SUPERANTIGENS
SUPERANTIGENS
Molecular Basis for Their Role in Human Diseases

Edited by
Malak Kotb
and John D. Fraser

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This book is dedicated to the memory of Edwin H. Beachey,
a great scientist, mentor, and friend
# CONTENTS

Contributors ........................................................................................................ ix
Preface ................................................................................................................ xi

## I. SUPERANTIGENS: WHAT IS NEW?
1. The Streptococcal Superantigens • John D. Fraser and Thomas Proft ........ 3
2. Staphylococcal and Streptococcal Superantigens: an Update • Patrick M. Schlievert and Gregory A. Bohach ...................... 21
3. Mycoplasma arthritidis-Derived Superantigen (MAM), a Unique Class of Superantigen That Bridges Innate and Adaptive Immunity • Barry C. Cole and Hong-Hua Mu ......................... 37
4. Viral Superantigens in Mice and Humans • Albert K. Tai and Brigitte T. Huber ............................................................... 59
5. Superantigens from Gram-Negative Bacteria and the Diseases That They Cause • Takehiko Uchiyama, Tohru Miyoshi-Akiyama, and Hidehiro Ueshiba .............................................................. 77

## II. SUPERANTIGEN STRUCTURE AND FUNCTION
7. Structural Evidence for Zinc and Peptide Dependence in Superantigen-Major Histocompatibility Complex Class II Interaction • Björn Walse ................................................................. 103
8. Superantigens: Structure, Function, and Diversity • Matthew D. Baker and K. Ravi Acharya .................................................. 121

## III. SUPERANTIGENS AND HUMAN DISEASES
9. Role of Superantigens in Skin Disease • Sang-Hyun Cho and Donald Y. M. Leung ................................................................. 139

## IV. EXPERIMENTAL MODELS FOR SUPERANTIGEN-MEDIATED DISEASES
10. Pathogenetic Mechanisms and Therapeutic Approaches in Superantigen-Induced Experimental Autoimmune Diseases • Andrej Tarkowski ................................................................. 159
11. Experimental Models of Superantigen-Mediated Neuropathology
   Malte E. Kornhuber, Alexander Emmer, Kristina Gerlach, and M.S. Staeger
   ........................................ 169

12. Novel Experimental Models for Dissecting Genetic Susceptibility
    of Superantigen-Mediated Diseases
    Eva Medina ............................ 183

V. THERAPEUTIC INTERVENTIONS IN SUPERANTIGEN-MEDIATED
   DISEASES

13. Intravenous Immunoglobulin Therapy in Superantigen-Mediated Toxic Shock
    Syndrome
    Anna Norrby-Teglund, Donald E. Low, and
    Malak Kotb  ........................................ 197

14. Broad-Spectrum Peptide Antagonists of Superantigen Toxins
    Revital Levy, Iris Nasie, Dalia Hillman, Gila Arad, and
    Raymond Kaempfer  ............................ 217

15. Small Nonpeptide Inhibitors of Staphylococcal Superantigen-Induced
    Cytokine Production and Toxic Shock
    Teresa Krakauer  ......................... 229

16. Countermeasures against Superantigens: Structure-Based Design
    of Bispecific Receptor Mimics
    Goutam Gupta and
    Meghan Kunkel  ................................ 245

Index ........................................ 255
CONTRIBUTORS

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ix
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Microbial superantigens are fascinating proteins that have structurally evolved to interact in a unique manner with host immune defense systems. These molecules are unusual in the sense that they can simultaneously activate cells involved in innate immunity as well as T cells, which normally mediate acquired immune responses. As a result of this unusual mode of interaction, superantigens have the capacity to stimulate large numbers of immune cells to release inflammatory mediators that, if uncontrolled, can inflict serious damage upon the host and may even cause death. Through our studies of the various superantigens, we have learned so much about immune system activation and regulation and about the various mechanisms by which different cells of the immune system interact and exchange biochemical signals that program their response and function.

Years prior to their designation as superantigens and the discovery of the mechanism by which they function, several laboratories had been studying these proteins and noticing the unconventional way by which they elicit immune activation. The massive proliferative response they elicit in resting leukocytes resembled that of polyclonal mitogens, yet the requirement for cells expressing HLA class II molecules to induce leukocyte activation resembled antigenic responses. Unlike conventional antigens, however, these molecules required no processing by antigen-presenting cells and their presentation to T cells was MHC unrestricted. These seemingly perplexing properties were resolved when it became evident that the superantigens interact in a unique manner with HLA class II as well as with specific elements within the variable region of the β chain of the αβ T cell receptor (TCR). Furthermore, it was found that superantigens use these receptors as a means to bring different types of cells closer, forcing them to interact and exchange activation signals that trigger biochemical cascades, resulting in the elaboration of potent inflammatory cytokine responses and massive T cell proliferation.

Shortly after their discovery, it was believed that all superantigens were alike, that they interact in the same way with immune cells, and that they cause similar diseases, namely toxic shock, serious skin infections, and food poisoning. A common remark was “if you’ve studied one superantigen, you’ve studied them all.” We now know that nothing could have been further from the reality of these molecules. The fact that bacteria like *Streptococcus pyogenes* have over twelve different superantigens suggested that these microbial proteins are functionally nonredundant.

Thousands of articles have been published on superantigens, with a marked increase in the past two years, underscoring the fact that the field has been advancing considerably. This, we believe, is a result of the advent of sophisticated technologies and bioinformatics tools that unraveled new structure-function information and considerable differences in the way that distinct superantigens interact with HLA class II and/or TCR molecules. These new discoveries provided an impetus for more in-depth studies of molecular features underlying differences in the biological function of superantigens, their tissue specificity and capacity to cause or exacerbate different diseases.
Although several outstanding books on superantigens have been published, we wanted this book to highlight several new and exciting findings. We assembled an outstanding team of scientists with highly diverse expertise but a common interest in superantigen structure, function, and biology. These authors brilliantly captured some of the latest advances in the field, presenting information on newly discovered superantigens in bacteria and viruses, demonstrating how some superantigens interact with receptors other than, or in addition to, HLA class II and TCR molecules, and proposing novel mechanisms for the association of certain superantigens with various types of acute and chronic diseases, including autoimmune diseases. Exciting developments in therapeutic modalities for superantigen-mediated diseases are also highlighted in this book. This latter aspect has been given some priority in recent years, particularly since certain superantigens, in the aerosolized form, have potential for use as biological weapons and in bioterrorism.

More importantly, we wanted the readers of this book to develop a better appreciation for how newly discovered structural variations among superantigens affect the mode by which they interact with immune cells. We hope that the readers will have a better understanding of how these structure/function differences may explain why different superantigens contribute to the initiation and/or exacerbation of distinct diseases, why certain ones are effective in some tissues but not others, and how the host’s genetic makeup can grossly alter the course of superantigen-mediated diseases. We also hope that the readers of this book will appreciate how this new information has informed the design and development of novel intervention strategies or suggested the use of existing modalities to ameliorate or modulate superantigen responses in severe acute infections or certain chronic illnesses.

On the flip side, however, the powerful immune-stimulating potential of certain superantigens may be exploited to modulate and direct the type of inflammatory responses in a way that increases the host’s efficiency in overcoming certain chronic diseases and infections. These new insights may provide information on disease mechanism and thereby focus efforts to develop effective therapeutics and intervention measures for superantigen-mediated illnesses.

Malak Kotb
John D. Fraser
INDEX

Allergic encephalomyelitis
experimental, 161
Antibodies
development of
superantigen mimetic peptide and, 224–225
induction in rabbits, 27
Antigenic peptide
interactions of superantigens and MHC class II
molecules, 112–113, Color Plates 8 and 9
Antigens
conventional
superantigens versus, 246–247, Color Plate 16
Arthritis
collagen-induced
murine
triggering and exacerbation of, 50–52
experimental, 161
induced by Mycoplasma arthritidis
in BALB/c and C3H/HeJ mice, 40, 41
septic, 162
Autoimmune diseases
development of
superantigens in, 162
experimental
impact of superantigens on, 160
human
role of superantigens in, 51–52, 236
superantigen-induced experimental
pathogenetic mechanisms in, 159–168
therapeutic approaches in, 159–168
superantigens in development of, 245
murine models to study, 190–191
Autoimmunity
M. arthritidis-derived superantigen and,
50–52

B-cell and T-cell superantigens
joint action of
in multiple sclerosis, 175–178
multiple sclerosis and, 180

B cells
activation by superantigens, 143
superantigens stimulating, 59–60

Bacterial superantigens. See Superantigens, bacterial

Baicalin, 239
Benzylpenicillin
in toxic shock syndrome, 204
Blood mononuclear cells
human peripheral
to study superantigens, 231–233
Bullous impetigo, 145

Cell receptor-toxin interaction
inhibitors of, 237
Cellular response
in vitro, 231–233
Central nervous system
oligoclonal immunoglobulin synthesis in
superantigens and, 175–178
Chimeras
affinity for superantigens
molecular modeling to improve, 251–252
cloning of, 250
design of, 249
future testing using, 253
molecular modeling of
and interactions, 250–251, Color Plate 18
pairwise contacts with superantigens, 252
rationale for therapy by, 248–249
superantigen specificity of, 250
type-specific inhibition of IL-2 release and cell
proliferation by, 250
Chimeric receptor mimics
rationale for therapy by, 248–249
Clindamycin
in toxic shock syndrome, 204–205
Corticosteroids
resistance to
staphylococcal superantigens and, 142
Costimulatory molecules
blocking of, 165
Crohn’s disease, 28
Cytokines
associated with sepsis, 202
inducible
in cells of M. arthritidis-injected mice, 40, 41
induction of
by streptococcal superantigens, 12
inhibitors of, 239
serum induced by Mycoplasma arthritidis in C3H/HeSnJ and C3H/HeJ mice, 41, 43 staphylococcal superantigen-induced production of small nonpeptide inhibitors of, 229–244

Cytomegalovirus superantigen activity associated with, 60

D-galactosamine to induce toxic shock, 233–234 D-galactosamine-sensitized mouse as model for studying lethality of superantigens, 220

Dermatitis atopic description of, 143 IgE antibodies and, 144 staphylococcal superantigens and, 143–144 staphylococcal superantigens in, 152 treatment of staphylococcal superantigens and, 141–142

Dexamethasone, 238


Doxycycline, 239

Drug design structure-based, 246

Eczema staphylococcal superantigens and, 143


Encephalomyelitis allergic experimental, 169 experimental allergic, 161

Endotoxins in staphylococcal scarlet fever, 145–146 pyrogenicity of superantigens and synergy with, 11

Enterotoxins staphylococcal. See Staphylococcal enterotoxins

Epstein-Barr virus superantigen activity associated with, 60

Erythema perineal recurrent toxin-mediated, 146–147

Exotoxins produced by Staphylococcus aureus and Streptococcus pyogenes, 247 term “superantigen” applied to, 21

Fever in superantigen-based disease, 245

Food poisoning, 245 staphylococcal superantigens and, 141–142

Gene expression of superantigen encephalitis, 175, 176–178

Genetic factors and host response to microbial superantigens, 183–184

Genistein, 238

Genome scanning identification of streptococcal superantigens by, 5

Group A Streptococcus disease invasive and effects of streptococcal superantigens on primates, 13 epidemiological studies of, 12–13 influence of host genetic background on, 14

Guttate psoriasis, 148–150

Human endogenous retrovirus-K18 Env provirus, 65

Human endogenous retrovirus-K18 Env superantigens, 64–66

Human endogenous retrovirus superantigens, 63

Human endogenous retrovirus-W Env protein superantigens, 63–64

Human immunodeficiency virus-1 superantigens, 63

Human immunodeficiency virus infection, 245

Immune activation signal transduction and, 231

Immune system superantigen interactions with, 246–247, Color Plate 16

Immunity adaptive, 59–75 broad-spectrum protective without immunization, 221–222 innate and adaptive M. arthritidis-derived superantigen interactions with, 40–48
protective humoral 
lack of 
in toxic shock syndrome, 204
Immunization 
broad-spectrum protective immunity without, 221–222
Immunodeficiency diseases 
superantigens promoting, 245
Immunoglobulin 
intravenous 
in superantigen-mediated toxic shock syndrome, 197–215 
mechanisms of action of 
in toxic shock syndrome, 202, 203
intravenous polyspecific 
in Kawasaki disease, 205
in toxic shock syndrome, 205–209
clinical studies of, 207–209
inhibition of T-cell activation by, 207
mechanistic actions of, 205–206
modulation of cytokine responses by, 206–207
Immunoglobulin synthesis 
oligoclonal 
in central nervous system 
superantigens and, 175–178
Impetigo 
bullous, 145
Infections 
as triggers for psoriasis, 148
methicillin-resistant *Staphylococcus aureus*, 217
staphylococcal 
pathogenic mechanisms in, 202–204
streptococcal 
pathogenic mechanisms in, 202–204
superantigen-mediated 
prevention and therapy of, 246
with autoimmune manifestations, 162
Inflammation 
superantigen-mediated 
and shock, 202
downregulation of 
to prevent disease, 163–164
Inflammatory diseases 
of nervous system 
superantigens and, 169
Interleukin 1 
as mediator of shock, 229, 235
Intravenous polyspecific immunoglobulin 
in Kawasaki disease, 205
in toxic shock syndrome, 205–209
clinical studies of, 207–209
inhibition of T-cell activation by, 207
mechanistic actions of, 205–206
modulation of cytokine responses by, 206–207
Joint action 
of B-cell and T-cell superantigens 
in multiple sclerosis, 175–178
Kawasaki disease, 14–15, 143
Linezolid 
in toxic shock syndrome, 204
Lymphomas 
cutaneous T-cell, 147
Major histocompatibility complex 
class II 
α-chain binding, 97–98, Color Plates 4, 5 and 6
and *M. arthritidis*-derived superantigen interaction, 38–39
as coreceptor for *M. arthritidis* signaling through Toll-like receptors, 46–48
β-chain binding, 98–99, Color Plates 4, 5 and 7
binding sites of, 108
blocking of, 165
cross-linking of, 99, Color Plate 7
interaction 
zinc and peptide dependence in, 103–120
microbial superantigens and, 160
superantigen binding to, 97, 98, Color Plate 4
class II molecules and T-cell receptor interactions, 183
β-chain of
zinc-dependent interaction of, 111–112
site of, 111, Color Plate 9
structure of, 248, Color Plate 16
superantigen binding to, 124–125, 229
variations on, 97–100
superantigen interaction with, 104–109, Color Plates 8 and 10, 247–248
multiple modes of, 124, Color Plate 12
T-cell receptor and, 114, Color Plate 10
Major histocompatibility complex II/staphylococcal enterotoxin B/T-cell receptor complex 
putative, 97–98, Color Plate 6
Major histocompatibility complex II-superantigen complexes 
comparision of, Color Plate 8
Major histocompatibility complex II/superantigen 
*SPE-C/T*-cell receptor complex 
putative, 98, Color Plate 7
Major histocompatibility complex II-superantigen-T cell receptors quaternary complex, Color Plate 10
Methicillin-resistant *Staphylococcus aureus* infection, 217
Microbial superantigens
characteristics of, 160
Mouse (Mice)
human HLA-transgenic
in studies of superantigen-induced disease, 187–188
MHC complex II-congeneric strains of, 187
protection and rescue from lethal shock, 220–221
transgenic
expressing human HLA and CD4 molecules, 189–190
Mouse models. See Murine models
Mouse strain specificity
in adaptive immune response to M. arthritidis-derived superantigen in vivo, 40–45
Mucosal surfaces
superantigen interaction at
causing human diseases, 29–30
Multiple sclerosis, 169, 245
and B-cell superantigens, 180
and T-cell superantigens, 180
as viral disease, 179–180
chronic degeneration and inflammation in, 169
further research strategies in, 181
joint action, B-cell and T-cell superantigens, 179
relapsing-remitting
axonal loss in, 170
Multiple sclerosis-associated retrovirus, 170
Murine herpesvirus-68
superantigen activity associated with, 60–61
Murine leukemia virus
host-derived superantigens and, 61
Murine mammary tumor virus superantigen, 62
Murine models
human HLA-transgenic
to study superantigen-induced disease, 187–188
MHC class II-congeneric
as experimental models, 186–187
to study superantigens in autoimmune disease development, 190–191
transgenic
to study superantigen-mediated disease, 185
Mycoplasma arthritidis, 37–38
disease induced by, 50–52
role of M. arthritidis-derived superantigen, 48–50
M. arthritidis-derived superantigen, 37–57, 113–114, 122, 190
and autoimmunity, 50–52
and Toll-like receptor interaction
regulation of TLR2 and IL-12p40 by, 45
early work on, 38
in vivo
mouse strain specificity in adaptive immune response to, 40–45
interactions with innate and adaptive immunity, 40–48
macrophage expression of TLR2 and TLR4 in response to, 44–45
regulation of B7–1 and B7–2 induced by mediated through Toll-like receptors, 46
role in disease induced by M. arthritidis, 48–50
selection of TLR-triggered cytokine profiles models for, 48, 49
signaling through Toll-like receptors with MHC II as coreceptor, 46–48
structural properties of class II MHC interaction, 38–39
T-cell receptor molecules interaction with, 39–40
to study genetic susceptibility to disease, 185–186
zinc and, 126, 127
Mycoplasma arthritidis-injected mice
inducible cytokine profiles in cells of treatment with anti-B7–1 antibody, 46, 47
inducible cytokines from, 40–41, 42–43
serum cytokines induced in, 41, 43
Mycoplasma arthritidis mitogen. See Mycoplasma arthritidis-derived superantigen
Mycoplasmas, 37–38
Necrotizing fasciitis
streptococcal toxic shock syndrome and, 209
Neonatal toxic shock syndrome-like exanthematous disease
and adult TSS
expansion of V2+ T cells in, 81, 82
and toxic shock syndrome
activation of TSST-1–reactive T cells in, Color Plate 2
general description of, 81–83
Nervous system disorders
streptococcal superantigens and, 28–29
Neuromuscular diseases
superantigens and, 180–181
Neuropathology
superantigen-mediated experimental models of, 169–182
Oligoclonal immunoglobulin synthesis
in central nervous system superantigens and, 175–178
Osmotic pump implantation
in experimental toxic shock syndrome and Y. pseudotuberculosis infection, 81, 83
Penicillin
  in toxic shock syndrome, 204–205
Pentoxyfylline, 239
Peptide antagonists
  broad-spectrum
  of superantigen toxins, 217–227
Peptide antigen
  and superantigen
  presentation differences, 246–247, Color Plate 16
Peptides
  and zinc dependence
  in superantigen MHC class II interaction, 103–120
  antagonist
    as novel superantigen domain, 223, Color Plates 13 and 14
  superantigen antagonist
    blocking superantigen toxins, 218
effective in vivo, 218–219
  in protection of mice from lethal shock, 220
  superantigen mimetic
    development of protective antibodies and, 224–225
Peripheral blood mononuclear cells
  human
    to study superantigens, 231–233
Plaque psoriasis
  chronic, 150–151
Protein A
  bacterial cell wall-expressed, 162
Protein therapeutics
  structure-based design of, 246
Proteins
  chimeric. See Chimeras
Psoriasis
  animal models of, 148
  chronic plaque, 150–151
  experimental, 162
  genetic predisposition to, 147
  guttate, 148–150
  immune mediation of, 147
  infections triggering, 148
  pathogenesis of, 147–148
  superantigens in
    potential role of, 151
Pyrogenic exotoxins
  from group A streptococci, 3–4
Rabies virus superantigens, 62
Receptor mimics
  chimeric. See Chimeras
Rheumatic fever
  acute, 14
  streptococcal superantigens and, 28
Scarlet fever
  staphylococcal, 145
Septic arthritis, 162
Shock
  in superantigen-based disease, 245
  lethal
    protection and rescue of mice from, 220–221
  SEB-induced
    small nonpeptide therapeutics for, 238
    staphylococcal exotoxin-induced treatment of, 236–237
Signal transduction
  and immune activation, 231
  inhibitors of, 237–238
  trimeric complex for, 130
Skin
  antigen-presenting cells of
    effects of superantigens on, 141
  pathophysiology of superantigens on, 139–143
  surfaces of
    superantigen interaction at
      causing human diseases, 29–30
  T cells migrating to
    effects of superantigens on, 141–142
Skin disease
  streptococcal superantigens in, 147–151
  superantigen-mediated
    immunologic features of, 140
    superantigens in, 139–156
Skin infections
  Staphylococcus aureus and, 28
Skin rashes
  in acute and systemic Y. pseudotuberculosis infection, 84–85
  in systemic illnesses
    superantigens and, 143
Splenocytes
  activated
    amplifying superantigen encephalitis, 171–173, 174
Staphylococcal enterotoxin A, 93
Staphylococcal enterotoxin-like toxins
  binding of, 126
Staphylococcal enterotoxins, 104, 105, 121, 229
  as model toxins for chimeric receptor mimics, 249
  food poisoning and, 27–28
  in autoimmune disorders, 190
  SEA, 217–219
  SEB, 217–219
acute lung injury caused by, 231
animal models of, 233–234
antagonist domain in, 223–224, Color Plate 15
as accessible to ligands, 223–224, Color Plate 15
human susceptibility to, 233
immunoglobulins against, 221, 222
in vivo testing of, 233
transcytosing of, 233
Staphylococcal food poisoning superantigens and, 27–28
Staphylococcal protein A, 160
Staphylococcal scalded skin syndrome, 145–146
Staphylococcal scarlatiniform eruption, 145–146
Staphylococcal scarlet fever, 145
Staphylococcal superantigen-like proteins, 93
allelic variations in, 96
Staphylococcal superantigens and MHC class II molecules, 229
and skin rashes, 143
and streptococcal superantigens update on, 21–36
binding to host cells, 230
division into subfamilies, 121–122
family tree of, 107
human diseases caused by, 235–236
in atopic dermatitis, 152
production of, 104
structure of, 247, Color Plate 17, 93
surface representation of, 122–124, Color Plate 11
toxic shock syndrome and, 199
Staphylococcus aureus, 103
bacterial infections and, 143
exotoxins produced by, 247
menstrual toxic shock syndrome and, 29–30
molecular structures of toxins from, 224
skin infections and, 28
toxic shock syndrome caused by, 197–198
virulence factors of, 200–201
Staphylococcus aureus infection methicillin-resistant, 217
Streptococcal infection
murine models in study of predisposing genetic factors, 186–187
Streptococcal mitogenic exotoxin, 121
Streptococcal pyogenic exotoxins, 121, 217–218
Streptococcal superantigen genes, 5–6
regulation of, 7–8
variation in, 6
Streptococcal superantigen SMEZ-2, 94–95, Color Plate 3
Streptococcal superantigens, 3–20, 121
and staphylococcal superantigens update on, 21–36
biochemical properties of, 9–10
cell receptor binding of, 10–11
cytokine induction by, 12
dimer-formation of, 10
division into subfamilies, 121–122
family tree of, 107
functional properties of, 7
identification by genome scanning, 5
in skin disease, 147–151
production of, 104
pyrogenicity of
and synergy with endotoxins, 11
structure of, 93
surface representation of, 122–124, Color Plate 11
toxic shock syndrome and, 199–202
Vβ specificity of, 6–7
Streptococcal toxic shock syndrome. See Toxic shock syndrome, streptococcal Streptococci
Group A
pyrogenic exotoxins from, 3–4
Streptococcus dysgalactiae-derived mitogen, 111
Streptococcus pyogenes, 103
exotoxins produced by, 247
molecular structures of toxins from, 224
smeZ family superantigens from, 224
toxic shock syndrome caused by, 198–199
virulence factors of, 200–201
Superantigen-chimera complexes, 250–251, Color Plate 18
Superantigen fold, 94–96, Color Plate 3
allelic variations in sequence decorate, 96
Superantigen toxins
broad-spectrum peptide antagonists of, 217–227
Superantigens
absorption and binding of, 103
activation of T cells by, 218
diseases caused by, 103
and MHC class II complexes, 247–248
comparison of, Color Plate 8
and neuromuscular diseases, 180–181
and superantigen-like proteins
OB-fold domain of, 95
architecture of, 93–102
as term applied to exotoxins, 21
association with human disease, 25–29
B-cell, 23
bacteria producing, 103
bacterial
crystal structure of, 104, 105
two domains of, 122
zinc-binding, 113–114
binding to MHC class II molecules, 124–125
binding to MHC-II and TCR
  variations on, 97–100
binding to T-cell receptor, 127–129, Color Plate 11
C-terminal β-grasp domain of, 95–96
categorization of, 24–25
countermeasures against, 245–254
definition of, 22–24
description of, 245–254
diseases mediated by. See Diseases, superantigen-mediated
downregulation of production of to prevent disease, 163
formation of, 124, Color Plate 12
four major groups of, 104
from gram-negative bacteria and disease caused by, 77–89
from various streptococci, 8–9
functions of, 93, 245–254
structure of and diversity of, 121–135
zinc in, 124–125, Color Plate 11, 122, 123
host-derived
murine leukemia virus and, 61
human disease caused by, 25–26
interaction at mucosal and skin surfaces in, 29–30
human diseases based on, 245
human endogenous retrovirus, 63
human endogenous retrovirus-K18 Env, 64–66
human endogenous retrovirus-W Env protein, 63–64
human immunodeficiency virus-1, 63
in complex with T-cell receptors, 247–248
in skin disease, 139–156
infections mediated by prevention and therapy of, 246
interaction with MHC class II molecules, 104–109, Color Plates 8 and 10
and antigenic peptide interactions, 112–113, Color Plates 8 and 9
multiple modes of, 124, Color Plate 12
T-cell receptor and, 114, Color Plate 10
interaction with Vβ-TCRs, 25
lethality of Nα-galactosamine-sensitized mouse as model for studying, 220
mechanism of stimulation of, 21–22
microbial characteristics of, 160
immunological response to, 183
murine mammary tumor virus, 62
neutralization of to prevent disease, 163–164
oligomerization of, 99–100
organisms encoding, 60
pathophysiology of on skin, 139–143
potential role in psoriasis, 151
prevention of interaction of, 165
prototypes, 247
pyrogenic family of, 160
pyrogenic toxin
categorization of, 24
rabies virus, 62
resistance to antagonist-mediated acquisition of, 221, 222, 224
role in human autoimmune disease, 51–52
sequence alignment of, 104, 106
specific tolerance to induction of, 165
staphylococcal. See Staphylococcal superantigens streptococcal. See Streptococcal superantigens structural features and idiosyncrasies of, 130–132
structure of, 247, Color Plate 17
function of and diversity of, 121–135
T-cell, 23–24
defining properties of, 23
use to benefit host, 165–166
versus conventional antigens, 246–247, Color Plate 16
viral
endogenous weak affinity model for, 66–68
exogenous and endogenous Vβ specificity of, 60–61
in mice and humans, 59–75
viral pathogens associated with, 60–61
T-cell and B-cell superantigens
joint action of in multiple sclerosis, 175–178
multiple sclerosis and, 180
T-cell lymphomas
cutaneous, 147
T-cell receptor molecules
M. arthritidis-derived superantigen interaction with, 39–40
T-cell receptors, 59
and MHC class II molecule interactions, 183
β-chain complexes
superantigen binding to, 97, 98, Color Plate 5
blocking of, 165
interaction and activation of superantigen interaction with MHC II molecules and, 114, Color Plate 10
structure of, 248, Color Plate 16
superantigen binding to, 127–129, Color Plate 11
variations on, 97–100
superantigens in complex with, 247–248
toxic shock syndrome toxin-1 binding, 128–129
T-cell superantigen
intracerebral
effects of, 170–171, 172–173
T cells
activation by superantigens, 183, 218
diseases caused by, 103
apoptosis of
during superantigen exposure, 164–165
migrating to skin
effects of superantigens on, 141–142
suppressor
in superantigen encephalitis, 173–175
Toll-like receptors
and M. arthritidis interaction
regulation of TLR2 and IL-12p40 by, 45
interaction of superantigens with, 48
M. arthritidis-induced regulation of B7–1 and B7–2 mediated through, 46
susceptibility to disease and, 52
Toxic shock syndrome, 143, 245
and neonatal toxic shock-like exanthematous disease
activation of TSST-1–reactive T cells in, Color Plate 2
expansion of V2 + T cells in, 81, 82
and staphylococcal superantigens, 199, 235–236
and streptococcal superantigens, 199–202, 235–236
as mediated by superantigens, 197
caused by Staphylococcus aureus, 197–198
caused by Streptococcus pyogenes, 198–199
clinical and epidemiological aspects of, 197–199
clinical definition of, 22
conventional therapy of, 204–205
general description of, 81–83
in humans and animal models
superantigens causing, 25–26
intraVenous immunoglobulin therapy in, 197–215
lack of protective humoral immunity in, 204
small nonpeptide inhibitors of, 229–244
streptococcal
and effects of streptococcal superantigens on primates, 13
and necrotizing fasciitis, 209
consequence of superantigen intoxication in clinical studies of, 13–14
epidemiological studies of, 13–14
influence of host genetic background on, 14
superantigen-induced cells and mediators participating in, 231, 232
Toxic shock syndrome-like exanthematous disease neonatal
and adult TSS
expansion of V2 + T cells in, 81, 82
and toxic shock syndrome
activation of TSST-1–reactive T cells in, Color Plate 2
general description of, 81–83
Toxic shock syndrome toxin-1, 105, 121, 199, 229
cartoon model of, Color Plate 1
mucosal penetration by, 29–30
structural differences of, 131
superantigen domain of, 223
T-cell receptor binding site of, 128–129
Tumor necrosis factor alpha
as mediator of shock, 229, 235
Vaginal mucosa
composition of, 29
Viral disease
multiple sclerosis as, 179–180
Viral pathogens
associated with superantigens, 60–61
Viral superantigen(s)
endogenous
weak
affinity model for, 66–68
exogenous and endogenous
Vβ specificity of, 60, 61
in mice and humans, 59–75
Working Group on Severe Streptococcal Infections, 198
Yersinia pseudotuberculosis-derived mitogen a
amino acid sequences of, 78
and mode of T-cell response-biased activation of T-cell
fraction, 80–81
reactive T cells
T-cell receptor Vβ repertoires of, 80
T-cell-dependent toxic effects of, 79–80
tertiary structure of, 79
Yersinia pseudotuberculosis-derived mitogens, 77–79, 122
production by Y. pseudotuberculosis strains, 84
T-cell activation by, 79–81
Yersinia pseudotuberculosis infection
acute and systemic
skin rashes in, 84–85
systemic
general description of, 83–85
pathogenic mechanism of, 86–87
T-cell receptor V expression in, 86

Zinc
and *M. arthritidis*-derived superantigen, 126, 127
and peptide dependence

in superantigen MHC class II interaction, 103–120
for interaction of superantigens and MHC molecules, 109–111
in superantigen function, 125–127, Color Plate 11, 122, 123
interaction of β-chain MHC class II molecules
dependence on, 111–112
site of, 111, Color Plate 9