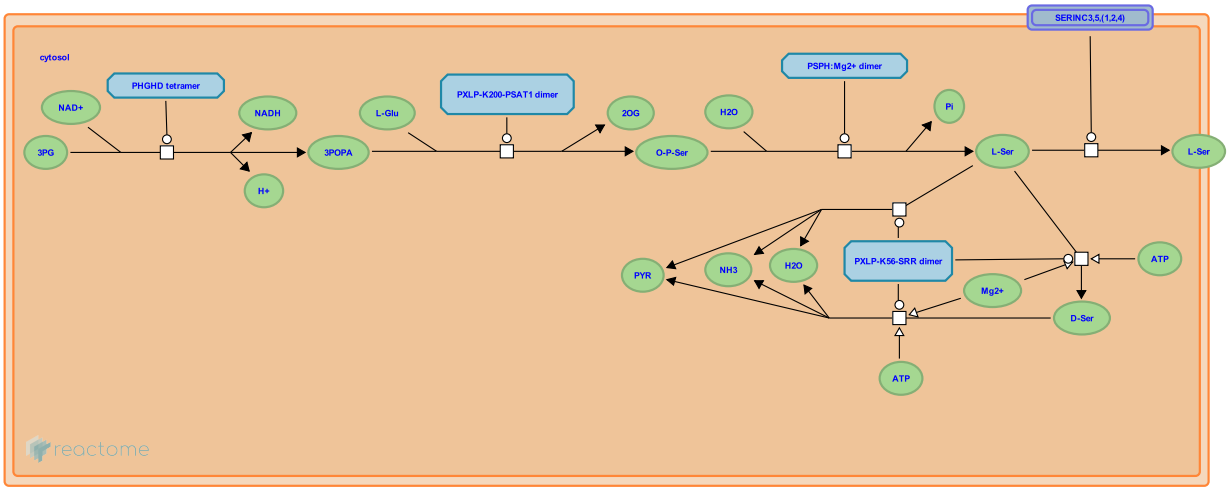
Serine biosynthesis



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21/11/2019

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

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. ↗

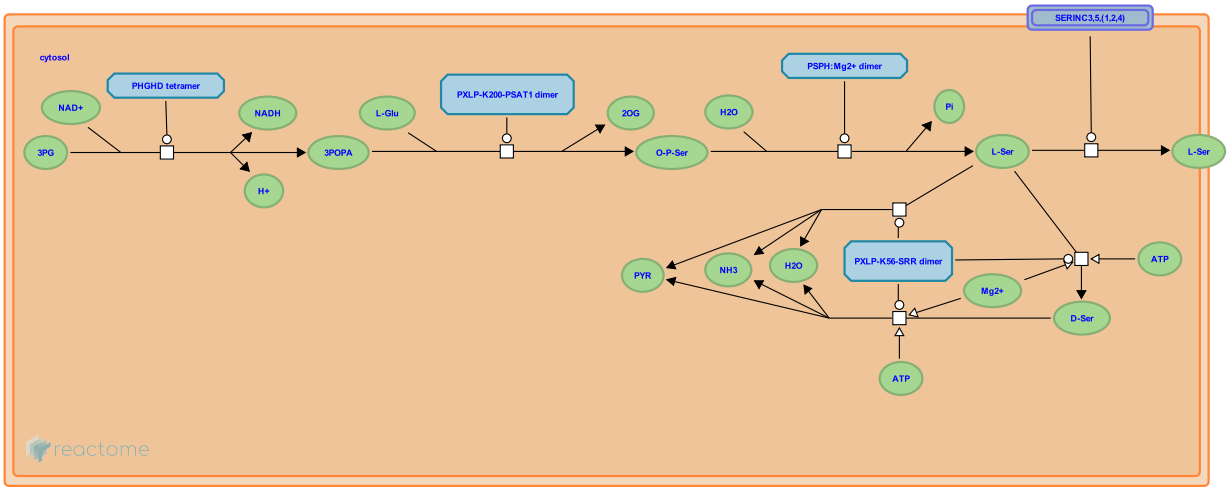
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Serine biosynthesis ↗

Stable identifier: R-HSA-977347

Compartments: cytosol



L-Serine is needed in human brain in large amounts as precursor to important biomolecules such as nucleotides, phospholipids and the neurotransmitters glycine and D-serine. The pathway for its synthesis starts with 3-phosphoglycerate and it later needs glutamate as an amination agent. Deficiencies in the participating enzymes lead to severe neurological symptoms that are treatable with serine if treatment starts early (de Koning & Klomp 2004).

Literature references

de Koning, TJ., Klomp, LW. (2004). Serine-deficiency syndromes. *Curr Opin Neurol, 17*, 197-204. ↗

Editions

2010-10-16	Authored	Stephan, R.
2010-10-18	Edited	Jassal, B.
2011-10-26	Reviewed	D'Eustachio, P.

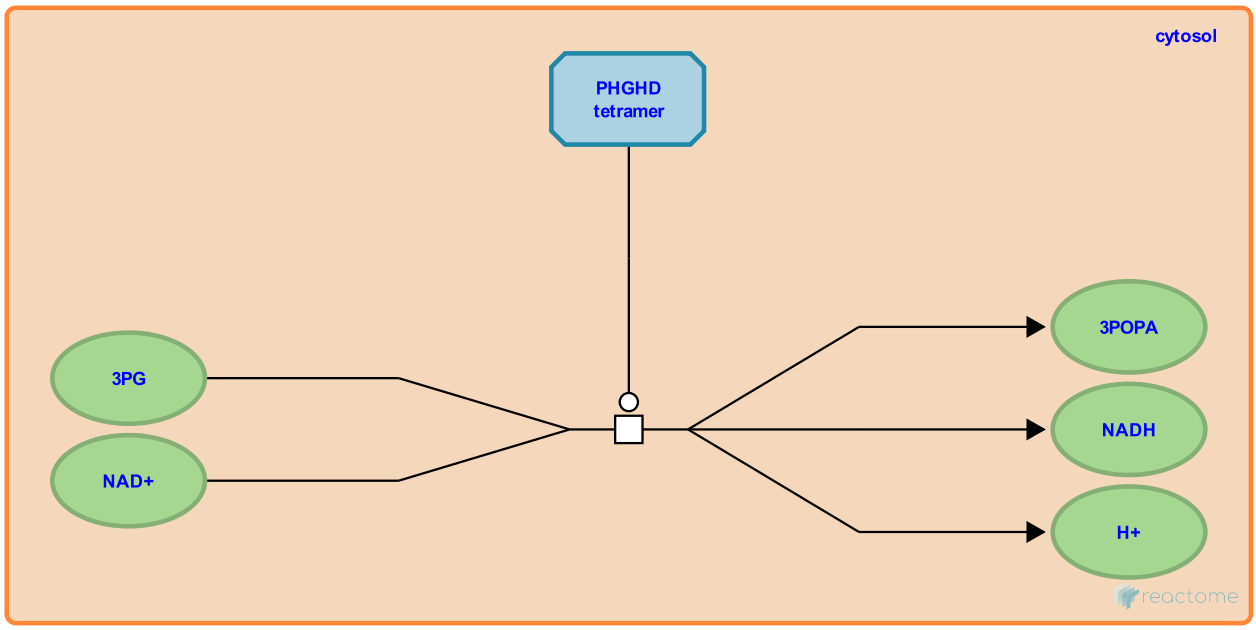
PHGHD tetramer dehydrogenates 3PG ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-977348

Type: transition

Compartments: cytosol



Serine biosynthesis starts from 3-phosphoglycerate, a glycolysis intermediate. Its dehydrogenation is catalysed by tetrameric phosphoglycerate dehydrogenase (PHGDH). (Tabatabaie et al. 2009).

Followed by: PXLP-K200-PSAT1 dimer transfers amino group from L-Glu to 3POPA

Literature references

Tabatabaie, L., de Koning, TJ., Geboers, AJ., van den Berg, IE., Berger, R., Klomp, LW. (2009). Novel mutations in 3-phosphoglycerate dehydrogenase (PHGDH) are distributed throughout the protein and result in altered enzyme kinetics. *Hum Mutat, 30*, 749-56. ↗

Editions

2010-10-16	Authored	Stephan, R.
2010-10-18	Edited	Jassal, B.
2011-10-26	Reviewed	D'Eustachio, P.

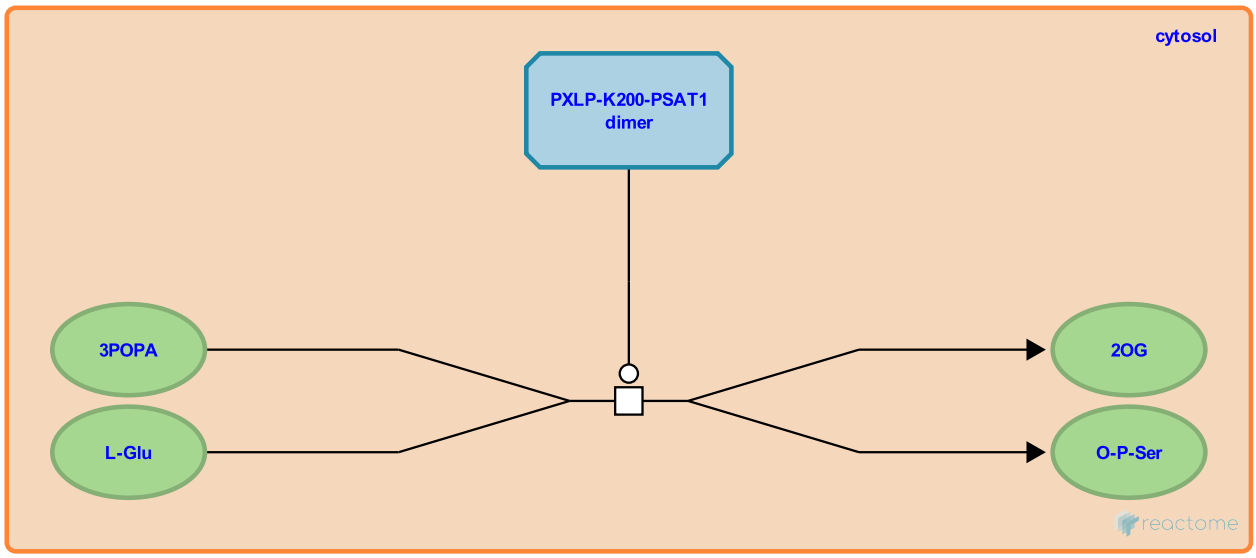
PXLP-K200-PSAT1 dimer transfers amino group from L-Glu to 3POPA ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-977333

Type: transition

Compartments: cytosol



The amino group needed for serine biosynthesis comes from glutamate (L-Glu). Its transfer onto 3-phosphonooxpyruvate (3POPA) is catalysed by PSAT1 dimer which needs pyridoxal phosphate (PXLP) as cofactor. (Baek et al. 2003)

Preceded by: PHGHD tetramer dehydrogenates 3PG

Followed by: PSPH:Mg2+ dimer dephosphorylates O-P-Ser

Literature references

Baek, JY., Jun, DY., Taub, D., Kim, YH. (2003). Characterization of human phosphoserine aminotransferase involved in the phosphorylated pathway of L-serine biosynthesis. *Biochem J, 373*, 191-200. ↗

Editions

2010-10-16	Authored	Stephan, R.
2010-10-18	Edited	Jassal, B.
2011-10-26	Reviewed	D'Eustachio, P.

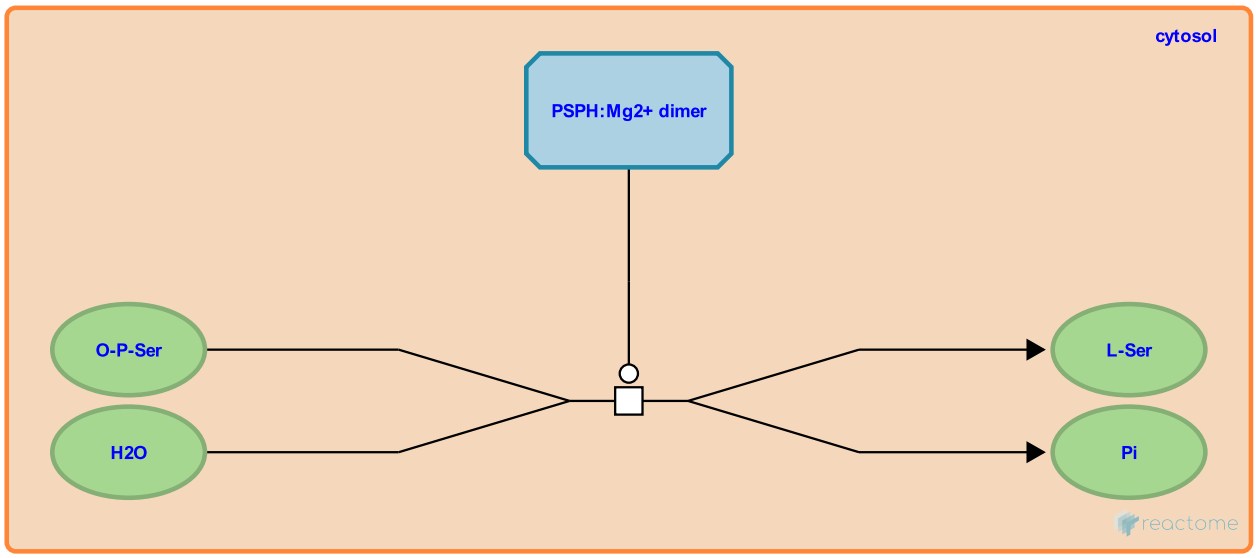
PSPH:Mg2+ dimer dephosphorylates O-P-Ser ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-977324

Type: transition

Compartments: cytosol



Dephosphorylation of O-phospho-L-serine to L-serine proceeds through a phospho-enzyme intermediate of the catalysing phosphatase PSP (Collet et al. 1997).

Preceded by: PXLP-K200-PSAT1 dimer transfers amino group from L-Glu to 3POPA

Followed by: SERINC3,5,(1,2,4) transport L-Ser from cytosol to plasma membrane, PXLP-K56-SRR dimer isomerises L-Ser to D-Ser

Literature references

Collet, JF., Gerin, I., Rider, MH., Veiga-da-Cunha, M., Van Schaftingen, E. (1997). Human L-3-phosphoserine phosphatase: sequence, expression and evidence for a phosphoenzyme intermediate. *FEBS Lett, 408*, 281-4. ↗

Editions

2010-10-16	Authored	Stephan, R.
2010-10-18	Edited	Jassal, B.
2011-10-26	Reviewed	D'Eustachio, P.

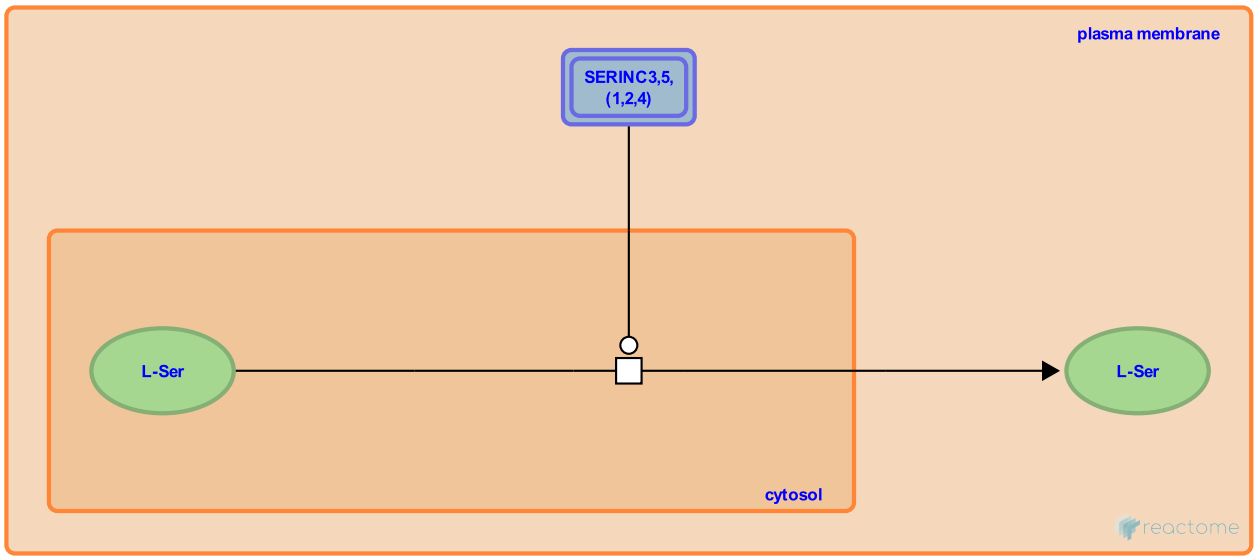
SERINC3,5,(1,2,4) transport L-Ser from cytosol to plasma membrane ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-8932980

Type: transition

Compartments: cytosol, plasma membrane



Serine incorporators 1-5 (SERINC1-5) are membrane-associated proteins that incorporate the polar amino acid serine (L-Ser) into membranes and facilitate the synthesis of the serine-derived lipids phosphatidylserine and sphingolipids. SERINC3 and 5 have recently been identified to be restrictors to HIV replication in human cells (Fackler 2015, Usami et al. 2015).

Preceded by: PSPH:Mg2+ dimer dephosphorylates O-P-Ser

Literature references

Fackler, OT. (2015). Spotlight on HIV-1 Nef: SERINC3 and SERINC5 Identified as Restriction Factors Antagonized by the Pathogenesis Factor. *Viruses, 7*, 6730-8. ↗

Usami, Y., Wu, Y., Göttlinger, HG. (2015). SERINC3 and SERINC5 restrict HIV-1 infectivity and are counteracted by Nef. *Nature, 526*, 218-23. ↗

Editions

2016-08-01	Authored, Edited	Jassal, B.
2016-08-12	Reviewed	D'Eustachio, P.

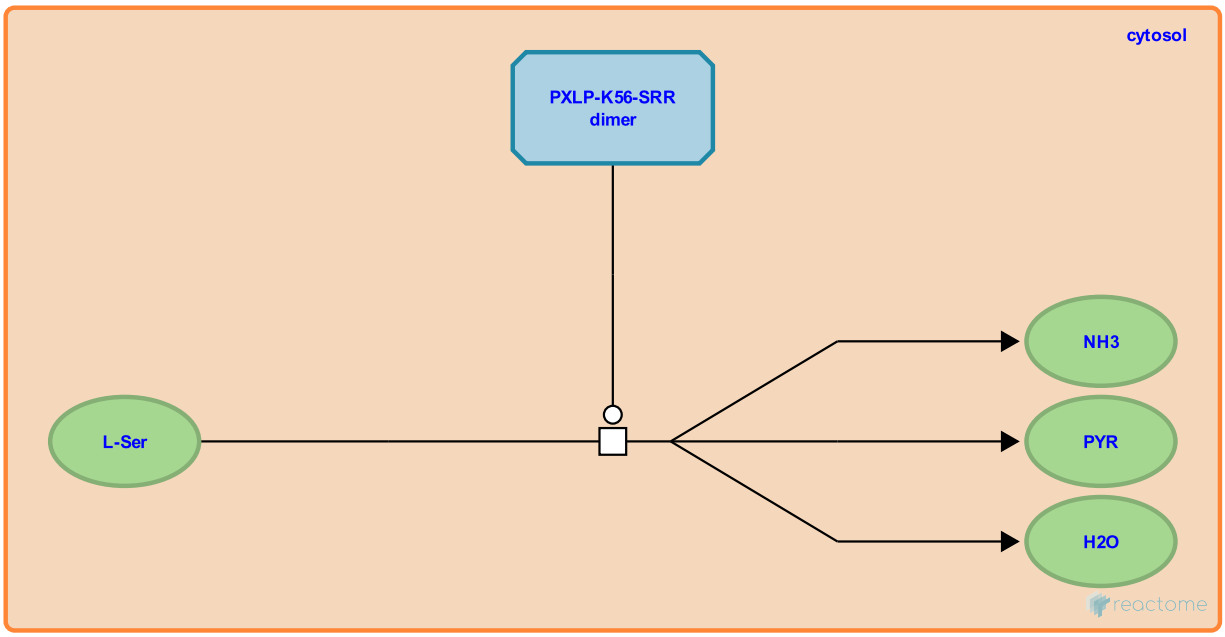
PXLP-K56-SRR dimer deaminates L-Ser ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-9034539

Type: transition

Compartments: cytosol



N-methyl D-aspartate (NMDA) receptors play a key role in excitatory neurotransmission, learning, memory and synaptic plasticity. Their activity is modulated by the agonist glutamate and by the co-agonists D-Serine (D-Ser) and glycine (gly). In human brain, dimeric serine racemase (SRR), a pyridoxal 5'-phosphate-dependent enzyme (Smith et al. 2010), is a bifunctional enzyme mediating mainly L-Serine catabolism by alpha,beta-elimination of water to form pyruvate (De Miranda et al. 2002, Foltyn et al. 2005). Part of L-Serine is not deaminated then SRR can also catalyse the isomerisation of L-Ser to D-Ser although this is very much a minor reaction. Thus, D-Ser homeostasis in neurons is modulated by SRR, and therefore indirectly, modulates NMDA receptors. Targeting SRR could find potential in neurodegenerative diseases (Canu et al. 2014). Mg2+ and ATP stimulate SRR (De Miranda et al. 2002).

Preceded by: PXLP-K56-SRR dimer isomerises L-Ser to D-Ser

Literature references

Foltyn, VN., Bendikov, I., De Miranda, J., Panizzutti, R., Dumin, E., Shleper, M. et al. (2005). Serine racemase modulates intracellular D-serine levels through an alpha,beta-elimination activity. *J. Biol. Chem., 280*, 1754-63. ↗

De Miranda, J., Panizzutti, R., Foltyn, VN., Wolosker, H. (2002). Cofactors of serine racemase that physiologically stimulate the synthesis of the N-methyl-D-aspartate (NMDA) receptor coagonist D-serine. *Proc. Natl. Acad. Sci. U.S.A., 99*, 14542-7. ↗

Editions

2017-08-03	Authored, Edited	Jassal, B.
2018-01-09	Reviewed	Wolosker, H.

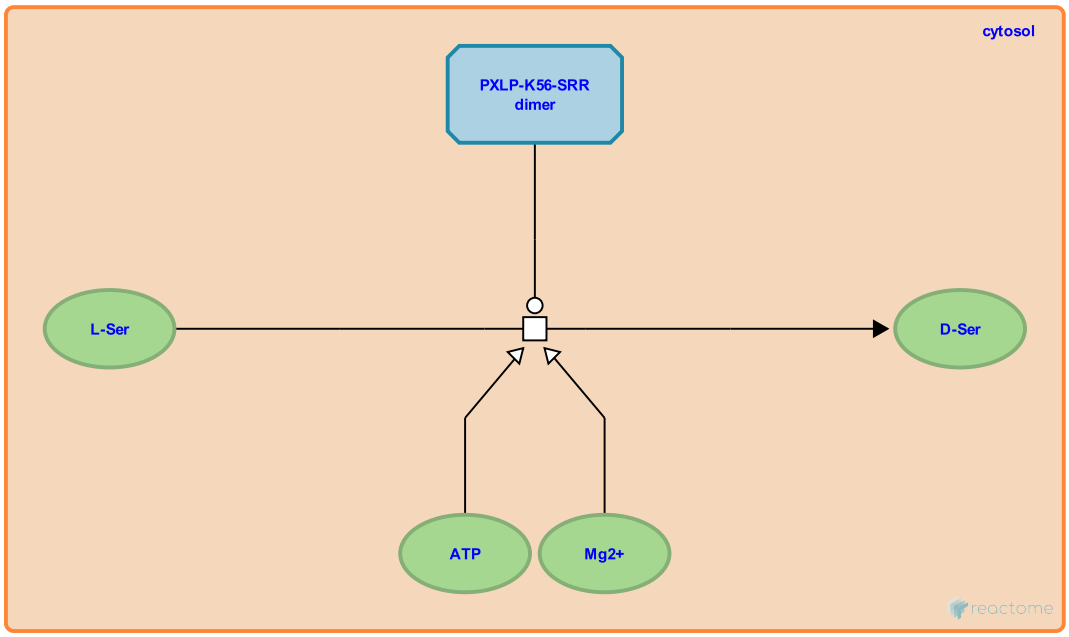
PXLP-K56-SRR dimer isomerises L-Ser to D-Ser ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-9014766

Type: transition

Compartments: cytosol



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Preceded by: PSPH:Mg2+ dimer dephosphorylates O-P-Ser

Followed by: PXLP-K56-SRR dimer deaminates D-Ser, PXLP-K56-SRR dimer deaminates L-Ser

Literature references

De Miranda, J., Santoro, A., Engelender, S., Wolosker, H. (2000). Human serine racemase: moleular cloning, genomic organization and functional analysis. *Gene, 256*, 183-8. ↗

Xia, M., Liu, Y., Figueroa, DJ., Chiu, CS., Wei, N., Lawlor, AM. et al. (2004). Characterization and localization of a human serine racemase. *Brain Res. Mol. Brain Res., 125*, 96-104. ↗

Editions

2017-08-03	Authored, Edited	Jassal, B.
2018-01-09	Reviewed	Wolosker, H.

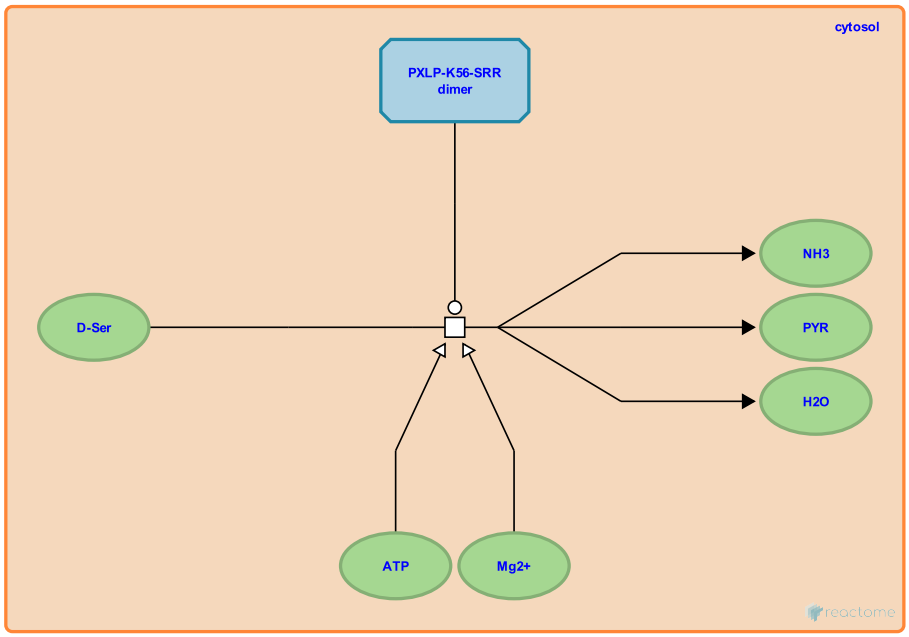
PXLP-K56-SRR dimer deaminates D-Ser ↗

Location: Serine biosynthesis

Stable identifier: R-HSA-9014741

Type: transition

Compartments: cytosol



N-methyl D-aspartate (NMDA) receptors play a key role in excitatory neurotransmission, learning, memory and synaptic plasticity. Their activity is modulated by the agonist glutamate and by the co-agonists D-Serine (D-Ser) and glycine (gly). In human brain, dimeric serine racemase (SRR), a pyridoxal 5'-phosphate-dependent enzyme (Smith et al. 2010), is a bifunctional enzyme mediating deamination and isomerisation of L-Serine. It can also catabolise D-Serine by alpha,beta-elimination of water to form pyruvate but at a rate 10-fold lower than for L-Serine (De Miranda et al. 2000, 2002, Foltyn et al. 2005). Thus, D-Ser homeostasis in neurons is modulated by SRR, and therefore indirectly, modulates NMDA receptors. Targeting SRR could find potential in neurodegenerative diseases (Canu et al. 2014). Mg2+ and ATP stimulate SRR (De Miranda et al. 2002).

Preceded by: PXLP-K56-SRR dimer isomerises L-Ser to D-Ser

Literature references

Foltyn, VN., Bendikov, I., De Miranda, J., Panizzutti, R., Dumin, E., Shleper, M. et al. (2005). Serine racemase modulates intracellular D-serine levels through an alpha,beta-elimination activity. *J. Biol. Chem., 280*, 1754-63. ↗

De Miranda, J., Panizzutti, R., Foltyn, VN., Wolosker, H. (2002). Cofactors of serine racemase that physiologically stimulate the synthesis of the N-methyl-D-aspartate (NMDA) receptor coagonist D-serine. *Proc. Natl. Acad. Sci. U.S.A., 99*, 14542-7. ↗

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2017-08-03	Authored, Edited	Jassal, B.
2018-01-09	Reviewed	Wolosker, H.

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