

SECOND EDITION

DNA Repair and Mutagenesis

SECOND EDITION

DNA Repair and Mutagenesis

Errol C. Friedberg

Department of Pathology, University of Texas
Southwestern Medical Center, Dallas, Texas

Richard D. Wood

Hillman Cancer Center, University of
Pittsburgh, Pittsburgh, Pennsylvania

Graham C. Walker

Department of Biology, Massachusetts
Institute of Technology, Cambridge,
Massachusetts

Roger A. Schultz

Department of Pathology, University of Texas
Southwestern Medical Center, Dallas, Texas

Wolfram Siede

Department of Cell Biology and Genetics,
University of North Texas Health Science
Center, Fort Worth, Texas

Tom Ellenberger

Department of Biological Chemistry and
Molecular Pharmacology, Harvard Medical
School, Boston, Massachusetts



**ASM
PRESS**

WASHINGTON, D.C.

Address editorial correspondence to ASM Press, 1752 N St. NW, Washington, DC 20036-2904, USA

Send orders to ASM Press, P.O. Box 605, Herndon, VA 20172, USA
Phone: 800-546-2416; 703-661-1593
Fax: 703-661-1501
E-mail: books@asmusa.org
Online: estore.asm.org

Copyright © 2006 ASM Press
American Society for Microbiology
1752 N St. NW
Washington, DC 20036-2904

Library of Congress Cataloging-in-Publication Data

DNA repair and mutagenesis / Errol C. Friedberg . . . [et al.].—2nd ed.
p. cm.

First ed. published in 1995, entered: Friedberg, Errol C.

Includes bibliographical references and index.

ISBN 1-55581-319-4

1. DNA repair. 2. Mutagenesis. I. Friedberg, Errol C. II. Friedberg, Errol C.
DNA repair and mutagenesis.

OH467.F753 2005
572.8'6459—dc22

2005045353

10 9 8 7 6 5 4 3 2 1

All rights reserved
Printed in the United States of America

Cover and interior design: Susan Brown Schmidler
Art rendering: Marty Burgin and Patrick Lane

Cover illustration: The MutS protein (red and white ribbon) is a sensor of mismatched base pairs in DNA (gold), coupling ATP turnover with mismatch recognition (1, 2). The disk-shaped MutS dimer encircles the bound DNA and stabilizes a sharp kink in the double helix. ATP binds to the dimer interface (bottom of figure) opposite the DNA and allosterically regulates DNA-binding affinity.

1. Lammers, M. H., A. Perrakis, J. Enzlin, H. H. K. Winterwerp, N. de Wind, and T. K. Sixma. 2000. The crystal structure of DNA mismatch repair protein MutS binding to a GT mismatch. *Nature* 407:711–717.

2. Obmolova, G., C. Ban, P. Hsieh, and W. Yang. 2000. Crystal structures of mismatch repair protein MutS and its complex with a substrate DNA. *Nature* 407:703–710.

For Rhonda, Jan, Jenny, Enid, Lisa, and Mary

About the Authors



(Left to right) Tom Ellenberger, Rick Wood, Roger Schultz, Errol Friedberg, Wolfram Siede, Graham Walker

Errol C. Friedberg, MD, received his training as a medical student at the University of the Witwatersrand, Johannesburg, South Africa, and did postdoctoral training in pathology and in biochemistry at Case Western Reserve University, Cleveland, Ohio. Following 19 years on the faculty at Stanford University, he assumed his present position as the Senator Betty and Dr. Andy Andujar Distinguished Chair in Pathology at the University of Texas Southwestern Medical Center at Dallas in 1990. He is the author of *DNA Repair* and is the senior author of the first edition of *DNA Repair and Mutagenesis*. He also authored *Cancer Answers—Encouraging Answers to 21 Questions You Were Always Afraid To Ask*, *Correcting the Blueprint of Life—an Historical Account of the Discovery of DNA Repair Mechanisms*, and *The Writing Life of James D. Watson*, and he edited and annotated the work *Sydney Brenner—My Life in Science*. He is the recipient of the Rous-Whipple Award from the American Society of Investigative Pathology and is a Fellow of the American Academy of Microbiology. He has contributed over 300 papers to the scientific literature, mainly on biological responses to DNA damage.

Graham C. Walker, PhD, is a Professor in the Department of Biology at the Massachusetts Institute of Technology. He has worked in the area of DNA repair and mutagenesis for 30 years and also carries out research on the *Rhizobium*-legume symbiosis and its relationship to chronic *Brucella* pathogenesis. He has been named an American Cancer Society Research Professor for his contributions to basic research and an HHMI Professor for his contributions to undergraduate education. He has been elected to the American Academy of Arts and Sciences and to the American Academy of Microbiology. He served as the Editor in Chief of *Journal of Bacteriology* for 10 years and is a member of various editorial boards. Long active in

undergraduate education, he was in charge of the undergraduate program in biology at MIT for 15 years, served as Housemaster of an MIT dormitory, was named a Margaret MacVicar Faculty Fellow for his undergraduate teaching, and has founded an HHMI Education Group. He has contributed over 250 papers to the scientific literature and is a coauthor of the first edition of *DNA Repair and Mutagenesis*.

Wolfram Siede, PhD, received his doctorate in microbiology from the University of Frankfurt, Frankfurt, Germany. He did his postdoctoral training in the Departments of Pathology at Stanford University and the University of Texas Southwestern Medical Center. In 1996, he became Assistant Professor in a joint appointment by the Department of Radiation Oncology and the Winship Cancer Institute at Emory University, Atlanta, Ga. He is currently Associate Professor and Graduate Advisor in the Department of Cell Biology and Genetics at the University of North Texas Health Science Center in Fort Worth. His research focus is on DNA repair, mutagenesis, and cell cycle regulation in yeast. He has published extensively on many aspects of eukaryotic DNA damage responses and is a coauthor of the first edition of *DNA Repair and Mutagenesis*.

Richard D. Wood, PhD, performed his graduate study in biophysics at the University of California, Berkeley, and obtained his PhD in 1981. This was followed by postdoctoral work at Yale University and at the Imperial Cancer Research Fund (ICRF) in the United Kingdom. After leading a research group at the Clare Hall Laboratories of the ICRF until 2001, he was appointed the Richard Cyert Professor of Molecular Oncology at the University of Pittsburgh. His research has focused on the molecular biology and

biochemistry of DNA repair and mutagenesis. He is a recipient of the Meyenburg Prize for Cancer Research, an elected member of the European Molecular Biology Organization (EMBO), and a Fellow of the Royal Society.

Roger A. Schultz, PhD, performed his graduate training in an interdepartmental program in genetics at Michigan State University in East Lansing in 1980. Following postdoctoral work in the Department of Pathology at Stanford University, he assumed a faculty position at the University of Maryland at Baltimore in the Division of Human Genetics in the School of Medicine. He moved to the McDermott Center for Human Growth and Development and the Department of Pathology at the University of Texas Southwestern Medical Center at Dallas in 1993. He has focused his research interests on human diseases with relevance to genomic instability. He served as Director of the Chromosome 15 DNA Sequencing Project within the Genome Sciences and Technology Center at UT Southwestern, again with a focus on human genomic integrity. More recently, he has added a more clinical focus to his activities as Associate Director of the Veripath Clinical Cytogenetic Laboratory at UT Southwestern.

Tom Ellenberger, DVM PhD, was trained as a veterinarian at Iowa State University before pursuing graduate studies in molecular biology and pharmacology at Harvard Medical School. Following postdoctoral studies in structural biology at Harvard College, he joined the faculty of Harvard Medical School in 1993, where he is the Hsien Wu and Daisy Yen Wu Professor of Biological Chemistry and Molecular Pharmacology. His research interests are focused on the structural enzymology of DNA repair, replication, and recombination processes.

Contents

Preface xxv
Abbreviations xxix

PART I **Sources and Consequences of DNA Damage 1**

- 1 | Introduction: Biological Responses to DNA Damage 3**
 - Historical Reflections 3
 - The Problem of Constant Genomic Insult 4
 - Biological Responses to DNA Damage 4
 - DNA Repair 4
 - DNA Damage Tolerance and Mutagenesis 5
 - Other Responses to DNA Damage 6
 - Disease States Associated with Defective Responses to DNA Damage 6

- 2 | DNA Damage 9**
 - Endogenous DNA Damage 9
 - Spontaneous Alterations in DNA Base Chemistry 9
 - Mismatches Created by DNA Replication Errors 24
 - Environmental DNA Damage 25
 - DNA Damage by Radiation 25
 - Chemical Agents That Damage DNA 35
 - DNA Damage and Chromatin Structure 48
 - UV Photoproduct Formation Is Influenced by Chromatin Structure and Binding of Other Proteins 48
 - Chromosomal Structure and Bound Proteins Can Protect against DNA Damage in Bacteria 49
 - Detection of DNA Damage by Proteins 50
 - Structural Information Is Encoded in DNA 50
 - Binding to Single-Stranded DNA 54
 - Locating Sites of DNA Damage 55
 - Summary and Conclusions 57

3	Introduction to Mutagenesis	71
	Mutations and Mutants: Some Definitions	71
	Point Mutations and Other Classes of Mutations	73
	Base Substitution Mutations	73
	Mutations Resulting from the Addition or Deletion of Small Numbers of Base Pairs	74
	Systems Used To Detect and Analyze Mutations	75
	Early Systems for the Analysis of Mutagenesis	75
	The Ames <i>Salmonella</i> Test: a Widely Used Reversion System	76
	<i>E. coli LacI</i> : an Example of a Forward Mutational System	77
	Other Examples of Forward Mutational Systems	78
	Special Systems To Detect Frameshift or Deletion Mutations	78
	Analysis of Mutagenesis in Mammalian Cells	79
	Use of Site-Specific Adducts	85
	Replication Fidelity and DNA Polymerase Structure	86
	Templated Information in DNA	86
	Energetics of Base Pairing	87
	Geometric Selection of Nucleotides during DNA Synthesis	87
	A Two-Metal-Ion Mechanism for DNA Synthesis	90
	Open and Closed Conformations of DNA Polymerases	92
	Importance of Base-Pairing Geometry versus Hydrogen Bonds	92
	Selection against Ribonucleotides	93
	Proofreading during DNA Synthesis	93
	Lesion Bypass by Error-Prone DNA Polymerases	95
	Conclusions about Replicative Fidelity	98
	Mechanisms Contributing to Spontaneous Mutagenesis	98
	Base Substitution Mutations Resulting from Misincorporation during DNA Synthesis	98
	Mutations Resulting from Misalignments during DNA Synthesis	99

PART 2

Correcting Altered Bases in DNA: DNA Repair 107

4	Reversal of Base Damage Caused by UV Radiation	109
	Direct Reversal Is an Efficient Strategy for Repairing Some Types of Base Damage Caused by UV Radiation	109
	Enzymatic Photoreactivation of Base Damage Caused by UV Radiation	109
	Not All Light-Dependent Recovery Effects Are Enzyme Catalyzed	110
	Enzymatic Photoreactivation Was Discovered by Accident	110
	Enzymes That Catalyze Photoreactivation of Cyclobutane Pyrimidine Dimers Are Members of an Extended Family of Blue-Light Receptor Proteins	112
	Pyrimidine Dimer-DNA Photolyases	112
	Distribution of Pyrimidine Dimer-DNA Photolyases in Nature	112
	Measuring and Quantitating Pyrimidine Dimer-DNA Photolyase Activity	113
	Properties and Mechanism of Action of Pyrimidine Dimer-DNA Photolyases	114
	Structural Studies of Pyrimidine Dimer-DNA Photolyases	119
	DNA Substrate Recognition and Electron Transfer by Photoproduct-DNA Photolyases	121
	Pyrimidine Dimer-DNA Photolyases from Other Organisms	123
	Therapeutic Use of Pyrimidine Dimer-DNA Photolyase for Protection against Sunlight	127
	(6-4) Photoproduct-DNA Photolyases	128
	(6-4) Photoproduct-DNA Photolyases Are Ubiquitous	128

- Mechanism of Action of (6-4) Photoproduct-DNA Photolyases 129
- The C-Terminal Region of (6-4) Photoproduct-DNA Photolyases Is Conserved 129
- Reduced Dihydroflavin Adenine Dinucleotide Is the Active Form of (6-4) Photoproduct-DNA Photolyase 131
- Photolyase/Blue-Light Receptor Family 131**
- Phylogenetic Relationships 132
- Repair of Thymine Dimers by a Deoxyribozyme? 132**
- Photoreactivation of RNA 133**
- Reversal of Spore Photoproduct in DNA 133**
- Formation of Spore Photoproduct 133
- Repair of Spore Photoproduct 134
- 5 Reversal of Alkylation Damage in DNA 139**
- Adaptive Response to Alkylation Damage in Bacteria 139**
- A Bit of History 139
- The Adaptive Response Defined 140
- Adaptation to Cell Killing and Adaptation to Mutagenesis Are Independent Processes 140
- Repair of O^6 -Alkylguanine and O^4 -Alkylthymine in DNA 141**
- A New DNA Repair Mechanism 141
- O^6 -Alkylguanine-DNA Alkyltransferases of *E. coli* 142
- Role of Ada Protein in the Adaptive Response to Mutagenesis 146
- O^6 -Alkylguanine-DNA Alkyltransferase II 150
- DNA Alkyltransferases in Other Organisms 152
- Repair of N1-Methyladenine and N3-Methylcytosine in DNA 157**
- alkB*⁺ Gene of *E. coli* 157
- Therapeutic Applications and Implications of the Repair of Alkylation Damage in DNA 161
- Genetic Polymorphisms in the O^6 -MGMT Gene 162
- Teleological Considerations Concerning the Reversal of Alkylation Base Damage in DNA 162
- Repair of a Specific Type of Single-Stranded DNA Break by Direct Reversal 162**
- Summary and Conclusions 163**
- 6 Base Excision Repair 169**
- DNA Glycosylases 169**
- Many DNA Glycosylases Are in the Helix-Hairpin-Helix Superfamily 171
- Uracil-DNA Glycosylases Remove Uracil from DNA 173
- Some DNA Glycosylases Remove Methylated Bases 180
- Several Enzymes Function To Limit Oxidized and Fragmented Purine Residues 186
- DNA Glycosylases That Remove Oxidized and Fragmented Pyrimidine Residues 191
- Some Organisms Have Pyrimidine Dimer-DNA Glycosylases 192
- Summary Comments on DNA Glycosylases 196
- Apurinic/Apyrimidinic Endonucleases 197**
- Exonuclease III (XthA) Family of AP Endonucleases 198
- Endonuclease IV (Nfo) Family of AP Endonucleases 200
- Postincision Events during Base Excision Repair 202**
- Gap Filling and Deoxyribosephosphate Removal in *E. coli* 202
- Gap Filling and Deoxyribosephosphate Removal in Mammalian Cells 203
- Several Mechanisms Control the Fidelity of Base Excision Repair in Mammalian Cells 204
- Structure and Mechanism of DNA Ligases 204

	Polynucleotide Kinase Phosphatase in Base Excision Repair	210
	Poly(ADP-Ribose) Polymerases in Base Excision Repair	210
	Sequential Interactions between Proteins in Base Excision Repair	213
	Base Excision Repair and Chromatin	214
7	Nucleotide Excision Repair: General Features and the Process in Prokaryotes	227
	Introduction to Nucleotide Excision Repair	227
	Historical Perspectives and Terminology	227
	Revised Nomenclature for Nucleotide Excision Repair	228
	Nucleotide Excision Repair in <i>E. coli</i>	228
	UvrABC DNA Damage-Specific Endonuclease of <i>E. coli</i>	229
	Damage-Specific Incision of DNA during Nucleotide Excision Repair in <i>E. coli</i>	229
	Recognition of Base Damage during Nucleotide Excision Repair in <i>E. coli</i>	238
	DNA Incision Is Bimodal during Nucleotide Excision Repair In Prokaryotes	244
	A Second Endonuclease Can Catalyze 3' DNA Incision during Nucleotide Excision Repair in <i>E. coli</i>	245
	Further Considerations about Nucleotide Excision Repair in Prokaryotes	247
	Postincisional Events during Nucleotide Excision Repair: Excision of Damaged Nucleotides, Repair Synthesis, and DNA Ligation	249
	Long-Patch Excision Repair of DNA	252
	DNA Ligation	253
	Miscellaneous Functions Possibly Associated with Nucleotide Excision Repair	253
	Nucleotide Excision Repair in Other Prokaryotes	253
	<i>Micrococcus luteus</i>	253
	<i>Deinococcus radiodurans</i>	253
	Other Organisms	254
	Nucleotide Excision Repair Proteins Can Be Visualized in <i>B. subtilis</i>	254
	Nucleotide Excision Repair Occurs in Some Members of the <i>Archaea</i>	255
	Coupling of Transcription and Nucleotide Excision Repair in <i>E. coli</i>	255
	<i>mfd</i> ⁺ Gene and Transcription Repair Coupling Factor	255
	Transcription Repair Coupling Factor Is Involved in Transcription Functions in the Absence of DNA Damage	257
	Detection and Measurement of Nucleotide Excision Repair in Prokaryotes	257
	Excision of Damaged Bases	257
	Measurement of Repair Synthesis	258
	Summary	260
8	Nucleotide Excision Repair in Eukaryotes: Cell Biology and Genetics	267
	Cell Biology of Nucleotide Excision Repair in Eukaryotes	269
	Experimental Demonstration of Nucleotide Excision Repair in Eukaryotic Cells	269
	Kinetics of Nucleotide Excision Repair in Eukaryotic Cells	274
	Genetics of Nucleotide Excision Repair in Eukaryotic Cells	274
	Mammalian Cells	274
	Genetics of Nucleotide Excision Repair in the Yeast <i>S. cerevisiae</i>	276
	Genetics of Nucleotide Excision Repair in Other Eukaryotes	278
	Genes and Proteins Involved in Nucleotide Excision Repair in Eukaryotes	281
	Mammalian XPA and Its Yeast Ortholog <i>RAD14</i>	281
	Replication Protein A	282
	Budding Yeast <i>RAD1</i> and <i>RAD10</i> , and the Mammalian Orthologs <i>XPF</i> and <i>ERCC1</i>	284
	Yeast <i>RAD2</i> and Its Mammalian Ortholog, <i>XPG</i>	291
	Yeast <i>RAD4</i> , Mammalian <i>XPC</i> , and Their Association with Rad23 Homologs	292

- Yeast and Mammalian Genes That Encode Subunits of TFIIH 296
MMS19 Gene and *MMS19* Protein 299
Yeast *RAD7* and *RAD16* Genes and Rad7 and Rad16 Proteins 299
DNA Damage-Binding Protein and the Gene Defective in XP Group E 301
Understanding the Mechanism of Nucleotide Excision Repair 303

9 Mechanism of Nucleotide Excision Repair in Eukaryotes 317

Biochemical Strategies for Dissection of the Nucleotide Excision Repair Mechanism 318

- Nucleotide Excision Repair in Cell Extracts 318
Permeabilized Cell Systems Can Identify Factors Involved in Nucleotide Excision Repair 320
Microinjection of DNA Repair Factors 321

Reconstitution of Nucleotide Excision Repair Defines the Minimal Components 322

- Nucleotide Excision Repair in Mammalian Cells Can Be Reconstituted with Purified Components 322
Reconstitution of the Incision Reaction of Nucleotide Excision Repair in *S. cerevisiae* with Purified Components 323

TFIIH in Nucleotide Excision Repair: Creation of an Open Intermediate for Dual Incision 323

- TFIIH Functions Independently in Nucleotide Excision Repair and in Transcription Initiation 323
TFIIH Harbors 10 Subunits and Two Enzymatic Activities 324
Core TFIIH Contains a Ring-Like Structure 325
TFIIH Performs Helix Opening in Transcription Initiation 325
TFIIH Performs Helix Opening during Nucleotide Excision Repair 326
Additional Functions of TFIIH 326

DNA Damage Recognition Mechanism in Nucleotide Excision Repair 327

- Different Lesions Have Different Repair Efficiencies and Sites of Dual Incision 327
XPC-RAD23B as a Distortion Recognition Factor in Nucleotide Excision Repair 328
Bipartite Mechanism of DNA Damage Recognition during Nucleotide Excision Repair 328
Role of *DDB* Protein in Nucleotide Excision Repair 331

Mechanisms of Assembly and Action of the Nucleotide Excision Repair Machinery 331

- Interactions between the Protein Components of Nucleotide Excision Repair 331
Nucleotide Excision Repair Subassemblies and Order of Action In Vitro 332
In Vivo Dynamics of Nucleotide Excision Repair 334

Repair Synthesis during Nucleotide Excision Repair 336

- DNA Polymerases δ and ϵ and Their Participation in Nucleotide Excision Repair 336
Proliferating-Cell Nuclear Antigen in Nucleotide Excision Repair 337
Replication Factor C in Nucleotide Excision Repair 338

Oligonucleotide Excision and Ligation in Nucleotide Excision Repair 339

- Oligonucleotide Excision during Nucleotide Excision Repair in Eukaryotes 339
DNA Ligation during Nucleotide Excision Repair in Eukaryotes 339

DNA Topoisomerases and Nucleotide Excision Repair 339

Modulation and Regulation of Nucleotide Excision Repair in Eukaryotes 340

- The Proteasome and Regulation of Nucleotide Excision Repair 340
Protein Phosphorylation Influences Nucleotide Excision Repair 342

Evolution of the Eukaryotic Nucleotide Excision Repair System 343

- Eukaryotic and Prokaryotic Nucleotide Excision Repair Mechanisms Use Similar Strategies 343

Most Eukaryotic Nucleotide Excision Repair Proteins Also Have Functions in Other Aspects of DNA Metabolism 343

10 Heterogeneity of Nucleotide Excision Repair in Eukaryotic Genomes 351

Influence of Chromatin and Higher-Order Structure on Nucleotide Excision Repair in Mammalian Cells 351

Chromatin Is Compactly Organized yet Subject to Dynamic Reorganization 351

Chromatin Remodeling and Nucleotide Excision Repair 354

Chromatin Reassembly Coupled to Nucleotide Excision Repair 356

Other Aspects of Intragenomic Heterogeneity of Nucleotide Excision Repair 358

Nucleotide Excision Repair in Transcribed versus Nontranscribed Regions 359

Introduction and Definition of Terms 359

Transcription-Coupled Nucleotide Excision Repair 360

Proteins That Participate in Transcription-Coupled Nucleotide Excision Repair 363

Cells Have Several Strategies To Deal with Stalled RNA Polymerase II 365

Biological Importance of Transcription-Coupled Nucleotide Excision Repair 368

Other Aspects of Transcription-Coupled Nucleotide Excision Repair 369

Summary 371

11 Alternative Excision Repair of DNA 379

Alternative Excision Repair Involving Endonuclease V 379

Endonuclease V of *E. coli* 379

Deoxyinosine 3' Endonuclease of *E. coli* 380

Endonuclease V and Deoxyinosine 3' Endonuclease of *E. coli* Are the Same Protein, Encoded by the *E. coli nfi*⁺ Gene 380

Endonuclease V of *E. coli* Is Conserved 380

Mammalian Homolog of Endonuclease V 381

Endonuclease V of *E. coli* Prevents Mutations Associated with Deamination of Bases 382

Nitrosating Agents Can Damage DNA 382

Endonuclease V of *E. coli* Prevents Cell Death Associated with the Presence of Hydroxylaminopurine in DNA 383

How Does Endonuclease V-Mediated Alternative Excision Repair Occur? 383

Alternative Excision Repair Mediated by Other Endonucleases 383

S. pombe DNA Endonuclease 383

S. pombe DNA Endonuclease in Other Organisms 384

What Is the Substrate Specificity of UVDE-Type Endonucleases? 385

Other Substrates Recognized by UVDE-Type Endonucleases 385

Uve1-Dependent Alternative Excision Repair of Mitochondrial DNA in *S. pombe* 385

How Does Uve1-Dependent Alternative Excision Repair Transpire? 386

Other Alternative Excision Repair Pathways? 386

Tyrosyl-DNA Phosphodiesterase: a Repair Reaction for Topoisomerase-DNA Complexes 387

Summary 387

12 Mismatch Repair 389

Early Biological Evidence for the Existence of Mismatch Repair 390

Genetic Phenomena Suggesting the Existence of Mismatch Repair 390

DNA Mismatch Repair in Prokaryotes 390

Mismatch Repair after Transformation of *S. pneumoniae* 391

In Vivo Analyses of Methyl-Directed Mismatch Repair in *E. coli* 392

Biochemical Pathway of *E. coli* Methyl-Directed Mismatch Repair 396

DNA Mismatch Repair in Eukaryotes 402

Early In Vivo Evidence Suggesting the Existence of Mismatch Repair in Yeasts and Fungi 402

MutS and MutL Homologs in Eukaryotic Cells 403

Defects in Mismatch Repair Genes Are Associated with Hereditary Nonpolyposis Colon Cancer 406

In Vitro Analyses of Mismatch Repair in Eukaryotic Cells 406

Relationship of Structure to Function of Mismatch Repair Proteins 409

MutS Structure 409

MutH Structure 411

MutL Structure 412

Unresolved Issues Concerning the Mechanism of Mismatch Repair 413

Molecular Basis of Strand Discrimination during Mismatch Repair 413

How Are Downstream Events Signaled in Mismatch Repair? 413

Effects of DNA Mismatch Repair on Genetic Recombination 416

Effect of Mismatch Repair on Recombination between Highly Homologous Sequences 416

Effects of Mismatch Repair on Recombination between Substantially Diverged Sequences 417

Effects of Mismatch Repair on Speciation, Adaptation, and Evolution 422

Possible Role for Mismatch Repair in Speciation 422

Cyclical Loss and Reacquisition of Mismatch Repair Play a Role in the Evolution of Bacterial Populations 422

Effects of Mismatch Repair on Adaptive Mutagenesis 423

Special Implications of Mismatch Repair Status for Pathogenic Bacteria 424

Mismatch Repair and Meiosis 424

Roles for Mismatch Repair Proteins in Gene Conversion and Antirecombination during Meiosis 424

Roles for Mismatch Repair Proteins in Promoting Crossovers during Meiosis 424

Mismatch Repair Proteins and DNA Damage Recognition 427

Mismatch Repair Proteins and Alkylation Damage 427

Oxidative DNA Damage and Mismatch Repair 429

Cisplatin DNA Damage and Mismatch Repair 429

Mismatch Repair and Other Forms of DNA Damage 429

Roles of Mismatch Repair Proteins in Somatic Hypermutation and Class Switch Recombination in the Immune Response 429

Somatic Hypermutation 430

Class Switch Recombination 430

Are the Effects of Mismatch Repair Proteins on Somatic Hypermutation and Class Switch Recombination Direct or Indirect? 430

Mismatch Repair and Cadmium Toxicity 430

Specialized Mismatch Repair Systems 431

Very-Short-Patch Mismatch Correction in *E. coli* Corrects G·T Mismatches Generated by Deamination of 5-Methylcytosine 431

Correction of G·T Mismatches Generated by Deamination of 5-Methylcytosine in Eukaryotes 433

MutY-Dependent Mismatch Repair 433

13 Repair of Mitochondrial DNA Damage 449

Mitochondrial DNA 449

The Mitochondrial Genome 449

Mitochondrial Mutagenesis 449

DNA Damage in the Mitochondrial Genome 451

Mitochondrial DNA Repair 451

Reversal of Base Damage in Mitochondrial DNA 452

Mitochondrial Base Excision Repair 452

Monitoring Loss of Damage from Mitochondrial DNA 453

Removal of Oxidative Damage from Mitochondrial DNA 453

Enzymes for Base Excision Repair in Mitochondrial Extracts 454

Short-Patch Base Excision Repair of Mitochondrial DNA 455

Age-Related Studies of Mitochondrial DNA Repair 455

Alternative Excision Repair Pathway in Mitochondria? 456

Recombinational Repair in Mitochondrial DNA? 457

Summary 457

PART 3

DNA Damage Tolerance and Mutagenesis 461

14 The SOS Responses of Prokaryotes to DNA Damage 463

The SOS Responses 463

Current Model for Transcriptional Control of the SOS Response 464

Physiological and Genetic Studies Indicate the Existence of the SOS System 465

Induced Responses 465

Genetic Studies of *recA* and *lexA* 466

Essential Elements of SOS Transcriptional Regulation 469

Proteolytic Cleavage of λ Repressor during SOS Induction 470

Induction of RecA Protein 471

LexA Protein Represses Both the *recA*⁺ and *lexA*⁺ Genes 471

LexA Protein Is Proteolytically Cleaved in a RecA-Dependent Fashion 472

Mechanism of LexA Repressor Cleavage 473

Similarities between LexA, λ Repressor, UmuD, and Signal Peptidase 476

Nature of the RecA Interactions Necessary for LexA, UmuD, and λ Repressor Cleavage 477

Identification of Genes in the SOS Network 478

Identifying SOS Genes by the Use of Fusions 478

Identifying SOS Genes by Searching for Potential LexA-Binding Sites 479

Identifying SOS Genes by Expression Microarray Analysis 479

Generation of the SOS-Inducing Signal In Vivo 481

Double-Strand Breaks Are Processed by the RecBCD Nuclease/Helicase To Give Single-Stranded DNA Needed for SOS Induction 483

Generation of Single-Stranded DNA by Bacteriophage, Plasmids, or Transposons Leads to SOS Induction 483

An SOS-Inducing Signal Is Generated when Cells Attempt To Replicate Damaged DNA 484

Regions of Single-Stranded DNA in Undamaged Cells 485

SOS Induction Caused by Mutations That Affect the Normal Processing of DNA 485

The Special Case of Phage ϕ 80 Induction 486

Modeling the SOS Signal 486

Additional Subtleties in the Transcriptional Regulation of the SOS Responses 486

Strength and Location of SOS Boxes 486

DinI, RecX, and PsiB Proteins and *isfA* Affect SOS Regulation by Modulating RecA-Mediated Cleavage Reactions 488

Other Regulatory Systems Can Affect the Expression of SOS-Regulated Genes 489

Physiological Considerations of the SOS Regulatory Circuit 489

Levels of Control of the SOS Response besides Transcriptional Regulation 491

A Physiological Look at the SOS Responses 491

SOS-Induced Responses That Promote Survival while Maintaining the Genetic Integrity of the Genome 491

SOS-Induced Responses That Promote Survival while Destabilizing the Genetic Integrity of the Genome 492

SOS-Induced Responses That Destabilize the Genetic Integrity of the Genome 493

SOS-Induced Cell Cycle Checkpoints 495

Miscellaneous Physiological Effects of SOS Induction 495

SOS Responses in Pathogenesis and Toxicology 496

Relationships of the SOS Responses to Pathogenesis 496

Use of Fusions to SOS Genes To Detect Genotoxic Agents 497

SOS Responses in Other Bacteria 497

15 Mutagenesis and Translesion Synthesis in Prokaryotes 509

SOS-Dependent Mutagenesis: Requirements for Particular Gene Products 510

SOS Mutagenesis by UV Radiation and Most Chemicals Is Not a Passive Process 510

UmuD and UmuC Proteins Are Important for UV Radiation and Chemical Mutagenesis 511

Multiple Levels of Post-Translational Regulation of UmuD Protein: New Dimensions to SOS Regulation 514

Inferences about the Mechanism of SOS Mutagenesis Based on Mutational Spectra and Site-Directed Adduct Studies 523

The Original *lacI* System: a Purely Genetic Means of Determining Mutational Spectra 523

Mutational Spectra Obtained by Direct DNA Sequencing 524

Factors Influencing the Mutational Spectrum for a Given Mutagen 524

Influence of Transcription-Coupled Excision Repair on Mutational Spectra 525

Identification of Premutagenic Lesions 525

More Complex Lesions as Premutagenic Lesions 532

SOS Mutator Effect 534

The Road to Discovering the Molecular Mechanism of SOS Mutagenesis 535

A Further Requirement for RecA Protein in SOS Mutagenesis besides Facilitating LexA and UmuD Cleavage 535

DNA Polymerases I and II Are Not Required for SOS Mutagenesis 536

Evidence Relating DNA Polymerase III to SOS Mutagenesis 536

Influence of the "Two-Step" Model for SOS Mutagenesis 537

Initial Efforts To Establish an In Vitro System for SOS Mutagenesis 537

UmuC-Related Proteins Are Found in All Three Kingdoms of Life 538

dinB, *umuDC*, and *mucAB* Encode Members of the Y Family of Translesion DNA Polymerases 539

Rev1 Catalyzes the Formation of Phosphodiester Bonds: Rad30 and Xeroderma Pigmentosum Variant Protein Are DNA Polymerases 539

DinB Is a DNA Polymerase 539

umuDC Encodes a Translesion DNA Polymerase, DNA Pol V, That Requires Accessory Proteins 540

mucAB Encodes a Translesion DNA Polymerase, DNA Pol R1, That Requires Accessory Proteins 542

The Structure of Family Y DNA Polymerases Accounts for Their Special Ability To Carry Out Translesion Synthesis 543

	Multiple SOS-Induced DNA Polymerases Can Contribute to SOS-Induced Mutagenesis	543
	Protein-Protein Interactions That Control the Activities of the <i>umuDC</i> and <i>dinB</i> Gene Products	543
	RecA and SSB Interactions with DNA Pol V	545
	Interactions of the β Sliding Clamp with DNA Polymerases V and IV	546
	Interactions of UmuD and UmuD' with Components of DNA Polymerase III	548
	How Is Polymerase Switching Controlled?	549
	What Is the Biological Significance of SOS Mutagenesis and Translesion Synthesis by Specialized DNA Polymerases?	551
	Translesion DNA Polymerases Can Contribute to Fitness and Survival in Two Ways	551
	Action of Translesion DNA Polymerases in Stationary Phase, Aging, and Stressed Bacteria	551
	SOS-Independent Mutagenesis	554
	Lesions That Do Not Require Induction of SOS Functions To Be Mutagenic	554
	The UVM (UV Modulation of UV Mutagenesis) Response	555
	Mutagenesis Resulting from the Misincorporation of Damaged Nucleotides	555
16	Recombinational Repair, Replication Fork Repair, and DNA Damage Tolerance	569
	DNA Damage Can Interfere with the Progress of Replication Forks and Lead to the Generation of Various Structures	570
	Formal Considerations	570
	The In Vivo Situation Is More Complicated	571
	Transient Partial Inhibition of DNA Replication after DNA Damage	573
	Various DNA Structures Resulting Directly or Indirectly from DNA Damage Can Be Processed by Homologous Recombination Proteins	574
	RecA Protein: a Protein with Mechanistic Roles in Homologous Recombination and DNA Repair	574
	Other Key Proteins with Roles in Homologous Recombination	579
	Recombinational Repair of Double-Strand Breaks in <i>E. coli</i>	584
	Model for Damage Tolerance Involving the Recombinational Repair of Daughter Strand Gaps	586
	Evidence Supporting the Model for Recombinational Repair of Daughter Strand Gaps	586
	Perspectives on Daughter Strand Gap Repair	590
	An Error-Free Process(es) Involving Recombination Functions Predominates over Mutagenic Translesion Replication in a Model In Vivo System	592
	Homologous Recombination Functions Play Critical Roles in the Stabilization and Recovery of Arrested or Collapsed Replication Forks	593
	Recognition of Fundamental Relationships between Replication and Recombination	593
	Possible Mechanisms for Regressing Replication Forks	598
	Models of Nonmutagenic Mechanisms for Restarting Regressed DNA Replication Forks Arrested by a Lesion Affecting Only One Strand of the DNA Template	599
	Models of Nonmutagenic Mechanisms for Restarting Regressed DNA Replication Forks Arrested by a Lesion or Blocks Affecting Both Strands of the DNA Template	602
	Recovery of DNA Replication after DNA Damage: "Inducible Replisome Reactivation/Replication Restart"	603
	Polymerases Participating in Inducible Replisome Reactivation/Replication Restart Revisited	603
17	DNA Damage Tolerance and Mutagenesis in Eukaryotic Cells	613
	Phenomenology of UV Radiation-Induced Mutagenesis in the Yeast <i>Saccharomyces cerevisiae</i>	613

- Insights from Mutational Spectra: the *SUP4-o* System 613
- Studies with Photoproducts at Defined Sites 615
- Untargeted Mutagenesis in *S. cerevisiae* Cells Exposed to UV Radiation 616
- Timing and Regulation of UV Radiation-Induced Mutagenesis 616

Phenomenology of UV Radiation-Induced Mutagenesis in Mammalian Cells 617

- DNA Replication in UV-Irradiated Cells 617
- Inducibility of Mutagenic Processes in Mammalian Cells? 621
- Mutational Specificity of UV Radiation-Induced Lesions 622
- Summary and Conclusions 629

Molecular Mechanisms of Eukaryotic DNA Damage Tolerance and Mutagenesis 629

- Genetic Framework in *S. cerevisiae* 629
- DNA Polymerase ζ 629
- Rev1 Protein 631
- DNA Polymerase η 632
- Other Vertebrate Lesion Bypass Polymerases 636
- Handling of DNA Lesions by Bypass Polymerases: Synopsis and Comparison with In Vivo Data 638
- Somatic Hypermutation 639
- The *RAD6* Epistasis Group Dissected: Defining Error-Prone and Error-Free Tolerance Mechanisms 642
- Role of PCNA in Orchestrating the Choice of Damage Tolerance Pathways 647

Summary and Conclusions 649

18 Managing DNA Strand Breaks in Eukaryotic Cells: Repair Pathway Overview and Homologous Recombination 663

Overview of Various Pathways for Double-Strand Break Repair in Eukaryotes 663

***Saccharomyces cerevisiae* as a Model System for Detecting Double-Strand Breaks and Their Repair 665**

Experimental Systems To Study Responses to Localized DNA Double-Strand Breaks 668

- The HO Endonuclease System 668
- Generation of Double-Strand Breaks in Conditional Dicentric Chromosomes 668
- I-SceI-Induced Targeted Double-Strand Breaks 669

Homologous Recombination 671

- End Processing as the Initiating Step 671
- Pairing and Exchanging of Homologous DNA: Rad51, Its Orthologs, Paralogs, and Interacting Partners 671
- Role of Cohesin Proteins 681
- The BRCA/Fanconi Pathway 682
- Holliday Structure Resolution 685

Synthesis-Dependent Strand Annealing and Break-Induced Replication 687

Single-Strand Annealing 688

Transcription and Recombination 689

UV Radiation-Stimulated Recombination 690

Repair of DNA Interstrand Cross-Links 690

- Interstrand Cross-Link Repair in *E. coli* 691
- Interstrand Cross-Link Repair in *S. cerevisiae* 692
- Interstrand Cross-Link Repair in Higher Eukaryotes 695

Summary 696

19	Managing DNA Strand Breaks in Eukaryotic Cells: Nonhomologous End Joining and Other Pathways	711
	Nonhomologous End Joining	711
	Introduction	711
	V(D)J Recombination	712
	Class Switch Recombination	714
	Roles of the Ku Proteins	715
	DNA-Dependent Protein Kinase	718
	Artemis: a Human SCID Syndrome Reveals a Player in Nonhomologous End Joining	721
	Ligation Step of Nonhomologous End Joining	722
	Synopsis: Model for Vertebrate Nonhomologous End Joining	724
	The Mre11-Rad50-NBS1/Xrs2 Complex	724
	Yeast Rad50, Mre11, and Xrs2 Function in Double-Strand Break Repair and Meiosis but Are Not Essential for Homologous Recombination	725
	Two MRN Complex Components Are Associated with Human Genomic Instability Syndromes	726
	Null Mutations of MRN Components Are Lethal in Mammalian Cells, and Hypomorphic Mutations Result in Severe Developmental Consequences	726
	Focus Formation of the MRN Complex at Sites of Double-Strand Breaks	727
	In Vitro DNA-Processing Activities of the MRN Complex	727
	The MRN Complex in Nonhomologous DNA End Joining: a Major Role in <i>S. cerevisiae</i> but Possibly Not in Vertebrates	728
	Role of the MRN Complex in Homologous Recombination	730
	Significance of Nuclease Activity	731
	Special Roles of the MRN Complex in Replication and Telomere Maintenance	731
	“Molecular Velcro” and Beyond: Models for MRN Action Based on Structural Analysis	733
	Conclusions	734
	Histone Modifications and Double-Strand Breaks	735
	Histone Phosphorylation	735
	Histone Acetylation	736
	Regulation of Pathway Choice	736
	Repair of Single-Strand Breaks	737
	Sources and Significance of Single-Strand Breaks	737
	Poly(ADP-Ribose) Polymerase as a Nick Sensor	738
	XRCC1 Is a Scaffold Protein Orchestrating Interactions among Multiple Single-Strand Break Repair Proteins	738

PART 4

Regulatory Responses to DNA Damage in Eukaryotes 751

20	Cell Cycle Checkpoints: General Introduction and Mechanisms of DNA Damage Sensing	753
	Cell Cycle Basics and the Emergence of the Checkpoint Concept	753
	Studying Checkpoints	757
	DNA Damage Sensing	758
	Defining Checkpoint-Triggering Damage and Sensor Proteins	758
	The ATM Protein as a Damage Sensor	760
	ATR Protein and Its Targeting Subunit	762
	PCNA- and RFC-Like Clamp and Clamp Loader Complexes	764

- Cross Talk between Sensors 765
- The MRN Complex Plays an Additional Role in Checkpoint Arrests 766
- Synopsis: Independent but Communicating Sensors Are Brought Together by Common Requirements 767
- Other Sensor Candidates 768
- Sensing UV Radiation Damage 768
- Damage Sensing in S Phase 769

21 | Cell Cycle Checkpoints: Signal Transmission and Effector Targets 779

Generation and Transmission of a Checkpoint-Activating Signal 779

- The Rad53^{Sc}/Cds1^{Sp}/CHK2^{Hs} Kinase 779
- Mediators Are Important for Activation of Rad53^{Sc}/Cds1^{Sp}/CHK2^{Hs} through DNA Structure Sensors 781
- Possible Mammalian Rad9^{Sc} Homologs 782
- S-Phase-Specific Activation of Rad53^{Sc}/Cds1^{Sp}/CHK2^{Hs} 783
- Chk1 Kinase: Different Roles in Different Organisms 783
- Activation of Chk1 Kinase in *S. pombe*, *X. laevis*, and Humans 784
- Summary: Pathways of Generating a Transmittable Damage Signal 784

Downstream Targets and Mechanisms That Regulate Cell Cycle Progression 785

- p53 as a Target of DNA Checkpoint Pathways 785
- DNA Damage-Induced G₁/S Arrest 791
- Modulation of S Phase in the Presence of DNA Damage 794
- DNA Damage-Induced G₂/M Arrest 798
- DNA Damage and the Regulation of M Phase 801
- Synopsis 802

Effector Targets That Modulate DNA Repair 802

- Repair Targets in Yeasts 802
- Repair Targets in Mammalian Cells 803

Other Regulatory Responses to DNA Damage 803

Summary 804

22 | Transcriptional Responses to DNA Damage 817

Introduction 817

- Phenotypic Characterization of Pathway Inducibility 817
- Analysis of Individual Genes 817
- Differential Screening 818
- Screens of Genome Arrays 818

***Saccharomyces cerevisiae* Genes Regulated in Response to DNA-Damaging Agents 818**

- Regulation of Ribonucleotide Reductase 818
- Inducibility of Genes Involved in DNA Repair and Damage Tolerance: a Look at Various Pathways 820
- Genome-Wide Approaches 823
- Synopsis: No Satisfying Answer to the Question of Significance 827

Vertebrate Genes Regulated in Response to DNA-Damaging Agents 828

- Overview 828
- p53 as a Transcription Factor 828
- E2F Transcription Factor Family 830
- Mammalian UV Radiation Response 831
- Transcriptional Response to Ionizing Radiation 835

Summary and Conclusions 837

- 23 | DNA Damage and the Regulation of Cell Fate 845**
- Adaptation and Cell Cycle Restart 846**
 - Damage Signaling and Adaptation in *Saccharomyces cerevisiae* 846
 - Adaptation and Cell Cycle Restart by Silencing of Downstream Effectors 847
 - Recovery in Multicellular Eukaryotes 847
 - Regulation of Apoptosis 848**
 - Introduction to Apoptotic Pathways 848
 - Activation of the Apoptosis Pathway by DNA Damage: the Roles of p53 Revisited 850
 - Role of DNA Damage Sensors and Transducers in Apoptosis 852
 - Additional Elements of DNA Damage-Induced Apoptosis 853
 - Senescence, Cancer, and the DNA Damage Connection 854**
 - Checkpoints and Cancer Therapy 856**

PART 5

Disease States Associated with Defective Biological Responses to DNA Damage 863

- 24 | Xeroderma Pigmentosum: a Disease Associated with Defective Nucleotide Excision Repair or Defective Translesion DNA Synthesis 865**
- A Huge Literature on Xeroderma Pigmentosum 865**
 - Primary Clinical Features 866**
 - Other Clinical Features 867
 - Incidence and Demographics 867**
 - Skin Cancer Associated with Xeroderma Pigmentosum 868**
 - Phenotypes of Xeroderma Pigmentosum Cells 868**
 - Chromosomal Abnormalities 868
 - Sensitivity to Killing by DNA-Damaging Agents 869
 - Hypermutability 869
 - Source of Mutations 869
 - Defective Nucleotide Excision Repair 870
 - Repair of Oxidative Damage and Its Relationship to Neurological Disorders in Xeroderma Pigmentosum 872
 - Defective Repair of Purine Cyclodeoxynucleosides 873
 - Genetic Complexity of Xeroderma Pigmentosum 874**
 - The Xeroderma Pigmentosum Heterozygous State 875
 - Molecular Pathology 875**
 - Xeroderma Pigmentosum from Genetic Complementation Group A 875
 - Xeroderma Pigmentosum from Genetic Complementation Group B 876
 - Xeroderma Pigmentosum from Genetic Complementation Group C 877
 - Xeroderma Pigmentosum from Genetic Complementation Group D 878
 - Xeroderma Pigmentosum from Genetic Complementation Group E 880
 - Mutations Have Only Been Found in the *DDB2* Gene in XP-E Group Cells 880
 - Xeroderma Pigmentosum from Genetic Complementation Group F 880
 - Xeroderma Pigmentosum from Genetic Complementation Group G 881
 - Summary 881
 - Unexplained Features of Xeroderma Pigmentosum 881
 - Cancer in Other Organs in Xeroderma Pigmentosum Individuals 881
 - Cancer Risk Assessment 882
 - Pathogenesis of Neurological Complications 882
 - Therapy 882

Mouse Models of Defective Nucleotide Excision Repair 882

- Mice Defective in the *Xpa* Gene 883
- Mice Defective in the *Xpc* Gene 884
- Mice Defective in the *Xpd* Gene 886
- Mice Defective in the *Xpe* Gene 886
- Mice Defective in the *Xpf* Gene 887
- Mice Defective in the *Xpg* Gene 887
- Mice Defective in the *Ercc1* Gene 887
- Mice Defective in the *Rad23A* and *Rad23B* Genes 887

Summary 887**25 Other Diseases Associated with Defects in Nucleotide Excision Repair of DNA 895****Cockayne Syndrome 895**

- Introduction 895
- Clinical Phenotypes 895
- Cellular Phenotypes 896
- Genetics 898

Other Clinical Entities Associated with Mutations in Cockayne Syndrome or XP Genes 905

- Cerebro-Oculo-Facio-Skeletal Syndrome 905
- UV Sensitive Syndrome 905
- Combined XP/CS Complex 906
- Allelic Heterogeneity in Xeroderma Pigmentosum 906
- Trichothiodystrophy 907
- The “Transcription Syndrome” Hypothesis of XP/CS and Trichothiodystrophy 909
- Direct Observations of Defective Transcription 910
- Molecular Defects in XP/CS and Trichothiodystrophy Cells 910
- Allele-Specific and Gene Dosage Effects in This Group of Diseases 912
- Skin Cancer in the Transcription Syndromes 913

Summary 913**26 Diseases Associated with Defective Responses to DNA Strand Breaks 919****Ataxia Telangiectasia (Louis-Bar Syndrome) 919**

- Clinical Features 919
- Cellular Phenotypes 920
- Identification of the Ataxia Telangiectasia-Mutated (*ATM*) Gene 924
- Atm* Mutant Mice 926

Nijmegen Breakage Syndrome 928

- Clinical Features 928
- Cellular Characteristics 928
- Identification of the Gene Mutated in Nijmegen Breakage Syndrome (*NBS1*) 929
- Nibrin and Nijmegen Breakage Syndrome Cellular Phenotypes 929
- Nbs1* Mutant Mice 929
- Genetic Heterogeneity 929
- Heterozygosity and Cancer Predisposition 930

Ataxia Telangiectasia-Like Disorder 930**DNA Ligase IV Mutations and Human Disease 930****Seckel Syndrome 930****Severe Combined Immunodeficiency 932**

- Clinical Features 933

Molecular Causes	934
Recombinase-Activating Gene Deficiencies (<i>RAG1</i> - or <i>RAG2</i> -Deficient Severe Combined Immunodeficiency)	935
Animal Models	935
Spinocerebellar Ataxia with Axonal Neuropathy	935

27 | Diseases Associated with Disordered DNA Helicase Function 947

Biochemistry of RecQ Helicases	947
Crystal Structures of DNA Helicases	949
Fluorescence Resonance Energy Transfer	950
DNA Helicases That Participate in DNA Replication	952
RecQ Helicases and Human Disease	953
RecQ Helicases in Model Organisms	953
RecQ Protein in <i>E. coli</i>	953
Yeast Homologs of RecQ	954
Bloom Syndrome	954
Clinical Features of Bloom Syndrome Include a Marked Cancer Predisposition	955
Autosomal Recessive Genetics of Bloom Syndrome	955
Chromosome Instability as a Hallmark of Bloom Syndrome Cells	955
Bloom Syndrome Cells Exhibit Defects Associated with the S Phase of the Cell Cycle	956
Bloom Syndrome Cells Manifest a Diversity of Subtle Defects in Enzymes Involved in DNA Repair	957
Somatic Recombination Events in Bloom Syndrome Cells Facilitate Mapping and Cloning of the <i>BLM</i> Gene	958
Interallelic Recombination and Its Potential Relevance to Bloom Syndrome	958
The <i>BLM</i> Gene Is a Member of the RecQ Family	958
Bloom Syndrome Heterozygotes May Be Predisposed to Cancer	959
The <i>BLM</i> Gene Product Is a RecQ-Like Helicase	960
<i>BLM</i> Gene Expression	960
BLM Protein Localization	961
Modulation of Sister Chromatid Exchange	961
Association of BLM with Other DNA Repair Functions	962
Models for the Study of BLM Function	963
The Molecular Function of BLM Protein	964
Werner Syndrome	965
Clinical Features	965
Genetics	966
Cellular Phenotype of Werner Syndrome Cells	966
Identification of the <i>WRN</i> Gene	966
WRN Protein Contains DNA Helicase and Exonuclease Activities	967
WRN Protein Interactions	967
WRN Expression	968
WRN Protein Function	968
Mutations in <i>RECQL4</i> Are Associated with Rothmund-Thomson Syndrome and RAPADILINO Syndrome	968
Clinical Features of Rothmund-Thomson Syndrome	968
Cellular Characteristics of Rothmund-Thomson Syndrome	968
Rothmund-Thomson Syndrome Patients Have Mutations in <i>RECQL4</i>	969
RAPADILINO Syndrome	969
Summary of Human Diseases Associated with Defects in the RecQ Family of DNA Helicase	971

28 | Additional Diseases Associated with Defective Responses to DNA Damage 979

- Hereditary Nonpolyposis Colon Cancer 980**
 - Clinical Presentation 980
 - Hereditary Nonpolyposis Colon Cancer and Microsatellite Instability 980
 - Hereditary Nonpolyposis Colon Cancer and Mismatch Repair 981
 - How Do Heterozygous Mutations Cause Cancer? 984
 - Mouse Models with Defects in Mismatch Repair Genes 985
 - Tumors in Homozygous Mutant Mice 985
- Fanconi Anemia 986**
 - Clinical Phenotypes 987
 - Genetics 988
 - Cellular Features 988
 - DNA Repair in Fanconi Anemia Cells 989
 - Genetic Complexity 989
 - Mouse Models 993
 - Final Comments 994

29 | Hereditary Diseases That Implicate Defective Responses to DNA Damage 1001

- Hereditary Cancer Predisposition Syndromes 1001**
 - Retinoblastoma 1004
 - Li-Fraumeni Syndrome 1006
 - Breast Cancer Predisposition Syndromes 1007
 - Predisposition to Gastrointestinal Tumors 1008
 - Skin Cancer Syndromes 1016
 - Additional Cancer Predisposition Syndromes 1018
- Disorders with Alterations in Chromatin Structure 1021**
 - Immunodeficiency-Centromeric Instability-Facial Anomalies Syndrome 1021
 - Roberts Syndrome 1023
 - Alpha-Thalassemia/Mental Retardation Syndrome, X-Linked 1025
 - Rett Syndrome 1025
 - Rubinstein-Taybi Syndrome 1026
 - Coffin-Lowry Syndrome 1026
 - Saethre-Chotzen Syndrome 1026
 - Dyskeratosis Congenita 1027
- DNA Repair and Its Association with Aging 1028**
 - Aging and the Age-Related Decline in DNA Repair 1028
 - Reversal of Aging and DNA Repair 1030
 - Array Analysis of Aging in Mammals 1030
 - Engineered Mouse Models for Aging 1030
 - Telomeres and Aging 1031
 - Hutchinson-Gilford Progeria Syndrome (Progeria) 1032
 - Down Syndrome (Trisomy 21) 1033

30 | DNA Polymorphisms in Gatekeeper and Guardian Genes 1049

- Human Genetic Variation 1050**
- DNA Structure/Repair-Related Methodologies for Single-Nucleotide Polymorphism Detection 1052**
 - Oligonucleotide Arrays 1052
 - Mismatch Repair Detection 1054
 - TDG/MutY Glycosylase Mismatch Detection 1054

MassEXTEND 1054
Stabilized Double D-Loops 1054

Assessing the Role of DNA Repair Gene Polymorphisms in Disease 1056

Statistics and Population-Based Studies 1056
Variability in DNA Repair Capacity 1057
Heterozygosity and DNA Repair Gene Mutations 1059
Heterozygosity for Genes Associated with Dominantly Inherited Disorders 1059
Heterozygosity for Genes Associated with Recessive Disorders 1061
Summarizing the Role of Heterozygosity 1061

DNA Repair Gene Polymorphisms 1062

DNA Repair Gene Single-Nucleotide Polymorphism Discovery 1062
Polymorphisms That Impact the Levels of Chemical-Induced DNA Damage 1062
Cytochrome P-450 Monooxygenase Gene 1062
Glutathione S-Transferase M1 Gene 1063
N-Acetyltransferase 2 Gene 1063
DNA Repair Gene Polymorphisms and Putative Cancer Risk 1064
Pharmacogenomics and DNA Repair Gene Polymorphisms 1067
Polymorphic Alleles and Functional Defects 1067
Summary 1070

Appendix 1081

Table 1 Nomenclature of DNA repair genes 1081
Table 2 Human hereditary diseases and defective cellular responses to DNA damage 1087

Index 1091

Preface

It has been a decade since the publication of the first edition of *DNA Repair and Mutagenesis*. It was noted in the preface then that “[I]n very recent times, progress in the DNA repair and mutagenesis fields has been particularly rapid. . . .” In fact, in recognition of the importance of mutagenesis as a fundamental aspect of DNA metabolism and the impressive gains made in our understanding of the intricate relationships between DNA repair and mutagenesis, the authors of the first edition elaborated the title *DNA Repair* used for the book published by W. H. Freeman in 1984.

The unabated progress of the DNA damage response field is reflected in further major changes in the present edition. The field has progressed to the point that a comprehensive treatment of the manifold responses to DNA damage (including sensing and signaling the presence of damage and other perturbations of DNA metabolism) now requires the efforts of an author group with expertise in multiple and diverse areas. Richard D. (Rick) Wood and Roger A. Schultz were invited to provide such expertise to bolster the team that wrote the first edition. Additionally, the inclusion of structural biologist Tom Ellenberger reflects our desire to incorporate the considerable recent contributions of protein structure to biology in general and the DNA repair field in particular. The six authors have labored to achieve a text that is seamlessly integrated.

The second edition of *DNA Repair and Mutagenesis* was initiated in late 1999. Our efforts to keep the final product manageable for the average reader notwithstanding, the size of the present work appropriately reflects the substantial growth of the field in the past decade. This edition is more a rewriting than a revision, and little of the text from the first edition remains. The first edition of *DNA Repair and Mutagenesis* comprised 14 chapters and contained about 400 illustrations. The present edition consists of 30 chapters divided into five major sections, and the text is adorned with more than 700 illustrations, including more than 80 structural representations. Additionally, more than ten thousand primary literature references are provided in full, reflecting the massive increase in the scientific literature through 2004.

We have strived to present readers with a comprehensive survey of the field, stressing basic principles wherever feasible but mainly describing the extensive progress achieved to date and highlighting the many problems remaining to be solved. We trust that our desire to represent the dynamic state of this active field of research will not hinder the primary educational purpose of this book, a basic text for advanced undergraduate and graduate students and a reference source for all students of DNA metabolism.

As was the case in the first edition, we have continued to present the field in a historical context, with the intent of sensitizing and inspiring students (and others) to the realities of how research progress unfolds and how ideas develop and attain maturity—or not. We have refrained

wherever possible from unadulterated dogma and from presenting the field of biological responses to DNA damage as anywhere near total clarification. While we are aware of presenting viewpoints that are sometimes controversial and even conflicting, we trust that readers, especially students, are not unduly confused or frustrated by our reluctance to always provide the final word, as it were. Rather, it is our hope that such controversies and complexities will inspire further studies.

The names of genes and their polypeptide products sometimes change with good reason as more is known about them and the families they belong to. Additionally, the value and utility of long-standing terminology are often challenged by new information. A textbook provides a valuable opportunity to address such revisions, and we have done so in some areas. However, we have consciously retained much original nomenclature in deference to historic recognition and popular usage.

No work of this sort can come to fruition without special assistance at every level. We owe an enormous debt of gratitude to many individuals for the help they have provided at every level of this labor. We have enjoyed scientific dialogues with an outstanding cadre of professional colleagues who have given unstintingly of their time, energy, and knowledge to review and discuss every chapter with us. In this respect, we owe particular thanks to Rafael Alvarez-Gonzalez, Carl Anderson, Daniel Bogenhagen, Rhona Borts, Vilhelm Bohr, Anne Casper, Stuart Clarkson, James Cleaver, Nils Confer, Richard Cunningham, Bruce Demple, Friederike Eckardt-Schupp, Andre Eker, Paula Fischhaber, Ann Ganesan, Myron Goodman, Thomas Glover, Philip Hanawalt, Ian Hickson, Peggy Hsieh, Sue Jinks-Robertson, Caroline Kisker, Beate Köberle, Nicole Kosarek, Y. W. Kow, Kenneth Kraemer, Susan LeDoux, Alan Lehmann, Michael Lieber, Tomas Lindahl, Sue Lovett, Carolina Marchetto, Lisa McDaniel, M. Stephen Meyn, Paul Modrich, Harvey Mohrenweiser, Robb Moses, Laura Niedernhofer, Shwetal Patel, Tony Pegg, Dean Rupp, Aziz Sancar, Gwen Sancar, Barbara Sedgwick, the late Erling Seeberg, Mutsuo Sekiguchi, Michael Smerdon, Kendrick Smith, Robert Sobol, David Stern, James Stivers, John Tainer, Gail Thomlinson, Takeshi Todo, Bennett van Houten, Harry van Steeg, Greg Verdine, Zhigang Wang, Bernard Weiss, Dale Wigley, Sam Wilson, Birgitte Wittschieben, John Wittschieben, Roger Woodgate, and Akira Yasui. Final responsibility naturally rests with us, and we apologize for any inaccuracies and omissions that remain in this publication. Readers are encouraged to inform us of these if and when they are discovered.

We particularly wish to acknowledge the outstanding artistic talent and the dedication and commitment of Marty Burgin, who also worked as illustrator for the first edition. This book is as much hers as ours. We are also extremely grateful to Patrick Lane, whose technological wizardry solved tricky problems in the rendering of crystal structures in shades of just two colors. We thank Jeff Holtmeier of ASM Press for providing his strong personal commitment and that of his staff throughout the production of this work. The magnificent job of editing of the manuscript by Yvonne Strong merits special mention. Thanks are also due to Susan Birch, Production Manager at ASM Press, and to Cathy Balogh and Susan Schmidler.

Each of us owes special thanks to particular individuals who provided indispensable logistical and spiritual support. E.C.F. thanks Angela Cepelis and Meredith Thomas for extraordinary secretarial and editorial assistance and Angela for her invaluable help in coordinating author meetings held in various parts of the country. He also thanks Rhonda Friedberg for editorial assistance and for unstinting moral support. For belief in the importance of the project and for help in bringing it to fruition, R.D.W. thanks his research group, as well as Enid Wood, Patrick Moore, Yuan Chang, Vesna Ropic-Otrin, Ron Herberman, and Arthur Levine. R.S. thanks Lisa McDaniel for extensive editorial assistance and expert help in coordinating and citing the literature and Carmencita Ordu for her invaluable secretarial support. G.W. thanks Jan and Gordon Walker for their cheerleading and understanding, Marianne White for her always cheerful help, Evelyn Witkin for her inspiration, and Priscilla Cooper, Judi Neal, Bill Broughton, and Anne Hills for their constant support. W.S. offers special thanks to Nina Patel and Gulnaz Bachlani.

Over the course of many meetings, most of which took place over weekends, as well as innumerable phone calls and e-mails, each of us came to know and respect our fellow authors from unique perspectives. We are unanimous in our view that the camaraderie and friendships forged through these meetings have enormously enriched our lives, not to mention our taste in fine beverages and the musical pursuits of some of us—such as they are!

ERROL C. FRIEDBERG

GRAHAM C. WALKER

WOLFRAM SIEDE

RICHARD D. WOOD

ROGER A. SCHULTZ

TOM ELLENBERGER

December 2004

Abbreviations

This text employs many standard (and some not so standard) abbreviations. In an effort to reduce confusion for the reader, abbreviations are spelled out in full when first employed in each chapter. Additionally, the following list includes the abbreviations most frequently used.

AAF	Acetylaminofluorine	MMS	Methyl methanesulfonate
ALL	Acute lymphoblastic leukemia	MNase	Micrococcal nuclease
AML	Acute myeloid leukemia	MSI	Microsatellite instability
AT	Ataxia telangiectasia	NER	Nucleotide excision repair
BER	Base excision repair	NHEJ	Nonhomologous end joining
BIR	Break-induced replication	4-NQO	4-Nitroquinoline 1-oxide
BPDE	Benzo[<i>a</i>]pyrene-diol-epoxide	NTP	Nucleoside triphosphate(s)
BrdU	5-Bromodeoxyuridine	OR	Odds ratio
BrU	5-Bromouracil	ORF	Open reading frame(s)
BS	Bloom syndrome	Pol	Polymerase
CHO	Chinese hamster ovary	(6-4)PP	(6-4) photoproduct(s)
CPD	Cyclobutane pyrimidine dimer(s)	RNAPII	RNA polymerase II
CS	Cockayne syndrome	ROS	Reactive oxygen species
dNTP	Deoxyribonucleoside triphosphate(s)	RR	Risk ratio
DSB	Double-strand break(s)	RS	Roberts syndrome
dsDNA	Double-stranded DNA	RT-PCR	Reverse transcription-polymerase chain reaction
EMS	Ethyl methanesulfonate	SCE	Sister chromatid exchange(s)
ESS	Enzyme-sensitive site(s)	SNP	Single-nucleotide polymorphism(s)
FA	Fanconi anemia	SSA	Single-strand annealing
FdU	5-Fluorodeoxyuridine	SSB	Single-strand break(s)
GFP	Green fluorescent protein	ssDNA	Single-stranded DNA
Gy	Gray	TC-NER	Transcription-coupled nucleotide excision repair
HNPPC	Hereditary nonpolyposis colon cancer	TLS	Translesion DNA synthesis
HR	Homologous recombination	TTD	Trichothiodystrophy
HU	Hydroxyurea	UAS	Upstream activating sequence(s)
ICL	Interstrand cross-link(s)	WS	Werner syndrome
IR	Ionizing radiation	XP	Xeroderma pigmentosum
MEF	Mouse embryonic fibroblast(s)		
MMC	Mitomycin C		
MMR	Mismatch repair		

Appendix

Table 1 Nomenclature of DNA repair genes^a

Pathway	Gene(s) in ^b :					Activity	
	<i>E. coli</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>	<i>Drosophila</i>	Human		
Base excision repair (BER) DNA glycosylases						Major altered base released:	
	<i>ung</i> ⁺	<i>UNG1</i>	<i>ung1</i> ⁺	—	<i>UNG</i>	U	
	—	—	—	<i>CG5285</i>	<i>SMUG1</i>	U, hydroxymethyl U	
	—	—	—	—	<i>MBD4 (MED1)</i>	U or T opposite G at CpG sequences	
	<i>mug</i> ⁺	—	<i>thp1</i> ⁺	<i>Thd1</i>	<i>TDG</i>	U, T, or ethenoC opposite G	
	<i>fpg</i> ⁺ (<i>mutM</i> ⁺)	<i>OGG1</i>	—	<i>Ogg1</i>	<i>OGG1</i>	8-oxoG opposite C	
	<i>mutY</i> ⁺	—	<i>myh1</i> ⁺	—	<i>MYH</i>	A opposite 8-oxoG	
	<i>nth</i> ⁺	<i>NTG1, NTG2</i>	<i>nth1</i> ⁺	<i>CG9272</i>	<i>NTHL1 (NTH1)</i>	Ring-saturated or fragmented pyrimidines	
	<i>alkA</i> ⁺ , <i>tagA</i> ⁺	<i>MAG1</i>	<i>mag1</i> ⁺ , <i>SPBC23G7.11</i>	—	<i>MPG (MAG, AAG)</i>	3-meA, ethenoA, hypoxanthine	
	<i>nei</i> ⁺	—	—	—	—	<i>NEIL1</i>	Thymine glycol
		—	—	—	—	<i>NEIL2</i>	Oxidative products of C, U
		—	—	—	—	<i>NEIL3</i>	Not known
	Other BER factors	<i>xthA</i> ⁺	<i>APN2 (ETH1)</i>	<i>apn2</i> ⁺	<i>Rrp1</i>	<i>APEX1 (HAP1, APE1, REF1)</i>	AP endonuclease
—		—	—	<i>ApII</i>	<i>APEX2 (APE2)</i>	AP endonuclease	
<i>nfo</i> ⁺		<i>APN1</i>	<i>apn1</i> ⁺	—	—	AP endonuclease	
—		—	—	<i>CG17227</i>	<i>LIG3</i>	DNA ligase	
—		—	—	<i>XRCC1</i>	<i>XRCC1</i>	Accessory factor for LIG3 and BER	
—		—	—	<i>Parp</i>	<i>PARP1 (ADPRT)</i>	Poly(ADP-ribose) polymerase	
—		—	—	—	<i>PARP2 (ADPRTL2)</i>	ADPRT-like enzyme	
Direct reversal of damage	<i>phrA</i> ⁺	<i>PHR1</i>	—	<i>phr</i>	—	CPD photolyase	
	—	—	—	<i>phr6-4</i>	—	(6-4) photolyase	
	—	—	<i>uve1</i> ⁺ (<i>uvde</i> ⁺)	—	—	UV damage endonuclease	
	<i>ada</i> ⁺ , <i>ogt</i> ⁺	<i>MGT1</i>	<i>SPAC1250.04c</i>	<i>agt</i>	<i>MGMT (AGT)</i>	O ⁶ -meG alkyltransferase	
	<i>alkB</i> ⁺	—	—	—	<i>ABH2</i>	Reversal of alkylation damage (1-meA and 3-meC)	

(continued)

Table 1 Nomenclature of DNA repair genes^a (continued)

Pathway	Gene(s) in ^b :					Activity	
	<i>E. coli</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>	<i>Drosophila</i>	Human		
					<i>ABH3 (DEPC-1)</i>	Reversal of alkylation damage (1-meA and 3-meC)	
Repair of DNA-protein cross-links		<i>TDP1</i>	<i>SPCP31B10.05</i>	<i>Tdp1</i>	<i>TDP1</i>	Removes covalently bound Topo I-DNA complexes	
Mismatch repair (MMR)	<i>mutS</i> ⁺	<i>MSH2</i>	<i>swi8</i> ⁺	<i>spell1 (spellchecker1)</i>	<i>MSH2</i>	Mismatch and loop recognition	
		<i>MSH3</i>	<i>swi4</i>	—	<i>MSH3</i>		
		<i>MSH6</i>	—	<i>CG7003</i>	<i>MSH6</i>		
	<i>mutL</i> ⁺				<i>mlh1</i>	<i>MLH1</i>	MutS homologs specialized for meiosis
						<i>MSH4</i>	
						<i>MSH5</i>	
		<i>PMS1</i>	<i>mlh1</i> ⁺	<i>pms2</i>		<i>PMS2</i>	MutL homologs, forming dimer
						<i>PMS1</i>	MutL homolog
						<i>MLH3</i>	MutL homologs of unknown function
					<i>PMS2L3</i>		
				<i>PMS2L4 (PMS6)</i>			
	<i>mutH</i> ⁺					GATC recognition	
	<i>uvrD</i> ⁺ (<i>mutU</i> ⁺)					Helicase aiding excision in MMR and NER	
Nucleotide excision repair (NER) DNA binding		<i>RAD4</i>	<i>rhp41</i> ⁺ , <i>rhp42</i> ⁺	<i>mus210</i>	<i>XPC</i>	Binds distorted DNA as complex	
		<i>RAD23</i>	<i>rhp23</i> ⁺	<i>Rad23</i>	<i>RAD23B (HR23B)</i>		
						<i>RAD23A (HR23A)</i>	RAD23B paralog
		<i>RAD14</i>	<i>rhp14</i> ⁺	<i>Xpac</i>	<i>XPA</i>		Binds DNA and proteins in preincision complex
		<i>uvrA</i> ⁺	—	—	—	—	Binds damaged DNA in complex with UvrB
		<i>uvrB</i> ⁺	—	—	—	—	Catalyzes unwinding in preincision complex
			<i>SSL2 (RAD25)</i>	<i>ercc3sp</i> ⁺	<i>hay (haywire)</i>	<i>XPB (ERCC3)</i>	3'-to-5' DNA helicase TFIIH subunit
TFIIH subunits		<i>RAD3</i>	<i>rad15</i> ⁺ (<i>rad5</i> ⁺)	<i>Xpd</i>	<i>XPB (ERCC2)</i>	5'-to-3' DNA helicase TFIIH subunit	
		<i>TFB1</i>	<i>tfb1</i> ⁺	<i>Tfb1</i>	<i>GTF2H1</i>	TFIIH subunit p62	
		<i>SSL1</i>	<i>ssl1</i> ⁺	<i>Ssl1</i>	<i>GTF2H2</i>	TFIIH subunit p44	
		<i>TFB4</i>	<i>tfb4</i> ⁺	<i>Tfb4</i>	<i>GTF2H3</i>	TFIIH subunit p34	
		<i>TFB2</i>	<i>tfb2</i> ⁺	<i>Tfb2</i>	<i>GTF2H4</i>	TFIIH subunit p52	
		<i>TFB5</i>		<i>CG31917</i>	<i>GTF2H5 (TTDA)</i>	TFIIH subunit p8	
		<i>KIN28</i>	—	<i>Cdk7</i>	<i>CDK7</i>	Kinase subunits of	
		<i>CCL1</i>	—	<i>CycH</i>	<i>CCNH</i>	TFIIH	
		<i>TFB3</i>	—	<i>Mat1</i>	<i>MNAT1 (MAT1)</i>	TFIIH subunit	
	NER nucleases		<i>uvrC</i> ⁺ , <i>cho</i> ⁺				3' and 5' incision nuclease
		<i>RAD2</i>	<i>rad13</i> ⁺	<i>mus201</i>	<i>XPB (ERCC5)</i>	3' incision nuclease	
		<i>RAD10</i>	<i>swi10</i> ⁺	<i>Ercc1</i>	<i>ERCC1</i>	5' incision nuclease subunits	
		<i>RAD1</i>	<i>rad16</i> ⁺	<i>mei9</i>	<i>XPF (ERCC4)</i>		

Table 1 (continued)

Pathway	Gene(s) in ^b :					Activity	
	<i>E. coli</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>	<i>Drosophila</i>	Human		
Other factors		<i>RAD28</i>	—	—	<i>CSA (CKN1, ERCC8)</i>	Cockayne syndrome; needed for TC-NER	
	<i>mfd</i> ⁺	<i>RAD26</i>	<i>rhp26</i> ⁺	—	<i>CSB (ERCC6)</i>	Cockayne syndrome; needed for TC-NER	
	—	—	<i>ddb1</i> ⁺	<i>Ddb1</i>	<i>DDB1</i>	p127 subunit of DDB	
	—	—	—	—	<i>DDB2 (XPE)</i>	p48 subunit of DDB, defective in XP-E	
		<i>RAD7</i>	<i>rhp7</i> ⁺		—	E3 ubiquitin ligase and damage binding	
		<i>RAD16</i>	<i>rhp16</i> ⁺		—		
		<i>MMS19</i>		<i>Mms19</i>	<i>MMS19L (MMS19)</i>	Transcription and NER	
DNA ligase I	<i>ligA</i> ⁺	<i>CDC9</i>	<i>cdc17</i> ⁺	<i>DNA-ligI</i>	<i>LIG1</i>	DNA joining	
Single-stranded-DNA-binding protein	<i>ssb</i> ⁺	<i>RFA1</i>	<i>ssb1</i> ⁺	<i>RpA-70</i>	<i>RPA1</i>	Binds ssDNA intermediates in recombination, NER, and gap-filling pathways	
		<i>RFA2</i>	<i>ssb2</i> ⁺	<i>RpA-30</i>	<i>RPA2</i>		
		<i>RFA3</i>	<i>ssb3</i> ⁺	<i>RpA-8</i>	<i>RPA3</i>		
Homologous recombination (HR)	<i>recA</i> ⁺	<i>RAD51</i>	<i>rhp51</i> ⁺	<i>Rad51 (spn-A)</i>	<i>RAD51</i>	Formation of protein filament to mediate homologous pairing	
					<i>RAD51L1 (RAD51B)</i>	Rad51 paralog	
				<i>spn-D</i>	<i>RAD51C (RAD51L2)</i>	Rad51 paralog	
					<i>RAD51L3 (RAD51D)</i>	Rad51 paralog	
		<i>DMC1</i>	<i>dmc1</i> ⁺	—	<i>DMC1</i>	Rad51 paralog for meiosis	
				<i>Rad51D</i>	<i>XRCC2</i>	DNA break and cross-link repair	
	<i>recB</i> ⁺ , <i>recC</i> ⁺ , <i>recD</i> ⁺					Generation of ssDNA to allow formation of RecA filament	
				<i>spn-B</i>	<i>XRCC3</i>	DNA break and cross-link repair	
	<i>recF</i> ⁺ , <i>recO</i> ⁺ , <i>recR</i> ⁺	<i>RAD52</i>	<i>rad22</i> ⁺ (<i>rad22a</i> ⁺), <i>rti1</i> ⁺ (<i>rad22b</i> ⁺)	—	<i>RAD52</i>	Accessory factor for recombination	
		<i>RAD54</i>	<i>rhp54</i> ⁺	<i>okra</i>	<i>RAD54L</i>	Accessory factor for recombination	
		<i>RDH54 (TID1)</i>	<i>rdh54</i> ⁺	—	<i>RAD54B</i>		
		<i>RAD55</i>	<i>rhp55</i> ⁺	—	—	Recombination mediator function	
		<i>RAD57</i>	<i>rhp57</i> ⁺	—	—		
		<i>RAD59</i>	—	—	—		
		<i>RHC18</i>	<i>rad18</i> ⁺				
						<i>BRCA1</i>	Recombination; E3 ubiquitin ligase
						<i>BRCA2 (FANCD1)</i>	Cooperation with RAD51, essential function
	<i>sbpC</i> ⁺	<i>RAD50</i>	<i>rad50</i> ⁺	<i>rad50</i>	<i>RAD50</i>	ATPase in complex with MRE11A, NBS1	
	<i>sbpD</i> ⁺	<i>MRE11</i>		<i>mre11</i>	<i>MRE11A</i>	3' exonuclease	
		<i>XRS2</i>	<i>nbs1</i> ⁺	<i>nbs</i>	<i>NBS1</i>	Mutated in Nijmegen breakage syndrome	
<i>ruvA</i> , <i>ruvB</i>					Branch migration of Holliday junctions		
<i>ruvC</i>		<i>(mus81-eme1)</i> ⁺ ?			Nuclease to cleave Holliday junctions		

(continued)

Table 1 Nomenclature of DNA repair genes^a (continued)

Pathway	Gene(s) in ^b :					Activity	
	<i>E. coli</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>	<i>Drosophila</i>	Human		
Nonhomologous end joining (NHEJ)		<i>YKU70 (HDF1)</i>	<i>pku70</i> ⁺	<i>Irbp</i>	<i>Ku70 (G22P1)</i>	DNA end binding	
		<i>YKU80 (HDF2)</i>	<i>pku80</i> ⁺	<i>Ku80</i>	<i>Ku80 (XRCC5)</i>	DNA end binding	
					<i>PRKDC (DNA-PKcs, XRCC7)</i>	DNA-dependent protein kinase catalytic subunit	
		<i>LIG4</i>		<i>ligase4</i>	<i>LIG4</i>	Ligase	
		<i>LIF4</i>			<i>XRCC4</i>	Ligase accessory factor	
				<i>Artemis (SNM1C)</i>	Nuclease		
Modulation of nucleotide pools	<i>MutT</i> ⁺	—	—	<i>CG10898</i>	<i>MTH1 (NUDT1)</i>	8-oxoGTPase	
	<i>Dut</i> ⁺			<i>dUTPase</i>	<i>DUT</i>	dUTPase	
					<i>p53R2</i>	p53-inducible ribonucleotide reductase small subunit 2	
DNA polymerases (catalytic subunits)	<i>polB</i> ⁺ (<i>dinA, pol II</i>)			—	<i>POLB</i>	Damage responses Pol β; BER in nuclear DNA	
		<i>MIP1</i>	<i>SPCC24B10.22</i> ⁺	<i>tam (tamas)</i>	<i>POLG</i>	Pol γ; replication and BER in mitochondrial DNA	
		<i>CDC2 (POL3)</i>	<i>cdc6</i> ⁺	<i>DNA-pold</i>	<i>POLD1</i>	Pol δ; NER and MMR	
		<i>POL2</i>	<i>cdc20</i> ⁺	<i>DNA-pole</i>	<i>POLE1</i>	Pol ε; NER and MMR	
		<i>REV3</i>	<i>rev3</i> ⁺	<i>mus205</i>	<i>REV3L (PSO1)</i>	DNA Pol ζ catalytic subunit	
		<i>REV7</i>	<i>SPAC12D12.09</i>	<i>rev7</i>	<i>REV7 (MAD2L2)</i>	DNA Pol β subunit	
		<i>REV1</i>	<i>SPBC1347.01c</i>	<i>Rev1</i>	<i>REV1L (REV1)</i>	dCMP transferase and other roles in TLS	
		<i>umuC</i> ⁺				Catalytic subunit of Pol V for lesion bypass	
		<i>RAD30</i>	<i>eso1</i> ⁺	<i>DNA-pollh</i>	<i>POLH</i>	Pol η; bypass of CPD, defective in XP-V	
					<i>POLI (RAD30B)</i>	Pol ι; lesion bypass	
		—	—	<i>mus308</i>	<i>POLQ</i>	Pol θ Lesion bypass; DNA crosslink repair?	
		<i>dinB</i> ⁺ (<i>Pol IV</i>)	—	—	<i>POLK (DINB1)</i>	Pol κ Lesion bypass	
			<i>POL4</i>	<i>SPAC2F7.06c</i>	—	<i>POLL</i>	Pol λ Gap filling during nonhomologous end joining
					—	<i>POLM</i>	
					—	<i>POLN (POL4P)</i>	Pol μ DNA cross-link repair?
		<i>POL5</i>	<i>pol5</i> ⁺				
DNA polymerase accessory factors	<i>dnaN</i> ⁺	<i>POL30</i>	<i>pcn1</i> ⁺	<i>mus209</i>	<i>PCNA</i>	Sliding clamp	
	<i>dnaX</i> ⁺ (γ-δ) complex	<i>CDC44</i>	<i>rfc1</i> ⁺	<i>Grf1</i>	<i>RFC1</i>	Clamp loader, large subunit	
Processing nucleases		<i>MUS81</i>	<i>mus81</i> ⁺	<i>mus81</i>	<i>MUS81</i>	Structure-specific nuclease subunits	
		<i>MMS4</i>	<i>eme1</i> ⁺	<i>MMS4 (CG12936)</i>	<i>EME1 (MMS4L)</i>		
	<i>polA</i> ⁺ (5' to 3' exo)	<i>RAD27 (RTH1)</i>	<i>rad2</i> ⁺	<i>I(3)04108</i>	<i>FEN1 (DNase IV)</i>	5' nuclease	
					<i>TREX1 (DNase III)</i>	3' exonuclease	
					<i>TREX2</i>	3' exonuclease	
		<i>recJ</i> ⁺ , <i>Exo1</i> ⁺	<i>EXO1</i>	<i>exo1</i> ⁺	<i>tos (tosca)</i>	<i>EXO1 (HEX1)</i>	Exonuclease for MMR and other pathways

Table 1 (continued)

Pathway	Gene(s) in ^b :					Activity
	<i>E. coli</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>	<i>Drosophila</i>	Human	
		<i>SPO11</i>		<i>meiW-68</i>	<i>SPO11</i>	Recombination endonuclease
	<i>nfi</i> ⁺ (<i>EndoV</i> ⁺)	—	<i>SPAC1F12.06c</i>	—	<i>ENDO V (FLJ35220)</i>	Incision 3' of hypoxanthine and uracil
Rad6 pathway		<i>RAD6</i>		<i>UbcD6</i>	<i>UBE2A (RAD6A)</i>	E2 ubiquitin-conjugating enzyme
					<i>UBE2B (RAD6B)</i>	E2 ubiquitin-conjugating enzyme
		<i>RAD18</i>	<i>rhp18</i> ⁺		<i>RAD18</i>	RING domain E3 ubiquitin ligase
		<i>HPR5 (SRS2, RADH)</i>	<i>srs2</i> ⁺			RING domain E3 ubiquitin ligase
		<i>RAD5 (SNM2, REV2)</i>				RING domain E3 ubiquitin ligase
		<i>MMS2</i>			<i>UBE2V2 (MMS2)</i>	DNA helicase
	<i>UBC13</i>			<i>UBE2N (UBC13, BTG1)</i>	E2 ubiquitin-conjugating complex	
Genes defective in diseases associated with sensitivity to DNA damaging agent	<i>recQ</i> ⁺	<i>SGS1</i>	<i>rqh1</i> ⁺ (<i>hus1</i> ⁺ , <i>rad12</i> ⁺)	<i>mus309</i>	<i>BLM</i>	Bloom syndrome helicase
				<i>CG7670 (exo only)</i>	<i>WRN</i>	Werner syndrome helicase / 3'-exonuclease
				<i>RecQ4</i>	<i>RECQL4</i>	Rothmund-Thomson syndrome
		<i>TEL1</i>	<i>tefu tel1</i> ⁺	<i>CG6535</i>	<i>ATM</i>	Ataxia telangiectasia
		<i>HNT3</i>	<i>SPCC18.09c</i>	<i>CG5316</i>	<i>APTX</i>	Ataxia-oculomotor apraxia syndrome (aprataxin; interaction with XRCC1, XRCC4)
	—	—	—	—	<i>FANCA</i>	Fanconi anemia gene
	—	—	—	—	<i>FANCB</i>	Fanconi anemia gene
	—	—	—	—	<i>FANCC</i>	Fanconi anemia gene
	—	—	—	<i>fancd2</i>	<i>FANCD2</i>	Fanconi anemia gene
	—	—	—	—	<i>FANCE</i>	Fanconi anemia gene
	—	—	—	—	<i>FANCF</i>	Fanconi anemia gene
	—	—	—	—	<i>FANCG (XRCC9)</i>	Fanconi anemia gene
	—	—	—	<i>CG12812</i>	<i>FANCL</i>	Ubiquitin ligase for monoubiquitination of FANCD2
Other genes related to DNA repair		<i>PSO2 (SNM1)</i>		<i>mus322</i>	<i>DCLRE1A (PSO2, SNM1)</i>	DNA cross-link repair nuclease
					<i>SNM1B (DCLRE1B)</i>	Related to SNM1
					<i>PNKP (PNK)</i>	Converts some DNA breaks to ligatable ends
				<i>mus301 (spn-C)</i>	<i>HEL308</i>	Similar to helicase domain of Mus308
Other conserved DNA damage response genes	—	<i>H2A</i>	<i>hta1</i> ⁺ , <i>hta2</i> ⁺	<i>His2av</i>	<i>H2AFX (H2AX)</i>	Histone, phosphorylated after DNA damage
	—	—	—	<i>p53</i>	<i>p53 (TP53)</i>	Transcription factor and DNA binding
		<i>MEC1</i>	<i>rad3</i> ⁺	<i>mei-41</i>	<i>ATR</i>	ATM- and PI3K-like essential kinase

(continued)

Table 1 Nomenclature of DNA repair genes^a (continued)

Pathway	Gene(s) in ^b :					Activity
	<i>E. coli</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>	<i>Drosophila</i>	Human	
		<i>LCD1 (DDC2)</i>	<i>rad26</i> ⁺	<i>mus304</i>	<i>ATRIP</i>	ATR interacting
		<i>RAD17</i>	<i>rad1</i> ⁺	<i>rad1</i>	<i>RAD1</i>	PCNA-like DNA damage sensor (9-1-1 complex)
		<i>DDC1</i>	<i>rad9</i> ⁺	<i>rad9</i>	<i>RAD9</i>	
		<i>MEC3</i>	<i>hus1</i> ⁺	<i>Hus1</i> -like	<i>HUS1</i>	RFC1-like DNA damage sensor
		<i>RAD24</i>	<i>rad17</i> ⁺	<i>Rad17</i>	<i>RAD17</i>	
		<i>RAD9</i>	<i>crb2</i> ⁺ (<i>rhp9</i> ⁺)			Checkpoint function
		<i>CHK1</i>	<i>chk1</i> ⁺ (<i>rad27</i> ⁺)	<i>grp (grapes)</i>	<i>CHEK1 (CHK1)</i>	Effector kinase
		<i>RAD53</i>	<i>cds1</i> ⁺	<i>lok (loki)</i>	<i>CHK2 (CHEK2)</i>	Effector kinase

^aEntries in Table 1 are organized according to DNA repair pathway, emphasizing functional orthologs. In many cases, but not all, these are also sequence or structural homologs. Caution is recommended in this respect, and the text should be consulted for details, together with public DNA sequence databases. For example, the major DNA glycosylase for removal of 7,8-dihydro-8-oxoguanine (8-oxoG) from DNA is encoded by *fpg*⁺ in *Escherichia coli* and *OGG1* in human cells, but the two gene products are not related by amino acid sequence and do not fall into the same structural family. The symbol “–” indicates that no ortholog is detected. Some DNA repair genes play roles in more than one pathway but are listed here only once for simplicity. HUGO-approved gene names (<http://www.gene.ucl.ac.uk/nomenclature>) are presented in nearly all cases, with a few of the commonly used synonyms provided in parentheses. The name used most commonly in this book is usually presented first here. See also the table “Human DNA Repair Genes” (http://www.cgal.icnet.uk/DNA_Repair_Genes.html). For *Drosophila*, official gene names from <http://flybase.bio.indiana.edu> are used. For *Schizosaccharomyces pombe*, official gene names from <http://www.genedb.org/genedb/pombe/index.jsp> are used. For *Saccharomyces cerevisiae*, official gene names from <http://www.yeastgenome.org/> are used. For *E. coli*, official gene names from <http://www.ncbi.nlm.nih.gov/> are used.

^bDashes indicate that no gene exists. Blank spaces indicate that the status is unknown.

Table 2 Human hereditary diseases and defective cellular responses to DNA damage**A. Human hereditary diseases with defective cellular responses to DNA damage**

Human disease	Gene(s)	Principal defective response	Principal clinical features
Xeroderma pigmentosum (XP)	<i>XPA-XPG; XPV</i>	Nucleotide excision repair (NER); translesion DNA synthesis	Dermatitis, freckling, skin cancer, sometimes neurological defects
Cockayne syndrome (CS)	<i>CSA, CSB</i>	Transcription-coupled NER	Post-natal developmental defects, neurological defects
Combined XP/CS complex (XP/CS)	<i>XPB, XPD, XPG</i>	NER and basal transcription by RNA polymerase II	Features of both XP and CS
Trichothiodystrophy (TTD)	<i>XPB, XPD, TTDA</i>	NER and basal transcription by RNA polymerase II	Photosensitivity, brittle hair, post-natal developmental defects, neurological defects
Cerebro-oculo-facio-skeletal (COFS) syndrome	<i>CSB</i>	Transcription-coupled NER	Post-natal developmental defects, neurological defects
UV-sensitive (UV ^s) syndrome	<i>CSB</i>	Transcription-coupled NER	Photosensitivity
Ataxia telangiectasia (AT)	<i>ATM</i>	Repair of DNA strand breaks	Cerebellar ataxia, defective immune function, neurological problems, predisposition to hematolymphoid cancer
Nijmegen breakage syndrome (NBS)	<i>NBS1</i>	Repair of DNA strand breaks	Developmental abnormalities, growth retardation, cancer predisposition
AT-like disorder (ATLD)	<i>MRE11A</i>	Repair of DNA strand breaks	Defective immune function, neurological problems, predisposition to hematolymphoid cancer
LIG4 syndrome	<i>LIG4</i>	Repair of DNA strand breaks	Defective immune function, neurological problems, predisposition to hematolymphoid cancer
Seckel syndrome	<i>ATR</i>	Chromosome stability in response to specific treatments	Developmental, immunological, and hematolymphoid abnormalities
Severe combined immunodeficiency (SCID)	<i>RAG1, RAG2, SNM1C (Artemis)</i>	V(D)J recombination	Severe immunodeficiency
Spinocerebellar ataxia with axonal neuropathy (SCAN1)	<i>TDP1</i>	Processing of topoisomerase-DNA intermediates	Neurodegeneration
Ataxia-ocular apraxia 1 (AOA1)	<i>APTX (Aprataxin)</i>	None known; possibly double-strand break repair	Neurodegeneration
Bloom syndrome (BS)	<i>BLM</i>	Resolution of stalled replication/transcription intermediates	Dwarfism, immunodeficiency, cancer predisposition
Werner syndrome (WS)	<i>WRN</i>	Resolution of stalled replication/transcription intermediates	Premature aging, cancer predisposition
Rothmund-Thomson syndrome (RTS)	<i>RECQL4</i>	Resolution of stalled replication/transcription intermediates	Skin, hair, and skeletal abnormalities, cancer

(continued)

Table 2 Human hereditary diseases with defective cellular responses to DNA damage (*continued*)**A.** Human hereditary diseases and defective cellular responses to DNA damage (*continued*)

Human disease	Gene(s)	Principal defective response	Principal clinical features
RAPADILINO syndrome (RS)	<i>RECQL4</i>	Resolution of stalled replication/transcription intermediates	Skeletal abnormalities
46BR syndrome	<i>LIG1</i>	Modest chromosome instability	Immunodeficiency, cancer
Hereditary nonpolyposis colon cancer (HNPCC)	<i>MLH1, MSH2, MSH6, PMS1, PMS2, MLH3, EXO1</i>	Mismatch repair	Colon and other cancers
Fanconi anemia (FA)	<i>FANCA, FANCB, FANCC, FANCD1, BRCA2, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCL</i>	Chromosomal stability, spontaneous and in response to cross-linking agents	Limb defects, anemia, cancer disposition
Hyper-IgM syndrome	<i>UNG</i>	Removal of uracil during class switch recombination	Immune deficiency

B. Human hereditary diseases implicated in defective cellular responses to DNA damage

Human disease	Gene(s)	Principal defective response	Principal clinical features
Retinoblastoma (RB)	<i>RBI</i>	Cell cycle response to DNA damage	Retinoblastoma and other cancers
Li-Fraumeni syndrome (LFS)	<i>p53, CHEK2</i>	Cell cycle response to DNA damage	Broad spectrum of cancer
Hereditary breast cancer	<i>BRCA1, BRCA2</i>	Cell cycle response to DNA damage	Breast and ovarian cancer
Familial adenomatous polyposis (FAP)	<i>APC</i>	Cell proliferation and chromosomal stability	Gastrointestinal cancer and thyroid cancer
MYH-associated polyposis (MAP)	<i>MYH</i>	None noted, despite mutations in a base excision repair gene	Gastrointestinal cancer
Juvenile polyposis syndrome (JPS)	<i>SMAD4, BMPRIA</i>	Cell-signaling and "landscaper" functions	Juvenile polyps and gastrointestinal malignancy
Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome	<i>PTEN</i>	Cell cycle responses and apoptosis (but not in response to DNA damage)	Breast, thyroid, and endometrial cancer
Peutz-Jeghers syndrome (PJS)	<i>STK11</i>	Cell cycle responses and apoptosis	Hamartomas, gastrointestinal and non-gastrointestinal tumors
Basal cell nevus syndrome (BCNS)	<i>PTCH2</i>	Cell-signaling pathways	Malignant melanoma
Cutaneous malignant melanoma	<i>CDKN2A, CDK4</i>	Cell cycle responses and apoptosis	Malignant melanoma

Table 2 (continued)**B. Human hereditary diseases implicated in defective cellular responses to DNA damage**

Human disease	Gene(s)	Principal defective response	Principal clinical features
Wilm's tumor (WT)	<i>WT1</i>	Transcriptional regulation	Pediatric kidney tumors
Hereditary papillary renal cell carcinoma (HPRCC)	<i>MET</i>	Cell signaling	Papillary renal cell carcinoma
von Hippel-Lindau (VHL)	<i>VHL</i>	Multiple associated functions, possibly defective in cell cycle regulation	Renal cell and other cancers
TSC Tuberous sclerosis complex	<i>TSC1, TSC2</i>	Cytoskeleton maintenance	Multiple hamartomas, renal cell cancer
Neurofibromatosis type 1 and type 2 (NF1, NF2)	<i>NF1, NF2</i>	RAS protein regulation or cytoskeleton maintenance	Neurofibrosarcoma and other tumors

Index

A

- A-rules, 615
- Abasic residues, *See* AP sites
- ABC transporter, 230
- Abf1 protein, *S. cerevisiae*, 342
- ABH genes, human, 157, 159, 161
- Acetaldehyde, 38–39
- Acetophenone, 34
- N-Acetoxy-2-acetyl-2-aminofluorene, 318, 358, 571, 896
- N-2-Acetyl-2-aminofluorene, 41–42, 245, 247, 513
- Acetylation
 - histones, 354–355, 736, 790, 1005
 - p53 protein, 790
- Acetyltransferase, 41
- N-Acetyltransferase, polymorphisms, 1063–1064
- Achondroplasia, 1027
- Acrolein, 40
- Activation loop, 780
- Activation-induced cytidine deaminase, 14, 641, 714
- Active rolling model, RecQ helicase activity, 951
- AD32 (intercalating agent), 247
- Ada box, 147, 149
- ADA gene, human, 934
- ada*⁺ gene
 - E. coli*, 140, 146–153, 183
 - Salmonella*, 153
- Ada protein, *see also* O⁶-Alkylguanine-DNA alkyltransferase
 - E. coli*, 146–150, 234
 - ada* regulon, 147, 149
 - alkylated, 146–147
 - conversion to transcriptional activator, 147–149
 - C-terminal domain, 147, 150–151
 - N-terminal domain, 147–148
 - regulatory function, 146
 - specificity, 149
- Ada regulon, *E. coli*, 147, 149
- adaA*⁺ gene, *B. subtilis*, 152
- adaB*⁺ gene, *B. subtilis*, 153
- Adaptation, 759, 845
 - cell cycle restart and, 846–847
 - multicellular eukaryotes, 847
 - S. cerevisiae*, 846–847
- Adaptive mutagenesis, 423–424, 552–553
- Adaptive mutation, 422, 639
- Adaptive response to alkylation damage,
 - bacteria, 139–150
 - adaptation to cell killing, 140
 - adaptation to mutagenesis, 140, 146–150
 - AlkA protein in, 182–184
 - definition, 140
 - evolutionary significance, 153
 - historical review, 139–140
 - termination, 150
- Adaptor proteins, 848
- Adenine
 - deamination, 9–11, 14–15
 - imidazole ring opening, 19
- Adenosyl radical, 134
- S-Adenosylmethionine, 4, 16, 37, 134
- Aflatoxin(s), 43–44
- Aflatoxin B₁, 44
 - mutagenicity, 76, 532
- Aflatoxin B₁-8,9-epoxide, 44
- Aging, 854–856
 - array analysis of aging in mammals, 1030
 - DNA repair and, 7, 1028–1034
 - age-related decline in DNA repair, 1028–1030
 - reversal of aging and DNA repair, 1030
 - mitochondrial theory, 455–456
 - mouse models, 1030–1031
 - oxidative DNA damage and, 22–23
 - somatic mutation theory, 854
 - telomeres and, 1031–1032
 - translesion DNA synthesis and, 551–552
- aidB*⁺ gene, *E. coli*, 147, 149
- AKT protein, 804
- Aldehydes, DNA-protein cross-links, 40
- alkA*⁺ gene, *E. coli*, 140, 147, 149, 172, 181–184
- AlkA protein, 181–184
 - adaptive response to alkylation damage, 182–184
 - helix-hairpin-helix motif, 183–184
 - structure, 183–185
- Alkaline elution method, detection of nucleotide excision repair, 272–273, 275
- Alkaline unwinding method, detection of nucleotide excision repair, 272–273
- alkB*⁺ gene, *E. coli*, 147, 157–160
 - homologs in higher organisms, 159–160
- AlkB protein
 - E. coli*, 161
 - reactions catalyzed, 158–159
 - sequence motif, 158
 - human, subcellular localization, 160
 - repair of alkylated RNA, 160
- Alkyl hydroperoxidase, NADPH-dependent, 21
- Alkyladenine, 37
- Alkylating agents, 35–38, 154
 - chemotherapeutics, 161–162
 - environmental, 37, 180–181
 - hypersensitivity in methylpurine-DNA glycosylase deficiency, 184–185
 - natural forms, 146, 153
 - reaction sites in DNA, 36–37
 - reversal of alkylation damage, 139–168
 - SOS-independent mutagenesis, 554
 - structures, 36
 - Swain-Scott constant, 37–38
 - tolerance in mammalian cells, 157
 - UVM response, 555
- Alkylation damage
 - adaptive response in bacteria, 139–150
 - adaptation to cell killing, 140
 - adaptation to mutagenesis, 140
 - AlkA protein in, 182–184
 - definition, 140
 - evolutionary significance, 153
 - historical review, 139–140
 - termination, 150
 - mammalian cells, 154
 - mtDNA, 451–452
 - repair, 139–168
 - O⁶-alkylguanine, 141–157
 - O⁴-alkylthymine, 141–157
 - 1-methyladenine, 157–162
 - 3-methylcytosine, 157–162
 - teleological considerations, 162
 - therapeutic applications and implications, 161–162
 - RNA, 160
- Alkylation resistance
 - mammals, 427–429
 - single-celled organisms, 427
- 3-Alkylcytosine, 37
- O²-Alkylcytosine, 37
- 3-Alkylguanine, 37
- O⁶-Alkylguanine, 37
- mammalian cells and tissues, 154–155
- premutagenic lesion, 554
- repair, 141–157
 - enzyme-catalyzed reversal, 139–168

- O*⁶-Alkylguanine-DNA alkyltransferase, *see also* Ada protein
A. arolicus, 154
A. fulgidus, 154
A. nidulans, 153
 Archaea, 153–154
B. subtilis, 151
E. coli, 142–146
 eukaryotes, 153
 genes for, 153
 human, 154
M. luteus, 152
 mammalian, 151, 154–156
 phosphorylation, 156
S. cerevisiae, 151, 153
Salmonella, 151
 therapeutic applications, 161–162
- O*⁶-Alkylguanine-DNA alkyltransferase I, (*O*⁶-AGT I), *E. coli*, 142
 compared to *O*⁶-AGT II, 152
 levels, 145–146
 mechanism of action, 143–145
 peak expression, 149
 repair of methylphosphotriesters, 144–145
 substrate specificity, 142–143
 suicide enzyme, 145
- O*⁶-Alkylguanine-DNA alkyltransferase II, (*O*⁶-AGT II), *E. coli*, 142, 146, 150–152
 biochemical properties, 151
 compared to *O*⁶-AGT I, 152
 functions, 151–152
- O*⁶-Alkylguanine-DNA methyltransferase, mitochondrial, 452
- Alkylphosphate, 37
- Alkylpurine-DNA glycosylase, *H. pylori*, 186
- 3-Alkylthymine, 37
- O*²-Alkylthymine, 37
- O*⁴-Alkylthymine, 37
 premutagenic lesion, 554–555
 repair, 141–157
 enzyme-catalyzed reversal, 139–168
- Allele, 71
- Allele number, 71
- Alpha particles, 26, 28
- Alternative excision repair, 4–5, 107, 379–388
D. radiodurans, 254, 384
 definition, 228
 endonuclease V, 379–383
 mtDNA, 385–386, 456–457
N. crassa, 385, 387
 oxidative base damage, 386–387
 topoisomerase-DNA complexes, 387
- Alu* elements, 420–421, 991
- α -Amanitin, 363
- Ames test, 76–77, 513
- Amethopterin, 13
- 9-Aminoacridine, 395
- 3-Aminobenzamide, 212–213
- 2-Aminopurine, 99, 395, 418
- Anaphase-promoting complex, 754, 801
- Ancient DNA, 23–24
- Aneuploidy, 667, 1011
- Angelicin, 40–41
- Animal models, *see also* Mouse models
 Bloom syndrome, 963–964
- Anthracycline, 247
- Antibody genes, *see also* V(D)J recombination
 class switch recombination, 429–430, 640, 714
 hypermutation, 13–14, 429–430
- Antimutator mutants, *S. cerevisiae*, 629
- Antioxidant(s), 17
- Antioxidant enzymes, 21–22
- Antley-Bixler syndrome, 1027
- AP endonuclease, 169–170, 192, 197–202, 213, 383
D. melanogaster, 199–200
E. coli, 198
 endonuclease IV (Nfo) family, 200–202
 exonuclease III (XthA), 198–200
 human, 198
 mitochondrial, 454–455
 reaction catalyzed, 171
S. cerevisiae, 198–199, 202
 single-strand break repair, 738–739
- AP lyase, 169–170, 172, 178, 191–192, 197, 199
 base excision repair, 202
 mitochondrial, 454–455
 reaction catalyzed, 171
- AP sites, 15–17, 38, 197, 247
 β -elimination, 15–17
 handling by bypass polymerases, 639
 as premutagenic lesion, 530–532
 repair, *see also* Base excision repair
 by exonuclease III, 198–199
 Rad1-Rad10 complex, 287–288
 structure, 171
 toxic consequences, 213
- AP-1, 156, 199
 adaptation in multicellular eukaryotes, 847
 apoptosis, 853
 transcriptional response to DNA damage, 835
 UV response in mammals, 831–832, 834
- APAF-1 adaptor protein, 848–850
- APC* gene, human, 189, 985, 1009–1012
- APC* protein, human, 1009–1012
 functional domains, 1010
- APE* gene, human, *see APEX1* gene, human
- Apert syndrome, 1027
- APEX1* gene, human, 199
- Apex1* gene, mouse, 199
- APEX1* protein
 base excision repair, 212, 214
 human, 55
 mammalian, 199–200, 204, 208
- Aphidicolin, 357, 407, 932, 961
- APN1* gene, *S. cerevisiae*, 202
- APOBEC (enzyme), 13–14
- Apoptosis, 4, 6, 22, 753, 845
 activation by DNA damage, 850–852
 apoptosome and downstream effectors, 849–850, 853
 apoptotic pathways, 848–850
 extrinsic and intrinsic, 848–849
 Cockayne syndrome, 898
 DNA damage sensors, 852–853
 Fanconi anemia, 989
 mismatch repair proteins and, 427–428
 mitochondria in, 450–451
 reactive oxygen species, 851
 regulation, 848–853
- Apoptosis-inducing factor, 850
- Apoptosome, 849–850
 nuclear, 853
- Aprataxin, 739, 936
- APRT* gene
 CHO cells, 81–82
 mouse, 83–86
- Apurinic site, *see* AP sites
- Apyrimidinic site, *see* AP sites
- Archaea
 DNA helicase, 288
 nucleotide excision repair, 255
- Arginine methyltransferase, 790, 851
- Aromatic amines, 41–42
- Artemis* gene, human, 934
- Artemis protein
 cell cycle regulation, 803
 deficiency, 935
 nonhomologous end joining, 721–722, 724, 728
 V(D)J recombination, 714
- Arylhydrocarbon hydroxylase, 43
- ASF1* gene, *S. cerevisiae*, 358
- Asf1 protein, *S. cerevisiae*, 779
- ASPP protein, 851
- AT, *see* Ataxia telangiectasia
- Ataxia telangiectasia (AT), 23, 620, 726, 756, 760, 791, 852, 919–928, 1087
 AT variants, 925
 cancer proneness, 925–926
 cell cycle, 922
 cellular phenotypes, 920–923, 928
 chromosomal abnormalities, 922–923
 clinical features, 919–920, 928, Color Plate 5
 complementation groups, 923–925
 DNA repair, 923
 genetic heterogeneity, 923–924
 homologous recombination, 922–923
 in vitro correction of cellular phenotypes, 924
 lymphoreticular system disease, 919–920
 mouse model, 926–928
 oxidative stress response, 923
 premature aging, 1029
 radioresistant DNA synthesis, 760, 920–922
 relationship to Bloom syndrome, 962–963
 sensitivity to ionizing radiation, 920
- Ataxia telangiectasia-like disorder (ATLD), 726, 796, 928, 930, 1087
- Ataxia with oculomotor apraxia, 739, 936, 1087
- ATLD, *see* Ataxia telangiectasia-like disorder
- ATM* gene, human, 760, 924–928, 962–963
 consequences of heterozygous mutations, 926
 DNA repair, 803
 heterozygotes, 1061
 mapping, 1050
 mutations, 925–926
- Atm* gene, mouse, 926–928
- ATM protein, 735, 762–763, 768, 781, 1016
 apoptosis, 852
 DNA damage sensor, 760–762
Drosophila homolog, 760
 G₂/M arrest, 799
 interaction with 53BP1, 782

- interaction with MRN complex, 767
mammalian, 759
phosphorylation, 761–762
phosphorylation of p53 protein, 788–789
S-phase arrest, 796–797
senescent cells, 855
transcriptional response to DNA damage, 835
V(D)J recombination, 761
yeast, 759
- ATP, in nucleotide excision repair, 232, 240, 248
- ATP hydrolysis, RecA protein, 579
- ATPase
CSB protein, 899
DNA-dependent, 250
DNA-independent, 230–231
- ATR gene, Seckel syndrome, 931–933
- ATR protein, 428–429, 780
ATR-ATRIP complex, 764
DNA damage sensor, 762–763
DNA repair, 803
G₁/S arrest, 794
mammalian, 759
phosphorylation of p53 protein, 788
senescent cells, 855
yeast, 759
- ATR-interacting proteins, 759
- ATRIP protein, 763
ATR-ATRIP complex, 764
ATRIP-RPA interactions, 763–764
- ATRX gene, human, 1025
- Attenuated familial adenomatous polyposis, 1009–1010
- Autoradiography, nucleotide excision repair, 267
- Auxotroph, 74–75
- Azaserine, 153
- 6-Azauracil, 366, 465
- B**
- Bacillus subtilis*
nucleotide excision repair, 254–255
SOS system, 498
spore photoproduct, *see* Spore photoproduct
spores, 33
translesion DNA synthesis, 549–550
- Bacterial persistence, 497
- Bacterial toxins, 47–48
- Bacteriophage, *see* phage entries
- BAK protein, 851–852
- Bannayan-Riley-Ruvalcaba syndrome, 1014–1015, 1088
- BARD1 protein, BRCA1-BARD1 complex, 788
- Basal cell carcinoma, 82
- Basal cell nevus syndrome, 1016–1018, 1088
- Base analog, 13
- Base excision repair, 4–5, 14, 17, 107, 140, 162, 169–226
AP endonucleases, 197–202
AP sites, 17
Bloom syndrome, 957
chromatin and, 214
DNA glycosylase, 169–197
DNA ligase, 204–210
fidelity in mammalian cells, 204
- gap filling and deoxyribosephosphate removal
E. coli, 202–203
mammalian cells, 203–204
long-patch pathway, 203, 212
mammalian cells, 270
mtDNA, 451–455
nomenclature of repair genes, 1081
poly(ADP-ribose) polymerase, 210–213
polymorphisms in repair genes, 1064
polynucleotide kinase phosphatase, 210–211
post-incision events, 202–213
replacement of single nucleotide, 203
S. cerevisiae, 821
S. pombe, 822
sequential interactions between proteins, 213–214
short-patch pathway, 203, 455
source of single-strand breaks, 737
transcriptional response to DNA damage, 821
- Base propenal, 46
- Base substitution mutation, 73–74
from misincorporation during DNA synthesis, 98–99
- Base-flipping, 56–57, 162, 432
AP site recognition, 200
endonuclease IV, 200–201
pyrimidine dimer-DNA photolyase, 120, 125, 194
- Base-pairing
energetics, 87
Hoogsteen base pairs, 87, 98, 637
Watson-Crick pairs, 87
- Basic fibroblast growth factor, 831
- BAX protein, 848, 850–853
- B-cell malignancy, uracil-DNA glycosylase deficiency, 179
- BCL proteins
apoptosis, 848–850
domain BH3-only, 848
BCNS gene, human, 1017
- Benzo[a]pyrene, 42, 637, 1063
- Benzo[a]pyrene diol epoxide, 43–44, 247, 363, 544, 571
- O⁶-Benzylguanine, 161–162
- β sliding clamp, 546–547
- β-Elimination, 15–17
- β-Hairpin structure, UvrB protein, 242
- β-Lactam antibiotics, 497
- BID protein, 849
- BIDS syndrome, 908–909
- Big Blue Mouse, 83
- 1,3-Bis(2-chloroethyl)-1-nitrosourea, 143, 247
- Bisulfite, 12
- B-K mole syndrome, 1018
- Bladder cancer, 1063–1066
- Bleomycin, 46, 200, 383, 533, 963, 1068
- BLM gene, human, 421, 947, 954–965
BLMash mutation, 959
gene expression, 960–961
heterozygotes, 1061
mapping and cloning, 958
mutations in Bloom syndrome, 959
- Blm gene, mouse, 963–964
- BLM protein
cellular localization, 961
chickens, 963
- DNA repair functions, 962
Drosophila ortholog, 963
FA core complex, 993
helicase activity, 958–960
human, molecular functions, 964–965
interaction with WRN protein, 967–968
- Bloom syndrome (BS), 209, 421, 947, 954–965, 1087
animal models, 963–964
autosomal recessive genetics, 955
biochemical abnormalities, 957
cancer predisposition, 955, 959–960, 971
cellular characteristics, 971
chromosome instability, 955–956, 962, 1061
clinical features, 955, 970, Color Plate 7
defects associated with S phase, 956–957
DNA repair, 957
heterozygotes, 959–960, 1061
interallelic recombination, 958
mismatch repair, 962
nucleotide excision repair, 957, 962
relationship to ataxia telangiectasia, 962–963
sister chromatid exchange, 954–956, 958, 961–962, 1061
somatic recombination, 958
- Blue-light receptor proteins, 112, 130–132
- BMPRIA gene, human, 1014
- bord*⁺ gene, *E. coli*, 481, 496
- Bovine AP endonuclease 1, 199
- 53BP1 protein, mammalian, 736, 782–783
- 46BR syndrome, 1088
- Branch migration, 665
- BRCA1 gene, human, 1007–1008
heterozygosity, 1060
mapping, 1050
pedigree analysis, 1008
polymorphisms, 1068
- BRCA1 protein, 682, 736, 782
activities, 682–683
BRCA1-BARD1 complex, 788
cell cycle regulation, 683
DNA repair, 682–683
G₂/M arrest, 799, 801
MRN complex and, 727–728
phosphorylation, 682, 797
protein-protein interactions, 683
S-phase arrest, 797
structure, 682–683
transcription, 683
ubiquitination, 683
- BRCA2 gene, human, 1007–1008
Fanconi anemia complementation group, 992–993
heterozygosity, 1060
mapping, 1050
polymorphisms, 1066
- BRCA2 protein, 682, 797
BRCA2DBD polypeptide, 684
DNA repair, 682
Fanconi anemia connection, 685
homologous recombination, 683–685
RAD51 interactions, 683–685
structure, 682–685
- BRCT domain, 682, 781–782, 847, 930
- Breakage-fusion cycle, 855
- Break-induced replication, 594, 663, 665, 687
- BIR mediators, 687

- Break-induced replication, (*continued*)
 HO-induced, 687
S. cerevisiae, 687
- Breast cancer, 204, 453, 1058, 1062, 1064
 ATM mutations, 926
 hereditary, 682, 1088
 predisposition syndromes, 1002, 1007–1008
- Brittle-hair syndromes, 907–909
 5-Bromodeoxyuridine, 258–260
 O⁶-(4-Bromothienyl)guanine, 161
 5-Bromouracil, 13, 35, 258–260, 395
- BrU-photolysis, 35
- BS, *see* Bloom syndrome
- Butter yellow, *see* *N,N*-Dimethyl-4-aminoazobenzene
- t*-Butyl hydroperoxide, 200, 385
 O⁶-Butylguanine, mtDNA, 452
- Bystander effect, 28
- C**
- CID protein, mammalian, 719
caa⁺ gene, *E. coli*, 487
- c-Abl kinase, 429
- CAC genes, *S. cerevisiae*, 357–358
- Cadmium toxicity, 430–431
- CAF1 protein, mammalian, 356–358
- Caffeine, 763, 857, 921
- Cairns model system, adaptive mutagenesis, 552–553
- Calicheamicin, 46, 533
- Caloric restriction, 22
- Caltractin, 294–295
- Camptothecin, 47, 737–738, 759, 770, 966
- Cancer, 14, *see also specific types*
 ataxia telangiectasia, 925–926
 cell cycle checkpoints and, 757
 DNA damage and, 7, 854–856
 oxidative DNA damage and, 22–23
 therapy, cell cycle checkpoints and, 856–857
Xpa mouse, 883–884
Xpc mouse, 886
- Cancer predisposition, 390, 828
 Bloom syndrome, 955, 959–960, 971
BRCA2 polymorphisms, 1066
 combinatorial effects of different polymorphisms, 1067
 DNA polymorphisms and, 1049–1080
 DNA repair capacity and, 1057–1059
 Fanconi anemia, 987–988
 hereditary syndromes, 1001–1021, *see also specific syndromes*
 Nijmegen breakage syndrome, 930
 Rothmund-Thomson syndrome, 968, 971
 Werner syndrome, 971
 xeroderma pigmentosum, 881–882
 risk assessment, 881–882
XPD polymorphisms, 1064–1066
XPG polymorphisms, 1066
XRCC1 polymorphisms, 1064
- Carbodiimide, 82
- Carboplatin, 36, 39
- Carcinogen(s)
 metabolism, 72, 1062–1071
 proximate, 42
 ultimate, 42
- Carcinogenesis, remote, 41
- Caretaker genes/proteins, 855, 1001
- Carmustine, 161
- Carney complex, 1002
- Casein kinase I, 789, 819
- Casein kinase II, 789
- β-CASP family, 693
- Caspase, 848
- Caspase-2, 853
- Caspase-3, 428, 849–850, 852
- Caspase-7, 849
- Caspase-8, 848
- Caspase-9, 849–850
- Catalase, 21–22, 989
 xeroderma pigmentosum, 873
- Cataract–microcephaly–failure-to-thrive–kyphoscoliosis syndrome, 910
- Catechol estrogens, 45–46
- β-Catenin, 1010–1011
- CBP acetyltransferase, 851
- CC-1065, 247
- CCL1* gene, *S. cerevisiae*, 279
- Ccl1 protein, *S. cerevisiae*, 324–325
- CCNH* gene, human, 279
- CCNH* protein, mammalian, 324
- CD3D* gene, human, 934
- CD45* gene, human, 934
- cdc1*⁺ gene, *S. pombe*, 1007
- CDC2* gene, *S. cerevisiae*, 336
- Cdc2 protein
 mammalian, 798
S. pombe, 798–799, 847
- Cdc5 protein, *S. cerevisiae*, 801
- CDC7 protein, CDC7-DBF4 complex, 794
- CDC8* gene, *S. cerevisiae*, 278, 823
- CDC9* gene, *S. cerevisiae*, 207, 272–273, 278–279, 755, 823
- CDC13* gene, *S. cerevisiae*, 755, 759
- CDC17* gene, *S. cerevisiae*, 823
- Cdc20 protein, *S. cerevisiae*, 801
- CDC25 protein, mammalian, G₂/M arrest, 799
- Cdc25 protein, *S. pombe*, 798–799
- CDC25A protein, vertebrates, 794
- Cdc28 protein, *S. cerevisiae*, 801
- Cdk inhibitors (Cki), 754, 792
- CDK1 protein, vertebrates, 792
- CDK2 kinase, vertebrates, 792–794
- CDK4* gene, human, 1018
- CDK4 kinase, vertebrates, 793
- CDK7* gene, human, 279
- CDK7 protein, mammalian, 324
- CDKN2A/CDNK2* gene, human, 1018
- Cds1 protein
S. pombe, 779–780, 783
X. laevis, 780
- cea*⁺ gene, *E. coli*, 487, 489
- Cell cycle
 ataxia telangiectasia, 922
 double-strand break repair and, 736–737
S. cerevisiae, 737, 754–757
- Cell cycle checkpoints, 4, 6, 620
 apoptosis and, 853
 cancer, 757
 cancer therapy and, 856–857
 cell cycle progression
 DNA damage-induced G₂/M arrest, 798–801
 G₁/S arrest, 791–794
 inhibition, 22
 regulation, 785–802
- regulation of M phase, 801–802
- S-phase response to DNA damage, 794–798
- checkpoint-triggering damage, 758–760
- DNA damage sensing, 758–771
 ATM protein, 760–762
 ATR protein, 762–763
 ATRIP-RPA interactions, 763–764
 cross talk between sensors, 765–766
 interactions of checkpoint clamp and clamp loader, 765
 MRN complex, 766–767
 9-1-1 complex, 764–765, 769–771
 PCNA, 764
 RFC-like clamp loader, 765
 S phase, 769–771
- DNA damage sensor proteins, 758–760
 effector targets
 downstream targets, 785–802
 modulation of DNA repair, 802–803
 p53, 785–791
- emergence of checkpoint concept, 753–758
- Fanconi anemia, 990
- mammalian Rad9 homologs, 782–783
- methods of study, 757–758
 synchronization of cells, 757
- sensing UV radiation damage, 768–769
- signal transmission, 758
 Chk1 kinase, 783–784
 generation and transmission of
 checkpoint-activating signal, 779
 mediators, 781–782
 Rad53/Cds1/CHK2 kinase, 779–780, 783
 summary, 784–785
- SOS-induced, 495
- transcriptional response to DNA damage and, 823, 826
- Xenopus*, 759–760
- Cell cycle restart
 adaptation and, 846–847
S. cerevisiae, 847
- Cell division, control by SOS-induced
 checkpoint, 495
- Cell fate, DNA damage effect, 845–862
- Cell size checkpoint, 804
- CENPF protein, 1004
- Centrin 2, 294–295
- Centrosome amplification, 845
- Cerebro-oculo-facio-skeletal (COFS) syndrome, 905, 1087
- CFK-activating kinase, phosphorylation of p53 protein, 789
- Charcot-Marie-Tooth disorder, 1033
- CHEK2* gene, human, 1007
- Chemicals, metabolism, 72, 1062–1071
- Chemical mutagenesis, 72
- Chi site, 580, 594
- Chiasmata, 425
- Chicken foot structure, Holliday junction, 571, 575, 595, 597, 601
- Chinese hamster ovary cells, nucleotide excision repair, 267–269, 275
- CHK1* gene, human, 1007
- Chk1 kinase
 activation, 784
 G₂/M arrest, 799, 801
 phosphorylation, 784
 phosphorylation of p53 protein, 789

- roles in different organisms, 783–784
S. cerevisiae, 847
S. pombe, 783, 798–799
 senescent cells, 855
- Chk1* mutant, mouse, 784
- CHK2 protein
 apoptosis, 852
 G₂/M arrest, 799
 human, 779–783
 phosphorylation, 781
 phosphorylation of p53 protein, 789
 senescent cells, 855
- Chk2 protein, *Drosophila*, 780
- Chl12 protein, *S. cerevisiae*, 770
- Chlorambucil, 36
- Chloroacetaldehyde, 176
- N*-(2-Chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea, 36, 143
- O*⁶-Chloroethylguanine, repair, 143
- Chloroethylnitrosourea, 152, 161
- Cho protein, *E. coli*, 245–247
 Cho homologs, 247, 492
M. hyopneumoniae, 247
- Chromatin
 assembly, 770
 base excision repair, 214
 MRN complex binding, 725
 nucleotide excision repair
 distribution of DNA damage and repair events, 355–357
 reassembly coupled to repair, 356–358
 remodeling, 354–356
 structural changes, 352–354
 organization into higher-order structures, 351–352
 remodeling enzymes, ATP-dependent, 354
 structure, alterations in hereditary diseases, 1021–1028
 structure and DNA damage, 48–49
 transcription, structural changes, 352–354
- Chromatin assembly factor 1, 356–358
- Chromatin immunoprecipitation technique, 40, 668–669
- Chromatin silencing, Ku proteins, 717
- Chromophore, pyrimidine dimer-DNA photolyase, 112, 115–116, 118–119
- Chromosomal abnormalities
 ataxia telangiectasia, 922–923
 Fanconi anemia, 988
 prevention by mismatch repair, 421
 xeroderma pigmentosum, 868–869
- Chromosome instability
 Bloom syndrome, 955–956, 962, 1061
 retinoblastoma, 1004
- Cip1 protein, vertebrates, 791
- Circadian rhythm, 131
- Cisplatin, 36, 38–39, 118, 247–248, 284, 330, 363, 385, 451, 989
 resistance, 429
- c-Jun N-terminal kinase, 429
 phosphorylation of p53 protein, 789
- cka*⁺ gene, *E. coli*, 489
- Claspin, 784
- Class switch recombination, antibody genes, 429–430, 640, 714
- CLN* genes, *S. cerevisiae*, 791
- ClpXP protease, 473, 491, 522
- Clustering analysis, 825
- CMM* genes, human, 1018
- Cockayne syndrome (CS), 23, 298, 364, 367–368, 834, 865, 895–905, 1087,
 see also XP/CS complex
 apoptosis, 898
 cellular phenotypes, 896–897
 clinical phenotypes, 895, Color Plate 2
 complementation groups, 898
 DNA repair, 896–897
 transcriptionally active DNA, 897–898
 genetics, 898–905
 group A, 898
 group B, 898
 mouse models, 903–905, 912
 oxidative base damage repair, 903
 premature aging, 1029–1030
 transcription-coupled nucleotide excision repair, 897–898, 901, 903
 UV sensitivity, 896
- Coding joint, V(D)J recombination, 712–714
- Coffin-Lowry syndrome, 1026
- COFS syndrome, see Cerebro-oculofacio-skeletal syndrome
- Cohesins, 681, 796
- Cold spot, 77
- Colicin EI, 489
- Colon cancer, 189–190, 204, 406, 433, 1065
 predisposition syndromes, 1008–1016
- Combined XP/CS, see XP/CS complex
- Comet assay
 double-strand break repair in *S. cerevisiae*, 667
 nucleotide excision repair, 273
- Complementarity-defining region, 640
- Completion problem, cell cycle, 754, 757
- Complex mutation, 99–100
- Conditional dicentric chromosomes, 668–669
- Conditional mutation, 74
- Constant denaturant capillary electrophoresis, 83
- Constitutively-stable DNA replication, 594
- Contingency loci, 424
- COP9 signalosome, 902–903
- Copy choice DNA replication, see Replication fork regression
- Cosmic radiation, 25
- Cowden syndrome, 1002, 1014–1015, 1088
- COX11* gene, *S. cerevisiae*, 693
- CpG islands, methylation, 154
- CPRI* gene, *S. cerevisiae*, 827
- Crb2 protein, *S. pombe*, 784, 847
- CREBBP* gene, human, 1026
- Crisis stage, 855
- Cross-link(s), 248, 663
 detection, 39
 DNA-DNA, 34
 interstrand, see Interstrand cross-link repair
 intrastrand, 38–39
 DNA-protein, 27, 34, 39–40, 47
 psoralen-induced, 40–41
- Cross-linking agents, 38–40
 sensitivity, 696
- Crossover, 665
 during meiosis, 424–427
- Crossover interference, 425
- Crotonaldehyde, 40
- Crouzon cutis gyrata of Beare and Stevenson, 1027
- Crouzon syndrome with acanthosis nigricans, 1027
- CRT1* gene, *S. cerevisiae*, 818–819
- Crt1 protein, *S. cerevisiae*, 826
- CRY* genes, see *hCRY1*; *hCRY2*; *mCry1*; *mCry2*
- Cryptochromes, 112
 in different kingdoms, 131
- CS, see Cockayne syndrome
- CSA gene, human, 279, 364, 899–900
- Csa* gene, mouse, 904–905
- CSA protein
 human, 302, 899–900
 cellular location, 902
 multimeric protein complex, 902–903
 RNA polymerase II transcription, 368, 900
 XAB2 protein interactions, 901
 mammalian, 364
- CSB* gene, human, 276, 279, 364, 898–899
- COFS syndrome, 905
- UV-sensitive syndrome, 906
- Csb* gene, mouse, 903–904
- CSB protein
 human, 898–899
 ATPase activity, 899
 interaction with RNA polymerase II, 900
 repair of oxidative base damage, 371, 903
 RNA polymerase II transcription, 368, 900
 transcription elongation, 369, 901
 ubiquitination of RNA polymerase II, 900–901
 XAB2 protein interactions, 901
 mammalian, 364, 366–368
- CTD kinase, 324–325
- CtIP protein, 801
- CTP:CMF phosphotransferase, 12
- CUL4A protein, 302
- Cullin 4a, 902–903
- Cut phenotype, *S. pombe*, 757
- Cutaneous malignant melanoma, 1018
- CY1* gene, *S. cerevisiae*, 76
- Cyclic AMP, mutagenesis in aging colonies, 552
- Cyclin(s), 754, 1018
- Cyclin A, 792, 830
- Cyclin B, 801
- Cyclin D, 792–793
- Cyclin E, 792–794
- Cyclin H, 324
- Cyclin-dependent kinase, 736–737, 753–754, 792, 990
 phosphorylation of p53 protein, 789
- Cyclobutane pyrimidine dimers, 12, see also Pyrimidine dimer-DNA glycosylase; Pyrimidine dimer-DNA photolyase
cis-syn form, 30, 115, 527–528, 615
 distribution in chromatin, 48–49
 DNA polymerase bypass of CPD lesions, 96, 98, 638
 formation, 29–32
 effect of DNA sequence context, 31–32
 inhibition of DNA polymerase III, 527
- lacI* gene, 31

- Cyclobutane pyrimidine dimers, (*continued*)
 local structure of DNA, 30
 locating in DNA, 31–32
 loss of radiolabeled dimers from DNA, 257–258
 mtDNA, 452
 nucleotide excision repair in eukaryotes, 274
 photoreactivation, 109–127
 photoreversal, 110
 photosensitized reactions, 34–35
 as premutagenic lesion, 525–529
 repair, *see also* Base excision repair;
 Nucleotide excision repair
 repair by deoxyribozyme, 132
 RNA, 133
 sunlight-induced, 35
trans-syn form, 30, 115, 528, 615
 UV irradiation of mammalian cells, 624
 UV radiation-induced mutagenesis of
Sup4-o in yeast, 615
 xeroderma pigmentosum cells, 869
 8,5'-Cyclodeoxyadenosine, 23, 27
 8,5'-Cyclodeoxyguanosine, 24, 27
 Cyclohexylcarbodiimide, 247
 Cyclophosphamide, 36
 Cyclopurine DNA adducts, 23, 873–874
CYP1A1 gene, human, 1062–1063
 Cystic fibrosis, *P. aeruginosa* infections, 424
 Cytidine deaminase, activation-induced
 deaminase, *see* Activation-induced
 cytidine deaminase
 Cytochrome *c*, apoptosis, 848–849, 853
 Cytochrome P-450 system, 41–44
 polymorphisms, 1062–1063
 Cytolethal distending toxin, 47–48
 Cytosine
 deamination, 4, 9–12, 14, 16, 432, 641
 antibody gene hypermutation, 13–14,
 641, 714
 defense against retroviruses, 13–14
 ionizing-radiation-mediated damage, 27
 methylation, 358–359
 Cytosine deaminase, 14
 Cytosine DNA methyltransferase, 56
 Cytosine glycol, 22
 Cytosine hydrate, 16, 33, 191
- D**
 Dacarbazine, 36, 161, 428
dam⁺ gene, *E. coli*, 393–395, 399, 402, 427,
 429, 485–486
 Dark repair, 227
dat1⁺ gene, *B. subtilis*, 152–153
 Daughter strand gap repair, 485, 593
 evidence for gaps in new DNA, 587–589
 evidence for recombinational events,
 589–590
 gap size, 588
 in vivo system, 592–593
 perspectives, 590–592
 protein in, 590
 RecA protein, 578, 586
 recombinational repair, 586–593
 DBF4 protein, CDC7-DBF4 complex, 794
 dbSNP (database), 1051
dcm⁺ gene, *E. coli*, 431–432
 Dcm methylase, 432
 dCMP deaminase, 12
dcry gene, *Drosophila*, 131
 dCTP deaminase, 12–13
DDI1 gene, *S. cerevisiae*, 821
 DDB protein
 mammalian, 342, 356
 nucleotide excision repair, 331
DDB1 gene, human, 279, 830, 880
 DDB1 protein
 homologs, 302–303
 human, 902–903
 mammalian, 302–303, 333
 regulation, 301
 ubiquitin ligase, 301–302, 331
DDB2 gene
 human, 279, 880
 mammalian, 301, 830, 837
 DDB2 protein, mammalian, 301–302, 333
 Ddc1 protein, *S. cerevisiae*, 764, 769
DDR gene, *S. cerevisiae*, 823–824
 Deamination, 382
 adenine, 9–11, 14–15
 bisulfite-induced, 12
 cytosine, 4, 9–14, 16, 432, 641
 deoxyadenosine, 382
 deoxycytidine, 382
 deoxyguanosine, 382
 guanine, 9–10, 14–15
 5-hydroxymethylcytosine, 14
 5-methylcytosine, 9–10, 14, 16, 390,
 431–433
 nitrous acid-induced, 12
 Death receptors, 848, 850
 Death-inducing signaling complex, 848
 Debrisoquine, 1062
DEF1 gene, *S. cerevisiae*, 367–368
Deinococcus radiodurans
 alternative excision repair, 254
 nucleotide excision repair, 253–254
 Deletion mutation, 73–75
 detection, 78–79
 from primer-template misalignment, 99
 Denaturing gradient gel electrophoresis, 82
denV⁺ gene, phage T4, 193–196
 denV protein, phage T4, 55, 194–195, 882
 Denys-Drash syndrome, 1019
 Deoxyadenosine, 379
 deamination, 382
 3-(Deoxyadenosin-*N*⁶-yl)-
 4-aminoquinoline-1-oxide, 45
 2'-Deoxy-6-(cystamine)-2-aminopurine,
 141
 Deoxycytidine, deamination, 382
 Deoxycytidyl transferase, Rev1, 631–632
 Deoxyguanosine, 42
 deamination, 382
N-(2'-Deoxyguanosin-8-yl)-*N*-acetyl-
 2-aminofluorene, 42
N-(2'-Deoxyguanosin-8-yl)-2-acetyl-
 2-aminofluorene, 532
 3-(Deoxyguanosin-*N*²-yl)-
 2-aminofluorene, 42
N-(2'-Deoxyguanosin-8-yl)-
 2-aminofluorene, 42
N-(Deoxyguanosin-8-yl)-
 4-aminoquinoline-1-oxide, 45
 3-(Deoxyguanosin-*N*²-yl)-
 4-aminoquinoline-1-oxide, 45
 Deoxyinosine 3' endonuclease, *E. coli*, 380
 Deoxynucleoside triphosphate, *see* dNTP
 Deoxyribose, at AP site, 15–17, 169–171,
 202–203, 211
 Deoxyribosephosphate lyase, DNA poly-
 merase β , 203
 Deoxyribozyme, thymine dimer repair, 132
 Depurination, 10, 15–17, 24, 169, 185
 Depyrimidination, 15–17, 169
 DeSanctis-Cacchione syndrome, 867
 Dexamethasone, 156
 1,2-Diacyl-*sn*-glycerol, 156
 4,6-Diamino-5-formamidopyrimidine, 19,
 22, 24, 27
 2,6-Diamino-4-hydroxy-5-
 formamidopyrimidine (FaPy), 19,
 22, 27–28, 190, 192
 2,6-Diamino-4-hydroxy-5-*N*-
 methylformamidopyrimidine,
 186–187, 387
 4,6-Diamino-5-*N*-
 methylformamidopyrimidine, 187
 2,6-Diaminopurine, 83
 Diamminedichloroplatinum(II), 318
 Di-(2-chloroethyl)sulfide, 35
 Diepoxybutane, 989
 Diethylnitrosamine, 37
 Differentiation, 846
 Difluorotoluene, 93
 Dihydrocytosine, 11
 5,6-Dihydrocytosine-6-sulfonate, 12
 Dihydrofolate reductase, 13
 8,9-Dihydro-8-(*N*7-guanyl)-9-
 hydroxyafatoxin B₁, 44
 7,8-Dihydro-8-oxoguanine, *see* 8-OxoG
 Dihydrothymine, 22
 removal, 192, 387
 5,6-Dihydro-5-(α -thyminyl)-thymine, *see*
 Spore photoproduct
 Dihydrouracil, 385
 removal, 387
 5,6-Dihydrouracil-6-sulfonate, 12
 Dihydrouridine, 11
 5,6-Dihydroxycytosine, 22
 5,6-Dihydroxydihydrothymine, *see*
 Thymine glycol
 Dimethyl sulfate, 180, 451
N,N-Dimethyl-4-aminoazobenzene, 41
 4-Dimethylbenzimidazole, 93
 1,2-Dimethylhydrazine, 37
 Dimethylnitrosamine, 37, 161
DIN genes, *S. cerevisiae*, 823–824
din⁺ genes, *E. coli*, 478–481, 487–488, 492,
 494, 496, 538, 543, 553
 DinB protein
E. coli, 538–539, 553
S. cerevisiae, 632
 DinI protein, *E. coli*, 491, 521
 regulation of RecA-mediated cleavage
 reactions, 488–489
 Dinitrogen trioxide, 383
 Dioxygenases, 157
 Direct photoreversal, 110
 Dislocation mutagenesis, 99
 Distamycin, 51
 Ditercalanum, 247
div⁺ gene, *E. coli*, 486, 495
DKC1 gene, human, 1027–1028
 D-loop, 594, 596, 602–603, 680
 DNA
 ancient, 23–24
 A-tract sequences, 53
 flexible molecule, 52–53

- methylation, 393–394, 1005, 1022–1025
after nucleotide excision repair, 358–359
mitochondrial, *see* Mitochondrial DNA
structural information encoded in, 50–54
undermethylated, 393
- DNA alkyltransferase, 56
eukaryotes, 153
prokaryotes, 152–153
- DNA damage, 9–69
activation of apoptosis, 850–853
alterations in base chemistry, 9–24
biological relevance, 28
biological responses, 4–6
cancer, 854–856
chromatin structure and, 48–49
constant genomic insult, 4
detection by proteins, 50–57
disease states associated with defective responses to, 6–7, 979–1047
endogenous, 4, 9–25
environmental, 4, 9, 25–48
historical reflections, 3–4
inhibition of DNA synthesis, 618–620
ionizing radiation, 4, 17, 24–29
lipid peroxidation products, 16, 20–21
locating sites of, 55–57
loss of bases, 15–17
major sites, 10
mismatches created by replication errors, 24–25
oxidative damage, *see* Oxidative damage
processing by homologous recombination proteins, 574–584
proteins protecting against, 49
regulation of cell fate, 845–862
regulatory responses, 114
senescence, 854–856
sensing, 758–771
SOS response, 463–497
spontaneous, handling by bypass polymerases, 639
strand breaks, *see* Strand breaks
transcriptional response, 817–844
under extreme conditions, 24
UV radiation, 4, 29–36
UV response in mammals, 831–835
- DNA damage checkpoint, UmuD and UmuC in, 519–520
- DNA damage tolerance, 4–6, 461
E. coli, 569–612
error-free, 642–646
error-prone, 642–646
eukaryotes, 629–649
translesion DNA synthesis, 509–510
- DNA damage-binding complex
regulation, 301
XP group E, 301–303
- DNA deoxyribosephosphodiesterase, 202–204
- DNA end-binding factor, 715–718
- DNA endonuclease, *see also specific enzymes*
Rad1–Rad10 complex, 285
Rad2 protein, 291
S. pombe, 383–386
- DNA glycosylase, 140, 169–197, *see also specific enzymes*
base excision repair, 213
bifunctional, 171, 190, 192, 202
E. coli, 172
helix-hairpin-helix motif, 171–174
human, 172
limiting oxidized and fragmented purine residues, 186–191
mechanism of action, 175
mismatch-specific, 176, 178
monofunctional, 171, 202
MutY and MYH, 189–190
OGG1, 190–191
reaction catalyzed, 170
release of free bases, 171
removal of methylated bases, 180–186
removal of oxidized and fragmented pyrimidine residues, 191–192
S. cerevisiae, 172
- DNA gyrase, 596
nucleotide excision repair, 253
- DNA helicase
archaeal, 288
defects in human hereditary diseases, 947–978
DNA replication, 952–953
Rad3 protein, 296–297
RecQ family, 947–978, *see also* RecQ helicase
replicative, 571
Srs2 protein of yeast, 645
TFIIH, 328–329
- DNA helicase II, *E. coli*, 250, 394
mismatch repair, 401–403
nucleotide excision repair, 250–251
orthologs, 253–254
- DNA ligase, 204, 454
ATP-dependent, 205
base excision repair, 170, 202–210
catalytic domain, 205–207
DNA-binding domain, 205–207
E. coli, 204–205
helix-hairpin-helix domain, 206
human, 208–210
mammalian, 207–208
mechanism of action, 204–210
mismatch repair, 403
mutations, 209–210
nucleotide excision repair, 253, 318, 339, 343
oligonucleotide-binding fold, 205–206
phage T7, 205–206
rejoining of strand breaks in DNA, 163
structure, 204–210
T. filiformis, 206–207
- DNA ligase I, 358
base excision repair, 207–209
Bloom syndrome, 957
mutations, 210
oligonucleotide-binding fold, 208
reconstitution of nucleotide exchange repair, 322
sister chromatid exchange formation, 962
- DNA ligase III, 212–214
base excision repair, 207–209
single-strand break repair, 738–739
- DNA ligase IV
base excision repair, 207–209
human, 722, 930–931
mutations, 210, 930–931
nonhomologous end joining, 722
S. cerevisiae, 737
XRCC4 protein-ligase IV complex, 722–723
- DNA ligation, 169
mice defective in, 723
- DNA methyltransferase, 821, 1022, 1025
- DNA mismatch correction, 157
- DNA photolyase, 56, 194, *see also*
Pyrimidine dimer-DNA photolyase;
(6-4) Photoproduct-DNA photolyase
monomerization of pyrimidine dimers, 110
transcriptional response to DNA damage, 820
- DNA polymerase
B family, 629
B. stearothersophilus, 89, 92, 94
deoxyribosephosphate activity, 204
error-prone
lesion bypass, 95–98
structure, 96–97
geometric selection of nucleotides, 87–90
incorporation of incorrect bases, 24–25
incorporation of uracil, 12
mammalian, 204
mechanism of action
importance of base-pairing geometry vs. hydrogen bonds, 92–93
induced-fit, 89–90
selection against ribonucleotides, 93
two-metal-ion, 90–92, 98
nomenclature of polymerase genes, 1084
open and closed conformations, 92
phage T4, 555
dynamic processivity, 550
phage T7, 89–90, 92–94
proofreading, 25, 87–88, 93–94, 98
sequence-specific pausing, 99
slippage, 980–982
SOS-induced, 543–544
structure, 86–98
Sulfolobus
Dbh polymerase, 96–97
Dpo4 polymerase, 96–98, 532
Taq, 89, 92–94
tool belt model, 550
X family, 637
Y family, 632, 636–637
- DNA polymerase I, *E. coli*, 89–91, 182, 244, 292, 431
functions, 536
gap filling in base excision repair, 202
Klenow fragment, *see* Klenow fragment
nucleotide excision repair, 229–243, 250–253
structure, 87–88
- DNA polymerase II, *E. coli*, 252, 479, 552, 601
functions, 536
inducible replisome/replication restart, 604
protein-protein interactions that control, 543–551
translesion DNA synthesis, 543
- DNA polymerase III, *E. coli*, 252, 551, 596
encounters with damaged DNA, 571
inhibition by cyclobutane pyrimidine dimers, 527
interaction with UmuD, 548–549
mismatch repair, 397, 402–403
mutations leading to SOS response, 486

- DNA polymerase III, (*continued*)
 SOS-dependent mutagenesis, 536–537
 UVM response, 555
- DNA polymerase 4, *S. cerevisiae*, 203, 723
- DNA polymerase IV, *see also* DinB protein
E. coli, 479, 494, 509, 539
 adaptive mutagenesis, 553
 interaction with β sliding clamp, 546–547
 protein-protein interactions that control, 543–551
 translesion DNA synthesis, 543
- DNA polymerase V, *E. coli*, 492, 494, 496, 509, 540–543, 551–552
 inducible replisome/replication restart, 604–605
 interaction with β sliding clamp, 546–547
 interaction with RecA and single-stranded DNA-binding proteins, 545–546
 protein-protein interactions that control, 543–551
 SOS-dependent mutagenesis, 543
- DNA polymerase α , 336, 830
S. cerevisiae, 339
- DNA polymerase β , 204, 208, 211–212, 214
 in cancer, 204
 deoxyribosephosphate lyase activity, 203
 errors, 204
 mammalian cells, 88–89, 92
 single-strand break repair, 738–739
 translesion synthesis, 638
- DNA polymerase γ , 204
- DNA polymerase δ , 203, 318
 human, 336–337
 mismatch repair, 407
 mitochondrial, 454–455, 638–639
 nucleotide excision repair, 322, 336–338
S. cerevisiae, 336–337, 339
- DNA polymerase ϵ , 318, 819
 DNA damage sensing, 771
 human, 336–337
 nucleotide excision repair, 322, 336–337
S. cerevisiae, 203, 336–337
- DNA polymerase ζ , 629–631, 638–639, 648, 822
 human, 631
S. cerevisiae, 629–631
 somatic hypermutation, 641
- DNA polymerase η , 539, 551, 632–636, 696, 823
 binding to PCNA, 648–649
 human, 95
 nuclear localization, 634
 one-step versus two-step reactions, 634–635
S. cerevisiae, 96–97, 509, 632, 635–636
 somatic hypermutation, 641
 translesion DNA synthesis, 632, 635–636, 638–639
 xeroderma pigmentosum, 632–634
- DNA polymerase θ , 637–639
- DNA polymerase ι , 204, 509, 636–637, 639, 641, 648
- DNA polymerase κ , 509, 637, 639, 648, 796
- DNA polymerase λ , 204, 723–724
- DNA polymerase μ , 637, 723–724
- DNA polymerase processivity protein, 496
- DNA polymorphisms, 1049–1080, *see also*
 Single-nucleotide polymorphisms
 N-acetyltransferase 2 gene, 1063–1064
 cytochrome P-450 monooxygenase gene, 1062–1063
 DNA repair genes, 1056–1057
 glutathione S-transferase M1 gene, 1063
 human genetic variation, 1050–1052
 impacting levels of chemical-induced DNA damage, 1062–1071
 restriction fragment length polymorphisms, 1050
 short tandem repeat sequences, 1050
- DNA recognition code, 51
- DNA repair, *see also specific types*
 aging and, 1028–1034
 ataxia telangiectasia, 923
 Bloom syndrome, 957
 cancer predisposition and, 1057–1059
 chromatin structure and, 50–57
 Cockayne syndrome, 896–897
 definitions, 4–5
 direct reversal of DNA damage, 5
 alkylation damage, 139–168
 base damage, 107, 109–138
 repair of single-stranded DNA breaks, 162–163
E. coli, RecA protein, 574–579
 error-free, 6
 error-prone, 6
 excision of damage, 5
 Fanconi anemia, 989
 mammalian cells, 803
 nomenclature of repair genes, 1081–1086
 somatic hypermutation and, 641
 trichothiodystrophy, 908–909
 yeast, 802–803
- DNA repair enzymes, *see also specific enzymes*
 activity on undamaged DNA, 114
 assay of individual enzymes, 319
 base-flipping, 56–57
 binding to single-stranded DNA, 54
 facilitated diffusion on DNA, 55
 interactions with p53 protein, 790
 levels in cells, 114–115
 locating sites of DNA damage, 55–57
 recognition of mismatched base pairs, 57
 regulation of expression, 114
 substrate selection, 55–56
- DNA repair genes
 heterozygosity, 1059
 genes for dominantly inherited disorders, 1059–1060
 genes for recessive disorders, 1061
 polymorphisms, 1062–1071
 functional defects, 1067–1070
 pharmacogenomics, 1067
 putative cancer risk, 1064–1067
 role in disease, 1056–1057
 statistics and population-based studies, 1056–1057
 variability in DNA repair capacity, 1057–1059
 single-nucleotide polymorphisms, 1062
- DNA sequence
 indirect readout, 53–54
 local structure of double helix, 50–51
- DNA sequencing
 bisulfite procedure, 12
 determination of mutational spectra, 524
 mutation identification, 85
- DNA synthesis, *see also DNA polymerases*
 arrested, 461, 465
 Cockayne syndrome, 897
 DNA helicase in, 952–953
 geometric selection of nucleotides, 87–90
 importance of base-pairing geometry vs. hydrogen bonds, 92–93
 incorporation of damaged nucleotide precursors, 25
 incorporation of incorrect bases, 24–25, 98–99
 mammalian cells exposed to DNA-damaging agents, 618–620
 MRN complex, 731–732
 mtDNA, 450
 non-semiconservative, *see* Repair synthesis
oriC-independent, 594, 603
 primer-template misalignment, 99–100
 radioresistant, *see* Radioresistant DNA synthesis
 recovery after DNA damage, 603–605
 relationship between replication and recombination, 593–598
 repair synthesis, *see* Repair synthesis
 replication errors, 72, 389
 replication of damaged DNA, SOS induction, 484–485
S. cerevisiae, 823
 selection against ribonucleotides, 93
 templated information in DNA, 86–87
 transcriptional response to DNA damage, 823
 transient inhibition after DNA damage, 573–574
 translesion, *see* Translesion DNA synthesis
 two-metal-ion mechanism, 90–92, 98
 uracil incorporation, 12–13
 after UV irradiation, 573–574
- DNA topoisomerase
 association with RecQ protein, 954
 DNA topoisomerase-DNA complex, repair reaction, 387
 nucleotide excision repair, 339–340
- DNA topoisomerase I, 213, 339, 770
 ataxia telangiectasia, 921
 interaction with WRN protein, 967
 nucleotide excision repair, 253
 source of single-strand breaks, 737
- DNA topoisomerase II, 213, 339, 770, 847
 ataxia telangiectasia, 921
 Bloom syndrome, 957
 G₁/S arrest, 794
- DNA topoisomerase III, 924, 963
- DNA topoisomerase inhibitors, 47, 961
- dnaB*⁺ gene, *E. coli*, 954
- DnaB protein, *E. coli*, 595–597, 952
- DNA-binding assay, pyrimidine dimer-DNA photolyase, 113
- DNA-binding proteins
 detection of DNA damage, 50–57
 DNA flexibility and, 52–53
 facilitated diffusion on DNA, 55
 indirect readout of DNA sequence, 53–54
 sequence-specific, 50–52

- single-stranded, *see* Single-stranded-DNA-binding proteins
 UvrA, 230–231
dnaC⁺ gene, *E. coli*, 484, 604
 DnaC protein, *E. coli*, 595–597
 DNA-deoxyribophosphodiesterase, 169–170
 DNA-dependent protein kinase
 apoptosis, 852
 cell cycle regulation, 803
 DNA damage sensor, 768
 histone phosphorylation, 735
 interaction with DNA, 719–720
 mouse *scid* mutant, 718–719
 multicellular eukaryotes, 847
 nonhomologous end joining, 718–721, 724
 phenotype of mice defective in, 720–721
 phosphorylation of p53 protein, 788
 transcriptional response to DNA damage, 835–837
 vertebrates, 847
dnaE⁺ gene, *E. coli*, 486
dnaF⁺ gene, *E. coli*, 486
 DnaG protein, *E. coli*, 595–596
dnaJ⁺ gene, *E. coli*, 239
dnaK⁺ gene, *E. coli*, 239
dnaN⁺ gene, *E. coli*, 486, 496
dnaQ⁺ gene, *E. coli*, 396, 485
dnaT⁺ gene, *E. coli*, 486
 DnaT protein, *E. coli*, 595–596
dnaZ⁺ gene, *E. coli*, 397
 DNMT1 protein, 1005
DNMT3B gene, human, 1022–1023
 dNTP, damaged, misincorporation, 555
 Dose fractionation, radiotherapy, 856
 Double D-loop formation assay, single-nucleotide polymorphisms, 1054–1056
 Double Holliday junction intermediate, 425
 Double-junction dissolution, 965
 Double-strand break(s), 29
 checkpoint response, 759–760, 766–767
 eukaryotes, 663–710
 experimental systems, 668–670
 conditional dicentric chromosomes, 668–669
 HO endonuclease, 668–669
 I-SceI-induced targeted, 669–670
 generation at replication fork, 570
 processing by RecBCD nuclease/helicase, 483
 radiation-induced, 27–28
S. cerevisiae, 665–669
 transcriptional response, 826–827
 site-specific, 668–669
 Double-strand break repair, 4–5, 28, 509,
see also Homologous recombination;
 Nonhomologous end joining
 cell cycle stage-dependent, 736–737
 eukaryotes, 663–665, 711–750
 histone modification, 735–736
 MRN complex, 724–735
 nonhomologous end joining, 664,
 711–724
 polymorphisms in repair genes, 1066
 recombinational repair, 584–585
 regulation of pathway choice, 726–727
S. cerevisiae, 665–667
 V(D)J recombination and, 714
 Down syndrome, premature aging, 1029,
 1033–1034
 Doxorubicin, 247
 Dpb protein, *S. cerevisiae*, 771
 DpiAB two-component system, 497
 Dps protein, *E. coli*, 49
dr1819 gene, *D. radiodurans*, 254
 Drcl protein, *S. cerevisiae*, 771
 Drug metabolism, 72, 1062–1071
DST1 gene, *S. cerevisiae*, 366
 dTMPase, 13
 Dulbecco, Renato, 111
 dUMP, incorporation into DNA, 12–13, 176
 dUMP kinase, 13
DUN1 gene, *S. cerevisiae*, 818–819, 823, 826
 Dun1 kinase, *S. cerevisiae*, 781, 819
 Duplication, 73
dut⁺ gene, *E. coli*, 12, 199
 dUTP pyrophosphatase, 17
 dUTPase, 12
 Dynamic recognition, base damage, 329
 Dyschromatosis symmetrica hereditaria, 867
 Dyskeratin, 1027–1028
 Dyskeratosis congenita, 1027–1028
 Dysplastic nevus syndrome, 1018
- ## E
- E7 protein, human papillomavirus, 793
 Early-onset ataxia with ocular motor
 apraxia, 936
 EcoRI, induction of SOS response, 486
 Effector caspase, 848
 Effector kinase, 759
 Effector protein, 779
 Electron microscopy, repair synthesis
 patches, 319–320
 Electron transport chain, 449–450
 Electrophilic reactants, DNA damage,
 41–46
 Elongation factor, FACT, 789
 Elongin C, 301, 342
 Elutriation, 757
 Embryonic development, 7
 Embryonic viability
Blm mutant mice, 963–964
 DNA polymerase ζ and, 631
 mice defective in DNA ligation, 723
Rb1 knockout mouse, 1005–1006
 Emery-Dreifuss muscular dystrophy, 1033
 End-joining pathway function, Rad1-
 Rad10 enzyme, 286–287
 End-labeling method, detection of NER at
 nucleotide resolution, 270–271
 Endonuclease II, *see* Exonuclease III (Xth)
 Endonuclease III, human, 172
 Endonuclease III (Nth), 196
E. coli, 172–173, 191–192
 helix-hairpin-helix motif, 191
 Endonuclease III-like I protein, mam-
 malian, 192
 Endonuclease IV (Nfo), 22, 200–202
 base-flipping, 200–201
E. coli, 200
 induction, 201
 mechanism of action, 200–201
 Endonuclease V
A. fulgidus, 380–381
 alternative excision repair, 379–383
E. coli, 379–383
 homologs, 380–382
 preventing cell death with hydroxy-
 laminopurine, 383
 preventing mutations associated with
 base deamination, 382
 mammalian, 381–382
T. maritima, 380–381
 Endonuclease VI, *see* Exonuclease III (Xth)
 Endonuclease VIII (Nei), *E. coli*, 172, 186,
 192
 Endonuclease VIII-like DNA glycosylase 1,
 172
 Endonuclease VIII-like DNA glycosylase 2,
 172
 Endonuclease VIII-like DNA glycosylase 3,
 172
 Endonuclease VIII-like proteins, mam-
 malian, 192
 Eneidyne, 46
 Environmental stress response, 826
 Enzymatic photoreactivation, *see*
 Photoreactivation
 Episomal shuttle vector, 81
 Epistasis, 276–278
 1,2-Epoxy-3-butene, 1063
 3,4-Epoxy-cyclopenta[*c,d*]pyrene, 532
 2,3-Epoxy-4-hydroxynonenal, 21
 ERCC genes, human, 275–276
 ERCC1 gene
 human, 279, 285, 881, 1051
 mammalian, 285–288, 837
 ERCC1 protein
 interstrand cross-link repair, 695
 mammalian, 285–288, 332
 binding and positioning DNA sub-
 strate, 290–291
 ERCC1-XPF enzyme, 286–287, 318,
 326–327, 333–334, 336, 360
 helix-hairpin-helix domain, 290
 protein domain structure, 288–291
 reconstitution of nucleotide excision
 repair, 322
 sequence similarity to XPF proteins,
 289
 ERCC2 gene, *see* XPD gene
 ERCC3 gene, *see* XPB gene
 ERCC5 gene, *see* XPG gene
 ERCC6 gene, *see* CSB gene
 Ergosterol desaturase, 693
 ERK motif, 288–289
 ERK1 gene, mammalian, 832
 Error-prone DNA repair, 510
Escherichia coli, *see also specific genes*
 DNA damage tolerance, 569–612
 homologous recombination, 569–612
 interstrand cross-link repair, 691–692
 mismatch repair, 390–402
 methyl-directed, 392–402
 very-short-patch repair, 431–432
 nucleotide excision repair, 228–253,
 343
 SOS response and, 491–492
 (6–4) photoproduct-DNA photolyase,
 121–123
 pyrimidine dimer-DNA photolyase,
 114–119
 binding to substrate, 116–117
 chromophores, 118–119
 enzymatic efficiency, 118

Escherichia coli, (continued)

- kinetics and thermodynamics of photoreactivation, 115
- light requirement, 115–116
- mechanism of action, 116–117, 119
- model substrates, 118
- nucleotide excision repair, 117–118
- protein, 115
- rate constants for photoreactivation, 116
- reactivation of RNA, 133
- structure, 119–121, 125–126
- Shiga toxin, 496
- SOS system, 463–497
- ESCO2* gene, human, 1025
- Esophageal cancer, 162, 1064, 1067
- ESS assay, 258
- Estrogen(s), DNA damage, 45–46
- Estrogen receptor alpha, 176, 326
- 1,*N*⁶-Ethenoadenine, removal, 181, 184–185, 203
- 3,*N*⁴-Ethenocytosine removal, 176, 178
- UVM response, 555
- Ethyl carbamate, 176
- Ethyl methanesulfonate, 35–36, 513, 554, 738
- 3-Ethyladenine, removal, 181
- S*-Ethylcysteine, 143
- 3-Ethyldeoxycytidine, 158
- O*⁶-Ethylguanine
 - mtDNA, 452–453
 - repair, 142–143
- N*-Ethyl-*N*-nitrosourea, 36–37, 154
- Ethylpurine adducts, 363
- Etoposide, 47, 339, 429, 794, 963, 966
- Ets1 protein, 326
- Evolution
 - bacteria, 422–423
 - cyclical loss and reacquisition of mismatch repair, 422–423
 - inducible mutagenesis, 551
 - nucleotide excision repair, 343
- Excision repair, *see* Alternative excision repair; Base excision repair; Nucleotide excision repair
- EXO1* gene
 - human, 982–983
 - S. cerevisiae*, 408
- Exo1* gene, mouse, 427
- Exocyclic etheno adducts, 20–21
- Exonuclease, 169
- Exonuclease I
 - eukaryotes, 408–409
 - yeast, 403, 427
- Exonuclease I, *E. coli*, 400–403
- Exonuclease III (Xth), 198–200
 - E. coli*, 198–199
 - homologs in other organisms, 199–200
 - structure, 200
 - repair of AP sites, 198–199
- Exonuclease VII, *E. coli*, 400–403
- Exonuclease X, *E. coli*, 400–403

F

- F' plasmid, SOS mutator effect, 534–535
- FA, *see* Fanconi anemia
- FA-associated polypeptides, 993

- Facilitated diffusion, proteins along DNA, 55
- FADD adaptor, 848, 850
- Familial adenomatous polyposis, 189–190, 980, 1002, 1008–1012
 - progression from adenoma to carcinoma, 1013
- Familial atypical multiple mole and melanoma syndrome, 1018
- Familial partial lipodystrophy, 1033
- FANCA* gene, human, 989–991
- FANCC* gene, human, 990
- FANCD1* gene, human, 696, 992–993
- FANCD1* protein, 1007
- FANCD2* gene, human, 932, 992, 1051
 - S*-phase arrest, 797
- FANCD2* protein, 685
- FANCE* gene, human, 992
- FANCF* gene, human, 992
- FANCG* gene, human, 991–992
- FANCL* gene, human, 993
- Fanconi anemia (FA), 696, 727, 797, 929, 979, 986–994, 1088
 - apoptosis, 989
 - BRCA2 protein connection, 685
 - cancer predisposition, 987–988
 - clinical features, 987–989, Color Plate 10
 - complementation groups, 989–990, 1007
 - DNA repair, 989
 - genetics, 988–993
 - heterozygotes, 1061
 - homologous recombination defect, 685
 - mouse models, 993–994
 - oxidative stress response, 989
- FaPy-DNA glycosylase, 172
- Far assay, 667
- FAS receptor, 850
- FEN1 protein, 292–293
 - base excision repair, 203, 212, 214
 - mammalian, 337, 714
- Fenton reaction, 18, 21
- FGFR* genes, human, 1027
- FHA domain, 780, 783
- Filamentation, *E. coli*, UV-induced, 465–466
- Flap endonuclease, 170, 383, 803
- FLAP endonuclease I, *see* FEN1 protein
- Flavin adenine dinucleotide (FAD) (6-4) photoproduct-DNA photolyase, 129–131
 - pyrimidine dimer-DNA photolyase, 112, 115–116, 118–119
- Fluorescence-activated cell sorting, 757
 - multiparameter, 757–758
- Fluorescence resonance energy transfer study, RecQ helicase, 950–952
- Fluorescently tagged proteins, visualization of nucleotide excision repair, 334–335
- 5-Fluorouracil, 465
 - removal, 175, 178
- Folate metabolism, 13
- Folic acid deficiency, 13
- Formamidopyrimidine(s), 34, 186
- Formamidopyrimidine-DNA glycosylase
 - E. coli*, 186–188
 - T. thermophilus*, 187
- N*-Formamidourea, 24, 26
- 5-Formyl-dUTP, 555
- Forward mutation, 72

- Forward mutational system, 77–79
- FOS* gene
 - human, 966
 - mammalian, 831–832, 834–835
- 14-3-3 protein
 - G₂/M arrest, 799–801
 - S. pombe*, 799
- Fowlpox virus, pyrimidine dimer-DNA photolyase, 127
- fpg*⁺ gene, *E. coli*, 55, 172, 186–188, 202
- Fragile-site expression, Seckel syndrome, 932–933
- Fragile X syndrome, 421
- Frameshift mutation, 73–75, 639–640
 - detection, 78–79
 - from primer-template misalignment, 99
- Free-radical-based DNA-cleaving agents, 46
- ftsI*⁺ gene, *E. coli*, 496
- ftsK*⁺ gene, *E. coli*, 486, 495
- FtsZ protein, *E. coli*, 495
- Fungi, mismatch repair, 402–406
- FUSE-binding protein, 911

G

- G₁ arrest, 757, 759, 766, 786
- G₂ arrest, 763
- G₂ checkpoint, 769–770
- G₁ cyclin, 791
- G₂/M arrest, 755–756, 759, 766, 768, 782, 784, 798–801
 - Cdc2* of *S. pombe*, 798–799
 - CDC25 protein, 799
 - mammalian cells, 799–802
 - S. cerevisiae*, 846
 - transcriptional targets of p53, 799–801
- G₂/M checkpoint, ataxia telangiectasia, 922
- G₁/S arrest, 791–794
 - vertebrates, 791–794
 - RB1 tumor suppressor, 793
 - two-wave response, 794–795
 - yeast, 791
- G₁/S checkpoint, ataxia telangiectasia, 922
- GADD45* gene, vertebrates, 791
- GADD45* protein
 - G₂/M arrest, 799–801
 - vertebrates, 802, 828, 830
- Gain-of-function mutation, 73
- galk*⁺ gene, *E. coli*, 80–81
- Gamma rays, 26
- Gardner syndrome, 1009
- Gastrointestinal tumors, predisposition syndromes, 1008–1016
- GATC sites, methylation, 393–394
- Gatekeeper genes/proteins, 855, 1001
 - DNA polymorphisms, 1049–1080
- Gcn4 protein, *S. cerevisiae*, 831–832
- GCTM1* gene, human, 1062
- Gene conversion, 390, 402–403, 417, 419, 424–427, 646, 665, 670
- Gene dosage effects, transcription syndromes, 912–913
- Genetic diversification, by mutation, 145
- Genetic instability, nonhomologous end joining and, 723
- Genetic variation, human, 1050–1053
- Genome, 71
 - constant genomic insult, 4
- Genome integrity, role of SOS system, 491–492

- Genomic instability syndromes, human, 726
- Genomic mutation rate, 72
- Genomic stability
maintenance, 389–390
mismatch repair and, 421–422
- Genotoxic agents
detection with SOS genes, 497
metabolism, 72, 1062–1071
- Genotype, 72
- Geometric selection, 87–90
- Germinal center, lymphoid tissue, 640
- gfp*⁺ gene, *B. subtilis*, 493
- GIS1* gene, *S. cerevisiae*, 124, 820
- Global excision repair, 228
- Global genome repair, 5, 228, 359
- Glove model, DNA damage recognition, 329
- Glutathione, 44–45
- Glutathione *S*-transferase, 41, 44
polymorphisms, 1063
- Glycophorin A locus, 966
- GO system, 188
- Gorlin syndrome, 1016–1018
- Gp4 protein, phage T7, 952
- Gray (Gy), 26
- groEL*⁺ gene, *E. coli*, 522
- groES*⁺ gene, *E. coli*, 522
- Growth factor(s), secretion in UV response, 831
- Growth factor receptors, 833
- grp* gene, *Drosophila*, 783–784
- grxA*⁺ gene, *E. coli*, 481
- GSTM1* gene, human, 1063
- GTF* genes, human, 279
- GTF2H proteins, mammalian, 324–326
- Guanine
deamination, 9–10, 14–15
imidazole ring opening, 19
- Guardian genes, DNA polymorphisms, 1049–1080
- gyrB*⁺ gene, *E. coli*, 597
- H**
- Halogenated pyrimidines, UV sensitivity, 35
- Hamartin, 1020
- HAP1* gene, human, 199
- Haploinsufficiency, 1059
- Haplotype, 1051
- Haplotype mapping, 1051
- HapMap, 1051–1052
- hay* gene, *D. melanogaster*, 298
- Hayflick limit, 855
- hCRY1* gene, human, 131
- hCRY2* gene, human, 131
- hda*⁺ gene, *E. coli*, 496
- HDAC11* gene, human, 1051
- Hdf proteins, *S. cerevisiae*, 716–718
- HDM2 protein, human, 787
- Head and neck cancer, 878, 1064–1065
- HEAT elements, 762
- Heat shock proteins, 199
- Hef enzyme, *P. furiosus*, 289–290
- Helicase, *see* DNA helicase
- Helix-hairpin-helix motif, 257
AlkA protein, 183–184
DNA glycosylases, 171–174, 178, 190
DNA ligase, 206
endonuclease III, 191
ERCC1 protein, 290–291
MutY protein family, 189
MYH protein family, 189
Helix-turn-helix motif, UvrA protein, 230–232
- Heme oxygenase, 21
- Heme peroxidase, 991
- Hereditary nonpolyposis colon cancer (HNPCC), 406, 979, 1009, 1088
clinical features, 980
genetic heterogeneity, 982–985
microsatellite instability, 980–981, 1050
mismatch repair, 980–986, 1060–1061
mouse models, 985–986
tumors in homozygous mutant mice, 985–986
- Herpesvirus-associated ubiquitin-specific protease, 788
- Heterochromatin, 55
- Heterochromatin repulsion, 1023–1024
- Heteroduplex DNA, 664–665
mismatch repair, 392–393
- Heteroduplex formation, 389
- Heterology index, 479
- Heromorphisms, 1050
- hex*⁺ genes, *S. pneumoniae*, 391–392, 398
- Hex-dependent mismatch repair, *S. pneumoniae*, 390–392
- High-negative interference, 390
- Histone(s), 48–49, 1021
acetylation, 354–355, 736, 790, 1005
H2AX, 55, 782
modification and double-strand breaks, 735–736
modification in apoptosis, 849
phosphorylation, 735–736
post-translational modifications, 355
transcriptional regulation, 353
ubiquitination, 642–643
- Histone acetylase, 176
- Histone acetyltransferase, 736, 790
- Histone code, 355
- Histone deacetylase, 790, 1022
- Histone H1, 351
H1.2 isoform, 853
phosphorylation, 735
- Histone H2A, 351–352, 354
phosphorylation, 735–736, 782
- Histone H2B, 351–352, 354
- Histone H3, 351–352, 354, 358
acetylation, 736
phosphorylation, 1026
- Histone H3 methyltransferase, 1022
- Histone H4, 351–352, 354, 358
acetylation, 736
- HMG-1 protein, 790
- HNPCC, *see* Hereditary nonpolyposis colon cancer
- HO endonuclease, 668–669, 759
S. cerevisiae, 846
- HO* gene, *S. cerevisiae*, 668–669
- Hodgkin's lymphoma, 161
- Holliday, Robin, 390
- Holliday junction, 425–426, 585, 665, 952
chicken foot structure, 571, 575, 595, 597, 601
cleavage by RuvABC, 602–603
Holliday structure resolution, 685–687
- Homeologous recombination, 664
- Homologous recombination
ataxia telangiectasia, 922–923
branch migration and resolution, 581–584
BRCA/Fanconi pathway, 682–685
BRCA2 protein in, 683–685
cohesins, 681
double-strand break repair, 736–737
E. coli, 569–612
RecA protein, 574–579
RecBCD pathway, 574
RecF pathway, 574
end processing as initiating step, 671
eukaryotes, 663–710
Holliday junction resolution, 685–687
inhibition by UmuD' and UmuC, 518
initiation, 579–581
interstrand cross-link repair, 691–692
MRN complex, 730–731
nomenclature of genes, 1083
pairing and exchanging of homologous DNA, 671–681
RecBCD helicase/nuclease, 574, 580
RecG protein, 583–584
RecJ nuclease, 581
RecQ helicase, 581, 685
replication and, 593–598
RuvABC protein, 581–583
S. cerevisiae, 822, 846
stabilization and recovery of
arrested/collapsed replication fork, 593–598
transcription and, 689–690
transcriptional response to DNA damage, 822
UV radiation-stimulated, 690
- Homologous recombination proteins, processing DNA damage, 574–584
- Homopolymeric runs, SOS-induced cells, 494
- Hoogsteen base pairs, 87, 98, 637
- Hormesis, 29
- Hormone metabolites, DNA damage, 45–46
- Host cell reactivation, 193, 227–228
- Hot spot, 14, 38, 75, 77–78, 432, 483, 523–524, 614–615, 639, 690
mtDNA, 453
p53 tumor suppressor gene, 628–629
UV irradiation of mammalian cells, 624
- HOT1* region, *S. cerevisiae*, 690
- Hpr1 protein, *S. cerevisiae*, 690
- HPRT* gene, mammalian, 81–82
UV mutagenesis, 625–626
- Human genetic variation, 1050–1052
- Huntington's disease, 421
- HuR protein, 786
- Hus1 protein, *S. pombe*, 764, 796
- Hutchinson-Gilford syndrome, 1029, 1032–1033
- Hydrogen peroxide, 17–23, 26, 49, 465, 496, 693, 738, 826
- 8-Hydroxyadenine, repair, 903
- N*-Hydroxyaminofluorene, 247
- 4-Hydroxyaminoquinoline 1-oxide, 45
- 5-Hydroxycytosine, removal, 187, 191
- 2-Hydroxy-dATP, 189
- 8-Hydroxy-5-deazaflavin, 112
- 8-Hydroxydeoxyadenosine, 989
- 8-Hydroxydeoxyguanosine, 23
- 5-Hydroxy-5,6-dihydrocytosine, 22
- 5-Hydroxy-5,6-dihydrothymine, 22, 34

6-Hydroxy-5,6-dihydrothymine, 27
 8-Hydroxyguanine, 23–24, 45; *see also* 8-OxoG
 5-Hydroxyhydantoin, 22, 24, 26
 Hydroxyl radical, 17–23, 26–28
 Hydroxylamine, 82
 5-Hydroxyl-dCTP, 555
 5-Hydroxyl-dUTP, 555
 5-Hydroxymethylcytosine, deamination, 14
 5-Hydroxy-5-methylhydantoin, 22
 removal, 191
 5-Hydroxymethyluracil, 14, 22, 24, 27
 removal, 177
 4-Hydroxynonenal, 20–21, 40
 4-Hydroxy-2-oxoglutarate aldolase, 496
 5-Hydroxythymine, 27
 6-Hydroxythymine radical, 19
 5-Hydroxyuracil, removal, 175, 387
 Hydroxyurea, 269, 685, 756, 766, 770, 779–780, 782, 796, 954
 Hyper-immunoglobulin M syndrome, 14, 1088
 Hypermutation, *see* Somatic hypermutation
 Hyperrecombination, 383, 389–390
S. cerevisiae, 690
 Hypochondroplesia, 1027
 Hypomorphic mutations, MRN components, 726
 Hypoxanthine, in DNA, 10–11, 14–15
 removal, 184–185, 203
 Hypoxanthine glycosylase, Bloom syndrome, 957

I

IκB kinase, 834
 IκB-α, ataxia telangiectasia, 924
 IAP proteins, apoptosis, 848, 853
 IBIDS syndrome, 908–909
 ICF gene, human, 1022
 Ichthyosis-cheek-eyebrow syndrome, 910
 Ichthyosis-follicularis-atrichia-photophobia syndrome, 910
 I-compounds, 23
ifsA⁺ gene, *E. coli*, 489
 IKK protein, 836
IL2RG gene, human, 934
IL7R gene, human, 934
 Immune system alterations
 DNA ligase I mutations, 210
 uracil-DNA glycosylase deficiency, 179
 Immunodeficiency-centromeric instability-facial anomalies syndrome, 1021–1023
 ImpC protein, *E. coli*, 488
 Inchworm-type model, translocation of
 DNA helicase, 950–951
 Indirect photoreversal, 110
 Indirect readout, DNA sequence, 53–54
 Induced mutagenesis, 72
 Induced stable DNA replication, 493, 594–595
 Inducible replisome reactivation/replication restart, 573, 603–605
 Initiation factor, eIF2α, 804
 Initiator caspase, 848
Ink4a gene, mouse, 904
 Inositol hexakisphosphate, 724, 760
 Insertion mutation, 73
 Insertion-deletion loops, 389, 397

intE⁺ gene, *E. coli*, 481
 Integrated shuttle vector, 81
 Interallelic recombination, Bloom syndrome, 958
 Intercalating agents, 12, 75, 248
 psoralens, 40–41
 Interchromatid recombination, 664
 Interchromosomal recombination, 664, 681
 Interleukin-1, 831
 Interleukin-6, 988
 International distress signal, 464
 Interspecies mating, bacterial, SOS response and, 494–495
 Interstrand cross-link repair, 690–696
 DNA polymerases, 696
E. coli, 691–692
 higher eukaryotes, 695–696
 models, 696–697
 homologous recombination, 691–692, 695–696
 homologs of *SNM/PSO* genes, 696
 nucleotide excision repair, 692, 695
 postreplication repair, 692–693, 696
S. cerevisiae, 692–694
 model, 693–694
SNM1-encoded nuclease, 693
 translesion synthesis, 692–693
 UvrABC endonuclease, 691–692
 Uvr-independent, 692
 Intracellular adhesion molecule 1, 913
 Intrachromosomal exchanges, 418
 Intrachromosomal recombination, 664
 Intra-S checkpoint, 770
 Intrastrand adduct, 38–39
 Inversion, 73
 Ionizing radiation
 annual dose to population of United States, 25
 DNA damage, 4, 17, 24–29
 base damage, 26–27
 direct effects, 26
 indirect effects, 26
 strand breaks, 27–28
 oxygen effect, 28
 radioadaptation, 836–837
 sensitivity in ataxia telangiectasia, 920
 transcriptional response to DNA damage in mammals, 835–837
 Iron, Fenton reaction, 18, 21
 Iron-dependent oxygenase, 158
 I-SceI endonuclease, 669–670
 I-SceI-induced targeted double-strand breaks, 669–670

J

Jackson-Weiss syndrome, 1027
JAK3 gene, human, 934
JNK gene, mammalian, 832, 835
JUN gene
 human, 901
 mammalian, 831–835
 Juvenile polyposis coli, familial, 1002, 1013–1014, 1088

K

KARP-1 gene, mammalian, 836
KARP-1 protein, mammalian, 719
katE⁺ gene, *E. coli*, 481

katG⁺ gene, *E. coli*, 481
 Keratosis-ichthyosis-deafness syndrome, 910
KIN17 gene, mammalian, 834
KIN28 gene, *S. cerevisiae*, 279
 Kin28 protein, *S. cerevisiae*, 324–325
 Kinetochore, 1004–1005
 Klenow fragment, 87–88, 92, 94
 KNTC2/HEC1 protein, 1005
 Ku proteins, 715–718, 737
 checkpoint response, 768
 chromatin silencing, 717
 DNA-dependent protein kinase, 718–721
 homologs in yeast, 716–718, 846
 in vitro properties, 715–716
 interaction with MRN complex, 729–730
 Ku-defective mice, 720–721
M. tuberculosis, 716
 mammalian, 836
 nonhomologous end joining, 715–718, 724
 rediscovery as repair proteins, 715–718
 telomere structure and, 717–718
 vertebrates, 847

L

L1 repeat elements, 1023
lacI system, *E. coli*, 77–78
 determination of mutational spectra, 523–524
lacZ-to-*lacI* fusions, 79–80
 mutational spectrum, 77–78
 Lactacystin, 340
lacZ⁺ gene, *E. coli*, 76
lacZ-to-*lacI* fusions, 79–80
 Lamins, 1033
 Landscape genes, 1004
 Laryngeal cancer, 1064
 Lcd1 protein, *S. cerevisiae*, 763, 783, 846
 Lesion bypass DNA polymerase, 95–98, *see also* DNA repair, error-prone
 Lethal mutation, 74
 Leukemia
 ataxia telangiectasia, 926
 Fanconi anemia, 987–988
 LexA box, *see* SOS box
lexA⁺ gene, *E. coli*, 230, 252, 463–469, 478–481, 486–487, 490–491, 511
lexA mutants, 467–469
lexA(Def) mutations, 468–470, 479, 514, 516, 535
lexA(Ind) mutations, 468, 471–472, 474, 478, 510–511, 553
lexA(Ts) mutations, 468–469, 471
 repression by LexA protein, 471–472
 LexA protein, *E. coli*, 233, 463–497
 autocleavage, 465, 473–474, 476
 binding to SOS boxes, 472–473
 C-terminal domain, 473
 fragment degradation by ClpXP protease, 473
 homology to UmuD and Muca, 514
 negative control element, 468
 N-terminal domain, 472–473
 proteolytic cleavage, 473–476
 RecA-mediated cleavage, 472–478, 489, 517–518
 repression of *recA*⁺ and *lexA*⁺ genes, 471–472
 structurally related proteins, 475–476

- LexA-binding sites, 479
 Lif proteins, *S. cerevisiae*, 722, 729, 737
 Li-Fraumeni syndrome, 780, 786, 1002, 1006–1007, 1088
 p53 protein, 1006–1007, 1059–1060
LIG1 gene
 human, 279, 1051
 mammalian, 207
LIG3 gene, mammalian, 207–208
LIG4 gene
 human, 930–931
 mammalian, 207
 Lig4 protein, *S. cerevisiae*, 722
 LIG4 syndrome, 1087
ligA⁺ gene, *E. coli*, 205
 Light repair, 227
 Limb girdle muscular dystrophy, 1033
 Linear energy transfer, 26
 Linker DNA, 48–49
 Lipid peroxidation products, 176
 alkylating agents, 37
 DNA damage, 16, 20–21, 39
 Liquid holding recovery, 249
lit⁺ gene, *E. coli*, 481
 Liver cancer, 161–162
LMNA gene, human, 1033
 Locus heterogeneity, xeroderma pigmentosum, 875
lon mutants, *E. coli*, 465, 485
 Lon protease, 491, 521–522
 Long-patch excision repair, 252–253, 601
 Loss of heterozygosity, 84
 Louis-Bar syndrome, *see* Ataxia telangiectasia
 Lung cancer, 161, 1062–1066
 Lymphoma, 640
 ataxia telangiectasia, 926
 mice defective in DNA ligation, 723
 Lymphoreticular system, disease in ataxia telangiectasia, 919–920
 Lynch syndrome II, *see* Hereditary non-polyposis colon cancer
- ## M
- M phase
 regulation, 801–802
 S. cerevisiae, 801
 MAD2 protein, human, 631
MAG1 gene, *S. cerevisiae*, 172, 821, 824–826
 Maintenance methylase, 358
 Malondialdehyde, 20
 Mammalian cells
 mutagenesis, 79–85
 identification of DNA fragment carrying mutations, 82–83
 intact animals, 83–85
 sequencing of mutated genes with PCR, 81–82
 shuttle vectors, 79–81
 transcriptional response to DNA damage, 828–837
 UV radiation-induced mutagenesis, 617–629
 chromosomal genes, 625–627
 cyclobutane pyrimidine dimers, 624
 hot spots, 624
 HPRT gene, 625–626
 inducibility of mutagenic process, 621–622
 mutant fixation in S phase, 617–618
 nucleotide excision repair, 624–625
 (6-4) photoproducts, 624
 replication in treated cells, 618–620
 specificity of induced lesions, 622–629
 targeted mutations, 622–623
 transition mutations, 623–624
 translesion synthesis, 620–621
 untargeted mutations, 622
 Mandibuloacral dysplasia, 1033
 MassARRAY system, 85, 1054
 Maternal inheritance, 449
 Mating-type switching, yeast, 280, 402–403, 667–669
 Maxicell procedure, 594
MBD4 gene, human, 172, 178
 MBD4 proteins
 deficiency, 179
 mammalian, 178–179
 yeast, 178
 MCM2–7 complex, mammalian, 952
mCRY1 gene, mouse, 131
mCRY2 gene, mouse, 131
 MDC1 protein
 mammalian, 782–783
 phosphorylation of p53 protein, 789
 MDM2 protein, regulation of p53 protein, 787–788, 793
 MEBP protein, 156
MEC1 gene, *S. cerevisiae*, 125, 756, 762, 826
 Mec1 protein
 S. cerevisiae, 762–764, 779, 781, 795–796, 803, 819, 846–847
 S. pombe, 783
MEC3 gene, *S. cerevisiae*, 125, 756
 Mec3 protein, *S. cerevisiae*, 764
MECP2 gene, 1025–1026
 Meiosis
 crossovers during, 424–427
 mismatch repair and, 424–427
 S. cerevisiae, 725
 Melanoma, 638, 904, 1064–1066, 1088
 familial, 1002, 1018
 Melphalan, 36
 Menadione, 201, 826
 Mer⁺ phenotype, 154–156
 Mer⁻ phenotype, 155–156
 Mer3 protein, *S. cerevisiae*, 426
 Merchloroethamine, 36
MET proto-oncogene, 1020
 Metabolism, genotoxic chemicals, 72, 1062–1071
 Metal salts, Fenton reaction, 18
 Metal-binding site, Ada protein, 147
 5,10-Methenyltetrahydrofolyl polyglutamate, pyrimidine dimer-DNA photolyase, 112, 115–116, 118–119
 Methotrexate, 13
 Methyl chloride, 37, 146, 153
 Methyl iodide, 146
 Methyl methanesulfonate (MMS), 36–37, 139, 180, 183, 199–200, 203, 278, 645, 770, 791, 819
 MMS-treated *S. cerevisiae*, 794–796
 Methyl radical, 37
 Methyl viologen, 201, 693
 1-Methyladenine, 16
 repair, 157–162
 by enzyme-catalyzed reversal, 139–168
 in RNA, 160
 3-Methyladenine, 16, 37, 141, 427
 removal, 178, 180–186
 7-Methyladenine, 181
 Methyladenine-DNA glycosylase, 172, 821
 E. coli, 173
 AlkA, 181–184
 TagA, 181, 183
 3-Methyladenine-DNA glycosylase I, 172
 3-Methyladenine-DNA glycosylase II, 172
 Methylating agents, 4, 37
 Methylation
 CpG islands, 155
 DNA, 393–394, 1005, 1022–1025
 after nucleotide excision repair, 358–359
 GATC sites, 393–394
 RNA, 160
 Methylation tolerance, 157
 Methyl-binding domain glycosylase 4, 172
S-Methylcysteine, 141–142
 3-Methylcytosine, 16
 repair, 157–162
 by enzyme-catalyzed reversal, 139–168
 in RNA, 160
 5-Methylcytosine
 deamination, 9–10, 14, 16, 390, 431–433
 formation in repair, 358
*O*²-Methylcytosine, removal, 181
 5-Methylcytosine-binding domain glycosylase 4, 433
 5-Methylcytosine hydrate, 33
 1-Methyldeoxyguanosine, 158
 Methyl-directed mismatch repair, *E. coli*, 390, 432
 biochemical pathway, 396–402
 excision and resynthesis of DNA, 397
 excision reaction, 399–401
 gene products in, 394–395
 in vitro assay, 396–397, 399
 in vivo analysis, 392–402
 initial steps, 399
 linear substrates, 400
 model for bidirectional repair, 401–402
 proteins, 403
 purification of proteins, 398
 repair of heteroduplex DNA, 392–393
 specificity in vivo, 395–396
 strand discrimination, 393–394, 398
 3-Methylguanine, removal, 181, 184
 7-Methylguanine, 16, 37, 141, 427
 removal, 178, 180–186
*O*⁶-Methylguanine, 16, 427–428
 mtDNA, 452
 premutagenic lesion, 554
 repair, 141–157, 181
*O*⁶-Methylguanine-DNA methyltransferase, 428–429, *see also O*⁶-MGMT gene;
 Ada protein
 Bloom syndrome, 957
 therapeutic applications, 161
 Methylhydrazines, 146
N-Methyl-*N'*-nitro-*N*-nitrosoguanidine, 35–36, 44–45, 139, 141, 146, 152, 154–156, 161, 229, 247, 427–428, 513, 532, 768
 4-(Methylnitrosamino)-1-butanone, 161
 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone, 1063
N-Methyl-*N*-nitrosourea, 35–37, 139, 146, 154, 157, 358, 451

- Methylphosphotriesters, 142
 repair, 144–145
 stereoisomers, 144
- Methylpurine-DNA glycosylase
 deficiency in mice, 184–185
 human, 184–185
 removal of alkylated bases, 185–186
 substrate specificity, 185–186
- Methyltartronylurea, 24, 26
 removal, 191
- 3-Methylthymine, 158
 O^2 -Methylthymine, removal, 181
 O^4 -Methylthymine, 427, 554–555
 repair, 141–157
- Methyltransferase, 141
- Methylurea, 37
mfd⁺ gene
B. subtilis, 256–257
E. coli, 255–256, 491–492, 525
- MGM101* gene, yeast, 457
- Mgmt* gene, mouse, 157
- O^6 -MGMT gene
 human, 154–155, 161
 genetic polymorphisms, 162
 mammalian, 154–155
 promoter region, 156
- MGT1* gene, *S. cerevisiae*, 153, 821, 824
- MHR1* gene, *S. cerevisiae*, 457
- MHY-DNA glycosylase, 189
- Microarray analysis
 aging in mammals, 1030
E. coli responses to mitomycin C, 481
 MMS-treated yeast, 824–826
 single-nucleotide polymorphisms,
 1052–1054
 SOS genes of *E. coli*, 479–481
 transcriptional responses to DNA damage, 818
- Microcystin-LR, 342
- Microsatellite DNA, SOS-induced cells, 494
- Microsatellite instability, 389–390, 406
 Bloom syndrome, 962
 hereditary nonpolyposis colon cancer,
 980–981, 1050
- MIG-DNA glycosylase, 189
- Minichromosome maintenance 2–7, 794
- Mismatch repair, 4–5, 25, 57, 107, 157,
 389–447
 adaptive mutagenesis and, 423–424
 alkylation resistance
 mammals, 427–429
 single-celled organisms, 427
 antirecombinational effects
 heteroduplex destruction model, 419
 heteroduplex rejection model, 419
 higher eukaryotes, 420–421
 during meiosis, 424–427
 prokaryotes, 417–419
S. cerevisiae, 419–420
 apoptosis, 850
 Bloom syndrome, 962
 cadmium toxicity and, 430–431
 checkpoint pathway, 768
 class switch recombination, 429–430
 correction of G-T mismatches, 433
 DNA damage recognition, 427–429
E. coli, 390–402, 431–432
 early biological evidence, 390
 eukaryotes, 402–409
 bidirectional excision capability, 407
 5' → 3' vs. 3' → 5' excision, 408–409
 exonuclease involvement, 408
 in vitro analysis, 406–409
 MutS and MutL homologs, 403–406
 PCNA, 407–409, 415
 strand specificity, 407
 in evolution, 422–423
 fungi, 402–406
 futile cycles, 428
 gene conversion and, 424–427
 genomic stability and, 421–422
 hereditary nonpolyposis colon cancer,
 406, 980–986, 1060–1061
 heterozygosity in mismatch repair genes,
 1060–1061
 long-patch, 391
 mechanism
 signaling downstream events, 413–416
 strand discrimination, 413
 unresolved issues, 413–414
 meiosis and, 424–427
 crossovers, 424–427
 methyl-directed, *see* Methyl-directed mismatch repair
 MutY-dependent, 433
N. meningitidis, 424
 nomenclature of repair genes, 1082
 origin of mismatched base pairs,
 389–390
 oxidative damage, 429
 in pathogenic bacteria, 424
 recombination and, 416–422
 in highly homologous sequences,
 416–417
 in substantially divergent sequences,
 417–422
S. cerevisiae, 402–406, 424
S. pneumoniae, 390–392
 somatic hypermutation, 429–430
 specialized systems, 431–433
 in speciation, 422
 structure-function relationships of repair
 proteins, 409–413
 targeting repair to one strand, 392
 very-short-patch repair, 431–432
- Mismatch repair detection, finding single-nucleotide polymorphisms,
 1054–1055
- Mismatch-specific DNA glycosylase, 176,
 178
- Missense mutation, 73
- Mitochondria, p53 in mitochondrial
 matrix, 851–852
- Mitochondrial DNA (mtDNA), 19
 damage in, 451–452
 defects in human diseases, 450
 human, 449
 maternal inheritance, 449
 mitochondrial genome, 449–450
 mutagenesis, 449–451
 oxidative damage, 22–23, 451–454, 456
 replication, 450
- Mitochondrial DNA repair, 451–459
 age-related, 455–456
 alternative excision repair, 385–386,
 456–457
 base excision repair, 451–455
 short-patch, 455
 Down syndrome, 1034
 monitoring, 453
 recombination repair, 457
 removal of oxidative damage, 453–454
 reversal of base damage, 452
- Mitochondrial proteins, 449
- Mitogen-activated protein kinase pathway
 G_2/M arrest, 799
 ionizing-radiation response in mammals,
 835
 phosphorylation of p53 protein, 789
 UV response in mammals, 832–834
- Mitomycin C, 36, 38, 200, 229, 247, 250,
 253–254, 429, 465, 494, 585, 686,
 929, 931, 989–991
 response in *E. coli*, 481
- Mitosis, human cells, 802
- Mitotic catastrophe, 845
- Mitotic death, 845
- Mitotic recombination, 419, 690
 MRN mutants, 731
 Rad1-Rad10 complex, 286–287
- Mitotic spindle, damaged, 757
- Mitotic spindle checkpoint, 802, 1005
- Mlh* gene, mouse, 987
- Mlh proteins, *S. cerevisiae*, 403–404, 425
- MLH* genes
 mammalian, 426–427, 430
S. cerevisiae, 405, 417, 419, 982
- MLH1* gene, human, 982–985, 1021, 1060
- MLH1* protein, human, 768, 962
- MLH3* gene, human, 982–983
- MMS2* gene, *S. cerevisiae*, 822
- Mms2 protein, *S. cerevisiae*, 645
- MMS19* gene, *S. cerevisiae*, 278–279, 299
- MNAT1* gene, human, 279
- MNAT1* protein
 human, 299
 mammalian, 324–325
- mol* genes, *E. coli*, 383
- Molecular chaperones, 491
- Molecular matchmakers
 in DNA metabolism, 239
 UvrA protein, 238–239
- Molybdopterin guanine dinucleotide,
 383
- Monoallelic mutational analysis,
 1011–1012
- Mosaic mutant clones, *S. cerevisiae*,
 616–617
- Mouse models
 aging, 1030–1031
 ataxia telangiectasia, 926–928
 Bloom syndrome, 963–964
 Cockayne syndrome, 903–905, 912
 Fanconi anemia, 993–994
 hereditary nonpolyposis colon cancer,
 985–986
 tumors in homozygous mutant mice,
 985–986
 retinoblastoma, 1005–1006
scid mouse, 718–719, 721, 935
 xeroderma pigmentosum, 882–887
- MPG* gene
 human, 172
 mammalian, 184
- Mpg* gene, mouse, 184–185
- Mrc1 protein, *S. cerevisiae*, 783
- MRE11 protein, mammalian, 726–727
- Mre11 protein, *S. cerevisiae*, 725
- MRE11A* gene, human, 930

- Mre11-Rad50-NBS/Xrs2 complex, *see* MRN complex
- MRN complex, 724–735, 770
ataxia telangiectasia-like syndrome, 930
binding to chromatin, 725
checkpoint arrest, 766–767
DNA-processing activities, 727–728
double-strand break repair, 724–735
focus formation at double-strand breaks, 727
homologous recombination, 730–731
human genomic instability syndromes, 726
hypomorphic mutations, 726
interaction with ATM protein, 767
interaction with Ku proteins, 729–730
mammalian, 726
MDC1 protein and, 782
model for action based on structural analysis, 733–734
Mre11-Rad50 interactions, 734
Nijmegen breakage syndrome, 929
nonhomologous end joining, 728–730
 in vitro studies, 728–729
 in vivo studies, 729–730
nuclease activity, 731
null mutations in components, 726
Rad50 structure, 733–734
replication, 731–732
S-phase arrest, 796–797
S. cerevisiae, 725–734
 break-induced replication, 687
 telomere maintenance, 731–732
 zinc hook, 734–735
- MSH genes
 mammalian, 426–427
 S. cerevisiae, 404–405, 417, 419–420, 427, 982
- Msh gene, mouse, 428, 987
- Msh proteins
 mouse, 430
 S. cerevisiae, 403–404, 419, 421–422, 425–426
- MSH2 gene, human, 982–985, 1021, 1060
- Msh2 gene, mouse, 421
- MSH2 protein, mammalian, 405–406
- MSH3 gene, human, 985
- MSH6 gene, human, 982–983, 985–986
- MTH1 gene, human, 189
- muc*⁺ genes, *Salmonella*, 77
- MucA protein, plasmid pKM101, homology to LexA and λ repressor, 514
- mucAB* gene, plasmid pKM101, 513–514
 translesion DNA polymerase, 542
- Muenke syndrome, 1027
- mug*⁺ gene, *E. coli*, 172, 176
- Mug-DNA glycosylase, 172
- Muir-Torre syndrome, *see* Hereditary non-polyposis colon cancer
- Multiple endocrine neoplasia, 1003
- MUS-38 gene, *N. crassa*, 387
- Mus81 protein, 803
 eukaryotes, as resolvase, 685–686
 S. cerevisiae, 426
- Mus304 protein, *Drosophila*, 763
- mus308* gene, *Drosophila*, 696
- mus309* gene, mouse, 963
- mus322* gene, *Drosophila*, 696
- Mustard gas, 35
- Muta Mouse, 83
- Mutagen, 72
- Mutagenesis, 5–6, 72
 adaptive, 423–424, 552–553
 analysis, 75–87
 bypass of arrested replication, 461
 chemical, 72
 dislocation, 99
 eukaryotes, 629–639
 induced, 72
 mammalian cells, 79–85
 identification of DNA fragment carrying mutations, 82–83
 insect animals, 83–85
 sequencing of mutated genes with PCR, 81–82
 shuttle vectors, 79–81
 from misincorporation of damaged nucleotides, 555
 mtDNA, 449–451
 replication fidelity, 86–98
 site-specific adducts, 85–86
 SOS-dependent, *see* SOS-dependent mutagenesis
 spontaneous, 72, 98–100
 Xpc mouse, 886
 UV radiation, 72
 two-hit kinetics, 468
 Weigle, *see* Weigle mutagenesis
- Mutant, definition, 71–75
- Mutation, 6, *see also specific types*
 clusters of discrete mutations, 99–100
 definition, 71–75
 detection and analysis
 Ames test, 76–77
 E. coli lacI system, 77–78
 early systems, 75–76
 frameshift or deletion mutations, 78–79
 mammalian cells, 79–85
 phage T4, 75
 reversion systems, 75–76
- Mutation avoidance, 389–390
 Hex-dependent mismatch repair, 392
- Mutation rate
 genomic, 72
 mtDNA, 450
- Mutational hot spot, *see* Hot spot
- Mutational spectra, 85
- determination
 direct DNA sequencing, 524
 lacI system, 523–524
 factors influencing, 524–525
 influence of transcription-coupled excision repair, 525–526
 lacI mutations, 77–78
 SUP4-o system, 613–615
- Mutator phenotype, 187, 189–190, 385, 389, 391–392, 395–397, 422–424, 494
- mutH*⁺ gene, *E. coli*, 394–399, 417
- MutH protein, *E. coli*, 402–403, 411–412, 416, 418
 endonuclease activity, 398–399
 purification, 398
 structure, 411–412
- mutL*⁺ gene
 E. coli, 394–397, 417–418, 427, 429, 432, 982
 cloning, 398
 Salmonella, 398
- MutL protein, 413–416
 E. coli, 402–403, 412–413, 418, 432
 purification, 398
 homologs in eukaryotes, 403–406, 768
 structure, 412–413
- mutS*⁺ gene
 E. coli, 394–397, 417–418, 423, 427, 429, 432, 481, 982
 cloning, 398
 homologs, 398
 Salmonella, 398
- MutS protein, 413–416
 E. coli, 397, 402–403, 409–411, 417–419, 432
 purification, 398
 homologs in eukaryotes, 403–406
 mammalian homologs, 768
 structure, 409–411
 T. aquaticus, 409–411
- mutT*⁺ gene, *E. coli*, 189
- MutT-DNA glycosylase
 helix-hairpin-helix motif, 189
 homologs, 189
 nucleotide pool sanitization, 189
- mutY*⁺ gene, *E. coli*, 172, 187, 433
- MutY homolog-DNA glycosylase, 172
 mitochondrial, 454
- MutY protein, *E. coli*, 55, 57
- MutY-dependent mismatch repair, 433
- MutY-DNA glycosylase, 172
 E. coli, 187–189
 helix-hairpin-helix motif, 189
 Mycobacterium tuberculosis, SOS system, 498
- MYH gene, human, 172, 189–190, 433, 1012–1014
- MYH-associated polyposis, 1012–1013, 1088
- MYH-DNA glycosylase, 191
 mitochondrial, 454
 predisposition to colon cancer, 189–190
- ## N
- NAD, interactions with p53 protein, 790
- NADH cytochrome P-450 reductase, 990
- Nalidixic acid, 250, 339
 SOS induction, 483
- Nasopharyngeal cancer, 1064
- NAT genes, human, 1062–1064, 1067
- NBS, *see* Nijmegen breakage syndrome
- NBS protein, *see* MRN complex
- NBS1* gene, human, 929
- NBS1* protein, mammalian, 726–727
- N-degron strategy, 278
- Necrosis, 845
- nedB*⁺ gene, *E. coli*, 481
- NEDDylation, p53 protein, 788
- nei*⁺ gene, *E. coli*, 172, 192
- NEIL genes
 human, 172
 mammalian, 192
- NEIL proteins, 186, 192, *see also endonuclease VIII-like DNA glycosylases*
- Neocarzinostatin, 46, 533
- Netropsin, 51
- Neu-Laxova syndrome, 905
- Neurofibromatosis
 type 1, 1003, 1020–1021, 1089
 type 2, 1003, 1020–1021, 1089
- Neurofibromin, 1021

- Neurospora crassa*, alternative excision repair, 387
- Neutral filter elution, double-strand break repair in *S. cerevisiae*, 665–667
- Neutral mutation, 73
- Neutral sucrose density gradient, double-strand break repair in *S. cerevisiae*, 665–667
- Nevoid basal cell carcinoma, 1003
- NF-κB
- apoptosis, 853
 - ataxia telangiectasia, 924
 - ionizing radiation response in mammals, 835–836
 - UV response in mammals, 834–835
- NF1* gene, human, 1021
- NF2* gene, human, 1021
- nfi*⁺ gene, *E. coli*, 380, 382–383
- nfo*⁺ gene, *E. coli*, 200, 202, 532
- Nibrin, 726, 929
- Nick translation, 244, 252
- Nijmegen breakage syndrome (NBS), 725–726, 766, 796, 928–930, 1087
- cancer predisposition, 930
 - cellular phenotypes, 928–929
 - clinical features, 928
 - genetic heterogeneity, 929
- 9-1-1 complex, 764–765, 769–771, 781, 796, 803
- Nitric oxide, 18–19, 496, 837
- Nitric oxide synthase, 19, 837
- Nitrofurantoin, 383
- Nitrogen mustard, 35–36, 38, 229, 247, 451, 465
- 4-Nitroquinoline 1-oxide, 45, 247, 253, 451, 512, 524, 693, 819, 824, 896, 963, 966, 968
- Nitrosamines, tobacco-specific, 44–45
- Nitrosating agents, 382–383
- Nitrosation, chemical, 146
- Nitrosoguanidine, 824
- Nitrous acid, 12, 38, 382
- Nocodazole, 827
- Noncrossovers, 425–426
- Nonhomologous end joining, 5, 664, 670, 688, 930
- antibody genes, 14
 - Artemis protein, 721–722, 724, 728
 - class switch recombination, 714
 - DNA ligase IV, 722
 - DNA-dependent protein kinase, 718–721, 724
 - double-strand break repair, 736–737
 - eukaryotes, 711–750
 - Ku proteins, 715–718, 724
 - ligation step, 722–723
 - MRN complex, 728–730
 - in vitro studies, 728–739
 - in vivo studies, 729–730
 - nomenclature of genes, 1084
 - S. cerevisiae*, 712
 - V(D)J recombination, 712–714
 - vertebrate model, 724
 - vertebrates, 712
 - Xenopus*, 711
 - XRCC4 protein, 722–723
- Nonsense mutation, 73–74
- Nonsense suppressor, 73–74
- Novobiocin, 339, 921
- NOXA protein, 850
- nrdA*⁺ gene, *E. coli*, 481
- NTG1* gene, *S. cerevisiae*, 172, 825
- Ntg1 protein, yeast, 453
- NTG2* gene, *S. cerevisiae*, 172, 825
- nth*⁺ gene, *E. coli*, 172, 191–192, 532
- NTHL1* gene, human, 172
- Nuclear irradiation, colocalization of NER proteins at repair sites, 335–336
- Nuclear receptors
- interaction with thymine-DNA glycosylase, 176
 - transactivation by TFIIF, 326–327
- Nuclear scaffold, 352–353
- Nucleoid, 49, 449
- Nucleosome, 48–49, 52, 155, 214, 351–352, 711, *see also* Chromatin; Histone entries
- action of chromatin remodeling enzymes, 354
 - position changes during nucleotide excision repair, 356
 - repair of DNA within, 319
- Nucleosome core particle, 351–352
- Nucleotide excision repair (NER), 4–5, 107
- A. thalania*, 280
 - aging and, 1029–1030
 - archaea, 255
 - assay, 257–260
 - autoradiography, 267
 - B. subtilis*, 254–255
 - bimodal, 228
 - Bloom syndrome, 957, 962
 - cell biology, 269–274
 - D. melanogaster*, 278–280
 - D. radiodurans*, 253–254
 - damage-specific incision of DNA, 272–273
 - alkaline elution and alkaline unwinding, 272–273, 275
 - comet technique, 273
 - incision in *cdc9* mutants of yeast, 272
 - defects, human hereditary diseases, 267, 895–918
 - DNA damage sensing, 768–769
 - E. coli*, 228–253, 343, *see also* UvrABC endonuclease
 - ATP in damage-specific incision, 248–249
 - conformation distortion in substrate recognition, 247–248
 - cross-links recognized by UvrABC endonuclease, 248
 - damage-specific incision of DNA, 229–238
 - DNA incision is bimodal, 244–245
 - DNA ligation, 253
 - functions possibly associated with, 253
 - inducible model, 252
 - post-incisional events, 249–252
 - recognition of base damage during, 238–244
 - second 3'-endonuclease, 245–247
 - SOS response and, 491–492
 - eukaryotes, 269–274, 317–350
 - cell extracts, 318–320, 337
 - detection at specific gene sequences, 360–361
 - direct observation of photoproduct excision, 270
 - DNA methylation, 358
 - error rate, 327
 - evolution, 343
 - excised photoproducts measured with specific antibodies, 271–272
 - excision of photoproducts, 270–272
 - experimental demonstration, 269–274
 - genes and proteins, 281–303
 - genetics, 274–281
 - heterogeneity, 351–377
 - influence of chromatin/chromosome structure, 351–359
 - kinetics, 274
 - lesions placed at specific sites in DNA, 320–321
 - loss of sites sensitive to pyrimidine dimer-specific enzymes, 270
 - measurement in individual DNA strands, 362
 - measurement of repair synthesis, 269–270
 - microinjection of repair factors, 321–322
 - modulation and regulation, 340–343
 - PCR and end labeling for detection, 270–271
 - permeabilized cell systems, 320–321
 - reactivation of damaged plasmid and viral DNA, 273–274
 - repair synthesis, 336–339
 - repetitive DNA, 358
 - schematic model, 318
 - transcribed vs. nontranscribed regions, 359–371
- H. influenzae*, 254
- historical perspective, 227–228, 267
- interstrand cross-link repair, 692, 695
- long-patch, 252–253
- M. genitalium*, 254
- M. luteus*, 253
- M. thermoautotrophicum*, 255
- mammalian cells, 273
- mechanism, 303
- mechanism in eukaryotes, 317–350
- assembly and action of NER machinery, 331–336
 - biochemical strategies to study, 318–322
 - bipartite mechanism of DNA damage recognition, 328–329
 - colocalization of proteins at repair sites, 335–336
 - creation of open intermediate for dual incision, 323–327
 - DDB protein, 331
 - distortion recognition, 328, 330–331
 - DNA damage recognition, 327–331
 - DNA ligation, 339
 - in vivo dynamics, 334–336
 - locations of incisions, 327–328
 - oligonucleotide excision, 339
 - oligonucleotide products, 320
 - order of action of factors, 333–334
 - PCNA, 337–338
 - preincision complex, 317
 - protein interactions, 331–332
 - protein phosphorylation, 342–343
 - recognition of damaged strand, 330–331
 - reconstitution of repair, 322–323
 - repair efficiency, 327

- replication factor C, 338–339
 subassemblies, 332–333
 substrates, 330–331
 topoisomerases, 339–340
 visualization of proteins, 334–335
N. crassa, 279
 nomenclature of repair genes,
 1082–1083
 operating on undamaged DNA, 247
P. fluorescens, 254
 plants, 280–281
 polymorphisms in repair genes,
 1064–1066
 prokaryotes, 227–266
 evolution, 343
 pyrimidine dimer-DNA photolyase in,
 117–118
R. sphaeroides, 254
 repair synthesis of DNA, 251
 revised nomenclature, 228
 rodent genetic complementation groups,
 275–276
S. cerevisiae, 269, 272–273, 276–278,
 281–303, 616–617, 692, 769, 820
 order of action of repair machinery,
 334
 reconstitution of incision reaction,
 323–324
S. pneumoniae, 254
S. pombe, 278–280
Salmonella, 254
 short-patch, 252
 terminology, 227–228
 TFIID, 275, 279, 296–299, 317, 322–327,
 329, 331–336, 339, 342–343,
 363–364
 transcriptional response to DNA damage,
 820–821, 829–830
 transcription-coupled, *see* Transcription-
 coupled nucleotide excision repair
 unimodal, 228
 UV-irradiated mammalian cells, 624–625
 vertebrates, 829–830
 xeroderma pigmentosum, 274–275,
 865–894
 Nucleotide incision repair, 387
 Nucleotide pool sanitization, 189
 Nucleotidyl hydrolase, 197
 Null mutation, 73
nuo⁺ gene, *E. coli*, 481
- O**
- oat*⁺ gene, *E. coli*, 146, 153
 Oculotrichodysplasia, 910
 Odds ratio, 1057
OGG1 gene
 human, 56, 172, 903
 mammalian, 453–456
 S. cerevisiae, 172
Ogg1 gene, mouse, 190–191
OGG1-DNA glycosylase, 202, 903
 helix-hairpin-helix motif, 190
 human, 191
 knockout mice, 190–191
 reaction catalyzed, 190
 removal of 7,8-dihydro-8-oxoguanine,
 190–191
ogt⁺ gene, *E. coli*, 151–152
 Okadaic acid, 342
- Oligonucleotide excision, nucleotide exci-
 sion repair, 339
 Oligonucleotide fragments, 228
 Oligonucleotide-binding fold, 54, 205, 208,
 283
 Omenn syndrome, 935
 Omp proteins, *E. coli*, 471, 497
 Oncogene, 627
orgK⁺ gene, *E. coli*, 481
oriC site, 574
oriC-independent DNA replication, 594,
 603
 Origin recognition complex, *S. cerevisiae*,
 771
 Osmium tetroxide, 82
 Oxazopyridocarbazole, 395
 Oxidative damage, 10, 16–23, 34–35, 46,
 386
 aging and, 1030
 alternative excision repair, 386–387
 cellular defenses against, 21–22
 mismatch repair, 429
 mtDNA, 451–454, 456
 repair in Cockayne syndrome, 903
 senescence and, 854
 xeroderma pigmentosum, 872–873
 Oxidative stress
 ataxia telangiectasia, 923
 Down syndrome, 1034
 Fanconi anemia, 989
 S. cerevisiae, transcriptional response, 826
 UVM response, 555
 8-OxoA, 22, 190
 8-Oxo-dATP, 189
 8-Oxo-dGTP, 555
 8-OxoG, 16, 19, 22, 27–28, 34–35
 control of effects of, 187–189
 incorporation into DNA, 25
 mtDNA, 452–456
 oxidation products, 555
 premutagenic lesion, 555
 removal, 186–187, 190–191, 203, 371
 repair, 903
 8-OxoG-DNA glycosylase, 172
 2-Oxoglutarate oxygenase, 158
 8-Oxo-GMP, 189
 8-Oxo-GTP, 189
 8-Oxoguanosine, 87
 Oxygen effect, 28
 Oxygen paradox, 16
 Oxygen radicals, *see* Reactive oxygen
 species
oxyR regulon, 22
- P**
- p14ARF* oncogene, 788
 p21 protein
 G₂/M arrest, 799–801
 G₁/S arrest, 791–793
 knockout mice, 793
 mammalian, binding to PCNA, 338
 senescent cells, 855
 transcriptional response to DNA damage,
 828–829
 UV response, 834
 p34 protein, 797
 p38 protein, 832, 853
p53 gene, 14, 156
 cancer cells, 856–857
 hot spot, 628–629
 human
 heterozygotes, 1059–1060
 mutations, 82, 1068
 mouse, 84
 skin cancer, 82, 627–629, 638, 877–878
 p53 protein, 421, 428
 accumulation in Bloom syndrome, 960
 acetylation, 790
 activation after UV exposure, 769
 adaptation in multicellular eukaryotes,
 847
 apoptosis, 850–853
 cell cycle checkpoint arrest, 759
 DNA repair, 803
 functions, 786
 G₂/M arrest, 799–801
 G₁/S arrest, 791, 793
 homologous recombination, 803
 interacting partners, 790–791
 Li-Fraumeni syndrome, 1006–1007,
 1059–1060
 mitochondrial, 851–852
 NEDDylation, 788
 paralogs and orthologs, 852
 phosphorylation, 788–790
 post-translational regulation, 786–790
 radioadaptation, 837
 regulation by MDM2, 787–788, 793
 regulation of nucleotide excision repair,
 829–830
 regulation of ribonucleotide reductase,
 819
 repression by, 829
 senescent cells, 855
 structure, 786
 sumoylation, 788
 target of checkpoint pathways, 785–791
 as transcription factor, 828–830, 835,
 850–851
 cell fate decisions, 851
 transcriptional activator, 786, 799–801
 ubiquitination, 787–788, 790
 p53-inducible genes, 851
 p63 protein, apoptosis, 852
 p73 protein, apoptosis, 852
 PAG608 protein, 851
 Pancytopenia, Fanconi anemia, 987
 Papillary renal cell carcinoma, hereditary,
 1002, 1020
 Paraganglioma and pheochromocytoma,
 hereditary, 1002
 Paranemic joints, 578
 Paraquat, *see* Methyl viologen
PARP1 gene, human, polymorphisms, 1067
Parp1 gene, mouse, 921
 Partial-loss-of-function mutation, 73
 Pathogenic bacteria
 mismatch repair, 424
 SOS response, 496–497
 PCNA, *see* Proliferating-cell nuclear antigen
 Pds protein, *S. cerevisiae*, 801
 Penetrance, 1056–1057
 Pentoxifylline, 857
 Peptidyl-propyl isomerase, phosphorylation
 of p53 protein, 789
Per1 gene, mouse, 131
 Peroxidase, 21
 Peroxiredoxin, 21–22
 Peroxynitrite anion, 19, 22

- PERP protein, 850–851
 Peutz-Jeghers syndrome, 1003, 1015–1016
 Pfeiffer syndrome, 1027
 Phage, SOS mutator effect, 535
 Phage ϕ 80, induction, 486
 Phage ϕ X174, SOS mutator effect, 535
 Phage 434, repressor protein, 54
 Phage λ
 prophage induction, 465–466
 recombination, 417
 repressor protein, 52
 UV-irradiated, 465–466, 510–511
 Phage λ repressor, 52, 465, 491
 dimerization, 470
 homology to UmuD and MucA, 514
 proteolytic cleavage during SOS induction, 470–471, 477–478
 structurally related proteins, 475–476
 Phage M13, SOS mutator effect, 535
 Phage PBS1, uracil-DNA glycosylase, 179–180
 Phage PBS2, uracil-DNA glycosylase, 179–180
 Phage T2, UV-inactivated, 193
 Phage T4
 denV protein, 50, 882
 mutagenesis, 75
 pyrimidine dimer-DNA glycosylase, 193–196
 UV-inactivated, 193
 Pharmacogenomics, 1067
 Phenazine methosulfate, 201
 Phenotype, 72
 Phorbol-12-myristate-13-acetate, 156
 Phosphatidylinositol 3-kinase family, 719, 735, 760–762, 781
 3' Phosphodiesterase, 170
 Phosphorylation
 BRCA1 protein, 682, 797
 histones, 735–736
 p53 protein, 788–790
 Photoantenna, 119
 Photobleaching technique, 334–335
 Photocatalyst, 119
 Photodynamic effect, 34
 Photolyase/cryptochrome genes, 112
 (6-4) Photoproduct, 30, 247
 Dewar isomers, 32, 35, 529–530, 639
 distribution in chromatin, 48–49
 handling by bypass polymerases, 638–639
 lacI gene, 32
 mtDNA, 452
 nucleotide excision repair in eukaryotes, 274
 photoreactivation, 109–112, 128–131
 as premutagenic lesion, 529–530
 simian virus 40 DNA, 32–33
 UV irradiation of mammalian cells, 624
 UV radiation, 32–33
 xeroderma pigmentosum cells, 869
 (6-4) Photoproduct-DNA photolyase, 112, 127–130
 active form, 131
 chromophores, 128–130
 C-terminal region, 129
 D. melanogaster, 128
 in different kingdoms, 131
 DNA substrate recognition, 121–123
 E. coli, 121–123
 electron transfer, 121–123
 homologs, 131
 mechanism of action, 129–130
 oxetane intermediate, 131
 phylogenetic relationships, 132
 ubiquitous nature, 128–129
 X. laevis, 129, 131
 zebrafish, 129
 Photoreactivation, 109–112, 227, *see also*
 (6-4) Photoproduct-DNA photolyase; Pyrimidine dimer-DNA photolyase
 discovery, 110–112
 enzymes that catalyze, 112
 RNA, 133
 Photoreversal, 194
 direct, 110
 indirect, 110
 sensitized, 110
 Photosensitization, 34–35
 Photosensitizer, 35
phr⁺ gene, *E. coli*, 114, 118, 479
PHR1 gene, *S. cerevisiae*, 123–124, 820
 regulators, 124–125
 transcriptional regulation, 123–124
 Phylogenetic relationships, photolyases, 132
 PIBIDS syndrome, 908–909
 PIDD protein, 853
PJS gene, human, 1015–1016
 Plants
 blue-light receptor genes, 131
 nucleotide excision repair, 280–281
 pyrimidine dimer-DNA photolyase, 127
 Plasmid, with DNA damage, nucleotide excision repair by host cells, 273–274, 318–319
 Plasmid pKM101, 77, 513–514, 517, 542
 Plasmid-based assays, double-strand break repair, 668–670
 Pleiotropic mutation, 72
 Plumbagin, 201
 PML body, 853, 961
Pms genes, mouse, 84–85, 987
PMS1 gene
 human, 982–984, 1060
 S. cerevisiae, 398, 404–405, 417, 419, 427, 823, 982
PMS1 protein
 human, 768
 mammalian, 406
Pms1 protein, *S. cerevisiae*, 404, 425
PMS2 gene, human, 983–984, 1060
PMS2 protein, human, 768
 Poikiloderma, 968
 Point mutation, 73
 SOS mutator effects, 494
POL2 gene, *S. cerevisiae*, 337
POL32 gene, *S. cerevisiae*, 638
polA⁺ gene, *E. coli*, 140, 182, 229, 234, 249, 397, 485–486, 494, 604
 polAex, 252
polB⁺ gene, *E. coli*, 252, 479–480, 487, 491–492, 496, 543, 552
polC⁺ gene, *E. coli*, 252
POLH gene, human, 1061
PolK gene, mouse, 637
 Polo-like kinase
 Cdc5, 801
 PLX1, 801
POLQ gene, mouse, 696
 Poly(ADP-ribose) polymerase (PARP), 1030
 apoptosis, 849–850
 base excision repair, 210–213
 PARP1, 208, 211–214, 719, 738, 849–850, 921
 DNA damage sensor, 768
 PARP2, 208, 211, 738
 single-strand break repair, 738
 sister chromatid exchange formation, 961
 Poly(ADP-ribosylation), inhibitors, 212
 Polycyclic aromatic hydrocarbons, 43–44, 1062
 Polymerase chain reaction (PCR)
 detection of NER at nucleotide resolution, 270–271
 ligation-mediated, assay of nucleotide excision repair, 270–271
 quantitative, assay of nucleotide excision repair, 258, 270
 sequencing mutated target genes, 81–82
 Polymorphisms, *see* DNA polymorphisms
 Polynucleotide kinase, 208, 723, 738
 Polynucleotide kinase phosphatase, base excision repair, 210–211
 PolyPhen (algorithm), 1067
 Post-meiotic segregation, 402, 417
 Postnatal development, 7
 Post-replication repair, 586, 642
 interstrand cross-link repair, 57, 692–693, 696
 Post-replicative gap filling, 4
 Post-switching segregation, mating type in yeast, 402–403
 ppGpp, 489
Prdx1 gene, mouse, 21
 Premature aging, *see also specific syndromes*
 progeroid syndromes, 23, 1029, 1032–1034
 Premature centromere separation, 1023–1024
 Premutagenic lesion, 72, 85–86
 O⁶-alkylguanine, 554
 O⁴-alkylthymine, 554–555
 AP sites, 530–532
 complex
 affecting both strands of DNA, 533
 closely spaced opposing photoproducts, 532–533
 cyclobutane pyrimidine dimers, 525–529
 identification, 525–532
 O⁶-methylguanine, 554
 8-oxoG, 555
 (6-4) photoproduct, 529–530
 Prereplication complex, 793
 Presynapsis, Rad51 protein of *S. cerevisiae*, 672–674
priA⁺ gene, *E. coli*, 485–486, 595, 604
 limited viability of mutants, 595, 597
 PriA protein, *E. coli*, 596, 600–603
 oriC-independent replication, 594
 restart of regressed replication fork, 603
 restart primosome, 595
 PriB protein, *E. coli*, 595–596
 PriC protein, *E. coli*, 595–596
 Primer-template misalignment, 99–100
 Primosome, 595
 restart, 595
 Procarbazine, 36, 428–429

- Procarcinogens, 1062
 Procaspase-9, 848–849
 Proflavine, 75
 Progeroid syndromes, 23, 1029, 1032–1034
 Programmed cell death, *see* Apoptosis
 Proliferating-cell nuclear antigen (PCNA), 176, 203, 214, 289–290, 318, 322, 337–338, 343
 binding to DNA polymerase η , 648–649
 binding to p21, 338
 DNA damage sensor, 764
 DNA damage tolerance, 647–649
 G₁/S arrest, 792
 interaction with WRN protein, 967
 ionizing-radiation inducible, 837
 mismatch repair, 403, 407–409, 415
 PCNA-like proteins, 759
 post-translational modification, 551
 S. cerevisiae, 647–649
 structure, 338
 sumoylation, 647–649
 ubiquitination, 647–649
 Promyelocytic leukemia protein, 853, 961
 Prophage induction, 465–466
 β -Propiolactone, 40
 Prostate cancer, 1065, 1067
 Proteasome, 340, 754
 human cells, 342
 26S, 340
 yeast, 340–342
 Protein, oxidized, 22
 Protein degradation, ubiquitin conjugation, 642–645
 Protein kinase, 779
 DNA-dependent, *see* DNA-dependent protein kinase
 Protein kinase 2, phosphorylation of p53 protein, 789
 Protein kinase C, 835, 924
 phosphorylation of p53 protein, 789
 Protein phosphatase
 Dis2 type 1, 847
 nucleotide excision repair, 342–343
 Protein truncation test, 1011
 Protein X, 469, 471
 Prototroph, 75
 Proximate carcinogen, 42
psiB⁺ gene, *E. coli*, 489
 PsiB protein, *E. coli*, regulation of RecA-mediated cleavage reactions, 488–489
PSO genes, *S. cerevisiae*, 693
 homologs in higher eukaryotes, 696
 Psoralens, 229, 247–248, 318, 692, 989
 cross-link formation, 40–41
 psoralen-plus-UV-A reaction, 40–41
 structure, 40–41
 Psoriasis, 1065
 Ptc proteins, *S. cerevisiae*, 847
PTCH2 gene, human, 1017–1018
PTEN gene, human, 1015
 PTEN tumor suppressor, 804
 Pterin, pyrimidine dimer-DNA photolyase, 112
 Pulsed-field gel electrophoresis, double-strand break repair in *S. cerevisiae*, 665–667
 PUMA protein, 850
 Purine(s)
 fragmented, 186–191
 ionizing-radiation-mediated damage, 27
 numbering of pyrimidine ring, 157–158
 oxidized, 186–191
 UV radiation-induced lesions, 33
 Purine cyclodeoxynucleosides, repair in xeroderma pigmentosum, 873–874
 Pyrimidine(s), numbering of pyrimidine ring, 157–158
 Pyrimidine dimer-DNA glycosylase, 31, 192–196
 absence in placental mammals, 196
 assay, 194
 B. sphaericus, 196
 Chlorella viruses, 196
 completion of BER initiated by, 202–213
 endonuclease III family, 196
 M. luteus, 192–193, 195–196, 253, 257–258, 270, 287
 N. mucosa, 196
 phage T4, 193–196, 229, 257–258, 270, 287
 Pyrimidine dimer-DNA photolyase, 112–127, 196
 A. nidulans, 112, 116, 119, 122–123, 126–127
 A. thaliana, 112, 123, 127–128
 absence in placental mammals, 127
 absorption and action spectra, 115–116
 C. reinhardtii, 127
 chromophore, 112, 115–116, 118–119
 C-terminal region, 129
 D. melanogaster, 123
 dark reaction, 115–116
 deazaflavin-type, 112, 116, 122
 detection and measurement
 DNA-binding assay, 113
 light-dependent loss of thymine-containing CPD, 113–114
 restoration of transforming ability of DNA, 113
 restriction enzyme analysis, 114
 distribution in nature, 112
 E. coli, 112, 114–119
 binding to substrate, 116–117
 cellular levels, 114
 chromophores, 118–119
 enzymatic efficiency, 118
 kinetics and thermodynamics of photoreactivation, 115
 light requirement, 115–116
 mechanism of action, 116–117, 119
 model substrates, 118
 nucleotide excision repair, 117–118
 protein, 115
 rate constants for photoreactivation, 116
 reactivation of RNA, 133
 structure, 119–121, 125–126
 folate-type, 112, 116, 122
 goldfish, 127
 H. halobium, 122–123, 126
 light reaction, 116
 M. thermoautotrophicum, 122–123, 126
 mechanism of action, 114–119
 base-flipping, 120, 125
 N. crassa, 123, 126
 phylogenetic relationships, 132
 plants, 127
 properties, 114–119
 S. acutus, 122–123
 S. cerevisiae, 116–117, 122–126
 kinetics, 127
 structure, 125–126
 S. griseus, 122–123, 126
 Salmonella, 123, 126
 structural studies, 119–121
 T. thermophilus, 120–123
 therapeutic use, 127–128
 viral, 127
 Pyrimidine hydrate, 33
 Pyrimidine-pyrimidone (6-4) photoproduct, *see* (6-4) Photoproduct
- ## Q
- Quinone oxidoreductase 1, 790
- ## R
- Rad (unit of radiation), 26
RAD1 gene, *S. cerevisiae*, 277–279, 284–291, 370, 692
Rad1 protein
 S. cerevisiae, 284–285, 371, 762
 N terminus, 288
 Rad1-Rad10 complex, 284–288, 318, 327, 343, 360
 single-strand annealing, 688–689
 S. pombe, 764, 796
RAD2 gene, *S. cerevisiae*, 124, 277–279, 291–292, 692
rad2⁺ gene, *S. pombe*, 386
Rad2 protein, *S. cerevisiae*, 291–292, 317–318, 327, 334, 367, 371, 820–821
 DNA junction-specific endonuclease, 291
RAD3 epistasis group, 277, 820
RAD3 gene, *S. cerevisiae*, 277, 279, 296–298, 692, 824
Rad3 protein
 S. cerevisiae, 296–298, 317, 324–326, 329, 332, 371
 DNA helicase, 296–297, 329
 S. pombe, 762, 784
RAD4 gene, *S. cerevisiae*, 277–279, 292–293, 692
Rad4 protein, *S. cerevisiae*, 292–294, 300, 334, 343, 363–364
 Rad4-Rad23 complex, 295–296, 317, 332
RAD5 gene, *S. cerevisiae*, 645, 693, 822
RAD6 epistasis group, 629, 642–646, 822
 transcriptional response to DNA damage, 822–823
RAD6 gene, *S. cerevisiae*, 642–644, 693, 822
 orthologs, 643
Rad6 protein
 S. cerevisiae, 645–647
 interaction with Rad18, 644–645
 ubiquitin-conjugating enzyme, 642–644
 S. pombe, 764
RAD7 gene, *S. cerevisiae*, 124, 277–279, 299–300
Rad7 protein, *S. cerevisiae*, 299–301, 334, 339, 342, 365, 821
 E3 ubiquitin ligase, 300–301
 Rad7-Rad16 complex, 300, 332, 339
RAD9 gene, *S. cerevisiae*, 125, 756
 cell cycle checkpoints, 755

- Rad9 protein
 human, 771, 793, 853
S. cerevisiae, 759, 779–781, 783–784, 819, 821
 mammalian homologs, 782–783
 phosphorylation, 781
- RAD10 gene, *S. cerevisiae*, 277, 279, 284–291, 692
- Rad10 protein, *S. cerevisiae*, 284–285, 334
 Rad1-Rad10 complex, 284–288, 318, 327, 343, 360
 single-strand annealing, 688–689
- rad13⁺* gene, *S. pombe*, 291
- RAD14 gene, *S. cerevisiae*, 278–279, 281–282
- Rad14 protein, *S. cerevisiae*, 282, 317, 332, 334, 343, 360, 371, 769
- RAD16 gene, *S. cerevisiae*, 277–279, 299–300, 693, 823
- Rad16 protein, *S. cerevisiae*, 299–301, 334, 339, 342, 365, 821
 E3 ubiquitin ligase, 300–301
 Rad7-Rad16 complex, 300, 332, 339
 ring finger protein, 300
- RAD17 gene, *S. cerevisiae*, 125, 756
- Rad17* gene, mouse, 765
- Rad17 protein
 human, 766
S. cerevisiae, 764, 803
S. pombe, 765–766, 796
- RAD18 gene
 eukaryotes, 696
S. cerevisiae, 822–823
- rad18⁺* gene, *S. pombe*, 386
- Rad18 protein, *S. cerevisiae*, 648
 interaction with Rad6, 644–645
- RAD19 gene, *S. cerevisiae*, 278
- RAD20 gene, *S. cerevisiae*, 278
- RAD21 gene, *S. cerevisiae*, 278
- RAD22 gene, *S. cerevisiae*, 278
- RAD23 gene, *S. cerevisiae*, 277–279, 294–295, 300, 823, 825
- Rad23* genes, mouse, 295, 887
- Rad23 protein, *S. cerevisiae*, 294–295, 300, 334, 343, 360
 interaction with proteasome, 340–341
 Rad4-Rad23 complex, 295–296, 317, 332
 ubiquitin-like domain, 340
- RAD23A and RAD23B proteins
 human, 294–295, 788
 mammalian, 326
 protection against proteasome action, 342
 reconstitution of nucleotide excision repair, 322
 XPC-RAD23B complex, 295, 317, 328, 331–335, 356, 363
- RAD24 gene, *S. cerevisiae*, 125, 756
- Rad24 protein, *S. cerevisiae*, 765, 770, 803, 821
- RAD25 gene, *S. cerevisiae*, 277, 299
- RAD26 gene, *S. cerevisiae*, 279, 364, 370
- Rad26 protein
S. cerevisiae, 364–371
S. pombe, 763
- RAD28 gene, *S. cerevisiae*, 364
- RAD30 gene, *S. cerevisiae*, 539, 632, 635–636, 822–823
- Rad30 protein
S. cerevisiae, 539
S. pombe, 632
- RAD50 protein, mammalian, 726
- Rad50 protein, *see also* MRN complex
S. cerevisiae, 725, 733–734
- RAD51 gene
 mammalian, 695
S. cerevisiae, 671–672, 822–823, 826
- RAD51 protein
 BRCA2 interactions, 683
 eukaryotes, as resolvase, 686–687
 mammalian, 735, 782, 803, 836
 mouse, 426
- Rad51 protein, *S. cerevisiae*, 577, 671–672, 677, 846
 ATPase, 672
 branch migration, 673–674
 break-induced replication, 687
 interaction with Rad52, 675–676
 meiosis-specific paralogs, 676–679
 orthologs, 671–672
 paralogs, 677
 presynapsis and synapsis, 672–674
 Rad51-Rad54 complex, 579–581
 regulation of expression, 672
 single-strand annealing, 688
 Srs2 antagonism, 679
 strand exchange, 672, 674
 structure, 672–673
 vertebrate paralogs, 677–679
- RAD51A/RAD51B/RAD51C protein, vertebrates, 677–679
 activities, 678–679
 targeted deletions, 678
- RAD52 epistasis group, 667, 679
- RAD52 gene, *S. cerevisiae*, cell cycle checkpoints, 755
- Rad52 protein, *S. cerevisiae*, 737, 846
 activity, 674–676
 break-induced replication, 687
 DNA-binding protein, 674–675
 homologs, 674
 interaction with Rad51, 675–676
 mediator protein, 675–676
 phosphorylation, 676
 single-strand annealing, 688–689
 structure, 674–675
- RAD53 gene, *S. cerevisiae*, 124–125, 756, 823, 1007
- Rad53 protein, *S. cerevisiae*, 769, 771, 779–780, 783, 791, 795–796, 819, 847
 phosphorylation, 779, 781
- RAD54 gene
 mammalian, 695, 836
S. cerevisiae, 822–823, 826
- Rad54 protein, *S. cerevisiae*
 break-induced replication, 687
 changing of DNA topology, 679–681
 paralogs, 681
 Rad51-Rad54 complex, 579–581
- Rad54B protein, human, 681
- Rad55 protein, *S. cerevisiae*, 677, 802
- Rad57 protein, *S. cerevisiae*, 677
- Rad59 protein, *S. cerevisiae*, break-induced replication, 687
- Rad60 protein, *S. pombe*, 802
- radA⁺* gene, *E. coli*, 585
- Radiation oncology, 856
- Radical SAM superfamily, 134
- Radioadaptation, 836–837
- Radionuclides, naturally occurring, 25
- Radioreistant DNA synthesis, 726
 ataxia telangiectasia, 760, 920–922
- RAF-1 protein, mammals, 835
- RAG1 gene
 human, 721–722, 934–935
 mammalian, 712–714
- RAG1 protein, vertebrates, 724
- RAG2 gene
 human, 721–722, 934–935
 mammalian, 712–714
- RAG2 protein, vertebrates, 724
- RAIDD protein, 853
- RAPADILINO syndrome, 947, 1088
 cellular characteristics, 971
 clinical features, 969–970
 mutation in *RECQL4* gene, 969
- RAS protein, mammalian, 833
- RB, *see* Retinoblastoma
- Rb1* gene, human, 1004–1006
- Rb1* gene, mouse, 1005–1006
- RB1 protein, 1004–1005
- RB1 tumor suppressor, G₁/S arrest, 793
- Rdh54 protein, *S. cerevisiae*, 681
- Reactive nitrate species, 383
- Reactive oxygen species, 4, 496
 apoptosis, 851
 breakdown, 17
 cellular defenses against, 21–22
 damage to mtDNA, 451
 DNA damage, 10, 16–23
 elimination by antioxidant enzymes, 21–22
 generation, 17
 by Fenton reactions, 18
 from nitric oxide, 18–19
 induced by ionizing radiation, 26, 836
 p53 regulation, 790
 reactivity, 17–18
 UV response in mammals, 833–834
- Rec1 protein, *U. maydis*, 764
- RecA coprotease, 477
- RecA* gene, *Dictyostelium*, 457
- recA⁺* gene, *E. coli*, 252, 463, 465–469, 478–481, 487, 491, 586–589, 591, 691
 DNA degradation in *recA* mutants, 594
recA mutants, 467–468
recA(Cpt^c) mutations, 467
recA(Def) mutations, 467, 470–471, 478–479, 510–511, 514, 535
recA441, 466, 468, 470–471, 511
 repression by LexA protein, 471–472
- RecA nucleotide-binding fold, 948
- RecA protein, *E. coli*, 418, 463–497
 ATP binding, 579
 ATP hydrolysis, 579
 cleavage of λ repressor, 470–471, 477–478
 cleavage of LexA protein, 472–478, 517–518
 cleavage of UmuD protein, 477–478, 489, 515–518, 604
- C-terminal domain, 574
 daughter strand gap repair, 586, 590
 DNA repair, 574–579
 double-strand break repair, 585
 eukaryotic equivalents, 671–672

- homologous pairing and strand exchange, 578–579
- homologs, 577
- in mitochondria, 457
 - in other bacteria, 497–498
- inducible replisome reactivation/replication restart, 603–605
- induction, 471
- interaction with DNA polymerase V, 545–546
- maintaining integrity of replication fork, 594
- N-terminal domain, 574
- oriC*-independent replication, 594
- RecA-ssDNA nucleoprotein filaments, 464–465, 474, 477–478, 518, 542, 545–546, 575–577
- recombination reactions, 574–579
- regulation of RecA-mediated cleavage, 488–489
- repair of daughter strand gaps, 578
- replication fork regression, 598–600
- SOS-dependent mutagenesis, 514–515, 535
- structure, 574
- structure-function relationships, 577–578
- translesion DNA synthesis, 542
- recB*⁺ gene, *E. coli*, 585
- RecBCD nuclease/helicase
- homologous recombination, 574, 580
 - processing double-strand breaks, 483
- recC*⁺ gene, *E. coli*, 585
- recF*⁺ gene, *E. coli*, 577, 585, 594, 601, 604
- RecF protein, *E. coli*
- daughter strand gap repair, 590
 - homologous recombination, 574
 - RecA-ssDNA nucleoprotein filament formation, 576–577
- recG*⁺ gene, *E. coli*, 583, 601
- RecG helicase, 952–953
- RecG protein
- E. coli*, 257, 597
 - daughter strand gap repair, 590
 - homologous recombination, 583–584
 - replication fork regression, 598–599
- T. maritima*, 584
- recJ*⁺ gene, *E. coli*, 202, 585, 594, 601
- RecJ nuclease, 400–403
- homologous recombination, 581
- recN*⁺ gene, *E. coli*, 479, 481, 487, 490, 496, 585
- recO*⁺ gene, *E. coli*, 600, 604
- RecO protein, *E. coli*, 596
- RecA-ssDNA nucleoprotein filament formation, 576–577
- Rec-less DNA degradation, 594
- recQ*⁺ gene, *E. coli*, 594, 601, 953–954
- RecQ helicase
- arginine finger, 948–949
 - association with topoisomerases, 954
 - B. stearothermophilus*, 949–950
 - biochemistry, 947–953
 - BLM* gene product, 958–960
 - crystal structure, 949–950
 - defects in human hereditary diseases, 947–978
 - E. coli*, 948, 953–954
 - fluorescence resonance energy transfer study, 950–952
 - heterozygous cells, 1061
 - homologous recombination, 581, 685
 - model organisms, 953–954
 - RecA-type fold, 948
 - WRN protein, 966–967
 - yeast homologs, 954
- RECQL4* gene, human
- RAPADILINO syndrome, 968–969
 - Rothmund-Thomson syndrome, 968–969
- RECQL5* gene, human, 968
- recR*⁺ gene, *E. coli*, 594, 601, 604
- RecR protein, *E. coli*, 596
- RecA-ssDNA nucleoprotein filament formation, 576–577
- RecX protein, *E. coli*, regulation of RecA-mediated cleavage reactions, 488–489
- Recombination, 5
- Bloom syndrome, 958
 - ERCC1-XPF complex, 287
 - homologous, *see* Homologous recombination
 - mismatch repair and, 416–422
 - in highly homologous sequences, 416–417
 - in substantially divergent sequences, 417–422
 - Rad1-Rad10 complex, 286–287
- Recombination proteins, stabilization and recovery of arrested/collapsed replication fork, 593–598
- Recombinational repair, 5, 569–612
- daughter strand gaps, 586–593
 - double-strand breaks, 584–585
 - E. coli*, 584–585
 - mtDNA, 457
- Recombination-dependent DNA replication, 594
- REF-1 protein, 790
- Rem* phenotype, *rad3* mutants of yeast, 298
- Remote carcinogenesis, 41
- Renal cell carcinoma, hereditary papillary, 1002, 1020
- Rep helicase, *E. coli*, 595, 950, 952
- Repair synthesis, 25, 169, 251–252
- cell extracts, 319
 - DNA in nucleosomes, 319
 - measurement, 258–260
 - nuclear excision repair in eukaryotes, 267–270, 336–339
 - patches visualized by electron microscopy, 319–320
 - repair patch size, 251
 - xeroderma pigmentosum, 870–871, 874
- Repairosome, 334
- Repetitive DNA, nucleotide excision repair, 358
- Replication, *see* DNA synthesis
- Replication factor C, *see* RFC protein
- Replication factory, 592
- Replication fidelity, 24–25
- Replication fork, 146, 214, 413, 770–771
- arrested/collapsed, 570–571
 - cells not exposed to DNA-damaging agents, 597
 - evidence for regression, 597–598
 - homologous recombination in stabilization and recovery, 593–598
 - lesion affecting one strand of DNA template, 599–602
 - mechanism for regression, 598–603
 - arrested/stalled, 571
 - blockage by RNA polymerase, 573
 - blocked, 569–612
 - collapsed, 570
 - encounters with damaged DNA
 - generation of complex DNA structures, 570–574
 - generation of double-strand breaks, 570–574
 - generation of single-strand gaps, 570–571, 586
 - lesions in double-stranded templates, 571–572
 - lesions in single-stranded templates, 571 - fork catastrophe, 796
 - Mac1/Rad53-dependent stabilization, 796
 - regressed
 - access of repair system to lesion, 599–601
 - lesion affecting both strands of DNA template, 602–603
 - nonmutagenic mechanisms for restarting, 599–603
 - template switch mechanism, 601–602 - regression, 4, 6, 571, 594–595
 - relationship of DNA lesions to, 591
- Replication fork regression, 4, 6, 571, 594–595
- Replication protein A, *see* RPA protein
- Replication restart, 573, 603–605
- Replication-coupling assembly factor, 358
- Replisome initiation, mammalian cells, 618–619
- Replisome, 550
- inducible replisome reactivation/replication restart, 573, 603–605
- Reprimo* gene, 801
- Resolvase, 665
- eukaryotes, 685–687
- Resolvase A, 686
- Respiration arrest, SOS response, 496
- Restart primosome, 595
- Restriction endonucleases, 55
- SOS response and, 495–496
- Restriction enzyme analysis, pyrimidine dimer-DNA photolyase, 114
- Restriction fragment length polymorphisms, human genetic variation, 1050
- Restriction point, 791
- Retinoblastoma (RB), 1001, 1003–1006, 1088
- chromosome instability, 1004
 - mouse model, 1005–1006
- Retinoic acid receptor, 176, 326
- Retrovirus, defense against, 13–14
- REV1* gene, *S. cerevisiae*, 823
- Rev1 protein, *S. cerevisiae*, 509, 539, 631–632, 638–639
- REV3* gene, *S. cerevisiae*, 629–631, 693, 823
- Rev3 protein, *S. cerevisiae*, DNA polymerase ζ , 629–631, 639
- REV7* gene, *S. cerevisiae*, 629–631
- Rev7 protein, *S. cerevisiae*, DNA polymerase ζ , 629–631

- REV3L* gene, eukaryotes, 696
 Reverse transcriptase, 89, 160
 Reversion mutation, 72
 Reversion system, mutation detection and analysis, 75–76
rex⁺ gene, *E. coli*, 489
 REX1 protein, *C. reinhardtii*, 299
RFA1 gene, *S. cerevisiae*, 279, 282–284, 823
Rfa1 protein, *S. cerevisiae*, 763, 797
RFA2 gene, *S. cerevisiae*, 279, 282–284, 823
Rfa2 protein, *S. cerevisiae*, 797
RFA3 gene, *S. cerevisiae*, 282–284
 RFC protein, 765
 eukaryotes, 407, 409, 415
 mammalian, 318, 322, 338
 nucleotide excision repair, 322, 338–339
 S. cerevisiae, 338–339, 343
 RFC-like clamp holder, 765
rhp51⁺ gene, *S. pombe*, 386
 Ribonucleotide reductase, 12, 481
 inhibition, 770
 transcriptional response to DNA damage, 818–819
 RING finger domain, 644–645
 Risk ratio, 1057
 R-loop, 594
 RNA
 photoreactivation, 133
 repair of alkylation damage, 160
 RNA editing, 13–14
 RNA polymerase, blockage of replication fork, 573
 RNA polymerase I, 327, 371
 CSB protein in transcription complex, 901
 RNA polymerase II, 275, 296, 324–325, 343
 S. cerevisiae, Rbp9 subunit, 370
 stalled, 365–368
 backing up after pausing, 366–367
 degradation, 367–368
 interaction with CSB and Rad26 proteins, 366
 Rad26 action, 365–366
 ubiquitination, 367–368
 transcription, 352–353
 CSA and CSB proteins and, 900
 transcription syndromes, 909–911
 ubiquitination, 900–901
 XAB2 protein interactions, 901
 RNA world, 23, 132
 RNase A, 82
 RNase H, 588–589
rnh⁺ genes, *E. coli*, 486, 588
RNR genes, *S. cerevisiae*, 818–819, 821, 823, 826, 854
 Roberts syndrome, 1023–1025, Color Plate 11
Roc1 protein, human, 902
 Rodent cells, UV radiation-induced mutagenesis, 626–627
 Rodent genetic complementation groups, nucleotide excision repair, 275–276
 Rothmund-Thomson syndrome, 23, 910, 947, 968–971, 1087
 cancer predisposition, 968, 971
 cellular characteristics, 968–969, 971
 clinical features, 968, 970, Color Plate 9
 mutation in *RECQL4* gene, 969
 premature aging, 1029
 RPA protein, 176, 282–284, 674–676, 765, 768, 784
 ATRIP-RPA interactions, 763–764
 binding to ssDNA, 954
 eukaryotes, 407, 409
 FA core complex, 993
 G₁/S arrest, 794
 inhibition of MRE11, 728
 mammalian
 nucleotide excision repair, 326, 331–334, 337
 restitution of nucleotide excision repair, 322
 oligonucleotide-binding fold, 283–284
 phosphorylation, 798
 S-phase arrest, 797–798
 S. cerevisiae, 317, 403, 846
 single-strand annealing, 688
RPA1 gene, human, 279, 282
RPA2 gene, human, 279, 282
RPA3 gene, human, 279, 282
RPB9 gene, *S. cerevisiae*, 370–371
RPH1 gene, *S. cerevisiae*, 124
Rpl1 protein, *S. cerevisiae*, 820
Rpn1 protein, *S. cerevisiae*, 294
RPN4 gene, *S. cerevisiae*, 825
Rqh protein, *S. pombe*, 954
Rrp1 protein, *D. melanogaster*, 199–200
 Rubinstein-Taybi syndrome, 1026
 RUD syndrome, 910
ruvA⁺ gene, *E. coli*, 479, 491, 496, 581–583
 RuvABC complex, *E. coli*, 418
 ATPase activity, 582–583
 daughter strand gap repair, 590
 Holliday junction cleavage, 602–603
 in homologous recombination, 581–583
ruvB⁺ gene, *E. coli*, 479, 496, 581–583
ruvC⁺ gene, *E. coli*, 581–583
- S**
- S checkpoint, ataxia telangiectasia, 922
 S9 mix, 77
 S phase
 defects in Bloom syndrome, 956–957
 DNA damage sensing, 769–771
 S-phase-specific sensors, 771
 intra-S checkpoint, 770, 922
 mutant fixation in mammalian cells, 617–618
 regulation in *S. cerevisiae*, 770
 response to DNA damage, 794–798
 checkpoint signaling and translesion synthesis, 796
 MMS-treated *S. cerevisiae*, 794–796, 824–826
 slowing of S-phase progression, 770
 S-phase arrest, 756, 767, 782
 RPA, 797–798
 vertebrates, 796–797
Saccharomyces cerevisiae, see also *specific genes*
 adaptation, 846–847
 base excision repair, 821
 cell cycle, 737, 754–757
 cell cycle restart, 847
 double-strand breaks, 668–669
 double-strand breaks and their repair, 665–667
 genetic framework, 629
 homologous recombination, 822, 846
 interstrand cross-link repair, 692–694
 Ku homologs, 716–718
 M phase, 801–802
 mismatch repair, 402–406, 424
 MMS-treated, 794–796
 MRN complex, 725–734
 N-degron strategy, 278
 nonhomologous end joining, 712
 nucleotide excision repair, 269, 272–273, 276–278, 281–303, 323–324, 616–617, 692, 769, 820
 pyrimidine dimer-DNA photolyase, 116–117, 122–126
 kinetics, 127
 structure, 125–126
 transcriptional response to DNA damage, 818–828
 UV radiation-induced mutagenesis, 613–617
 photoproducts at defined sites, 615
 SUP4-o system, 613–615
 untargeted mutagenesis, 616
Sae2 protein, *S. cerevisiae*, 803
 Saethre-Chotzen syndrome, 1026–1027
SAP130 protein, 302
sbc⁺ genes, *E. coli*, 202, 400, 585
sbmC⁺ gene, *E. coli*, 481, 496
 SCF complex, 754, 794
Schizosaccharomyces pombe
 DNA endonuclease, 383–386
 mtDNA, alternative excision repair, 385–386
 nucleotide excision repair, 278–280
 UVDE endonuclease, 383–386
 Uve1 protein, 456–457
 Schwannomin, 1021
 SCID, see Severe combined immunodeficiency
scid mouse, 718–719, 721, 935
scid-like phenotype, human, 721–722
SCKL1 gene, human, 931
 Screening, 72
 Seckel syndrome, 763, 930–932, 1087, Color Plate 6
 Second-order selection, 423
 Securin, 790, 801
 Selection, 72
 Senescence, 845–846, 854–856
 human cells, 854–855
 mouse models, 1030–1031
 Sensitized photoreversal, 110
 Sensitizer molecule, 34
 Separase, 681, 801
 Septation, bacterial, 495
 Seryl-tRNA synthetase, 45
 Severe combined immunodeficiency (SCID), 932–935, 1087
 Artemis deficiency, 935
 clinical features, 933
 molecular causes, 934–935
 mouse model, 935
 recombinase-activating gene deficiency, 935
SGS1 gene, *S. cerevisiae*, 954
Sgs1 protein, *S. cerevisiae*, 421, 771, 954
 Shiga toxin, 496
 Short tandem repeat sequences, human genetic variation, 1050
 Short-patch excision repair, 252

- mitochondrial, 455
- Shuttle vector
 analysis of mutagenesis in mammalian cells, 79–81
 episomal, 81
 integrated, 81
 mutational spectra of UV-induced lesions, 622
 reactivation, 621–622
 transiently replicating, 80–81
- SIFT (algorithm), 1067
- Signal joint, V(D)J recombination, 712–714
- Signal peptidase, 475–477
- Signal transduction, 6
 cell cycle checkpoints, 758
- Signalosome, 902–903
- Silent mutation, 73
- Single-end invasion intermediate, 425
- Single-nucleotide polymorphisms
 detection
 MassEXTEND, 1054
 mismatch repair detection, 1054–1055
 oligonucleotide arrays, 1052–1054
 stabilized double-D-loop method, 1054–1056
 TDG/MutY glycosylase mismatch method, 1054
 DNA repair genes, 1062
 human genetic variation, 1051–1052
- Single-strand annealing, 663, 665, 688–689
- Single-strand break(s), 665
 radiation-induced, 27–28, 162
 recombinogenic effect, 667
 repair by direct rejoining, 162–163
 sources and significance, 737–738
- Single-strand break repair, 4–5, 737–739
 poly(ADP-ribose) polymerase, 738
 XRCC1 protein, 738–739
- Single-strand gap
 generation at replication fork, 570–571, 586
 repair, 509
- Single-strand invasion, 665
- Single-stranded DNA (ssDNA)
 cell cycle checkpoint arrest, 759
 RecA-ssDNA nucleoprotein filaments, 464–465, 474, 477–478, 518, 542, 545–546, 575–577
 SOS induction, 483–485
 undamaged cells, 485
- Single-stranded-DNA-binding proteins, 54, 397, 402–403, 596
 interaction with DNA polymerase V, 545–546
 oligonucleotide/oligosaccharide-binding fold, 54
 replication protein A, 282–284
- Singlet states, 34
- Sir proteins, *S. cerevisiae*, 717
- SIR2 deacetylase, 790
- Sister chromatid(s), repair involving, 681
- Sister chromatid cohesion, 730, 1025
- Sister chromatid exchange, 868
 Bloom syndrome, 954–956, 958, 961–962, 1061
- Site-specific adduct, 85–86
- Site-specific double-strand breaks, 668–669
- Sjögren-Larsson syndrome, 910
- Skin cancer, 161, 1064–1065
- p53* gene in, 627–629, 638, 877–878
 predisposition syndromes, 1016–1018
 transcription syndromes, 913
 xeroderma pigmentosum, 627, 866–868, 882, 913, 1017
Xpa mouse, 883
Xpc Trp53 mouse, 885–886
- SMAD4* gene, human, 1014
- Small acid-soluble proteins, 133–134
- SMC proteins, 733, 802
 cohesins, 681
- SMC1* gene, vertebrates, 796–797
- Sml1 protein, *S. cerevisiae*, 819
- SMO* gene, human, 1018
- SMUG1* DNA glycosylase, 172
- SMUG1* gene, human, 172
- SNM* genes, *S. cerevisiae*, 693
 homologs in higher eukaryotes, 696
- SNM1 protein, mammalian, 782
- Snm1 protein
 mouse, 721
 yeast, 721
- Sod2* gene, mouse, 1030
- Sodium bisulfite, 12
- Somatic hypermutation, 14, 429–430, 639–642
 DNA repair and, 641
- Somatic mutation
 aging and, 854
 significance of DNA damage for, 641–642
 translesion synthesis and, 641
- Somatic recombination, Bloom syndrome, 958
- SOS box, 230, 464, 471, 490
 LexA binding, 472–473
 strength and location, 486–487
- SOS chromotest, 497
- SOS genes, 230, 478–481
 detection of genotoxic agents, 497
 identification
 expression microarray analysis, 479–481
 searching for LexA-binding sites, 479
 use of fusions, 478–479
 plasmid-encoded gene, 479
- SOS mutator effect, 494
 cells not exposed to exogenous DNA-damaging agents, 543
 chromosomal loci, 534–535
 F' plasmid, 534–535
 single- and double-stranded phages, 535
- SOS system, 248, 250, 252, 383, 463
B. subtilis, 498
E. coli, 463–497
 bacterial persistence, 497
 destabilization of genome, 492–495
 double-strand breaks processed by RecBCD nuclease/helicase, 483
 essential elements, 469–478
 fully induced, 489–490
 fully repressed, 489–490
 generation of inducing signal in vivo, 481–486
 genetic studies, 465–469
 increased excision of transposable elements, 493–494
 increased transposition, 493–494
 indirect induction, 484, 491
 induced responses, 465–466
 induction by ssDNA, 483–485
- induction during replication of damaged DNA, 484–485
 induction of cell cycle checkpoints, 495
 induction of RecA protein, 471
 LexA cleavage, 472–476
 LexA protein binds to SOS boxes, 472–473
 maintenance of genome integrity, 491–492
 model for transcriptional control, 464–465
 modeling SOS signal, 486
 mutations in stationary-phase/aging cells, 494
 phage ϕ 80 induction, 486
 physiological considerations, 465–469, 489–496
 post-translational control, 491
 proteolytic cleavage of λ repressor, 470–471
 respiration arrest, 496
 restriction endonucleases and, 495–496
 similarities between LexA, λ repressor, UmuD, and signal peptidase, 475–477
 stimulation of interspecies mating in bacteria, 494–495
umuDC genes, 513
 gram-negative bacteria, 497–498
 induction, 490
 by mutations that affect DNA processing, 485–486
M. tuberculosis, 498
 pathogenic bacteria, 496–497
 split phenotypes, 490
- SOS-dependent mutagenesis
 bacterial, 511
 biological significance, 551–553
 DNA polymerase III, 526–527
 in vitro system, 537–538
 induction, 510–511
 mechanism, 522–539
 mutational spectra, 523–535
 post-translational regulation of UmuD, 514–523
 RecA protein, 514–515, 535
 RecA-mediated cleavage of UmuD, 516–517
 requirements for particular gene products, 510–523
 site-directed adduct studies, 523–535
 SOS-induced DNA polymerase, 543–544
 translational regulation of UmuD, 517–518
 two-step model, 537
 UmuD and UmuC protein, 511–514, 518
- SOS-independent mutagenesis, 554–555
- soxRS* regulon, 22
- SP lyase, *B. subtilis*, 134
- SP1 protein, ionizing radiation response in mammals, 835
- Spd1 protein, 302
- Speciation, mismatch repair in, 422
- spi*⁺ gene, *B. subtilis*, 134
- spi*⁻ selection, 83–84
- Spinocerebellar ataxia with axonal neuropathy, 47, 387, 935–937, 1087
- Split phenotypes, SOS response, 490

- Spo1 protein, *S. cerevisiae*, 425
 Spo11 protein, *S. cerevisiae*, 667, 725
 Spontaneous mutagenesis, 72
 Spore, *B. subtilis*, 49
 Spore photoproduct, 33–34, 49, 133–134
 formation, 133–134
 repair, 134
 structure, 133
 Sporulation, *S. cerevisiae*, 642–643
 SRC kinase, mammalian, 833
 SRS2 gene, *S. cerevisiae*, 645, 679, 822
 Srs2 protein, *S. cerevisiae*, 679, 687–688, 846
 Srs2 suppressor, *S. cerevisiae*, 645
ssb⁺ gene, *E. coli*, 479
 SSL1 gene, *S. cerevisiae*, 277–279, 298–299
 Ssl1 protein, *S. cerevisiae*, 299, 324–325, 332
 SSL2 gene, *S. cerevisiae*, 278, 298–299
 Ssl2 protein, *S. cerevisiae*, 298–299, 317, 324–326, 332
ssp⁺ genes, *B. subtilis*, 134
 STAGA complex, 302
 START site, yeast, 791
 Staurosporine, 857
 STK11/LKB1 gene, human, 1015–1016
 Stomach cancer, 1064, 1067
 Stop codon, 73
 Strand breaks, *see also* Double-strand break(s); Single-strand break(s)
 chemical and enzymatic agents, 46–48
 defective repair in human genetic diseases, 919–946
 eukaryotic cells, 663–710
Streptococcus pneumoniae
 Hex-dependent mismatch repair, 390–392
 transformation, 391–392
 Streptonigrin, 961
 Streptozotocin, 37, 146, 153, 451
 Styrene, 1063
sulA⁺ gene, *E. coli*, 465, 469, 479–481, 485–487, 490–491, 495
 Sulfotransferase, 41
 Sulfur mustards, 38
 SUMO protein, 647–649, 967
 Sumoylation
 p53 protein, 788
 PCNA, 647–649
 Sunlight, DNA damage, 35
 SUP4-o system, *S. cerevisiae*
 mutational spectra, 613–615
 photoproducts at defined sites, 615
 untargeted mutations, 616
 Supercoiling, replication fork regression, 598–599
 Superoxide dismutase, 21–22, 201, 854, 957, 1030, 1034
 copper/zinc, 928
 manganese, 836
 Superoxide radical, 17–23, 26, 201
supF gene, 78, 81
 Swain-Scott constant, 37–38
 Swil protein, *S. pombe*, 783
 Synapsis, Rad51 protein of *S. cerevisiae*, 672–674
 Synaptonemal complex, 725
 Synthesis-dependent strand annealing, 426, 585, 665, 687

T
tagA⁺ gene, *E. coli*, 172, 181, 183
 Tandem repeat DNA, SOS-induced cells, 494
 Targeted mutation, 72
 UV irradiation of mammalian cells, 622–623
 Tautomycin, 342
 Taxol, 857
 TDG gene, human, 172
 TDG/MutY glycosylase mismatch method, finding single-nucleotide polymorphisms, 1054
 TDP1 gene
 human, 47, 936
 S. cerevisiae, 387
 Tell protein, *S. cerevisiae*, 766, 779, 781
 Telomerase, 421, 687, 718, 732, 854–855, 966, 1027, 1031–1033
 Telomerase RNA, 1027
 Telomere, 287, 717, 723, 759, 966
 aging and, 1031–1032
 Ku proteins and telomere structure, 717–718
 MRN complex in telomere maintenance, 731–732
 Telomere capping proteins, 717–718, 723, 732
 Telomere erosion, *S. cerevisiae*, transcriptional response, 826–827
 Telomere healing, 718
 Telomere position effect, 717
 Telomere shortening, 854–855, 1031
 Telomeric recombination, 421
 Temozolomide, 35, 161, 428
 Temperature-sensitive mutation, 74
 Template switching mechanism, 595, 665
 error-free DNA damage tolerance, 646
 template switch at regressed replication fork, 601–602
 TERC gene
 human, 1027–1028
 mammals, 1031
 Terminal deoxynucleotidyltransferase, 714, 724
 TERT gene, mammals, 1031–1032
 Testicular tumor, 876
 TFB genes, *S. cerevisiae*, 277, 279, 299
 Tfb proteins, *S. cerevisiae*, 324–325, 332
 TFIIH, 900, 909–913
 core subunits contain ring-like structure, 325
 DNA helicase activity, 328–329
 enzymatic activities, 324–325
 functions, 343
 human, 876, 878–879
 mammalian, 317
 damaged-strand recognition, 331
 restitution of nucleotide excision repair, 322
 nucleotide excision repair, 275, 279, 296–299, 323–324, 360
 helix opening, 326
 localization at repair sites, 336
 protein interactions, 332
 subassemblies, 332–334
 RNA polymerase I transcription, 327
 S. cerevisiae, 317, 324–325, 334
 subunits, 296–299, 324–325
 transactivation of nuclear receptors, 326–327
 transcription initiation, 323–324
 helix opening, 325–326
 TFC complex, 302
 TGFBR2 gene, human, 984–985
 α-Thalassemia/mental retardation syndrome, X-linked, 1025
 β-Thalassemia trait, 910
 Thanatophoric dysplasia, 1027
 Thermophiles, DNA damage under extreme conditions, 24
 6-Thioguanine selection, 83
 Thioredoxin, 21
 30-nm fiber, 352
 Thymidine dihydrodimer, 24
 Thymidine-tyrosine cross-link, 27
 Thymidylate synthase, 12, 146–147
 Bloom syndrome, 957
 Thymine
 deamination of 5-methylcytosine, 10, 14
 ionizing-radiation-mediated damage, 27
 Thymine glycol, 16, 19, 22, 24, 26, 28, 33, 247
 removal, 191–192
 repair, 903
 Thymine glycol-DNA glycosylase I, 172
 Thymine glycol-DNA glycosylase II, 172
 Thymine hydrate, removal, 191
 Thymine-DNA glycosylase, 172, 176, 433
 interaction with nuclear receptors, 176
 interaction with XPC-RAD23B, 176
 S. pombe, 176
 Thymineless death, 953
 Thymine-thymine dimers, *see* Cyclobutane pyrimidine dimers
 TID3 gene, *S. cerevisiae*, 1005
 T-loop, 732
 Tobacco-specific nitrosamines, 44–45
 Top1 protein, *S. cerevisiae*, 783
top⁺ gene, *E. coli*, 253
 TOP1 gene, *S. cerevisiae*, 759
 TOP3 gene, human, 924
 TopBP1 protein, human, 771
 Topoisomerase, *see* DNA topoisomerase
 Transcription
 chromatin structure and, 352–354
 homologous recombination and, 689–690
 response to DNA damage, 803–804
 role of CSB protein, 900–902
 Transcription elongation factor, SII, 366–367, 370
 Transcription factor, 49, 51, 55
 AP-1, 156, 199, 831–832, 835
 ATR-3, 837
 CREB, 832
 E2F, 793, 850, 853
 transcriptional response to DNA damage, 830–831, 836
 E2F1, 302
 EGR-1, 836
 Gcn4, 51, 831–832
 MIZ-1, 847
 SP1, 719
 TFIIH, *see* TFIIH
 TIF-IB, 327
 Yap1, 826
 Transcription repair coupling factor, 255–257, 366, 525

- Transcription syndromes, 909–910
 allele-specific and gene dosage effects, 912–913
 skin cancer, 913
- Transcriptional regulation, 753
 Ada protein, 146–150
 SOS response, 464–465
- Transcriptional response to DNA damage, 817–844
 analysis of individual genes, 817–818
 cell cycle checkpoints and, 823, 826
 differential screening, 818
 mammals
 ionizing radiation, 835–837
 radioadaptation, 846–847
 transcription factors, 835–836
 pathway inducibility, 817
- S. cerevisiae*, 818–828
 base excision repair, 821
 checkpoint pathway, 823, 826
DDR and *DIN* genes, 823–824
 DNA synthesis, 823
 double-strand breaks, 826–827
 genome-wide approaches, 823–827
 homologous recombination, 822
 inducibility of genes, 820–823
 nucleotide excision repair, 820–821
 photolyase, 820
RAD6 epistasis group, 822–823
 ribonucleotide reductase, 818–819
 telomere erosion, 826–827
 transcripts in MMS-treated yeast, 824–826
- screens of genome arrays, 818
- UV radiation response, *see* UV response, mammalian
- vertebrates, 828–837
 nucleotide excision repair, 829–830
 p53 as transcription factor, 828–830, 835
 transcription factor E2F, 830–831
 transcriptional profiling, 828–829
- Transcriptional response to oxidative stress, *S. cerevisiae*, 826
- Transcription-coupled nucleotide excision repair, 4–5, 107, 228, 255, 317, 322, 359–365, 525
- B. subtilis*, 362
 biological importance, 368–369
 Cockayne syndrome, 897–898, 901, 903
D. discoideum, 363
E. coli, 362
 evolution, 343
 genome context dependence, 371
 mammalian cells, 360–362
 mediated by RNA polymerase II, 370
 mutation spectra and, 525–526
 proteins that participate in, 363–364
 RNA polymerase I-transcribed genes, 371
S. cerevisiae, 362–363
 with stalled RNA polymerase II, 365–368
 transcription-blocking lesions, 363
 yeast *rad26* mutants, 370
- Transformation, *S. pneumoniae*, 391–392
 high-efficiency, 391
 low-efficiency, 391
- Transformation assay, pyrimidine dimer-DNA photolyase, 113
- Transgenic mice
 analysis of mutagenesis, 83
- gpt* delta, 83
 models of aging, 1030–1031
- Transiently replicating shuttle vector, 80–81
- Transition mutation, 11, 73
 UV irradiation of mammalian cells, 623–624
- Translation, response to DNA damage, 803–804
- Translesion DNA polymerase, 539–543
 aging and, 551–553
 contribution to fitness and survival, 551–552
 stationary-phase bacteria, 551–553
 stressed bacteria, 551–552
- Translesion DNA synthesis, 4, 492–493, 509–510, 593
 biological significance, 551–553
 bypass polymerases, 629–639
 checkpoint signaling, 796
 control of polymerase switching, 549–551
 DNA polymerase η , 632–636
 DNA polymerases, 539–543, 638
 handling of AP sites, 639
 handling of photoproducts, 638–639
 handling of spontaneous DNA damage, 638–639
 induction, 510–511
 interstrand cross-link repair, 692–693
 protein-protein interactions that control, 543–551
 replicative polymerases, 638
 somatic hypermutation and, 641
 UV-irradiated mammalian cells, 620–621
 xeroderma pigmentosum, 865–894
- Transplatin, 247
- Transposable elements, excision, effect of SOS response, 493–494
- Transposase, 494
- Transposition, *E. coli*, effect of SOS response, 493–494
- Transversion mutation, 19, 73, 187, 189
- TRF proteins, 854–855
- Trichorhexis nodosa, 907
- Trichoschisis, 907
- Trichothiodystrophy (TTD), 23, 865, 878–879, 907–909, 1087
 cancer proneness, 913
 clinical features, 907–908, Color Plate 4
 DNA repair, 908–909
 molecular defects, 910–912
 premature aging, 1029
 transcription syndrome, 909–910
- Triplet expansion, 421
- Triplet states, 34–35
- Trisomy 21, *see* Down syndrome
- tRNA genes, 371
 mitochondrial, 449–450
- Trp53* gene, mouse, 885–886, 1030
- trpA*⁺ gene, *E. coli*, 75
- TSC* genes, human, 1020
- TTD, *see* Trichothiodystrophy
- TTD* gene, human, 909
- Tid* gene, mouse, 912
- TTDA* gene, human, 907, 912
- Tuberin, 1020
- Tuberous sclerosis complex, 1003, 1020, 1089
- Tumor necrosis factor alpha, 989
- Tumor suppressor gene, 627
- Tumorigenesis, MBD4-deficient mice, 179
- Turcot syndrome, 1009
- Twain-supercoil-domain model, 353
- TWIST* gene, human, 1026–1027
- Ty element, 824
- Tyrosine kinase, p53 regulator, 790
- Tyrosine phosphorylation, 754
- Tyrosyl-DNA phosphodiesterase 1, 387, 936
- ## U
- UBC13* gene, *S. cerevisiae*, 822
- Ubc13 protein, *S. cerevisiae*, 645
- UBI14* gene, *S. cerevisiae*, 642, 822–823
- Ubiquitin, 294, 822
- Ubiquitin ligase, 367
 E2, *S. cerevisiae*, 642–644
 E3, 300–302, 331, 342, 683, 754, 788, 801, 902–903
 parkin-like, 787–788
- Ubiquitination
 BRCA1 protein, 683
 MMs2-Ubc13-Rad5 system, 645
 p53 protein, 787–788, 790
 PCNA, 647–649
 RNA polymerase II, 900–901
- Ubiquitination pathway, 340–342
- Ubiquitin-conjugating enzyme variant proteins, 645
- UBR1* gene, *S. cerevisiae*, 642
- UCN01, 857
- UDP-glucuronosyltransferase, 41
- u*-gene reactivation, 193
- ugi*⁺ gene, PBS phage, 179–180
- Ultimate carcinogen, 42
- UME6* gene, *S. cerevisiae*, 124
- Ume6 protein, *S. cerevisiae*, 820
- umuC*⁺ gene, *E. coli*, 511–514
 homologs on pKM101, 513–514
 isolation and characterization of mutants, 512
 phenotype of mutants, 512–513
- UmuC protein, *E. coli*
 in DNA damage checkpoint, 519–520
 inhibition of homologous recombination, 518
 post-translation control, 521–523
 purification, 537–538
 related proteins in three kingdoms of life, 538–540
 SOS control, 513
 SOS-dependent mutagenesis, 511–514
- umuD*⁺ gene, *E. coli*, 511–514
 homologs on pKM101, 513–514
 isolation and characterization of mutants, 512
 phenotype of mutants, 512–513
- UmuD protein
E. coli, 465, 491, 496
 autodigestion, 491
 in DNA damage checkpoint, 519–520
 homology to LexA and λ repressor, 514
 inducible replisome/replication restart, 604
 interaction with DNA polymerase III, 548–549

- UmuD protein, (*continued*)
 post-translational regulation, 514–523, 551
 RecA-mediated cleavage, 477–478, 489, 515–518, 604
 SOS control, 513
 SOS-dependent mutagenesis, 511–514
 structurally related proteins, 475–476
 structure of UmuD₂ and UmuD', 520–521
 translation regulation, 517–518
 UmuD', 515, 517–518
 UmuD' inhibition of homologous recombination, 518
Salmonella, 517
 umuDC⁺ operon, *E. coli*, 479, 487–488, 490–492, 494–495, 497, 535–539
 induction for SOS mutagenesis, 518
 replication restart, 603
 SOS control, 513
 UmuDC protein, *E. coli*, 535–539
 translesion DNA polymerase, 540–542
 UNG gene, human, 172, 175
 ung⁺ gene, *E. coli*, 12, 172–173, 175
 UNG1 gene, *S. cerevisiae*, 172
 Unscheduled DNA synthesis, *see* Repair synthesis
 Untargeted mutation, 72
 UV irradiation of mammalian cells, 622
 UV irradiation of *S. cerevisiae*, 616
 Upstream activating sequence, 820
 Upstream repressing sequence, 820–821
 Uracil, in DNA, 9–14, 385
 from deamination of cytosine, 9–14, 432
 folate metabolism and, 13
 incorporation during replication, 12–13
 removal, 17, *see also* Uracil-DNA glycosylase
 by uracil-DNA glycosylases, 173–180
 when mispaired with guanine, 176
 Uracil glycol, removal, 191
 Uracil-DNA glycosylase, 12–13, 17, 56–57, 172
A. aeolicus, 178
Archaea, 174, 177–178
 deficiency, 178–179
E. coli, 55, 173–175, 178, 180
 family 1, 175–177
 family 2, 176–177
 family 3, 177
 family 4, 177
 family 5, 177–178
 helix-hairpin-helix motif, 178
 herpes simplex virus, 175
 human, 175
M. jannaschii, 178
 mammalian, 55, 174–175, 178
 B-cell malignancies and altered immune system, 179
 MBD4 proteins, 178–179
 mechanism of action, 180
 mismatch-specific, 433
 mitochondrial, 454
 phyletic distribution, 174
 protein inhibitors, 179–180
 removal of uracil from DNA, 173–180
S. cerevisiae, 174
S. pombe, 174
 somatic hypermutation, 641
 structure, binding pocket, 180
 thermophiles, 174, 178
 Urea residue, 24, 26, 28, 190
 removal, 191–192
 β-Ureidoisobutyric acid, removal, 192
 UV radiation, *see also* SOS-dependent mutagenesis
 cyclobutane pyrimidine dimers, *see* Cyclobutane pyrimidine dimers
 damage to mtDNA, 451
 DNA containing halogenated pyrimidines, 35
 DNA cross-links, 34
 DNA damage, 4, 29–36
 distribution in chromatin, 48–49
 solar wavelengths, 35
 genes with increased transcript levels, 482
 lesions involving purines, 33
 mutagenesis, 72
 mutational spectra, 523–524
 (6-4) photoproduct, *see* (6-4) Photoproduct
 photosensitization of DNA, 34–35
 psoralen-plus-UV-A reaction, 40–41
 pyrimidine hydrate, 33
 radiation spectrum, 29
 recovery from, 227–228
 reversal of base damage, 109–138
 sensing UV radiation damage, 768–769
 spore photoproduct, *see* Spore photoproduct
 stimulation of recombination, 690
 T-even phages, 193
 thymine glycol, 33
 UVM response, 555
 xeroderma pigmentosum cells, 869
 UV radiation-induced mutagenesis
 mammalian cells, 617–629
 chromosomal genes, 625–627
 cyclobutane pyrimidine dimers, 624
 DNA polymerase ζ, 631
 hot spots, 624
 HPRT gene, 625–626
 inducibility of mutagenic process, 621–622
 mutant fixation in S phase, 617–618
 nucleotide excision repair and, 624–625
 (6-4) photoproducts, 624
 replication in treated cells, 618–620
 specificity of induced lesions, 622–629
 targeted mutations, 622–623
 transition mutations, 623–624
 translesion synthesis, 620–621
 untargeted mutations, 622
 rodent cells, 626–627
S. cerevisiae, 613–617
 photoproducts at defined sites, 615
 SUP4-o system, 613–615
 timing and regulation, 616–617
 untargeted mutagenesis, 616
 two-hit kinetics, 468
 UV response, mammalian, 831–835
 AP-1 and, 831–832, 834
 cytoplasmic vs. DNA damage signals, 834–835
 immediate-early response genes, 831
 intermediate-response genes, 831
 NK-κB, 834–835
 signals originating in cell membrane, 832–834
 slow-response genes, 831
 UVDE endonuclease
N. crassa, 386
S. pombe, 383–386
 substrate specificity, 385
 UVDE-like endonuclease, mitochondrial, 454
 uve1⁺ gene, *S. pombe*, 384–386
 Uve1 protein, *S. pombe*, 456–457, 820
 UVM response, *E. coli*, 555
 UV-mimetic, 896
 uvrA⁺ gene
B. subtilis, 493, 586–587, 591
D. radiodurans, 254
E. coli, 229–230, 479, 486–487, 490–492, 601
 UvrA protein
B. subtilis, localization within cells, 255
E. coli, 230–233, 343
 amino acid sequence, 230–231
 ATP binding, 232
 ATPase activity, 230–231
 binding of dimer to DNA, 232–233
 binding to various types of base damage, 233
 dimerization, 232
 DNA helicase activity of (UvrA)₂UvrB, 241, 243
 DNA-binding protein, 230–232
 helix-turn-helix motif, 230–232
 interaction with UvrB, 238
 loading UvrB on damaged DNA, 240
 molecular matchmaker, 238–239
 nucleotide excision repair, 228–243
 orthologs, 253–254
 translocation of (UvrA)₂UvrB complex, 241
 (UvrA)₂UvrB complex, 239–243
 zinc finger motif, 230–232
 UvrABC DNA damage-specific endonuclease, *see* UvrABC endonuclease
 UvrABC endonuclease, 228, 484
 cross-link recognition, 248
E. coli, 229–253
 substrates, 247
 interstrand cross-link repair, 691–692
 uvrB⁺ gene, *E. coli*, 229, 233–234, 484, 486–487, 490, 492
 promoters, 233–234
 UvrB protein
B. caldotenax, 235
 crystal structure, 235–237
E. coli, 231, 234, 343
 amino acid sequence, 235
 β-hairpin structure, 242
 binding to DNA, 248
 conformation change in DNA, 240
 cryptic ATPase activity, 241, 243
 damage-specific binding, 243
 delivery to sites of DNA damage, 240
 DNA helicase activity of (UvrA)₂UvrB, 241, 243
 homology to UvrC, 234
 interaction with UvrA, 238
 monomer or dimer, 234–235
 nucleotide excision repair, 228–253
 orthologs, 253–254
 protolytic cleavage site, 234

- structure, 234
translocation of (UvrA)₂UvrB complex, 241
(UvrA)₂ UvrB complex, 239–243
UvrBC complex, 244
UvrB-damaged DNA proreincision complex, 239–240, 243
UvrB-DNA preincision complex, 239–240, 243, 248
T. thermophilus, 234–235
uvrC⁺ gene, *E. coli*, 229, 237–238, 479
UvrC protein, *E. coli*, 231, 234, 238, 245–247, 343, 381
affinity for UvrB-DNA complex, 238
DNA incisions, 245
forms, 247
homology to UvrB, 234
nucleotide excision repair, 228–253
orthologs, 253–254
UvrBC complex, 244
uvrD⁺ gene, *E. coli*, 229, 249–250, 394–395, 397, 401, 417, 479, 485–487, 490–492, 494, 585
UvrD protein, *E. coli*, *see* DNA helicase II, *E. coli*
uvrY⁺ gene, *E. coli*, 491
UV-sensitive syndrome, 905–906, 1087
- V**
V(D)J recombination, 639–640, 718, 720, 724, 930, 935
antibody genes, 712–714
ataxia telangiectasia, 926, 928
ATM protein, 761
double-strand break repair and, 714
RAG-mediated cleavage and joint formation, 712–714
Vertebrates, nucleotide excision repair, 829–830
Very-short-patch mismatch repair, 14, 57
E. coli, 431–432
VHL gene, human, 1020
Vinyl chloride, 176
Viral probe
mutational spectra of UV-induced lesions, 622
reactivation, 621–622
Virus, UV-irradiated, nucleotide excision repair by host cells, 273–274
von Hippel-Lindau disease, 1003, 1020, 1089
von Recklinghausen disease, *see* Neurofibromatosis, type 1
VP16, 921
Vsr endonuclease, 431–433
vsr⁺ gene, *E. coli*, 431–432
- W**
WAF1 gene, vertebrates, 791–792
WAGR syndrome, 1019
Watson, James, 3
Weigle mutagenesis, 466, 468, 510–511, 514–515, 621
Weigle reactivation, 466, 468, 510–511, 621
Werner syndrome, 23, 929, 965–968, 1087
cancer predisposition, 971
cellular phenotype, 966, 971
clinical features, 965–966, 970, Color Plate 8
genetics, 966
heterozygotes, 1061
premature aging, 1029, 1033
Wilms' tumor, 1003, 1018–1020, 1089
Wortmannin, 763
WRN gene, human, 961, 965–968
heterozygotes, 1061
identification, 966–967
WRN protein, 929
DNA helicase and exonuclease activities, 967
expression, 968
function, 968
protein interactions, 967–968
WT1 gene, human, 1019–1020
- X**
X rays, 26
XAB2 gene, human, 901
Xanthine, 10, 15
Xenopus laevis
cell cycle checkpoint arrest, 759–760
nonhomologous end joining, 711
xerC⁺ gene, *E. coli*, 486, 495, 597
xerD⁺ gene, *E. coli*, 486, 495, 597
Xeroderma pigmentosum (XP), 82, 95, 267, 865–894, 979, 1087, *see also* XP/CS complex
cancer, 881–882
cellular phenotypes, 868–874
chromosomal abnormalities, 868–869
classical, 870, 875
clinical features, 866–867, Color Plate 1
complementation groups, 874–875
genetic complexity, 874–875
group A, 870–876
group B, 870–871, 874–877, 907
group C, 870–875, 877–878
group D, 298, 870–875, 878–879, 907
group E, 301–303, 868, 870–875, 880
group F, 285–288, 870–871, 874–875, 880–881
group G, 870–871, 874–875, 881
heterozygotes, 1061
hypermutability of cells, 869–870
incidence and demographics, 867–868
killing cells with DNA-damaging agents, 869
literature, 865–866
molecular pathology, 875–881
mouse model, 882–887
neurological complications, 866–867, 872, 882
nucleotide excision repair, 274–275, 870–872, 882–887
repair of cyclodeoxynucleosides, 873–874
repair of oxidative damage, 872–873
skin cancer, 627, 866–868, 882, 913, 1017
source of mutations, 869–870
therapy, 882
unexplained features, 881
variant form, 621, 696, 875, 1061
DNA polymerase η , 632–634
Xeroderma pigmentosum variant protein, 539
- XP, *see* Xeroderma pigmentosum
XP/CS complex, 865, 876, 878, 906, 1087
allele-specific and gene dosage effects, 912–913
cancer proneness, 913
clinical features, Color Plate 3
molecular defects, 910–912
transcription syndrome, 909–910
XPA gene
human, 275, 279, 875–876, 881
mammalian, 281
Xpa gene, mouse, 883–884
XPA protein, mammalian, 281, 317, 326, 331–333, 336, 343, 360, 367
binding to DNA, 281–282
fluorescently tagged, 335
reconstitution of nucleotide excision repair, 322
XPB gene
human, 275–276, 279, 875–877, 881, 906–907, 911, 1034
trichothiodystrophy, 907, 909
mammalian, 298–299
XPB protein, mammalian, 317, 324–326, 336
phosphorylation, 343
XPC gene
human, 275, 279, 875, 877–878, 881, 1051
polymorphisms, 1069–1071
mammalian, 293–294, 837
vertebrates, 830
Xpc gene, mouse, 884–886
spontaneous mutagenesis, 886
XPC protein
human, 294
mammalian, 292–296, 326, 333, 343, 363, 368–369
fluorescently tagged, 335
proteosomal degradation, 342
reconstitution of nucleotide excision repair, 322
XPC-RAD23B complex, 176, 295, 317, 328, 331–335, 356, 363
XPD gene
human, 275–277, 279, 875, 878–879, 906–907, 910–912, 1034, 1051
COFS syndrome, 905
polymorphisms, 1064–1069, 1071
trichothiodystrophy, 907, 909
mammalian, 296–298
Xpd gene, mouse, 886
XPD protein
human, 913
mammalian, 298, 317, 324, 326, 329
XPE gene, human, 275, 301, 875, 880
Xpe gene, mouse, 886
XPF gene, human, 275, 279, 285–288, 875, 880–881
Xpf gene, mouse, 887
XPF protein, mammalian, 332
ERCC1-XPF enzyme, 286–287, 318, 326–327, 333–334, 336, 360
interstrand cross-link repair, 695
N terminus, 288
nuclease domain, 288–289
reconstitution of nucleotide excision repair, 322
sequence similarity to ERCC1 protein, 289

- XPF protein, mammalian, (*continued*)
 structural organization of XPF nuclease family, 289–290
- XPF-like nucleases, 289–290
- XPG* gene
 human, 275–276, 279, 875, 881, 906–907, 910–912
 polymorphisms, 1066
 mammalian, 292–293
 isolation, 291–292
 mutations, 292
- Xpg* gene, mouse, 887, 912
- XPG protein
 human, 912
 mammalian, 292, 317–318, 326–327, 332–334, 336, 360, 367
 reconstitution of nucleotide excision repair, 322
 structure-specific nuclease, 282
- XPV* gene, human, 275, 633–634, 875
- XRCC1* gene
 human, 738, 1034
- polymorphisms, 1064, 1067–1069
 mammalian, 837
- XRCC1* protein
 base excision repair, 207–208, 211–214
 single-strand break repair, 738–739
 sister chromatid exchange formation, 961
- vertebrates
 activities, 678–679
 targeted deletions, 678
- XRCC2* protein, vertebrates, 677–679
- XRCC3* gene, human, 1066, 1069
- XRCC3* protein, vertebrates, 677–679
 activities, 678–679
 targeted deletions, 678
- XRCC4* protein
 nonhomologous end joining, 722–723
XRCC4 protein-ligase IV complex, 722–723
- XRCC7* gene, mammalian, 719
- XRCC9* gene, human, 991
- Xrs2 protein, *see also* MRN complex
- S. cerevisiae*, 725, 729
- xthA*⁺ gene, *E. coli*, 198–200, 453, 532
- Y**
- yaf*⁺ genes, *E. coli*, 538
- ydjM*⁺ gene, *E. coli*, 487
- ydjQ*⁺ gene, *E. coli*, 245–247, 492
- Yeast, *see Saccharomyces cerevisiae*;
Schizosaccharomyces pombe
- yeeF*⁺ gene, *E. coli*, 481
- Yin yang 1 protein, 788
- Yku proteins, *S. cerevisiae*, 716–718
- ysdAB*⁺ gene, *E. coli*, 496
- Z**
- Zinc finger domain
 Ada protein, 147
 UvrA protein, 230–232
- Zinc hook, MRN complex, 734–735
- Zip proteins, *S. cerevisiae*, 426