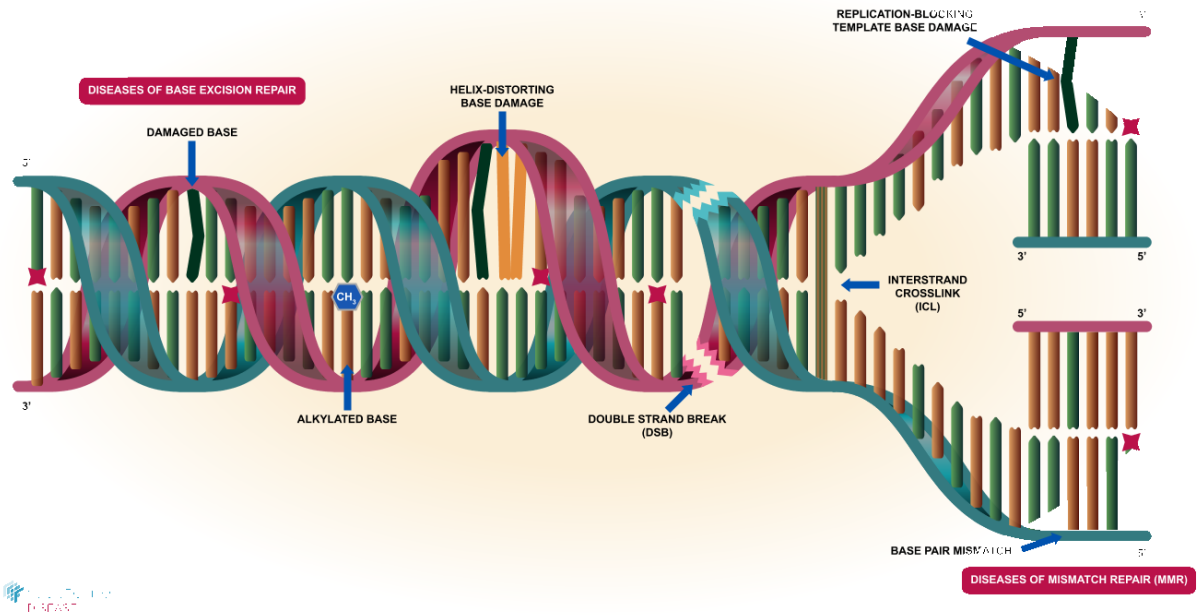
Diseases of DNA repair



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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.

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Literature references

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Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

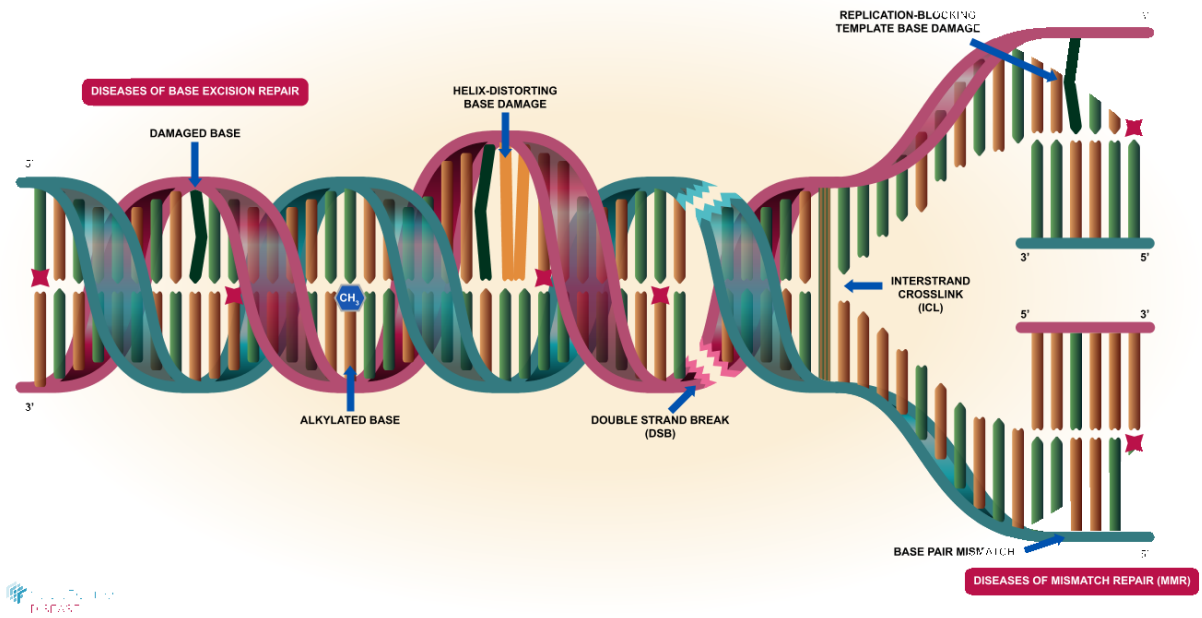
Reactome database release: 74

This document contains 3 pathways (see Table of Contents)

Diseases of DNA repair ↗

Stable identifier: R-HSA-9675135

Diseases: genetic disease



Inherited and sporadic defects in genes that encode proteins that participate in DNA repair give rise to genetic instability that can lead to malignant transformation or trigger cellular senescence or apoptosis. Inherited defects in DNA repair genes are the underlying cause of familial cancer syndromes and premature ageing syndromes. Sporadic defects in DNA repair genes are frequently found in tumors. For review, please refer to Tiwari and Wilson 2019.

We have so far annotated diseases of mismatch repair and diseases of base excision repair.

Defects in mammalian DNA mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6) result in microsatellite instability (MSI) and reduced fidelity during replication and repair steps. Defective variants of MMR genes are associated with sporadic cancers with hypermutation phenotype as well as hereditary cancer syndromes such as Lynch syndrome (hereditary non-polyposis colorectal cancer) and constitutional mismatch repair deficiency syndrome (CMMRD). MSI is an important predictor of sensitivity to cancer immunotherapy. For review, please refer to Pena-Diaz and Rasmussen 2016, Sijmons and Hofstra 2016, Tabori et al. 2017, Baretti and Le 2018.

Germline mutations, single nucleotide polymorphisms (SNPs) and somatic mutations in several genes involved in base excision repair (BER), a DNA repair pathway where a damaged DNA base is excised and replaced with a correct base, are involved in the development of cancer and several oxidative stress-related diseases. For review, please refer to Fu et al. 2012, Fletcher and Houlston 2010, Brenerman et al. 2014, Patrono et al. 2014, and D'Errico et al. 2017.

Literature references

Fu, D., Calvo, JA., Samson, LD. (2012). Balancing repair and tolerance of DNA damage caused by alkylating agents. *Nat. Rev. Cancer, 12*, 104-20. ↗

Baretti, M., Le, DT. (2018). DNA mismatch repair in cancer. *Pharmacol. Ther., 189*, 45-62. ↗

D'Errico, M., Parlanti, E., Pascucci, B., Fortini, P., Baccarini, S., Simonelli, V. et al. (2017). Single nucleotide polymorphisms in DNA glycosylases: From function to disease. *Free Radic. Biol. Med., 107*, 278-291. ↗

Tiwari, V., Wilson, DM. (2019). DNA Damage and Associated DNA Repair Defects in Disease and Premature Aging. *Am. J. Hum. Genet., 105*, 237-257. ↗

Sijmons, RH., Hofstra, RMW. (2016). Review: Clinical aspects of hereditary DNA Mismatch repair gene mutations. *DNA Repair (Amst.), 38*, 155-162. ↗

Editions

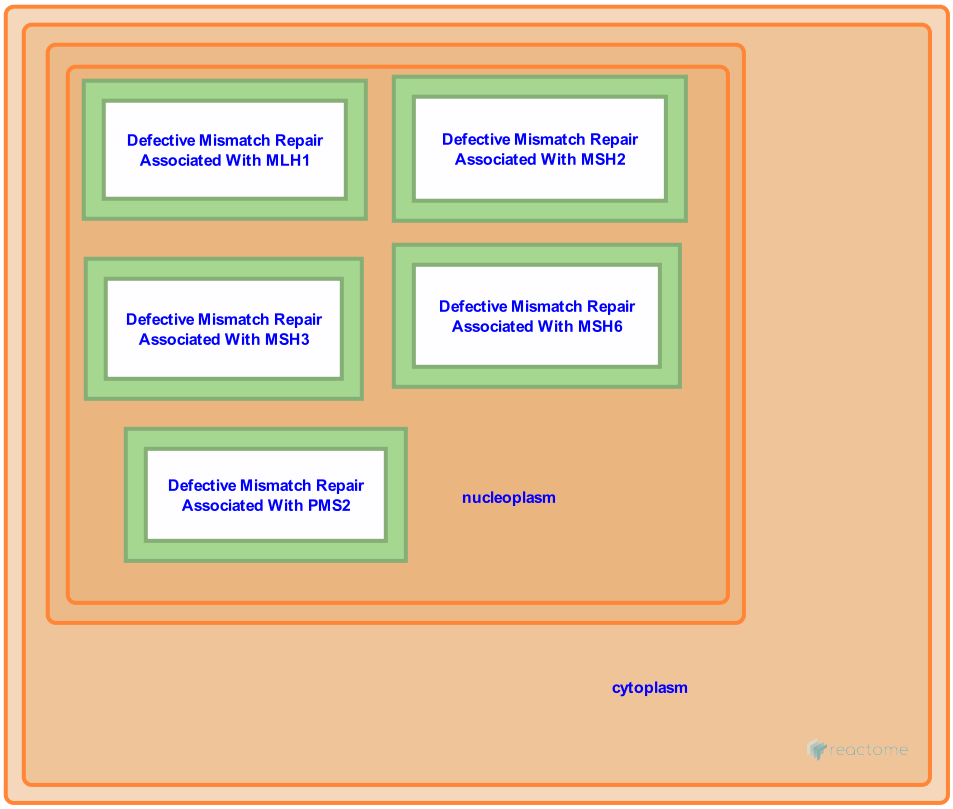
2020-02-21	Authored	Orlic-Milacic, M.
2020-02-24	Reviewed	D'Eustachio, P.
2020-02-24	Edited	Orlic-Milacic, M.

Diseases of Mismatch Repair (MMR) ↗

Location: Diseases of DNA repair

Stable identifier: R-HSA-5423599

Diseases: cancer



Defects in mammalian DNA mismatch repair (MMR) genes (MLH1, PMS2, MSH2, and MSH6) are characterized by microsatellite instability and reduced fidelity during replication and repair steps. The MMR proteins interact with each other to execute steps within the mismatch repair pathway. Defective variants of these proteins are associated with nonpolyposis colorectal cancer. The MutS proteins are thought to directly contact double-stranded DNA, scanning along the genomic DNA for mismatches analogous to a "sliding clamp" until they encounter a base pair containing a mismatch. The MutS proteins interact with multiple proteins including other MLH and MutL, the later have significant amino acid identify and structural similarity to the MLH proteins, as well as RPA, EXO1, RFC, possibly HMGB1, and other less well-characterized proteins.

With respect to the mutator function, the MSH2/MutSaplha heterodimer is thought primarily to repair single-base substitutions and 1 bp insertiondeletion mutations, while MSH2/MutSbeta is thought primarily to repair 1-4 bp insertiondeletion mutations. The MLH and MutL heterodimer proteins interact with heterodimers of MutS proteins to help catalyze different functions. MLH1:MutLalpha is the primary complex that interacts with both MutS alpha and beta complex in mechanisms thought to be relevant to cancer prevention. Recent studies suggest that MLH1:MLH3 may also contributes to some of these processes as well, but in all mechanisms tested to a lesser degree than MLH1:PMS2.

Literature references

Chao, EC., Lipkin, SM. (2006). Molecular models for the tissue specificity of DNA mismatch repair-deficient carcinogenesis. *Nucleic Acids Res., 34,* 840-52. ↗

Editions

2014-03-03	Authored	Gillespie, ME.
2016-11-01	Reviewed	Arora, S.
2017-02-27	Edited	Gillespie, ME.

Diseases of Base Excision Repair ↗

Location: Diseases of DNA repair

Stable identifier: R-HSA-9605308

Diseases: cancer

Germline mutations, single nucleotide polymorphisms (SNPs) and somatic mutations in several genes involved in base excision repair (BER), a DNA repair pathway where a damaged DNA base is excised and replaced with a correct base, are involved in the development of cancer and several other oxidative stress-related diseases. For review, please refer to Fu et al. 2012, Fletcher and Houlston 2010, Brenerman et al. 2014, Patrono et al. 2014, and D'Errico et al. 2017.

Literature references

Fu, D., Calvo, JA., Samson, LD. (2012). Balancing repair and tolerance of DNA damage caused by alkylating agents. *Nat. Rev. Cancer, 12*, 104-20. ↗

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D'Errico, M., Parlanti, E., Pascucci, B., Fortini, P., Baccarini, S., Simonelli, V. et al. (2017). Single nucleotide polymorphisms in DNA glycosylases: From function to disease. *Free Radic. Biol. Med., 107*, 278-291. ↗

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Editions

2018-05-12	Authored	Orlic-Milacic, M.
2018-08-09	Edited	Orlic-Milacic, M.

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