Pyrimidine catabolism

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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


Reactome database release: 70

This document contains 1 pathway and 17 reactions (see Table of Contents)
Pyrimidine catabolism

Stable identifier: R-HSA-73621

In parallel sequences of three reactions each, thymine is converted to beta-aminoisobutyrate and uracil is converted to beta-alanine. Both of these molecules are excreted in human urine and appear to be normal end products of pyrimidine catabolism (Griffith 1986; Webster et al. 2001). Mitochondrial AGXT2, however, can also catalyze the transamination of both molecules with pyruvate, yielding 2-oxoacids that can be metabolized further by reactions of branched-chain amino acid and short-chain fatty acid catabolism (Tamaki et al. 2000). The importance of these reactions in normal human pyrimidine catabolism has not been well worked out.

**Literature references**


**Editions**

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TMP, (d)UMP, uridine 2' monophosphate, or uridine 3'-monophosphate + H2O => thymidine, deoxyuridine, or uridine + orthophosphate [NT5M]

**Location:** Pyrimidine catabolism

**Stable identifier:** R-HSA-109514

**Type:** transition

**Compartments:** mitochondrial matrix

5'3'-Nucleotidase, mitochondrial (NT5M) is the major nucleotidase of human mitochondria, catalyzing the hydrolysis of TMP, uridine 2', 3', and 5'-monophosphates, and dUMP to yield the corresponding (deoxy)nucleosides and orthophosphate. It may play a central role in "substrate cycles" to regulate mitochondrial deoxynucleotide levels, especially in non-dividing cells (Rampazzo et al. 2000; Gallinaro et al. 2002). The active form of the enzyme is a homodimer, with an absolute requirement for Mg++ (Rampazzo et al. 2000; Rinaldo-Matthis et al. 2002).

**Literature references**


**Editions**

2010-02-05 Revised D'Eustachio, P.
5'-nucleotidase (NT5E) associated with the plasma membrane catalyzes the reactions of extracellular CMP, TMP, or UMP with H2O to yield the corresponding nucleoside and orthophosphate. The active enzyme is a glycolipid-anchored dimer (Misumi et al. 1990; Thompson et al. 1987; Zimmerman 1992)

**Literature references**


**Editions**

2010-02-05  Revised  D'Eustachio, P.
(d)CMP, TMP, or (d)UMP + H2O => (deoxy)cytidine, thymidine, or (deoxy)uridine + orthophosphate (NT5C3)

Location: Pyrimidine catabolism

Stable identifier: R-HSA-109449

Type: transition

Compartments: cytosol

Cytosolic 5'-nucleotidase 3 (NTSC3) catalyzes the hydrolysis of pyrimidine nucleoside monophosphates (d)CMP, TMP, and (d)UMP to nucleosides plus orthophosphate. While the enzyme appears to be present in many tissues, it is especially abundant in erythrocytes, where it may function to remove excess pyrimidine nucleotides generated by nucleic acid breakdown, while sparing purine nucleotides needed for red cell energy metabolism. Deficiencies in the enzyme are associated with a form of hemolytic anemia and its inactivation by heavy metals may be responsible for some hematological abnormalities associated with lead poisoning (Marinaki et al. 2001; Rees et al. 2003). The active form of the enzyme is a monomer. It has an absolute requirement for Mg++, and is inactive against purine nucleotides (Amici et al. 1997; Amici and Magni 2002).

Literature references


Editions

2010-02-05 Revised D'Eustachio, P.
(d)CMP, TMP, or (d)UMP + H2O => (deoxy)cytidine, thymidine, or (deoxy)uridine + orthophosphate (NT5C1A)

Location: Pyrimidine catabolism

Stable identifier: R-HSA-109380

Type: transition

Compartments: cytosol

Cytosolic 5'-nucleotidase IA (NT5C1A) catalyzes the hydrolysis of (deoxy)cytidine monophosphate, thymidine monophosphate and (deoxy)uridine monophosphate to the corresponding nucleosides plus orthophosphate. The enzyme is allosterically activated by ADP (Hunsucker et al. 2001). The human enzyme is inferred to be a homotetramer with one Mg++ ion bound per subunit based on its similarity to the pigeon heart enzyme (Bianchi and Spychala 2003; Sala-Newby et al. 1999; Skladanowski and Newby 1990).

Literature references


Editions

2010-02-05 Revised D'Eustachio, P.
TMP, uridine 2', 3', or 5' monophosphates, or deoxyuridine 3' or 5' monophosphates + H2O \rightarrow thymidine or (deoxy)uridine + orthophosphate [NT5C]

Location: Pyrimidine catabolism

Stable identifier: R-HSA-109480

Type: transition

Compartments: cytosol

Cytosolic 5'3'-nucleotidase (NT5C) catalyzes the hydrolysis of uridine 2', 3', and 5' monophosphates, deoxyuridine 3' and 5' monophosphates, and thymidine monophosphate to yield the corresponding (deoxy)nucleosides and orthophosphate. The active form of the enzyme is a homodimer, with an absolute requirement for Mg++ (Hoglund and Reichard 1990; Rampazzo et al. 2000). This enzyme appears to play a central role in the "substrate cycles" that regulate cytosolic deoxynucleotide levels (Gazziola et al. 2001).

Literature references


Editions

2010-02-05 Revised D'Eustachio, P.
(deoxy)uridine + orthophosphate <=> uracil + (deoxy)ribose 1-phosphate (UPP)

**Location:** Pyrimidine catabolism

**Stable identifier:** R-HSA-74376

**Type:** transition

**Compartments:** cytosol

Cytosolic uridine phosphorylase (isoforms UPP1 and UPP2) catalyzes the reversible reactions of uridine or deoxyuridine with orthophosphate to yield uracil and ribose 1-phosphate or deoxyribose 1-phosphate (Watanabe and Uchida 1995; Johansson, 2003). The active form of UPP1 is a dimer (Roosild et al. 2009).

**Literature references**


**Editions**

2010-02-05 Revised D'Eustachio, P.
thymidine or deoxyuridine + orthophosphate ⇌ thymine or uracil + 2-deoxy-D-ribose 1-phosphate [TYMP]

**Location:** Pyrimidine catabolism

**Stable identifier:** R-HSA-112265

**Type:** transition

**Compartments:** cytosol

Cytosolic thymidine phosphorylase (TYMP) catalyzes the reversible reactions of thymidine or deoxyuridine with orthophosphate to form thymine or uracil and 2-deoxy-D-ribose 1-phosphate. The active form of the enzyme is a homodimer (Desgranges et al. 1981; Norman et al. 2004; Usuki et al. 1992).

**Literature references**


**Editions**

2010-02-05 Revised D'Eustachio, P.
Cytosolic dihydropyrimidine dehydrogenase catalyzes the reaction of uracil and NADPH + H+ to form 5,6-dihydrouracil and NADP+. The mechanism of the human reaction is inferred from that of the well-characterized pig enzyme (Yokota et al. 1994).

Followed by: 5,6-dihydrouracil + H2O => beta-ureidopropionate

Literature references


Editions

2010-02-05 Revised D'Eustachio, P.
5,6-dihydrouracil + H2O => beta-ureidopropionate

**Location:** Pyrimidine catabolism

**Stable identifier:** R-HSA-73589

**Type:** transition

**Compartments:** cytosol

Cytosolic dihydropyrimidinase tetramer catalyzes the reaction of 5,6-dihydrouracil and water to form 3-ureidopropionate (Hamajima et al. 1998).

**Preceded by:** uracil + NADPH + H+ => 5,6-dihydrouracil + NADP+

**Followed by:** beta-ureidopropionate + H2O => beta-alanine + NH4+ + CO2

**Literature references**


**Editions**

2010-02-05  Revised  D'Eustachio, P.
beta-ureidopropionate + H2O => beta-alanine + NH4+ + CO2

Location: Pyrimidine catabolism

Stable identifier: R-HSA-73591

Type: transition

Compartments: cytosol

Cytosolic 3-ureidopropionase catalyzes the reaction of 3-ureidopropionate and water to form beta-alanine, CO2, and NH3 (van Kuilenberg et al. 2004).

Preceded by: 5,6-dihydrouracil + H2O => beta-ureidopropionate

Followed by: Mitochondrial uptake of beta-alanine

Literature references


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Mitochondrial uptake of beta-alanine

**Location:** Pyrimidine catabolism

**Stable identifier:** R-HSA-909765

**Type:** omitted

**Compartments:** cytosol, mitochondrial matrix

**Inferred from:** Mitochondrial uptake of beta-alanine (Rattus norvegicus)

The mitochondrial uptake of cytosolic beta-alanine in human cells is inferred from the corresponding process known to occur in rat (Tamaki et al. 2000).

**Preceded by:** beta-ureidopropionate + H2O => beta-alanine + NH4+ + CO2

**Followed by:** beta-alanine + pyruvate => 3-oxopropanoate + alanine

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Mitochondrial AGXT2 tetramer catalyzes the reaction of beta-alanine and pyruvate to form 3-oxopropanoate and alanine. While the human mitochondrial AGXT2 enzyme has been characterized experimentally in other respects (Rodionov et al. 2010), its ability to catalyze this transamination reaction is inferred from the properties of its rat homologue.

**Preceded by:** Mitochondrial uptake of beta-alanine

**Literature references**


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thymine + NADPH + H+ => 5,6-dihydrothymine + NADP+

Location: Pyrimidine catabolism

Stable identifier: R-HSA-73616

Type: transition

Compartments: cytosol

Cytosolic dihydropyrimidine dehydrogenase catalyzes the reaction of thymine and NADPH + H+ to form 5,6-dihydrothymine and NADP+. The mechanism of the human reaction is inferred from that of the well-characterized pig enzyme (Yokota et al. 1994).

Followed by: 5,6-dihydrothymine + H2O => beta-ureidoisobutyrate

Literature references


Editions

2010-02-05 Revised D'Eustachio, P.
5,6-dihydrothymine + H2O => beta-ureidoisobutyrate

Location: Pyrimidine catabolism

Stable identifier: R-HSA-73618

Type: transition

Compartments: cytosol

Cytosolic dihydropyrimidinase tetramer catalyzes the reaction of 5,6-dihydrothymine and water to yield 3-ureidoisobutyrate (Hamajima et al. 1998).

Preceded by: thymine + NADPH + H+ => 5,6-dihydrothymine + NADP+

Followed by: beta-ureidoisobutyrate + H2O => 3-aminoisobutyrate + NH4+ + CO2

Literature references


Editions

2010-02-05 Revised D'Eustachio, P.
beta-ureidoisobutyrate + H2O => 3-aminoisobutyrate + NH4+ + CO2

Location: Pyrimidine catabolism

Stable identifier: R-HSA-73620

Type: transition

Compartments: cytosol

Cytosolic UPB1 (beta-ureidopropionase) catalyzes the reaction of 3-ureidoisobutyrate and H2O to form (R)-3-aminoisobutyrate, CO2, and NH3 (Tamaki et al. 2000; van Kuilenburg et al. 2004).

Preceded by: 5,6-dihydrothymine + H2O => beta-ureidoisobutyrate

Followed by: Mitochondrial uptake of (R)-3-aminoisobutyric acid

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Mitochondrial uptake of (R)-3-aminoisobutyric acid

Location: Pyrimidine catabolism

Stable identifier: R-HSA-909755

Type: omitted

Compartments: cytosol, mitochondrial matrix

Inferred from: Mitochondrial uptake of (R)-3-aminoisobutyric acid (Rattus norvegicus)

The mitochondrial uptake of cytosolic (R)-3-aminoisobutyric acid in human cells is inferred from the corresponding process known to occur in rat (Tamaki et al. 2000).

Preceded by: beta-ureidoisobutyrate + H2O => 3-aminoisobutyrate + NH4+ + CO2

Followed by: (R)-3-aminoisobutyric acid + pyruvate => 2-methyl-3-oxopropanoate + alanine

Literature references


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(R)-3-aminoisobutyric acid + pyruvate => 2-methyl-3-oxopropanoate + alanine

Location: Pyrimidine catabolism

Stable identifier: R-HSA-909780

Type: transition

Compartments: mitochondrial matrix

Inferred from: (R)-3-aminoisobutyric acid + pyruvate => 2-methyl-3-oxopropanoate + alanine (Rattus norvegicus)

Mitochondrial AGXT2 tetramer catalyzes the reaction of (R)-3-aminoisobutyric acid and pyruvate to form 2-methyl-3-oxopropanoate and alanine. While the human mitochondrial AGXT2 enzyme has been characterized experimentally in other respects (Rodionov et al. 2010), its ability to catalyze this transamination reaction is inferred from the properties of its rat homologue.

Preceded by: Mitochondrial uptake of (R)-3-aminoisobutyric acid

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Introduction

Pyrimidine catabolism

TMP, (d)UMP, uridine 2’ monophosphate, or uridine 3’-monophosphate + H2O => thymidine, deoxyuridine, or uridine + orthophosphate [NT5M]

CMP or TMP or UMP + H2O => cytidine, thymidine, or uridine + orthophosphate [NT5E]

(d)CMP, TMP, or (d)UMP + H2O => (deoxy)cytidine, thymidine, or (deoxy)uridine + orthophosphate (NT5C3)

(d)CMP, TMP, or (d)UMP + H2O => (deoxy)cytidine, thymidine, or (deoxy)uridine + orthophosphate (NT5C1A)

TMP, uridine 2’, 3’, or 5’ monophosphates, or deoxyuridine 3’ or 5’ monophosphates + H2O => thymidine or (deoxy)uridine + orthophosphate [NT5C]

(deoxy)uridine + orthophosphate <=> uracil + (deoxy)ribose 1-phosphate (UPP)

thymidine or deoxyuridine + orthophosphate <=> thymine or uracil + 2-deoxy-D-ribose 1-phosphate [TYMP]

uracil + NADPH + H+ => 5,6-dihyuracil + NADP+

5,6-dihydrouracil + H2O => beta-ureidopropionate

beta-ureidopropionate + H2O => beta-alanine + NH4+ + CO2

Mitochondrial uptake of beta-alanine

beta-alanine + pyruvate => 3-oxopropanoate + alanine

thymine + NADPH + H+ => 5,6-dihydrothymine + NADP+

5,6-dihydrothymine + H2O => beta-ureidoisobutyrate

beta-ureidoisobutyrate + H2O => 3-aminoisobutyrate + NH4+ + CO2

Mitochondrial uptake of (R)-3-aminoisobutyric acid

(R)-3-aminobutyric acid + pyruvate => 2-methyl-3-oxopropanoate + alanine