Phosphate bond hydrolysis by NUDT proteins

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04/03/2019
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: 67

This document contains 1 pathway and 13 reactions (see Table of Contents)

https://www.reactome.org
Enzymes that belong to the NUDT (Nudix) superfamily catalyze the hydrolysis of phosphodiester bonds in molecules including nucleoside triphosphates and diphosphates and nucleotide sugars. Family members are defined by the presence of an amino acid sequence motif shared with the E. coli MutT gene product, and are involved in diverse physiological processes (Mildvan et al. 2005; McLennan 2006).

The hydrolysis of nucleoside di and triphosphates whose purine bases have been oxidized or deaminated may protect the cell from the mutational damage that would occur if modified deoxyribonucleotides were incorporated into DNA and from the aberrant protein synthesis that would occur if modified ribonucleotides were incorporated into mRNA (Iyama et al. 2010; Takagi et al. 2012). The hydrolysis of ADP ribose may prevent the aberrant spontaneous ADP ribosylation of cellular proteins that could occur were this molecule to accumulate to high levels in the cell (Perraud et al. 2003; Shen et al. 2003). This hypothesis is further supported by the demonstration that mice lacking NUDT1 show an increased lifetime incidence of liver and other tumors compared to normal controls, and that rapidly metabolizing tumor cells in culture are killed under conditions where synthesis of NUDT1 protein is suppressed or its catalytic activity is inhibited (Gad et al. 2014; Huber et al. 2014).

**Literature references**


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https://www.reactome.org
NUDT1 hydrolyses 8-oxo-dGTP to 8-oxo-dGMP

Location: Phosphate bond hydrolysis by NUDT proteins

Stable identifier: R-HSA-2395849

Type: transition

Compartments: cytosol

NUDT1 (MTH1) catalyzes the reaction of 8-oxo-dGTP and water to form 8-oxo-dGMP and PPi (pyrophosphate). Four NUDT1 proteins have been identified, encoded by a single gene with alternative start codons (Oda et al. 1999). The shortest of these, NUDT1 p18, has been biochemically (Sakumi et al. 1993; Takagi et al. 2012) and structurally (Mishima et al. 2004) characterized and shown to catalyze hydrolysis of 8-oxo-dGTP. The active enzyme is a monomer associated with a magnesium ion (Mishima et al. 2004). The longer isoforms all consist of the p18 polypeptide with aminoterminal extensions and are presumed to be active as well but have not been experimentally characterized. The p18 isoform is predominantly cytosolic (Kang et al. 1995). Its expression prevents the accumulation of oxo-guanine bases in DNA in mutant mouse cells lacking endogenous NUDT1 activity (Yoshimura et al. 2003).

Together, these data support the hypothesis that by cleaving 8-oxo-dGTP and thus preventing its incorporation into DNA NUDT1 provides a physiologically important defense against mutagenesis due to oxidative stress. This hypothesis is further supported by the demonstration that mice lacking NUDT1 show an increased lifetime incidence of liver and other tumors compared to normal controls, and that rapidly metabolizing tumor cells in culture are killed under conditions where synthesis of NUDT1 protein is suppressed or its catalytic activity is inhibited (Gad et al. 2014; Huber et al. 2014).

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NUDT15 hydrolyses 8-oxo-dGTP to 8-oxo-dGMP

Location: Phosphate bond hydrolysis by NUDT proteins

Stable identifier: R-HSA-2395869

Type: transition

Compartments: cytosol

NUDT15 (MTH2) catalyzes the reaction of 8-oxo-dGTP and water to form 8-oxo-dGMP and PPi (pyrophosphate). Cai et al. (2003) first identified this activity in studies of the homologous mouse protein; the activity of the human NUDT15 protein has since been confirmed experimentally (Takagi et al. 2012).

Literature references


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NUDT15 hydrolyses 8-oxo-dGDP to 8-oxo-dGMP

**Location:** Phosphate bond hydrolysis by NUDT proteins

**Stable identifier:** R-HSA-2395876

**Type:** transition

**Compartments:** cytosol

NUDT15 (MTH2) catalyzes the reaction of 8-oxo-dGDP and water to form 8-oxo-dGMP and Pi (orthophosphate) (Takagi et al. 2012). The subcellular location of NUDT15 has not been established but is assumed to be cytosolic like NUDT1.

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NUDT18 hydrolyses 8-oxo-dGDP to 8-oxo-dGMP

Location: Phosphate bond hydrolysis by NUDT proteins

Stable identifier: R-HSA-2395879

Type: transition

Compartments: cytosol

NUDT18 (MTH3) catalyzes the reaction of 8-oxo-dGDP and water to form 8-oxo-dGMP and Pi (orthophosphate) (Takagi et al. 2012). The subcellular location of NUDT18 has not been established but is assumed to be cytosolic like NUDT1.

Literature references

NUDT18 hydrolyses 8-oxo-GDP to 8-oxo-GMP

**Location:** Phosphate bond hydrolysis by NUDT proteins

**Stable identifier:** R-HSA-2395873

**Type:** transition

**Compartments:** cytosol

NUDT18 (MTH3) catalyzes the reaction of 8-oxo-GDP and water to form 8-oxo-GMP and Pi (orthophosphate) (Takagi et al. 2012). The subcellular location of NUDT18 has not been established but is assumed to be cytosolic like NUDT1.

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NUDT18 hydrolyses 8-OH-dADP to 8-OH-dAMP

Location: Phosphate bond hydrolysis by NUDT proteins

Stable identifier: R-HSA-2395965

Type: transition

Compartments: cytosol

NUDT18 (MTH3) catalyzes the reaction of 8-hydroxy-dADP and water to form 8-hydroxy-dAMP and Pi (orthophosphate) (Takagi et al. 2012). The subcellular location of NUDT18 has not been established but is assumed to be cytosolic like NUDT1.

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https://www.reactome.org
NUDT1 hydrolyses 2-OH-dATP to 2-OH-dAMP

**Location:** Phosphate bond hydrolysis by NUDT proteins

**Stable identifier:** R-HSA-2395818

**Type:** transition

**Compartments:** cytosol

NUDT1 (MTH1) catalyzes the reaction of 2-hydroxy-dATP and water to form 2-hydroxy-dAMP and PPI (pyrophosphate). Four NUDT1 proteins have been identified, encoded by a single gene with alternative start codons (Oda et al. 1999). The shortest of these, NUDT1 p18, has been shown to catalyze hydrolysis of 2-hydroxy-dATP (Fujikawa et al. 1993; Sakai et al. 2002). The active enzyme is a monomer associated with a magnesium ion (Mishima et al. 2004). The longer isoforms all consist of the p18 polypeptide with aminoterminal extensions and are presumed to be active as well but have not been experimentally characterized. The p18 isoform is predominantly cytosolic (Kang et al. 1995). Its expression prevents the accumulation of modified adenosine bases in DNA in mutant mouse cells lacking endogenous NUDT1 activity (Yoshimura et al. 2003).

Together, these data support the hypothesis that by cleaving 2-hydroxy-dATP and thus preventing its incorporation into DNA, NUDT1 provides a physiologically important defense against mutagenesis due to oxidative stress. This hypothesis is further supported by the demonstration that mice lacking NUDT1 show an increased lifetime incidence of liver and other tumors compared to normal controls, and that rapidly metabolizing tumor cells in culture are killed under conditions where synthesis of NUDT1 protein is suppressed or its catalytic activity is inhibited (Gad et al. 2014; Huber et al. 2014).

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**NUDT1 hydrolyses 2-OH-ATP to 2-OH-AMP**

**Location:** Phosphate bond hydrolysis by NUDT proteins

**Stable identifier:** R-HSA-2395872

**Type:** transition

**Compartments:** cytosol

NUDT1 (MTH1) catalyzes the reaction of 2-hydroxy-ATP and water to form 2-hydroxy-AMP and PPI (pyrophosphate). Four NUDT1 proteins have been identified, encoded by a single gene with alternative start codons (Oda et al. 1999). The shortest of these, NUDT1 p18, has been shown to catalyze hydrolysis of 2-hydroxy-dATP (Fujikawa et al. 2001). The active enzyme is a monomer associated with a magnesium ion (Mishima et al. 2004). The longer isoforms all consist of the p18 polypeptide with aminoterminal extensions and are presumed to be active as well, but have not been experimentally characterized. The p18 isoform is predominantly cytosolic (Kang et al. 1995).

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NUDT16 hydrolyses dIDP to dIMP

**Location:** Phosphate bond hydrolysis by NUDT proteins

**Stable identifier:** R-HSA-2509793

**Type:** transition

**Compartments:** nucleoplasm

NUDT16 dimer catalyzes the reaction of dIDP and water to form dIMP and Pi (orthophosphate). Mg++ is required for enzymatic activity. The protein is mostly located in the nucleus and concentrated in the nucleolus, where it can also mediate the decapping of U8 small nucleolar RNA (Iyama et al. 2010; Peculis et al. 2007).

**Literature references**


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NUDT16 hydrolyses IDP to IMP

**Location:** Phosphate bond hydrolysis by NUDT proteins

**Stable identifier:** R-HSA-2509816

**Type:** transition

**Compartments:** nucleoplasm

NUDT16 dimer catalyzes the reaction of IDP and water to form IMP and Pi (orthophosphate). Mg++ is required for enzymatic activity. The protein is mostly located in the nucleus and concentrated in the nucleolus, where it can also mediate the decapping of U8 small nucleolar RNA (Iyama et al. 2010; Peculis et al. 2007).

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Cytosolic NUDT5 hydrolyses ADP-ribose to R5P and AMP

Location: Phosphate bond hydrolysis by NUDT proteins

Stable identifier: R-HSA-2393939

Type: transition

Compartments: cytosol

Cytosolic NUDT5 dimer (ADP-ribose pyrophosphatase) catalyzes the hydrolysis of ADP-ribose to form AMP and D-ribose 5-phosphate. Each NUDT5 subunit is associated with three magnesium ions (Zha et al. 2006, 2008). NUDT5 also catalyzes the hydrolysis of 8-oxo-dGTP but with a strongly alkaline pH optimum (Ito et al. 2011) so the physiological relevance of this reaction is unclear and it is not annotated here.

Literature references


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Mitochondrial NUDT9 hydrolyses ADP-ribose to R5P and AMP

Location: Phosphate bond hydrolysis by NUDT proteins

Stable identifier: R-HSA-2393954

Type: transition

Compartments: mitochondrial matrix

Mitochondrial NUDT9 (ADP-ribose pyrophosphatase) catalyzes the hydrolysis of ADP-ribose to form AMP and D-ribose 5-phosphate. The active enzyme is the longer of two isoforms generated by alternative splicing and is a monomer complexed with two magnesium ions (Perraud et al. 2003; Shen et al. 2003).

Literature references


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Manganese-dependent ADP-ribose/CDP-alcohol diphosphatase (ADPRM:Mn2+) can mediate the hydrolysis of ADP-ribose and less efficiently, CDP-alcohols and 2',3'-cAMP (Cabezas et al. 2015).

**Literature references**


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