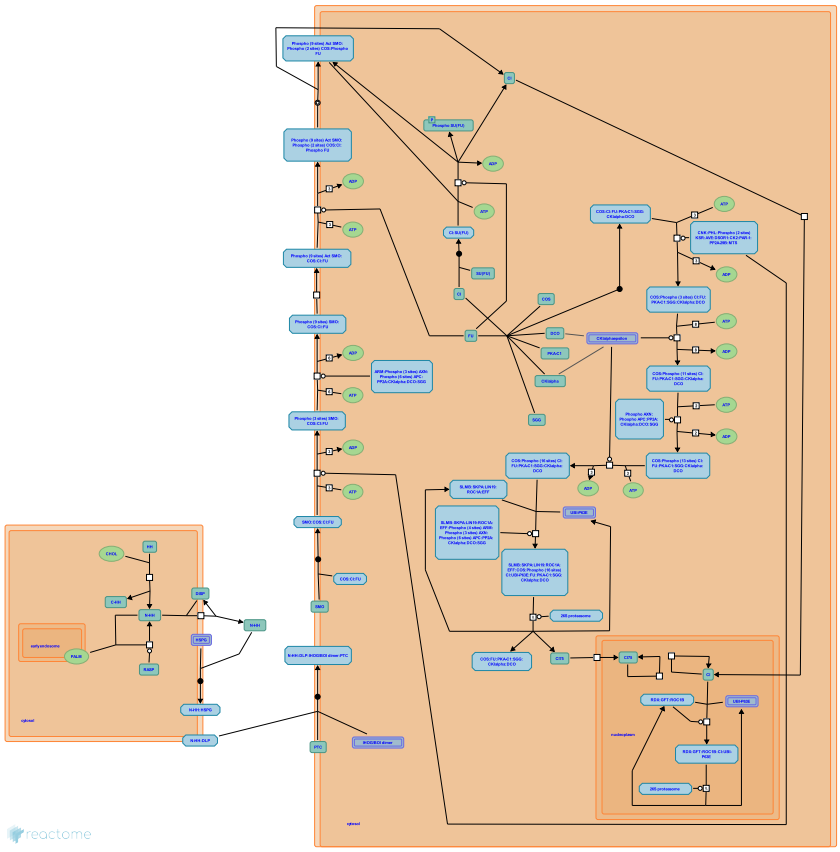
Hedgehog pathway



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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.

14/09/2024

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. ↗

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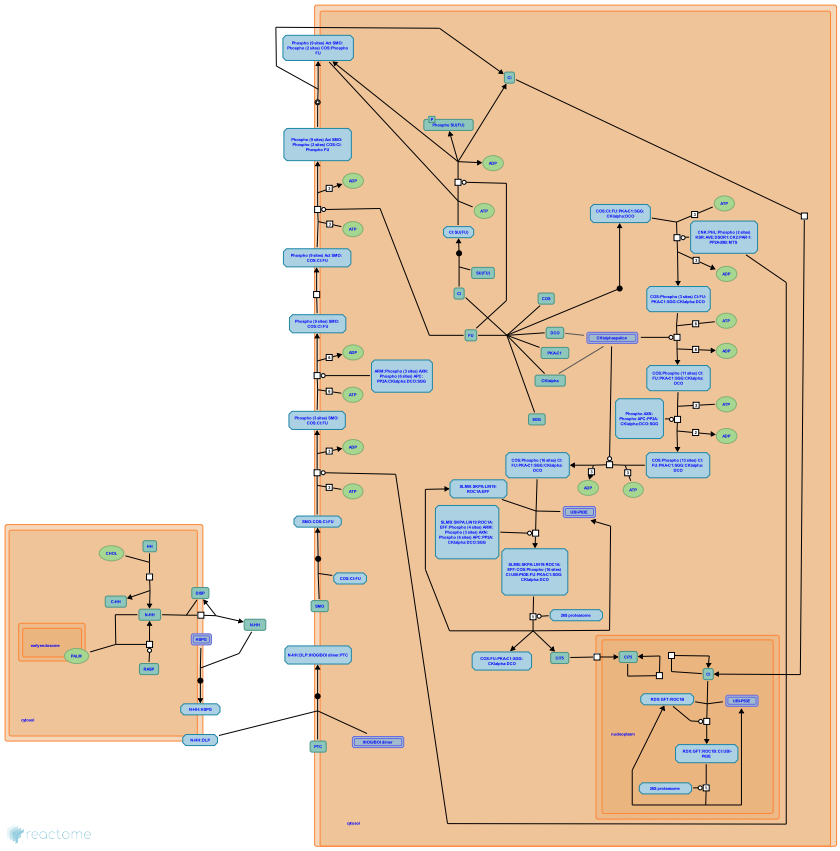
Reactome database release: 89

This document contains 4 pathways (see Table of Contents)

Hedgehog pathway ↗

Stable identifier: R-DME-209392



In the Hedgehog signalling pathway, as in the Wingless pathway, there are two main sets of signalling events. One comes into play when the Hedgehog (N-HH) ligand is bound to its cell surface receptor, Patched (PTC) and the other set occurs when the ligand isn't bound to it.

In Hedgehog sending cells, full-length Hedgehog ligand (HH) undergoes an autoprocessing event culminating in cleavage of itself into an N-terminal fragment (N-HH) modified by cholesterol and a C-terminal fragment (C-HH) which is no longer used in the pathway. N-HH is further processed through the action of the protein-cysteine N-palmitoyltransferase, Rasp (RASP), which palmitoylates the ligand. N-HH is secreted extracellularly with the assistance of the membrane protein, Dispatched (DISP). Efficient movement of N-HH requires heparan sulphate proteoglycans (HSPGs) such as Dally (DALLY) and Dally-like protein (DLP), which can aid the accumulation of N-HH at the cell surface and facilitate intercellular transport of ligand.

In cells not exposed to HH, the transmembrane protein PTC inhibits the transmembrane residing Smoothened (SMO). In the cytosol, full-length Cubitus Interruptus protein (CI) forms a complex with the Suppressor of Fused protein (SU(FU)) and the large kinesin-like scaffold protein, Costal2 (COS), which also binds the Ser/Thr protein kinase, Fused (FU). COS recruits the Ser/Thr kinases: protein kinase A (PKA-C1); Shaggy (SGG); casein kinase I alpha (CKIalpha); and casein kinase I epsilon (DCO). These phosphorylate CI which is now recognised by Slimb (SLMB) which is part of the SCF ubiquitin ligase complex. CI is ubiquitinated and partially degraded by the proteasome resulting in a truncated CI (CI75) which transports to the nucleus where it acts as a repressor of transcription.

However, if N-HH ligand is in the vicinity of the Hedgehog receiving cell, it binds to PTC, reducing the inhibiting effect PTC has on SMO. This leads to increased phosphorylation of SMO by PKA-C1 and CKIalpha, accompanied by a conformational change, increased stability and enhanced surface accumulation. CI associates with SMO via COS and is no longer efficiently phosphorylated and proteolysed after SMO activation. FU, COS and SU(FU) are phosphorylated and full-length CI gains greater access to the nucleus, where it activates transcription.

Literature references

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Cohen MM, Jr. (2003). The hedgehog signaling network. *Am J Med Genet A, 123*, 5-28.

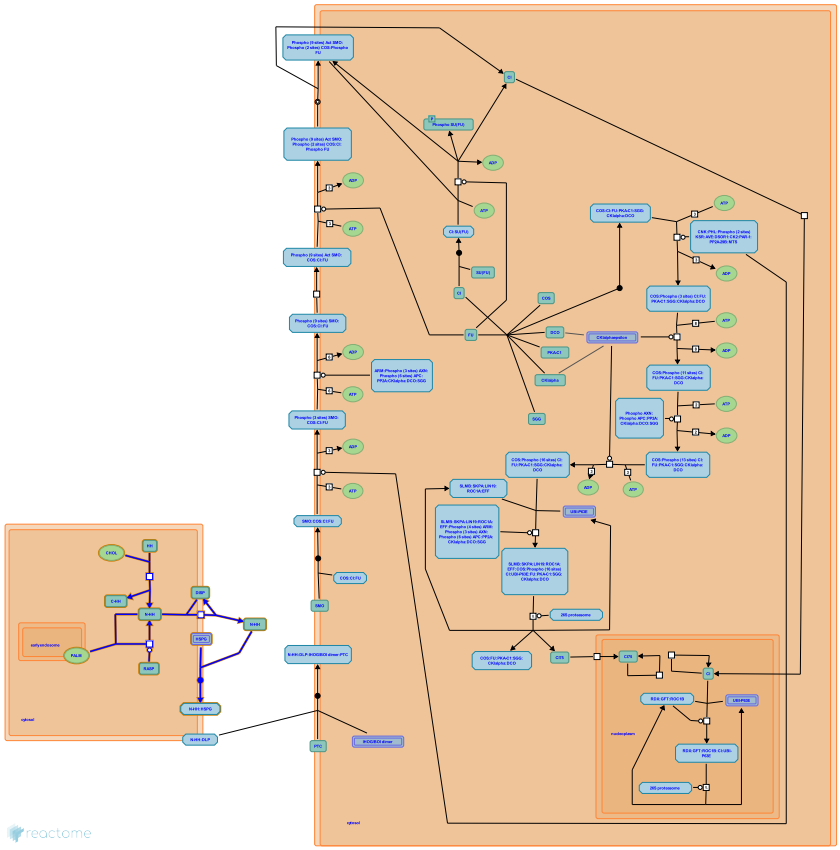
Editions

2006-12-07	Authored, Edited	Williams, MG.
2008-03-17	Reviewed	Kalderon, D.

Formation and transport of the N-HH ligand ↗

Location: Hedgehog pathway

Stable identifier: R-DME-209471



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Cohen MM, Jr. (2003). The hedgehog signaling network. *Am J Med Genet A, 123*, 5-28. ↗

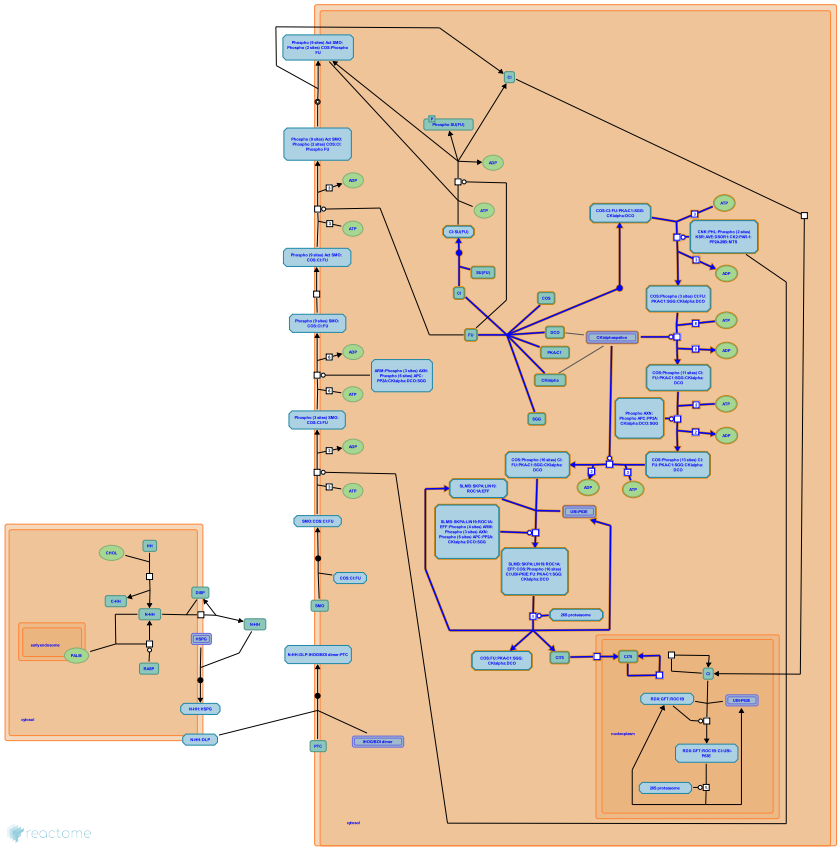
Editions

2006-12-07	Authored	Williams, MG.
2006-12-08	Edited	Williams, MG.
2008-03-17	Reviewed	Kalderon, D.

N-HH ligand not bound to PTC receptor complex ↗

Location: Hedgehog pathway

Stable identifier: R-DME-209446



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Cohen MM, Jr. (2003). The hedgehog signaling network. *Am J Med Genet A, 123*, 5-28. ↗

Editions

2006-12-07	Authored	Williams, MG.
2006-12-08	Edited	Williams, MG.
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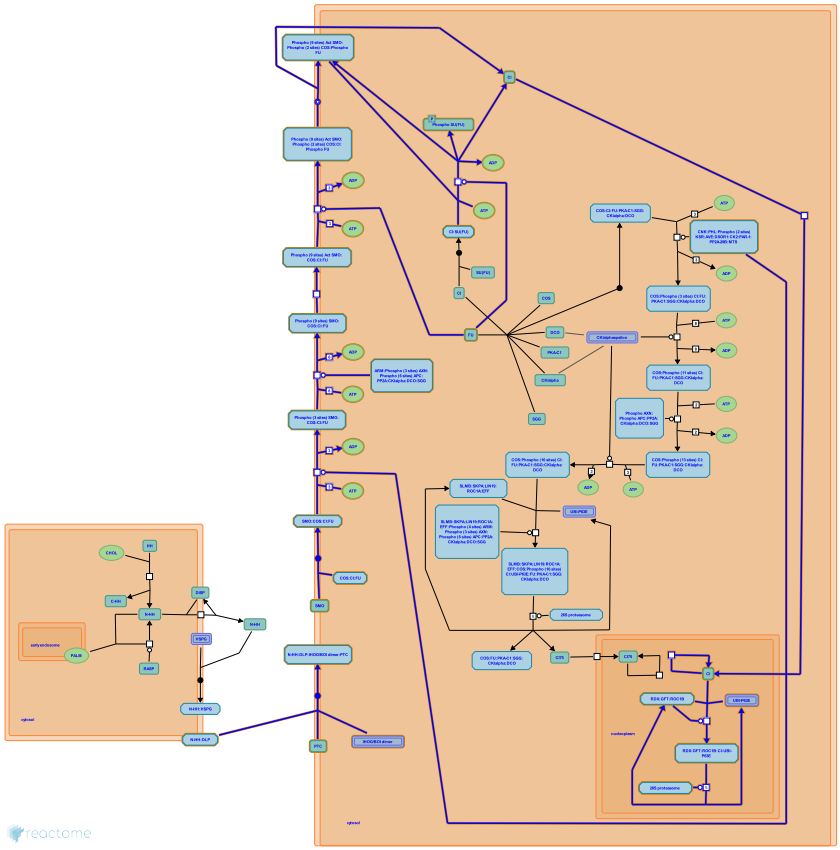
N-HH ligand bound to PTC receptor complex ↗

Location: Hedgehog pathway

Stable identifier: R-DME-209452



Spatzle (SPZ) dimer binding leads to Toll (TL) receptor homodimerisation and activation.

Literature references

Cohen MM, Jr. (2003). The hedgehog signaling network. *Am J Med Genet A, 123*, 5-28. ↗

Editions

2006-12-07	Authored	Williams, MG.
2006-12-08	Edited	Williams, MG.
2008-03-17	Reviewed	Kalderon, D.

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