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SnapShot: DNA Mismatch Repair

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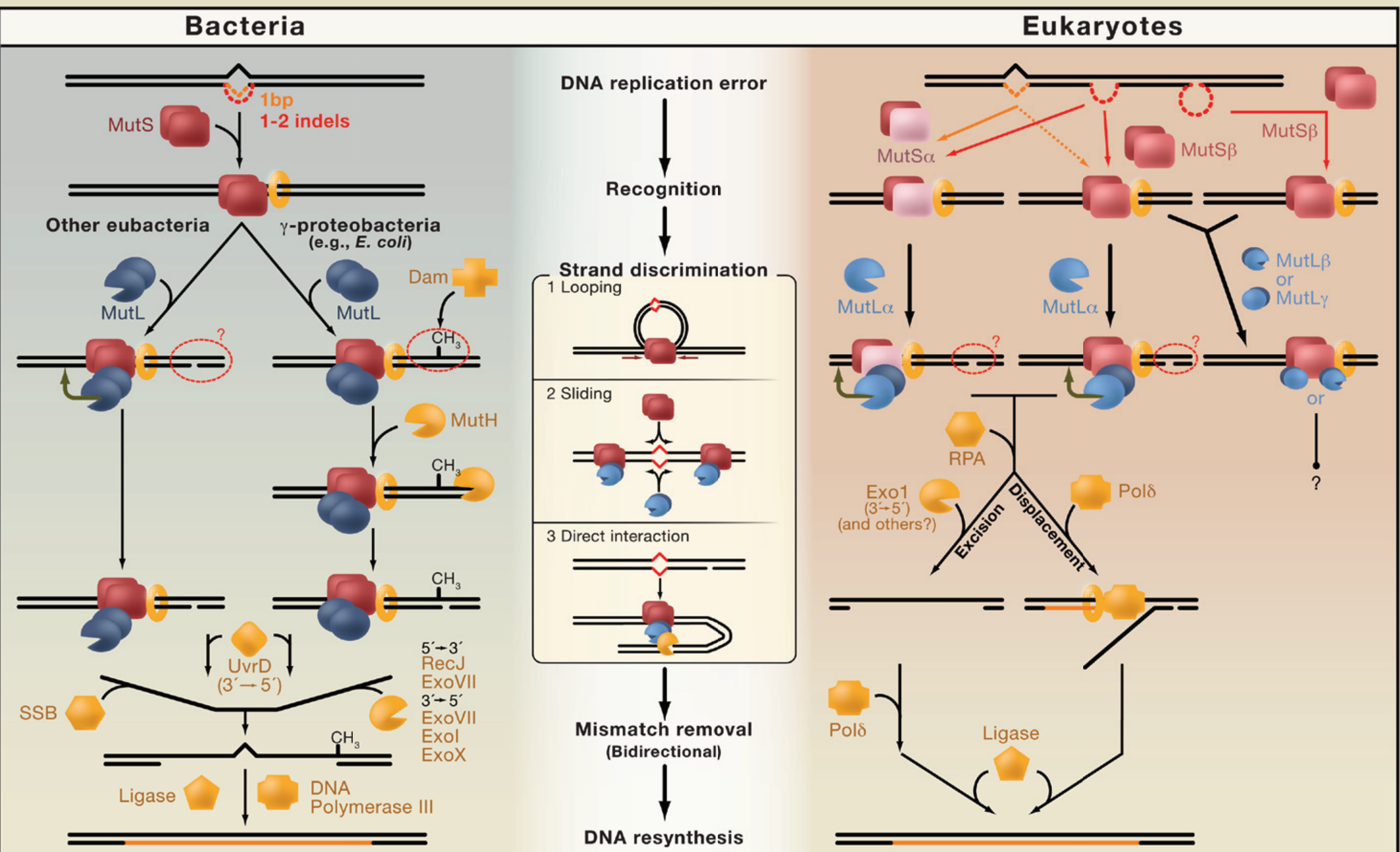

	MutS homologs	MutL homologs	Nucleases	Clamp loaders	Sliding clamps	ssDNA binding	Ligases	DNA pols	Other factors
Other Eubacteria	MutS, MutS2, MutS3, MutS4	MutL	RecJ, EvoVII	γ-cplx	β clamp	SSB	lig	DpolII	UvrD
γ-proteo-bacteria	MutS	MutL	MutH, RecJ, EvoVII, ExoI, ExoX	γ-cplx	β clamp	SSB	LigA	DpolII	UvrD, Dam
Archaea	MutS1, MutS4, MutS5	MutL							
Vertebrates	Msh2, Msh3, Msh6	Mlh1, Pms1, Mlh3, Pms2	Exo1	RFC	PCNA	RPA	Lig1	Polδ	
Insects	Spel1, Msh6	Mlh1, Pms2	Exo1	RFC	PCNA	RPA	Lig1	Polδ	
Fungi	Msh1, Msh2, Msh3, Msh6	Mlh1, Mlh2, Mlh3, Pms1	Exo1	RFC	PCNA	RPA	lig	Polδ	
Plants	Msh1, Msh2, MutS2, Msh3, Msh6, Msh7	Mlh1, Mlh3, Pms1	Exo1	RFC	PCNA	RPA	Lig1	Polδ	

	Structures	Notes
Dam	2G1P 1.85 Å *E. coli*	32 kDa monomer; adenine-specific DNA methylase (GATC) important in repair, replication, and transcription
γ-complex	1JR3 2.70 Å *E. coli*	200 kDa heterodimer; clamp loader, ATPase; binds β clamp, DpolII, DNA, and ATP; loads β-clamp onto primed DNA
RFC	1SXJ 2.85 Å *S. cerevisiae*	211 kDa heteropentamer; clam[p] loader, ATPase; binds PCNA, DNA, and ATP, loads PCNA ont[o] primed DNA
β clamp	1MMI 1.85 Å *E. coli*	81 kDa dimer; sliding clamp processivity factor; binds ssDN[A], DpolII, MutS, and MutL; also known as DNA pol III β subunit
PCNA	1AXC 2.60 Å *H. sapiens*	95 kDa trimer; sliding clamp processivity factor; binds ssDN[A], Exo1, Fen1, Lig1, Msh3, Msh6, DNA pols α/δ/ε and others
MutS	1W7A 2.27 Å *E. coli*	180 kDa dimer; ATPase; DNA mismatch recognition, antirecombination; binds DNA mismatches, MutL, β clamp, AT[P]
MutSα	2O8D 3.00 Å *H. sapiens*	221 kDa heterodimer; ATPase; binds DNA mismatches, ATP, MSH1, PCNA, and BRCA1; als[o] active in meiotic recombination
MutL	1B63/1X9Z 1.90/2.10 Å *E. coli*	135 kDa dimer; ATPase, endonuclease (except in γ-proteobacteria); binds MutS, MutH, β clamp, UvrD, Vsr, ATP
MutH	2AOR 2.00 Å *E. coli*	28 kDa monomer; hemimethylation-directed endonuclease; binds MutL
UvrD	2IS6 2.20 Å *E. coli*	82 kDa monomer; 3′ to 5′ DNA helicase; binds PCNA; also involved in base excision repair also known as DNA helicase II
ExoI	3C94 2.70 Å *E. coli*	54 kDa monomer; 3′ to 5′ DNA exonuclease; also known as SbcB
RecJ	1IR6 2.90 Å *E. coli*	63 kDa monomer; 5′ to 3′ DNA exonuclease; also involved in initiation of recombination
SSB	1QVC 2.20 Å *E. coli*	79 kDa tetramer; binds ssDNA (cooperative), ExoI, RecO, UDG and DNA poll III; also active in replication and recombination
RPA	1JMC 2.40 Å *H. sapiens*	90 kDa heterotrimer; facilitates DNA synthesis, enhances excision, protects template DN[A] binds ssDNA, DNA polα, PCNA
LigA	2OWO 2.30 Å *E. coli*	73 kDa monomer; NAD⁺ or ATP-dependent DNA ligase; binds nicked dsDNA; also known as DnaL or lig
Lig1	1X9N 3.00 Å *H. sapiens*	102 kDa monomer; NAD⁺ or ATP-dependent DNA ligase; binds nicked dsDNA, PCNA, UBC, and MRE11A

See online version for legend and references.

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Mismatch Repair in Bacteria and Eukaryotes

Mismatch repair in the bacterium *Escherichia coli* is initiated when a homodimer of MutS binds as an asymmetric clamp to DNA containing a variety of base-base and insertion-deletion mismatches. The MutL homodimer then couples MutS recognition to the signal that distinguishes between the template and nascent DNA strands. In *E. coli*, the lack of adenine methylation, catalyzed by the DNA adenine methyltransferase (Dam) in newly synthesized GATC sequences, allows *E. coli* MutH to cleave the nascent strand. The resulting nick is used for mismatch removal involving the UvrD helicase, single-strand DNA-binding protein (SSB), and excision by single-stranded DNA exonucleases from either direction, depending upon the polarity of the nick relative to the mismatch. DNA polymerase III correctly resynthesizes DNA and ligase completes repair.

In bacteria lacking Dam/MutH, as in eukaryotes, the signal for strand discrimination is uncertain but may be the DNA ends associated with replication forks. In these bacteria, MutL harbors a nick-dependent endonuclease that creates a nick that can be used for mismatch excision. Eukaryotic mismatch repair is similar, although it involves several different MutS and MutL homologs: MutSα (MSH2/MSH6) recognizes single base-base mismatches and 1–2 base insertion/deletions; MutSβ (MSH2/MSH3) recognizes insertion/deletion mismatches containing two or more extra bases. There are three eukaryotic MutL heterodimers: MutLα (in humans MLH1/PMS2; in yeast MLH1/PMS1), MutLβ (MLH1/MLH3), and MutLγ (human MLH1/PMS1; yeast MLH1/MLH2). The eukaryotic MutS and MutL heterodimers have partial overlap in substrate specificity. MutLα and MutLβ have endonuclease activity, with the active sites present in human PMS2 (yeast PMS1) and human MLH3. The resulting nick can be used for excision by the double-strand DNA 5′-exonuclease activity of Exo1. No helicase has yet been implicated in eukaryotic mismatch repair. Other exonucleases may perform excision, or the mismatch may be removed by strand displacement synthesis. DNA is resynthesized by DNA polymerase δ.

Protein Structures

Also depicted are structures of proteins involved in DNA mismatch repair (including Protein Data Bank ID, resolution, and species) among the many that are now available. Future studies will likely add to this list, possibly including proteins involved in excision, termination, and coordination of mismatch repair with nucleosome reloading and chromatin remodeling after replication.

Evolutionary Conservation

The table provides information on the evolutionary conservation of mismatch repair proteins. Additional notes: grey icons indicate genes found only in subset of species; MSH1 in fungi is involved in mitochondrial DNA repair and is derived from β-proteobacterial MutS via horizontal gene transfer from ancestral mitochondria; MutS in plants is derived from cyanobacterial MutS, is associated with chloroplasts, and is present in varying copy numbers; in archaea the general mismatch repair pathway is unknown, although MutS and MutL family members are found in limited species, likely due to horizontal gene transfer from bacteria. For archaeal MutS5, no mismatch repair-specific DNA binding has been reported.

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