HS-GAG 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.

16/11/2022

https://reactome.org
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 1 pathway and 14 reactions (see Table of Contents)

https://reactome.org
Lysosomal degradation of glycoproteins is part of the cellular homeostasis of glycosylation (Winchester 2005). The steps outlined below describe the degradation of heparan sulfate/heparin. Complete degradation of glycoproteins is required to avoid build up of glycosaminoglycan fragments which can cause lysosomal storage diseases. The proteolysis of the core protein of the glycoprotein is not shown here.

**Literature references**


**Editions**

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HS-GAGs translocate to the lysosome for degradation

**Location:** HS-GAG degradation

**Stable identifier:** R-HSA-2024084

**Type:** omitted

**Compartments:** plasma membrane, lysosomal lumen

As part of the natural turnover of GAGs, extracellular HSPGs are endocytosed to the lysosome to be degraded (Winchester 2005).

**Followed by:** Heparanase (HPSE) cleaves heparan sulfate from its proteoglycan (lysosome)

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Heparanase (HPSE) cleaves heparan sulfate from its proteoglycan (lysosome)

**Location:** HS-GAG degradation

**Stable identifier:** R-HSA-1667005

**Type:** transition

**Compartments:** lysosomal lumen

Heparanase (HPSE) is an endoglycosidase that cleaves heparan sulfate (HS) from its HS proteoglycan (HSPG) (Toyoshima & Nakajima 1999; Okada et al. 2002). The formation of a heterodimer of 8kDa and 50kDa subunits cleaved from the 65kDa form is required for enzyme activity (Levy-Adam et al. 2003) and this proteolytic cleavage occurs in the lysosome (Goldshmidt et al. 2002). Acidic conditions within the lysosome optimises HPSE activity.

**Preceded by:** HS-GAGs translocate to the lysosome for degradation

**Followed by:** IDUA hydrolyses Heparan sulfate chain(1)

**Literature references**


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Heparanase 2 (HPSE2) binds heparan sulfate proteoglycans

Location: HS-GAG degradation

Stable identifier: R-HSA-1678694

Type: binding

Compartments: plasma membrane, extracellular region

Heparanase 2 (HPSE2) (McKenzie et al. 2000) is a membrane-bound protein with ~40% sequence similarity to heparanase (HPSE). While HPSE2 binds HS proteoglycans strongly, it has no endoglycosidase activity and cannot cleave heparan sulfate (HS) from HS proteoglycan. Studies of cultured cells suggest that HPSE2 may also block targeting of HPSE and HS-proteoglycan to lysosomes (Levy-Adam et al. 2010). Defects in HPSE2 are the cause of urofacial syndrome (UFS) (MIM:236730) (Daly et al. 2010, Pang et al. 2010).

Literature references


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An L-iduronic acid residue can be cleaved from either heparan sulfate or dermatan sulfate by the lysosomal enzyme alpha-L-iduronidase (IDUA) (Scott et al. 1991). Defects in IDUA are the cause of mucopolysaccharidosis type IH (MPS IH, Hurler syndrome, MIM:607014), mucopolysaccharidosis IH/S (MPSIH/S, HurlerScheie syndrome, MIM:607015) and mucopolysaccharidosis type IS (MPSIS, Scheie syndrome, MIM:607016) (LeeChen et al. 1999).

Preceded by: Heparanase (HPSE) cleaves heparan sulfate from its proteoglycan (lysosome)

Followed by: SGSH hydrolyses Heparan sulfate chain(2)

Literature references


N-sulphoglucosamine sulphohydrolase (SGSH) hydrolys the sulfate group from the terminal N-sulphoglucosamine residue of heparan sulfate (Scott et al. 1995). Defects in SGSH cause mucopolysaccharidosis type II A (MPSIIIA, MIM:252900), also called Sanfilippo syndrome A (Weber et al. 1997).

**Preceded by:** IDUA hydrolys Heparan sulfate chain(1)

**Followed by:** HGSNAT oligomer acetylates Heparan sulfate chain(3)

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HGSNAT oligomer acetylates Heparan sulfate chain(3)

**Location:** HS-GAG degradation

**Stable identifier:** R-HSA-1678660

**Type:** transition

**Compartments:** lysosomal lumen, cytosol, lysosomal membrane

Heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT) acetylates the non-reducing terminal alpha-glucosamine residue of heparan sulfate. This is a critical reaction for the degradation of heparan sulfate because there is no enzyme that can act on the unacetylated glucosamine molecule. The mechanism by which HGSNAT uses cytosolic acetyl-CoA to transfer the acetyl group to the lysosomal luminal substrate is unknown (Fan et al. 2006). A catalytically inactive 77kDa precursor is transported to the lysosome and is cleaved into a 29kDa N-terminal alpha-chain and a 48kDa C-terminal beta-chain, which are assembled into active 440kDa oligomers in the lysosomal membrane (Durand et al. 2010). Defects in HGSNAT cause mucopolysaccharidosis type IIIC (MPSIIIC, MIM:252930), also called Sanfilippo C syndrome (Fan et al. 2006, Hrebicek et al. 2006).

**Preceded by:** SGSH hydrolyses Heparan sulfate chain(2)

**Followed by:** NAGLU hydrolyses Heparan sulfate chain(4)

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https://reactome.org
Alpha-N-acetylglucosaminidase (NAGLU) hydrolyses the non-reducing, terminal N-acetyl-D-glucosamine residue from heparan sulfate. The active form of the enzyme (77kDa) is derived from a 82kDa precursor (Weber et al. 1996). Defects in NAGLU cause of mucopolysaccharidosis type IIIB (MPSIIIB, MIM:252920) also known as Sanfilippo syndrome type B (Beesley et al. 2005).

Preceded by: HGSNAT oligomer acetylates Heparan sulfate chain(3)

Followed by: IDS hydrolyses Heparan sulfate chain(5)

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**IDS hydrolyses Heparan sulfate chain(5)**

**Location:** HS-GAG degradation

**Stable identifier:** R-HSA-1678650

**Type:** transition

**Compartments:** lysosomal lumen

Iduronate 2sulfatase (IDS) hydrolyses 2-sulfate groups from Iduronate 2-sulfate units of heparan sulfate. Defects in IDS are the cause of mucopolysaccharidosis type II (MPSII, MIM:309900), also called Hunter syndrome (Wilson et al. 1990).

**Preceded by:** NAGLU hydrolyses Heparan sulfate chain(4)

**Followed by:** IDUA hydrolyses Heparan sulfate chain(6)

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**Preceded by:** IDS hydrolyses Heparan sulfate chain(5)

**Followed by:** SGSH hydrolyses Heparan sulfate chain(7)

**Literature references**


N-sulphoglucosamine sulphohydrolase (SGSH) hydrolyses the sulfate group from the terminal N-sulphoglucosamine residue of heparan sulfate (Scott et al. 1995). Defects in SGSH cause mucopolysaccharidosis type IIIA (MPSIIIA, MIM:252900), also called Sanfilippo syndrome A (Weber et al. 1997).

**Preceded by:** IDUA hydrolyses Heparan sulfate chain(6)

**Followed by:** HGSNAT oligomer acetylates Heparan chain(1)

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HGSNAT oligomer acetylates Heparan chain(1)

Location: HS-GAG degradation

Stable identifier: R-HSA-2090085

Type: transition

Compartments: lysosomal lumen, cytosol, lysosomal membrane

Heparan-alpha-glucosaminide N-acetyltransferase (HGSNAT) acetylates another non-reducing terminal alpha-glucosamine residue of heparan sulfate. This is a critical reaction for the degradation of heparan sulfate because there is no enzyme that can act on the unacetylated glucosamine molecule. The mechanism by which HGSNAT uses cytosolic acetyl-CoA to transfer the acetyl group to the lysosomal luminal substrate is unknown (Fan et al. 2006). A catalytically inactive 77kDa precursor is transported to the lysosome and is cleaved into a 29kDa N-terminal alpha-chain and a 48kDa C-terminal beta-chain, which are assembled into active 440kDa oligomers in the lysosomal membrane (Durand et al. 2010). Defects in HGSNAT cause mucopolysaccharidosis type IIIC (MPSIIIC, MIM:252930), also called Sanfilippo C syndrome (Fan et al. 2006, Hrebicek et al. 2006).

Preceded by: SGSH hydrolyses Heparan sulfate chain(7)

Followed by: NAGLU hydrolyses heparan chain(2)

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NAGLU hydrolyses heparan chain(2)

Location: HS-GAG degradation

Stable identifier: R-HSA-2090038

Type: transition

Compartments: lysosomal lumen

Alpha-N-acetylgalcosaminidase (NAGLU) also hydrolyses another non-reducing, terminal N-acetyl-D-glucosamine residue from heparan sulfate. The active form of the enzyme (77kDa) is derived from an 82kDa precursor (Weber et al. 1996). Defects in NAGLU cause Mucopolysaccharidosis type IIIB (MPSIIIB, MIM:252920), also known as Sanfilippo syndrome type B (Beesley et al. 2005).

Preceded by: HGSNAT oligomer acetylates Heparan chain(1)

Followed by: GUSB tetramer hydrolyses CS/HS precursor

Literature references


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GUSB tetramer hydrolyses CS/HS precursor

**Location:** HS-GAG degradation

**Stable identifier:** R-HSA-1678854

**Type:** transition

**Compartments:** lysosomal lumen

The tetrameric lysosomal enzyme beta-glucuronidase hydrolyses glucuronate from heparan or the linker chain (Oshima et al. 1987). L-aspartic acid is an inhibitor of enzyme activity (Kreamer et al. 2001).

**Preceded by:** NAGLU hydrolyses heparan chain(2)

**Followed by:** GLB1 hydrolyses linker chain(2)

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GLB1 hydrolyses linker chain(2)

**Location:** HS-GAG degradation

**Stable identifier:** R-HSA-2090079

**Type:** transition

**Compartments:** lysosomal lumen

Beta-galactosidase (GLB1) can cleave terminal galactose residues from the linker chain sequence of glycosaminoglycans (Asp et al. 1969). Defects in GLB1 causes the lysosomal storage diseases GM1 gangliosidosis (Yoshida et al. 1991) and Morquio syndrome B (Oshima et al. 1991).

**Preceded by:** GUSB tetramer hydrolyses CS/HS precursor

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[https://reactome.org](https://reactome.org)
Table of Contents

Introduction

1 HS-GAG degradation

2 HS-GAGs translocate to the lysosome for degradation

3 Heparanase (HPSE) cleaves heparan sulfate from its proteoglycan (lysosome)

4 Heparanase 2 (HPSE2) binds heparan sulfate proteoglycans

5 IDUA hydrolyses Heparan sulfate chain(1)

6 SGSH hydrolyses Heparan sulfate chain(2)

7 HGSNAT oligomer acetylates Heparan sulfate chain(3)

8 NAGLU hydrolyses Heparan sulfate chain(4)

9 IDS hydrolyses Heparan sulfate chain(5)

10 IDUA hydrolyses Heparan sulfate chain(6)

11 SGSH hydrolyses Heparan sulfate chain(7)

12 HGSNAT oligomer acetylates Heparan chain(1)

13 NAGLU hydrolyses heparan chain(2)

14 GUSB tetramer hydrolyses CS/HS precursor

15 GLB1 hydrolyses linker chain(2)

Table of Contents