Defective HDR through Homologous Recombination (HRR) due to PALB2 loss of function

Masson, JY., Milano de Souza, L., Orlic-Milacic, M., Pospiech, H., Winqvist, R.

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.

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

13/11/2022
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: 82

This document contains 3 pathways (see Table of Contents)

https://reactome.org
Defective HDR through Homologous Recombination (HRR) due to PALB2 loss of function

Stable identifier: R-HSA-9701193

Compartments: nucleoplasm

Diseases: cancer

Biallelic loss-of-function mutations in PALB2 results in Fanconi anemia subtype N (FA-N), which is phenotypically very similar to Fanconi anemia subtype D1, caused by biallelic loss-of-function of BRCA2 (Reid et al. 2007). FA-D1 and FA-N are characterized by developmental abnormalities, bone marrow failure and childhood cancer susceptibility, especially childhood solid tumors, such as Wilms tumor and medulloblastoma. Monoallelic PALB2 loss-of-function is an underlying cause of hereditary breast cancer in particular, but inactivating PALB2 mutations are also to a lesser extent found in some other cancer types, including pancreatic cancer (Erkko et al. 2007, Erkko et al. 2008, Antoniou et al. 2014, Yang et al. 2020). Germline PALB2 mutations are somewhat less frequent than those occurring in BRCA1 and BRCA2, but cause a comparably high risk of developing breast cancer. Therefore, PALB2 is a high-risk breast cancer predisposing gene (Nepomuceno et al. 2021).

PALB2 interacts with both BRCA1 and BRCA2, and serves as a bridge that connects BRCA2 with BRCA1 at sites of DNA double-strand break repair (DSBR). PALB2 also interacts directly with DNA and takes part in the regulation of RAD51-mediated homologous recombination (Buisson et al. 2010; Dray et al. 2010). PALB2 loss-of-function mutations can affect its interaction with BRCA1 when they affect the N-terminal coiled-coil domain that is necessary for BRCA1 binding (Sy et al. 2009, Foo et al. 2017). Mutations in the coiled-coil domain can also affect PALB2 self-interaction, recruitment to double-strand break sites, homologous recombination repair and RAD51 foci formation (Buisson and Masson 2012). PALB2 missense mutants that do not bind to BRCA1 can still be recruited to DSBR sites, probably through interaction with other proteins involved in DSBR, but they are unable to restore efficient gene conversion in PALB2-deficient cells and they render cells hypersensitive to the DNA damaging agent mitomycin C (Sy et al. 2009), with some variants also presenting sensitivity to PARP inhibitors (Foo et al. 2017).

Mutations evaluated so far in the central region of PALB2, which contains the ChAM motif and the MRG15-binding region, have shown no functional impact on the protein.

Mutations affecting the C-terminal WD40 domain of PALB2 impair its ability to interact with BRCA2, RAD51 and/or RAD51C (Erkko et al. 2007, Park et al. 2014, Simhadri et al. 2019). In addition, disruption of the WD40 domain can lead to the exposure of a nuclear export signal (NES), leading to cytoplasmic translocation of PALB2 (Pauty et al. 2017). Mutations affecting the C-terminal domain of PALB2 are more frequent than mutations that affect the N-terminus and have been observed, as germline mutations, in familial breast cancer and in Fanconi anemia, but somatic mutations also occur in sporadic cancers. Cells that express PALB2 mutants defective in BRCA2, RAD51 and/or RAD51C binding show reduced ability to perform DSBR via homologous recombination repair, form fewer RAD51 foci at DSBR sites, and are sens-
itive to DNA crosslinking agents such as mitomycin C (Erkko et al. 2007, Parker et al. 2014).


**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020-10-09</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2021-02-25</td>
<td>Reviewed</td>
<td>Pospiech, H., Winqvist, R.</td>
</tr>
<tr>
<td>2021-03-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2021-07-25</td>
<td>Reviewed</td>
<td>Masson, JY., Milano de Souza, L.</td>
</tr>
<tr>
<td>2021-08-05</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of BRCA1 binding function

**Location:** Defective HDR through Homologous Recombination (HRR) due to PALB2 loss of function

**Stable identifier:** R-HSA-9704331

**Compartments:** nucleoplasm

**Diseases:** cancer

Mutations in the N-terminal coiled-coil domain of PALB2 (amino acids 9-44), involved in self-interaction and BRCA1 binding, impair the interaction of PALB2 with BRCA1 (Sy et al. 2009, Foo et al. 2017, Boonen et al. 2020). Phosphorylation of PALB2 by ATR on serine residue S59 promotes BRCA1-PALB2 interaction and the localization of PALB2 to DNA damage sites (Buisson et al. 2017). Mutations in the coiled-coil domain can also affect PALB2 self-interaction, recruitment to double-strand break sites, homologous recombination repair, and RAD51 foci formation (Buisson and Masson 2012). PALB2 missense mutants that do not bind to BRCA1 can still be recruited to DNA double-strand break repair (DSBR) sites, probably through interaction with other proteins involved in DSBR, but they are unable to restore efficient gene conversion in PALB2-deficient cells and they render cells hypersensitive to the DNA damaging agent mitomycin C (Sy et al. 2009). Some variants in this region are also sensitive to PARP inhibitors (Foo et al. 2017).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020-10-09</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2021-02-25</td>
<td>Reviewed</td>
<td>Pospiech, H., Winqvist, R.</td>
</tr>
<tr>
<td>2021-03-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2021-07-25</td>
<td>Reviewed</td>
<td>Masson, JY., Milano de Souza, L.</td>
</tr>
<tr>
<td>2021-08-05</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of BRCA2/RAD51/RAD51C binding function

Location: Defective HDR through Homologous Recombination (HRR) due to PALB2 loss of function

Stable identifier: R-HSA-9704646

Compartments: nucleoplasm

Diseases: cancer

Mutations affecting the C-terminal WD40 domain of PALB2 (amino acids 853-1186) impair its ability to interact with BRCA2, RAD51 and/or RAD51C (Erkko et al. 2007, Park et al. 2014). In addition, disruption of the WD40 domain can lead to the exposure of the nuclear export signal (NES) and cytoplasmic translocation of PALB2 (Pauty et al. 2017). Mutations affecting the C-terminal domain of PALB2 are more frequent than mutations that affect the N-terminus and have been observed, as germline mutations, in familial breast cancer and in Fanconi anemia, but somatic mutations also occur in sporadic cancers. Cells that express PALB2 mutants defective in BRCA2, RAD51 and/or RAD51C binding show reduced ability to perform DSBR via homologous recombination repair, form fewer RAD51 foci at DSBR sites, and are sensitive to DNA crosslinking agents such as mitomycin C (Erkko et al. 2007, Park et al. 2014).

Literature references


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2020-10-09</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2021-02-25</td>
<td>Reviewed</td>
<td>Pospiech, H., Winqvist, R.</td>
</tr>
<tr>
<td>2021-03-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2021-07-25</td>
<td>Reviewed</td>
<td>Masson, JY., Milano de Souza, L.</td>
</tr>
<tr>
<td>2021-08-05</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>

https://reactome.org
Table of Contents

Introduction 1

- Defective HDR through Homologous Recombination (HRR) due to PALB2 loss of function 2

- Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of BRCA1 binding function 4

- Defective HDR through Homologous Recombination Repair (HRR) due to PALB2 loss of BRCA2/RAD51/RAD51C binding function 6

Table of Contents 8