Hh mutants that don't undergo autocatalytic processing are degraded by ERAD
**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.

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**Literature references**


Reactome database release: 70

This document contains 1 pathway and 6 reactions (see Table of Contents)

https://reactome.org
Hh signaling is required for a number of developmental processes, and mutations that disrupt the normal processing and biogenesis of Hh ligand can result in neonatal abnormalities. SHH is one of a number of genes that have been associated with the congenital disorder holoprosencephaly, which causes abnormalities in brain and craniofacial development (Roessler et al, 2009; reviewed in Roessler and Muenke, 2011). SHH variants associated with the condition affect the autocatalytic processing of the precursor and dramatically impair the production of the secreted active Hh-Np, abrogating signaling (reviewed in Pan et al, 2013).

**Literature references**


**Editions**

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HPE SHH variants don't undergo autoproteolytic cleavage

Location: Hh mutants that don't undergo autocatalytic processing are degraded by ERAD

Stable identifier: R-HSA-5358460

Type: transition

Compartments: endoplasmic reticulum lumen

Diseases: holoprosencephaly

Holoprosencephaly (HPE) is a congenital brain disorder that results in abnormal formation and septation of the central nervous system during development. Genetic studies have implicated more than 10 chromosomal locations in the development of HPE, and 7 contributing genes, including SHH have been identified (Belloni et al, 1996; reviewed in Roessler and Muenke, 2011). Missense and truncation mutations in SHH that impair Hh signaling have been identified in cases of HPE. Many of the mutations cluster in regions of the protein that contribute to the autoproteolytic cleavage of the precursor. Because this processing is required for the production of Hh-Np (the active signaling molecule), Hh-processing mutants abolish Hh ligand secretion and Hh signaling. Mutations of residues in the conserved G-C-F motif containing the catalytic cysteine, and of residues in the sterol recognition region (SRR) in the C-terminus of Hh have been identified in HPE and abrogate ligand secretion and signaling and are thought to disrupt the cleavage reaction in the ER (Roessler et al, 2009; Traiffort et al, 2004; Maity et al, 2005; Chen et al, 2011; Huang et al, 2013).

Literature references


Editions

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Hh processing variants bind lectins

**Location:** Hh mutants that don't undergo autocatalytic processing are degraded by ERAD

**Stable identifier:** R-HSA-5362450

**Type:** binding

**Compartments:** endoplasmic reticulum membrane

**Diseases:** holoprosencephaly

Like the WT C-terminal fragment of Hh, processing-defective variant precursors of full-length Hh are also targeted for degradation by the endoplasmic reticulum-associated degradation (ERAD) pathway (Chen et al, 2011; Huang et al, 2013). This pathway delivers N-glycosylated ER-resident substrates to a retrotranslocation channel, where they are ubiquitinated and translocated to the cytosol for proteasome-mediated degradation in an ATP-ase dependent fashion (reviewed in Vembar and Brodsky, 2008). Recognition and targeting of ER proteins for the ERAD pathway depends at least in part by modification and binding of the glycosyl groups, and as is the case for the WT C-terminal fragment, lectins OS9 and ERLEC1 are required for the degradation of processing-defective variants of Hh (Chen et al, 2011). OS9 and ERLEC1 may target substrates to the retrotranslocation channel by virtue of their interaction SEL1, an ER membrane protein with established roles in the ERAD pathway (Christianson et al, 2008; Mueller et al, 2008; Hosokawa et al, 2008; Hosokawa et al, 2009).

**Followed by:** Hh processing variants are recruited to SEL1:SYVN at the ER membrane

**Literature references**

## Editions

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Hh processing variants are recruited to SEL1:SYVN at the ER membrane

**Location:** Hh mutants that don't undergo autocatalytic processing are degraded by ERAD

**Stable identifier:** R-HSA-5387386

**Type:** binding

**Compartments:** endoplasmic reticulum membrane

**Diseases:** holoprosencephaly

As is the case for the WT Hh C-terminal fragment, siRNA depletion of SEL1 and SYVN1 inhibits the degradation of processing-defective Hh mutants, suggesting these versions of Hh are also targets for ERAD-mediated degradation (Chen et al, 2011; Huang et al, 2013).

**Preceded by:** Hh processing variants bind lectins

**Followed by:** Hh processing variants are ubiquitinated

**Literature references**


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**Hh processing variants are ubiquitinlated**

**Location:** Hh mutants that don't undergo autocatalytic processing are degraded by ERAD

**Stable identifier:** R-HSA-5483238

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol

**Diseases:** holoprosencephaly

Processing-defective SHH variants are ubiquitinlated by SYVN1 (Chen et al, 2011).

**Preceded by:** Hh processing variants are recruited to SEL1:SYVN at the ER membrane

**Followed by:** Hh processing variants are translocated to the cytosol in a VCP-dependent manner

**Literature references**


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**Hh processing variants are translocated to the cytosol in a VCP-dependent manner**

**Location:** Hh mutants that don't undergo autocatalytic processing are degraded by ERAD

**Stable identifier:** R-HSA-5387389

**Type:** transition

**Compartments:** cytosol

**Diseases:** holoprosencephaly

Depletion of the ATPase VCP results in the stabilization of processing-defective Hh variants in the ER lumen, supporting the notion that, as is the case for the WT Hh C-terminal fragment, these peptides are also substrates for ERAD (Chen et al, 2011; Huang et al, 2013).

**Preceded by:** Hh processing variants are ubiquitinated

**Followed by:** processing defective Hh variants are degraded by the proteasome

**Literature references**


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After retrotranslocation to the cytosol, processing-defective Hh variants are degraded by the proteasome (Chen et al, 2011; Huang et al, 2013).

**Preceded by:** Hh processing variants are translocated to the cytosol in a VCP-dependent manner

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