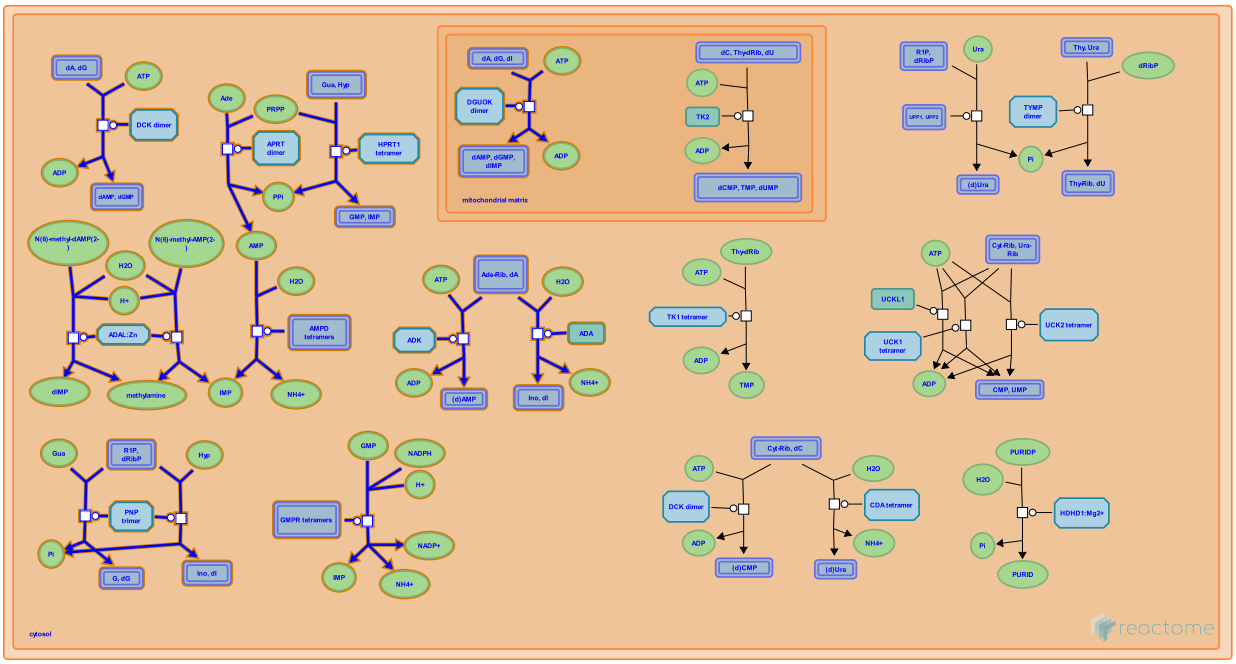
Purine salvage



D'Eustachio, P., Graves, L., Jassal, B., Rush, MG.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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.

17/05/2024

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. ↗

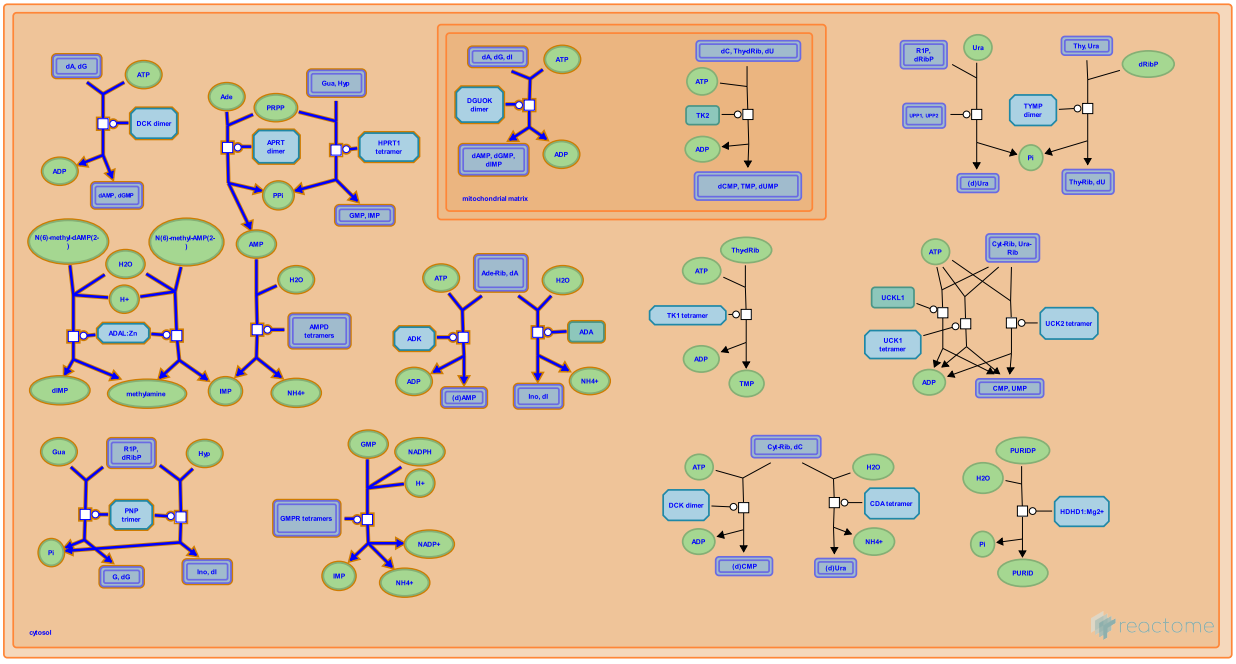
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Purine salvage ↗

Stable identifier: R-HSA-74217



Nucleosides and free bases generated by DNA and RNA breakdown are converted back to nucleotide monophosphates, allowing them to re-enter the pathway of purine biosynthesis and interconversiohn. Under normal conditions, DNA turnover is limited and deoxyribonucleotide salvage operates at a correspondingly low level (Watts 1974).

Literature references

Watts, RW. (1974). Molecular variation in relation to purine metabolism. *J Clin Pathol Suppl (R Coll Pathol), 8*, 48-63. ↗

Editions

2003-07-17	Authored	Jassal, B.
2010-02-06	Revised	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

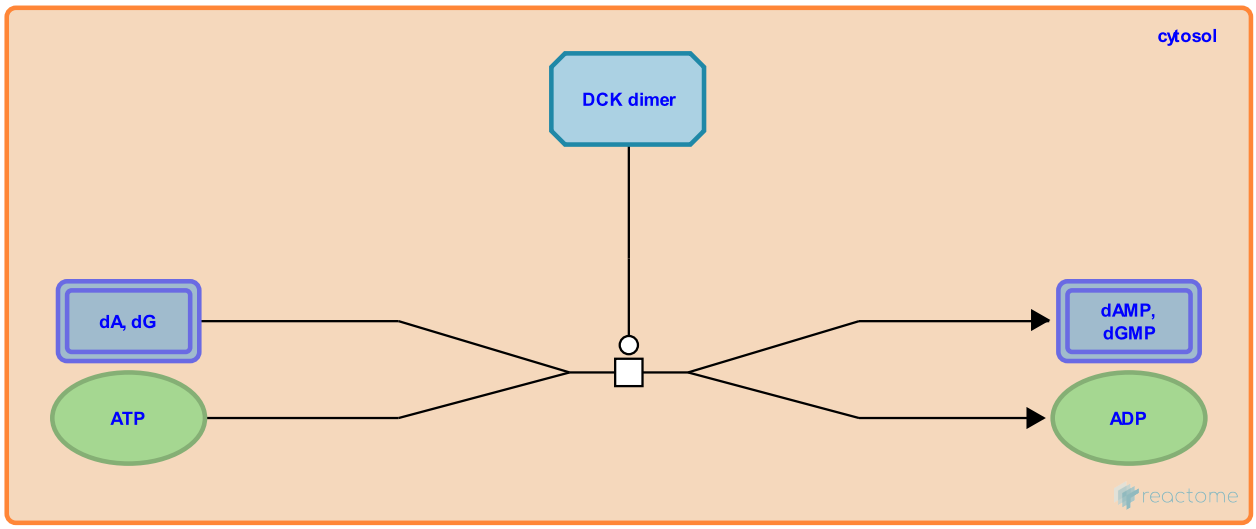
deoxyadenosine or deoxyguanosine + ATP => dAMP or dGMP + ADP (DCK) ↗

Location: Purine salvage

Stable identifier: R-HSA-109671

Type: transition

Compartments: cytosol



Cytosolic deoxycytidine kinase (DCK) catalyzes the reactions of deoxyadenosine and deoxyguanosine with ATP to form the corresponding nucleotide monophosphates and AMP, The enzyme is a dimer (Bohman and Eriksson 1988; Datta et al. 1989). While the enzyme can be found in nuclei of cultured cells expressing high levels of a tagged recombinant protein, its normal location appears to be cytosolic (Hatzis et al. 1998).

Literature references

Bohman, C., Eriksson, S. (1988). Deoxycytidine kinase from human leukemic spleen: preparation and characterization of the homogeneous enzyme. *Biochemistry, 27*, 4258-4265. ↗

Talianidis, I., Jullig, M., Petrakis, TG., Hatzis, P., Al-Madhoon, AS., Eriksson, S. (1998). The intracellular localization of deoxycytidine kinase. *J Biol Chem, 273*, 30239-30243. ↗

Datta, NS., Fox, IH., Hurley, MC., Shewach, DS., Mitchell, BS. (1989). Human T-lymphoblast deoxycytidine kinase: purification and properties. *Biochemistry, 28*, 114-123. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

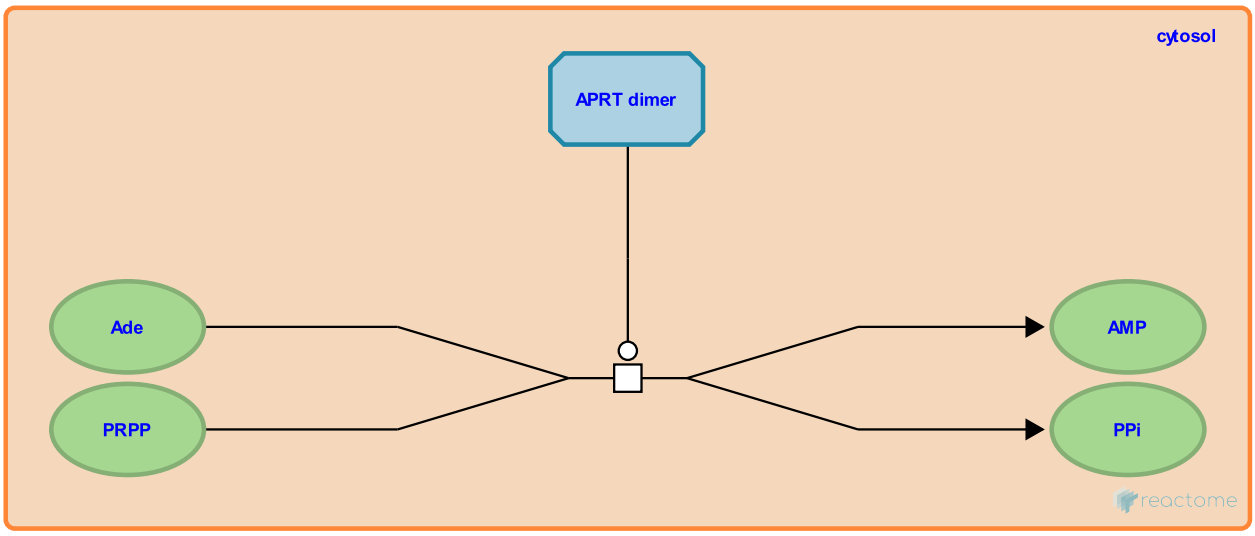
APRT catalyzes the conversion of adenine to AMP ↗

Location: Purine salvage

Stable identifier: R-HSA-74213

Type: transition

Compartments: cytosol



Cytosolic APRT dimer catalyzes the reaction of adenine and 5-phospho-alpha-D-ribose 1-diphosphate to form AMP and pyrophosphate (Holden et al. 1979; Silva et al. 2008).

Followed by: AMP + H2O => IMP + NH4+ (AMPD)

Literature references

Thiemann, OH., Silva, CH., Iulek, J., Silva, M. (2008). Structural complexes of human adenine phosphoribosyltransferase reveal novel features of the APRT catalytic mechanism. *J Biomol Struct Dyn, 25*, 589-97. ↗

Holden, JA., Meredith, GS., Kelley, WN. (1979). Human adenine phosphoribosyltransferase. Affinity purification, subunit structure, amino acid composition, and peptide mapping. *J Biol Chem, 254*, 6951-5. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

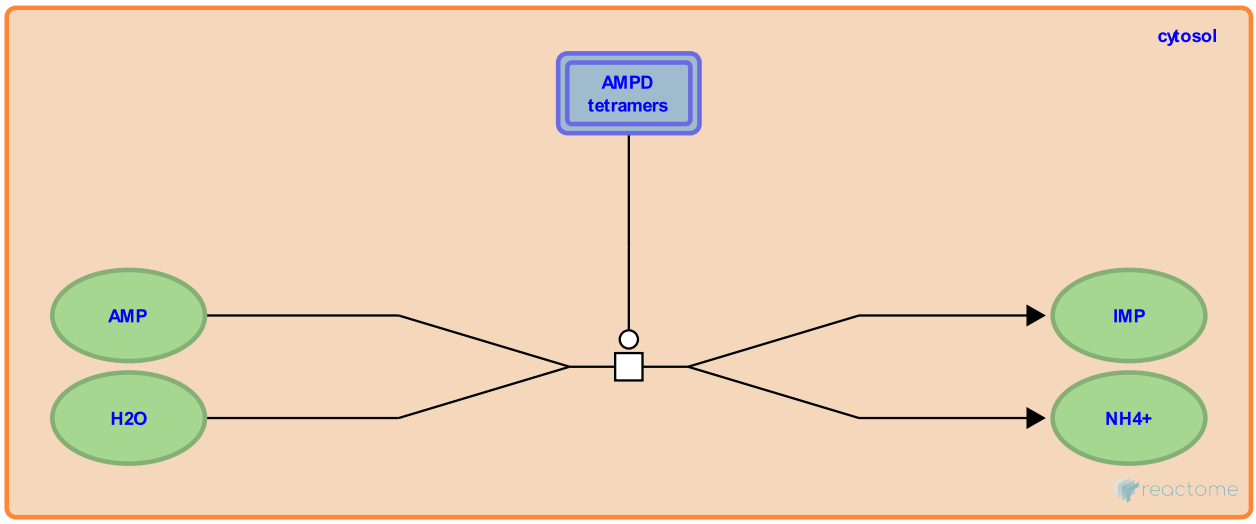
AMP + H2O => IMP + NH4+ (AMPD) ↗

Location: Purine salvage

Stable identifier: R-HSA-76590

Type: transition

Compartments: cytosol



Cytosolic AMP deaminase (AMPD) catalyzes the hydrolysis of AMP to yield IMP and ammonia. Three isoforms of AMPD, E, L, and M, have been identified that differ in their expression patterns in the body. All occur as tetramers and all have qualitatively the same catalytic activity, however (Bausch-Jurken et al. 1992; Mahnke-Zizelman et al. 1998).

Preceded by: APRT catalyzes the conversion of adenine to AMP

Literature references

Mahnke-Zizelman, DK., Morisaki, T., Bausch-Jurken, MT., Sabina, RL. (1992). Molecular cloning of AMP deaminase isoform L. Sequence and bacterial expression of human AMPD2 cDNA. *J Biol Chem, 267*, 22407-13. ↗

Tullson, PC., Mahnke-Zizelman, DK., Sabina, RL. (1998). Novel aspects of tetramer assembly and N-terminal domain structure and function are revealed by recombinant expression of human AMP deaminase isoforms. *J Biol Chem, 273*, 35118-25. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

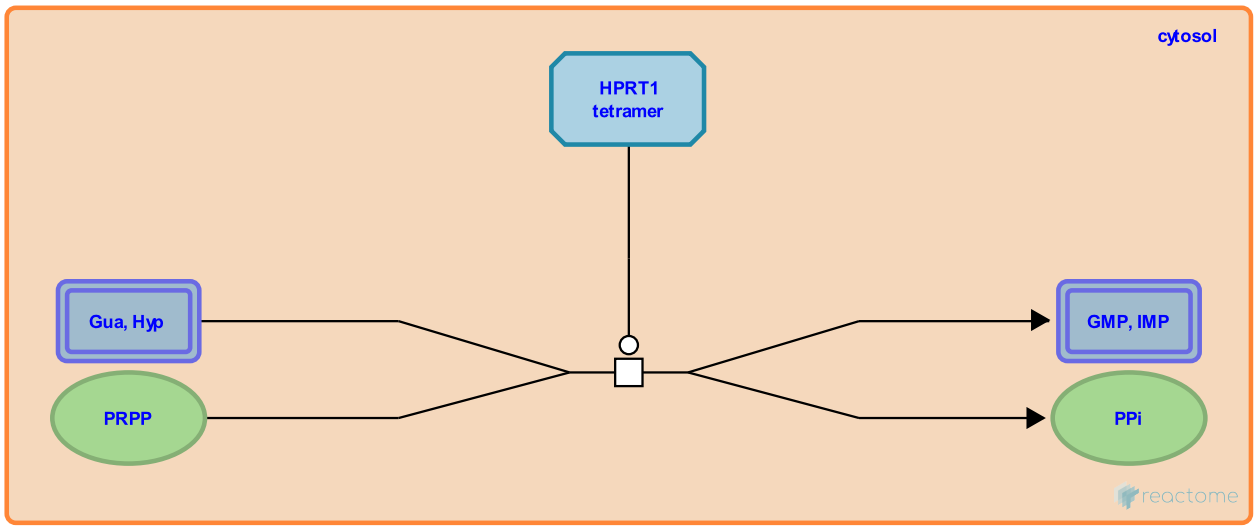
HPRT1 catalyzes the conversion of guanine or hypoxanthine to GMP or IMP ↗

Location: Purine salvage

Stable identifier: R-HSA-74215

Type: transition

Compartments: cytosol



Cytosolic hypoxanthine-guanine phosphoribosyltransferase (HPRT1) tetramer catalyzes the reactions of guanine or hypoxanthine with PRPP to form GMP ir IMP and pyrophosphate (Holden and Kelley 1978; Jolly et al. 1983).

Followed by: GMP + NADPH + H+ => IMP + NADP+ + NH4+ (GMPR,GMPR2)

Literature references

Bohlen, P., Esty, AC., Jolly, DJ., Hunkapillar, T., Johnson, GG., Berg, P. et al. (1983). Isolation and characterization of a full-length expressible cDNA for human hypoxanthine phosphoribosyl transferase. *Proc Natl Acad Sci U S A, 80*, 477-81. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

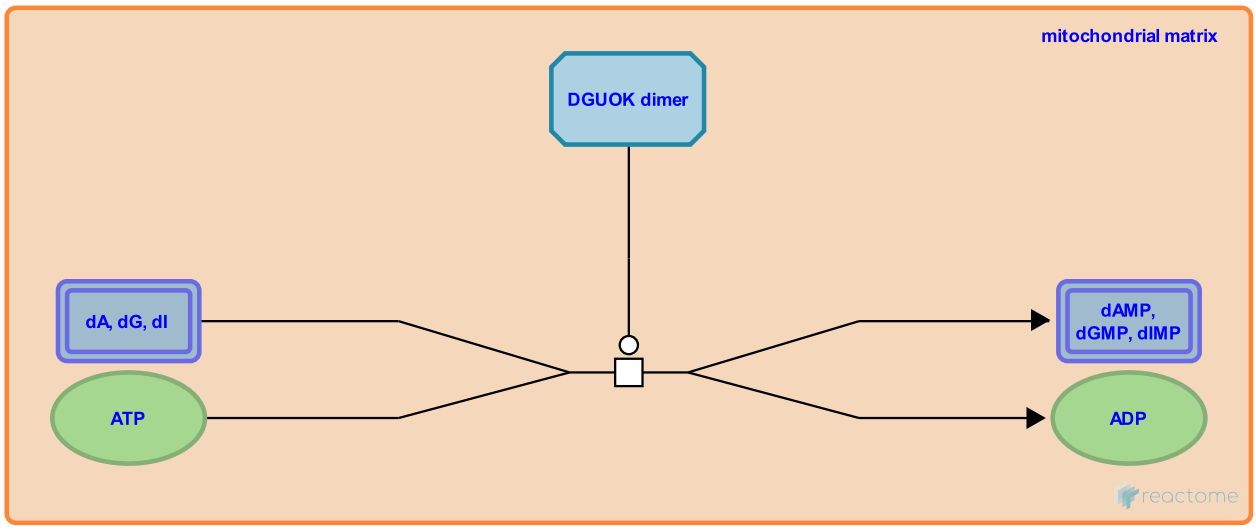
dA, dG, or dI + ATP => dAMP, dGMP, or dIMP + ADP (DGUOK) ↗

Location: Purine salvage

Stable identifier: R-HSA-74207

Type: transition

Compartments: mitochondrial matrix



Mitochondrial deoxyguanosine kinase (DGUOK) catalyzes the reactions of deoxyadenosine, deoxyguanosine, and deoxyinosine with ATP to form the corresponding nucleotide monophosphates and ADP (Park and Ives 1988; Johansson and Karlson 1996). Crystallographic studies of the human enzyme have confirmed its dimeric structure and allowed identification of key amino acid residues responsible for its substrate specificity (Johansson et al. 2001).

Literature references

Karlsson, A., Johansson, M. (1996). Cloning and expression of human deoxyguanosine kinase cDNA. *Proc Natl Acad Sci USA, 93*, 7258-7262. ↗

Park, I., Ives, DH. (1988). Properties of a highly purified mitochondrial deoxyguanosine kinase. *Arch Biochem Biophys , 266*, 51-60. ↗

Knecht, W., Eklund, H., Piskur, J., Munch-Petersen, B., Ramaswamy, S., Ljungcrantz, C. et al. (2001). Structural basis for substrate specificities of cellular deoxyribonucleoside kinases. *Nat Struct Biol, 8*, 616-620. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

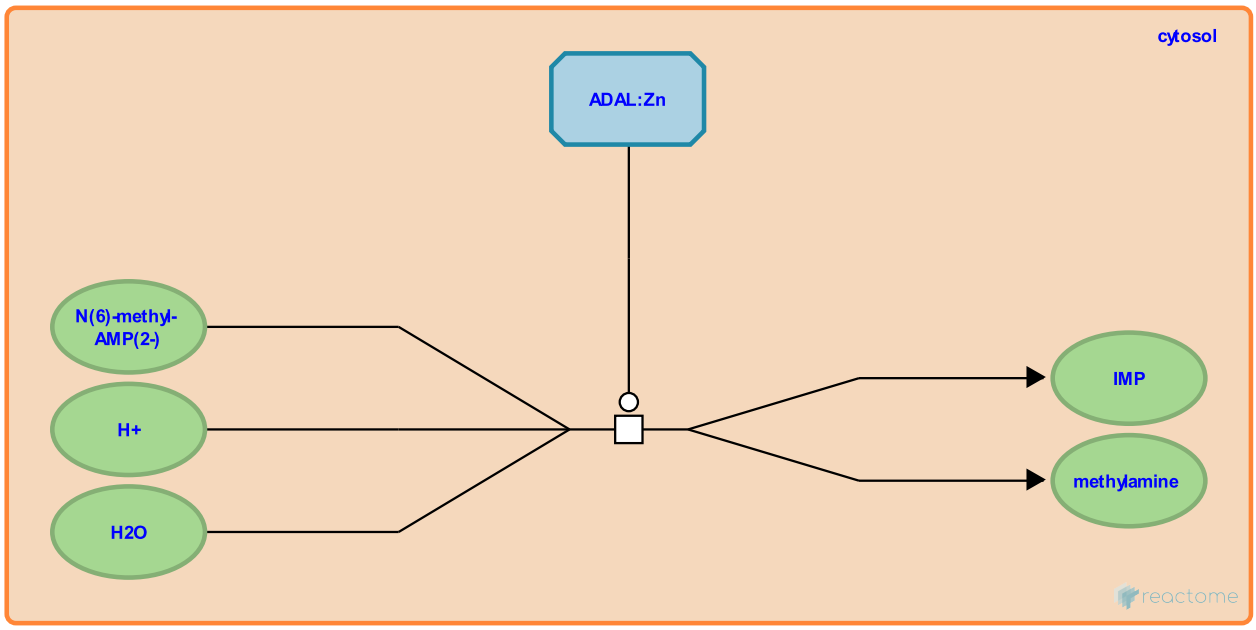
ADAL1 hydrolyzes N6-methyl-AMP to IMP and methylamine ↗

Location: Purine salvage

Stable identifier: R-HSA-2161187

Type: transition

Compartments: cytosol



Cytosolic ADAL (Adenosine DeAminase-Like) catalyzes the reaction of N6-methyl-AMP and water to form IMP and methylamine. The active form of the enzyme is a protein monomer complexed with a zinc ion (Murakami et al. 2011). Scaletti et al. (2021) suggest that under physiological conditions this reaction could enable the detoxification and salvage of methylated adenosine nucleotides.

Literature references

Vallin, KS., Jemth, AS., Scaletti, ER., Stenmark, P., Helleday, T., Sarno, A. et al. (2020). MutT homologue 1 (MTH1) removes N6-methyl-dATP from the dNTP pool. *J Biol Chem, 295*, 4761-4772. ↗

Furman, PA., Sofia, MJ., Du, J., Bao, H., Murakami, E., Mosley, RT. (2011). Adenosine deaminase-like protein 1 (ADAL1): characterization and substrate specificity in the hydrolysis of N(6)- or O(6)-substituted purine or 2-aminopurine nucleoside monophosphates. *J Med Chem, 54*, 5902-14. ↗

Editions

2012-03-14	Authored	D'Eustachio, P.
2012-03-16	Edited	D'Eustachio, P.
2012-03-16	Reviewed	Jassal, B.
2021-05-21	Revised	D'Eustachio, P.

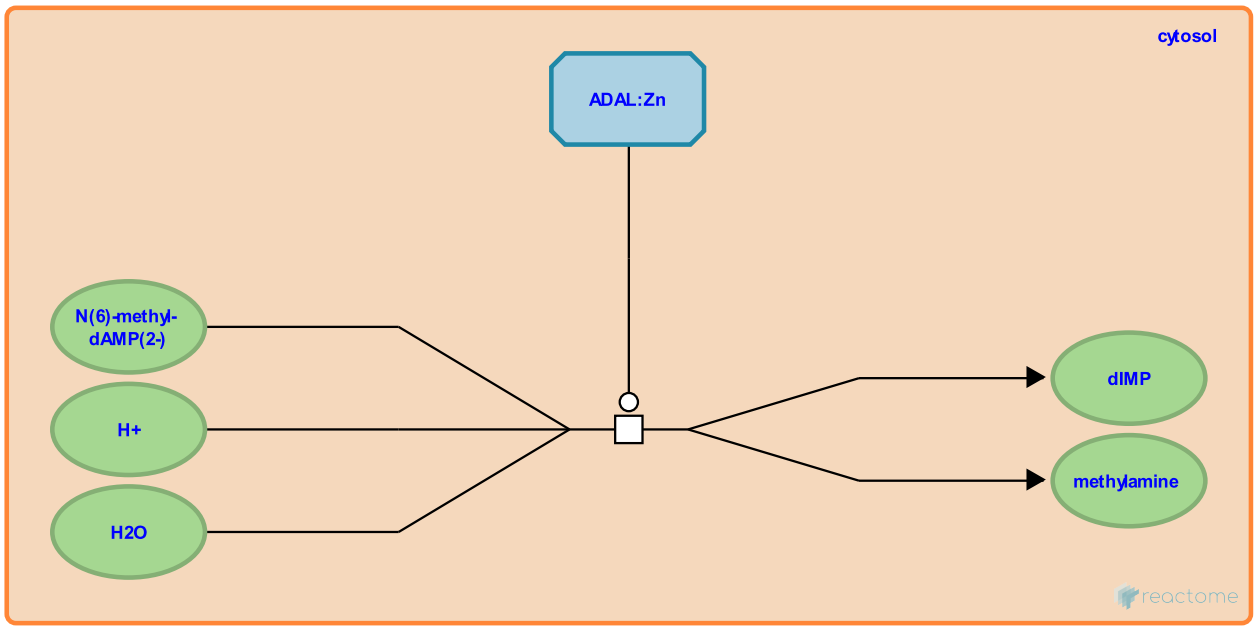
ADAL1 hydrolyzes N6-methyl-dAMP to dIMP and methylamine ↗

Location: Purine salvage

Stable identifier: R-HSA-9731661

Type: transition

Compartments: cytosol



Cytosolic ADAL (Adenosine DeAminase-Like) catalyzes the reaction of N6-methyl-dAMP and water to form dIMP and methylamine. The active form of the enzyme is a protein monomer complexed with a zinc ion (Murakami et al. 2011). Scaletti et al. (2021) suggest that under physiological conditions this reaction could enable the detoxification and salvage of methylated adenosine nucleotides.

Literature references

Vallin, KS., Jemth, AS., Scaletti, ER., Stenmark, P., Helleday, T., Sarno, A. et al. (2020). MutT homologue 1 (MTH1) removes N6-methyl-dATP from the dNTP pool. *J Biol Chem, 295*, 4761-4772. ↗

Furman, PA., Sofia, MJ., Du, J., Bao, H., Murakami, E., Mosley, RT. (2011). Adenosine deaminase-like protein 1 (ADAL1): characterization and substrate specificity in the hydrolysis of N(6)- or O(6)-substituted purine or 2-aminopurine nucleoside monophosphates. *J Med Chem, 54*, 5902-14. ↗

Editions

2021-05-21	Authored, Edited	D'Eustachio, P.
2021-05-25	Reviewed	Jassal, B.

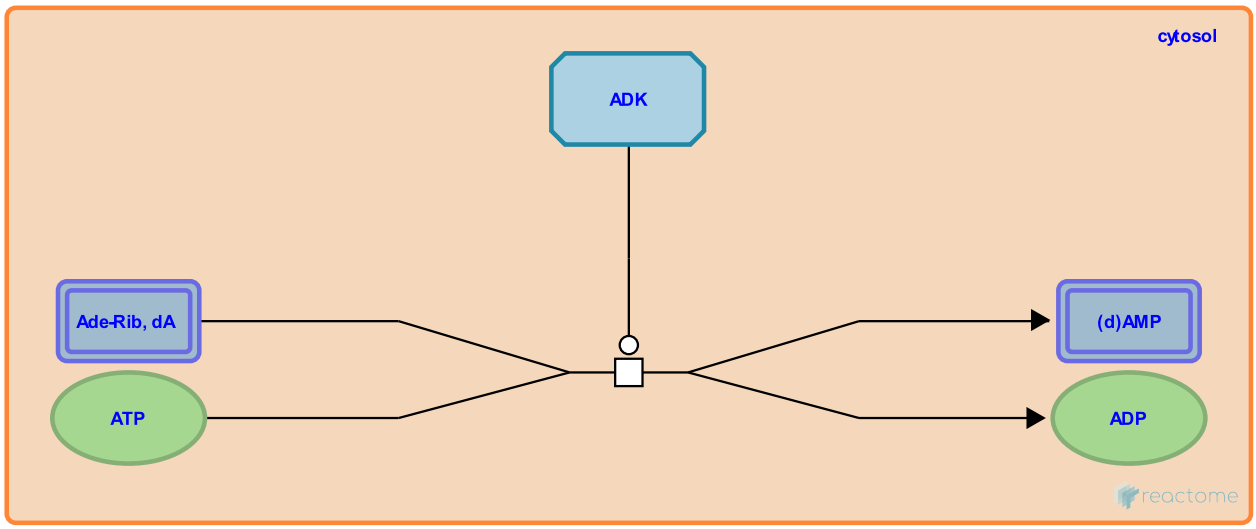
(2'-deoxy)adenosine + ATP => (d)AMP + ADP (ADK) ↗

Location: Purine salvage

Stable identifier: R-HSA-109624

Type: transition

Compartments: cytosol



Cytosolic adenosine kinase (ADK) catalyzes the reactions of adenosine and deoxyadenosine with ATP to yield the corresponding nucleotide monophosphates and ADP (Andres and Fox 1979). The enzyme is substantially more active on adenosine than deoxyadenosine in vitro (Hurley at al. 1985) though studies of cultured cells suggest that both reactions may be physiologically relevant (Hershfield et al. 1982). The enzyme is a monomer complexed with magnesium (Mathews et al. 1998).

Literature references

Ealick, SE., Mathews, II., Erion, MD. (1998). Structure of human adenosine kinase at 1.5 A resolution. *Biochemistry, 37*, 15607-20. ↗

Bagnara, AS., Williams, SR., Fetter, JE., Small, WC., Hershfield, MS., Wasson, DB. et al. (1982). Effects of mutational loss of adenosine kinase and deoxycytidine kinase on deoxyATP accumulation and deoxyadenosine toxicity in cultured CEM human T-lymphoblastoid cells. *J Biol Chem, 257*, 6380-6386. ↗

Lin, B., Fox, IH., Hurley, MC. (1985). Regulation of deoxyadenosine and nucleoside analog phosphorylation by human placental adenosine kinase. *J Biol Chem, 260*, 15675-15681. ↗

Fox, IH., Andres, CM. (1979). Purification and properties of human placental adenosine kinase. *J Biol Chem, 254*, 11388-11393. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

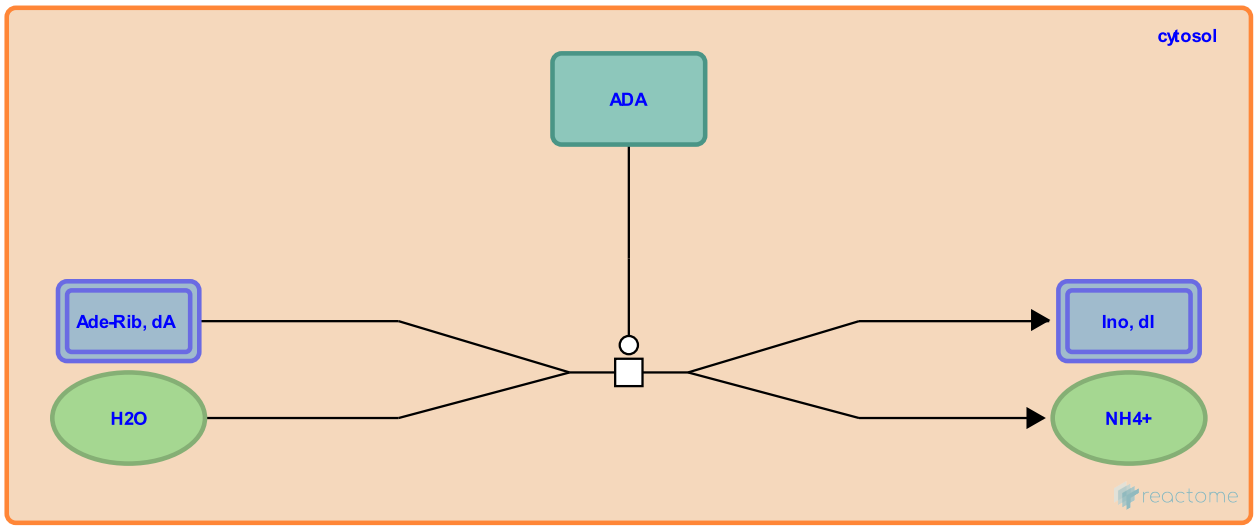
ADA catalyzes the deamination of (deoxy)adenosine ↗

Location: Purine salvage

Stable identifier: R-HSA-74241

Type: transition

Compartments: cytosol



Cytosolic adenosine deaminase (ADA) catalyzes the hydrolysis of 2'deoxyadenosine and adenosine to yield deoxyinosine and inosine, respectively, plus ammonia (Akeson et al. 1988). Unpublished crystallographic data (PDB 3IAR) indicate that the human enzyme is a monomer.

Literature references

Hutton, JJ., States, JC., Wiginton, DA., Akeson, AL., Dusing, MR. (1988). Mutant human adenosine deaminase alleles and their expression by transfection into fibroblasts. *J Biol Chem, 263*, 16291-6. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

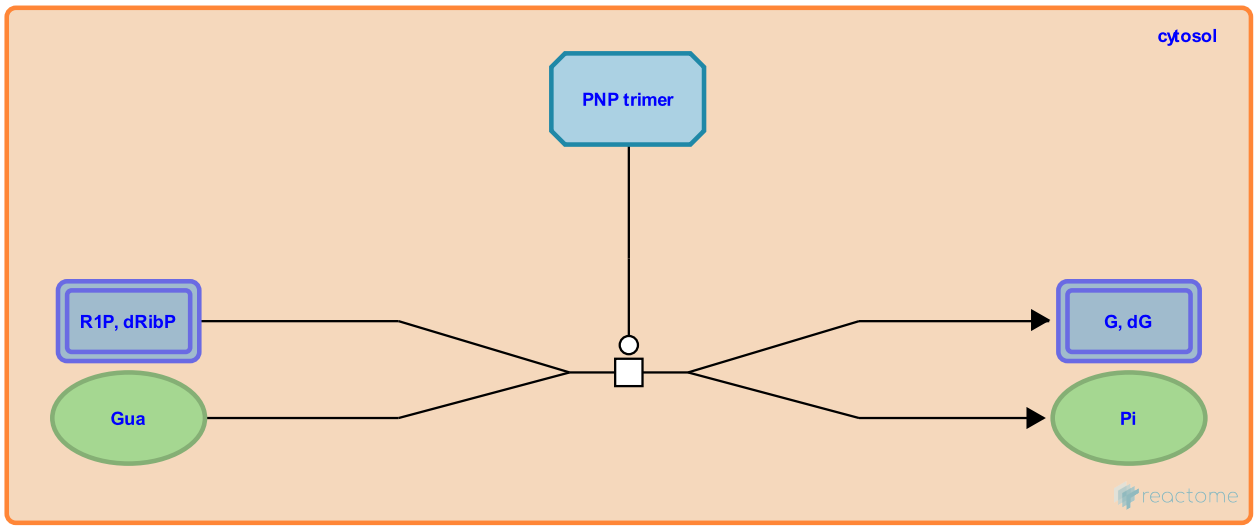
PNP catalyzes the conversion of guanine and (deoxy)ribose to (deoxy)guanosine ↗

Location: Purine salvage

Stable identifier: R-HSA-112034

Type: transition

Compartments: cytosol



Cytosolic purine nucleoside phosphorylase (PNP) trimer catalyzes the reversible reaction of guanine with ribose 1-phosphate or deoxyribose 1-phosphate to form guanosine or deoxyguanosine and orthophosphate (Ealick et al. 1990; Wiginton et al. 1980). While PNP is active with either ribose 1-phosphate or deoxyribose 1-phosphate in vitro, levels of deoxyribose 1-phosphate are normally low in vivo, limiting the extent of this reaction. PNP deficiency in vivo is associated with defects in purine metabolism and leads to immunodeficiency (Williams et al. 1987).

Literature references

Williams, SR., Gekeler, V., McIvor, RS., Martin, Jr, DW. (1987). A human purine nucleoside phosphorylase deficiency caused by a single base change. *J Biol Chem, 262*, 2332-2338. ↗

Hutton, JJ., Wiginton, DA., Coleman, MS. (1980). Characterization of purine nucleoside phosphorylase from human granulocytes and its metabolism of deoxyribonucleosides. *J Biol Chem, 255*, 6663-6669. ↗

Cook, WJ., Habash, J., Greenhough, TJ., Babu, YS., Carter, DC., Parks, Jr, RE. et al. (1990). Three-dimensional structure of human erythrocytic purine nucleoside phosphorylase at 3.2 A resolution. *J Biol Chem, 265*, 1812-1820. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

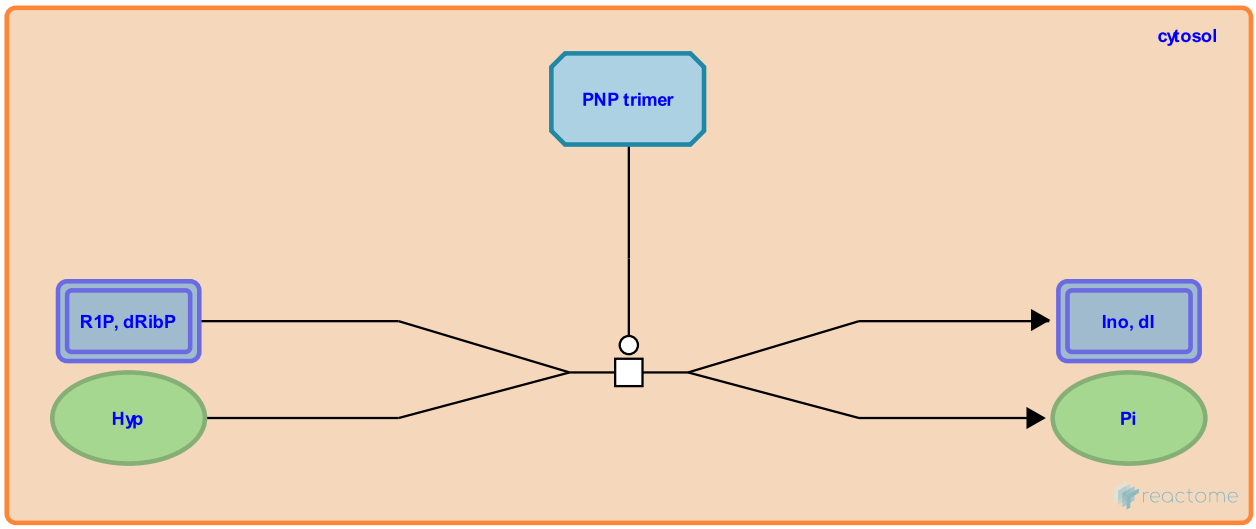
PNP catalyzes the conversion of hypoxanthine and (deoxy)ribose to (deoxy)inosine ↗

Location: Purine salvage

Stable identifier: R-HSA-112033

Type: transition

Compartments: cytosol



Cytosolic purine nucleoside phosphorylase (PNP) trimer catalyzes the reversible reaction of hypoxanthine with ribose 1-phosphate or deoxyribose 1-phosphate to form inosine or deoxyinosine and orthophosphate (Ealick et al. 1990; Wiginton et al. 1980). While PNP is active with either ribose 1-phosphate or deoxyribose 1-phosphate in vitro, levels of deoxyribose 1-phosphate are normally low in vivo, limiting the extent of this reaction. PNP deficiency in vivo is associated with defects in purine metabolism and leads to immunodeficiency (Williams et al. 1987).

Literature references

Williams, SR., Gekeler, V., McIvor, RS., Martin, Jr, DW. (1987). A human purine nucleoside phosphorylase deficiency caused by a single base change. *J Biol Chem, 262*, 2332-2338. ↗

Hutton, JJ., Wiginton, DA., Coleman, MS. (1980). Characterization of purine nucleoside phosphorylase from human granulocytes and its metabolism of deoxyribonucleosides. *J Biol Chem, 255*, 6663-6669. ↗

Cook, WJ., Habash, J., Greenhough, TJ., Babu, YS., Carter, DC., Parks, Jr, RE. et al. (1990). Three-dimensional structure of human erythrocytic purine nucleoside phosphorylase at 3.2 A resolution. *J Biol Chem, 265*, 1812-1820. ↗

Editions

2010-02-06	Revised	D'Eustachio, P.

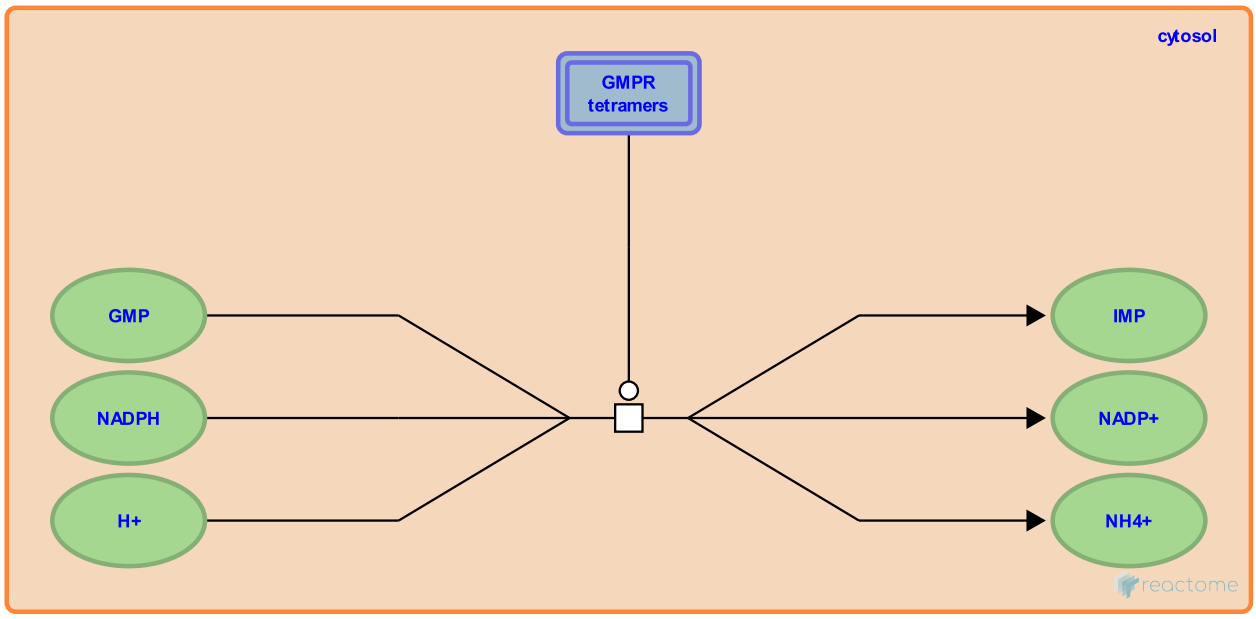
GMP + NADPH + H+ => IMP + NADP+ + NH4+ (GMPR,GMPR2)

Location: Purine salvage

Stable identifier: R-HSA-514604

Type: transition

Compartments: cytosol



Cytosolic GMP reductase (GMPR) catalyzes the reaction of GMP and NADPH + H+ to yield IMP and NADP+ + NH4+ (Spector et al. 1979; Deng et al. 2002). Two GMPR proteins have been identified, GMPR and GMPR2. Both proteins form homotetramers (GMPR - unpublished crstallographic data PDB 2BLE; GMPR2 - Li et al. 2006).

Preceded by: HPRT1 catalyzes the conversion of guanine or hypoxanthine to GMP or IMP

Literature references

Deng, Y., Qiu, R., Gu, X., Chen, F., Li, J., Xie, Y. et al. (2006). Crystal structure of human guanosine monophosphate reductase 2 (GMPR2) in complex with GMP. *J Mol Biol, 355*, 980-8.

Gu, S., Deng, Y., Wang, Y., Huang, Y., Ying, K., Gu, X. et al. (2002). NADPH-dependent GMP reductase isoenzyme of human (GMPR2). Expression, purification, and kinetic properties. *Int J Biochem Cell Biol, 34*, 1035-50.

Miller, RL., Jones, TE., Spector, T. (1979). Reaction mechanism and specificity of human GMP reductase. Substrates, inhibitors, activators, and inactivators. *J Biol Chem, 254*, 2308-15.

Editions

2010-02-18	Authored, Edited	D'Eustachio, P.
2024-03-06	Reviewed	Rush, MG., Graves, L.

Table of Contents

Introduction 1

Purine salvage 2

- deoxyadenosine or deoxyguanosine + ATP => dAMP or dGMP + ADP (DCK) 3
- APRT catalyzes the conversion of adenine to AMP 4
- AMP + H2O => IMP + NH4+ (AMPD) 5
- HPRT1 catalyzes the conversion of guanine or hypoxanthine to GMP or IMP 6
- dA, dG, or dI + ATP => dAMP, dGMP, or dIMP + ADP (DGUOK) 7
- ADAL1 hydrolyzes N6-methyl-AMP to IMP and methylamine 8
- ADAL1 hydrolyzes N6-methyl-dAMP to dIMP and methylamine 9
- (2'-deoxy)adenosine + ATP => (d)AMP + ADP (ADK) 10
- ADA catalyzes the deamination of (deoxy)adenosine 11
- PNP catalyzes the conversion of guanine and (deoxy)ribose to (deoxy)guanosine 12
- PNP catalyzes the conversion of hypoxanthine and (deoxy)ribose to (deoxy)inosine 13
- GMP + NADPH + H+ => IMP + NADP+ + NH4+ (GMPR,GMPR2) 14

Table of Contents 15