Diseases of Base Excision Repair

Boldogh, I., Doetsch, PW., Kuiper, RP., Nakabeppu, Y., Orlic-Milacic, M., Rivera Polo, B., Sampath, H., Vlahopoulos, S., Zhou, J., de Voer, RM.

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

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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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Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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

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Diseases of Base Excision 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

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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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Brenerman, BM., Illuzzi, JL., Wilson, DM. (2014). Base excision repair capacity in informing healthspan. *Carcinogenesis, 35*, 2643-52. ↗

Editions

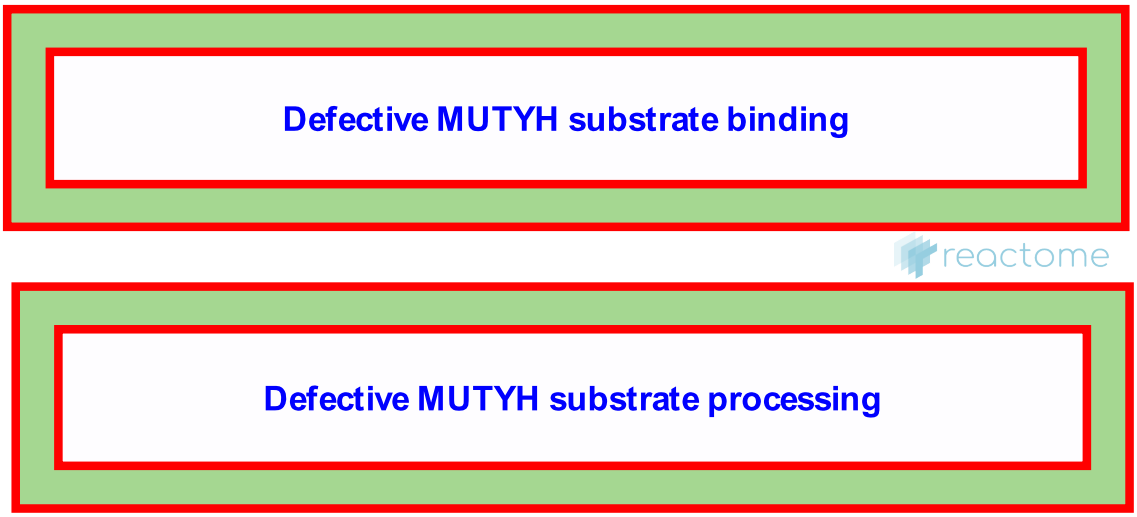
2018-05-12	Authored	Orlic-Milacic, M.
2018-08-09	Edited	Orlic-Milacic, M.

Defective Base Excision Repair Associated with MUTYH ↗

Location: Diseases of Base Excision Repair

Stable identifier: R-HSA-9605310

Diseases: cancer, colorectal cancer, familial adenomatous polyposis



MUTYH gene is located on chromosome 1 and encodes a DNA glycosylase involved in base excision repair (BER). MUTYH (MYH) functions as an adenine DNA glycosylase and removes adenines and 2-hydroxyadenines on the newly synthesized DNA strand mispaired with guanines or 8-oxoguanines. 8-oxogunanines are produced by oxidation of guanines in DNA or by incorporation of 8-oxodGTP from the nucleotide pool into the newly synthesized DNA strand. Germline mutations in MUTYH cause the MUTYH-associated polyposis (MAP), a syndrome that resembles the familial adenomatous polyposis (FAP) syndrome, caused by mutations in the APC tumor suppressor gene. MAP is also known as the familial adenomatous polyposis 2 (FAP2) (OMIM:608456). MAP-affected individuals are predisposed to development of multiple colorectal adenomas and colorectal cancer. MAP is largely inherited in an autosomally recessive manner, with both MUTYH alleles affected. The predisposition of heterozygous MUTYH mutation carriers to MAP has not been completely ruled out (Fleischmann et al. 2004).

MUTYH is most frequently affected by missense mutations in MAP patients, with two major mutations, Y165C and G382D, reported in about 80% of MAP patients of European origin. In Japanese patients, the most frequently reported mutation was Q324H (Yanaru-Fujisawa et al. 2008). Residues Y165C and G382D in the abundant MUTYH isoform MUTYH alpha-3 (MUTYH-3), used in the majority of functional studies, correspond to Y176C and G393D, respectively, in the canonical UniProt isoform (MUTYH alpha-1) and to Y179C and G396, respectively, in the longest NCBI isoform, which is used as a reference isoform in the database InSiGHT (International Society for Gastrointestinal Hereditary Tumours Database). However, both the canonical UniProt and NCBI MUTYH isoforms are expressed at very low levels or not at all (Plotz et al. 2012). In addition to the isoform MUTYH alpha-3, the other two abundant MUTYH isoforms are MUTYH beta-3 and MUTYH gamma-3 (Plotz et al. 2012), which differ from MUTYH alpha-3 in the first exon used. Exons 1-alpha and 1-beta contain sequences that resemble a mitochondrial targeting signal (MTS). It was reported that MUTYH alpha-3 and MUTYH beta-3 predominantly localize to mitochondria, while MUTYH gamma-3 predominantly localizes to the nucleus (Takao et al. 1999). However, a nuclear localization signal is located at the C-terminus of all MUTYH isoforms and other studies suggested that all isoforms can localize to the nucleus and only a small fraction of MUTYH is targeted to the mito-

chondria (Ohtsubo et al. 2000, Ichinoe et al. 2004). A small number of functional studies of MUTYH mutants uses the MUTYH isoform gama-3 (Goto et al. 2010, Shinmura et al. 2012). Nuclear localization of MUTYH may be affected by a splicing site variant (Tao et al. 2004).

MAP, compared with APC-associated FAP, is characterized by a later age of onset and a smaller number and size of polyps. Germline MUTYH mutations are associated with an increased incidence of duodenal polyps, gastric cancer, melanoma, breast cancer, dental and dermoid cysts, and osteomas. MUTYH mutations are rarely reported in the sporadic colorectal cancer. Tumors that develop in MAP patients are characterized with an excess of G:C -> T:A transversions in tumor suppressor genes, such as APC, and oncogenes, such as KRAS, which is a consequence of MUTYH functional impairment.

A single nucleotide polymorphism (SNP) at the splice donor site was reported to affect translation efficiency of MUTYH transcript, but its relevance for cancer predisposition has not been clarified (Yamaguchi et al. 2002). Catalytic activity of MUTYH and its mutants may be affected by posttranslational modifications (Parker et al. 2003, Kundu et al. 2010). Some MUTYH mutations reported in colorectal cancer do not affect MUTYH catalytic activity but disrupt the interaction of MUTYH with other proteins involved in DNA repair (Tominaga et al. 2004, Turco et al. 2013).

For review, please refer to Chow et al. 2004, Nielsen et al. 2011, Venesio et al. 2012, Mazzei et al. 2013.

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Editions

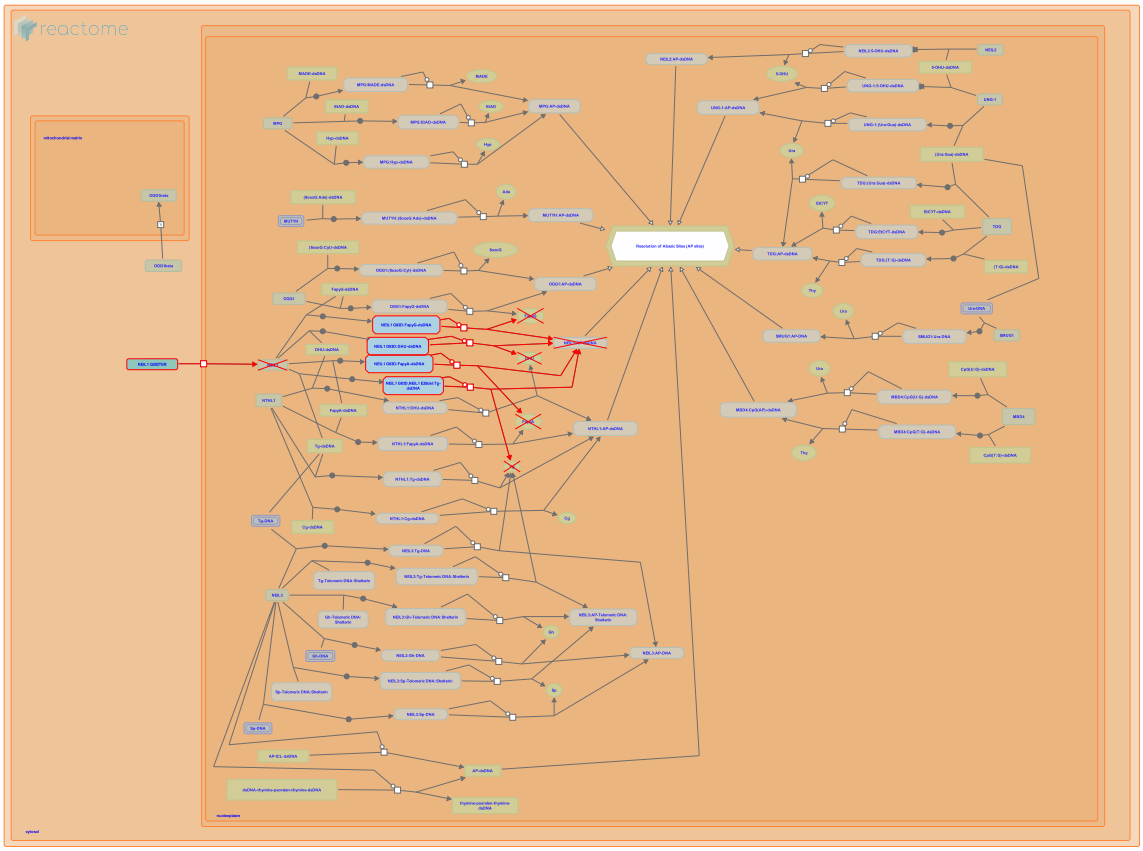
2018-05-12	Authored	Orlic-Milacic, M.
2018-06-28	Reviewed	Nakabeppu, Y.
2018-06-29	Edited	Orlic-Milacic, M.

Defective Base Excision Repair Associated with NEIL1 ↗

Location: Diseases of Base Excision Repair

Stable identifier: R-HSA-9616334

Diseases: cancer



NEIL1 is an enzyme with dual DNA glycosylase and beta/delta lyase activity involved in base excision repair pathway (BER), the primary repair pathway for oxidative DNA damage. NEIL1 can detect and remove DNA damage resulting from oxidation of adenine, guanine and thymine, in the form of 4,6-diamino-5-formamidopyrimidine (FapyA), 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), and thymine glycol (Tg), respectively. NEIL1 can also detect and remove dihydrouracil (DHU), which results from deamination of cytosine. Several low frequency NEIL1 polymorphisms, present in about 1% of general population in the United States have been reported. Different polymorphisms have different effects on NEIL1 function, and it was suggested that NEIL1 polymorphisms and NEIL1 deficiency or haploinsuficiency may be involved in predisposition to cancer and in metabolic syndrome (Roy et al. 2007, Vartanian et al. 2006, Sampath et al. 2011, Prakash et al. 2014). One polymorphism, NEIL1 G83D, is associated with primary sclerosing cholangitis and cholangiocarcinoma (Forsbring et al. 2009). NEIL1 G83D variant exhibits impaired DNA glycosylase activity towards different damaged DNA bases (Roy et al. 2007, Prakash et al. 2014) and induces genomic instability (Galick et al. 2017).

NEIL1 E28del, an in frame deletion variant of NEIL1 reported in gastric (stomach) cancer, where glutamate at position 28 is deleted, does not cleave Tg from damaged DNA (Shinmura et al. 2004).

NEIL1 Q282TER, a NEIL1 variant which lacks the putative nuclear localization signal (NLS), localizes to the cytosol and is therefore not able to access damaged DNA substrates, but its involvement in cancer is uncertain (Shinmura et al. 2015).

Reduced expression of NEIL1 and NEIL2 genes, accompanied with increased NEIL3 gene expression was

detected in various cancers. NEIL1 gene silencing by promoter hypermethylation may be one of the underlying mechanisms for reduced NEIL1 expression in cancer (Shinmura et al. 2016).

Infection with the Hepatitis C virus (HCV) leads to decreased NEIL1 expression in liver cells, through an unknown mechanism (Pal et al. 2010).

Mice that are double knockout for Neil1 and Nthl1 genes accumulate DNA damage in the form of FapyA and FapyG and are more prone to development of lung adenocarcinoma than single Neil1 or Nthl1 gene knockouts (Chan et al. 2009). Another study reported that Neil1 knockout mice did not show a predisposition to tumour formation, and neither did double knockouts of Neil1 and Neil2, nor triple knockouts of Neil1, Neil2 and Neil3. Neil1 knockout mice are obese, consistent with the metabolic syndrome, but double knockouts of Neil1 and Neil2 do not display obesity (Rolseth et al. 2017).

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Editions

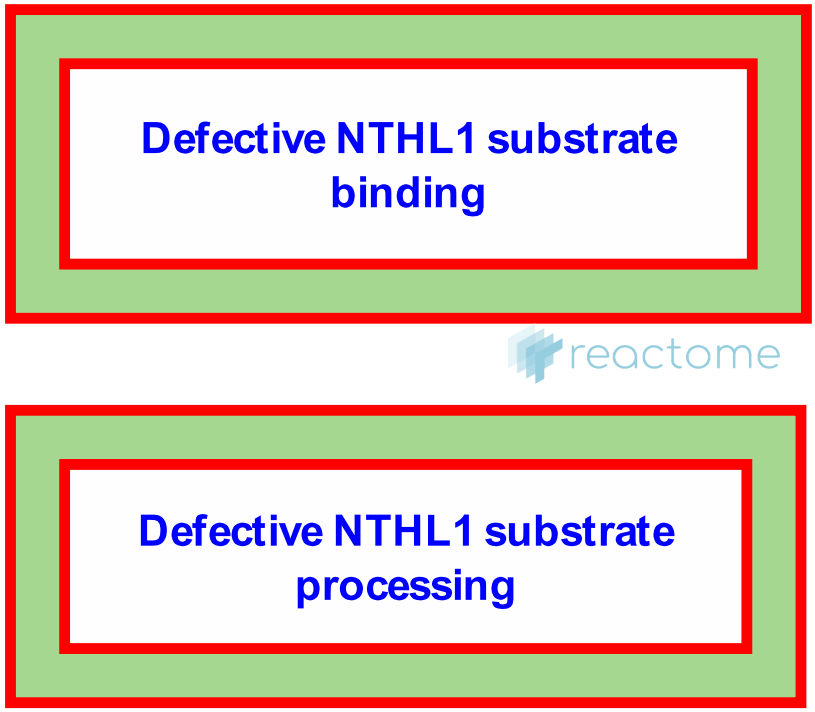
2018-11-27	Authored	Orlic-Milacic, M.
2019-01-03	Reviewed	Sampath, H.
2019-01-05	Edited	Orlic-Milacic, M.

Defective Base Excision Repair Associated with NTHL1 ↗

Location: Diseases of Base Excision Repair

Stable identifier: R-HSA-9616333

Diseases: cancer



NTHL1 is a DNA N-glycosylase that catalyzes the first step in base excision repair (BER), the primary repair pathway for oxidative DNA damage. NTHL1 can recognize and remove oxidized cytosine, adenine and thymine, in the form of cytosine glycol (Cg), 4,6-diamino-5-formamidopyrimidine (FapyA), and thymine glycol (Tg), respectively. NTHL1 can also recognize and remove dihydrouracil (DHU), produced by cytosine deamination. Germline mutations that impair function of NTHL1 predispose affected patients to a cancer syndrome (NTHL1 syndrome) that involves adenomatous polyposis and colorectal cancer, similar to MUTYH-associated polyposis (MAP), but also causes development of tumors in other organs, such as breast, bladder, skin, uterus and brain. Only patients with mutations in both alleles of NTHL1 are affected, indicative of an autosomally recessive inheritance (Weren et al. 2015, Rivera et al. 2015, Broderick et al. 2017, Grolleman et al. 2019). Some common NTHL1 polymorphisms may results in reduced NTHL1 function, but predisposition of affected individuals to cancer has not been studied in full (Galick et al. 2013). Mice that are double knockout for Neil1 and Nthl1 genes accumulate DNA damage in the form of FapyA and FapyG and are more prone to development of lung adenocarcinoma than single Neil1 or Nthl1 gene knockouts (Chan et al. 2009). Biallelic loss-of-function mutations in NTHL1 result in a mutational signature characterized by C>T transitions at non-CpG sites (Grolleman et al. 2019). For review, please refer to Weren et al. 2018.

Besides loss-of-function mutations, NTHL1 is amplified and overexpressed in some cancers. NTHL1 overexpression leads to genomic instability in non-transformed human bronchial epithelial cells and may lead to malignant transformation (Limpose et al. 2018).

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Chan, MK., Ocampo-Hafalla, MT., Vartanian, V., Jaruga, P., Kirkali, G., Koenig, KL. et al. (2009). Targeted deletion of the genes encoding NTH1 and NEIL1 DNA N-glycosylases reveals the existence of novel carcinogenic oxidative damage to DNA. *DNA Repair (Amst.), 8*, 786-94. ↗

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Weren, RD., Ligtenberg, MJ., Geurts van Kessel, A., de Voer, RM., Hoogerbrugge, N., Kuiper, RP. (2018). NTHL1 and MUTYH polyposis syndromes: two sides of the same coin?. *J. Pathol., 244*, 135-142. ↗

Editions

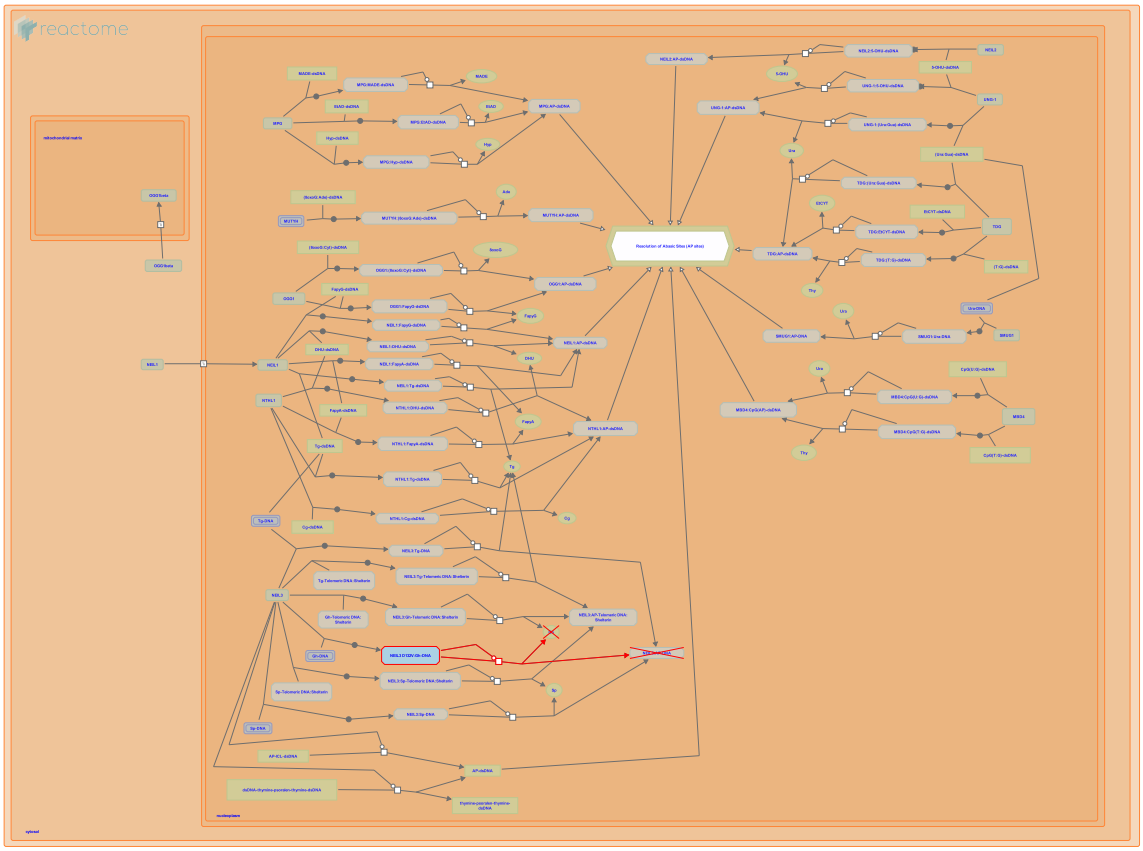
2018-12-13	Authored	Orlic-Milacic, M.
2019-01-14	Reviewed	Kuiper, RP.
2019-01-17	Edited	Orlic-Milacic, M.
2019-01-31	Reviewed	Doetsch, PW.
2019-02-19	Reviewed	Rivera Polo, B.
2019-02-21	Reviewed	de Voer, RM.

Defective Base Excision Repair Associated with NEIL3 ↗

Location: Diseases of Base Excision Repair

Stable identifier: R-HSA-9629232

Diseases: autoimmune hypersensitivity disease



NEIL3 is a DNA N-glycosylase involved in base excision repair (BER), the primary repair pathway for oxidative DNA damage. NEIL3 can detect and remove oxidized guanine, in the form of 5-guanidinohydatoin and spiroiminodihydantoin, and oxidized thymine, in the form of thymine glycol. NEIL3 has a preference for single strand DNA (ssDNA) and is implicated in repair of oxidative DNA damage at telomeres (Zhou et al. 2013). A NEIL3 disease variant NEIL3 D132 is unable to cleave 5 guanidinohydantoin (Gh) from oxidatively damaged DNA. Individuals harboring a NEIL3 D132V homozygous mutation are predisposed to development of autoimmune diseases (Massaad et al. 2016) and NEIL3 depletion is also associated with an increase in telomere damage and loss (Zhou et al. 2017). NEIL3 unhooks DNA interstrand cross-links (ICLs) during DNA replication. NEIL3 resolves psoralen- and abasic site-induced ICLs in a Fanconi anemia (FA) pathway-independent manner (Semlow et al. 2016, Martin et al. 2017).

A polymorphism in one of the NEIL3 gene splice sites may increase the risk of myocardial infarction (Skarpengland et al. 2015). NEIL3 expression in the heart increases after heart failure in humans and after myocardial infarction in mouse disease models. Neil3 knockout mice show increased mortality after myocardial infarction, but there is no increase in the amount of DNA damage in Neil3 knockout hearts. In the heart, NEIL3 may function in the epigenetic regulation of gene expression and facilitate transcriptional response to myocardial infarction (Olsen et al. 2017). NEIL3 mRNA expression is increased in human carotid plaques and Neil3 deficiency accelerates plaque formation in Apoe knockout mice, but it appears that this is not correlated with oxidative DNA damage (Skarpengland et al. 2016).

The function of NEIL3 in removal of hydantoins from single strand DNA may be important for removal of replication blocks in proliferating cells. Mouse embryonic fibroblasts and neuronal stem cell derived

from Neil3 knockout mouse embryos show decreased proliferation capacity and increased sensitivity to DNA damaging agents (Rolseth et al. 2013). NEIL3 may be required for maintenance of adult neurogenesis, as Neil3 knockout mice exhibit learning and memory deficits and synaptic irregularities in the hippocampus (Regnell et al. 2012). In addition, NEIL3 deficient neuronal stem cells exhibits signs of premature senescence (Reis and Hermanson 2012) and Neil3 knockout mice show reduced ability to augment neurogenesis to repair damage induced hypoxia ischemia (Sejersted et al. 2011).

Mice that are triple knockout for Neil1, Neil2 and Neil3 do not show a predisposition to tumour formation or changes in telomere length (Rolseth et al. 2017).

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Editions

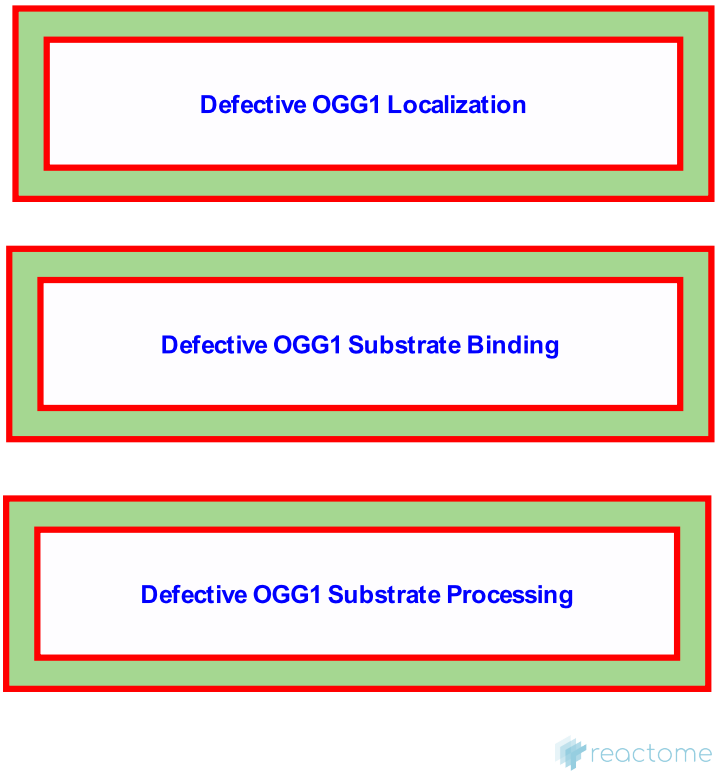
2019-01-05	Authored	Orlic-Milacic, M.
2019-02-11	Reviewed	Zhou, J.

Defective Base Excision Repair Associated with OGG1 ↗

Location: Diseases of Base Excision Repair

Stable identifier: R-HSA-9656249

Diseases: cancer, Alzheimer's disease



OGG1 is the main DNA glycosylase responsible for removal of 8-oxoguanine (8oxoG), the most frequent type of oxidative DNA damage, from DNA and initiation of the base excision repair (Klungland et al. 1999, Minowa et al. 2000). A frequent OGG1 polymorphism increases the risk of breast and lung cancer in affected individuals, and inactivating mutations in OGG1 have been reported in various cancer types and in Alzheimer's disease. Ogg1 knockout mice are predisposed to cancer. For review, please refer to Boiteux et al. 2017.

Literature references

Boiteux, S., Coste, F., Castaing, B. (2017). Repair of 8-oxo-7,8-dihydroguanine in prokaryotic and eukaryotic cells: Properties and biological roles of the Fpg and OGG1 DNA N-glycosylases. *Free Radic. Biol. Med., 107*, 179-201. ↗

Klungland, A., Rosewell, I., Hollenbach, S., Larsen, E., Daly, G., Epe, B. et al. (1999). Accumulation of premutagenic DNA lesions in mice defective in removal of oxidative base damage. *Proc. Natl. Acad. Sci. U.S.A., 96*, 13300-5. ↗

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Editions

2019-07-30	Authored	Orlic-Milacic, M.
2019-10-02	Reviewed	Vlahopoulos, S.
2019-10-08	Reviewed	Boldogh, I.
2019-10-10	Edited	Orlic-Milacic, M.

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