Homologous Recombination

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INTRODUCTION

Genetic recombination is a fundamental process in biology that operates continually to shape and reshape the genomes of all organisms. It rearranges genes or parts of genes both within and between chromosomes, limits the divergence of repeated DNA sequences, guides the proper segregation of chromosomes at cell division, and promotes repair of damaged DNA. It provides therefore a potent evolutionary force that serves both to promote genetic diversity and to conserve genetic identity. Recent years have seen remarkable progress in our understanding of recombination reactions. Much of this progress stems from the pioneering genetic and molecular analysis initiated by A. J. Clark and P. Howard-Flanders some 30 years ago when the first recombination gene, *recA*, was identified in *Escherichia coli* and shown to be involved in repair of DNA damage (29, 74). RecA is the most crucial component for the homologous (also known as "general") recombination reaction, and the study of its properties over the last 15 years has laid the foundations for in vitro analysis. The number of genes linked with recombination has now grown substantially. Many have been studied in detail, and the point has been reached where we can begin to understand the sequence of protein-DNA interactions that give rise to recombinants in crosses or which lead to repair of chromosomal damage. Homologs and analogs of *E. coli* genes have been discovered in a wide range of bacteria and viruses. More recently, RecA-like proteins have been discovered in yeasts and higher eukaryotes, including humans, which suggests that a similar reaction mechanism operates in all organisms (159, 204, 205). The genetics and biochemistry of homologous recombination have been the subject of excellent recent reviews (30, 92, 246). We focus here on recombination during genetic exchange in *E. coli* and *Salmonella typhimurium* (official designation, *Salmonella enterica* serovar Typhimurium) and on related aspects of DNA repair. Recombinational exchanges associated with other types of DNA rearrangement (site specific, transpositional) are reviewed elsewhere in this volume (see chapters 124, 125, and 140). Aspects of recombination leading to chromosomal rearrangements are reviewed in detail in chapter 120, and recombinational repair is discussed in further detail in chapter 121.

HOMOLOGY AND RECOMBINATION

Homologous recombination involves exchanges between DNA molecules (or parts thereof) of identical or nearly identical sequence for considerable distances along their length. How "long" do these homologous sequences have to be? As mentioned above, RecA function, which brings about pairing of homologous strands (see below), is central to the homologous reaction. Figure 1 illustrates the relationship between the requirement for RecA and the length of homology in a variety of recombination systems. For homologies greater than 1 kb, it is generally observed that virtually all crossover events are RecA mediated. For smaller homologies, however, it is now clear that RecA-independent mechanisms can come into play. It is also evident that homology-dependent crossovers, in some cases RecA dependent, occur between homologies as short as 23 bases (Fig. 1) although more substantial frequencies of events are not observed unless homologies are in the 50- to 100-base range (82, 193, 203, 244). The functions required to produce the RecA-independent homologous crossovers are not known at present. Length of homology is clearly a factor, but the structures of the particular replicons involved

must also be important (Fig. 1), and various replication-related activities are probably involved (see references to Fig. 1). In all of the recombination systems discussed below, the lengths of homology involved are in the 1-kb range or greater and the events are almost always RecA dependent.

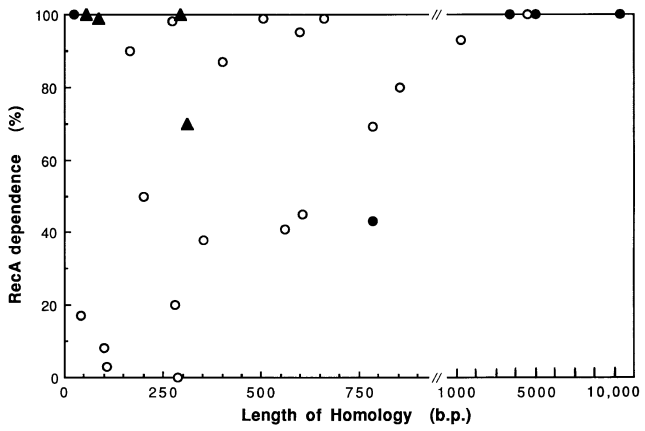

FIGURE 1 RecA dependence of recombination frequency or rate on length of DNA homology between recombining substrates, using various recombination systems. Open circles refer to tandem or inverted duplications on ColE1-derived replicating plasmids (15, 39, 42, 86, 101, 123, 124, 140, 144, 166, 193, 223, 258, 260, 261). Closed circles refer to duplications on the chromosome or large F-prime factors (24, 109, 123, 132, 187, 193, 195). Closed triangles refer to recombination between a plasmid and infecting λ (red-) bacteriophage (82, 194, 244). Absolute recombination frequencies range from 2.3 x 10^{-6} to 1.5 x 10^{-1}, depending on the system and the length of homology involved.

HETERODUPLEX JOINTS

Exchanges between homologous DNA molecules require breakage and reunion of DNA chains and generally, although not always, conserve the integrity of the chromosome. The precision of recombination is achieved by the simple expedient of pairing complementary single strands from each molecule to form a heteroduplex joint. Proper base pairing registers homology and thus provides the key to this “legitimate” exchange. Illegitimate and homeologous exchanges (i.e., between regions of poor homology) can be aborted at this stage by enzymes that recognize base pair mismatches and dismantle the heteroduplex intermediate.

Three kinds of reactions have been considered for the production of heteroduplex joints. The first involves annealing of homologous single-strand tails created at DNA ends to form a recombinant with an internal heteroduplex joint (Fig. 2a). The second stems from the Holliday model (71), which invokes a reciprocal exchange between two duplexes of single strands of the same polarity (Fig. 2b). When the exchanged strands are nicked, they are free to interwind with their complements and form plectonemic heteroduplex joints which link the two molecules together at the point of strand crossover via a Holliday junction (71). The symmetrical Holliday structure remains central to most current models of recombination, even if some other features of the original Holliday model have been found wanting (215). Further processing of the Holliday intermediate by symmetrical strand cleavage (resolution) and religation leads to recombinant molecules of either the crossover type (splices), where there is an exchange of flanking DNA arms, or noncrossover type (patches), where the DNA arms retain their parental configurations. In the absence of any chain breaks, an unstable, noninterwound paranemic joint is formed.

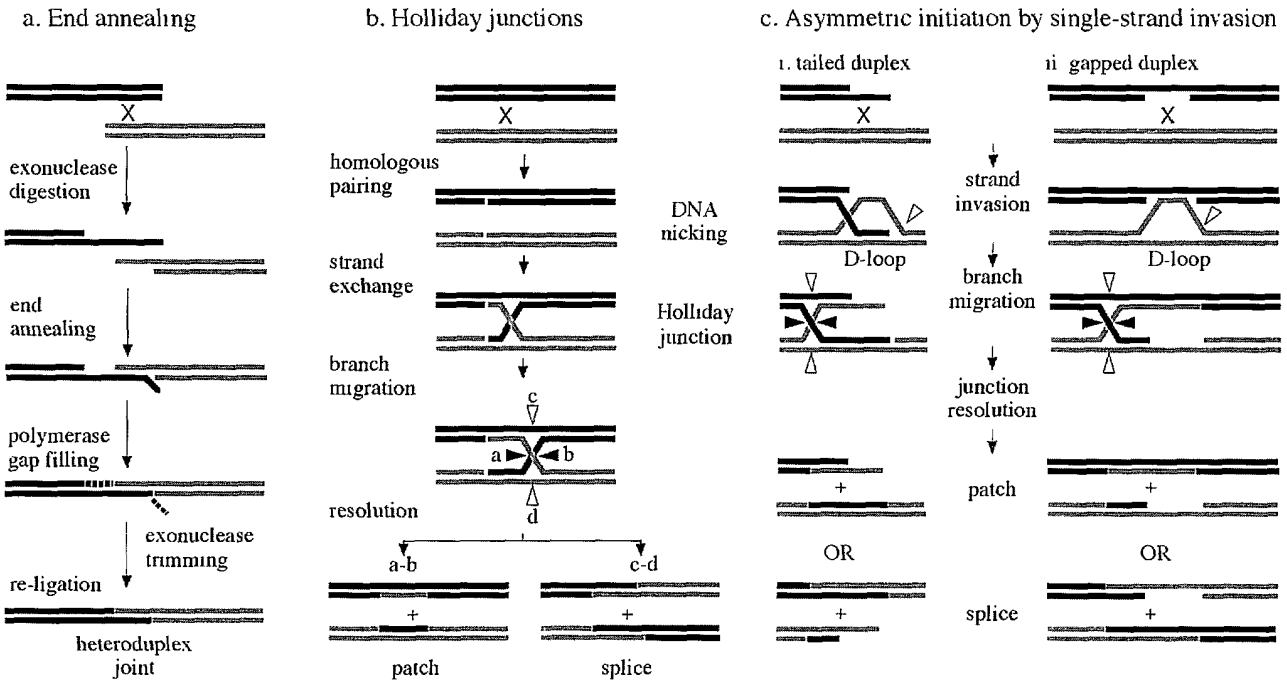

FIGURE 2 Schematic diagrams showing possible molecular mechanisms for the formation of heteroduplex joints. Arrowheads indicate sites of strand nicking.

The third involves interactions between intact and partially duplex molecules with either a single-strand tail or a gap (Fig. 2c). The single-stranded region invades the intact duplex and pairs with its complement, displacing the other strand into a D-loop. A tailed substrate can lead directly to a plectonemic joint, although the extent of the D-loop is limited by tortional stress. A gapped substrate will run into a similar problem but is also limited to a paranemic joint until there is further strand cutting. In both cases, the initial exchange is asymmetric and leads to a three-strand joint. Strand cutting coupled with migration of the branch point into duplex-duplex regions leads to a Holliday junction, which can then be resolved.

Three-strand junctions are likely to be particularly important early intermediates in recombination since most exchanges in vivo are probably initiated by single-stranded regions of DNA (110). Invasion by a 3′ tailed molecule also provides a link with DNA replication by priming new DNA synthesis. The two 3′ ends flanking a double-strand break or gap can be coordinated to recover the missing information as shown in Fig. 3 (5, 224). These reactions lead to Holliday junctions which can be resolved as before or aborted to allow annealing of the extended 3′ ends, at least in theory.

In essence, therefore, homologous recombination can be viewed as a sequence of reactions that form and then resolve heteroduplex intermediates. Recombination in vivo is complicated by the diversity of substrates encountered, the large number of genes involved, some of which have redundant activities, the overlap with repair of damaged DNA, and the possibility of diverting intermediates into replicative pathways. However, the picture is clearing as the biochemical activities of the proteins involved are revealed, allowing them to be linked with a particular stage or stages in the recombination reaction. Before we turn to the enzymology, we shall describe the genes identified and some of the genetic and molecular studies that have shown their involvement with recombination reactions. We concentrate mainly on the *E. coli* system and mention comparisons with *S. typhimurium* in a later section.

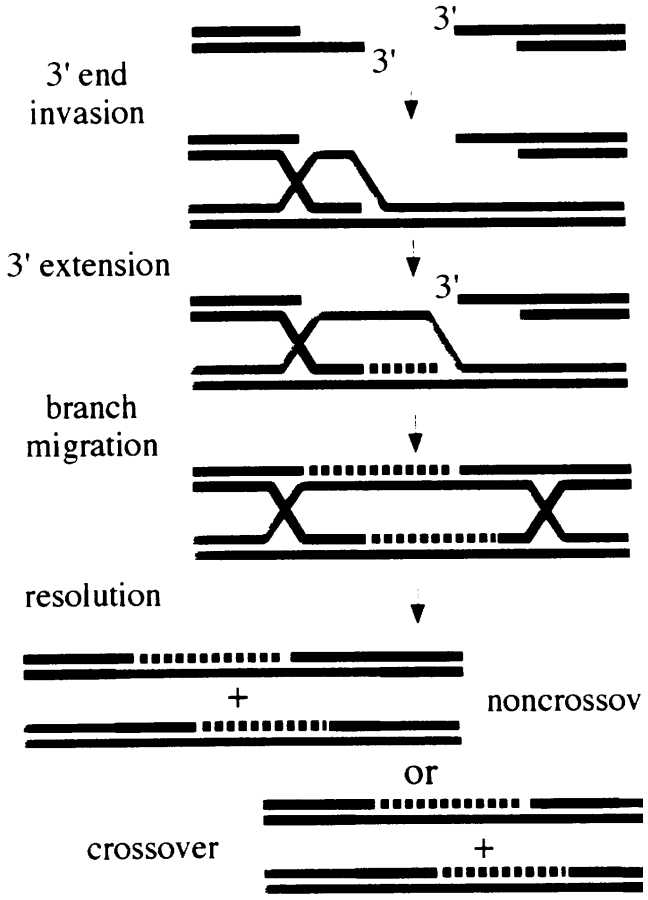

FIGURE 3 Model for repair of a DNA double-strand break by d'-end invasion of an intact duplex coupled with DNA synthesis (dashed line).

GENETIC ANALYSIS

Recombination Genes

The first gene (*recA*) was identified by mutations that block recombination in Hfr × F^- crosses (29). This seminal work also revealed *recA* mutants to be sensitive to radiation, which established a direct link between recombination and repair. A screening of other radiation-sensitive mutants quickly revealed additional *recA* alleles and two new recombination genes, *recB* and *recC* (49, 74, 256). Since those early studies, mutations in more than 30 other genes have been have been shown to affect recombination. Table 1 summarizes what is known about these genes and their products. With the exception of *recA, recB,* and *recC,* mutations in these genes have little (<10-fold) or no effect on the efficiency of recombinant formation in Hfr crosses. Many were identified initially through defects in repair (e.g., *lexA, recN, recQ, recR, ruv*) or in some other aspect of DNA metabolism (*gyrAB, helD, lig, polA, ssb*). Others were discovered through mutations that increase (hyperrecombination phenotype) or reduce recombination in certain types of genetic crosses (*recO, mutH, mutL, mutS, topA, uvrD, xse*) or in particular genetic backgrounds (*recF, recJ, recE, recT*). *recD* was found through its effect on DNA breakdown and plasmid stability. Several other genes involved with various aspects of DNA metabolism have been linked with recombination but have no obvious role in the formation of recombinants (*dam, dut, xth, rdgB*). Mutations at these loci confer a hyper-Rec phenotype (33, 88, 137, 263).

Suppressors

The defects in conjugational recombination and DNA repair in *recB* and *recC* strains are suppressed by mutations called *sbcA* located within the defective Rac prophage. These suppressors appear to be promoter mutations that activate expression of the *recE* gene of Rac and also of *recT*, which partly overlaps the C-terminal end of *recE* (31). The product of *recE* (exonuclease VIII [ExoVIII]) is thought to replace ExoV (the product of *recB*, *recC*, and *recD*) in the presynaptic stage of recombination. A second class of *recBC* suppressors was identified in strains lacking the Rac prophage. These were found to carry mutations in *sbcB*, which encodes exonuclease I, a 3′-to-5′ single-stranded DNA (ssDNA) exonuclease (99). *sbcB* suppressors are missense mutations eliminating the 3′-to-5′ ssDNA exonuclease but which leave ExoI protein with some unspecified activity needed to restore recombination and repair. Deletions, and other *sbcB* null mutations (*xonA*), restore repair but not recombination (168). Genetic analysis of recombination-proficient *recBC sbcB* strains revealed an additional mutation in a gene called *sbcC* (114). The *sbcC* mutation is needed for full suppression of *recBC* and accumulates spontaneously during the growth of *recBC sbcB* strains because it improves viability. Mutations in another gene, *sbcD*, located immediately downstream of *sbcC* have the same effect (60). Interestingly, strains carrying mutations in *sbcC* or *sbcD* alone provide improved hosts for the propagation of λ phages carrying a long palindrome in their DNA (21, 60). SbcC and SbcD proteins together specify an ATP-dependent exonuclease active on double-stranded DNA (dsDNA) (J. Connelly and D. R. F. Leach, unpublished data) which, like ExoI, may destroy potential substrates for recombination in strains lacking ExoV (94). They may also form part of a postreplicative surveillance mechanism for the repair of large DNA secondary structures (hairpins and cruciforms) arising from various misalignments of single strands at the replication fork (104).

TABLE 1 *E. coli* recombination genes, suppressors, and related functions[a]

Gene	Location	Product (kDa)	Activity	Function	Mutant phenotype	Reference(s)
Recombination genes						
recA	60.8	37.8	DNA binding; makes RecA-DNA filament; ATPase; coprotease	DNA pairing and strand exchange; SOS control; SOS inducible	Rec$^-$ and repair deficient; SOS noninducible	29, 92, 246
recB	63.6	135	Subunits RecBCD-dsDNA (ExoV) and ssDNA exonuclease and endonuclease, ATPase, DNA helicase; Chi recognition	Makes 3′ tailed duplex DNA via helicase and strand-specific exonuclease	Reduced DNA breakdown; inactive Chi. Null *recBC* strains are cRec$^-$ and repair defective and have low viability; *recD* strains are hRec.	49, 92, 228, 255
recC	63.7	125				
recD	63.5	67				
recE	30.4	96	5′-3′ dsDNA exonuclease (ExoVIII)	Resects duplex molecules to give 3′ ssDNA tails	Rec$^-$ and repair defective in *recBC sbc* strains	80, 87
recF	83.5	40	Binds ATP and DNA	Helps RecA synaptic filament; SOS induction	Reduced repair, pRec$^-$; cRec$^-$ in *recBC sbc* strains	72, 86, 92, 236
recG	82.4	76	DNA binding; 3′-5′ junction helicase	Branch migration of strand exchange intermediates	Reduced Rec and repair; synergistic with *ruv*	115, 251, 253
recJ	65.4	53	5′-3′ ssDNA exonuclease	Makes 3′ tailed duplex DNA for RecA?	pRec$^-$ and cRec$^-$ and repair defects in *recBC recD* strains	125, 128
recN	59.1	64	ATP binding	Unknown; SOS inducible	Defective repair; cRec$^-$ in certain strains	116, 120, 169
recO	58.0	26	ssDNA binding and renaturation	Helps RecA synaptic filament	Reduced repair, pRec$^-$; cRec$^-$ in *recBC sbc* strains	86, 149, 236
recQ	86.3	70	3′-5′ DNA helicase	Unwinds duplex DNA; SOS inducible	cRec$^-$ in *recBC sbcBC* strains	152, 237
recR	10.6	22	ATP binding	Helps RecA synaptic filament; SOS induction	Reduced repair, pRec$^-$; cRec$^-$ in *recBC sbc* strains	133, 134, 236
recT	30.4	33	ssDNA binding and renaturation	Promotes DNA pairing	Reduced Rec and repair in *recBC* and *recBC sbc* strains	31, 65
rusA	12.3	14	Endonuclease; cleaves Holliday junctions	Resolution of Holliday intermediates	None detected	201
ruvA	41.9	22	DNA binding, specifically to Holliday junctions	Holliday junction recognition; SOS inducible	MC^s γ-ray^s UV^s. SOS-induced cell filamentation; reduced viability, reduced or abortive Rec; synergistic with *recG*	162, 200, 220, 249
ruvB	41.9	37	5′-3′ junction-DNA helicase	Branch migration of Holliday junctions; SOS inducible		
ruvC	42.0	19	Endonuclease; cleaves Holliday junctions	Resolution of Holliday junctions		
Suppressors						
sbcA[b]	30.4		See *recE* and *recT*	Activates expression of *recE* and *recT*	Suppression of *recB* and *recC*	8
sbcB	44.9	53	3′-5′ ssDNA exonuclease	Inactivation of ExoI	Partial suppression of *recBC*	98, 168
sbcC	8.9	118	ATP-dependent exonuclease?	Unknown	Cosuppressors of *recB* and *recC*	60, 114, 153
sbcD	8.9	45				
rus-1	12.3			IS*2* insertion activates *rusA*	Suppressor of *ruvA*, *ruvB*, and *ruvC*	135; —[c]

(Table continues)

TABLE 1 *Continued*

Gene	Location	Product (kDa)	Activity	Function	Mutant phenotype	Reference(s)
srfA = *recA*	60.8		Modified RecA	Improved ssDNA binding	Suppression of *recF, recO,* and *recR*	238, 243
srgA	88.5		Unknown		Suppressor of *recG* linked to *prtA*	—[d]
srjB	22.1		See *helD*	Inactivation of topoisomerase I	Partial suppression of *recJ*	127
srjC	86.1		See *uvrD*	Alteration of helicase II activity	Partial suppression of *recJ* with *srjB*	127
xonA	44.9	53	See *sbcB*	Inactivation of ExoI	Suppression of repair defect in *recBC* strains	168
Replication- and repair-related genes						
gyrA	50.3	97	Subunits of DNA topoisomerase II	Negative supercoiling of DNA	Reduced pRec	242
gyrB	83.5	90				
helD	22.1	75	DNA helicase IV	Unwinds 3′ tailed duplex DNA	Rec$^-$ with *uvrD*	145
lexA	91.6	24	Binds promoters of SOS genes	Repressor of SOS genes	Altered SOS control	240
lig	54.5	75	DNA ligase	Sealing DNA nicks	Defective repair and Rec	91, 107
mutH	63.9	25	Binds hemimethylated GATC	Mismatch repair	Mutator; hRec	51, 147
mutL	94.7	70	Assembly of MutHLS	Postsynaptic monitoring of hDNA?	Mutator; hRec	51, 147, 257
mutS	61.5	97	Binds DNA base pair mismatches	Postsynaptic monitoring of hDNA?	Mutator; hRec	51, 147, 257
polA	87.2	103	DNA polymerase I	Repair DNA synthesis	UV and MMS sensitive; hRec	63, 88
prtA	88.5	76	3′-5′ DNA helicase; binds *pas* DNA sequences	Assembles active primosomes for DNA synthesis	UV sensitive; reduced recombination; defective growth and cell division; chronic SOS induction	105, 106, 138, 155, 156
ssb	92.0	19	ssDNA binding	Melts secondary structure in ssDNA	Altered Rec and repair	146
topA	28.6	100	DNA topoisomerase I	Formation of plectonemic joints?	Sensitive to DNA damage; pRec$^-$	45, 57
uvrD	86.1	82	DNA helicase II	dsDNA and hDNA unwinding? SOS inducible	UV^s MMS^s; mutator and hRec	51, 111, 136, 143, 148, 263
xseA	56.5	52	Subunit of DNA exonuclease VII	ExoVII degrades linear ssDNA in the 5′-3′ direction	Defective repair and recombination; hRec	22, 133

[a]Associated genes/functions are grouped by vertical lines. Additional references are given in the text. Abbreviations: MC, mitomycin; MMS, methyl methanesulfonate; Rec, recombination; cRec, conjugational recombination; pRec, plasmid recombination; hRec, hyperrecombination; hDNA, heteroduplex DNA; superscript s, sensitive; superscript –, deficient.
[b]Not a gene; defines mutations in the Rac prophage which activate *recET*.
[c]Mahdi et al., unpublished
[d]A. A. Aldeib, A. A. Mahdi, and R. G. Lloyd, unpublished data.

Mandal et al. (135) described a suppressor of *ruv* mutations. DNA sequence analysis identified the mutation, *rus-1,* as an IS*2* insertion within an open reading frame (*orf151*) encoding a protein of unknown function (A. A. Mahdi, T. N. Mandal, G. J. Sharples, and R. G. Lloyd, unpublished data). Approximately 500 bp downstream is another *orf* encoding a 14-kDa protein which functions as a Holliday junction resolvase, like RuvC (201). Overproduction of the resolvase suppresses *ruvA, ruvB,* and *ruvC* mutations (201) (Mahdi et al., unpublished). The structural gene for the resolvase has been named *rusA,* while the IS*2* insertion upstream has been renamed *orf151*::IS*2.* The insertion most likely functions as a suppressor by promoting expression of *rus.* IS*10,* which has an outward-facing promoter, also suppresses *ruv* mutations when inserted upstream of *rusA* (Mahdi et al., unpublished).

Certain functional alleles of *recA* act as partial suppressors of *recF* mutations. In the case of *recA803* (= *srfA*), the mutation increases RecA's affinity for ssDNA and improves its ability to compete with SSB (129, 130). *recA803* also partially suppresses *recO* and *recR* mutations (243). Weak suppressors of *recJ* (*srj*) have been identified as alleles of *helD* or *uvrD,* revealing a possible role for these helicases in recombination (127). A link with DNA replication has been revealed by a suppressor (*srgA*) of *recG* located in or near *priA* (A. A. Aldeib and R. G. Lloyd, unpublished data). The PriA protein is involved in primosome assembly and translocation. Like RecG, it binds specific secondary structures in DNA and has 3′-to-5′ DNA helicase activity (106, 155, 253).

Recombination Systems

Before mentioning some of the molecular events particular to the three best-studied recombination systems (Hfr crosses, plasmids, and λ crosses), it should be emphasized at the outset that a large variety of approaches to the analysis of recombination have been used, both in vivo and in vitro, and the functional requirements for these systems have been found to vary widely. In Table 2 we list the majority of the in vivo systems of homologous exchange which have been used in *E. coli* and *S. typhimurium* to date. The systems which involve rearrangements of the haploid (and/or partially diploid) chromosome are reviewed in much more detail in chapter 120.

MOLECULAR ANALYSIS OF GENETIC EXCHANGE

Conjugational Recombination

Conjugation has been used primarily for genetic analysis of recombination. It has also provided some molecular insights, although these have been limited because of the poorly defined nature of the DNA substrate(s) involved. During conjugation, a single strand of donor (Hfr or F-prime) DNA is transferred to an F^- recipient, where it provides a template for lagging-strand synthesis (see chapter 126). While transfer is in progress, the leading 5′ end is probably attached to DNA helicase I at the site of DNA transfer so that in effect a growing loop of partially duplex DNA is presented to the recipient. When mating terminates, the transferred DNA is released as a linear fragment with a ~40-kb segment of F-plasmid DNA extending from *oriT* at the leading end and a single-strand overhang of variable length at the distal 3′ end because of the failure to complete the complementary strand by lagging-strand synthesis. Recombinants arise from exchanges between this fragment and the circular recipient chromosome (see references 117 and 211 for recent reviews).

Siddiqi and Fox (207) were able to demonstrate covalent joining of single strands of donor and recipient DNA. The recombinant molecules detected were consistent with displacement of single strands of recipient DNA by the strands of the donor. These exchanges incorporated donor fragments ranging from about 0.15 to 3 kb. Intriguingly, the donor strand appeared to be mostly joined to newly synthesized recipient DNA, suggesting that the exchange is connected with replication. We postpone

further discussion of this feature of recombination until a later section. No insertions of dsDNA were observed. However, the experiments were biased toward detecting single-strand insertions. Long double-strand insertions in particular would not have been revealed by the analysis conducted. More recent studies with both *E. coli* and *S. typhimurium* have provided compelling genetic evidence for such exchanges (117, 141, 211). In matings where a relatively short section of Hfr DNA is transferred, most recombinants inherit the Hfr DNA in a single section, with the two exchanges needed for integration located near the ends of the transferred fragment. The focusing of exchanges near the ends is less marked in matings where a longer fragment is transferred. Multiple exchanges are also noticeably more frequent (117). The single-strand insertions detected by Siddiqi and Fox (207) probably reflect the joints made by the splice exchanges associated with double-stranded Hfr DNA integration (117). Double-strand insertion is also supported by the fact that recombinant formation requires the activity of Holliday junction resolvases (112).

Birge and Low (17) detected recombinant DNA by measuring β-galactosidase in crosses between strains carrying different, noncomplementing, *lacZ* mutant alleles. Enzyme production depends on RecA-mediated recombination to form transcribable *lacZ*$^+$ DNA. However, they also found that while the yield of lacZ+ recombinant colonies was reduced 100-fold or more in recB or recC strains, enzyme production was reduced by 2-fold at most. They concluded that recombination could initiate by an efficient recBC-independent mechanism but that the intermediates formed could not be processed to viable products. The production of these transcribable intermediates was shown subsequently to require the functions of recF, recO, and recJ (119). These observations confirmed earlier predictions that different protein-DNA substrate combinations provide alternative routes for the initiation of recombination (25–27).

Plasmid Recombination

Plasmid molecules have been used extensively for the analysis of recombination. Initial studies focused on exchanges between plasmids or within circular dimers and revealed a requirement in the wild type for *recA*, *recF, recJ, recO,* and *recR* but not for *recB, recC,* or *recD* (14, 86, 101, 128, 133). With increasing refinement of the substrate and the use of *recBC sbcA* or *recBC sbcBC* strains, most of the remaining genes have been implicated in the formation of recombinants (84, 96, 128, 158, 226, 227, 259). The *recF, recJ, recO,* and *ssb* genes have also been implicated in mismatch repair of plasmid heteroduplexes (53).

TABLE 2 In vivo or semi-in vivo recombination systems and *rec* gene dependence (*E. coli* and/or *S. typhimurium*)

Recombination system	Rec function requirement[a]			Reference(s)
	Major	Minor or none	Inhibitory	
Occurring during vegetative growth				
Chromosomal duplications				
Formation	*recA*	*recB*[b]		67, 195
Formation, homeologous	*recA, recB*	*mutH, uvrD, recF*	*recF*[c], *mutL, mutS*	109, 167, 187
Resolution (deletion)	*recA* [*recB* or *recF*]	[*recB* or *recF*]		3, 24, 132
Inversion	*recA, recB*			193, 195
Long-range gene conversion (starved cells)	*recA, recB, gyrB, osmZ*	*recF, sbcB, xseA, recN, recQ,* (*ruvA*), (*ruvC*)	*uvrD, dam, dut, xth, sbcB*[d]	44, 88, 89, 262, 263
F-prime–chromosome	*recA, recB*			32, 254
F-prime–chromosome (starved cells)	*recA, recB polA*, SOS			214
Plasmid-chromosome				—[e]
Plasmid-plasmid (intra- or inter-)				
In *rec*$^+$	*recA, recF, recJ, recO, recR, ssb, topA*	*recB, recC, recN, ruvB*[f], *mutH, mutL*	*recD, uvrD*	14, 35, 36, 42, 54, 56, 57, 79, 84, 86, 101, 126, 157, 166, 260, 261
In *recBC*$^-$ *sbcA*$^{-g}$	*recE,* (*recF*), (*recJ*), *recN, recO, recQ, ruvB, mutS*	*recA*	*recBC*	35, 42, 54, 101, 128, 226, 260
In *recBC*$^-$ *sbcBC*$^{-g}$	*recA, recF, recJ, recO, ruvB, mutS*	*recN, recQ*		128
Plasmid, in vivo restriction, in *recBC*$^-$ *sbcA*$^-$	*recE*		*recA*	158, 208, 209
Occurring following gene transfer				
Conjugation				
Hfr × F$^-$ (*rec*$^+$)	*recA, recB, recC,* [*recG* or *ruvA*], *recF*[d,j], *recJ*[d,j], *recO*[d,j]	*recD, recE, recF*[h], [*recG* or *ruvA*], *recJ, recN, recO, recQ*[h], *recR, recB*[l], *ruvC, uvrD, helD*	*mutH*[i], *mutL*[i], *mutS*[i], *uvrD*[i]	17, 51, 113, 115–119, 133, 135, 186
Hfr × F$^-$ (*recBC*$^-$ *sbcA*$^-$)	*recA, recE, recF, recG, recJ, recO, recQ, recR, recT, uvrD, helD*	*recN*		116, 118, 133, 145
Hfr × F$^-$ (*recBC*$^-$ *sbcB*$^-$ *sbcC*$^-$)	*recA, recF, recJ, recN, recO, recQ, recR, ruvA, ruvB, ruvC,* (*recG*), [*uvrD* or *helD*]	[*uvrD* or *helD*]	*sbcB, sbcC*	13, 116, 118, 133, 135, 145, 152
Hfr × F$^-$ (*recD*$^-$)	*recA, recC, recG, recJ, recN*	*recF, recO, recQ, recR, ruvB*		116, 117, 120, 126, 133
(F′ × F$^-$) × F$^-$	*recA*	*recB, recC*		64, 254
Hfr ×F$^-$/plasmid				170
F′ × F$^-$/plasmid				170
Transformation				
Linear chromosomal	*recA*		*recBC*	37, 70, 160, 161
Linearized plasmid				
In *rec*$^+$	*recA, recJ*	*recB, recC, recF*		223
In *recBC*$^-$ *sbcA*$^{-g}$	*recE, recT*	*recA, recBCD, recF, recG, recJ, recO, recN, recQ, recR, ruvB, mutS*		84, 97, 128, 223, 226
In *recBC*$^-$ *sbcBC*$^{-g}$	*recA, recF, recJ, recO, recQ*	*recN, ruvB, mutS*		55, 58, 128
Heteroduplex plasmid	*recF, recJ, ssb*	*recA, recBC, recN,* (*recO*), *ruv*		53, 56, 58
Generalized transduction	*recA, recB, recC, ruvB*	*recD, recF, recJ, recO, recN, recQ, sbcB, dam, uvrD, xth*	*sbcB*[d] *sbcCD*[k]	13, 68, 126, 139, 154, 256, 262, 263
Specialized transduction				
To chromosome	*recA, recJ*[j,l], *uvrD*[j,l]	*recB, recF, recJ*[j]	*sbcB*[d]	43, 66, 172–174, 192, 239, 245
To nonconjugative plasmid	*recA, recB*[l]	*recB*	*recB*[i], *sbcB*[d]	170
To F′ factor	*recA, recBC, recD, traY, traI*			20a, 170–173, 196
To (F′ × F$^-$) (conjuduction)	*recA*	*recB*		173

(Table continues)

TABLE 2 *Continued*

Recombination system		Rec function requirement[a]	Reference(s)
To another transducing phage	*recA, ssb*[j]	*recB*[j]	52, 61, —[m]
Phage infection			
Phage crosses	See text		
Phage-prophage crosses			
Homoimmune[a]	*recA*	*recB, recF*	52, 73, 108
Heteroimmune	*recA, red*		18
Tandem-duplication phage resolution[l]	*recF*	*recB*	66
Inverted repeat on phage	*recA, recB, polA*	*recF, dnaB*	50, 83

[a]Major requirement: greater than fivefold decrease in singly mutant strain. Gene symbols within brackets indicate little effect unless doubly mutant. Gene symbols within parentheses indicate approximate fivefold decrease. Gene symbols as in the text, Table 1, chapter 109, and chapter 126.
[b]The number of apparent gene conversions, however, is greatly reduced in *recB*$^-$.
[c]In *mutL*$^-$ or SOS-constitutive background.
[d]In *recB*$^-$ background; partial activity of *sbcB* may be required.
[e]See chapter 137.
[f]Ruv activity is required for some plasmid recombination events of the double-crossover type (28).
[g]Plasmid recombination occurs more than 10-fold more frequently in *recBC*$^-$ *sbcA*$^-$ or *recBC*$^-$ *sbcBC*$^-$ than in a *rec*$^+$ background.
[h]Whereas blocks in RecF or RecQ function have little effect on the frequency of recombination in this background, the average distance between crossovers, using *recF*$^-$ *recQ*$^-$ strains, is much greater than with *rec*$^+$ strains (103, 117).
[i]Mutation in any of these genes results in elevated intragenic recombinant production (51).
[j]Transcribable intermediate.
[k]In *recB*$^-$ *sbcB*$^-$ background, *E. coli.*
[l]Damage induced.
[m]M. Capage, R. D. Porter, A. Kolodkin, and K. B. Low, unpublished data.

In strains lacking ExoV, plasmids tend to recombine with a higher than normal frequency, forming higher oligomers and linear multimers, which causes problems at cell division and often leads to plasmid loss (16, 34, 95). Plasmid recombination in *recBC sbcA* strains is particularly unusual in that it proceeds without RecA and requires instead RecE and RecT (96, 128, 226). λ Redβ protein will also substitute for RecA in *recBC sbcBC* strains (14). The absence of ExoV is thought to conserve DNA ends generated by rolling-circle plasmid replication, which then provoke exchanges with other molecules (14, 34). However, Takahashi et al. (227) suggested an alternative mechanism for *recBC sbcBC* strains, first postulated for λ crosses (see Fig. 4, next section), in which a nonreciprocal break-join event (half-crossover or nonconservative exchange) between two molecules creates a recombinant molecule plus DNA ends that can stimulate further rounds of recombination. Successive rounds of nonreciprocal break-join exchanges have also been used to explain gene conversion without crossing over in this genetic background (259).

Several groups have used plasmid substrates to investigate the effect of DNA ends on recombination (84, 96, 126, 128, 158, 208, 209, 223, 226, 227). A double-strand break or gap is introduced into the substrate within a region of homology. The formation of a recombinant requires recircularization of the molecule. Because of the destructive effect of ExoV on linear DNA molecules, these studies have been restricted largely to *recD, recBC sbcA,* and *recBC sbcBC* strains. Recombination appears to be stimulated 10- to 100-fold by the DNA ends created. In the *recBC sbcA* background, or other strains carrying an *sbcA* mutation, there is evidence of efficient gap repair by a conservative mechanism involving copying of the intact homolog (gene conversion), with or without crossing over of flanking DNA (Fig. 3). Repair requires RecE and RecT but is independent of most other recombination proteins, including RecA, RuvC, and RecG (96, 226). The absence of any clear requirement for Holliday junction resolvases suggests that 3′ strands flanking the gap invade the intact homolog and are then extended by new DNA synthesis to recover the missing information before being reannealed (96). However, the possibility that Holliday junctions are formed but are resolved by some unknown activity cannot be excluded. No gap repair has been detected in other backgrounds. Double-strand breaks stimulate recombination in *recBC sbcBC* strains but via successive rounds of nonreciprocal break-join exchanges of the type first detected with phage λ (217, 219, 226).

Recombination of Phage l

The effect of DNA ends on recombination has received particular attention in phage λ crosses, where exchanges can be monitored by genetic and physical methods. Double-strand breaks are introduced naturally at *cos* sites by the packaging enzyme terminase which remains bound to the left end of λ DNA (as normally drawn) during the maturation process. The right end is free and provides a potent initiator of recombination, as do the DNA ends flanking a cut made by a restriction enzyme (for reviews, see references 206 and 231). λ encodes two proteins that catalyze homologous recombination, Redα or λ exonuclease, which digests duplex DNA in the 5′-to-3′ direction to leave 3′ overhangs, and Redβ, which catalyzes homologous pairing and strand annealing (151). When replication is blocked, recombination catalyzed by the Red system is focused near λ's right end. Stahl et al. (217) proposed a nonreciprocal break-join model for the exchange in which a 3′ single-strand tail generated at the right end by λ exonuclease invades an intact homolog to form a D-loop (Fig. 4). Appropriate nicks and ligations, coupled with limited DNA synthesis to extend the 3′ end, lead to a recombinant molecule which can be packaged from the terminase-bound *cos* at the left end (216, 231). The invaded homolog makes a minor contribution to the recombinant molecule at the right end. If replication is allowed, exchanges are more evenly distributed. This is explained by the fact that the tips of rolling circles are randomly distributed across the chromosome and can therefore initiate exchanges at any point (217).

When λ's own systems for recombination are disabled by *red* and *int* mutations, recombinants are produced by the enzymes of its host, *E. coli.* This normally requires *recA,* and to a lesser extent *recB* and *recC,* and also mutation of λ *gam,* which inhibits ExoV. In *recBC sbcA* strains, λ recombines efficiently without RecA and relies instead on the RecE and RecT proteins, which are functional analogs of λ's Redα and Redβ proteins (27, 87). Indeed, recombination in this background is almost indistinguishable from that catalyzed by λ's Red system (231). Recombination in *recBC sbcBC* strains is efficient and proceeds by a double-chain break and rejoin mechanism. However, in this case it requires RecA and RecJ. The 5′-to-3′ exonuclease activity of RecJ, coupled with RecQ or another helicase, is thought to provide the initiating 3′ tail. Recent studies have demonstrated an additional need for the RecF, RecO, and RecR proteins and to a lesser extent RecQ, if a small reading frame encoding a protein of 15 kDa is deleted from λ's *ninR* region (190, 191). Overexpression of the 15-kDa protein from plasmid constructs allows recombination of λΔ*nin5* phages in *recBC sbcBC* strains mutant for *recF, recO,* or *recR* but does nothing for the host (191).

Recombination of λ *red gam* phages in wild-type hosts is thought to be initiated by RecBCD enzyme entering the DNA at the right end. However, exchanges are distributed across the chromosome, even when replication is blocked. Presumably, the potent dsDNA exonuclease activity (ExoV) of RecBCD enzyme causes extensive degradation of the DNA before recombination can initiate. However, the situation changes dramatically when a Chi sequence (5′-GCTGGTGG-3′) is present in the λ DNA such that RecBCD entering at the right end encounters Chi from the 3′ end. In this case, exchanges are focused near Chi and decrease in a gradient extending leftward for some 10 kb (102).

Chi DNA Sequences and RecBCD Activity

The Chi octamer occurs with a surprisingly high frequency in the *E. coli* chromosome and is found on average every 5 kb or so along the DNA. However, its orientation is nonrandom. The majority are encountered from the 3′ end as drawn above when looking in the direction of the replication origin (*oriC*). The disparity, which is evident in all DNA segments examined, varies considerably and can reach as much as 9:1 (19; A. Kerr and R. G. Lloyd, unpublished analysis). Chi is not present in λ but may arise by mutation at several loci. Much of what is known about Chi sequences and their genetic activity has been derived from studies with Chi^+ phages (for reviews, see references 210 and 213). Chi

interacts specifically with RecBCD and is inactive in strains lacking this enzyme (218). RecBCD is a potent DNA helicase and exonuclease that acts on molecules with flush or nearly flush duplex ends (228). An early model of RecBCD-Chi interaction suggested that when RecBCD encounters a Chi from the 3′ end, the strand containing Chi is cleaved specifically to the right of the Chi sequence and is displaced as the enzyme continues to unwind the DNA to initiate recombination by invading an intact homolog (210).

A rather different model in which Chi acts to modulate the nuclease activity of RecBCD is supported by more recent studies (40, 41, 182). According to this model, RecBCD unwinds and rapidly degrades the strand ending 3′ as it tracks along the molecule, occasionally nicking the strand ending 5′. When it encounters Chi in the correct orientation, it pauses momentarily and the nuclease activity is modulated, possibly through loss of the RecD subunit, such that the strand ending 3′ is no longer degraded but is displaced as a single-strand tail as the RecBC(D) enzyme resumes duplex unwinding and nicking of the 5′-ending strand. The 3′ tail exposed by RecBCD then acts as a substrate for initiation as before (see reference 92 for a review). The model is consistent with the effect of Chi on λ crosses and with the phenotype of *recD* mutants, which lack ExoV activity but retain RecBC function (2). λ recombination occurs with a high frequency in *recD* strains and is insensitive to Chi (23, 230). The exchanges observed are also focused near the initiating dsDNA end when replication is blocked, as might be expected in the absence of ExoV degradation.

RecBCD enzyme is a potent exonuclease (ExoV) and is responsible for the rapid degradation of the chromosome in *recA* cells following irradiation with UV light (74). Modulation of this activity is likely to be important therefore in times of stress. Recent studies have shown that Chi sequences protect linear DNA from ExoV degradation, both in *cis* and in *trans,* which is consistent with a model in which RecBCD is modulated by Chi (38, 100). More than one encounter with Chi may be needed to modulate RecBCD (229). However, full protection against degradation requires RecA. Presumably, RecA engages the 3′ end exposed by RecBC(D) in a recombination reaction, preventing other exonucleases from gaining access (100).

Chi sequences are likely to influence the location of exchanges in *E. coli* crosses presenting linear DNA substrates, as they do in λ. Mutation of *recD,* which inactivates both ExoV and Chi, has been seen to cause polarized changes in linkage in P1 transductional crosses. As with λ, more of the transductants appear to have exchanges near the ends of the transduced DNA fragment than is the case in crosses with *recD*$^+$ strains (120). The tendency for exchange near the ends of Hfr DNA fragments in conjugational crosses may also reflect Chi activity (117, 211, 229). However, the frequent recovery of recombinants from exchanges that seem to have ignored several Chi sites in tandem suggests that another way can be found to initiate conjugational recombination that does not involve RecBCD activity at ends (117) (Kerr and Lloyd, unpublished analysis).

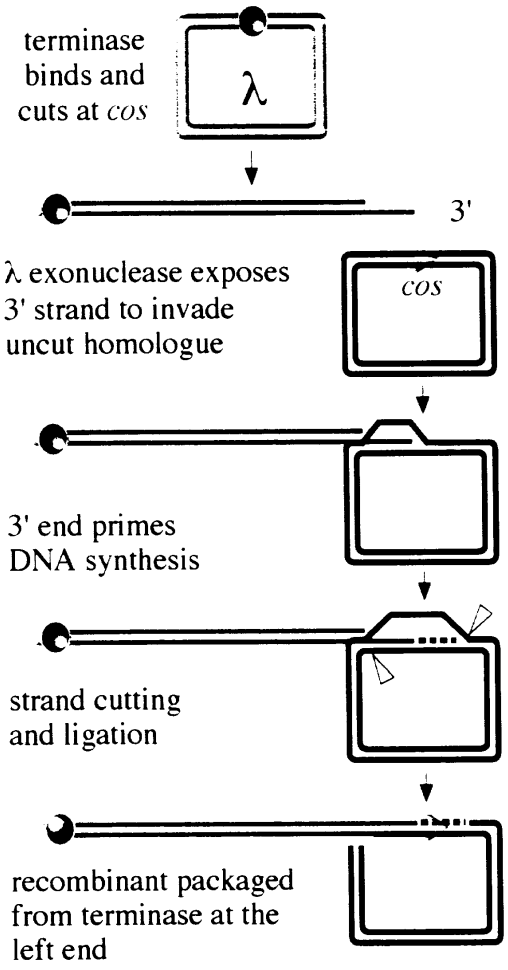

FIGURE 4 Model of break-join recombination catalyzed by the λ Red system. Terminase bound at *cos* is shown as a shaded circle. Arrowheads indicate sites of strand nicking. New DNA synthesis primed by the invading 3' end is shown as a dashed line.

Recombination Pathways

Early studies in *E. coli* were influenced by the idea that conjugational recombination proceeds via one of three largely independent and rather loosely defined molecular pathways called RecBC (later called RecBCD), RecE, and RecF after the first genes linked with these pathways. The RecBCD pathway was thought to predominate in the wild type since single mutations in *recB* or *recC* blocked conjugational recombination, whereas mutations in *recE* or *recF* had little effect. By the same criterion, RecE and RecF were defined as operating in *recBC sbcA* and *recBC sbcBC* strains (25–27). Further genes were classified according to the pathway or pathways in which they acted. However, it soon became clear that the RecE and RecF pathways had many genes in common. The genetic requirements for recombination in the wild type also varied according to the recombination system examined and often involved elements of the RecE and RecF pathways. Furthermore, certain mutations which alone have no substantial effect on conjugational recombination do so when combined in the same strain (e.g., *recG* and *ruv*, *helD* and *uvrD*, or *recD*, *recJ*, and *recN*), thus revealing a degree of functional redundancy (112, 116, 120, 126, 145). The increasing focus on

enzymology has also revealed many features at the molecular level that are similar in wild-type, *recBC sbcA*, and *recBC sbcBC* strains. The time has come therefore to abandon the original "three-pathway" concept and concentrate instead on the enzymology of the recombination reaction. The reader should remember primarily that the three-pathway concept was invoked to refer to three different functional configurations for conjugational recombination, and the use of these terms for other genetic systems distorts and confuses their meaning.

ENZYMOLOGY OF GENETIC EXCHANGE

We have already described how strand exchange and the formation of a heteroduplex joint provide the key to recombination. The enzymology can be considered therefore in terms of the reactions needed to prepare DNA for strand exchange (presynapsis), to catalyze homologous pairing and strand transfer (synapsis), and to process the heteroduplex intermediates into mature products (postsynapsis).

Presynapsis

Molecular studies have provided abundant evidence of the important role of DNA ends as initiators of recombination. The reason for this is now quite clear. RecA and other proteins like RecT that catalyze the synaptic stage need single strands in order to assemble on DNA before they can initiate pairing (93, 246). Ends provide entry points for exonucleases and DNA helicases to expose single strands for these synaptic proteins.

As described already, RecBCD enzyme can expose a 3′ single-strand tail at a duplex end by preferential degradation of the 5′-ending strand after an encounter with Chi. RecJ nuclease, which is required for recombination in the absence of RecBCD, particularly in *recBC sbcBC* strains, may similarly expose a 3′ tail when coupled with RecQ helicase, which is also required for recombination in this background (125). The helicases provided by *helD* and *uvrD* are possible alternatives to RecQ. In *recBC sbcA* strains, RecJ is needed for some systems of recombination but not others (96, 128). The RecE nuclease activated in this background provides another way of producing 3′ tailed duplexes.

All three exonucleases generate a 3′ single-strand tail, the end apparently favored by RecA during synapsis in vitro (see below). ExoI, the product of *sbcB*, digests ssDNA in the 3′-to-5′ direction and is a potent inhibitor of recombination in *recBC* mutants but not in the wild type or in *recD* or *recBC sbcA* strains. The reasons for these differences are not clear. ssDNA generated by RecJ may be exposed to ExoI, whereas RecBC(D) enzyme may hold on to the displaced 3′ end during the unwinding. Similarly, the 3′ end produced by RecE may be protected by the synaptic reaction catalyzed by its RecT partner (65). In the wild type, 5′ single-strand tails may also be exposed following RecBCD-Chi interactions and may allow recombination to initiate in the presence of ExoI (see reference 183).

Duplex ends are unlikely to be the only initiators of recombination in vivo. In conjugational crosses, a 3′ tail is likely to occur naturally at the distal end of the transferred Hfr DNA. However, this may not survive to initiate recombination except perhaps in strains lacking both ExoI and ExoV. Extensive single-strand gaps may arise in DNA following replication of damaged templates or during repair of mismatched bases (147, 184; see chapter 121). Similarly, ssDNA is likely to be exposed, at least transiently, during conjugational DNA transfer.

In order to be recombinogenic, ssDNA has to be made available to the synaptic proteins, RecA and RecT. In the case of RecT, assembly of the presynaptic complex may be coupled with strand exposure by RecE (65). RecA, on the other hand, is likely to have to compete with SSB, *E. coli*'s ssDNA binding protein. SSB stimulates strand exchange catalyzed by RecA in vitro by removing secondary structure from ssDNA and preventing DNA aggregation by RecA. However, the level of SSB is critical and too much inhibits the

reaction (reviewed by Kowalczykowski and Eggleston [93]). Recent studies have suggested that the RecF, RecO, and RecR proteins act together and help RecA overcome any inhibitory effect of SSB in vivo. Mutations in *recF*, *recO*, and *recR* confer similar phenotypes, show no additive interactions, and can be suppressed partly by mutations that increase RecA's affinity for ssDNA (119, 120, 133, 189, 243). RecF and RecO both bind ssDNA (62, 131), while RecO and RecR have been shown to interact in vivo and in vitro and to help RecA promote strand exchange in the presence of SSB (189, 236). It seems likely that these proteins help RecA to displace SSB, allowing RecA to form a synaptic filament. This may provide a way of directing single-strand intermediates into recombination and away from replication (30).

Once ssDNA has been made available, RecA monomers bind cooperatively to the DNA and polymerize in the 5′-to-3′ direction to form a helical nucleoprotein filament that can extend to adjacent duplex regions. The assembly, structure, and properties of the RecA-DNA filament have been described in detail (48, 92, 93, 175, 221, 222, 246). The filament has two functions. First, it activates the SOS response by interacting with LexA, UmuD, and, if present, certain phage repressors and catalyzes their cleavage by autodigestion (241). Cleavage of LexA induces synthesis of many proteins involved in DNA repair, including RecA itself and also RecN, RecQ, and RuvAB (see chapter 89). Second, it catalyzes the homologous pairing and strand exchange stage of recombination.

Synapsis

RecA is the only protein known to catalyze homologous pairing in *E. coli* in the absence of RecT or Redβ, and without it homologous recombination is essentially undetectable. The RecA-ssDNA filament searches for homology by a mechanism that is still not entirely clear but which involves repeated association and dissociation of naked duplex DNA with the filament by non–Watson-Crick base pairing (93, 175–178). Once homologous contacts are made, the duplex is drawn into alignment with the DNA in the filament and the two molecules are paired (76, 77). This has the important consequence of partly unwinding the duplex and extending its length by ~50% compared with normal B-form DNA. The DNA within the filament is already extended. Extending the DNA is critical for the next stage when the paired molecules are driven rapidly to exchange strands and form a paranemic joint. However, the joint is mobile, and when it encounters a strand end, the exchanged strands are free to interwind and form a stable heteroduplex joint. When pairing initiates within a single-stranded region bound by RecA, the exchange leads to a three-stranded junction. However, in duplex-duplex pairings, the exchange is reciprocal and generates a four-stranded Holliday junction when both molecules are nicked in strands of the same polarity. Strand exchange is unidirectional and proceeds with the same 5′-to-3′ polarity as the polymerization of RecA on the initiating single strand.

The mode of action of RecT is less clear. It promotes strand exchange between dsDNA and circular ssDNA in the presence of RecE by a reaction that depends on digestion of the linear duplex by RecE to expose an ssDNA tail, followed by RecT annealing of this tail to the ssDNA circle. Strand exchange can then continue without RecE (65). That RecT is able to promote strand exchange is supported by the ability of *sbcA recA* strains to catalyze double-strand gap repair, a reaction that requires invasion of a homologous duplex by the ends flanking the gap in order to prime DNA synthesis and recover the lost information (96, 226).

Postsynapsis

Following the synaptic stage, RecA can extend the heteroduplex as naked duplex DNA is spooled in one end of the filament and heteroduplex DNA is spilled out the other while the filament grows at the 3′ end and dissociates at the 5′ end (175). Strand exchange continues in the 5′-to-3′ direction but, unlike the initial synaptic exchange, requires hydrolysis of ATP. It also proceeds more slowly.

In *E. coli* two other enzymes, RuvAB and RecG, have evolved to help drive postsynaptic strand exchange (247, 252). Both act catalytically to drive branch migration of Holliday junctions along the DNA. RuvAB is a novel DNA helicase targeted to junction DNA (78, 164, 165, 220, 233–235). A

tetramer of RuvA binds specifically to the junction, folds it into an open configuration (Fig. 5a), and targets the assembly of a hexamer ring of RuvB on each of two homologous arms (Fig. 5b). These rings are asymmetric and face each other across the RuvA-junction complex. The two arms are then rotated through the static RuvAB complex in a reaction driven by ATP hydrolysis that locally unwinds the DNA and moves the junction point along the molecule (69, 163, 220). The RuvB hexamer rings assembled on DNA are also able to remove RecA filaments and therefore may have an additional postsynaptic function in clearing up the DNA when RecA function is completed (1).

RecG behaves in many ways like RuvAB. It is a DNA-dependent ATPase, binds specifically to model Holliday junctions, and dissociates these structures in reactions which depend on hydrolysis of ATP. It also drives branch migration of Holliday intermediates made by RecA (121, 121a, 202, 251). RecG will also unwind partial duplex substrates. The processivity of unwinding is low compared with RuvAB and proceeds with the opposite (3′-to-5′) polarity (253). The helicase activity is improved by incorporating a junction into the substrate, in which case the activity is targeted to the junction point (253). The similar properties of RecG and RuvAB are reflected in vivo, where both enzymes seem to provide overlapping activities to promote recombination and repair (112). However, there is no indication yet that RecG assembles into a structure resembling the RuvB rings. Indeed, the available evidence suggests otherwise (252).

To complete the recombination reaction, it is necessary to remove any junctions linking the substrate molecules together. Two enzymes, RuvC and RusA, have been linked with this stage. RuvC is an endonuclease that resolves Holliday intermediates into recombinant products by a dual-incision activity targeted specifically to junctions which cleaves two strands of the same polarity. RuvC acts as a dimer and folds the junction in a unique configuration that allows the noncrossover strands to be cleaved (Fig. 5c) (4, 9, 10, 225). Cleavage is favored at sequences with the consensus 5′-$^{A/}_{TTT\downarrow}{}^{G/}_{C\text{-}3'}$ (197). Genetic studies indicate that the RuvAB-mediated branch migration reaction is linked intrinsically with the resolution of recombination intermediates by RuvC protein (135). One of the principal functions of RuvAB may be to locate junctions at these sequences (197). RusA behaves remarkably like RuvC, although these proteins show no obvious similarity at the amino acid level. It cleaves junctions by a dual-incision mechanism targeted to particular sequences and leaves ligatable nicks in the DNA (201). However, it does not have the same sequence specificity.

Formation and Resolution of Junctions by RecG

Several observations suggest that RecG is not a simple alternative to RuvAB. First, both *recG* and *ruv* single mutants are sensitive to radiation and somewhat deficient in recombination (113, 162). Second, RecG cannot substitute for RuvAB to facilitate junction resolution by RuvC (135). Third, there is a functional overlap between RecG and RuvC, which indicates that RecG may function to resolve junctions independently of the RuvABC pathway (112). A clue as to how RecG could eliminate junctions has come from studies showing that RecG inhibits heteroduplex formation by RecA in vitro by driving branch migration in the reverse direction to that driven by RecA strand exchange. This has been observed in four-strand reactions (251) but is even more apparent in three-strand reactions (250). In contrast, RuvAB promotes RecA strand exchange in the four-strand reaction (233, 251) but has no effect on the three-strand reaction under the conditions reported (250). The reverse polarity of RecG is presumably dictated by some feature of the RecA filament or of its folding of the junction, since it is not observed with junction intermediates free of RecA. Reverse branch migration has the potential to remove Holliday junctions in vivo by aborting the initial exchange, provided nicks in the DNA remain unsealed. Such an activity may have a significant role both in recombinational repair of UV damage and in eliminating unproductive exchanges in genetic crosses (186, 251).

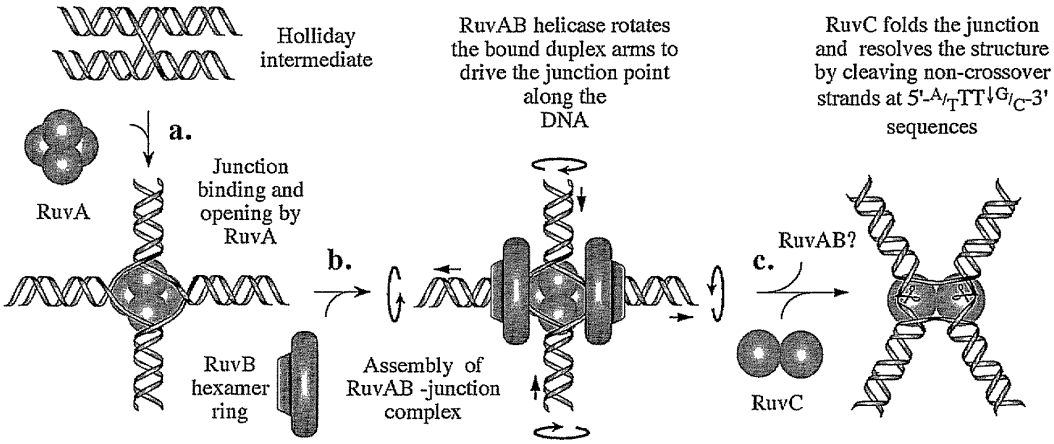

FIGURE 5 Processing Holliday junctions. (a) Junction binding by a tetramer of RuvA and folding of the junction to a square planar configuration. (b) Assembly of RuvB hexamer rings and formation of a RuvAB-junction complex. The arrows next to the arms show the direction of travel as the DNA is rotated through the static RuvAB complex (163). (c) Antiparallel configuration of the RuvC-junction complex resolved by cleavage of noncrossover strands (10).

It is patently obvious however that RecG cannot abort all exchanges initiated by RecA. If the directionality of branch migration by RecG is determined by the RecA filament, RecG could either abort or promote exchanges, depending on the initiating ssDNA substrate. These possibilities are illustrated in Fig. 6, where we consider recombination initiated by tailed duplex molecules. If the tail ends 5′, then RecA will readily catalyze an exchange from the three-stranded region into the duplex-duplex region of the two homologs. It is this class of exchange that RecG would abort by driving the junction back to the initiating single-stranded end (Fig. 6a). However, if the tail ends 3′, then the initial exchange is likely to be constrained to the three-stranded region as the RecA filament extends very poorly onto the duplex in this direction and tends to be discontinuous (198, 199). Reverse branch migration catalyzed by RecG would in this case help to push the exchange into the duplex-duplex region (Fig. 6b). The biological significance of these activities is perhaps best illustrated in the context of DNA repair.

RECOMBINATIONAL EXCHANGES IN DNA REPAIR

Mutations in most of the genes listed in Table 1, either alone or in combination with others, increase sensitivity to DNA damage and often reduce cell viability, from which it is clear that enzymes involved in recombination must have a vital role in repair. Recombination has been shown to repair two types of DNA lesion, double-chain breaks and single-strand gaps.

DNA End Repair and Priming of DNA Replication

The *recB, recC, ruv,* and *recG* genes are needed to maintain cell viability during normal growth. Strains carrying combinations of mutations in these genes are particularly sick, with viable cells often accounting for fewer than 20% of the total (20, 112, 115, 162, 186). The involvement of RecBCD, RuvABC, and RecG in cell viability implies that DNA double-chain breaks are a fact of life for *E. coli* and that their repair requires recombination enzymes to initiate exchanges at DNA ends and remove Holliday junctions. These exchanges must require RecA, but the effect of *recA* mutations on viability is noticeably less marked than that of *recBC* or *ruv* mutations. How can this be? Kuzminov et al. (100) have recently argued that the major double-strand lesion encountered during normal growth is a single end formed when a replication fork collapses after running into a single-strand break. They suggest that RecBCD-Chi interactions, plus RecA, allow the end to reinvade the intact duplex and restore the

replication fork (see Fig. 7b). The frequency of Chi sites and their nonrandom orientation makes this a particularly attractive possibility. In the absence of RecA, the broken arm can be degraded, allowing replication to resume again at *oriC*. Presumably, this is better than having no RecBCD to initiate the exchange—a surviving broken arm is likely to cause problems during the next round of replication—or no Ruv or RecG to process Holliday junctions.

The collapse of replication forks is likely to be exacerbated following exposure to DNA-damaging agents. Thus, DNA synthesis comes to a rapid halt following irradiation with UV light but resumes again after a short delay by a mechanism that involves RecA and induction of the SOS response (81). Kogoma and coworkers have recently shown that part of the process of recovery involves a new type of DNA synthesis (inducible stable DNA replication) primed initially by a 3′ single-strand tail from the end of a broken chromosome (5–7, 85). They propose that double-chain breaks are induced following SOS induction, particularly at sites called *oriM* within *oriC* and *ter* but also elsewhere when a replication fork encounters a single-strand break in the template. The DNA ends are processed by RecBCD-Chi interactions to produce 3′ single-strand tails or by other enzymes once RecBCD has been modulated and other proteins are induced to protect ssDNA. RecA-mediated invasion of an intact homolog creates a D-loop, which is extended as the 3′ end primes new DNA synthesis (Fig. 7a). DnaB helicase and DnaG primase are then recruited to the displaced ssDNA to prime lagging-strand synthesis. Resolution of the Holliday junction created as strand exchange is pushed into the duplex region of the invading DNA allows the D-loop to be converted into a bidirectional replication fork or to restore a collapsed fork as described by Kuzminov et al. (100), depending on the orientation of strand cleavage (Fig. 7b) (5, 100).

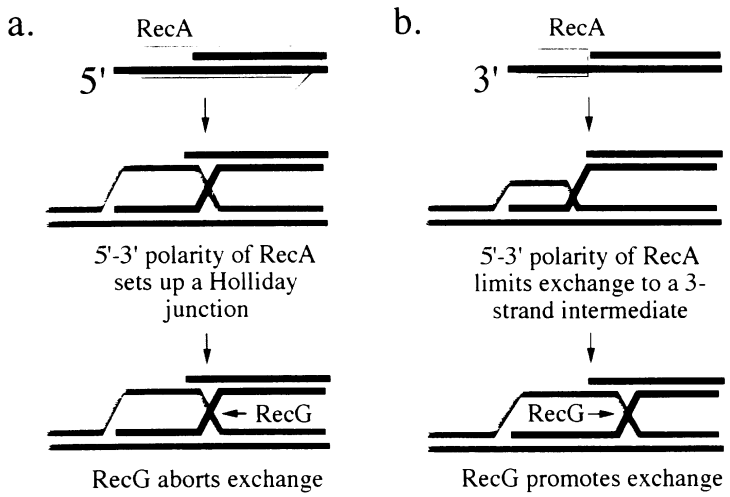

FIGURE 6 Model showing possible recombinogenic and antire-combinogenic activities of RecG being dictated by the polarity of RecA and of the ssDNA initiating exchange. (a) pairing initiated by a 5' tailed duplex; (b) pairing initiated by a 3' tailed duplex. The polar RecA filament is indicated by the shaded arrow. The polarity of RecG-driven branch migration is assumed to be dictated by RecA.

The events envisaged during inducible stable DNA replication can also accommodate a model for double-strand break repair (DSBR) as in Fig. 7c (5). It is here that we can consider further the relative activities of Ruv and RecG. Mutations in these genes dramatically alter the amount of DNA synthesis associated with end invasion, which implies that their products normally have an important role in this type of repair (6). As with other DSBR models (Fig. 3) (180, 224), the invading 3′ tail has the crucial role of priming repair synthesis. The three-strand intermediate generated by the exchange has to be processed before repair can be completed, and any junctions linking the two molecules have to be

removed. In the presence of RecA, RuvAB has little effect or no effect on three-strand intermediates in vitro, at least under one set of conditions (250), although under similar conditions it readily drives branch migration of four-strand Holliday intermediates (233, 251). Likewise, RuvC cleaves Holliday junctions but not equivalent three-strand junctions in the presence of RecA (12). RecG, however, does act on three-strand intermediates and has the right polarity in the presence of RecA to propel the initial exchange into duplex-duplex regions, forming a more stable Holliday junction which could be resolved subsequently by RuvABC. It is perhaps significant therefore that *recG* mutants are noticeably more sensitive to ionizing radiation than they are to UV light (115).

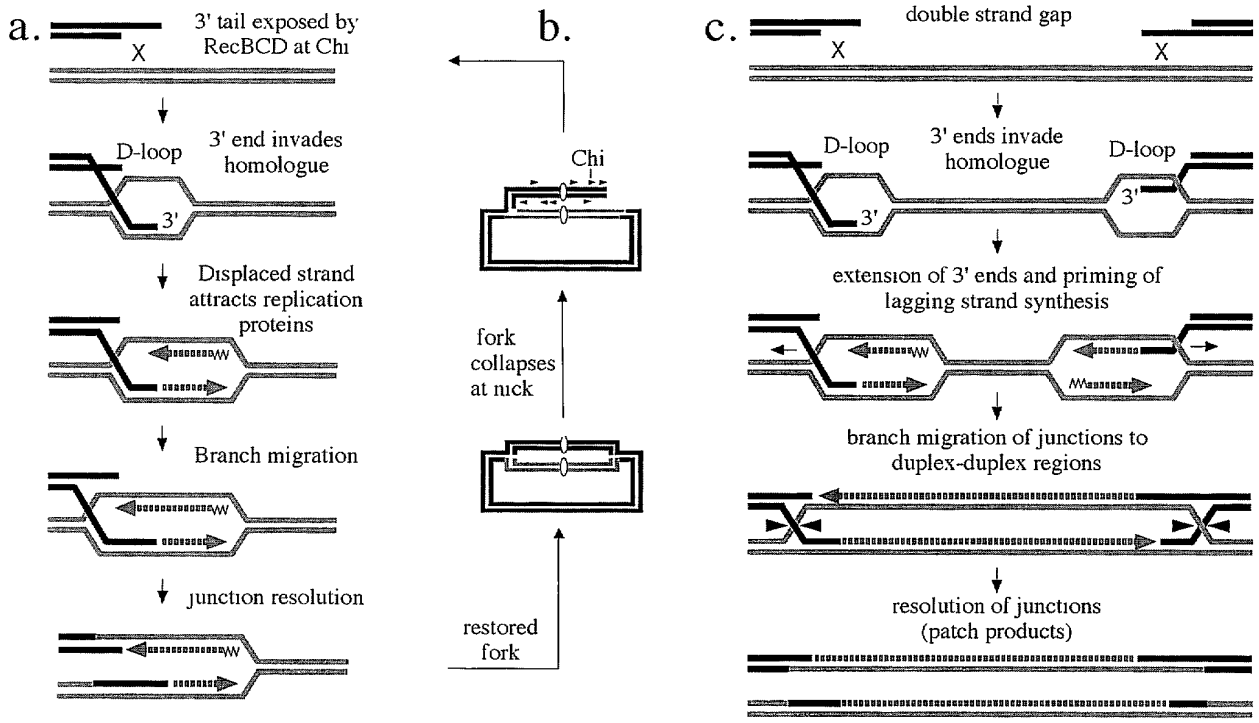

FIGURE 7 DNA replication primed by recombination. (a) Formation of a replication fork by invasion of duplex DNA by a 3′ tailed duplex. RNA primers are shown by a jagged line and new DNA is shown by a dashed line arrowed to indicate the polarity of synthesis. (b) Repair of a collapsed replication fork by the mechanism shown in panel a. The two arms are differentiated by shading. White ovals represent *oriC*, the origin of replication. The nonrandom distribution of Chi is indicated by small arrowheads and is shown for only the broken arm of the replication fork. (c) Model for repair of a double-strand gap by the coordinated invasion of an intact duplex by the two 3′ ends flanking the gap. Arrowheads at Holliday junctions identify the strands cleaved during resolution.

Although RecA seems to favor strand invasion by a 3′ end, and this fits with the known polarity of the major exonucleases linked with recombination, there is no obvious reason why strand invasion by a 5′ tail should not occur, at least occasionally. Studies in vitro support this possibility (46). In terms of DSBR, the invasion of a 5′ tail into a homologous duplex, being unable to prime repair DNA synthesis, would serve no purpose unless the exchange extended into duplex-duplex regions to create a Holliday junction, which would bring the 3′ end into play. 5′ invasion should provide an efficient route to a Holliday junction because of the polarity of RecA strand exchange. However, RecG would counter the exchange. If the two 3′ ends flanking a break or gap are extended before RecG drives reverse branch migration, they could possibly anneal to close the DNA. RecG might also inhibit growth of the RecA filament and thereby limit the risk of sequestering all of the RecA in one exchange. Such an activity is likely to be especially important when a minimum of two exchanges is needed, as with DSBR, and also conjugation and transduction.

Gap Repair

Howard-Flanders and colleagues were the first to propose that recombination plays an essential role in DNA repair by catalyzing exchanges with the undamaged sister duplex. They showed that discontinuities arise in newly synthesized DNA following UV irradiation of excision repair-defective cells and found that these discontinuities, which occur opposite the lesion (pyrimidine dimer) in the template strand, are closed by a mechanism that depends on *recA* (75, 184). One possible mechanism for this postreplication gap repair (Fig. 8) is based on the ideas proposed originally by Rupp et al. (185) and modified subsequently to take into account the properties of RecA (248). A RecA filament polymerizes at the gap and promotes homologous pairing and strand exchange with the undamaged sister molecule. Polymerization and strand exchange proceed 5′ to 3′ toward the lesion in the template strand and can presumably extend past the lesion to form a Holliday junction. The junction point can be pushed further into the duplex by RecA alone or aided by RuvAB. Strand transfer past the lesion closes the gap and provides a template for the UvrABCD excision system to repair the damaged strand, while the original 3′ end transferred to the donor duplex can be used to close the gap created by the exchange. Resolution of the junction and ligation complete repair.

The need to resolve junctions is clear and is consistent with the UV sensitivity of strains deficient in the known resolvases, particularly *ruv* mutants. Cleavage of the Holliday junction in either of the two possible orientations by the RuvABC system is likely to be the most common route since dimers become distributed and therefore diluted throughout the daughter chromosomes during subsequent growth of excision-deficient cells (59). This is most easily explained by crossing over between damaged and undamaged regions. However, if the DNA remains nicked, RecG could reverse strand exchange to remove the junction. Indeed, the combined activities of RecA, RuvAB, and RecG could provide a different mechanism for the replisome to bypass the original lesion in the template strand. The 3′ end at the collapsed replication fork could be switched by RecA and RuvAB to pair with the undamaged daughter strand, where it could prime DNA synthesis. After clearing the lesion, RecG could switch it back again to resume normal replication (47).

Exchanges initiated by RecA at strand gaps have also been proposed as a mechanism for the efficient initiation of conjugational recombination seen in *recBC* mutant cells, where ExoI activity is likely to inhibit initiation by 3′-end invasion (117, 119, 122). The failure to produce viable recombinants in these strains can be attributed to sequestering of RecA by the exchange, coupled with degradation of the unprotected ends of the Hfr DNA fragment. Cells lacking ExoV retain appreciable nuclease activity (181), and Kuzminov et al. (100) have shown that unprotected DNA ends are degraded quite rapidly when RecA is absent. The chances of having a second exchange, initiated at a gap, to integrate the Hfr DNA into a viable recombinant may therefore be rather limited.

RECOMBINATION FUNCTIONS: *S. TYPHIMURIUM* VERSUS *E. COLI*

Considerable progress has been made in the genetic analysis of recombination in *S. typhimurium*. Homologs of the *E. coli recA, recB, recC, recD, recF, recJ, recN, sbcB, sbcC,* and *sbcD* genes and an additional (unstable) suppressor of *recB* mutations (*sbcE*) have been found in *S. typhimurium* (see chapter 110). Since there is no equivalent to a Rac prophage known in *S. typhimurium* LT2, there are no known *recE* or *recT* genes in this organism and no “RecE pathway.”

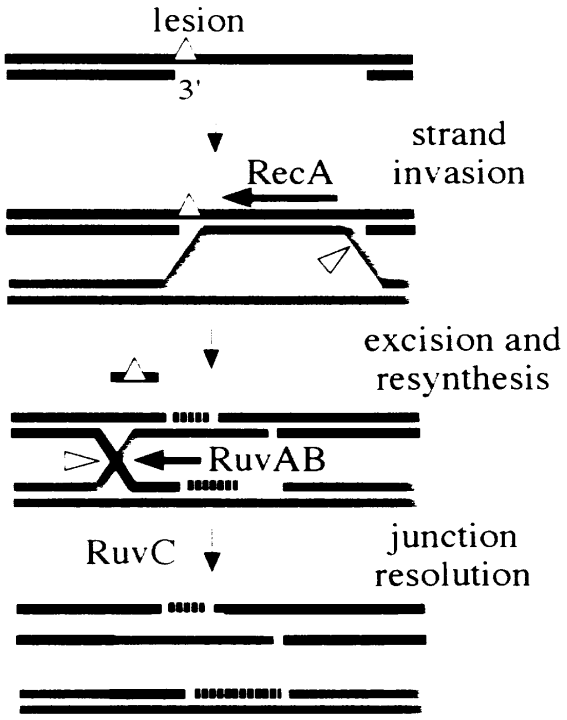

FIGURE 8 Model for gap repair by the combined activity of RecA, excision enzymes, and RuvABC. The lesion in the template strand is indicated by a vertical triangle. The direction of RecA and RuvAB strand exchange is indicated by the shaded arrows. Cleavage by RuvC (open arrowhead) is shown to give patch products but could equally lead to crossovers by cutting the other pair of strands.

Generally, the corresponding functions in the two species have been found to be highly homologous and can complement each other in most assays (see, for example, reference 188). One interesting difference in functional requirement is that *sbcB* mutations in *S. typhimurium* do not require an accompanying *sbcC* (or *sbcD*) mutation in order to restore *recB* mutant cells to a Rec^+ UV^r MC^r phenotype. However, an additional *sbcC* or *sbcD* mutation is required to recover from the high lethal sectoring observed in *recB* or *recB recC* mutant cells (13). Interestingly, the transductional recombination proficiency in *recB sbcB sbcC(D)* strains can be 16-fold greater than that in the wild-type (*rec*$^+$ *sbc*$^+$) background, and the UV resistance is also greater (13). This is reminiscent of the recombination levels much higher than the wild type in *recBC sbcBC E. coli* strains for certain recombinational systems (173, 192). A further difference in the RecB-related functional dependence in *S. typhimurium* is that the recombination stimulation by Chi sequences is much less than that in *E. coli* (212).

MISMATCH REPAIR AND INTERSPECIFIC CROSSES

E. coli and *S. typhimurium* encode homologous systems for the repair of single-base mismatches during replication (see chapter 121). It has been found that genetic blocks in the functions involved in this system (*dam, mutH, mutL, mutS, uvrD*) have marked effects on frequencies of recovery of certain classes of recombinants, often increasing them considerably (51, 89, 90, 111). Interestingly, a block in this mismatch repair pathway dramatically increases interspecific recombinant production in *S. typhimurium* Hfr $\times$ *E. coli* F^- crosses (by 1,000-fold; the recombination frequency is still 100-fold lower than in an equivalent intraspecific cross) (179). Since the chromosomal transfer of DNA between *S.*

typhimurium and *E. coli* is very similar in frequency to that with *E. coli* × *E. coli* (as measured by zygotic induction), it is reasonable to conclude that recombinogenic events initiated in the interspecific crosses are aborted by action (nicking, unwinding, and strand degradation) of the mismatch repair system on the many mismatches expected in heteroduplex joints formed between the nonidentical (~16% divergence) parental DNA molecules. Recent studies have also linked SOS induction and particular recombination genes in the formation of interspecific recombinants (142). There are various implications for effects of the mismatch repair system on the rate of horizontal gene transfer and evolution (142, 179).

CONCLUSIONS AND OUTLOOK

The exchanges that bring about recombination in genetic crosses and that repair damaged DNA show a remarkable similarity at the molecular level. Perhaps this is not surprising given that recombination in bacteria probably evolved to meet the demands of repair. Indeed, the formation of recombinants in genetic crosses could be viewed in many, if not all, cases simply as an exercise in DNA repair. How can the cell, or more precisely RecBCD, tell whether it is engaging the end of a DNA molecule introduced from an Hfr during conjugation or the broken arm of a collapsed replication fork? A similar question arises at gaps.

The key stage in the exchange is the formation of a heteroduplex joint. With certain exceptions, these exchanges are catalyzed by the RecA filament, a structure that has evolved to overcome the natural tendency of Watson-Crick strands to remain paired and at the same time to make use of this tendency to ensure homologous exchange. The solution is so elegant that it has been retained throughout evolution (11, 159, 204). However, it is not the only recombination protein to assemble into a multimeric machine. The RecBCD complex has evolved a dual role. It can function as a rampant nuclease to rapidly destroy linear DNA, which may be important for removing extraneous (foreign) sequences, or it can deliver a single strand to RecA for the initiation of exchange after some modulation by Chi. The helical rings formed by RuvB are quite remarkable. Compared with RecA, they are blockbusters, but may also be capable of some refinement, as they may well deliver Holliday junctions, and RuvC, to particular sequences where they can be resolved. The RecF, RecO, and RecR proteins also interact, but so far we know little of what they do. The enzymology of other recombination enzymes is also far from complete. RecN is a mystery remaining to be solved.

Protein complexes highlight the need for precision in the recombination reaction. We are only beginning to understand the interactions that keep these structure in tune with each other and that coordinate their activities with other complexes involved in replication and perhaps transcription. Connoisseurs of phage T4 have long been familiar with this problem (150). Enzymologists will be kept busy for a long time. Precision at the DNA level must be monitored within the heteroduplex joint to make sure that the exchanges are legitimate. RecA is not perfect, and recent studies indicate that the MutHLS mismatch repair system may monitor its fidelity during the exchange (179, 257). How it does so remains to be established.

A final note of caution is needed, however. It is tempting to conclude that recombination proceeds normally via the formation and subsequent resolution of Holliday junctions. It is significant that Ruv mutants are not particularly deficient in conjugational recombination and not at all in some types of crosses. Although the addition of a *recG* mutation does block the conjugational process, the reason why is not obvious since it alone cannot resolve a junction to give crossovers. RusA is not the answer either since strains deleted for both *ruvC* and *rusA* remain proficient in recombination, at least of the conjugational and plasmid type (A. A. Mahdi and R. G. Lloyd, unpublished data). It may be that a significant number of exchanges are of the nonreciprocal break-join type described in phage λ or that Holliday junctions can be resolved by topoisomerase (232). It is also significant that λ recombination has so far shown no requirement for any enzyme that resolves Holliday junctions, although

intermediates of this type have been detected under certain conditions. Strains lacking both RuvC and RusA remain to be tested. It is also possible that a gene for another resolvase may lurk somewhere in the *E. coli* or λ genome or that we still have a lot to learn.

ACKNOWLEDGMENTS

We thank our colleagues who provided unpublished information and apologize to those whose work has been referred to only indirectly through citations to reviews and other articles. R.G.L. is supported by grants from the Medical Research Council, the Science and Engineering Research Council, the Wellcome Trust, and the Royal Society. K.B.L. is supported by grant CA39238 from the USPHS.

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