Scavenging of heme from plasma

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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.

14/11/2022
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 1 pathway and 12 reactions (see Table of Contents)

https://reactome.org
Scavenging of heme from plasma

Stable identifier: R-HSA-2168880

Compartments: extracellular region, endocytic vesicle membrane, plasma membrane

Free heme is damaging to tissues as it intercalates into biologic membranes, perturbing lipid bilayers and promoting the conversion of low-density lipoprotein to cytotoxic oxidized products. Moreover, it represents a source of redox-active iron that, participating in the Fenton reaction, generates oxygen radicals (reviewed in Gutteridge 1989). Free heme in plasma is mainly generated from hemoglobin released by circulating erythrocytes in pathologic conditions associated with intravascular hemolysis. Free hemoglobin in plasma is scavenged by the extracellular protein haptoglobin. Haptoglobin is produced by the liver and secreted into the plasma. Haptoglobin binds dimers of hemoglobin subunits rather than the intact tetramer (reviewed in Nielsen et al. 2010, Levy et al. 2010, Ascenzi et al. 2005, Madsen et al. 2001). The resulting haptoglobin:hemoglobin complex is then bound by CD163, expressed on plasma membranes of monocytes and macrophages, and endocytosed. When the buffering capacity of plasma haptoglobin is overwhelmed, heme is released from methemoglobin and it is bound by albumin and then transferred to hemopexin (reviewed in Chiabrando et al. 2011, Nielsen et al. 2010, Tolosano et al. 2010, Ascenzi et al. 2005, Tolosano and Altruda 2002). Hemopexin is produced mainly in the liver. Once secreted into the plasma, hemopexin binds heme and the hemopexin:heme complex is then preferentially delivered to liver hepatocytes, bound by LRP1 (CD91) and endocytosed.

Literature references


https://reactome.org


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Haptoglobin binds Hemoglobin

Location: Scavenging of heme from plasma

Stable identifier: R-HSA-2168885

Type: binding

Compartments: extracellular region

Haptoglobin is an acute phase protein. It is produced by the liver and secreted into the plasma where it binds alpha-beta dimers of hemoglobin (Hamaguchi et al. 1971, Nagel and Gibson 1971, Tsapis et al. 1978, reviewed in Chiabrando et al. 2011). Haptoglobin monomers contain alpha and beta chains cleaved from a single proprotein and bonded by cystine disulfide bonds. The monomers further associate into dimers by disulfide-bonding and beta strand swapping (Andersen et al. 2012). Each haptoglobin dimer can bind two hemoglobin dimers, each containing hemoglobin alpha and hemoglobin beta.

Followed by: Haptoglobin:Hemoglobin binds CD163

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**Haptoglobin:Hemoglobin binds CD163**

**Location:** Scavenging of heme from plasma

**Stable identifier:** R-HSA-2168883

**Type:** binding

**Compartments:** plasma membrane, extracellular region

The CD163 receptor binds the haptoglobin:hemoglobin complex (Kristiansen et al. 2001, Madsen et al. 2004, Nielsen et al. 2007). After binding, the CD163:haptoglobin:hemoglobin complex is internalized by endocytosis and is degraded in the lysosome. CD163 is found on the membranes of monocytes and macrophages.

**Preceded by:** Haptoglobin binds Hemoglobin

**Followed by:** Hemoglobin:Haptoglobin:CD163 is endocytosed

**Literature references**


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https://reactome.org
The CD163:haptoglobin:hemoglobin complex is endocytosed (Schaer et al. 2006, Kristiansen et al. 2001) by monocytes or macrophages. CD163 is constitutively endocytosed by monocytes independently of ligand binding (Schaer et al. 2006). Upon endocytosis, the receptor–ligand complex enters early endosomes where haptoglobin:hemoglobin complexes are released from CD163. The receptor then recycles to the cell surface while haptoglobin:hemoglobin complexes continue through the endocytic pathway to end up in lysosomes where the protein moieties and the ligand are degraded.

**Preceded by:** Haptoglobin:Hemoglobin binds CD163

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Haptoglobin-related Protein binds Hemoglobin

**Location:** Scavenging of heme from plasma

**Stable identifier:** R-HSA-2168889

**Type:** binding

**Compartments:** extracellular region

Haptoglobin-related protein (HRP) is present in human serum in a complex known as trypanosome lytic factor-1 (TLF-1) that contains APOL1, APOA1, and HDL3. The HPR subunit of the complex binds hemoglobin with an unknown stoichiometry (Shiflett et al. 2005, Nielsen et al. 2006, Widener et al. 2007, Harrington et al. 2009).

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https://reactome.org
Ferriheme is transferred from Albumin to Hemopexin

Location: Scavenging of heme from plasma

Stable identifier: R-HSA-2168887

Type: transition

Compartments: extracellular region

Despite the lower affinity of ferriheme for albumin than for hemopexin, ferriheme initially associates with albumin, presumably because the molar concentration of albumin in plasma is considerably greater than that of hemopexin. Ferriheme is transferred directly from serum albumin to hemopexin (Morgan et al. 1976, Pasternack et al. 1983, Pasternack et al. 1985).

Followed by: LRP1 (CD91) binds Hemopexin:heme

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Ferriheme is transferred from Methemoglobin to Hemopexin

**Location:** Scavenging of heme from plasma

**Stable identifier:** R-HSA-2168884

**Type:** dissociation

**Compartments:** extracellular region

When haptoglobin capacity to buffer hemoglobin is overwhelmed, hemoglobin undergoes a rapid conversion to methemoglobin. Ferriheme is transferred directly from methemoglobin to hemopexin (Miller et al. 1996, Mauk and Mauk 2010).

**Followed by:** LRP1 (CD91) binds Hemopexin:heme

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Hemopexin binds Hemes

Location: Scavenging of heme from plasma

Stable identifier: R-HSA-2168886

Type: binding

Compartments: extracellular region

Hemopexin binds either ferriheme b or ferroheme b, however the stability of the complex containing ferriheme b is greater than the stability of the complex containing ferroheme b (Morgan 1976, Pasternack et al. 1983, Solar et al. 1989, Miller and Shaklai 1999, Rosell et al. 2005, Mauk and Mauk 2010).

Followed by: LRP1 (CD91) binds Hemopexin:heme

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LRP1 (CD91) binds Hemopexin:heme

**Location:** Scavenging of heme from plasma

**Stable identifier:** R-HSA-2168897

**Type:** binding

**Compartments:** plasma membrane, extracellular region

Once formed in the plasma, the hemopexin:heme complex is rapidly cleared from circulation and it is taken up by the liver (Smith and Morgan 1984, Smith and Morgan 1985, Tolosano et al. 2010, Vinchi et al. 2008), where heme is degraded by heme oxygenases. In mouse, rat and rabbit several experimental evidences led to the postulation of a specific receptor on hepatocytes with high affinity for the hemopexin:heme complex (Smith and Morgan 1981, Smith and Morgan 1984, Smith et al., 1988, Smith et al., 1991), but such a receptor has not been identified to date. The only known hemopexin:heme receptor is LRP1 (CD91) that is ubiquitously expressed and has a low affinity for the complex. LRP1 is a multi-ligand scavenger receptor, involved in endocytosis in some cells types, for example macrophages, and in signaling in other cell types (reviewed in Boucher and Herz 2011). LRP1 is known to act in the metabolism of lipoprotein and it is expressed in several cell types including macrophages, hepatocytes and neurons. Among several ligands, LRP1 (CD91) can bind the hemopexin:heme complex (Hvidberg et al. 2005).

**Preceded by:** Hemopexin binds Hemes, Ferriheme is transferred from Albumin to Hemopexin, Ferriheme is transferred from Methemoglobin to Hemopexin

**Followed by:** LRP1:Hemopexin:heme is endocytosed

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The LRP1:hemopexin:heme complex is endocytosed and the complex is dissociated in lysosomes, leading to heme uptake. Heme is then degraded by heme oxygenases. Whereas LRP1 is subsequently recycled to the plasma membrane, the destiny of hemopexin is controversial. Some studies have suggested that hemopexin can be recycled as an intact molecule to the extracellular milieu (Smith and Morgan, 1979). However, it has also been proposed that following hepatic uptake of heme from hemopexin:heme, varying proportions of the protein are either returned to the circulation or degraded in the liver (Potter et al., 1993). Recently, Hvidberg et al. have shown that most hemopexin is degraded in lysosomes (Hvidberg et al., 2005).

Preceded by: LRP1 (CD91) binds Hemopexin:heme

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Alpha1-Microglobulin binds heme

Location: Scavenging of heme from plasma

Stable identifier: R-HSA-2168888

Type: binding

Compartments: extracellular region

Alpha-1-Microglobulin binds heme b (Allhorn et al. 2002, Larsson et al. 2004). The crystal structure of the complex indicates that each microglobulin molecule binds 2 heme molecules and the microglobulin:heme complex trimerizes (Siebel et al. 2012).

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Alpha-1-Microglobulin is cleaved

**Location:** Scavenging of heme from plasma

**Stable identifier:** R-HSA-2203516

**Type:** omitted

**Compartments:** extracellular region

Both hemoglobin and the cytosolic face of erythrocytes are able to catalyze the cleavage of Alpha-1-Microglobulin in the IgA:Alpha-1-Microglobulin complex present in serum (Allhorn et al. 2002). The reaction produces truncated Alpha-1-Microglobulin, which is able to bind and degrade heme. About half of the circulating Alpha-1-Microglobulin is covalently bound to IgA.

**Followed by:** Truncated Alpha-1-Microglobulin binds heme

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Truncated Alpha-1-Microglobulin binds heme

Location: Scavenging of heme from plasma

Stable identifier: R-HSA-2168881

Type: binding

Compartment: extracellular region

Truncated Alpha-1-Microglobulin binds heme b and then degrades heme b by an unknown mechanism (Allhorn et al. 2002). The crystal structure of the untruncated Alpha1-Microglobulin:heme complex indicates that each Alpha1-Microglobulin molecule binds 2 heme molecules and the Alpha1-Microglobulin molecules trimerize (Siebel et al. 2012).

Preceded by: Alpha-1-Microglobulin is cleaved

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