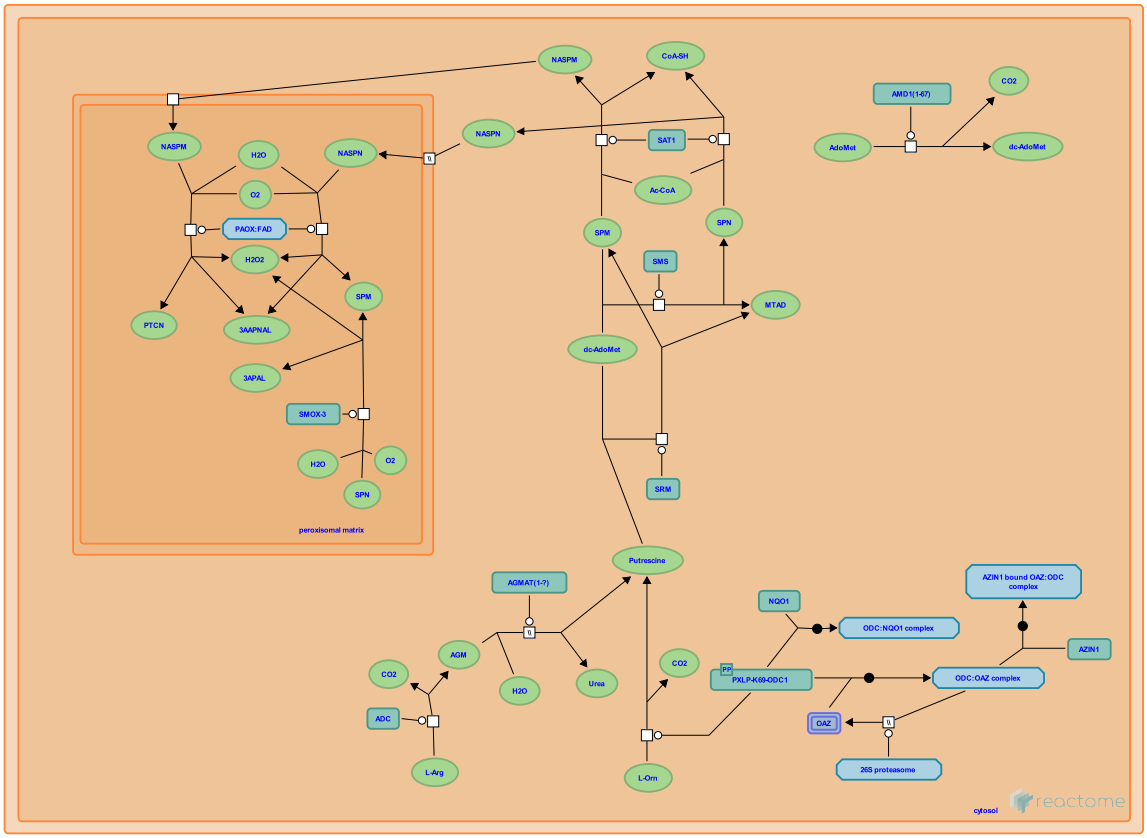
Metabolism of polyamines



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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.

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.

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. ↗

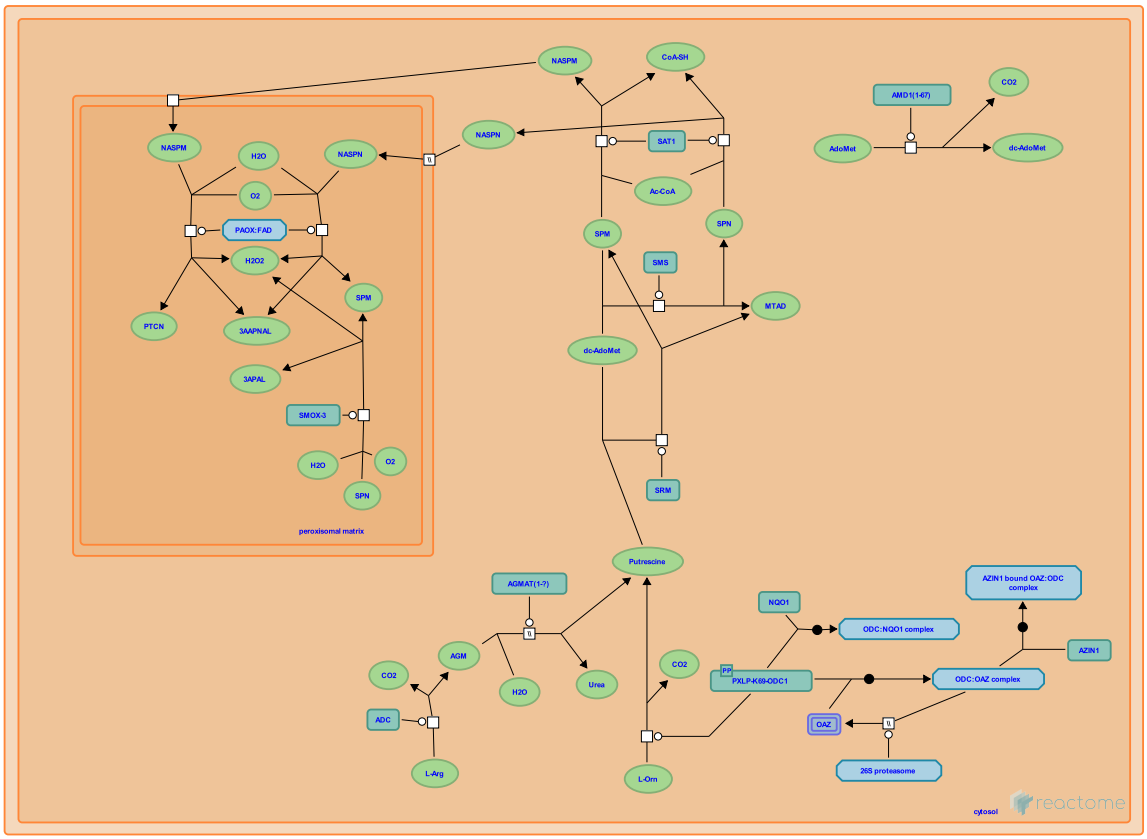
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Metabolism of polyamines ↗

Stable identifier: R-HSA-351202

Compartments: cytosol, peroxisomal matrix



Polyamines is a family of molecules (i.e. putrescine, spermine, spermidine) derived from ornithine according to a decarboxylation/condensative process. More recently, it has been demonstrated that arginine can be metabolised according to the same pathway leading to agmatine formation. Polyamines are essential for the growth, the maintenance and the function of normal cells. The complexity of their metabolism and the fact that polyamines homeostasis is tightly regulated support the idea that polyamines are essential to cell survival. Multiple abnormalities in the control of polyamines metabolism might be implicated in several pathological processes (Moinard et al., 2005). Legend for the following figure:

Literature references

Medina, MA., Urdiales, JL., Sánchez-Jiménez, F. (2001). Polyamine metabolism revisited. *Eur J Gastroenterol Hepatol, 13*, 1015-9. ↗

Hillary, RA., Pegg, AE. (2003). Decarboxylases involved in polyamine biosynthesis and their inactivation by nitric oxide. *Biochim Biophys Acta, 1647*, 161-6. ↗

de Bandt, JP., Cynober, L., Moinard, C. (2005). Polyamines: metabolism and implications in human diseases. *Clin Nutr, 24*, 184-97. ↗

Editions

2008-05-21	Authored	Gopinathrao, G.
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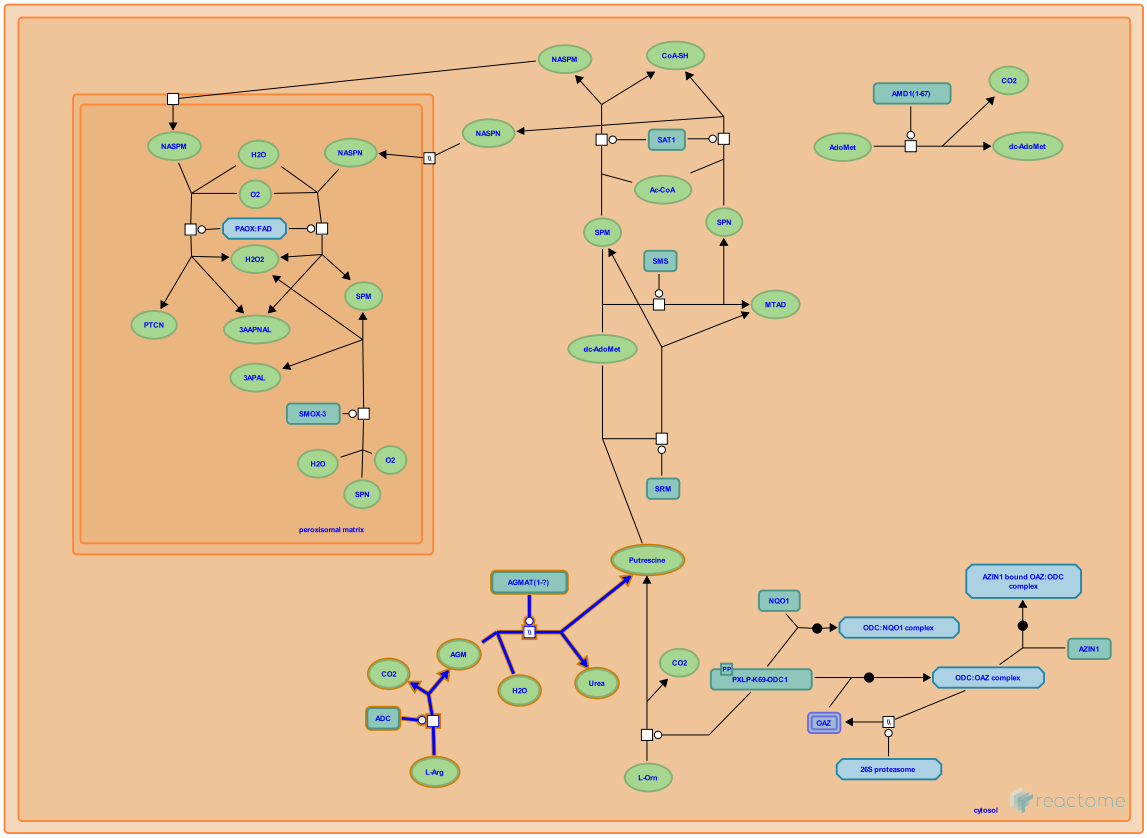
2017-03-22	Edited	D'Eustachio, P.

Agmatine biosynthesis ↗

Location: Metabolism of polyamines

Stable identifier: R-HSA-351143

Compartments: cytosol



Agmatine is an amine that is formed by decarboxylation of L-arginine by the enzyme arginine decarboxylase (ADC) and hydrolyzed by the enzyme agmatinase to putrescine. Agmatine binds to several target receptors in the brain and has been proposed as a novel neuromodulator (Reghunathan 2006). Agmatine has the potential to serve in the coordination of the early and repair phase pathways of arginine in inflammation (Satriano, 2003).

Literature references

Morris SM, Jr. (2003). Vertebrate agmatinases: what role do they play in agmatine catabolism?. *Ann N Y Acad Sci, 1009*, 30-3. ↗

Satriano, J. (2003). Agmatine: at the crossroads of the arginine pathways. *Ann N Y Acad Sci, 1009*, 34-43. ↗

de Bandt, JP., Cynober, L., Moinard, C. (2005). Polyamines: metabolism and implications in human diseases. *Clin Nutr, 24*, 184-97. ↗

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2006-04-27	Edited	Gopinathrao, G.
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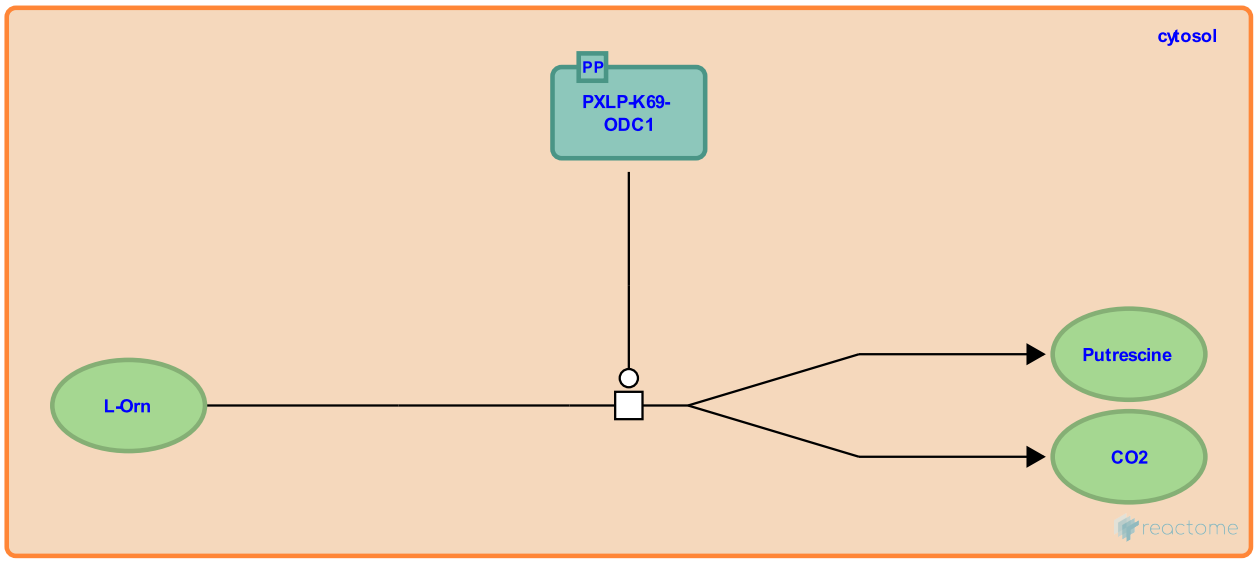
ornithine => putrescine + CO2 ↗

Location: Metabolism of polyamines

Stable identifier: R-HSA-70692

Type: transition

Compartments: cytosol



L-ornithine is converted into putrescine by ODC holoenzyme complex.Putrescine is subsequent used for polyamine synthesis.

Followed by: Putrescine + dc-Adenosyl methionine => Spermidine + 5'-methylthioadenosine

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). The hyperornithinemias, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1857-1895.

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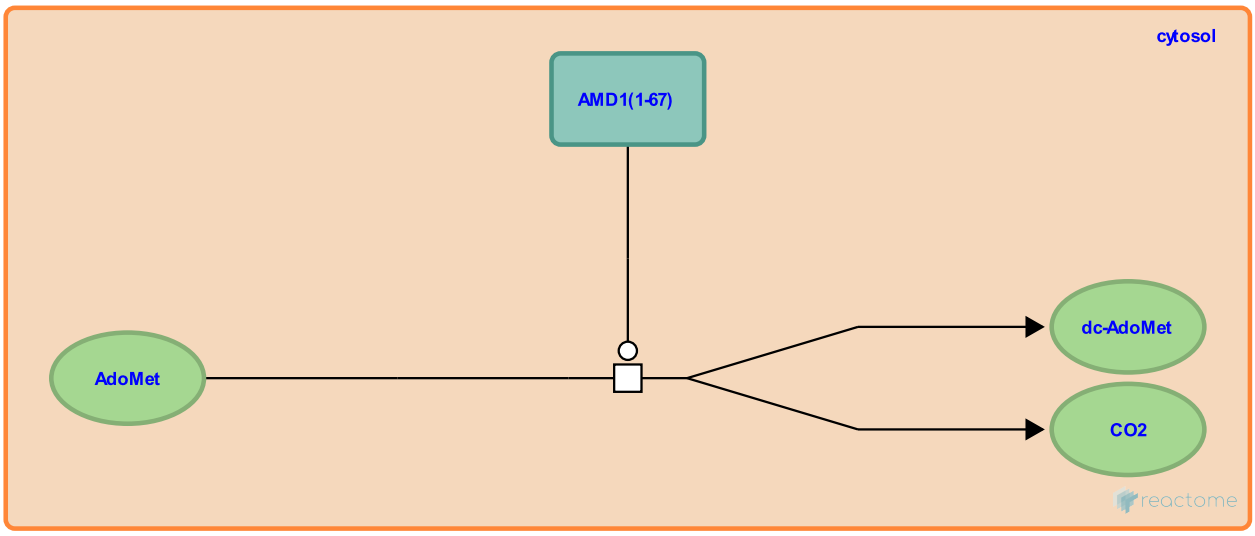
S-Adenosyl methionine <=> Decarboxylated-Adenosyl methionine + CO2 ↗

Location: Metabolism of polyamines

Stable identifier: R-HSA-351222

Type: transition

Compartments: cytosol



S-Adenosylmethionine decarboxylase belongs to a small class of amino acid decarboxylases that use a covalently bound pyruvate as a prosthetic group. It is an essential enzyme for polyamine biosynthesis and provides an important target for the design of anti-parasitic and cancer chemotherapeutic agents. It catalyzes the formation of the aminopropyl group donor in the biosynthesis of the polyamines spermidine and spermine. These pyruvoyl-dependent decarboxylases also form amines such as histamine, decarboxylated S-adenosylmethionine, phosphatidylethanolamine (a component of membrane phospholipids), and -alanine (a precursor of coenzyme A), which are all of critical importance in cellular physiology and provide important targets for drug design.

Followed by: dc-Adenosyl methionine + Spermidine => Spermine + 5'-methylthioadenosine, Putrescine + dc-Adenosyl methionine => Spermidine + 5'-methylthioadenosine

Literature references

Kapoor, P., Pegg, AE., Ekstrom, JL., Ealick, SE., Secrist JA, 3rd., Tolbert, WD. et al. (2001). The structural basis for substrate specificity and inhibition of human S-adenosylmethionine decarboxylase. *Biochemistry, 40*, 9484-94. ↗

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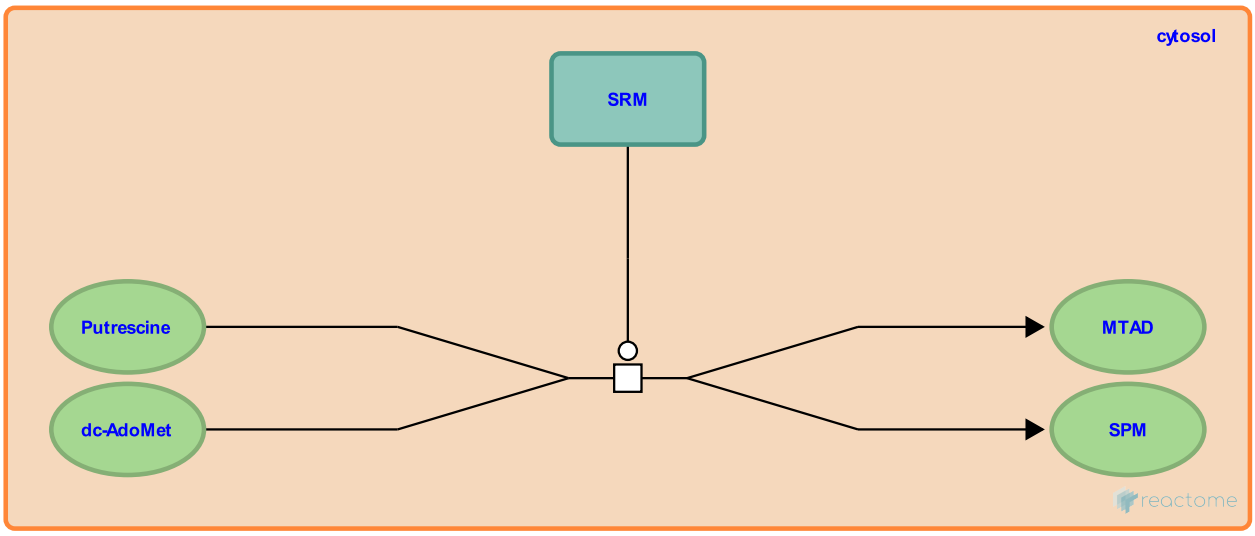
Putrescine + dc-Adenosyl methionine => Spermidine + 5'-methylthioadenosine ↗

Location: Metabolism of polyamines

Stable identifier: R-HSA-351215

Type: transition

Compartments: cytosol



Spermidine synthase is one of four enzymes in the polyamine-biosynthetic pathway and carries out the final step of spermidine biosynthesis. This enzyme catalyzes the conversion of putrescine to spermidine using decarboxylated S-adenosylmethionine as the cofactor.

Preceded by: ornithine => putrescine + CO2, S-Adenosyl methionine <=> Decarboxylated-Adenosyl methionine + CO2

Followed by: dc-Adenosyl methionine + Spermidine => Spermine + 5'-methylthioadenosine

Literature references

Alhonen, L., Myöhänen, S., Wahlfors, J., Kauppinen, L., Jänne, J. (1991). Human spermidine synthase gene: structure and chromosomal localization. *DNA Cell Biol, 10*, 467-74. ↗

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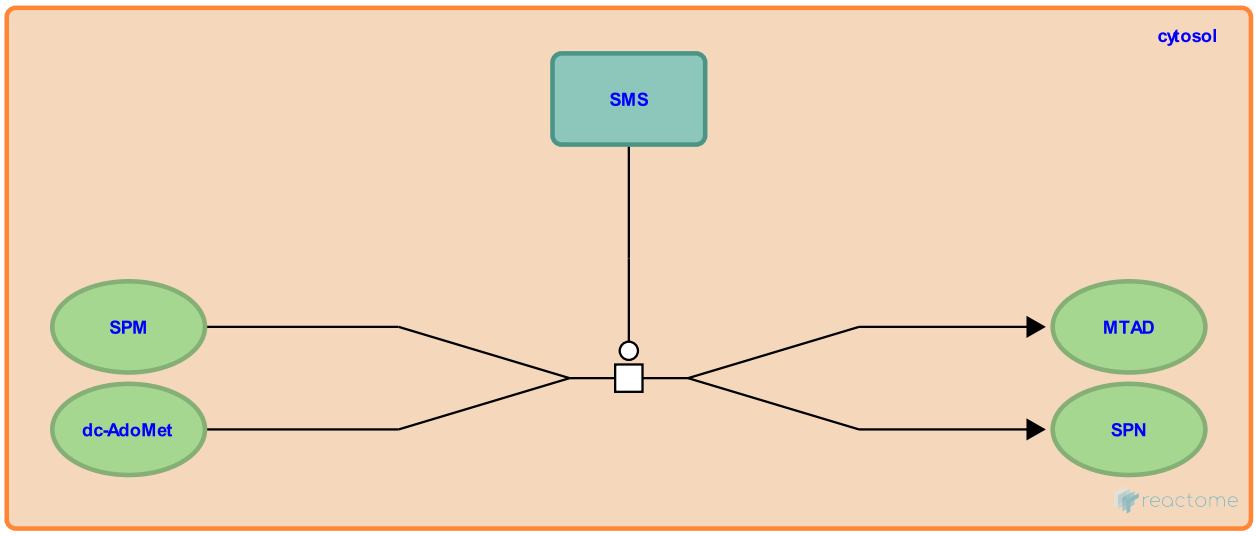
dc-Adenosyl methionine + Spermidine => Spermine + 5'-methylthioadenosine ↗

Location: Metabolism of polyamines

Stable identifier: R-HSA-351210

Type: transition

Compartments: cytosol



The protein encoded by this gene belongs to the spermidine/spermine synthases family. This gene encodes an ubiquitous enzyme of polyamine metabolism. Defects in SMS are the cause of Snyder-Robinson syndrome (SRS).

Preceded by: Putrescine + dc-Adenosyl methionine => Spermidine + 5'-methylthioadenosine, S-Adenosyl methionine <=> Decarboxylated-Adenosyl methionine + CO2

Literature references

Keinänen, T., Korhonen, VP., Halmekytö, M., Alhonen, L., Myöhänen, S., Eloranta, T. et al. (1995). Molecular cloning of a cDNA encoding human spermine synthase. *DNA Cell Biol, 14*, 841-7. ↗

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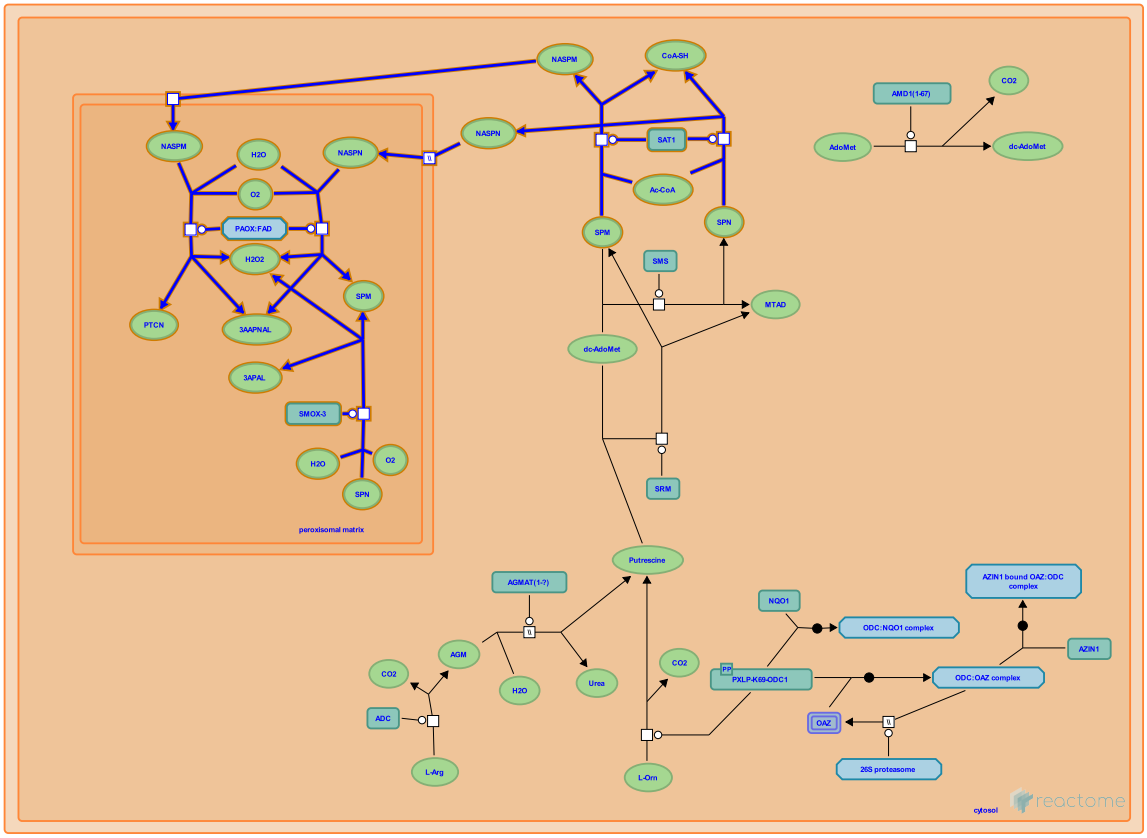
Interconversion of polyamines ↗

Location: Metabolism of polyamines

Stable identifier: R-HSA-351200

Compartments: peroxisomal matrix, cytosol



The reactions catalyzed by aminopropyl-transferases annotated above are generally irreversible. But spermine and spermidine can be recycled respectively into spermidine and putrescine. These events require the formation of N-acetylated intermediates, N1-acetylspermine and N1-acetylspermidine catalyzed by a cytosolic acetyl-CoA:spermidine/spermine N1-acetyl-tranferase (SSAT) enzyme.
Subsequently, polyamine-oxidase (PAO), a FAD enzyme present in the peroxysomes, yields a polyamine with release of an aldehyde (3-acetamindopropanal) and H2O2.
In addition, SMOX, a FAD-dependent, polyamine oxidase (PAOh1/SMO) that can efficiently use spermine as a substrate and is involved in interconversion reactions.

Literature references

Medina, MA., Urdiales, JL., Sánchez-Jiménez, F. (2001). Polyamine metabolism revisited. *Eur J Gastroenterol Hepatol, 13*, 1015-9. ↗

Seiler, N. (2004). Catabolism of polyamines. *Amino Acids, 26*, 217-33. ↗

Hillary, RA., Pegg, AE. (2003). Decarboxylases involved in polyamine biosynthesis and their inactivation by nitric oxide. *Biochim Biophys Acta, 1647*, 161-6. ↗

de Bandt, JP., Cynober, L., Moinard, C. (2005). Polyamines: metabolism and implications in human diseases. *Clin Nutr, 24*, 184-97. ↗

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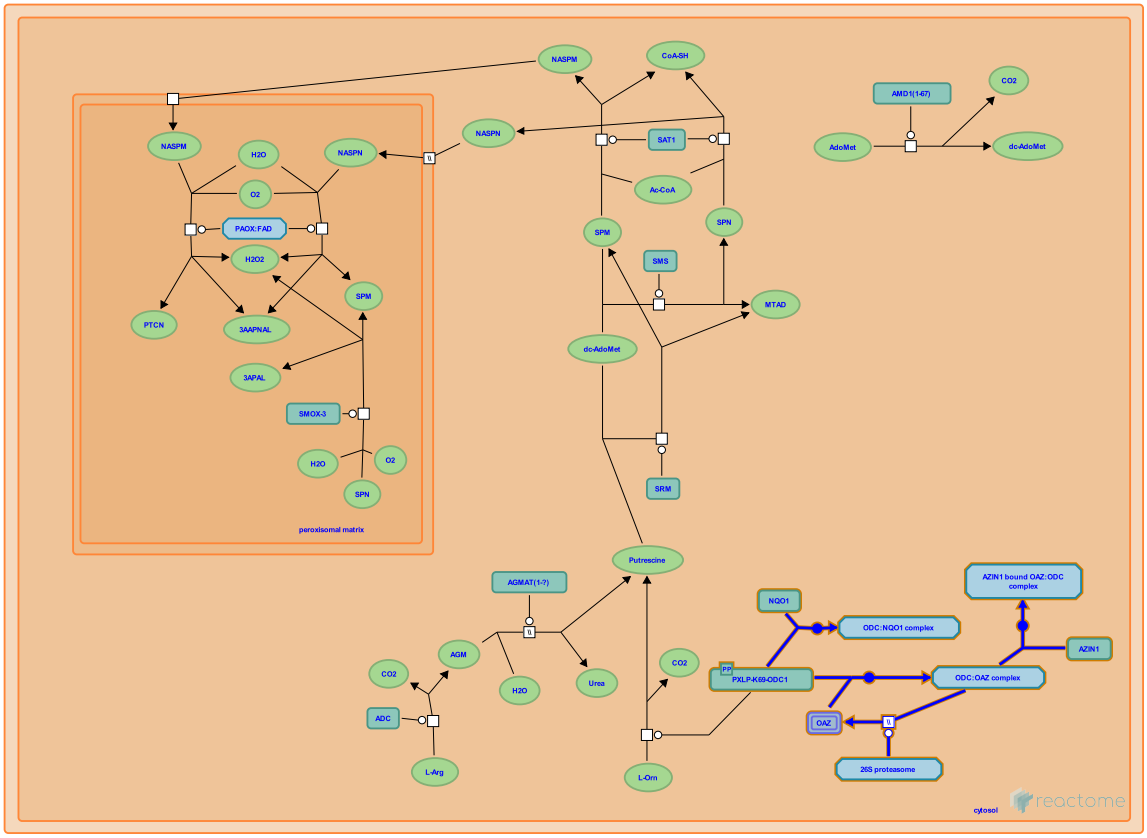
Regulation of ornithine decarboxylase (ODC)

Location: Metabolism of polyamines

Stable identifier: R-HSA-350562

Compartments: cytosol



Polyamines increase the production of antizyme (AZ). The carboxy-terminal half of antizyme interacts with ODC, generating an inactive AZ:ODC heterodimer complex. A carboxy-terminal domain of ODC is exposed only within the heterodimer, and is the target for subsequent degradation. A domain within the amino-terminal portion of antizyme provides a function needed for efficient degradation of ODC by the proteasome.
The proteasome cycle starts with the processing of AZ:ODC, sequestering ODC and then degrading it to peptides but releasing AZ. AZ participates in additional rounds of binding and degradation. Antizyme-mediated inhibition and destruction of ODC reduces synthesis of polyamines. Additionally, antizyme also inhibits polyamine transport into the cell. Antizyme production is reduced, completing the regulatory circuit (Coffino, 2001).
The following illustration is adapted from a minireview by Pegg, 2006; J. Biol. Chem., Vol. 281, Issue 21, 14529-14532.

Literature references

Shaul, Y., Kahana, C., Asher, G. (2005). Mechanisms of protein degradation: an odyssey with ODC. *Cell Cycle, 4*, 1461-4.

Murakami, Y., Tanaka, K., Hayashi, S., Matsufuji, S., Tanahashi, N. (2000). Degradation of ornithine decarboxylase by the 26S proteasome. *Biochem Biophys Res Commun, 267*, 1-6.

Pegg, AE. (2006). Regulation of ornithine decarboxylase. *J Biol Chem, 281*, 14529-32.

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Table of Contents