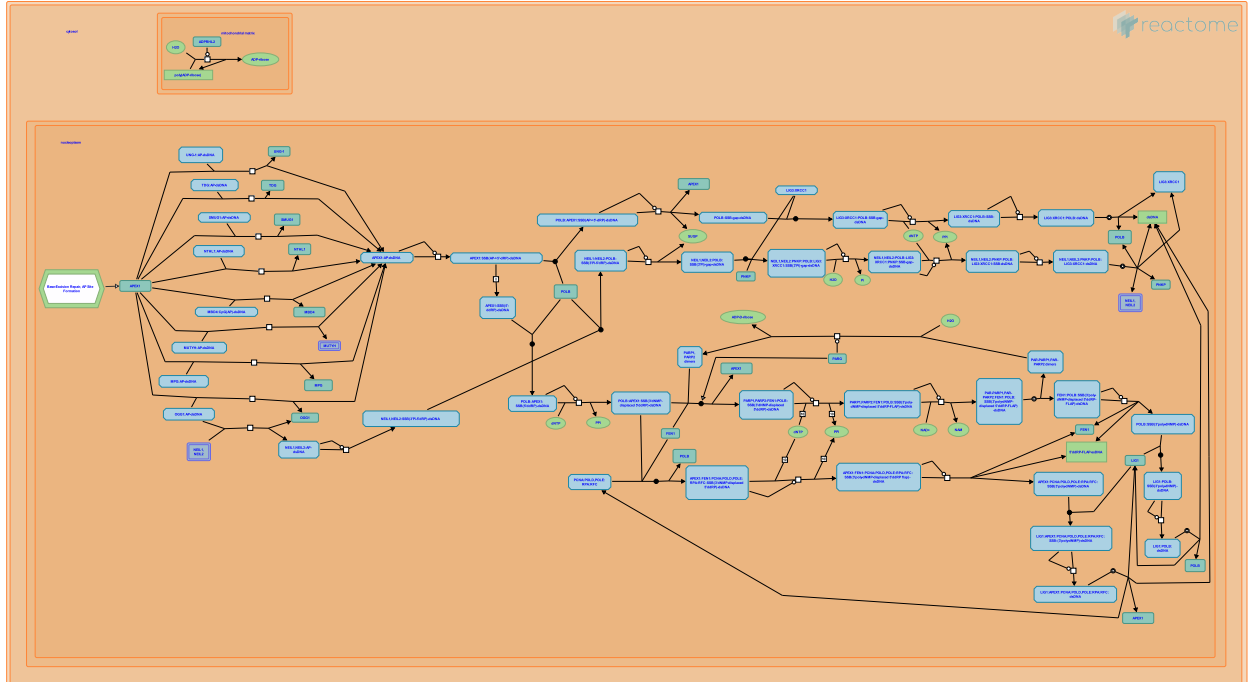


Resolution of Abasic Sites (AP sites)



Borowiec, JA., Matthews, L., Orlic-Milacic, M.

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](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/licenses/).

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](https://reactome.org/textbook/).

09/05/2024

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. [↗](#)

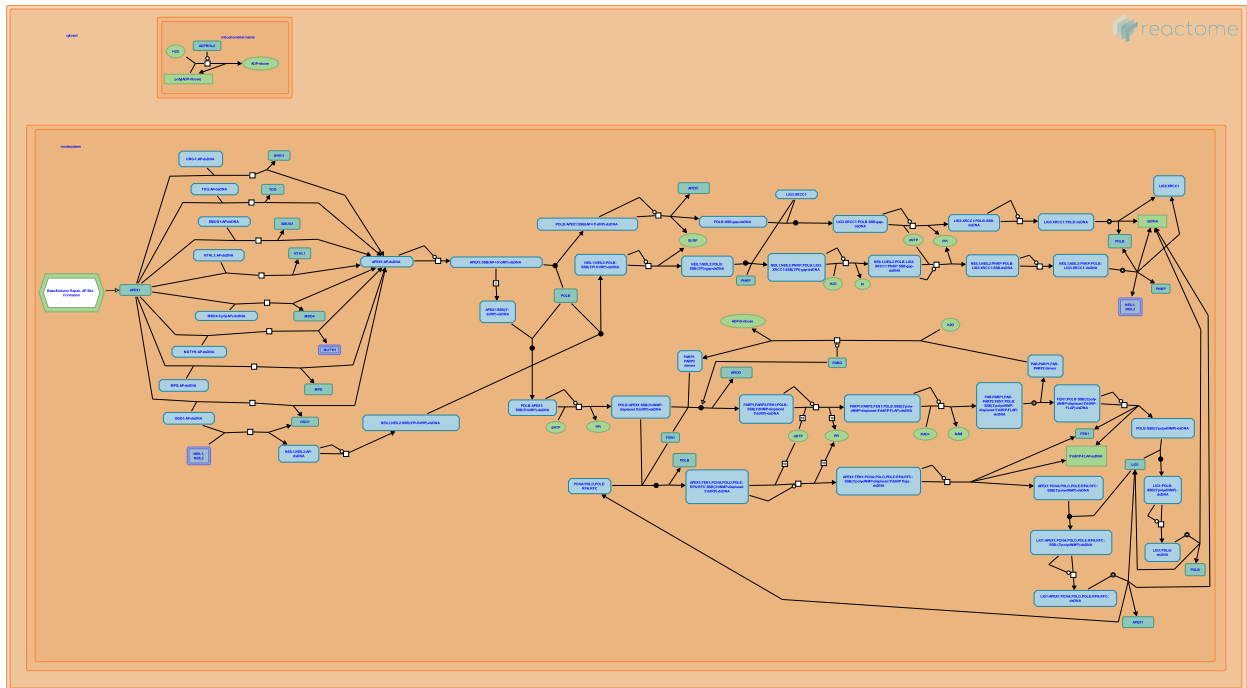
Reactome database release: 88

This document contains 5 pathways and 1 reaction ([see Table of Contents](#))

Resolution of Abasic Sites (AP sites) ↗

Stable identifier: R-HSA-73933

Compartments: nucleoplasm



Resolution of AP sites can occur through the single nucleotide replacement pathway or through the multiple nucleotide patch replacement pathway, also known as the long-patch base excision repair (BER). Except for the APEX1-independent resolution of AP sites via single nucleotide base excision repair mediated by NEIL1 or NEIL2 (Wiederhold et al. 2004, Das et al. 2006), single nucleotide and multiple-nucleotide patch replacement pathways are both initiated by APEX1-mediated displacement of DNA glycosylases and cleavage of the damaged DNA strand by APEX1 immediately 5' to the AP site (Wilson et al. 1995, Bennett et al. 1997, Masuda et al. 1998). The BER proceeds via the single nucleotide replacement when the AP (apurinic/aprimidinic) deoxyribose residue at the 5' end of the APEX1-created single strand break (SSB) (5'dRP) can be removed by the 5'-exonuclease activity of DNA polymerase beta (POLB) (Bennett et al. 1997). POLB fills the created single nucleotide gap by adding a nucleotide complementary to the undamaged DNA strand to the 3' end of the SSB. The SSB is subsequently ligated by DNA ligase III (LIG3) which, in complex with XRCC1, is recruited to the BER site by an XRCC1-mediated interaction with POLB (Kubota et al. 1996). BER proceeds via the multiple-nucleotide patch replacement pathway when the AP residue at the 5' end of the APEX1-created SSB undergoes oxidation-related damage (5'ddRP) and cannot be cleaved by POLB (Klungland and Lindahl 1997). Long-patch BER can be completed by POLB-mediated DNA strand displacement synthesis in the presence of PARP1 or PARP2, FEN1 and DNA ligase I (LIG1) (Prasad et al. 2001). When the PCNA-containing replication complex is available, as is the case with cells in S-phase of the cell cycle, DNA strand displacement synthesis is catalyzed by DNA polymerase delta (POLD) or DNA polymerase epsilon (POLE) complexes, in the presence of PCNA, RPA, RFC, APEX1, FEN1 and LIG1 (Klungland and Lindahl 1997, Dianova et al. 2001). It is likely that the 9-1-1 repair complex composed of HUS1, RAD1 and RAD9 interacts with and coordinates components of BER, but the exact mechanism and timing have not been elucidated (Wang et al. 2004, Smirnova et al. 2005, Guan et al. 2007, Balakrishnan et al. 2009).

Literature references

- Toueille, M., Hübscher, U., Smirnova, E., Markkanen, E. (2005). The human checkpoint sensor and alternative DNA clamp Rad9-Rad1-Hus1 modulates the activity of DNA ligase I, a component of the long-patch base excision repair machinery. *Biochem. J.*, 389, 13-7. ↗
- Dianova, II., Bohr, VA., Dianov, GL. (2001). Interaction of human AP endonuclease 1 with flap endonuclease 1 and proliferating cell nuclear antigen involved in long-patch base excision repair. *Biochemistry*, 40, 12639-44. ↗
- Lindahl, T., Kubota, Y., Nash, RA., Klungland, A., Schär, P., Barnes, DE. (1997). Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein. *EMBO J*, 15, 6662-70. ↗

Wilson, DM., Wong, D., Bennett, RA., Demple, B. (1997). Interaction of human apurinic endonuclease and DNA polymerase beta in the base excision repair pathway. *Proc Natl Acad Sci U S A*, 94, 7166-9. [↗](#)

Bennett, RA., Demple, B., Masuda, Y. (1998). Dynamics of the interaction of human apurinic endonuclease (Ape1) with its substrate and product. *J Biol Chem*, 273, 30352-9. [↗](#)

Editions

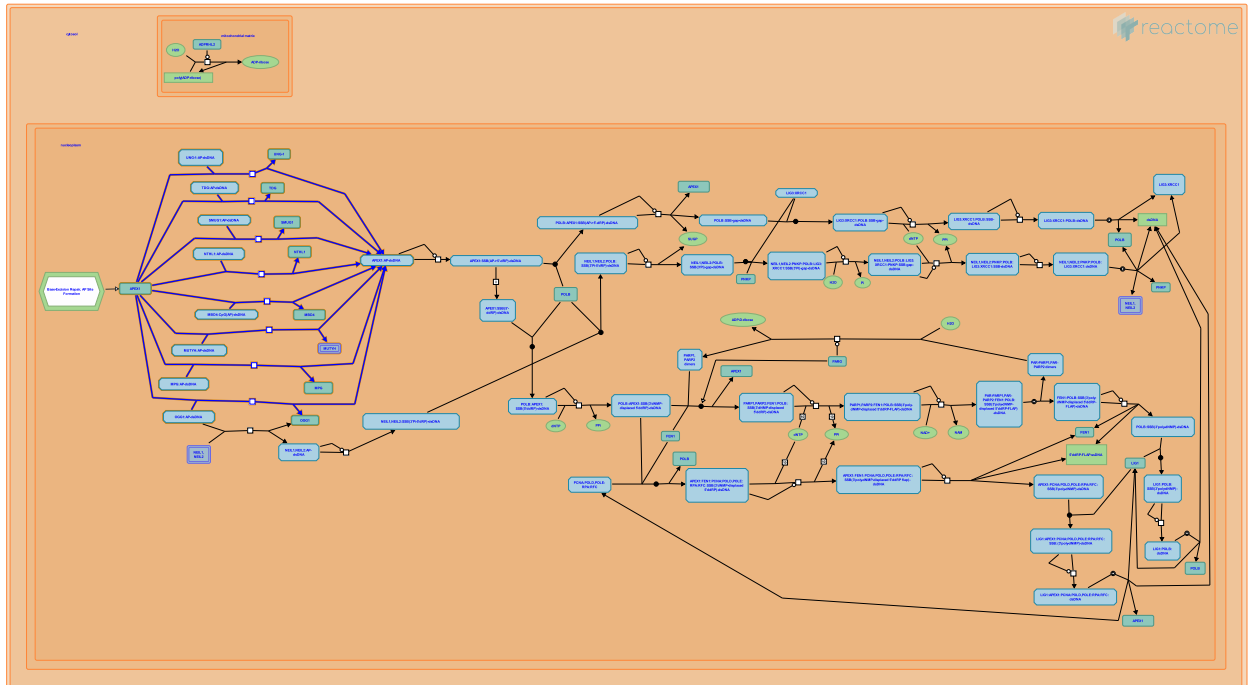
2004-02-03	Authored, Edited	Matthews, L.
2014-12-04	Edited, Revised	Orlic-Milacic, M.
2014-12-22	Reviewed	Borowiec, JA.

Displacement of DNA glycosylase by APEX1 ↗

Location: Resolution of Abasic Sites (AP sites)

Stable identifier: R-HSA-110357

Compartments: nucleoplasm



Following cleavage of the damaged base, DNA glycosylase is displaced by APEX1, an AP endonuclease (Parikh et al. 1998).

Literature references

Tainer, JA., Bharati, S., Krokan, HE., Mol, CD., Slupphaug, G., Parikh, SS. (1998). Base excision repair initiation revealed by crystal structures and binding kinetics of human uracil-DNA glycosylase with DNA. *EMBO J*, 17, 5214-26. ↗

Editions

2004-02-03	Authored, Edited	Mathews, L.
2014-12-04	Edited, Revised	Orlic-Milacic, M.
2014-12-22	Reviewed	Borowiec, JA.

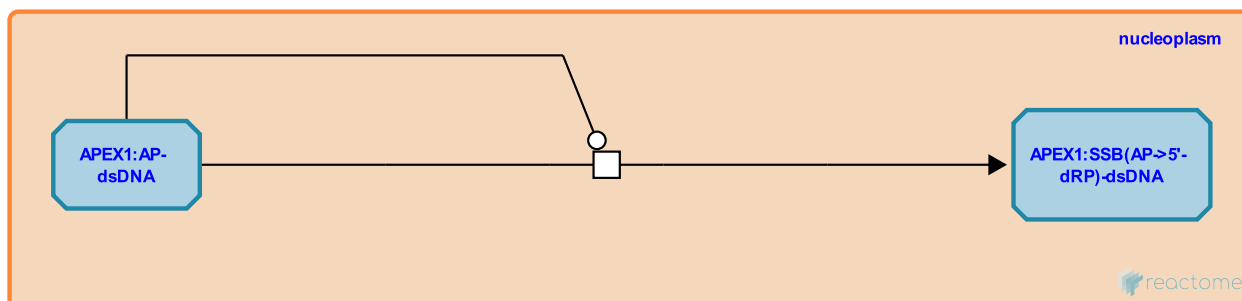
APEX1 mediates endonucleolytic cleavage at the 5' side of the AP site ↗

Location: [Resolution of Abasic Sites \(AP sites\)](#)

Stable identifier: R-HSA-110359

Type: transition

Compartments: nucleoplasm



APEX1 (APE1, HAP1), a DNA apurinic/aprimidinic (AP) site DNA lyase, cleaves the DNA strand sugar-phosphate backbone 5' to the AP site generated by DNA glycosylases or that forms by spontaneous loss of a base, producing a DNA strand with a 3'-terminal unsaturated sugar and a DNA strand with a terminal abasic 5'-deoxyribosephosphate (5'-dRP) as cleavage products (Wilson et al. 1995, Bennett et al. 1997, Masuda et al. 1998, Parikh et al. 1998).

Literature references

Tainer, JA., Bharati, S., Krokan, HE., Mol, CD., Slupphaug, G., Parikh, SS. (1998). Base excision repair initiation revealed by crystal structures and binding kinetics of human uracil-DNA glycosylase with DNA. *EMBO J*, 17, 5214-26. ↗

Wilson, DM., Wong, D., Bennett, RA., Demple, B. (1997). Interaction of human apurinic endonuclease and DNA polymerase beta in the base excision repair pathway. *Proc Natl Acad Sci U S A*, 94, 7166-9. ↗

Wilson, DM., Grollman, AP., Demple, B., Takeshita, M. (1995). Incision activity of human apurinic endonuclease (Ape) at abasic site analogs in DNA. *J. Biol. Chem.*, 270, 16002-7. ↗

Bennett, RA., Demple, B., Masuda, Y. (1998). Dynamics of the interaction of human apurinic endonuclease (Ape1) with its substrate and product. *J Biol Chem*, 273, 30352-9. ↗

Editions

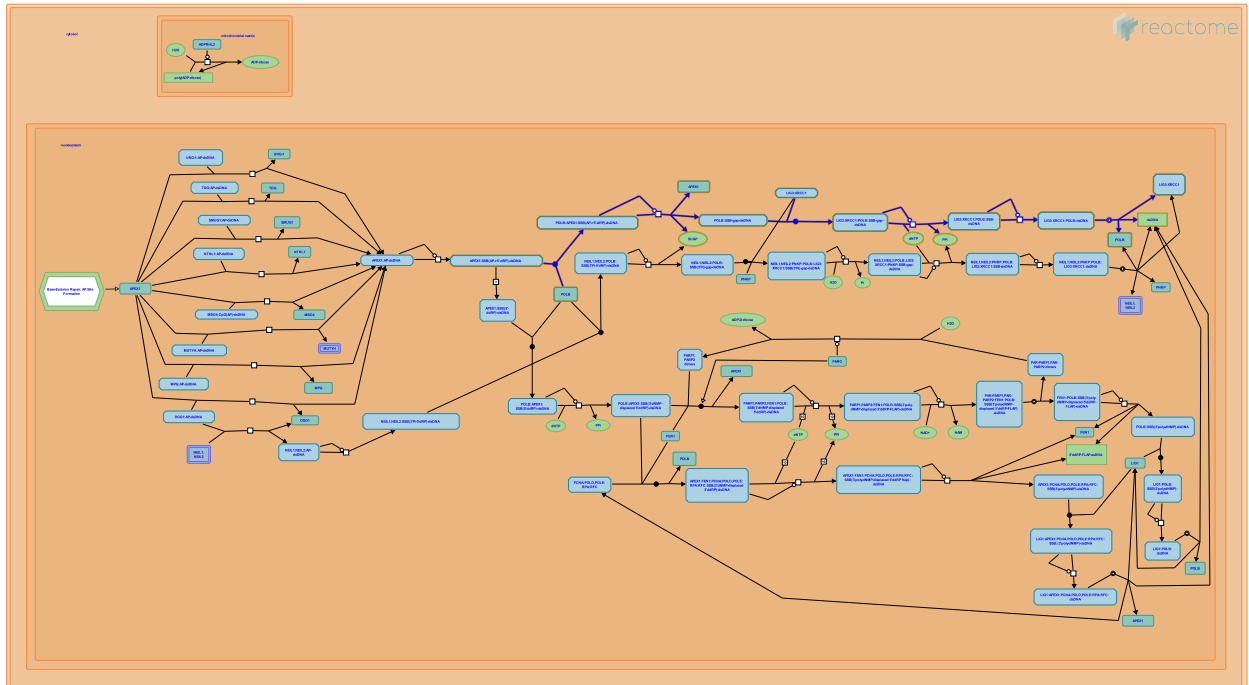
2004-02-03	Authored, Edited	Matthews, L.
2014-12-04	Edited	Orlic-Milacic, M.
2014-12-22	Reviewed	Borowiec, JA.

Resolution of AP sites via the single-nucleotide replacement pathway ↗

Location: Resolution of Abasic Sites (AP sites)

Stable identifier: R-HSA-110381

Compartments: nucleoplasm



The single nucleotide replacement pathway of base excision repair appears to facilitate the repair of most damaged bases. Following DNA glycosylase mediated cleavage of the damaged base, the endonuclease APEX1 is recruited to the site of damage where it cleaves the 5' side of the abasic (AP) deoxyribose residue. DNA polymerase beta (POLB) then cleaves the 3' side of the AP sugar phosphate, thus excising the AP residue. APEX1 is subsequently released, the XRCC1:LIG3 complex is recruited, and POLB mediates the synthesis of the replacement residue. Following LIG3 mediated ligation of the replaced residue, the XRCC1:LIG3 complex dissociates from DNA (Lindahl and Wood, 1999). An alternative BER pathway is employed when the structure of the terminal sugar phosphate is such that it cannot be cleaved by the AP lyase activity of POLB.

Literature references

Lindahl, T., Wood, RD. (1999). Quality control by DNA repair. *Science*, 286, 1897-905. ↗

Editions

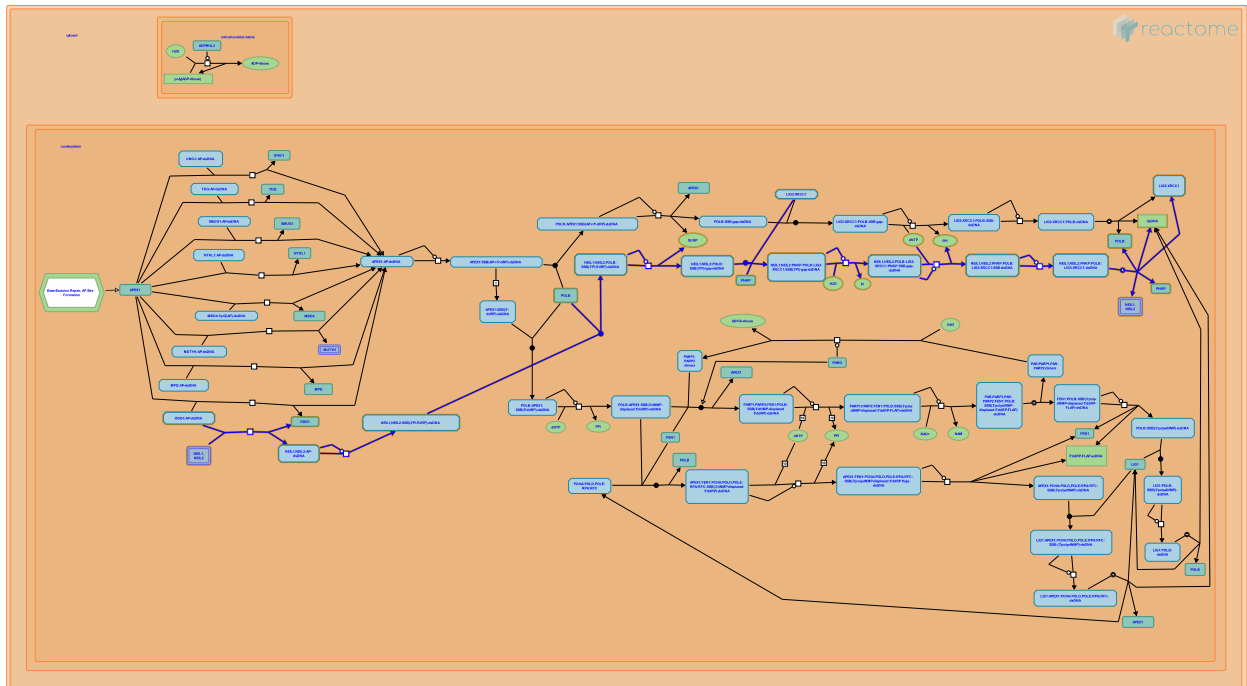
2004-02-03	Edited	Matthews, L.
2004-02-09	Authored	Matthews, L.
2014-12-04	Edited, Revised	Orlic-Milacic, M.
2014-12-22	Reviewed	Borowiec, JA.

APEX1-Independent Resolution of AP Sites via the Single Nucleotide Replacement Pathway ↗

Location: Resolution of Abasic Sites (AP sites)

Stable identifier: R-HSA-5649702

Compartments: nucleoplasm



NEIL1 and NEIL2 have a dual DNA glycosylase and beta/delta lyase activity. The AP (apurinic/aprimidinic) site-directed lyase activity of NEIL1 and NEIL2 is their major physiological role, as they can act on AP sites generated spontaneously or by other DNA glycosylases. NEIL1 or NEIL2 cleave the damaged DNA strand 5' to the AP site, producing a 3' phosphate terminus (3'Pi) and a 5' deoxyribose phosphate terminus (5'dRP). DNA polymerase beta (POLB) excises 5'dRP residue but is unable to add the replacement nucleotide to DNA with the 3'Pi end. PNKP, a DNA 3' phosphatase, removes 3'Pi and enables POLB to incorporate the replacement nucleotide, which is followed by ligation of repaired DNA strand by XRCC1:LIG3 complex (Whitehouse et al. 2001, Wiederhold et al. 2004, Das et al. 2006).

Literature references

- Karimi-Busheri, F., Wang, H., Weinfeld, M., Mitra, S., Hazra, TK., Kedar, P. et al. (2006). NEIL2-initiated, APE-independent repair of oxidized bases in DNA: Evidence for a repair complex in human cells. *DNA Repair (Amst.)*, 5, 1439-48. ↗
- Taylor, RM., Whitehouse, CJ., Weinfeld, M., Lasko, DD., Zhang, H., Thistlethwaite, A. et al. (2001). XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair. *Cell*, 104, 107-17. ↗
- Karimi-Busheri, F., Weinfeld, M., Mitra, S., Wiederhold, L., Izumi, T., Hazra, TK. et al. (2004). AP endonuclease-independent DNA base excision repair in human cells. *Mol. Cell*, 15, 209-20. ↗

Editions

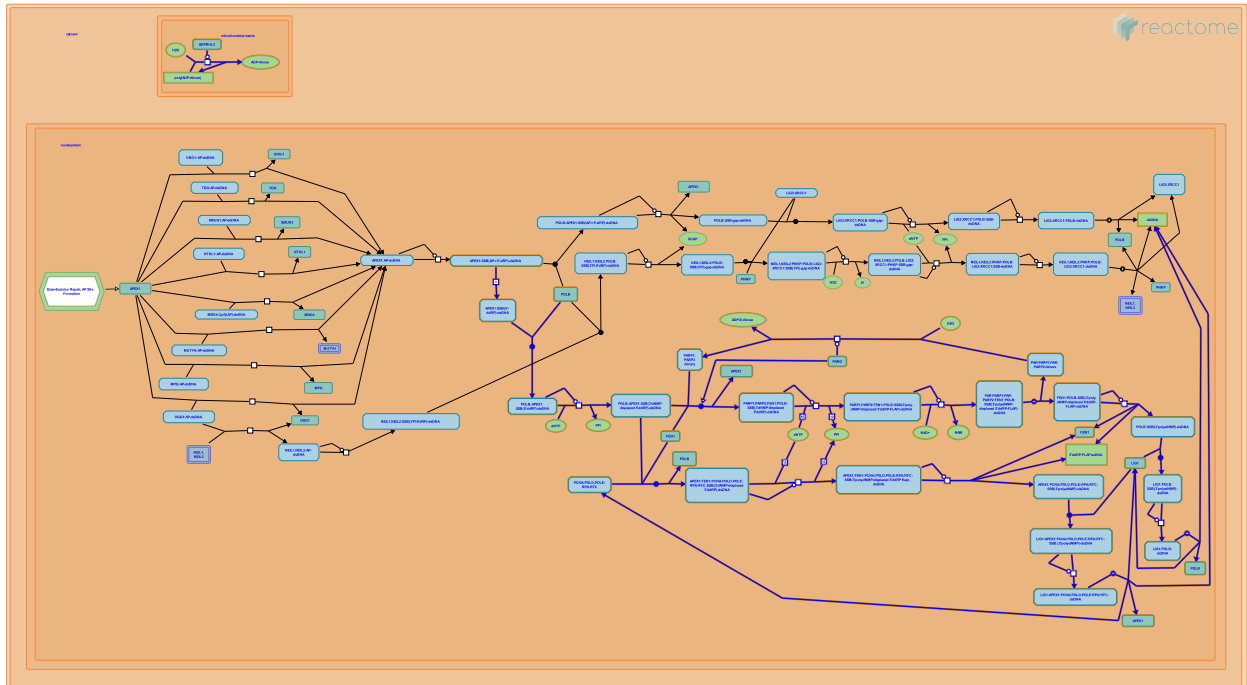
2014-12-04	Authored, Edited	Orlic-Milacic, M.
2014-12-22	Reviewed	Borowiec, JA.

Resolution of AP sites via the multiple-nucleotide patch replacement pathway ↗

Location: Resolution of Abasic Sites (AP sites)

Stable identifier: R-HSA-110373

Compartments: nucleoplasm



While the single nucleotide replacement pathway appears to facilitate the repair of most damaged bases, an alternative BER pathway is evoked when the structure of the 5'-terminal sugar phosphate is such that it cannot be cleaved through the AP lyase activity of DNA polymerase beta (POLB). Under these circumstances, a short stretch of residues containing the abasic site is excised and replaced (Dianov et al., 1999). Following DNA glycosylase-mediated cleavage of the damaged base, the endonuclease APEX1 is recruited to the site of damage where it cleaves the 5' side of the abasic deoxyribose residue, as in the single nucleotide replacement pathway. However, POLB then synthesizes the first replacement residue without prior cleavage of the 5'-terminal sugar phosphate, hence displacing this entity. Long-patch BER can be completed by continued POLB-mediated DNA strand displacement synthesis in the presence of PARP1 or PARP2, FEN1 and DNA ligase I (LIG1) (Prasad et al. 2001). When the PCNA-containing replication complex is available, as is the case with cells in the S-phase of the cell cycle, DNA strand displacement synthesis is catalyzed by DNA polymerase delta (POLD) or DNA polymerase epsilon (POLE) complexes, in the presence of PCNA, RPA, RFC, APEX1, FEN1 and LIG1 (Klungland and Lindahl 1997, Dianova et al. 2001). In both POLB-dependent and PCNA-dependent DNA displacement synthesis, the displaced DNA strand containing the abasic sugar phosphate creates a flap structure that is recognized and cleaved by the flap endonuclease FEN1. The replacement residues added by POLB or POLD/POLE are then ligated by the DNA ligase I (LIG1) (Klungland and Lindahl, 1997; Matsumoto et al., 1999).

Literature references

- Bohr, VA., Kenny, MK., Dianov, GL., Jensen, BR. (1999). Replication protein A stimulates proliferating cell nuclear antigen-dependent repair of abasic sites in DNA by human cell extracts. *Biochemistry*, 38, 11021-5. ↗
- Lindahl, T., Wood, RD. (1999). Quality control by DNA repair. *Science*, 286, 1897-905. ↗
- Dianova, II., Bohr, VA., Dianov, GL. (2001). Interaction of human AP endonuclease 1 with flap endonuclease 1 and proliferating cell nuclear antigen involved in long-patch base excision repair. *Biochemistry*, 40, 12639-44. ↗
- Vande Berg, BJ., Wilson, SH., Kim, SJ., Kedar, P., Yang, XP., Lavrik, OI. et al. (2001). DNA polymerase beta -mediated long patch base excision repair. Poly(ADP-ribose)polymerase-1 stimulates strand displacement DNA synthesis. *J. Biol. Chem.*, 276, 32411-4. ↗

Lindahl, T., Klungland, A. (1997). Second pathway for completion of human DNA base excision-repair: reconstitution with purified proteins and requirement for DNase IV (FEN1). *EMBO J*, 16, 3341-8. [↗](#)

Editions

2004-02-03	Edited	Matthews, L.
2004-02-09	Authored	Matthews, L.
2014-12-04	Edited, Revised	Orlic-Milacic, M.
2014-12-22	Reviewed	Borowiec, JA.

Table of Contents

Introduction	1
☒ Resolution of Abasic Sites (AP sites)	2
☒ Displacement of DNA glycosylase by APEX1	4
☒ APEX1 mediates endonucleolytic cleavage at the 5' side of the AP site	5
☒ Resolution of AP sites via the single-nucleotide replacement pathway	6
☒ APEX1-Independent Resolution of AP Sites via the Single Nucleotide Replacement Pathway	7
☒ Resolution of AP sites via the multiple-nucleotide patch replacement pathway	8
Table of Contents	10