Ligand-receptor interactions

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18/11/2019
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: 70

This document contains 1 pathway and 4 reactions (see Table of Contents)
Repression of Hh signaling in the absence of ligand depends on the transmembrane receptor protein Patched (PTCH), which inhibits Smoothened (SMO) activity by an unknown mechanism. This promotes the proteolytic processing and/or degradation of the GLI family of transcription factors and maintains the pathway in a transcriptionally repressed state (reviewed in Briscoe and Therond, 2013). In the absence of ligand, PTCH is localized in the cilium, while SMO is largely concentrated in intracellular compartments. Upon binding of Hh to the PTCH receptor, PTCH is endocytosed, relieving SMO inhibition and allowing it to accumulate in the primary cilium (Marigo et al, 1996; Chen and Struhl, 1996; Stone et al, 1996; Rohatgi et al, 2007; Corbit et al, 2005; reviewed in Goetz and Anderson, 2010). In the cilium, SMO is activated by an unknown mechanism, allowing the full length transcriptional activator forms of the GLI proteins to accumulate and translocate to the nucleus, where they bind to the promoters of Hh-responsive genes (reviewed in Briscoe and Therond, 2013).

In addition to PTCH, three additional membrane proteins have been shown to bind Hh and to be required for Hh-dependent signaling in vertebrates: CDON (CAM-related/downregulated by oncogenes), BOC (brother of CDO) and GAS1 (growth arrest specific 1) (Yao et al, 2006; Okada et al, 2006; Tenzen et al, 2006; McLellan et al, 2008; reviewed in Kang et al, 2007; Beachy et al, 2010; Sanchez-Arrones et al, 2012). CDON and BOC, homologues of Drosophila Ihog and Boi respectively, are evolutionarily conserved transmembrane glycoproteins that have been shown to bind both to Hh ligand and to the canonical receptor PTCH to promote Hh signaling (Okada et al, 2006; Yao et al, 2006; Tenzen et al, 2006, McLellan et al, 2008; Izzi et al, 2011; reviewed in Sanchez-Arrones et al, 2012). Despite the evolutionary conservation, the mode of ligand binding by CDON/Ihog and BOC/Boi is distinct in vertebrates and invertebrates. High affinity ligand-binding by CDON/Ihog and BOC/Boi is distinct in vertebrates and invertebrates. High affinity ligand-binding by CDON and BOC requires Ca2+, while invertebrate ligand-binding is heparin-dependent (Okada et al, 2006; Tenzen et al, 2006; McLellan et al, 2008; Yao et al, 2006; Kavran et al, 2010). GAS1 is a vertebrate-specific GPI-anchored protein that similarly binds both to Hh ligand and to the
PTCH receptor to promote Hh signaling (Martinelli and Fan, 2007; Izzi et al, 2011; reviewed in Kang et al, 2007). CDON, BOC and GAS1 have partially overlapping but not totally redundant roles, and knock-out of all three is required to abrogate Hh signaling in mice (Allen et al, 2011; Izzi et al, 2011; reviewed in Briscoe and Therond, 2013).

Literature references


Editions

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Hh-Npp binds BOC:PTCH1

Location: Ligand-receptor interactions

Stable identifier: R-HSA-5632653

Type: binding

Compartments: plasma membrane

Inferred from: Shh binds Boc:Ptch1 (Mus musculus)

Hh pathway activation depends upon the binding of Hh ligand to the PTCH transmembrane receptor (Chen and Struhl, 1996; Marigo et al, 1996; Stone et al, 1996). Ligand binding relieves the PTCH-dependent inhibition of SMO, allowing SMO to concentrate in the primary cilium and promoting the accumulation of the full-length form of the GLI transcriptional proteins (reviewed in Briscoe and Therond, 2013). PTCH also binds constitutively to the transmembrane protein BOC (brother of CDO), one of three vertebrate co-receptors required for Hh signaling in mice (Izzi et al, 2011; Allen et al, 2011; reviewed in Sanchez-Arrones et al, 2012). BOC interacts with PTCH through the first and second of the BOC fibronectin type 3 (FNIII) repeats, and with SHH through the third FNIII repeat, suggesting the formation of a ternary complex in the presence of ligand (Okada et al, 2006; Izzi et al, 2011). Although GAS1 similarly binds to both PTCH and Hh, it is not co-immunoprecipitated with BOC, suggesting the formation of separate receptor:co-receptor complexes (Izzi et al, 2011; Allen et al, 2011; reviewed in Briscoe and Therond, 2013).

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https://reactome.org
**Hh-Npp binds CDON and PTCH**

**Location:** Ligand-receptor interactions  
**Stable identifier:** R-HSA-5632652  
**Type:** binding  
**Compartments:** ciliary membrane

CDON is a transmembrane glycoprotein that binds directly to Hh ligand and is required in conjunction with PTCH, BOC and GAS1 to promote Hh signaling (Tenzen et al, 2006; McLellan et al, 2008; Kavran et al, 2010; Bae et al, 2011; reviewed in Beachy et al, 2010; Sanchez-Arrones et al, 2012). Conserved fibronectin type III repeats in the extracellular region of CDON and BOC are required for interaction with both Hh ligand and the PTCH receptor and also for interactions between BOC, CDON and GAS1 (Okada et al, 2006; Izzi et al, 2011; Bae et al, 2011). The manner in which each of these co-receptors interact and contribute to Hh signaling is not fully elucidated, but knockout of all three is required to abrogate Hh signaling in mice (Allen et al, 2007; Allen et al, 2011; Izzi et al, 2011; reviewed in Sanchez-Arrones et al, 2012).

**Literature references**


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Hh-Npp binds GAS1 and PTCH

**Location:** Ligand-receptor interactions

**Stable identifier:** R-HSA-5632649

**Type:** binding

**Compartments:** plasma membrane

GAS1 is a vertebrate-specific Hh coreceptor that binds directly to Hh ligand to promote signaling (Martinelli and Fan, 2007; McLellan et al, 2008; Izzi et al, 2011; Pineda-Alvarez et al, 2012). GAS1 interacts directly with PTCH as well as BOC and CDON and contributes in an unclearly defined manner to Hh signal transduction (Martinelli and Fan, 2007; Allen et al, 2007; Izzi et al, 2011; Allen et al, 2011; reviewed in Sanchez-Arrones et al, 2012).

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HHIP binds Hedgehog

Location: Ligand-receptor interactions

Stable identifier: R-HSA-445448

Type: binding

Compartments: extracellular region, plasma membrane

HHIP is a Hh-binding transmembrane protein that antagonizes Hh signaling by sequestering the ligand away from PTCH. HHIP is also a downstream target gene of Hh signaling, establishing a negative feedback loop that limits the extent of signaling (Chuang et al, 1999; Chuang et al, 2003; Bosanac et al, 2009; Bishop et al, 2009; Holtz et al, 2013). HHIP binds to all three Hh ligands, and also exists in a secreted form, which also sequesters ligand (Chuang et al, 1999; Coulombe et al, 2004). HHIP expression is altered in some cancers that show upregulated Hh signaling (Olsen et al, 2004; Tada et al, 2008; Tojo et al, 2002).

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