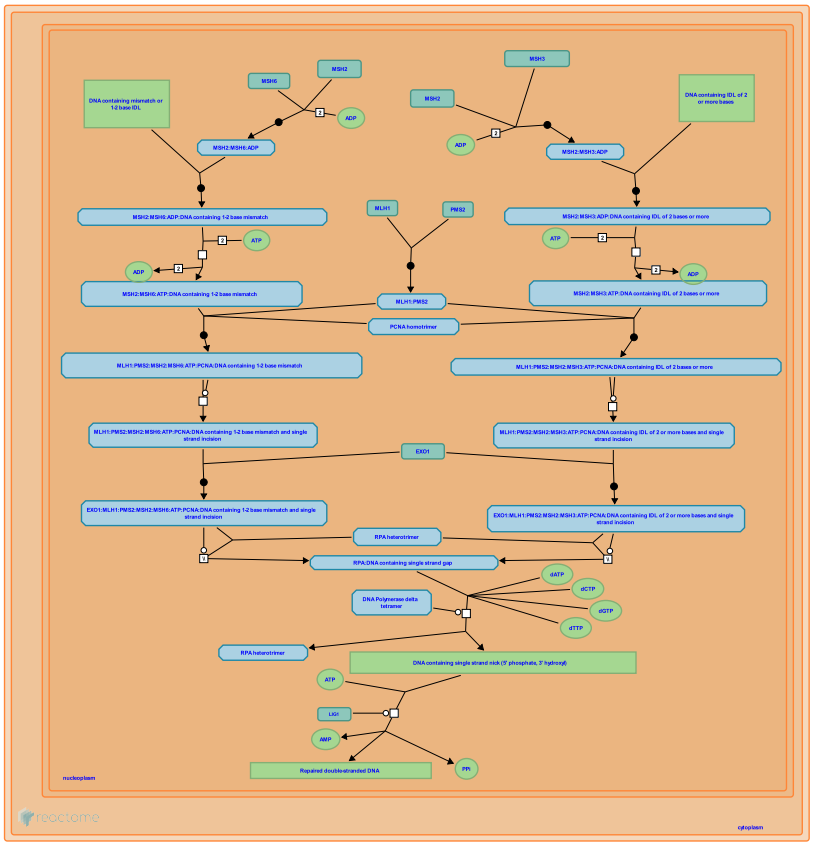
Mismatch Repair



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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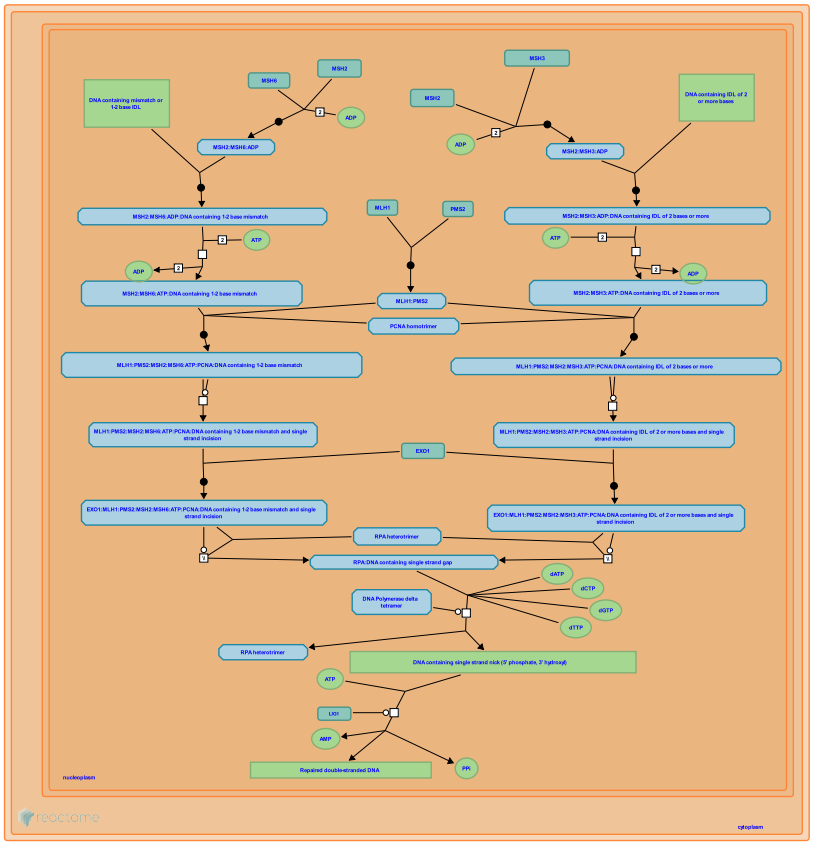
Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Mismatch Repair ↗

Stable identifier: R-HSA-5358508



The mismatch repair (MMR) system corrects single base mismatches and small insertion and deletion loops (IDLs) of unpaired bases. MMR is primarily associated with DNA replication and is highly conserved across prokaryotes and eukaryotes. MMR consists of the following basic steps: a sensor (MutS homologue) detects a mismatch or IDL, the sensor activates a set of proteins (a MutL homologue and an exonuclease) that select the nascent DNA strand to be repaired, nick the strand, exonucleolytically remove a region of nucleotides containing the mismatch, and finally a DNA polymerase resynthesizes the strand and a ligase seals the remaining nick (reviewed in Kolodner and Marsischkny 1999, Iyer et al. 2006, Li 2008, Fukui 2010, Jiricny 2013).
Humans have 2 different MutS complexes. The MSH2:MSH6 heterodimer (MutSalpha) recognizes single base mismatches and small loops of one or two unpaired bases. The MSH2:MSH3 heterodimer (MutSbeta) recognizes loops of two or more unpaired bases. Upon binding a mismatch, the MutS complex becomes activated in an ATP-dependent manner allowing for subsequent downstream interactions and movement on the DNA substrate. (There are two mechanisms proposed: a sliding clamp and a switch diffusion model.) Though the order of steps and structural details are not fully known, the activated MutS complex interacts with MLH1:PMS2 (MutLalpha) and PCNA, the sliding clamp present at replication foci. The role of PCNA is multifaceted as it may act as a processivity factor in recruiting MMR proteins to replicating DNA, interact with MLH1:PMS2 and Exonuclease 1 (EXO1) to initiate excision of the recently replicated strand and direct DNA polymerase delta to initiate replacement of bases. MLH1:PMS2 makes an incision in the strand to be repaired and EXO1 extends the incision to make a single-stranded gap of up to 1 kb that removes the mismatched base(s). (Based on assays of purified human proteins, there is also a variant of the mismatch repair pathway that does not require EXO1, however the mechanism is not clear. EXO1 is almost always required, it is possible that the exonuclease activity of DNA polymerase delta may compensate in some situations and it has been proposed that other endonucleases may perform redundant functions in the absence of EXO1.) RPA binds the single-stranded region and a new strand is synthesized across the gap by DNA polymerase delta. The remaining nick is sealed by DNA ligase I (LIG1).
Concentrations of MMR proteins MSH2:MSH6 and MLH1:PMS2 increase in human cells during S phase and are at their highest level and activity during this phase of the cell cycle (Edelbrock et al. 2009). Defects in MSH2, MSH6, MLH1, and PMS2 cause hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome) (reviewed in Martin-Lopez and Fishel 2013).

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Editions

2014-03-28	Authored, Edited	May, B.
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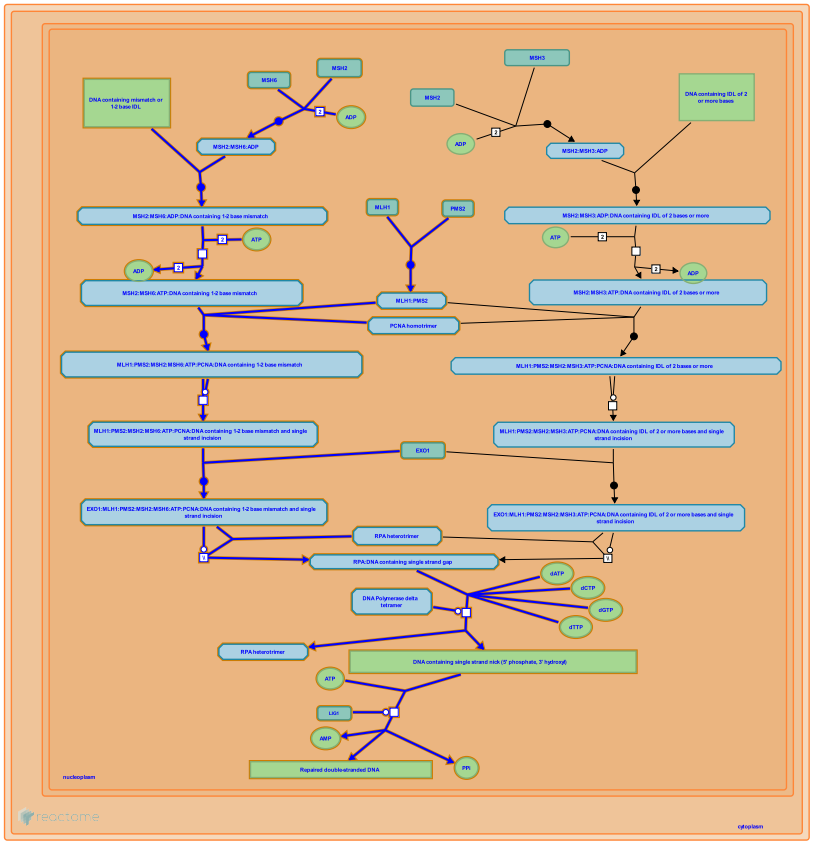
Mismatch repair (MMR) directed by MSH2:MSH6 (MutSalpha) ↗

Location: Mismatch Repair

Stable identifier: R-HSA-5358565



MSH2:MSH6 (MutSalpha) binds single base mismatches and unpaired loops of 1-2 nucleotides (reviewed in Edelbrock et al. 2013). Human cells contain about 6-fold more MSH2:MSH6 than MSH2:MSH3 (MutSbeta), which mediates repair of larger mismatches, and an imbalance in the ratio can cause a mutator phenotype (Drummond et al. 1997, Marra et al. 1998). The MSH6 subunit is responsible for binding the mismatch, which activates MSH2:MSH6 to exchange ADP for ATP, adopt the conformation to allow movement on the DNA, and interact with downstream effectors PCNA, MLH1:PMS2 and EXO1. The interaction with PCNA initiates excision of the recently replicated strand. MLH1:PMS2 has endonucleolytic activity and makes a nick that is enlarged to a gap of hundreds of nucleotides by EXO1. DNA is polymerized across the gap by DNA polymerase delta and the remaining nick is sealed by DNA ligase I.

Literature references

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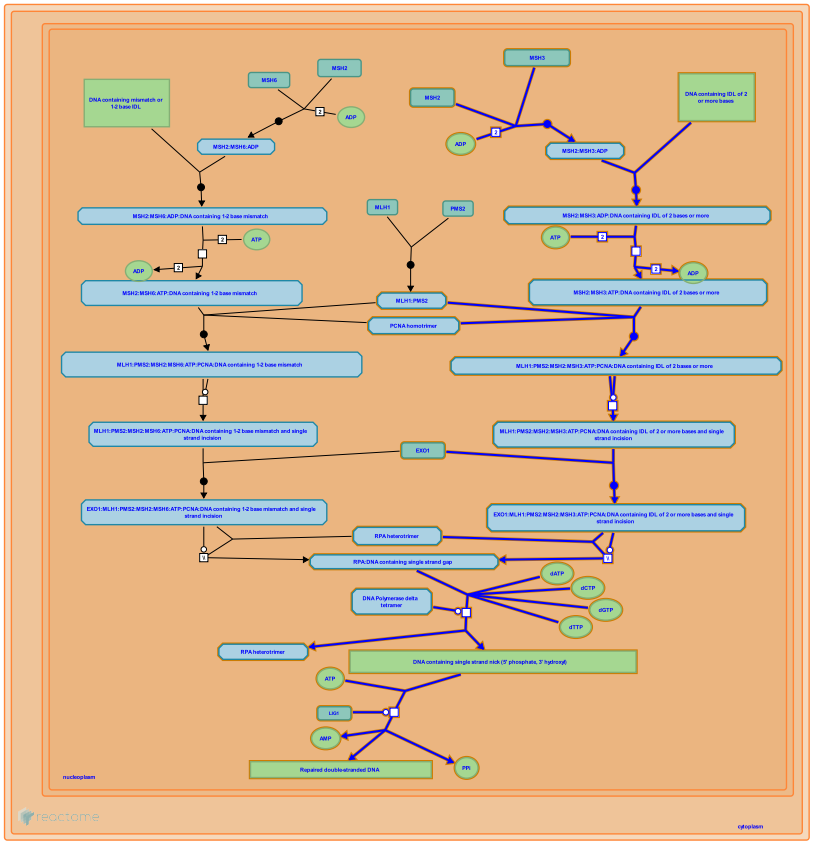
Mismatch repair (MMR) directed by MSH2:MSH3 (MutSbeta) ↗

Location: Mismatch Repair

Stable identifier: R-HSA-5358606



MSH2:MSH3 (MutSbeta) binds unpaired loops of 2 or more nucleotides (Palombo et al. 1996, Genschel et al. 1998). Human cells contain about 6-fold more MSH2:MSH6 than MSH2:MSH3 (MutSbeta) and an imbalance in the ratio can cause a mutator phenotype (Drummond et al. 1997, Marra et al. 1998). Binding of the mismatch activates MSH2:MSH3 to exchange ADP for ATP, adopt the conformation to allow movement along the DNA, and interact with downstream effectors PCNA, MLH1:PMS2 and EXO1. The interaction with PCNA initiates excision of the recently replicated strand. MLH1:PMS2 makes a nick that is enlarged to a gap of hundreds of nucleotides by EXO1. DNA is polymerized across the gap by DNA polymerase delta and the remaining nick is sealed by DNA ligase I.

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