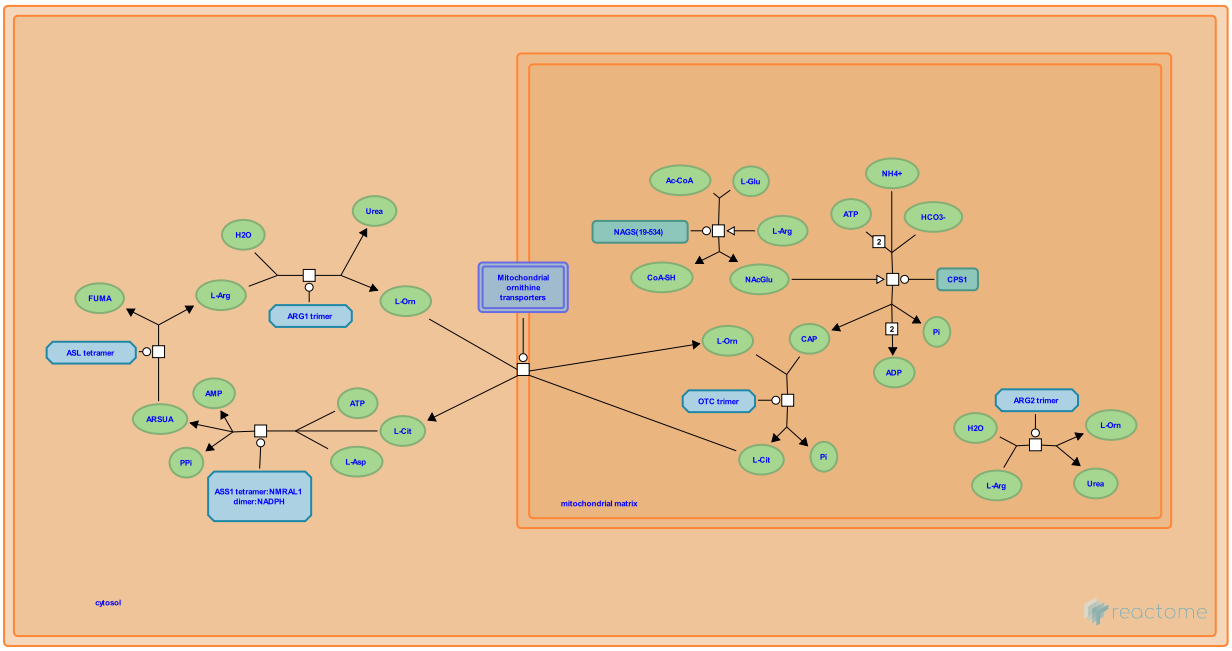
Urea cycle



D'Eustachio, P., Jassal, B.

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

26/04/2024

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. ↗

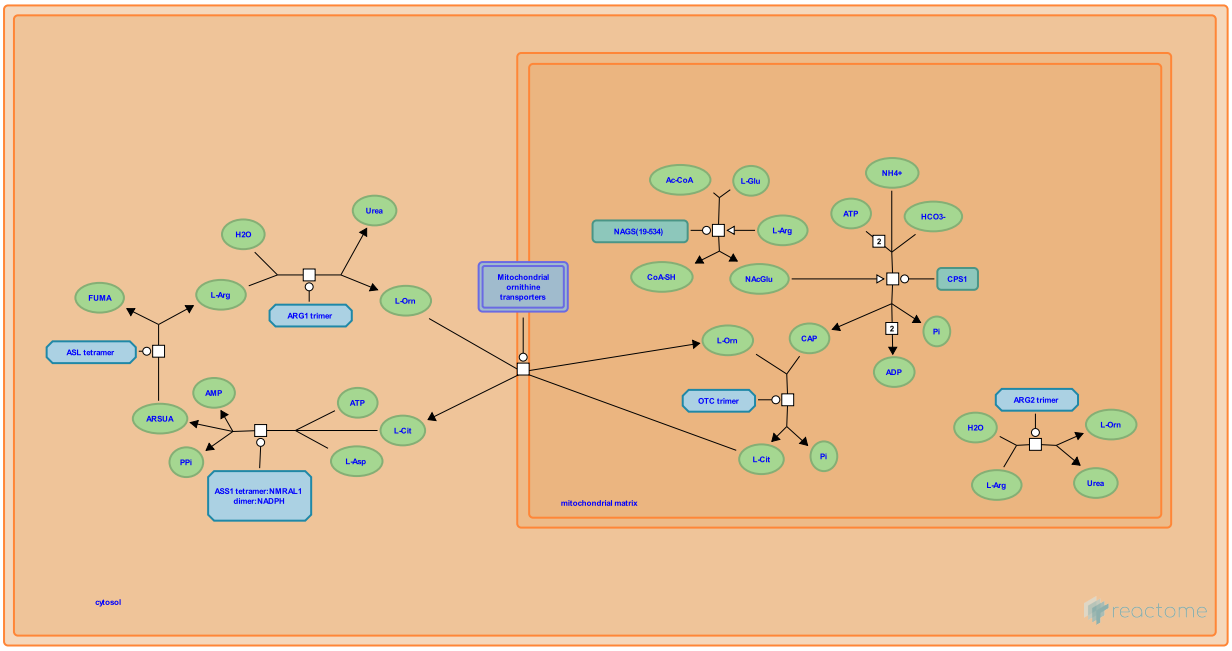
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Urea cycle ↗

Stable identifier: R-HSA-70635



The urea cycle yields urea, the major form in which excess nitrogen is excreted from the human body, and the amino acid arginine (Brusilow and Horwich 2001). It consists of four reactions: that of ornithine and carbamoyl phosphate to form citrulline, of citrulline and aspartate to form argininosuccinate, the cleavage of argininosuccinate to yield fumarate and arginine, and the cleavage of arginine to yield urea and re-form ornithine. The carbamoyl phosphate consumed in this cycle is synthesized in the mitochondria from bicarbonate and ammonia, and this synthesis in turn is dependent on the presence of N-acetylglutamate, which allosterically activates carbamoyl synthetase I enzyme. The synthesis of N-acetylglutamate is stimulated by high levels of arginine. Increased levels of free amino acids, indicated by elevated arginine levels, thus stimulate urea synthesis.

Two enzymes catalyze the hydrolysis of arginine to yield ornithine and urea. Cytosolic ARG1 is the canonical urea cycle enzyme. Mitochondrial ARG2 likewise catalyzes urea production from arginine and may have a substantial sparing effect in patients lacking ARG1 enzyme, so its reaction is annotated here although the role of ARG2 under normal physiological conditions remains unclear.

Literature references

Beaudet, AL., Scriver, CR., Sly, WS., Valle, D. (2001). Urea cycle enzymes, The Metabolic and Molecular Bases of Inherited Disease, 8th ed. *McGraw Hill*, 1909-1963.

Editions

2003-06-24	Authored	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.
2024-03-06	Edited	D'Eustachio, P.

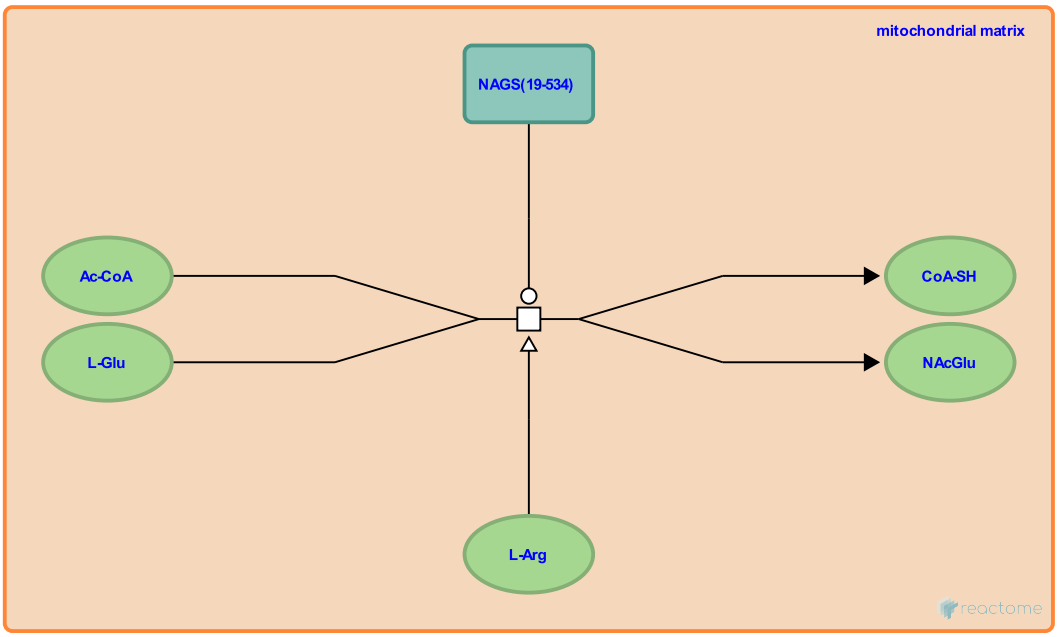
glutamate + acetyl CoA => N-acetyl glutamate + CoA ↗

Location: Urea cycle

Stable identifier: R-HSA-70542

Type: transition

Compartments: mitochondrial matrix



Mitochondrial N acetylglutamate synthetase (NAGS) catalyzes the reaction of glutamate and acetyl-CoA to form N-acetylglutamate and CoA. NAGS is activated by arginine and the N-acetylglutamate produced in the reaction in turn is required to activate carbamoyl synthetase I. Consistent with this regulatory role in urea synthesis, NAGS mutations in humans are associated with hyperammonemia (Caldovic et al. 2002; Morizono et al. 2004).

Followed by: 2 ATP + NH4+ + HCO3- => 2 ADP + orthophosphate + carbamoyl phosphate [mitochondrial]

Literature references

Tuchman, M., Shi, D., Caldovic, L., Morizono, H. (2004). Mammalian N-acetylglutamate synthase. *Mol Genet Metab, 81*, S4-11. ↗

Tuchman, M., Malamy, MH., Allewell, NM., Yu, X., Shi, D., Gracia Panglao, M. et al. (2002). Cloning and expression of the human N-acetylglutamate synthase gene. *Biochem Biophys Res Commun, 299*, 581-6. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.

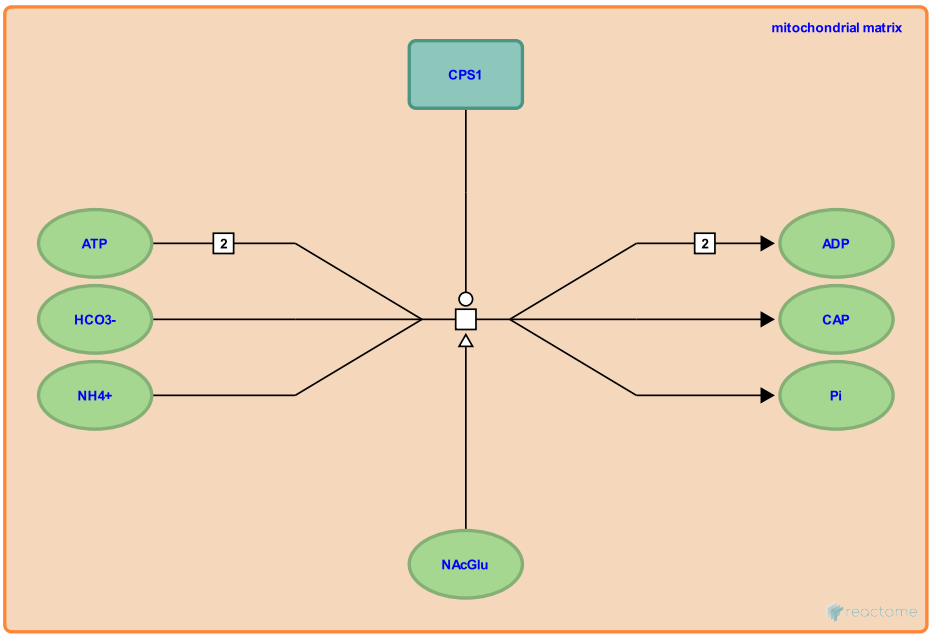
2 ATP + NH4+ + HCO3- => 2 ADP + orthophosphate + carbamoyl phosphate [mitochondrial] ↗

Location: Urea cycle

Stable identifier: R-HSA-70555

Type: transition

Compartments: mitochondrial matrix



At the beginning of this reaction, 1 molecule of 'NH4+', 1 molecule of 'HCO3-', and 1 molecule of 'ATP' are present. At the end of this reaction, 1 molecule of 'Carbamoyl phosphate', 1 molecule of 'ADP', and 1 molecule of 'Orthophosphate' are present.

This reaction takes place in the 'mitochondrial matrix' and is mediated by the 'carbamoyl-phosphate synthase (ammonia) activity' of 'carbamoyl-phosphate synthetase I dimer'.

Preceded by: glutamate + acetyl CoA => N-acetyl glutamate + CoA

Followed by: carbamoyl phosphate + ornithine => citrulline + orthophosphate

Literature references

Pierson, DL., Brien, JM. (1980). Human carbamylphosphate synthetase I. Stabilization, purification, and partial characterization of the enzyme from human liver. *J Biol Chem, 255*, 7891-5. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.

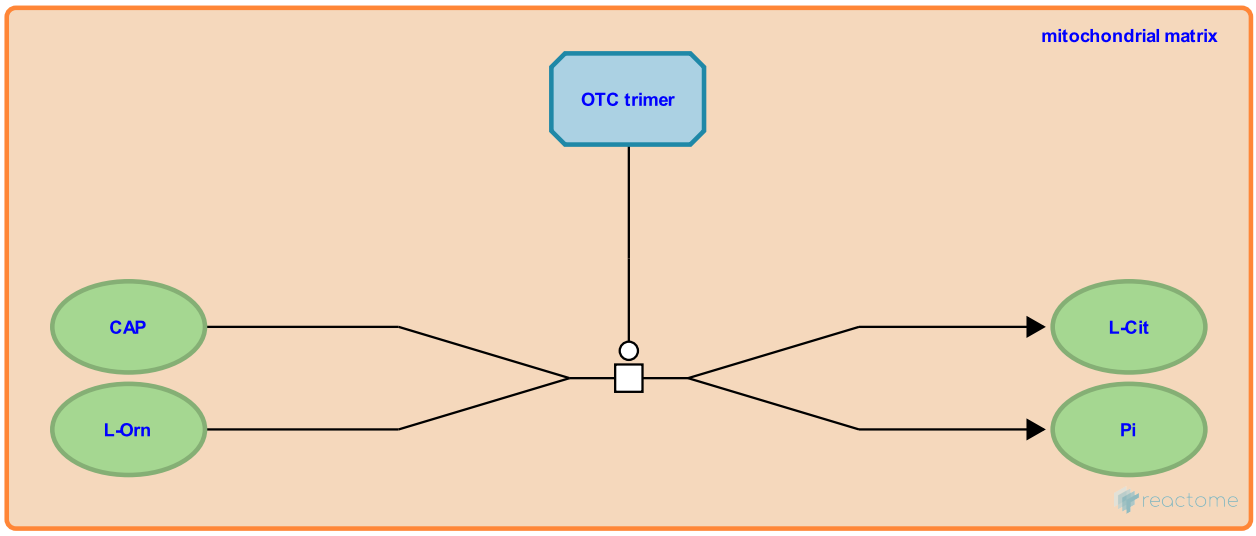
carbamoyl phosphate + ornithine => citrulline + orthophosphate ↗

Location: Urea cycle

Stable identifier: R-HSA-70560

Type: transition

Compartments: mitochondrial matrix



Mitochondrial ornithine transcarbamoylase (OTC) catalyzes the reaction of ornithine and carbamoyl phosphate to form citrulline (Horwich et al. 1984). The enzyme is a homotrimer (Shi et al. 2001).

Preceded by: ornithine (cytosolic) + citrulline (mitochondrial) => ornithine (mitochondrial) + citrulline (cytosolic), 2 ATP + NH4+ + HCO3- => 2 ADP + orthophosphate + carbamoyl phosphate [mitochondrial]

Followed by: ornithine (cytosolic) + citrulline (mitochondrial) => ornithine (mitochondrial) + citrulline (cytosolic)

Literature references

Doolittle, RF., Konigsberg, W., Kalousek, F., Kraus, JP., Williams, KR., Fenton, WA. et al. (1984). Structure and expression of a complementary DNA for the nuclear coded precursor of human mitochondrial ornithine transcarbamylase. *Science, 224*, 1068-74. ↗

Tong, L., Tuchman, M., Allewell, NM., Yu, X., Shi, D., Morizono, H. (2001). Human ornithine transcarbamylase: crystallographic insights into substrate recognition and conformational changes. *Biochem J, 354*, 501-9. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.

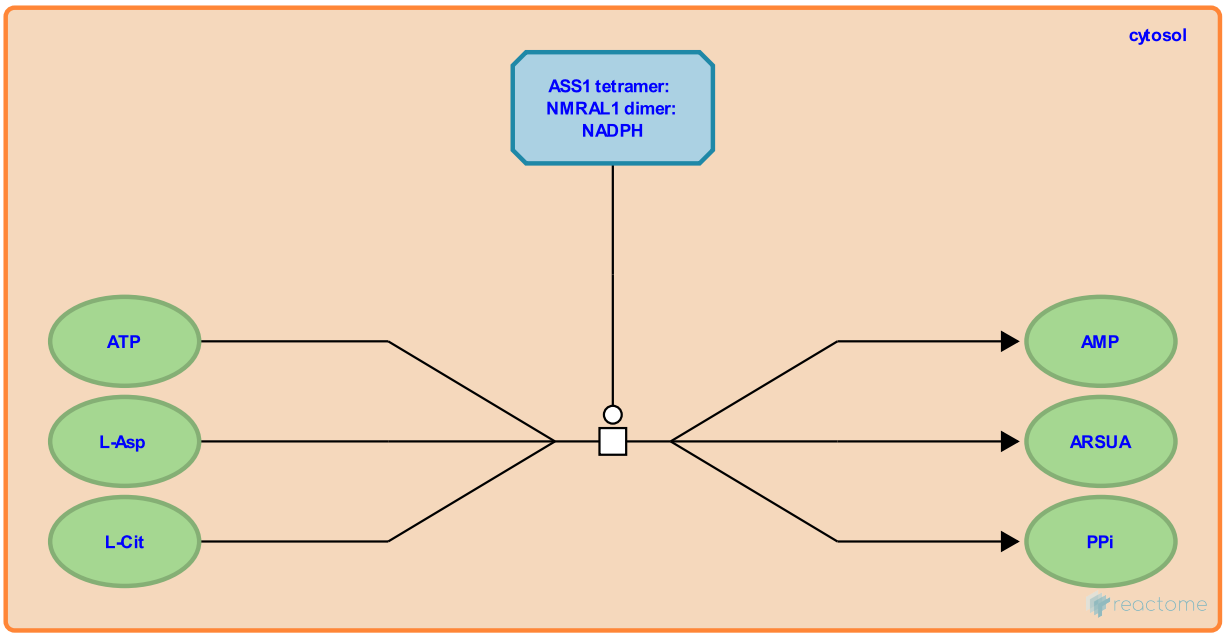
ASS1 tetramer:NMRAL1 dimer:NADPH transforms L-Asp and L-Cit to ARSUA ↗

Location: Urea cycle

Stable identifier: R-HSA-70577

Type: transition

Compartments: cytosol



Cytosolic argininosuccinate synthase (ASS1 tetramer) catalyzes the reaction of aspartate (L-Asp), citrulline (L-Cit), and ATP to form argininosuccinate (ARSUA), AMP, and pyrophosphate (PPi). The function of the human enzyme in vivo is inferred from the hypercitrullinemia observed in patients with defective forms of the enzyme (e.g., Engel et al. 2009). The enzyme is active as a homotetramer (O'Brien 1980; Karlberg et al. 2008) and binds NmrA-like family domain-containing protein 1 (NMRAL1). NMRAL1 is a redox sensor protein that can undergo restructuring and subcellular redistribution in response to changes in intracellular NADPH/NADP+ levels. Under normal NADPH levels, it can form an asymmetrical dimer with one subunit occupied by one NADPH molecule, hiding the binding site for ASS1 thus impairing its activity and reducing the production of nitric oxide (Zheng et al. 2007, Zhao et al. 2008).

Preceded by: ornithine (cytosolic) + citrulline (mitochondrial) => ornithine (mitochondrial) + citrulline (cytosolic)

Followed by: argininosuccinate <=> fumarate + arginine

Literature references

Zheng, X., Li, Y., Li, H., Luo, M., Zhao, Y., Zhang, J. et al. (2008). An NADPH sensor protein (HSCARG) down-regulates nitric oxide synthesis by association with argininosuccinate synthetase and is essential for epithelial cell viability. *J. Biol. Chem., 283*, 11004-13. ↗

Uppenberg, J., Holmberg-Schiavone, L., Flores, A., Hammarström, M., Högbom, M., Collins, R. et al. (2008). Structure of human argininosuccinate synthetase. *Acta Crystallogr D Biol Crystallogr, 64*, 279-86. ↗

Häberle, J., Engel, K., Höhne, W. (2009). Mutations and polymorphisms in the human argininosuccinate synthetase (ASS1) gene. *Hum Mutat, 30*, 300-7. ↗

O'Brien, WE. (1980). Isolation and characterization of argininosuccinate synthetase from human liver. *Biochemistry, 18*, 5353-6. ↗

Zheng, X., Dai, X., Lu, F., Luo, M., Yao, D., Gu, X. et al. (2007). Restructuring of the dinucleotide-binding fold in an NADP(H) sensor protein. *Proc. Natl. Acad. Sci. U.S.A., 104*, 8809-14. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.
2015-11-19	Revised	Jassal, B.

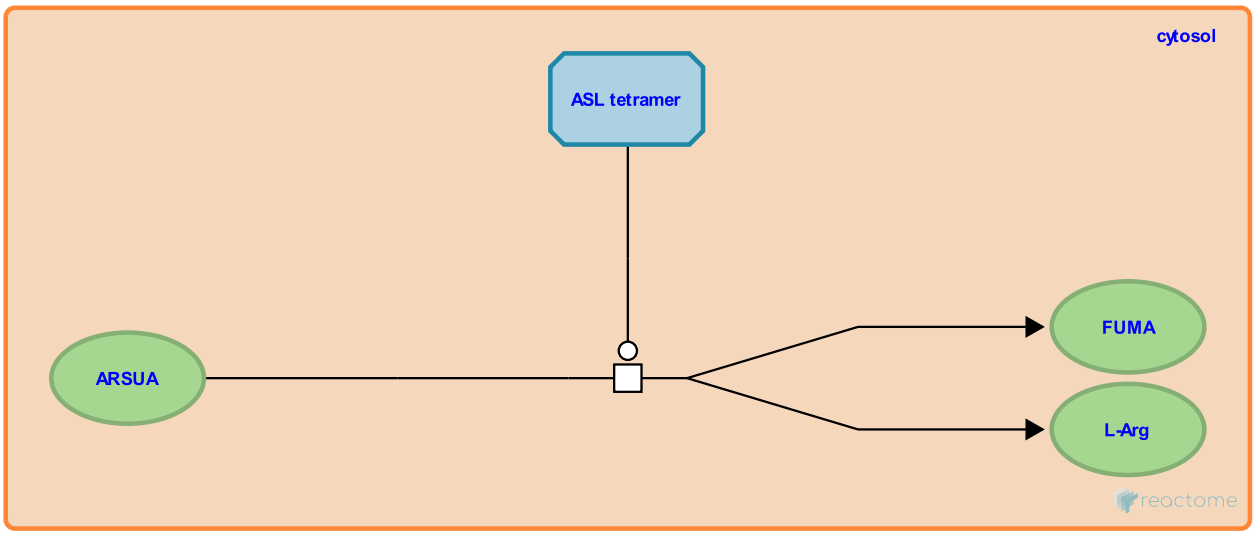
argininosuccinate <=> fumarate + arginine ↗

Location: Urea cycle

Stable identifier: R-HSA-70573

Type: transition

Compartments: cytosol



Cytosolic argininosuccinate lyase (ASL) catalyzes the reversible reaction of argininosuccinate to form fumarate and arginine. The enzyme is a homotetramer (Turner et al. 1997). The function of the human enzyme in vivo is inferred from the defective argininosuccinate lyase enzyme activity observed in patients with mutant forms of the ASL gene (e.g., Walker et al. 1990).

Preceded by: ASS1 tetramer:NMRAL1 dimer:NADPH transforms L-Asp and L-Cit to ARSUA

Followed by: arginine + H2O => ornithine + urea [ARG1]

Literature references

Howell, PL., Turner, MA., McInnes, RR., Simpson, A. (1997). Human argininosuccinate lyase: a structural basis for intragenic complementation. *Proc Natl Acad Sci U S A, 94*, 9063-8. ↗

McCloskey, DA., McInnes, RR., Simard, LR., Walker, DC. (1990). Molecular analysis of human argininosuccinate lyase: mutant characterization and alternative splicing of the coding region. *Proc Natl Acad Sci U S A, 87*, 9625-9. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.

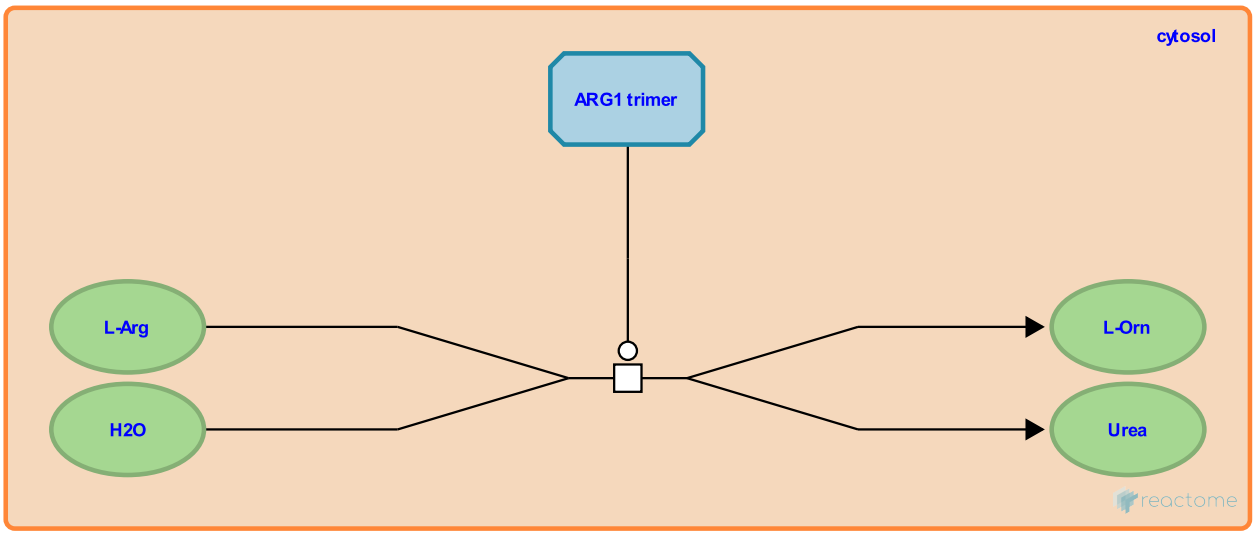
arginine + H2O => ornithine + urea [ARG1] ↗

Location: Urea cycle

Stable identifier: R-HSA-70569

Type: transition

Compartments: cytosol



Cytosolic Arginase 1 (ARG1) trimer catalyzes the hydrolysis of arginine to yield ornithine and urea (DiCostanzo et al. 2005). Patients expressing mutated forms of the enzyme with diminished in vitro arginase activity can accumulate arginine to pathogenic levels in the blood (e.g., Uchino et al. 1995).

Preceded by: argininosuccinate <=> fumarate + arginine

Followed by: ornithine (cytosolic) + citrulline (mitochondrial) => ornithine (mitochondrial) + citrulline (cytosolic)

Literature references

Centeno, F., Rodriguez, PC., Mora, A., Christianson, DW., Di Costanzo, L., Ochoa, AC. et al. (2005). Crystal structure of human arginase I at 1.29-A resolution and exploration of inhibition in the immune response. *Proc Natl Acad Sci U S A, 102*, 13058-63. ↗

Shapira, SK., Matsuda, I., Uchino, T., Lambert, M., Smit, LM., Qureshi, IA. et al. (1995). Molecular basis of phenotypic variation in patients with argininemia. *Hum Genet, 96*, 255-60. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.
2010-01-15	Revised	D'Eustachio, P.

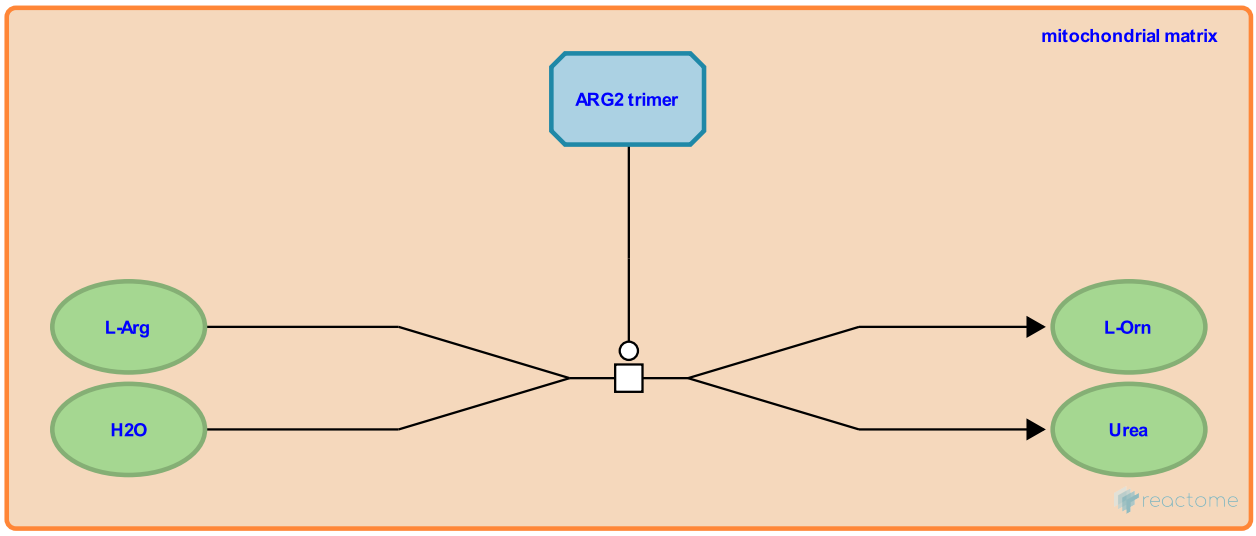
arginine + H2O => ornithine + urea [ARG2] ↗

Location: Urea cycle

Stable identifier: R-HSA-452036

Type: transition

Compartments: mitochondrial matrix



Arginase 2 (ARG2) trimer catalyzes the hydrolysis of arginine to form urea and ornithine (Cama et al. 2003). ARG2 is localized to the mitochondrion (Gotoh ea 1996). The enzyme is expressed in many tissues in addition to liver and while its function appears to mitigate the effects of ARG1 deficiency on urea synthesis, its normal physiological roles have not been fully defined (Iyer et al. 1998).

Literature references

Iyer, RK., Cederbaum, SD., Vockley, JG., Kern, RM., Jenkinson, CP., Grody, WW. (1998). The human arginases and arginase deficiency. *J Inherit Metab Dis, 21*, 86-100. ↗

Gotoh, T., Takiguchi, M., Terada, K., Mori, M., Nagasaki, A., Sonoki, T. (1996). Molecular cloning of cDNA for non-hepatic mitochondrial arginase (arginase II) and comparison of its induction with nitric oxide synthase in a murine macrophage-like cell line. *FEBS Lett, 395*, 119-22. ↗

Traish, AM., Cama, E., Shin, H., Emig, FA., Christianson, DW., Kim, NN. et al. (2003). Human arginase II: crystal structure and physiological role in male and female sexual arousal. *Biochemistry, 42*, 8445-51. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.

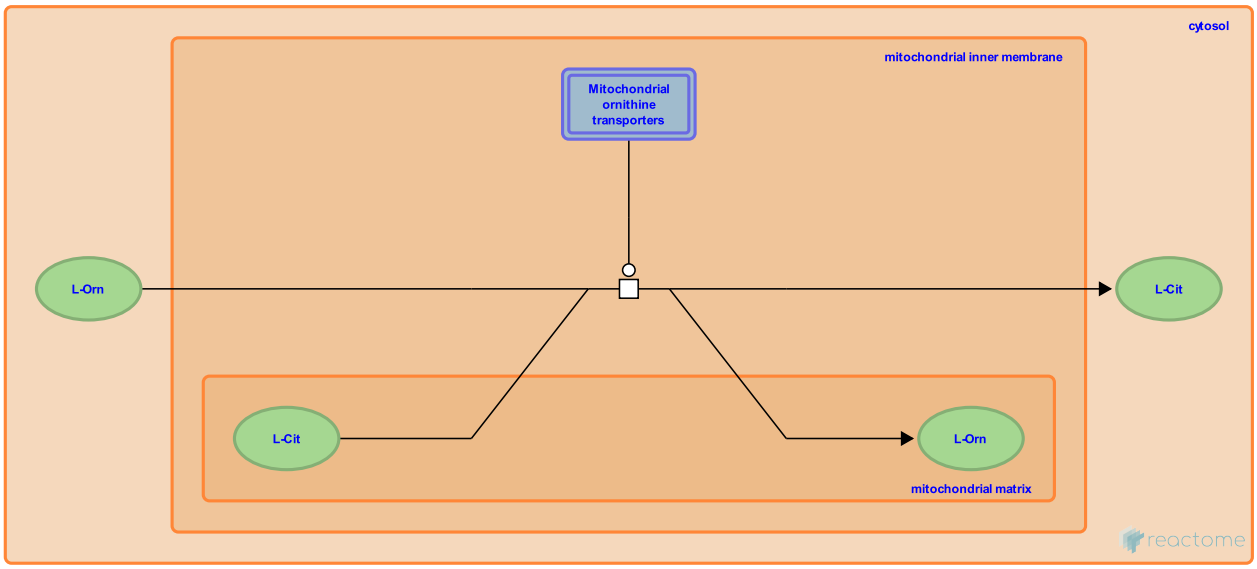
ornithine (cytosolic) + citrulline (mitochondrial) => ornithine (mitochondrial) + citrulline (cytosolic) ↗

Location: Urea cycle

Stable identifier: R-HSA-70634

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix, cytosol



The mitochondrial ornithine transporters SLC25A15 and SLC25A2 mediate the exchange of cytosolic ornithine for citrulline from the mitochondrial matrix. SLC25A15 was the first protein shown to have this function, identified because mutations in the protein are associated with elevated levels of ammonia, ornithine, and citrulline in affected individuals (Camacho et al. 1999). The second transporter, SLC25A2, identified later, is also expressed in normal cells and their apparently partly redundant function may explain the relatively mild symptoms associated with SLC25A15 deficiency compared to other defects of the urea cycle (Fiermonte et al. 2003).

Preceded by: arginine + H2O => ornithine + urea [ARG1], carbamoyl phosphate + ornithine => citrulline + orthophosphate

Followed by: ASS1 tetramer:NMRAL1 dimer:NADPH transforms L-Asp and L-Cit to ARSUA, carbamoyl phosphate + ornithine => citrulline + orthophosphate

Literature references

Goodman, BK., Camacho, JA., Obie, C., Biery, B., Valle, D., Lambert, M. et al. (1999). Hyperornithinaemia-hyperammonaemia-homocitrullinuria syndrome is caused by mutations in a gene encoding a mitochondrial ornithine transporter. *Nat Genet, 22*, 151-8. ↗

Fiermonte, G., Dolce, V., Walker, JE., Palmieri, F., David, L., Dionisi-Vici, C. et al. (2003). The mitochondrial ornithine transporter. Bacterial expression, reconstitution, functional characterization, and tissue distribution of two human isoforms. *J Biol Chem, 278*, 32778-83. ↗

Andrade, D., Rioseco-Camacho, N., Camacho, JA., Kong, J., Porter, J. (2003). Cloning and characterization of human ORNT2: a second mitochondrial ornithine transporter that can rescue a defective ORNT1 in patients with the hyperornithinemia-hyperammonemia-homocitrullinuria syndrome, a urea cycle disorder. *Mol Genet Metab, 79*, 257-71. ↗

Editions

2003-06-24	Authored, Edited	D'Eustachio, P.

Table of Contents