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DNA Mismatch Repair Systems: Mechanisms and Applications in Biotechnology

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Mismatch repair systems: Mechanisms and specificities

The detection of mispaired or unpaired bases in DNA is a central element of mutation avoidance (Radman *et al.*, 1979) genetic recombination (Jones, Wagner and Radman, 1987a) and speciation (Rayssiguier, Thaler and Radman, 1989). Mispaired or unpaired bases may arise as a result of replication errors, strand exchange between homologous but non-identical sequences or deamination of 5-methyl-cytosine (5-meC) to thymine. Both replication errors and deaminations of 5-meC are changes in DNA sequences which, if not rectified, will give rise to heritable mutations.

Mismatch repair systems can be divided in two broad classes on the basis of their mechanisms of action (for reviews, see Radman and Wagner, 1986; Claverys and Lacks, 1986; Modrich, 1991). The long patch mismatch repair (LPMR) systems act by removing a number of nucleotides (often 1000–3000) from one strand of a DNA double helix in the region of a mispaired or unpaired base (Wildenberg and Meselson, 1975; Wagner and Meselson, 1976; Mejean and Claverys, 1984; Brooks *et al.*, 1989). The resulting gap is then filled by DNA synthesis (Lahue, Au and Modrich, 1989; Brooks *et al.*, 1989). Short patch mismatch repair (SPMR) systems act by removing only the mismatched nucleotide or the mismatched nucleotide and a few surrounding nucleotides (Lieb, 1983; Jones, Wagner and Radman, 1987a,c; Radicella, Clark and Fox, 1988; Au *et al.*, 1988, 1989; Hennecke *et al.*, 1992).

Long patch mismatch repair systems are often referred to as 'generalized' mismatch repair systems because they act to repair many of the different mismatches formed as replication errors, i.e. mismatches formed as a result of errors in the polymerase nucleotide selection process which escape detection by the polymerase proofreading system (Radman and Wagner, 1986; Jones, Wagner and Radman, 1987b). Long patch mismatch repair systems also

Abbreviations: dGTP-ase, deoxyguanosine triphosphate; LPMR, long patch mismatch repair; 5-meC, 5-methyl-cytosine; SPMR, short patch mismatch repair.

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recognize and repair small (1–4 base) addition and deletion errors (Dohet, Wagner and Radman, 1986; Gasc, Sicard and Claverys, 1989; Parker and Marinus, 1992). Except for those systems requiring recombinational interactions between homologous DNA duplexes, any mismatch repair system whose mission is the correction of replication errors must be able to discriminate newly synthesized strands from parental strands and act specifically to preserve the sequence of the latter. Such strand discrimination is accomplished in *Escherichia coli* and some other bacteria by restricting LPMR to regions of DNA where one strand is undermethylated (Wagner and Meselson, 1976) with respect to adenine methylation of GATC sequences (Radman *et al.*, 1980; Pukkila *et al.*, 1983). The adenines in GATC sequences in non-replicating *E. coli* DNA are normally methylated (Marinus and Morris, 1973). This methylation inhibits the *E. coli* LPMR system (Radman *et al.*, 1980; Pukkila *et al.*, 1983). However, adenine methylation lags somewhat behind replication such that, immediately behind the replication fork, newly synthesized strands are transiently undermethylated (Lyons and Schendel, 1984). It is in this region that LPMR can act to remove replication errors. Another basis of strand discrimination in bacteria and in other organisms may be the discontinuities in newly synthesized DNA strands (Claverys and Lacks, 1986; Laengle-Rouault, Maenhaut-Michel and Radman, 1987; Lahue, Su and Modrich, 1987; Holmes, Clark and Modrich, 1990; Thomas, Roberts and Kunkel, 1991). In any event, it appears that LPMR systems generally act in the vicinity of the replication fork, although it has been shown that they do not require replication for their action (Radman and Wagner, 1986).

Short patch mismatch repair systems, which are considered to be 'specialized' mismatch repair systems, can act on non-replicating DNA to repair specific mismatches in a directed fashion (for a review, see Modrich, 1991). Two such systems have been identified in *E. coli*. One repairs only those G:T mismatches which result, or which could have resulted, from the deamination of 5-meC (Lieb, 1983; Jones, Wagner and Radman, 1987a,c; Zell and Fritz, 1987). Thus, this SPMR system acts only on a specific base (T) of a specific mismatch (G:T) at a specific position (the cytosine methylation position) in a specific sequence (a tetranucleotide sequence derived from the pentanucleotide cytosine methylase recognition sequence, CCWGG) (Lieb, Allen and Reid, 1986).

The other *E. coli* SPMR system acts on G:A mismatches to repair them to G:C (Au *et al.*, 1988; Radicella, Clark and Fox, 1988; Tsai-Wu, Radicella and Lu, 1991). This system apparently evolved because many G:A mismatches are not well recognized by the LPMR system (Dohet, Wagner and Radman, 1985; Jones, Wagner and Radman, 1987b), even though G:A mismatches are among the most common mistakes of DNA polymerases (Fersht and Knill-Jones, 1983). Because SPMR systems are not strand-directed, only those G:A mismatches in which A is on the newly synthesized strand will be repaired in such a way as to remove the replication error. In those cases where A is on the template strand, the action of this system would fix the mutation. However, the dGTPase activity of the polymerase-associated MutT protein (Akiyama *et al.*, 1989; Bhatnagar and Bessman, 1988) may function to prevent the

formation of G:template-A mismatches during replication and, thus, eliminate them as potential substrates for the SPMR system. Moreover, the MutT protein is likely to be involved in prevention of mutagenic incorporation of oxidatively damaged substrates for DNA synthesis such as the 8-oxoguanine triphosphate (Maki and Sekiguchi, 1992), whereas the MutY protein may prevent adenine misincorporation opposite 8-oxoG in the template (Michaels *et al.*, 1992).

The existence of mismatch repair was originally postulated to account for genetic marker effects in the studies of genetic recombination (Holliday, 1964; Ephrussi-Taylor and Gray, 1966) and it has been found that elements of both LPMR and SPMR do have a significant impact on the outcome of genetic recombination events (Jones, Wagner and Radman, 1987a). A key intermediate in the process of genetic recombination is a hybrid or heteroduplex overlap – a region of DNA in which one strand of the double helix is derived from each of the two recombining molecules (see *Figure 1*). It is this hybrid overlap that aligns recombining molecules and assures that recombination will occur only between homologous sequences. Mismatches will be formed whenever sequences that are not completely identical are included within the hybrid overlap (*Figure 1*). Whenever mismatches within hybrid overlaps are substrates for SPMR, they will be repaired according to the rules of the particular system involved (see *Figure 1*). It is this type of repair that is responsible for the elevated recombination of close markers (high negative interference) (Lieb, 1983; Jones, Wagner and Radman, 1987c; Meselson, 1988; Raposa and Fox, 1987; Dzidic and Radman, 1989) and will generally result in diversification of related, but non-identical, sequences (*Figure 1*).

Initially, it was not at all clear what, if any, role LPMR plays in genetic recombination. In fact, it was suggested that LPMR does not operate at all on recombinational intermediates (Lieb, 1981, 1983; Gussin, Rosen and Wulff, 1981). Such might be the case if the mismatch repair process was completely inhibited by methylation of GATC sequences. However, it has been demonstrated that, at least *in vitro*, LPMR proceeds sequentially and only breaking of the DNA strand containing the incorrect base, one of the later steps, requires unmethylated GATC sequences (Laengle-Rouault, Maenhaut-Michel and Radman, 1987; Au, Welsh and Modrich, 1992). Thus, the early steps of LPMR, including mismatch recognition, will occur even in fully methylated DNA. Given the structure of recombinational intermediates, it may be that the strand discontinuities in the donor DNA preceding and following the donor strand exchange serve to direct LPMR to the incoming strand and result in the strand being removed whenever it creates mismatches with the recipient strand (*Figure 1*). Thus, LPMR will prevent recombination between non-homologous sequences by 'aborting' the recombination process or by destroying the heteroduplex intermediate (Jones, Wagner and Radman, 1987c; Rayssiguier, Thaler and Radman, 1989; Shen and Huang, 1989; see *Figure 1*).

The 'editing' of recombinational intermediates and suppression of recombination by LPMR can account for the stability of eukaryotic genomes in which there are hundreds of thousands of dispersed repeated genetic elements.

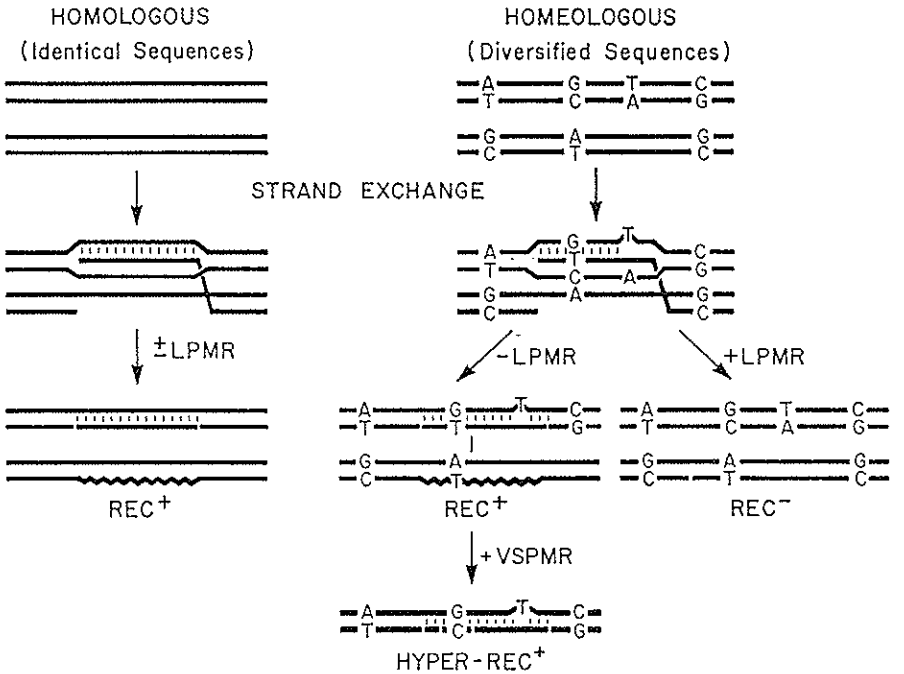

Figure 1. Specific prevention of recombination between partially homologous (homeologous) DNAs by the LPMR systems and hyper-recombination of specific allelic point mutations by the SPMR systems. LPMR proteins act by aborting the mismatched intermediates (hybrid DNA joints) generated by recombination proteins, thus creating the 'REC-' phenotype. Under LPMR-deficient conditions, the barrier to homeologous recombination is broken, allowing for inter-repeat and inter-species recombination (see text). An active SPMR (or VSPMR) can further process the mismatched intermediate to generate fine structure diversity at the nucleotide sequence level (HYPER-REC phenotype).

However, the repeated elements are sufficiently diverged (2–15%) that hybrid overlaps formed between them will contain mismatches and therefore, be substrates for action by a LPMR system. Long patch mismatch repair can prevent homologous interactions between repeated DNA sequences (Petit *et al.*, 1991) and between genomes of closely related species (Rayssiguier, Thaler and Radman, 1989), thereby protecting an organism against deleterious chromosomal rearrangements and acting as an effective genetic barrier between related species (Radman, 1991). *Escherichia coli* mutants deficient in mismatch detection proteins (MutS and MutL) show an increased rate of duplication and deletion formation as a result of recombination between copies of repeated, diverged sequences (Petit *et al.*, 1991). In addition, mutations which suppress LPMR allow interspecies *E. coli/Salmonella typhimurium* recombination at about 10% of intraspecies levels (*mut*+ bacteria allow only about 0.001% of intraspecies levels) (Rayssiguier, Thaler and Radman, 1989; Rayssiguier, Dohet and Radman, 1991). This high efficiency of hybrid DNA formation involving non-identical sequences provides substrates for SPMR and thus can result in high recombination frequencies (Jones, Wagner and Radman, 1987c).

Implications and applications of mismatch repair systems in genetic engineering and biotechnology

The ability to control the fidelity of DNA replication and recombination processes by controlling LPMR and SPMR opens new doors in biotechnology, genetic engineering and medicine. Not only is it now possible to use powerful mutator mutants (i.e. mutants deficient in LPMR and SPMR) to alter DNA sequences rapidly but randomly, but it is also possible to generate new genes and even new species by allowing heretofore forbidden recombination between related genes and species. Recombination between diverged DNA seuqences coding for proteins of similar function can be facilitated under LPMR-deficient conditions to allow 'protein engineering' analogous to the strategies employed in nature to generate diversity in the immune (Reynaud *et al.*, 1987), histocompatibility (Jaulin *et al.*, 1985) and parasite surface antigen (Thon, Baltz and Eisen, 1989) systems (*Figure 2*). In these systems, partially homologous DNA sequences act as donor sequences to a single expressed 'mosaic' gene. In addition, in yeast plasmid transformation experiments, recombination between diverged genes produced mosaic genes which coded for enzymes with altered specificities (Mezard, Pompon and Nicolas, 1992; Goguel, Delahodde and Jacq, 1992). By selecting appropriate donor sequences, it should be possible to set up similar systems of directed evolution in LPMR-deficient bacteria to create 'new' genes coding for new or improved proteins. Because the initial donor sequences can be selected by virtue of their ability to code for functional proteins, most recombinants will presumably be functional, an enormous advantage over current systems of random mutagenesis. Thus, it will be necessary only to select or screen for the desired alteration (e.g. improved stability, increased activity or altered specificity) from among a population of bacterial (or phage) clones coding for functional proteins. Recombinational repair between broken diverged (homeologous) genes is frequent in yeast plasmid transformation experiments, in which it was demonstrated that the resulting mosaic genes encode for enzymes with altered specificities (Mezard, Pompon and Nicolas, 1992; Goguel, Delahodde and Jacq, 1992).

The process of creating new genes can perhaps be made even more efficient by performing some of the steps *in vitro*. For example, heteroduplex DNA can be formed *in vitro* between two diverged genes (Abastado *et al.*, 1984) and be used to transfect LPMR-deficient *E. coli*. The heteroduplexes will then be substrates for SPMR, which will act to generate 'patchwork' sequences, which will represent increased repertoires of recombination products between the two genes.

Inhibition of LPMR will allow cloning of partially homologous genes from diverse species. By preparing a 'probe' sequence from a previously cloned gene of identical function to the desired gene (and, therefore, presumably partially homologous to it), it will be possible, by means of recombination between partially homologous sequences, to extract efficiently the desired gene from a library of genes of a given species. Obviously, such a procedure is not restricted to coding sequences, but may be used to obtain any partially

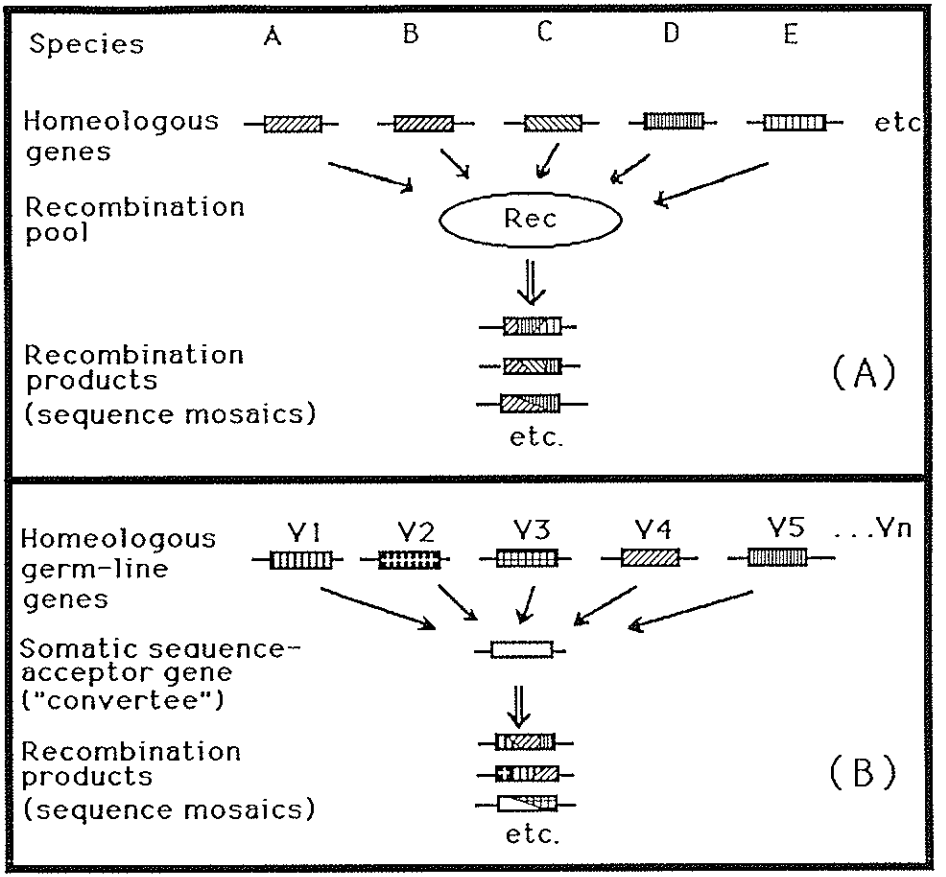

Figure 2. 'Instant evolution' of genes and the encoded proteins by maximized homeologous recombination in the absence of LPMR and with active SPMR systems (see *Figure 1*). Box B presents an oversimplified version of natural systems generating protein diversity through gene conversion processes (see text). Box A illustrates how one can mimic such diversification processes by homeologous recombination of cloned genes in bacteria that are LPMR−, SPMR+.

homologous sequences from any species. A similar method was previously developed, but did not employ LPMR-deficient bacteria and, therefore, was inefficient due to the high fidelity of genetic recombination in wild-type *E. coli* (Seed, 1983).

The same principle can serve as a basis for gene inactivation. An inactive but partially homologous sequence to the gene in question can be constructed and, under LPMR-deficient conditions, allowed to recombine with the target gene to inactivate it. The ability to inactivate genes selectively can be useful in gene mapping and may eventually have diagnostic or therapeutic applications, particularly as it becomes possible to inhibit, perhaps transiently, LPMR in higher organisms. If, as suggested by Radman (1988, 1989, 1991), mitotic recombination is prevented by the differential sequence polymorphisms carried by the two homologous chromosomes, then gene replacement, gene inactivation or 'gene therapy' by homologous recombination with exogenous DNA may also be prevented by the sequence polymorphism carried by the target plant, animal or human cells. Using cloned 'isogenic'

DNA sequences (from the same genetic background as the recipient cells) (Te Riele, Maandag and Berns, 1992) or inactivating mismatch detection and/or repair proteins may be necessary for efficient gene 'targeting' or 'therapy'.

The ability to remove genetic barriers between species by allowing them to recombine under LPMR-deficient conditions, as has been demonstrated in *Escherichia–Salmonella* crosses (Rayssiguier, Thaler and Radman, 1989), means that it is now possible to create new species of micro-organisms. The potential applications appear almost limitless. Attenuated live vaccines can be created by selectively recombining pathogenic bacteria, such as *Salmonella* and *Shigella*, with *E. coli* to create non-pathogenic strains that retain the immunogenicity of the pathogens. It may also be possible to create universal salmonella-based vectors for any antigen presentation which could be used as oral vaccines illiciting mucosal immunity (McGhee *et al.*, 1992).

Finally, it has been demonstrated that the mismatch-binding proteins, such as the bacterial MutS protein, can be used to detect substitution and small addition/deletion mutations. Such applications have wide ranging potentials for diagnosing human hereditary and somatic genetic diseases and in the study of polymorphism in human and other genomes (R. Wagner and M. Radman, unpublished).

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References

ABASTADO, J.-P., CAMI, B., HUYNH DINH, T., IGOLEN, J. AND KOURILSKY, P. (1984). Processing of complex heteroduplexes in *Escherichia coli* and *Cos-1* monkey cells. *Proceedings of the National Academy of Sciences, USA* **81**, 5792–5796.

AKIYAMA, M., MAKI, H., SEKIGUCHI, M. AND HORIUCHI, T. (1989). A specific role of MutT protein; to prevent dG.dA mispairing in DNA replication. *Proceedings of the National Academy of Sciences, USA* **86**, 3949–3952.

AU, K.G., WELSH, K. AND MODRICH, P. (1992). Initiation of methyl-directed mismatch repair. *Journal of Biological Chemistry* **267**, 12 142–12 148.

AU, K.G., CABRERA, M., MILLER, J.H. AND MODRICK, P. (1988). *Escherichia coli mutY* gene product is required for specific A-G to C-G mismatch correction. *Proceedings of the National Academy of Sciences, USA* **85**, 9163–9166.

AU, K.G., CLARK, S., MILLER, J.H. AND MODRICH, P. (1989). The *Escherichia coli* mutY gene encodes an adenine glycosylase active on G-A mispairs. *Proceedings of the National Academy of Sciences, USA* **86**, 8877–8881.

BHATANAGAR, S.K. AND BESSMAN, M.J. (1988). Studies on the mutator gene, *mutT* of *Escherichia coli*: molecular cloning of the gene, purification of the gene product, and identification of a novel nucleoside triphosphatase. *Journal of Biological Chemistry* **263**, 8953–8957.

BROOKS, P., DOHET, C., ALMOUZNI, G., MÉCHALI, M. AND RADMAN, M. (1989). Mismatch repair involving localised DNA synthesis in Xenopus egg extracts. *Proceedings of the National Academy of Sciences, USA* **86**, 4425–4429.

CLAVERYS, J.-P. AND LACKS, S.L. (1986). Heteroduplex deoxyribonucleic acid base

mismatch repair in bacteria. *Annual Review of Microbiology* **50**, 133–165.

DOHET, C., WAGNER, R. AND RADMAN, M. (1985). Repair of defined single base pair mismatches in *E. coli*. *Proceedings of the National Academy of Sciences, USA* **82**, 503–505.

DOHET, C., WAGNER, R. AND RADMAN, M. (1986). Methyl-directed repair of frameshift mutations in heteroduplex DNA. *Proceedings of the National Academy of Sciences, USA* **83**, 3395–3397.

DZIDIC, S. AND RADMAN, M. (1989). Genetic requirements for hyperrecombination by very short patch mismatch repair: involvement of *E. coli* DNA polymerase I. *Molecular and General Genetics* **217**, 254–256.

EPHRUSSI-TAYLOR, H. AND GRAY, T.C. (1966). Genetic studies of recombining DNA in pneumococcal transformation. *Journal of General Physiology* **49**, 211–231.

FERSHT, A.R. AND KNILL-JONES, J.W. (1983). Contribution of 3′→5′ exonuclease activity of DNA polymerase III holoenzyme from *Escherichia coli* to specificity. *Journal of Molecular Biology* **165**, 669–682.

GASC, A.M., SICARD, M. AND CLAVERYS, J.-P. (1989). Repair of single- and multiple-substitution mismatches during recombination in *Streptococcus pneumoniae*. *Genetics* **121**, 29–36.

GOGUEL, V., DELAHODDE, A. AND JACQ, C. (1992). Connections between RNA splicing and DNA intron mobility in yeast mitochondria: RNA maturase and DNA endonuclease switching experiments. *Molecular and Cellular Biology* **12**, 696–705.

GUSSIN, G.N., ROSEN, E.D. AND WULFF, D.L. (1981). Mapability of very close markers of bacteriophage lambda. *Genetics* **96**, 1–24.

HENNECKE, F., KOLMAR, H., BRUENDEL, K. AND FRITZ, H.-J. (1992). The vsr gene product of *E. coli* K-12 is a strand- and sequence-specific DNA mismatch endonuclease. *Nature* **353**, 776–778.

HOLLIDAY, R. (1964). A mechanism for gene conversion in fungi. *Genet Res* **5**, 282–304.

HOLMES, J.J., CLARK, S. AND MODRICH, P. (1990) Strand-specific mismatch correction in nuclear extracts of human and *Drosophila melanogaster* cell lines. *Proceedings of the National Academy of Sciences, USA* **87**, 5837–5841.

JAULIN, C., PERRIN, A., ABASTADO, J.-P., DUMAS, B., PAPAMETHEAKIS, J. AND KOURILSKY, P. (1985). Polymorphism in mouse and human class I *H-2* and *HLA* genes is not the result of random independent point mutations. *Immunogenetics* **22**, 453–470.

JONES, M., WAGNER, R. AND RADMAN, M. (1987a). Mismatch repair of deaminated 5-methyl-cytosine. *Journal of Molecular Biology* **194**, 155–159.

JONES, M., WAGNER, R. AND RADMAN, M. (1987b). Repair of a mismatch is influenced by the base composition of the surrounding nucleotide sequence. *Genetics* **115**, 605–610.

JONES, M., WAGNER, R. AND RADMAN, M. (1987c). Mismatch repair and recombination in *E. coli*. *Cell* **50**, 621–626.

LAENGLE-ROUAULT, F., MAENHAUT-MICHEL, G. AND RADMAN, M. (1987). GATC sequences, DNA nicks and the mutH function in *Escherichia coli* mismatch repair. *EMBO Journal* **6**, 1121–1127.

LAHUE, R.S., AU, K.G. AND MODRICH, P. (1989). DNA mismatch correction in a defined system. *Science* **245**, 160–164.

LAHUE, R.S., SU, S.-S. AND MODRICH, P. (1987). Requirement for d(GATC) sequences in *Escherichia coli mutHLS* mismatch correction. *Proceedings of the National Academy of Sciences, USA* **84**, 1482–1486.

LIEB, M. (1981). A fine structure map of spontaneous and induced mutations in the lambda repressor gene, including insertions of IS elements. *Molecular and General Genetics* **184**, 364–371.

LIEB, M. (1983). Specific mismatch correction in bacteriophage lambda crosses by very short patch repair. *Molecular and General Genetics* **191**, 118–125.

LIEB, M., ALLEN, E. AND REID, D. (1986). Very short patch mismatch repair in phage lambda: repair sites and length of repair tracts. *Genetics* **114**, 1041–1060.

LYONS, S. AND SCHENDEL, P.F. (1984). Kinetics of methylation in *Escherichia coli* K-12. *Journal of Bacteriology* **159**, 421–423.

MAKI, H. AND SEKIGUCHI, M. (1992). MutT protein specifically hydrolyses a potent mutagenic substrate for DNA synthesis. *Nature* **355**, 273–275.

MARINUS, M.G. AND MORRIS, N.R. (1973). Isolation of deoxyribonucleic acid methylase mutants of *Escherichia coli K-12*. *Journal of Bacteriology* **114**, 1143–1150.

MCGHEE, J.R., MESTECKY, J., DERTZBAUGH, M.T., ELDRIDGE, J.H., HIRASAVA, M. AND KIYONO, H. (1992). The mucosal immune system: from fundamental concepts to vaccine development. *Vaccine* **10**, 75–88.

MEJEAN, V. AND CLAVERYS, J.-P. (1984). Effect of mismatched base pairs on the fate of donor DNA in transformation of *Streptococcus pneumoniae*. *Molecular and General Genetics* **197**, 467–471.

MESELSON, M. (1988). Methyl-directed repair of DNA mismatches. In *Recombination of the Genetic Material* (K.B. Low, Ed.), pp. 91–113. Academic Press, San Diego, CA.

MEZARD, C., POMPON, D. AND NICOLAS, A. (1992). Recombination between similar but not identical DNA sequences during yeast transformation occurs within short stretches of identity. *Cell* **70**, 659–670.

MICHAELS, M.L., CRUZ, C., GROLLMAN, A.P. AND MILLER, J.H. (1992). Evidence that MutY and MutM combine to prevent mutations by an oxidatively damaged form of guanine in DNA. *Proceedings of the National Academy of Sciences, USA* **89**, 7022–7025.

MODRICH, P. (1991). Mechanisms and biological effects of mismatch repair. *Annual Review of Genetics* **25**, 229–253.

PARKER, B.O. AND MARINUS, M.G. (1992). Repair of DNA heteroduplexes containing small heterologous sequences in *Escherichia coli*. *Proccedings of the National Academy of Sciences, USA* **89**, 1730–1734.

PETIT, M.-A., DIMPFL, J., RADMAN, M. AND ECHOLS, H. (1991). Control of chromosomal rearrangements in *E. coli* by the mismatch repair system. *Genetics* **129**, 327–332.

PUKKILA, P.J., PETERSON, J., HERMAN, G., MODRICH, P. AND MESELSON, M. (1983). Effects of high levels of DNA adenine methylation on methyl-directed mismatch repair in *Escherichia coli*. *Genetics* **104**, 571–582.

RADICELLA, J.P., CLARK, E.A. AND FOX, M.S. (1988). Some mismatch repair activities in *Escherichia coli*. *Proceedings of the National Academy of Sciences, USA* **85**, 9674–9678.

RADMAN, M. (1988). Mismatch repair and genetic recombination. In *Genetic Recombination* (R. Kutcherlapati and G.R. Smith, Eds), pp. 169–192. American Society for Microbiology, Washington, DC.

RADMAN, M. (1989). Mismatch repair and the fidelity of genetic recombination. *Genome* **31**, 68–73.

RADMAN, M. (1991). Avoidance of inter-repeat recombination by sequence divergence and a mechanism of neutral evolution. *Biochimie* **73**, 357–361.

RADMAN, M. AND WAGNER, R. (1986). Mismatch repair in *Escherichia coli*. *Annual Review of Genetics* **20**, 523–538.

RADMAN, M., VILLANI, G., BOITEUX, S., KINSELLA, A.R., GLICKMAN, B.W. AND SPADARI, S. (1979). Replication fidelity: mechanisms of mutation evoidance and mutation fixation. *Cold Spring Harbor Symposia on Quantum Biology* **43**, 937–946.

RADMAN, M., WAGNER, R.E., GLICKMAN, B.W. AND MESELSON, M. (1980). DNA methylation, mismatch correction and genetic stability. In *Progress in Environmental Mutagenesis* (M. Alacevic, Ed.), pp. 121–130. Elsevier, Amsterdam.

RAPOSA, S. AND FOX, M.S. (1987). Some features of base pair mismatch and heterology repair in *Escherichia coli*. *Genetics* **117**, 381–390.

RAYSSIGUIER, C., DOHET, C. AND RADMAN, M. (1991). Interspecific recombination between *Escherichia coli* and *Salmonella typhimurium* occurs by the RecBCD pathway. *Biochimie* **73**, 371–374.

RAYSSIGUIER, C., THALER, D.S. AND RADMAN, M. (1989). The barrier to recombination between *Escherichia coli* and *Salmonella typhimurium* is disrupted in mismatch-repair mutants. *Nature* **342**, 396–401.

REYNAUD, C.-A., ANQUEZ, V., GRIMAL, H. AND WEILL, J.-C. (1987). A hyperconversion mechanism generates the chicken light chain preimmune repertoire. *Cell* **48**, 379–387.

SEED, B. (1983). Purification of genomic sequences from bacteriophage libraries by recombination and selection in vivo. *Nucleic Acids Research* **11**, 2427–2445.

SHEN, P. AND HUANG, H.V. (1989). Effect of base pair mismatches on recombination via the RecBCD pathway. *Molecular and General Genetics* **218**, 358–360.

TE RIELE, H., MAANDAG, E.R. AND BERNS, A. (1992). Highly efficient gene targeting in embryonic stem cells through homologous recombination with isogenic DNA constructs. *Proceedings of the National Academy of Sciences, USA* **89**, 5128–5132.

THOMAS, D.C., ROBERTS, J.D. AND KUNKEL, T.A. (1991). Heteroduplex repair in extracts of human HeLa cells. *Journal of Biological Chemistry* **266**, 3744–51.

THON, G., BALTZ, T. AND EISEN, H. (1989). Antigenic diversity by the recombination of pseudogenes. *Genes Dev* **3**, 1247–1254.

TSAI-WU, J.-J., RADICELLA, J.P. AND LU, A.-L. (1991). Nucleotide sequence of the *Escherichia coli micA* gene required for A/G-specific mismatch repair: identity of MicA and MutY. *Journal of Bacteriology* **173**, 1902–1910.

WAGNER, R. AND MESELSON, M. (1976).Repair tracts in mismatched DNA heteroduplexes. *Proceedings of the National Academy of Sciences, USA* **73**, 4135–4139.

WILDENBERG, J. AND MESELSON, M. (1975). Mismatch repair in heteroduplex DNA. *Proceedings of the National Academy of Sciences, USA* **72**, 2202–2206.

ZELL, R. AND FRITZ, H.-J. (1987). DNA mismatch-repair in *Escherichia coli* counteracting the hydrolytic deamination of 5-methylcytosine residues. *EMBO Journal* **6**, 1809–1815.