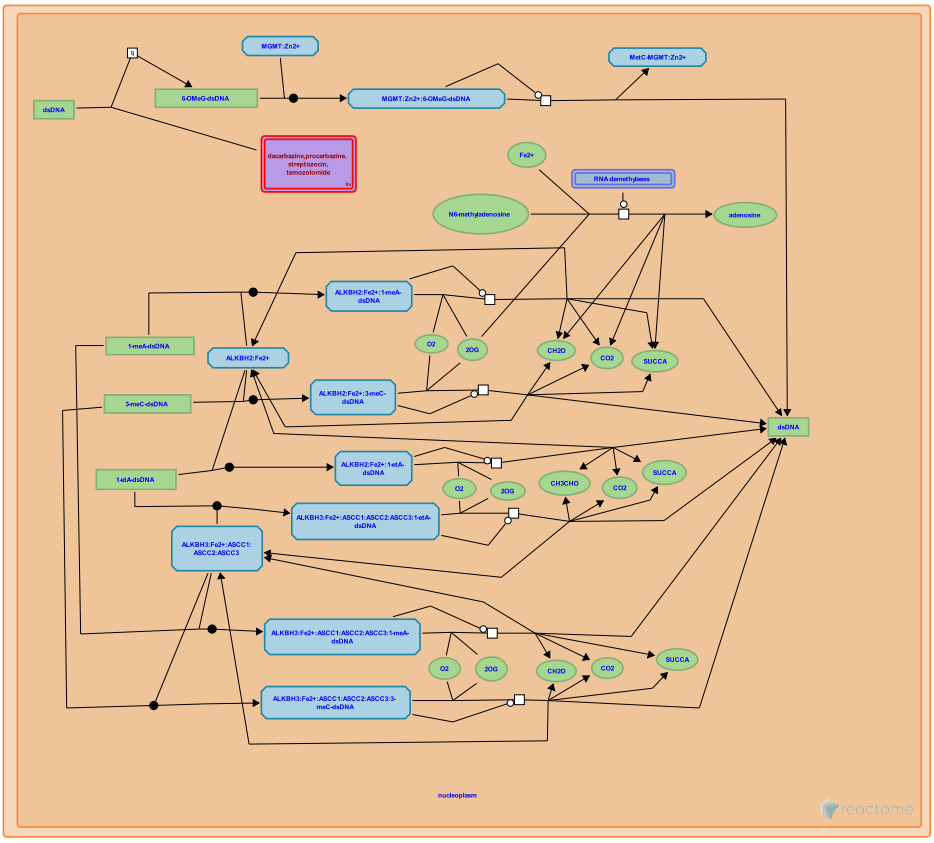
DNA Damage Reversal



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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).

Literature references

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. ↗

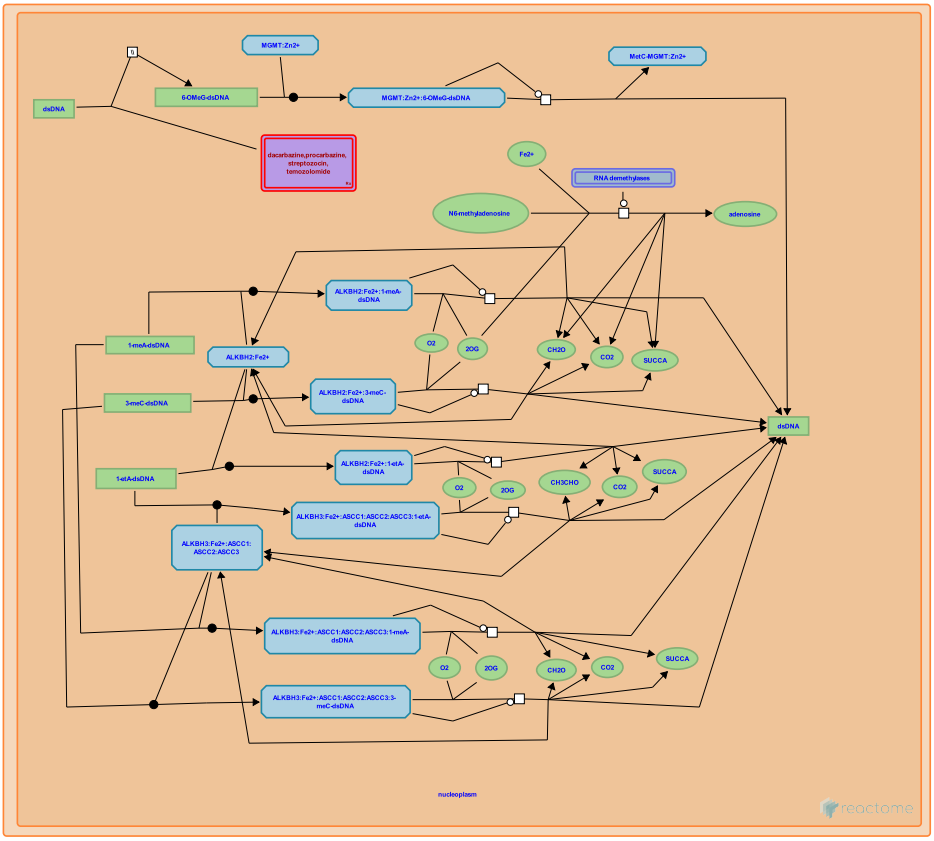
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

DNA Damage Reversal ↗

Stable identifier: R-HSA-73942

Compartments: nucleoplasm



DNA damage can be directly reversed by dealkylation (Mitra and Kaina 1993). Three enzymes play a major role in reparative DNA dealkylation: MGMT, ALKBH2 and ALKBH3. MGMT dealkylates O-6-methylguanine in a suicidal reaction that inactivates the enzyme (Daniels et al. 2000, Rasimas et al. 2004, Duguid et al. 2005, Tubbs et al. 2007), while ALKBH2 and ALKBH3 dealkylate 1-methyladenine, 3-methyladenine, 3-methylcytosine and 1-ethyladenine (Duncan et al. 2002, Dango et al. 2011).

Literature references

Pegg, AE., Tainer, JA., Tubbs, JL. (2007). DNA binding, nucleotide flipping, and the helix-turn-helix motif in base repair by O6-alkylguanine-DNA alkyltransferase and its implications for cancer chemotherapy. *DNA Repair (Amst.), 6*, 1100-15. ↗

Daniels, DS., Kanugula, S., Tainer, JA., Mol, CD., Arvai, AS., Pegg, AE. (2000). Active and alkylated human AGT structures: a novel zinc site, inhibitor and extrahelical base binding. *EMBO J., 19*, 1719-30. ↗

Rasimas, JJ., Pegg, AE., Ropson, IJ., Dalessio, PA., Fried, MG. (2004). Active-site alkylation destabilizes human O6-alkylguanine DNA alkyltransferase. *Protein Sci., 13*, 301-5. ↗

Rice, PA., He, C., Duguid, EM. (2005). The structure of the human AGT protein bound to DNA and its implications for damage detection. *J. Mol. Biol., 350*, 657-66. ↗

Xiong, LJ., Park, K., Mosammaparast, N., Dango, S., Shi, Y., Gygi, S. et al. (2011). DNA unwinding by ASCC3 helicase is coupled to ALKBH3-dependent DNA alkylation repair and cancer cell proliferation. *Mol. Cell, 44*, 373-84. ↗

Editions

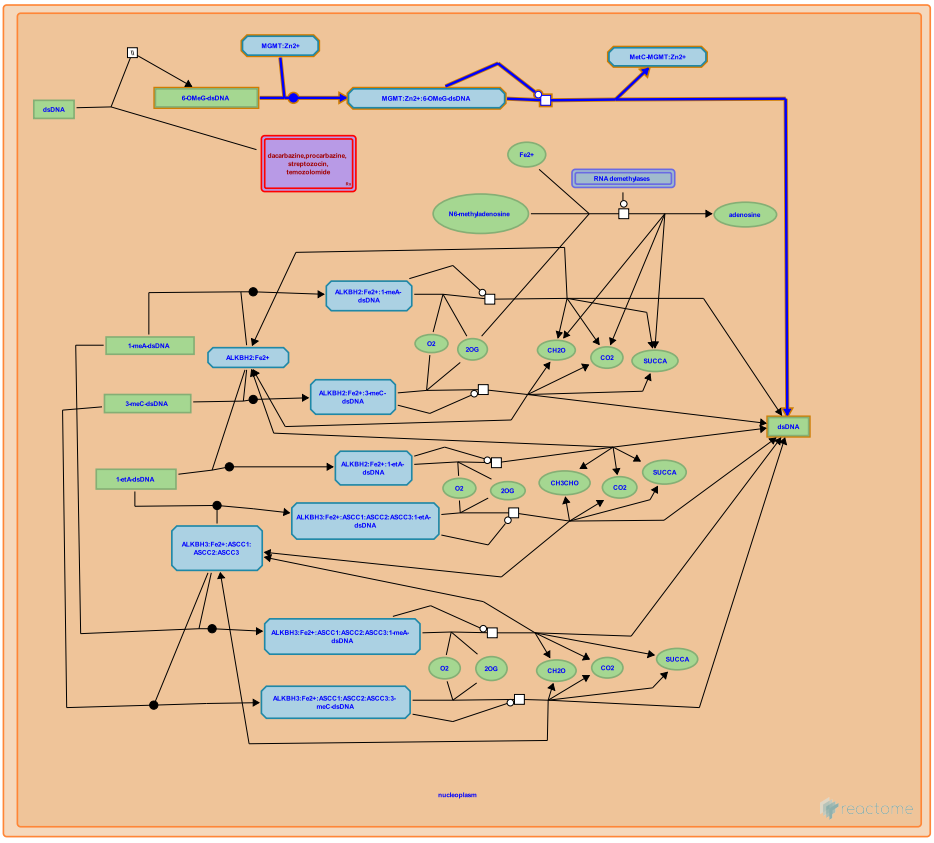
2004-02-04	Edited, Reviewed	Joshi-Tope, G.
2004-02-04	Authored	Pegg, AE.
2014-12-16	Edited, Revised	Orlic-Milacic, M.
2015-02-06	Reviewed	Gillespie, ME.

MGMT-mediated DNA damage reversal ↗

Location: DNA Damage Reversal

Stable identifier: R-HSA-5657655

Compartments: nucleoplasm



Reactive cellular catabolites can cause DNA damage by 6-O-methylation of guanine. 6-O-methylguanine can pair ambiguously with both C and T, and cause transition mutations. Active reversal of such damage can be facilitated by MGMT, a protein that has 6-O-methylguanine-DNA methyltransferase activity (Mitra and Kaina 1993).

Literature references

Mitra, S., Kaina, B. (1993). Regulation of repair of alkylation damage in mammalian genomes. *Prog Nucleic Acid Res Mol Biol, 44*, 109-42. ↗

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2004-02-04	Edited, Reviewed	Joshi-Tope, G.
2004-02-04	Authored	Pegg, AE.
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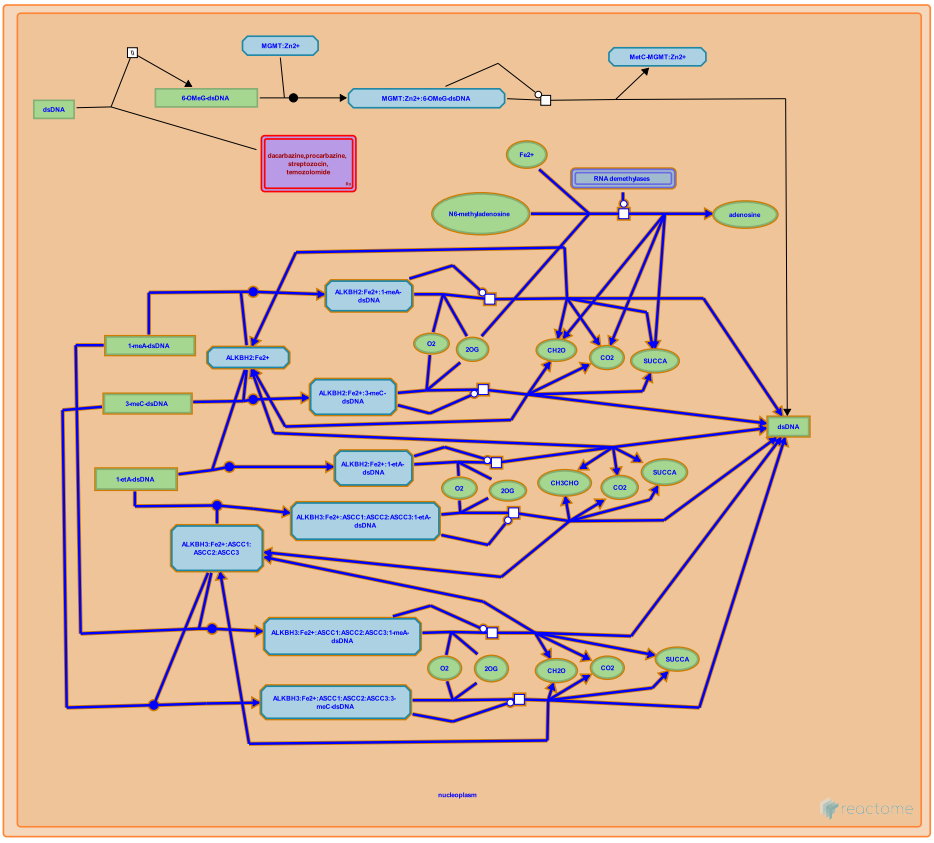
2015-02-06	Reviewed	Gillespie, ME.

Reversal of alkylation damage by DNA dioxygenases ↗

Location: DNA Damage Reversal

Stable identifier: R-HSA-73943

Compartments: nucleoplasm



DNA in cells is susceptible to different types of cytotoxic and mutagenic damage caused by alkylating agents. These genotoxic chemicals generate major lesions like 1-methyladenine, 3-methyladenine, 3-methylcytosine and O6-methylguanine in DNA. Cells have built in repair mechanisms against such toxic molecules. For example, 3-methyladeninie-DNA glycosylases excise some methylated bases while MGMT/hAGT protein transfers alkyl groups from others lesions onto cysteine residues. E.coli AlkB protein has a unique function wherein 1-methyladenine and 3-methylcytosine are demethylated by a combination of oxidative decarboxylation and hydroxylation activities. AlkB and its human orthologs, ALKBH2 (ABH2) and ALKBH3 (ABH3) belong to alpha-ketoglutarate deoxygenase family of enzymes that oxidize chemically inert compounds in the presence of alpha-ketoglutarate, oxygen and ferrous ions. As a byproduct of these chemical reactions, formaldehyde is released in the case of methylated lesions and acetaldehyde in the case 1-ethyladenine in DNA. CO2 and succinate are also released in an intermediate step not shown in the following illustration. Unlike other mechanisms which involve some kind of nuclease activities, this type of repair mechanism leaves the repaired bases intact by just removing the reactive alkyl groups that get bound to the bases thereby effecting accurate restoration of damaged DNA sequences (Trewick et al. 2002, Duncan et al. 2002, Sedgwick 2004).

Literature references

Lindahl, T., Henshaw, TF., Hausinger, RP., Sedgwick, B., Trewick, SC. (2002). Oxidative demethylation by Escherichia coli AlkB directly reverts DNA base damage. *Nature, 419*, 174-8. ↗

Sedgwick, B. (2004). Repairing DNA-methylation damage. *Nat Rev Mol Cell Biol, 5*, 148-57. ↗

Lindahl, T., Duncan, T., Bates, PA., Sedgwick, B., Trewick, SC., Koivisto, P. (2002). Reversal of DNA alkylation damage by two human dioxygenases. *Proc Natl Acad Sci U S A, 99*, 16660-5. ↗

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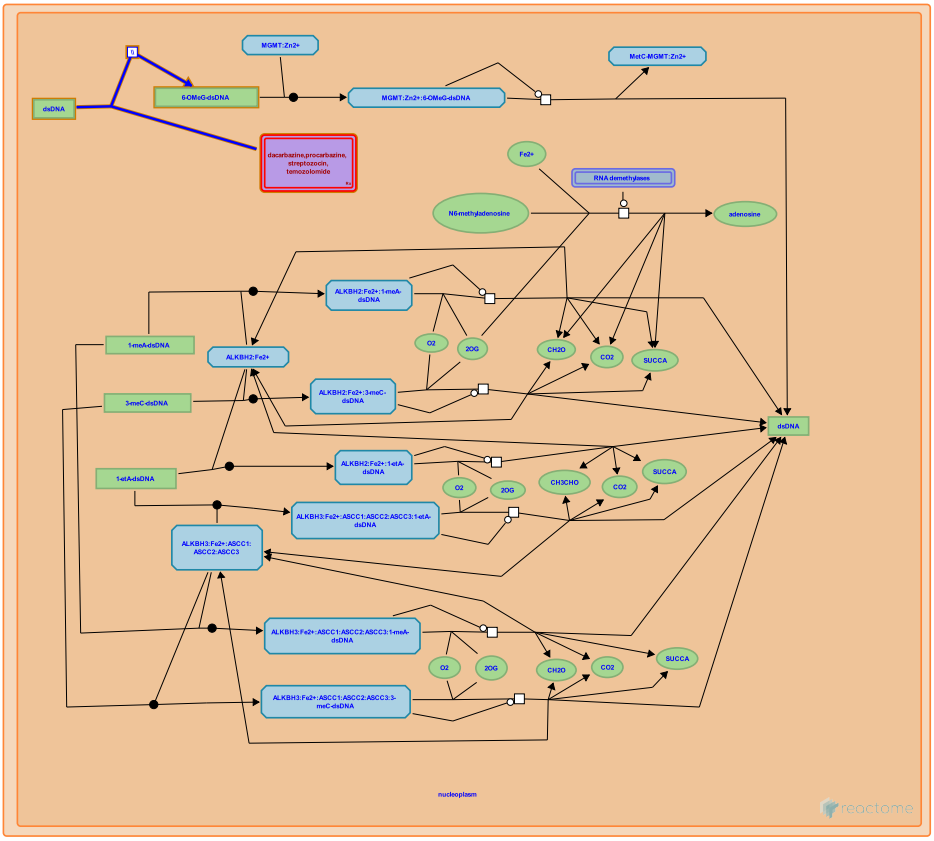
Reversible DNA damage induced by alkylating chemotherapeutic drugs ↗

Location: DNA Damage Reversal

Stable identifier: R-HSA-9729902



This pathway describes how chemotherapeutic drugs commonly used in cancer treatment produce alkylating DNA damage that is repaired through the DNA damage reversal pathway. For review, please refer to Fu et al. 2012.

Literature references

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

Editions

2021-05-28	Authored	Orlic-Milacic, M.
2021-07-28	Reviewed	Kadambat Nair, S.
2021-08-06	Edited	Orlic-Milacic, M.

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