Glyoxylate metabolism and glycine degradation

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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.

17/11/2022
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: 82

This document contains 2 pathways and 20 reactions (see Table of Contents)
Glyoxylate is generated in the course of glycine and hydroxyproline catabolism and can be converted to oxalate. In humans, this process takes place in the liver. Defects in two enzymes of glyoxylate metabolism, alanine:glyoxylate aminotransferase (AGXT) and glycerate dehydrogenase/glyoxylate reductase (GRHPR), are associated with pathogenic overproduction of oxalate (Danpure 2005). The reactions that interconvert glycine, glycolate, and glyoxylate and convert glyoxylate to oxalate have been characterized in molecular detail in humans. A reaction sequence for the conversion of hydroxyproline to glyoxylate has been inferred from studies of partially purified extracts of rat and bovine liver but the enzymes involved in the corresponding human reactions have not been identified.

**Literature references**

Unknown hydroxyproline carrier transports cytosolic HPRO into the mitochondrial matrix

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-6784213

Type: uncertain

Compartments: mitochondrial matrix, cytosol

Cytosolic hydroxyproline (HPRO) is transported into the mitochondrial matrix in a saturable process distinct from the one responsible for proline uptake. The carrier that mediates this process has not been identified, however (Atlante et al. 1996).

Followed by: PRODH2:FAD dimer dehydrogenates HPRO to 1-pyrroline-3-hydroxy-5-carboxylate

Literature references


Editions

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PRODH2: FAD dimer dehydrogenates HPRO to 1-pyrroline-3-hydroxy-5-carboxylate

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6784224

**Type:** transition

**Compartments:** mitochondrial inner membrane, mitochondrial matrix

PRODH2 dimer dehydrogenates hydroxyproline (HPRO) to form 1-pyrroline-3-hydroxy-5-carboxylate (Adams & Goldstone 1960). The enzyme is associated with FAD and ubiquinone (not annotated here) is the likely electron acceptor (Summitt et al. 2015). The mitochondrial localization of the reaction is inferred from studies of HPRO catabolism in rat and bovine systems (Adams & Frank 1980), and the localization of PRODH2 to the inner mitochondrial membrane is inferred from that of the homologous mouse protein (Da Cruz et al. 2003).

**Preceded by:** Unknown hydroxyproline carrier transports cytosolic HPRO into the mitochondrial matrix

**Followed by:** Spontaneous hydrolysis of 1-pyrroline-3-hydroxy-5-carboxylate to 4-OH-L-glutamate semi-aldehyde

**Literature references**


### Editions

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Spontaneous hydrolysis of 1-pyrroline-3-hydroxy-5-carboxylate to 4-OH-L-glutamate semialdehyde

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6784402

**Type:** transition

**Compartments:** mitochondrial matrix

The spontaneous hydrolysis of 1-pyrroline-3-hydroxy-5-carboxylate to form 4-OH-L-glutamate semialdehyde is inferred from the behavior of the analogous intermediate of proline catabolism (Moxley et al. 2011).

**Preceded by:** PRODH2:FAD dimer dehydrogenates HPRO to 1-pyrroline-3-hydroxy-5-carboxylate

**Followed by:** ALDH4A1 dimer dehydrogenates 4-OH-L-glutamate semialdehyde to 4-OH-L-glutamate

**Literature references**


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https://reactome.org
**ALDH4A1 dimer dehydrogenates 4-OH-L-glutamate semialdehyde to 4-OH-L-glutamate**

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6784399

**Type:** transition

**Compartments:** mitochondrial matrix

Mitochondrial delta-1-pyrroline-5-carboxylate dehydrogenase (ALDH4A1) catalyzes the reaction of 4-hydroxy-L-glutamate gamma-semialdehyde and NAD+ to form 4-hydroxyglutamate and NADH + H+. ALDH4A1 also catalyzes the corresponding reaction of proline catabolism, as shown in biochemical and structural studies (Adams & Goldstone 1960; Srivastava et al. 2012), and mutations in ALDH4A1 disrupt both catabolic processes in human patients (Valle et al. 1979).

**Preceded by:** Spontaneous hydrolysis of 1-pyrroline-3-hydroxy-5-carboxylate to 4-OH-L-glutamate semialdehyde

**Followed by:** PXLP-K279-GOT2 dimer transaminates 4-OH-L-glutamate to 4-hydroxy-2-oxoglutarate (HOG)

**Literature references**


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[https://reactome.org](https://reactome.org)
GOT2 dimer transaminates 4-OH-L-glutamate (4-OH-L-Glu) and oxaloacetate (OA) to form 4-hydroxy-2-oxoglutarate (HOG) and L-Asp. The ability of human GOT2 to catalyze this reaction has been inferred from studies of its rat homologue (Maitra & Dekker 1964).

**Preceded by:** ALDH4A1 dimer dehydrogenates 4-OH-L-glutamate semialdehyde to 4-OH-L-glutamate

**Followed by:** HOGA1 tetramer aldol-cleaves 4-OH-2-oxoglutarate (HOG) to glyoxylate and pyruvate

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HOGA1 tetramer aldol-cleaves 4-OH-2-oxoglutarate (HOG) to glyoxylate and pyruvate

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6784423

**Type:** transition

**Compartments:** mitochondrial matrix

Mitochondrial HOGA1 aldol-cleaves 4-OH-2-oxoglutarate (HOG) to glyoxylate and pyruvate. The biochemical details of the enzyme are inferred from the properties of its well-studied rat homologue (Maitra & Dekker 1964). The mature protein lacks a 25-residue mitochondrial targeting sequence and forms a homotetramer (Riedel et al. 2011).

**Preceded by:** PXLP-K279-GOT2 dimer transaminates 4-OH-L-glutamate to 4-hydroxy-2-oxoglutarate (HOG)

**Followed by:** Mitochondrial AGXT2 tetramer transaminates glyoxylate and alanine to glycine and pyruvate, An unknown carrier transports mitochondrial glyoxylate to the cytosol

**Literature references**


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Mitochondrial AGXT2 tetramer transaminates glyoxylate and alanine to glycine and pyruvate

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-904864

**Type:** transition

**Compartments:** mitochondrial matrix

Mitochondrial AGXT2 (alanine-glyoxylate transaminase 2) catalyzes the irreversible reaction of glyoxylate and alanine to form glycine and pyruvate (Rodionov et al. 2010). The active form of the enzyme is inferred to be a homotetramer from the properties of the homologous rat protein, which has been purified and characterized in vitro (Tamaki et al. 1990). Most conversion of glyoxylate to glycine in vivo appears to occur in the peroxisome, catalyzed by AGXT, and the physiological role of the AGXT2 reaction is unclear.

**Preceded by:** HOGA1 tetramer aldol-cleaves 4-OH-2-oxoglutarate (HOG) to glyoxylate and pyruvate

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An unknown carrier transports mitochondrial glyoxylate to the cytosol

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-6784436

Type: uncertain

Compartments: mitochondrial matrix, cytosol

Glyoxylate generated in the mitochondrion can enter the cytosol but the carrier that mediates its entry has not been identified (Wanders et al. 2016).

Preceded by: HOGA1 tetramer aldol-cleaves 4-OH-2-oxoglutarate (HOG) to glyoxylate and pyruvate

Followed by: An unknown carrier transports cytosolic glyoxylate to the peroxisome

Literature references


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An unknown carrier transports cytosolic glyoxylate to the peroxisome

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6784434

**Type:** uncertain

**Compartments:** peroxisomal matrix, cytosol

Cytosolic glyoxylate can enter the peroxisome but the carrier that mediates its entry has not been identified (Wanders et al. 2016).

**Preceded by:** An unknown carrier transports mitochondrial glyoxylate to the cytosol

**Followed by:** glyoxylate + alanine => glycine + pyruvate [peroxisome], glyoxylate + NADPH + H+ => glycolate + NADP+, Conversion of glyoxylate to oxalate

**Literature references**


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**glycine + O2 → glyoxylate + H2O2 + NH4+**

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-389821

**Type:** transition

**Compartments:** peroxisomal matrix

Peroxisomal D-amino-acid oxidase catalyzes the reaction of glycine, water, and O2 to form glyoxylate, H2O2, and NH4+. The active form of the enzyme is a homodimer and has FAD as a cofactor (Kawazoe et al. 2006; Molla et al. 2006).

**Preceded by:** glyoxylate + alanine → glycine + pyruvate [peroxisome]

**Followed by:** Conversion of glyoxylate to oxalate, glyoxylate + NADPH + H+ → glycolate + NADP+, glyoxylate + alanine → glycine + pyruvate [peroxisome]

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Peroxisomal DDO (D-aspartate oxidase) catalyzes the oxidation of D-Asp (D-aspartate) to OA (oxaloacetate) with the formation of H2O2. The human enzyme is a monomer with an FAD cofactor (Katane et al. 2010, 2015; Setoyama & Miura 1997), as is its well-characterized bovine homolog (Negri et al. 1992). Its peroxisomal location is inferred from studies in cultured cells of fusion proteins containing the carboxy-terminal peptide sequence of DDO (Amery et al. 1998).

**Literature references**


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glyoxylate + alanine $\Rightarrow$ glycine + pyruvate [peroxisome]

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-389684

**Type:** transition

**Compartments:** peroxisomal matrix

Alanine-glyoxylate transaminase (AGXT) catalyzes the irreversible reaction of glyoxylate and alanine to form glycine and pyruvate (Danpure and Jennings 1988). The active form of the enzyme is a homodimer (Zhang et al. 2003) with one molecule of pyridoxal phosphate bound to each subunit (Coulter-Mackie et al. 2005). Mutations in this enzyme are associated with primary hyperoxaluria type I. Mutant alleles encode both catalytically inactive proteins and active ones that are mis-localized to mitochondria (Purdue et al. 1990; Takada et al. 1990).

**Preceded by:** glycine + O2 $\Rightarrow$ glyoxylate + H2O2 + NH4+, HAO1 tetramer oxidizes glycolate to glyoxylate, An unknown carrier transports cytosolic glyoxylate to the peroxisome

**Followed by:** glycine + O2 $\Rightarrow$ glyoxylate + H2O2 + NH4+

**Literature references**


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glyoxylate + NADPH + H+ => glycolate + NADP+

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-389826

**Type:** transition

**Compartments:** peroxisomal matrix

Peroxisomal GRHPR catalyzes the reaction of glyoxylate and NADPH + H+ to form glycolate and NADP+. The active form of the enzyme is a monomer (Rumsby and Cregeen 1999); mutations in it are associated with primary hyperoxaluria type II (Cramer et al. 1999).

**Preceded by:** glycine + O2 => glyoxylate + H2O2 + NH4+, An unknown carrier transports cytosolic glyoxylate to the peroxisome

**Followed by:** HAO1 tetramer oxidizes glycolate to glyoxylate

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PXMP2 trimer transports glycolate from cytosol to peroxisomal matrix

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-8953430

Type: transition

Compartments: peroxisomal membrane

Inferred from: Pxmp2 trimer transports glycolate from cytosol to peroxisomal matrix (Mus musculus)

Peroxisomal membrane protein 2 (PXMP2) homotrimer is inferred from the properties of its mouse homolog to form a channel in the peroxisomal membrane that allows the passage of glycolate and other molecules with molecular masses less than 200 Da between the cytosol and the peroxisomal matrix (Rokka et al. 2009; Wanders et al. 2016).

Followed by: HAO1 tetramer oxidizes glycolate to glyoxylate

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HAO1 tetramer oxidizes glycolate to glyoxylate

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-389842

**Type:** transition

**Compartments:** peroxisomal matrix

Peroxisomal hydroxyacid oxidase 1 catalyzes the reaction of glycolate and O2 to form glyoxylate and H2O2. The active form of the enzyme is associated with FMN and is a tetramer (Jones et al. 2000; Murray et al. 2008; Vignaud et al. 2007; Williams et al. 2000).

**Preceded by:** PXMP2 trimer transports glycolate from cytosol to peroxisomal matrix, glyoxylate + NADPH + H+ => glycolate + NADP+

**Followed by:** Conversion of glyoxylate to oxalate, glyoxylate + alanine => glycine + pyruvate [peroxisome]

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https://reactome.org
Conversion of glyoxylate to oxalate

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-389862

Type: transition

Compartments: peroxisomal matrix

Peroxisomal hydroxyacid oxidase 1 catalyzes the reaction of glyoxylate to form oxalate. The active form of the enzyme is associated with FMN and is a tetramer (Jones et al. 2000; Murray et al. 2008; Vignaud et al. 2007; Williams et al. 2000).

Preceded by: glyoxylate + O2 => glyoxylate + H2O2 + NH4+, HA01 tetramer oxidizes glycolate to glyoxylate, An unknown carrier transports cytosolic glyoxylate to the peroxisome

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Glycine degradation

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-6783984

The simplest amino acid, glycine, is catabolised by several different pathways. The major pathway is via the glycine cleavage system, comprising dimeric P protein (GLDC), T protein (AMT, GCST), dimeric L protein (DLD) and H protein (GCSH) (Kikuchi et al. 2008).

Literature references


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LIPT2 transfers octanoyl group to GCSH

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-6793590

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial matrix

Lipoate is an essential cofactor for five redox reactions; four in oxoacid dehydrogenases (active in energy metabolism and amino acid metabolism) and one in the glycine cleavage system (GCS). Lipoate synthesis in mitochondria requires three steps. In the first step, mitochondrial lipoamyltransferase 2 (LIPT2) transfers an octanoyl group bound to an acyl-carrier protein (most likely NDUFA1, acyl-carrier protein, ACP) to mitochondrial glycine cleavage system H protein (GCSH) at lysine 107. The human protein is thought to function in the same way as yeast LIP2 (Schonauer et al. 2009).

Followed by: LIAS:2(4Fe-4S) transforms octanoyl-K107-GCSH to lipoyl-K107-GCSH

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LIAS:2(4Fe-4S) transforms octanoyl-K107-GCSH to lipoyl-K107-GCSH

Location: Glyoxylate metabolism and glycine degradation

Stable identifier: R-HSA-6793591

Type: transition

Compartments: mitochondrial matrix

Lipoate is an essential cofactor for five redox reactions; four in oxoacid dehydrogenases (active in energy metabolism and amino acid metabolism) and one in the glycine cleavage system (GCS). Lipoate synthesis in mitochondria requires three steps. In the second step, mitochondrial lipoyl synthase (LIAS) mediates the radical-mediated insertion of two sulfur atoms into the C-6 and C-8 positions of the octanoyl moiety bound to glycine cleavage system H protein (GCSH), transforming the octanoyl moiety to a lipoyl moiety. LIAS requires two 4Fe-4S clusters as cofactor which act as the sulfur donors in the reaction (Morikawa et al. 2001). Defects in LIAS causes neonatal-onset epilepsy, defective mitochondrial energy metabolism, and glycine elevation (Mayr et al. 2011).

Preceded by: LIPT2 transfers octanoyl group to GCSH

Followed by: LIPT1 transfers lipoyl group from lipoyl-GCSH to DHs

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LIPT1 transfers lipoyl group from lipoyl-GCSH to DHs

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6792572

**Type:** transition

**Compartments:** mitochondrial matrix

Lipoate is an essential cofactor for two enzymes from energy metabolism (alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase) and three from amino acid metabolism (branched-chain ketoacid dehydrogenase, 2-oxoadipate dehydrogenase, and the glycine cleavage system). Lipoate synthesis in mitochondria requires three steps. In the third step, mitochondrial lipoyltransferase 1 (LIPT1) catalyses the transfer of a lipoyl group from lipoyl-K107-GCSH to lysine residue(s) of lipoate-dependent enzymes (Fujiwara et al. 1999). Defects in LIPT1 reduce lipoylation of pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase, causing a cofactor disorder of mitochondrial energy metabolism (Soreze et al. 2013, Tort et al. 2014).

**Preceded by:** LIAS:2(4Fe-4S) transforms octanoyl-K107-GCSH to lipoyl-K107-GCSH

**Literature references**


**Editions**

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GNMT tetrramer transfers methyl group from AdoMet to Gly to form AdoHcy and SARC

**Location:** Glyoxylate metabolism and glycine degradation

**Stable identifier:** R-HSA-6798317

**Type:** transition

**Compartments:** cytosol

Cytosolic glycine N-methyltransferase (GNMT) catalyses the transfer of a methyl group from S-adenosylmethionine (AdoMet) to glycine (Gly) to form sarcosine (SARC, aka N-methylglycine) with the concomitant production of S-adenosylhomocysteine (AdoHcy) (Pakhomova et al. 2004).

**Literature references**


**Editions**

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  - Unknown hydroxyproline carrier transports cytosolic HPRO into the mitochondrial matrix
  - PRODH2:FAD dimer dehydrogenates HPRO to 1-pyrroline-3-hydroxy-5-carboxylate
  - Spontaneous hydrolysis of 1-pyrroline-3-hydroxy-5-carboxylate to 4-OH-L-glutamate semialdehyde
  - ALDH4A1 dimer dehydrogenates 4-OH-L-glutamate semialdehyde to 4-OH-L-glutamate
  - PXLP-K279-GOT2 dimer transaminates 4-OH-L-glutamate to 4-hydroxy-2-oxoglutarate (HOG)
  - HOGA1 tetramer aldol-cleaves 4-OH-2-oxoglutarate (HOG) to glyoxylate and pyruvate
  - Mitochondrial AGXT2 tetramer transaminates glyoxylate and alanine to glycine and pyruvate
  - An unknown carrier transports mitochondrial glyoxylate to the cytosol
  - An unknown carrier transports cytosolic glyoxylate to the peroxisome
  - glycine + O2 => glyoxylate + H2O2 + NH4+
  - DDO oxidizes D-Asp to OA
  - glyoxylate + alanine => glycine + pyruvate [peroxisome]
  - glyoxylate + NADPH + H+ => glycolate + NADP+
  - PXMP2 trimer transports glycolate from cytosol to peroxisomal matrix
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- Glycine degradation
  - LIPT2 transfers octanoyl group to GCSH
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