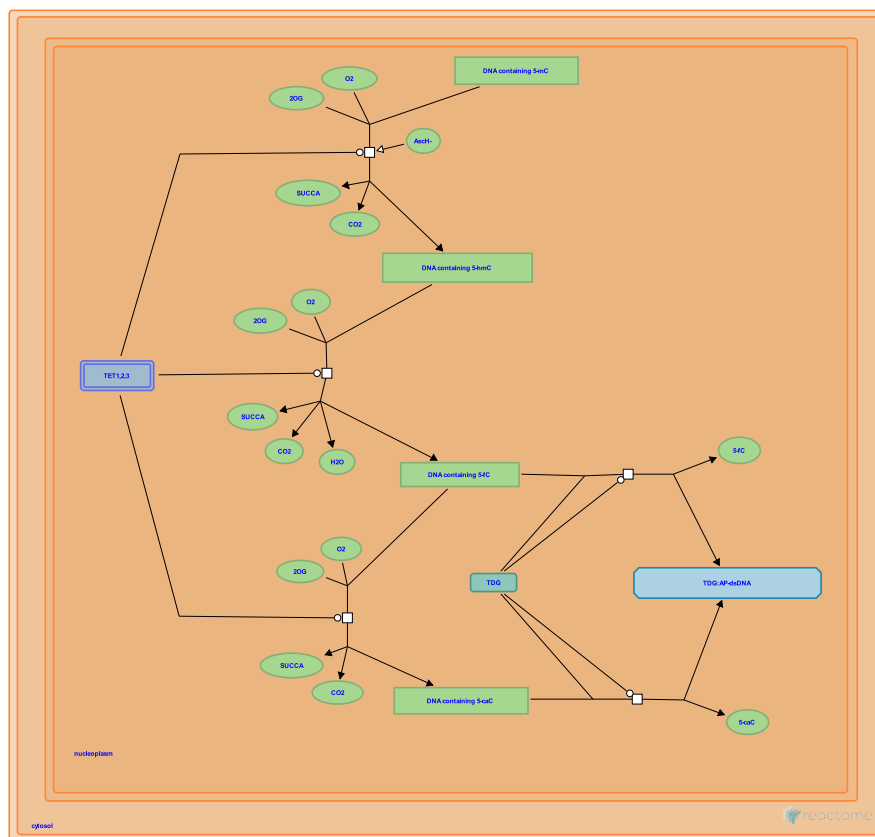


TET1,2,3 and TDG demethylate DNA



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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/).

25/04/2024

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.

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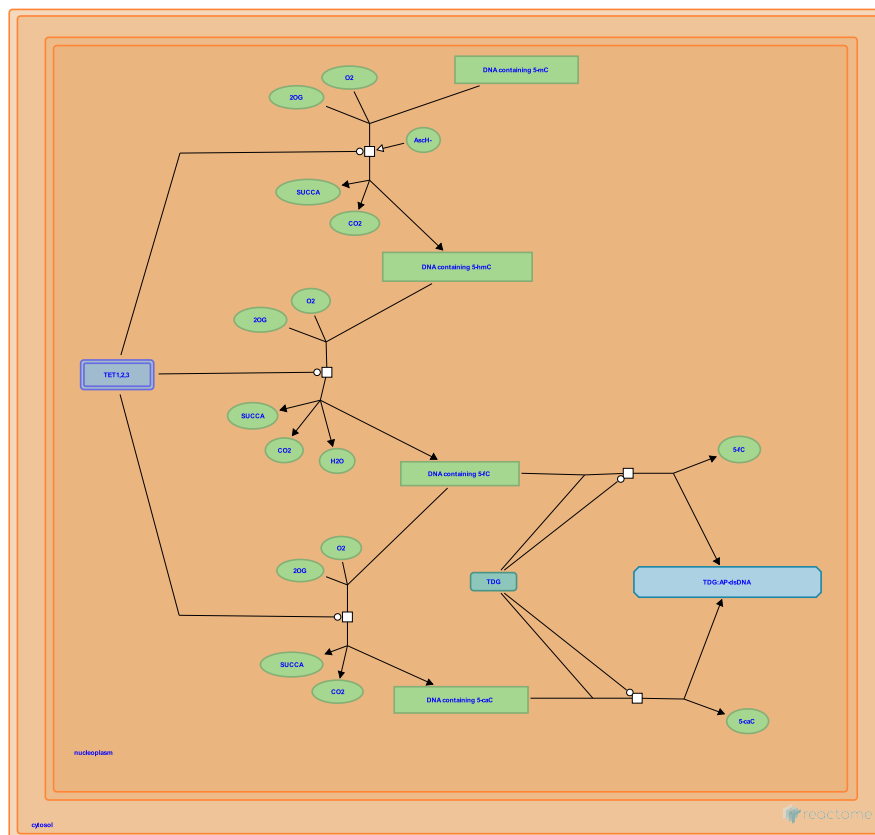
Reactome database release: 88

This document contains 1 pathway and 5 reactions ([see Table of Contents](#))

TET1,2,3 and TDG demethylate DNA ↗

Stable identifier: R-HSA-5221030

Compartments: nucleoplasm



About 2-6% of all cytosine residues and 70-80% of cytosine residues in CG dinucleotides in mammalian cells are methylated at the 5 position of the pyrimidine ring. The cytosine residues are methylated by DNA methyltransferases after DNA replication and can be demethylated by passive dilution during subsequent replication or by active modification of the 5-methylcytosine base. Cytosine demethylation is developmentally regulated: one wave of demethylation occurs in primordial germ cells and one wave occurs by active demethylation in the male pronucleus after fertilization.

Some mechanisms of active demethylation remain controversial, however progressive oxidation of the methyl group of 5-methylcytosine followed by base excision by thymine DNA glycosylase (TDG) has been reproducibly demonstrated *in vivo* (reviewed in Wu and Zhang 2011, Franchini et al 2012, Cadet and Wagner 2013, Kohli and Zhang 2013, Ponnaluri et al. 2013, Rasmussen and Helin 2016). Ten-eleven translocation proteins TET1, TET2, and TET3 are dioxygenases that first oxidize 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC) (Tahiliani et al. 2009, Ito et al. 2010), which is found in significant quantities and specific genomic locations in stem cells and neurons (Kinney and Pradhan 2013). TET proteins can further oxidize 5-hmC to 5-formylcytosine (5-fC) and then 5-carboxylcytosine (5-caC) (He et al. 2011, Ito et al. 2011). G:5-fC and G:5-caC base pairs are recognized by TDG, which excises the 5-fC or 5-caC and leaves an abasic site.

TET1 in mouse is expressed in neurons and its expression depends on neuronal activity (Guo et al. 2011, Kaas et al. 2013, Zhang et al. 2013). TET1 is also found in embryonic stem cells (Ficz et al. 2011, Koh et al. 2011, Wu et al. 2011) and in primordial germ cells of mice, where it plays a role in erasure of imprinting (Yamaguchi et al. 2013). TET3 is expressed in oocytes and zygotes of mice and is required for demethylation in the male pronucleus (Gu et al. 2011, Iqbal et al. 2011). TET2 is the most highly expressed TET family protein in hemopoietic stem cells and appears to act as a tumor suppressor. TET2 is also expressed in embryonic stem cells (Koh et al. 2011).

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Editions

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2014-02-21	Reviewed	Mukherji, M.

TET1,2,3 oxidizes 5-methylcytosine to 5-hydroxymethylcytosine ↗

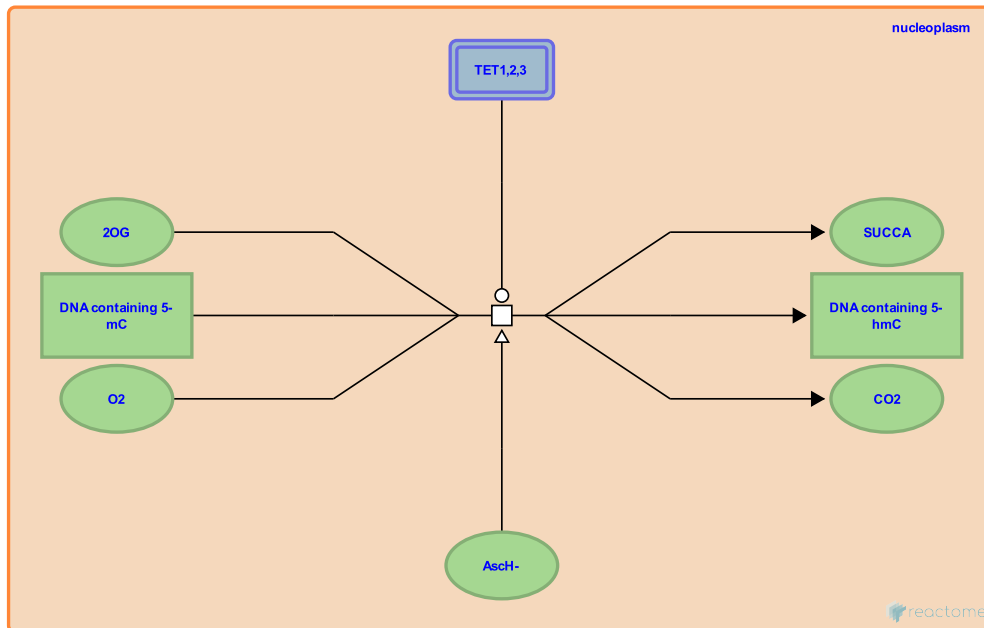
Location: TET1,2,3 and TDG demethylate DNA

Stable identifier: R-HSA-5221014

Type: transition

Compartments: nucleoplasm

Inferred from: Tet1,2,3 oxidizes 5-methylcytosine to 5-hydroxymethylcytosine (Mus musculus)



TET1, TET2, and TET3 each oxidize the 5-methyl group of 5-methylcytosine (5-mC) in DNA using molecular oxygen and 2-oxoglutarate as substrates and Fe(II) as a cofactor to yield 5-hydroxymethylcytosine (5-hmC), carbon dioxide, and succinate (Tahiliani et al. 2009, inferred from mouse in Ito et al. 2010). As inferred from mouse, sodium ascorbate (vitamin C) is required for full activity of these enzymes, presumably to maintain the ferrous state of iron (Fe²⁺) by acting as a reducing agent (Blaschke et al. 2013, Minor et al., 2013). The crystal structure of TET2 indicates that it binds specifically to 5-mC in CG dinucleotides and flips the base out of the helix into proximity of the catalytic Fe(II) where it is oxidized (Hu et al. 2013). TET3 is expressed in murine oocytes and zygotes and is implicated in demethylation of the male pronucleus after fertilization (Iqbal et al. 2011). As inferred from mouse, TET1 and TET2 appear to participate in differentiation of stem cells. TET1, TET2, and TET3 are involved in establishing the increased level of 5-hmC that is characteristic of adult neurons (Guo et al. 2011, inferred from mouse in Hahn et al. 2013). TET2 is expressed in hematopoietic cells where it appears to act as a tumor suppressor (Ko et al. 2010).

Followed by: TET1,2,3 oxidizes 5-hydroxymethylcytosine to 5-formylcytosine

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TET1,2,3 oxidizes 5-hydroxymethylcytosine to 5-formylcytosine ↗

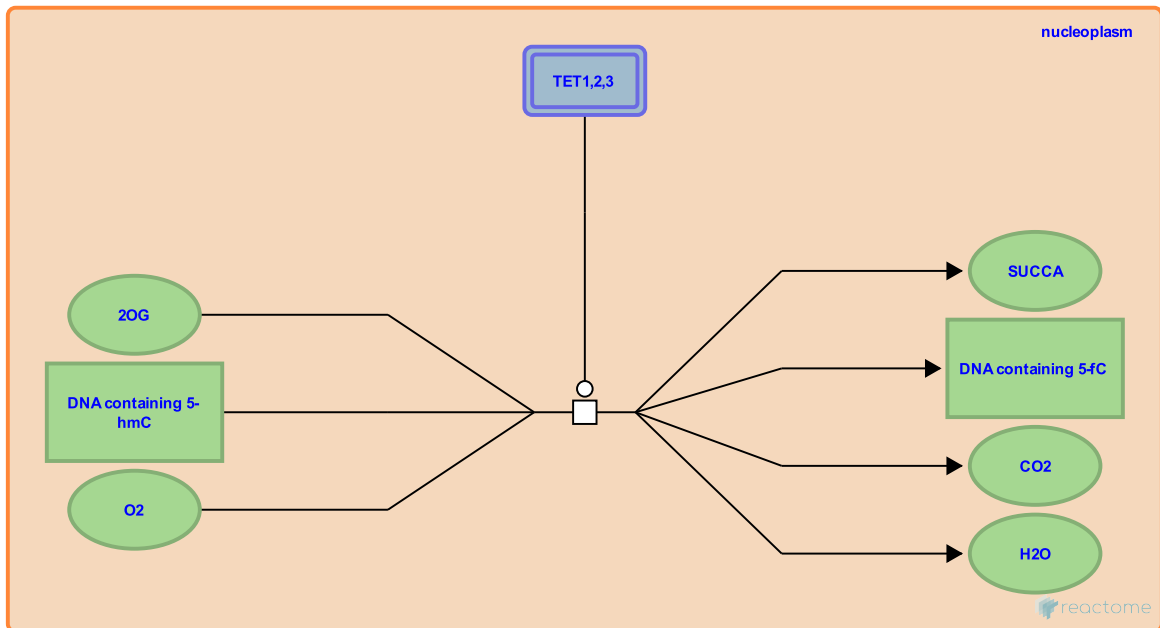
Location: TET1,2,3 and TDG demethylate DNA

Stable identifier: R-HSA-5220990

Type: transition

Compartments: nucleoplasm

Inferred from: Tet1,2,3 oxidizes 5-hydroxymethylcytosine to 5-formylcytosine (Mus musculus)



As inferred from mouse, TET1, TET2, and TET3 oxidize 5-hydroxymethylcytosine (5-hmC) in DNA using molecular oxygen and 2-oxoglutarate to yield 5-formylcytosine (5-fC), carbon dioxide, and succinate.

Preceded by: TET1,2,3 oxidizes 5-methylcytosine to 5-hydroxymethylcytosine

Followed by: TET1,2,3 oxidizes 5-formylcytosine to 5-carboxylcytosine, TDG excises 5-formylcytosine

Literature references

Ponnaluri, VK., Mukherji, M., Maciejewski, JP. (2013). A mechanistic overview of TET-mediated 5-methylcytosine oxidation. *Biochem. Biophys. Res. Commun.*, 436, 115-20. ↗

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TET1,2,3 oxidizes 5-formylcytosine to 5-carboxylcytosine ↗

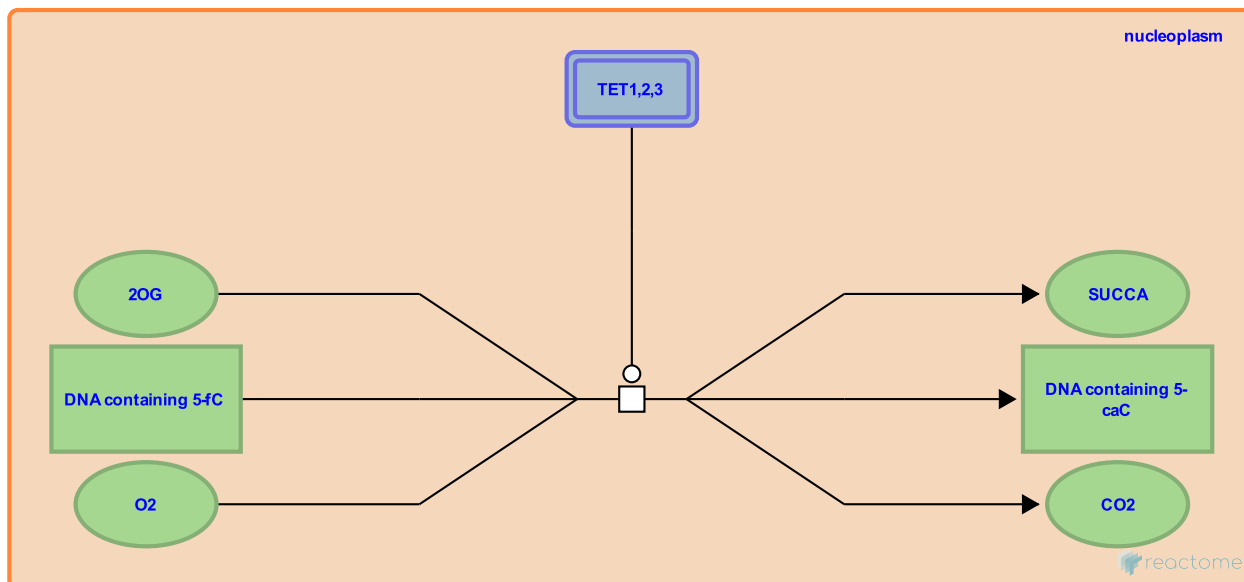
Location: TET1,2,3 and TDG demethylate DNA

Stable identifier: R-HSA-5220952

Type: transition

Compartments: nucleoplasm

Inferred from: Tet1,2,3 oxidizes 5-formylcytosine to 5-carboxylcytosine (Mus musculus)



As inferred from mouse, TET1, TET2, and TET3 each oxidize 5-formylcytosine (5-fC) in DNA using molecular oxygen and 2-oxoglutarate to yield 5-carboxylcytosine (5-caC).

Preceded by: TET1,2,3 oxidizes 5-hydroxymethylcytosine to 5-formylcytosine

Followed by: TDG excises 5-carboxylcytosine

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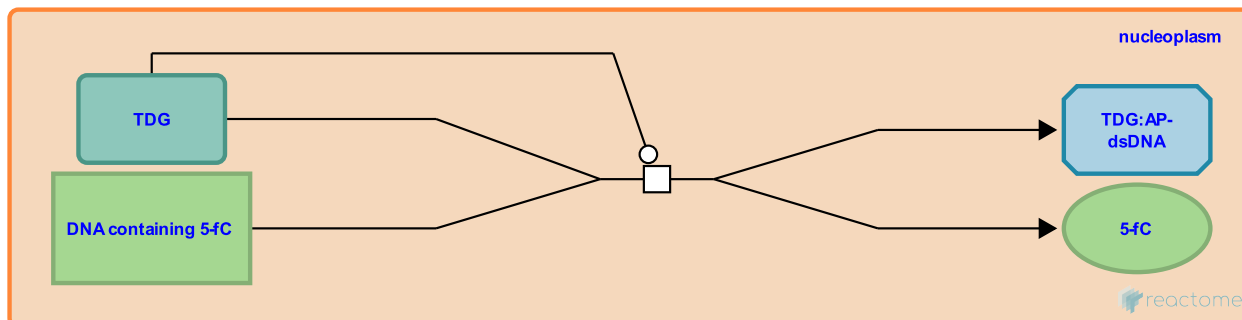
TDG excises 5-formylcytosine ↗

Location: [TET1,2,3 and TDG demethylate DNA](#)

Stable identifier: R-HSA-5220959

Type: transition

Compartments: nucleoplasm



Thymine DNA glycosylase (TDG) excises 5-formylcytosine (5-fC) from DNA (Maiti and Drohat 2011, Zhang et al. 2012, inferred from mouse in He et al. 2011) by flipping the base out of the helix and cleaving the N-glycosidic bond to leave an abasic site (apurinic/aprimidinic site, AP site). TDG interacts with the G opposite the excised base and remains bound to the abasic site (Maiti et al 2008). Dissociation of TDG from DNA is the rate-limiting step of the reaction.

Preceded by: [TET1,2,3 oxidizes 5-hydroxymethylcytosine to 5-formylcytosine](#)

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2013-12-29	Authored, Edited	May, B.
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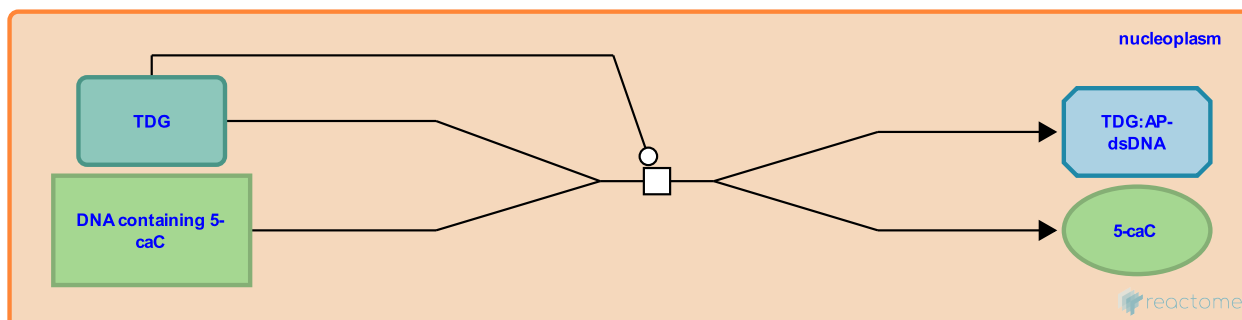
TDG excises 5-carboxylcytosine ↗

Location: [TET1,2,3 and TDG demethylate DNA](#)

Stable identifier: R-HSA-5221061

Type: transition

Compartments: nucleoplasm



Thymine DNA glycosylase (TDG) excises 5-carboxylcytosine (5-caC) from DNA (Maiti and Drohat 2011, Hashimoto et al. 2012, Zhang et al. 2012, inferred from mouse in He et al. 2011) by flipping the base out of the helix and cleaving the N-glycosidic bond to leave an abasic site (apurinic/aprimidinic site, AP site) (Hashimoto et al. 2012, Zhang et al. 2012). TDG interacts with the G opposite the excised base and remains bound to the abasic site (Maiti et al. 2008). Dissociation of TDG from DNA is the rate-limiting step of the reaction.

Preceded by: [TET1,2,3 oxidizes 5-formylcytosine to 5-carboxylcytosine](#)

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- Li, BZ., Tang, Q., Sun, Y., Jia, Y., Li, X., Chen, Z. et al. (2011). Tet-mediated formation of 5-carboxylcytosine and its excision by TDG in mammalian DNA. *Science*, 333, 1303-7. ↗
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