Diseases of Mismatch Repair (MMR)

Defective Mismatch Repair Associated With MLH1
Defective Mismatch Repair Associated With MSH2
Defective Mismatch Repair Associated With MSH3
Defective Mismatch Repair Associated With MSH6
Defective Mismatch Repair Associated With PMS2

nucleoplasm

cytoplasm

Arora, S., Gillespie, ME.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

05/07/2020
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).

Literature references


Reactome database release: 73

This document contains 6 pathways (see Table of Contents)
Diseases of Mismatch Repair (MMR)

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

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-03-03</td>
<td>Authored</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2016-11-01</td>
<td>Reviewed</td>
<td>Arora, S.</td>
</tr>
<tr>
<td>2017-02-27</td>
<td>Edited</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
Defective Mismatch Repair Associated With MLH1

Location: Diseases of Mismatch Repair (MMR)

Stable identifier: R-HSA-5545483

Compartments: nucleoplasm

Diseases: cancer

The MLH1:PMS2 complex is homologous to the E. coli MutL gene and is involved in DNA mismatch repair. Heterozygous mutations in the MLH1 gene result in hereditary nonpolyposis colorectal cancer-2 (Papadopoulous et al., 1994).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-11-10</td>
<td>Authored</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2016-11-01</td>
<td>Reviewed</td>
<td>Arora, S.</td>
</tr>
<tr>
<td>2017-02-27</td>
<td>Edited</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
MSH2 is homologous to the E. coli MutS gene and is involved in DNA mismatch repair (MMR) (Fishel et al., 1994). Heterozygous mutations in the MSH2 gene result in hereditary nonpolyposis colorectal cancer-1. Variants of MSH2 are associated with hereditary nonpolyposis colorectal cancer. Alteration of MSH2 is also involved in Muir-Torre syndrome and mismatch repair cancer syndrome.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-11-10</td>
<td>Authored</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2016-11-01</td>
<td>Reviewed</td>
<td>Arora, S.</td>
</tr>
<tr>
<td>2017-02-27</td>
<td>Edited</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
Defective Mismatch Repair Associated With MSH3

Location: Diseases of Mismatch Repair (MMR)

Stable identifier: R-HSA-5632927

Compartments: nucleoplasm

Diseases: cancer

MSH3 forms a heterodimer with MSH2 to form the MSH3:MSH2 complex, part of the post-replicative DNA mismatch repair system. This complex initiates mismatch repair by binding to a mismatch and then forming a complex with MutL alpha heterodimer. This gene contains a polymorphic 9 bp tandem repeat sequence in the first exon. Defects in this gene are a cause of susceptibility to endometrial cancer.

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-11-10</td>
<td>Authored</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2016-11-01</td>
<td>Reviewed</td>
<td>Arora, S.</td>
</tr>
<tr>
<td>2017-02-27</td>
<td>Edited</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
Defective Mismatch Repair Associated With MSH6

Location: Diseases of Mismatch Repair (MMR)

Stable identifier: R-HSA-5632968

Compartments: nucleoplasm

Diseases: cancer

MSH6 encodes a G/T mismatch-binding protein encoded by a gene localized to within 1 megabase of the related hMSH2 gene on chromosome 2. Unlike other mismatch repair genes, the MSH6 deficient cells showed alterations primarily in mononucleotide tracts, indicating the role MSH6 plays in maintaining the integrity of the human genome. Cells deficient in MSH6, accrue mutations in tracts of repeated nucleotides. MSH6 defects seem to be less common than MLH1 and MSH2 defects. They have been mostly observed in atypical HNPCC families and are characterized by a weaker family history of tumor development, higher age at disease onset, and low degrees of microsatellite instability (MSI) that predominantly involving mononucleotide runs.

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-11-10</td>
<td>Authored</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2016-11-01</td>
<td>Reviewed</td>
<td>Arora, S.</td>
</tr>
<tr>
<td>2017-02-27</td>
<td>Edited</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
Defective Mismatch Repair Associated With PMS2

Location: Diseases of Mismatch Repair (MMR)

Stable identifier: R-HSA-5632987

Compartments: nucleoplasm

Diseases: cancer

PMS2 heterodimerizes with MLH1 to form the MutL alpha complex involved in DNA mismatch repair. Mutations in this PMS2 are associated with hereditary nonpolyposis colorectal cancer, Turcot syndrome, and are a cause of supratentorial primitive neuroectodermal tumors.

Heterozygous truncating mutations in PMS2 play a role in a small subset of hereditary nonpolyposis colorectal carcinoma (Lynch syndrome, HNPCC-like) families. PMS2 mutations lead to microsatellite instability with carriers showing a microsatellite instability high phenotype and loss of PMS2 protein expression in all tumors.

Literature references


## Table of Contents

Introduction 1

- Diseases of Mismatch Repair (MMR) 2
  - Defective Mismatch Repair Associated With MLH1 4
  - Defective Mismatch Repair Associated With MSH2 5
  - Defective Mismatch Repair Associated With MSH3 6
  - Defective Mismatch Repair Associated With MSH6 7
  - Defective Mismatch Repair Associated With PMS2 8

Table of Contents