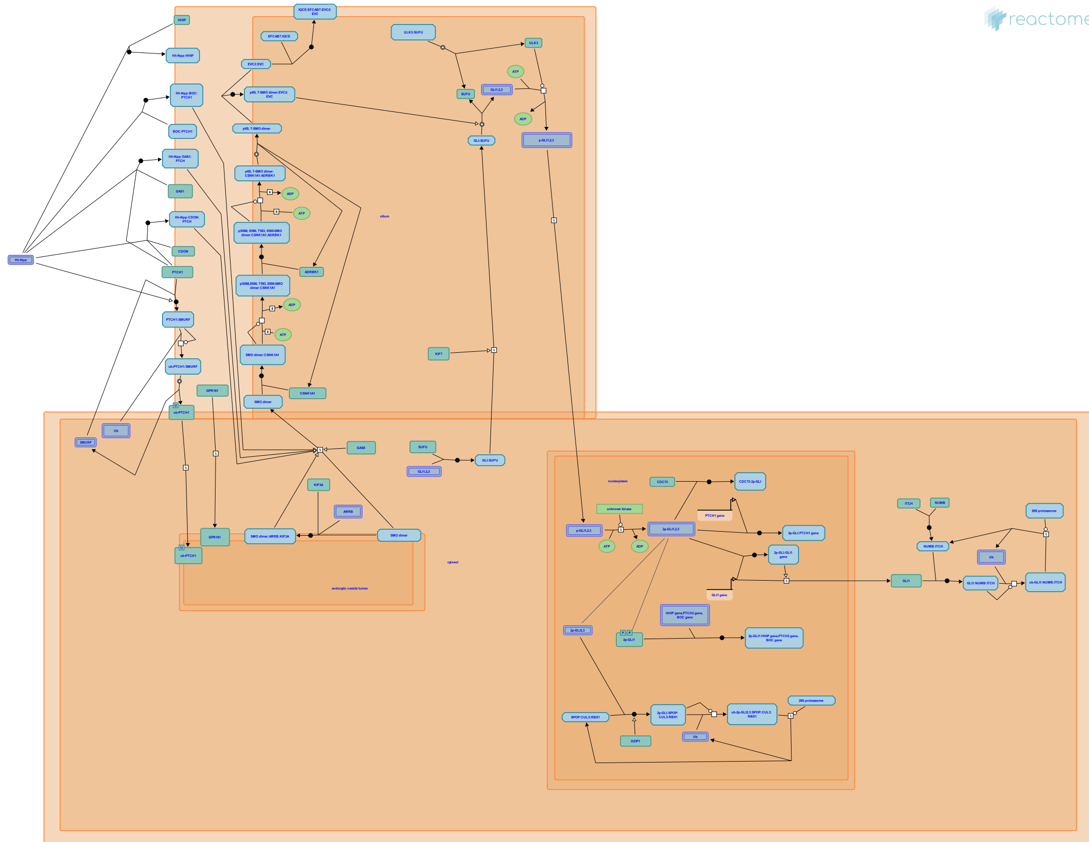
reactome

Hedgehog 'on' state



Gillespie, ME., Liu, Y C., Rothfels, K.

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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.

25/04/2024

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.

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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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Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46,* D649-D655. ↗

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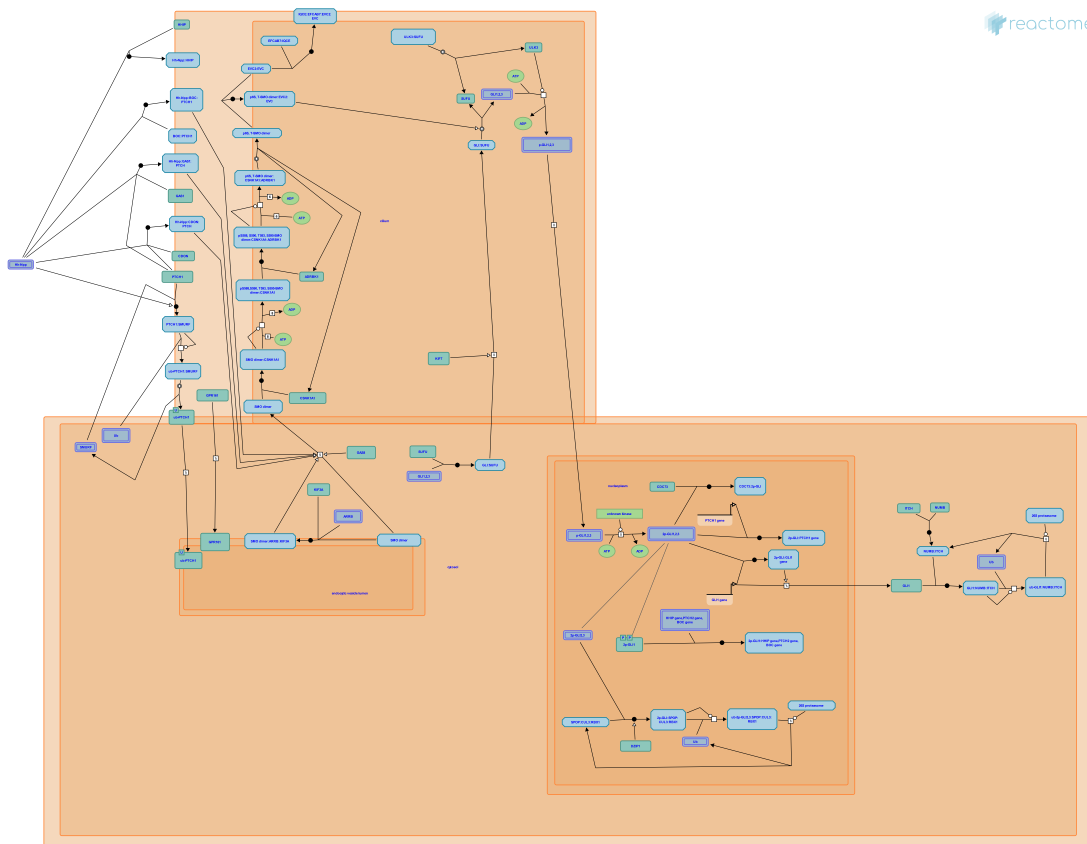
Reactome database release: 88

This document contains 4 pathways and 20 reactions (see Table of Contents)

Hedgehog 'on' state ↗

Stable identifier: R-HSA-5632684



Hedgehog is a secreted morphogen that has evolutionarily conserved roles in body organization by regulating the activity of the Ci/Gli transcription factor family. In Drosophila in the absence of Hh signaling, full-length Ci is partially degraded by the proteasome to generate a truncated repressor form that translocates to the nucleus to represses Hh-responsive genes. Binding of Hh ligand to the Patched (PTC) receptor allows the 7-pass transmembrane protein Smoothened (SMO) to be activated in an unknown manner, disrupting the partial proteolysis of Ci and allowing the full length activator form to accumulate (reviewed in Ingham et al, 2011; Briscoe and Therond, 2013).
While many of the core components of Hh signaling are conserved from flies to humans, the pathways do show points of significant divergence. Notably, the human genome encodes three Ci homologues, GLI1, 2 and 3 that each play slightly different roles in regulating Hh responsive genes. GLI3 is the primary repressor of Hh signaling in vertebrates, and is converted to the truncated GLI3R repressor form in the absence of Hh. GLI2 is a potent activator of transcription in the presence of Hh but contributes only minimally to the repression function. While a minor fraction of GLI2 protein is processed into the repressor form in the absence of Hh, the majority is either fully degraded by the proteasome or sequestered in the full-length form in the cytosol by protein-protein interactions. GLI1 lacks the repression domain and appears to be an obligate transcriptional activator (reviewed in Briscoe and Therond, 2013).
Vertebrate but not fly Hh signaling also depends on the movement of pathway components through the primary cilium. The primary cilium is a non-motile microtubule based structure whose construction and maintenance depends on intraflagellar transport (IFT). Anterograde IFT moves molecules from the ciliary base along the axoneme to the ciliary tip in a manner that requires the microtubule-plus-end directed kinesin KIF3 motor complex and the IFT-B protein complex, while retrograde IFT back to the ciliary base depends on the minus-end directed dynein motor and the IFT-A complex. Genetic screens have identified a number of cilia-related proteins that are required both to maintain Hh in the 'off' state and to transduce the signal when the pathway is activated (reviewed in Hui and Angers, 2011; Goetz and Anderson, 2010).

Literature references

Hui, CC., Angers, S. (2011). Gli proteins in development and disease. *Annu. Rev. Cell Dev. Biol.*, *27*, 513-37. ↗

Nakano, Y., Ingham, PW., Seger, C. (2011). Mechanisms and functions of Hedgehog signalling across the metazoa. *Nat. Rev. Genet.*, *12*, 393-406. ↗

Thérond, PP., Briscoe, J. (2013). The mechanisms of Hedgehog signalling and its roles in development and disease. *Nat. Rev. Mol. Cell Biol.*, *14*, 416-29. ↗

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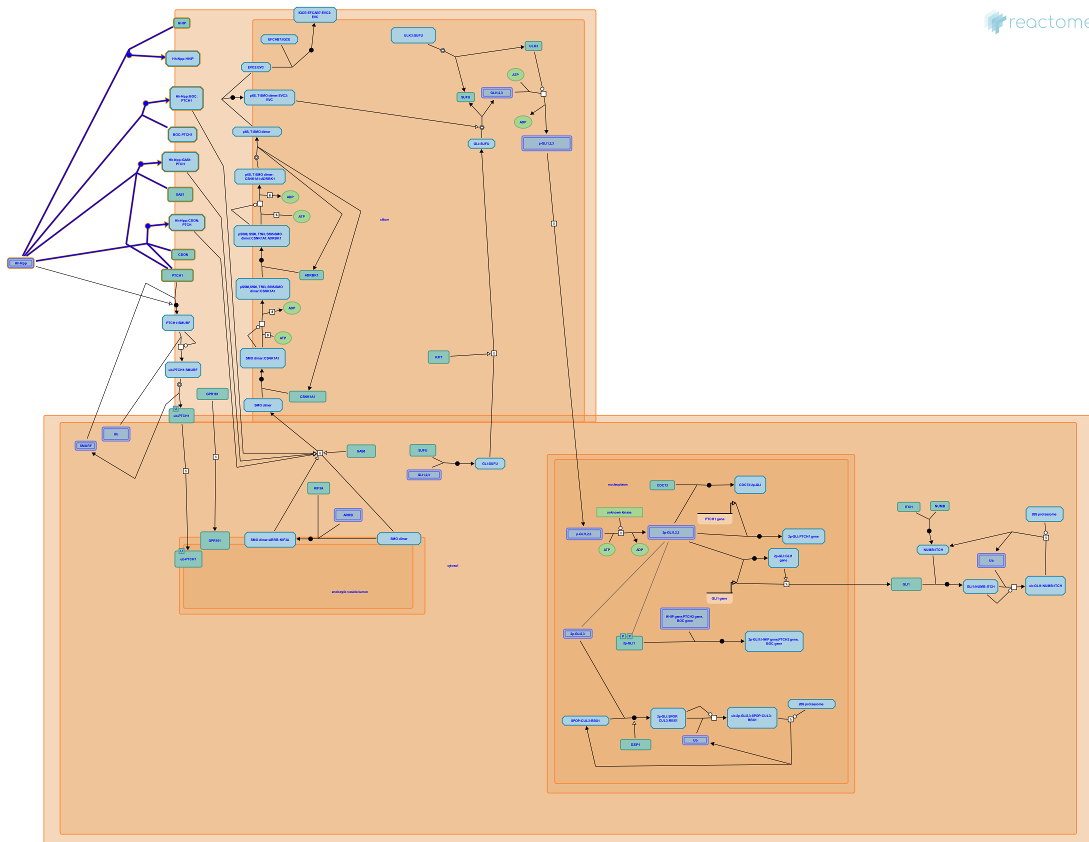
Editions

2014-08-07	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

Ligand-receptor interactions ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5632681



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 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

Kavran, JM., Oladosu, OO., Leahy, DJ., Mulepati, S., Ward, MD. (2010). All mammalian Hedgehog proteins interact with cell adhesion molecule, down-regulated by oncogenes (CDO) and brother of CDO (BOC) in a conserved manner. *J. Biol. Chem., 285*, 24584-90. ↗

Beachy, P., Lum, L., Yao, S. (2006). The ihog cell-surface proteins bind Hedgehog and mediate pathway activation. *Cell, 125*, 343-57. ↗

Davey, RA., Cunningham, JM., Marigo, V., Zuo, Y., Tabin, CJ. (1996). Biochemical evidence that patched is the Hedgehog receptor. *Nature, 384*, 176-9. ↗

Hymowitz, SG., Beachy, PA., Leahy, DJ., Lazarus, RA., Siebold, C. (2010). Interactions between Hedgehog proteins and their binding partners come into view. *Genes Dev., 24*, 2001-12. ↗

Thérond, PP., Briscoe, J. (2013). The mechanisms of Hedgehog signalling and its roles in development and disease. *Nat. Rev. Mol. Cell Biol., 14*, 416-29. ↗

Editions

2014-10-20	Authored	Rothfels, K.
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2014-11-09	Reviewed	Liu, Y C.

SMURF1/2 bind PTCH1 ↗

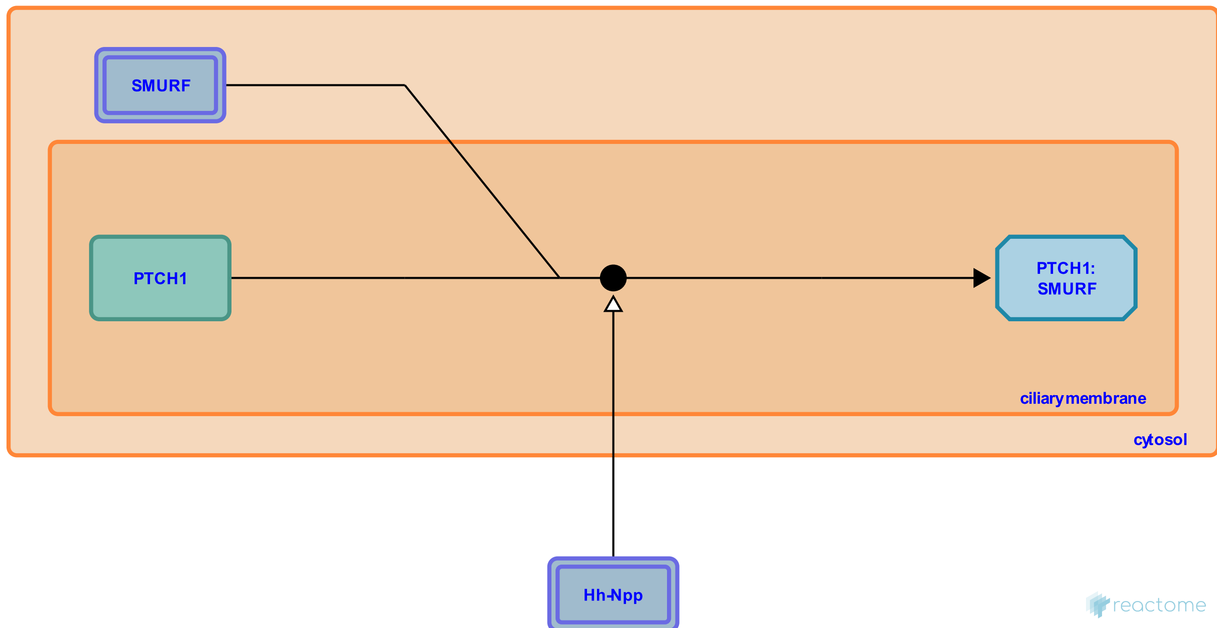
Location: Hedgehog 'on' state

Stable identifier: R-HSA-5632646

Type: binding

Compartments: ciliary membrane

Inferred from: Smurf1/2 bind Ptch1 (Mus musculus)



Hh stimulation promotes PTCH1 clearance from the primary cilium to endocytic compartments (Rohatgi et al, 2007; reviewed in Nowaza et al, 2013). Receptor internalization is required for pathway activation, and additionally limits the duration and range of Hh signaling by sequestering the ligand inside the cell (Rohatgi et al, 2007; Incardona et al, 2000; Incardona et al, 2002; Denef et al, 2000; Huang et al, 2013; Yue et al, 2014). Upon Hh pathway activation, the E3 ligases SMURF1 and SMURF2 bind to two PPXY motifs in the C-terminal tail of PTCH1 to promote its ubiquination, endocytosis and degradation. In Drosophila, SMURF-mediated ubiquitination of PTCH is depends on an interaction between SMURF and activated SMO, but this does not appear to be true in vertebrates where PTCH1 turnover is SMO-independent (Yue et al, 2014; Huang et al, 2013; Lu et al, 2006). In flies, SMURF-dependent ubiquitination preferentially downregulates ligand-unbound receptor and is thus believed to regulate downstream signaling by altering the ratio of bound to unbound receptor on the cell surface; this aspect of PTCH1 downregulation has not been examined in detail in vertebrate cells (Huang et al, 2013; Casali and Struhl, 2004; Yue et al, 2014).

Followed by: SMURF1/2 ubiquitinates PTCH1

Literature references

Kornberg, TB., Liu, S., Lu, X. (2006). The C-terminal tail of the Hedgehog receptor Patched regulates both localization and turnover. *Genes Dev., 20*, 2539-51. ↗

Gruenberg, J., Roelink, H., Incardona, JP. (2002). Sonic hedgehog induces the segregation of patched and smoothened in endosomes. *Curr. Biol., 12*, 983-95. ↗

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Struhl, G., Casali, A. (2004). Reading the Hedgehog morphogen gradient by measuring the ratio of bound to unbound Patched protein. *Nature, 431*, 76-80. ↗

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Editions

2014-10-20	Authored	Rothfels, K.
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2014-11-09	Reviewed	Liu, Y C.

SMURF1/2 ubiquitinates PTCH1 ↗

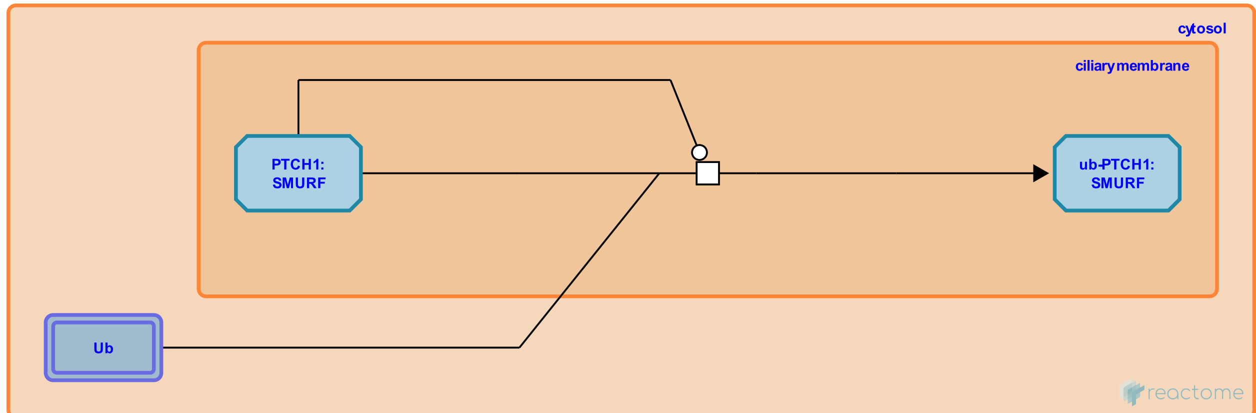
Location: Hedgehog 'on' state

Stable identifier: R-HSA-5632648

Type: transition

Compartments: ciliary membrane

Inferred from: Smurf1/2 ubiquitinates Ptch1 (Mus musculus)



SMURF 1 and 2 are required in a redundant manner for the ligand-dependent ubiquitination of the C-terminal tail of PTCH. Ubiquitination is required for PTCH1 clearance from the primary cilium to endocytic compartments for degradation, allowing downstream pathway activation (Rohatgi et al, 2007; Yue et al, 2014; Huang et al, 2013).

Preceded by: SMURF1/2 bind PTCH1

Followed by: SMURF1/2 dissociates from ub-PTCH1

Literature references

Zhang, YE., Shen, QH., Tang, LY., Chen, Y., Yue, S., Zhang, Z. et al. (2014). Requirement of Smurf-mediated endocytosis of Patched1 in Sonic Hedgehog signal reception. *Elife*, e02555. ↗

Wang, H., Liu, F., Sun, L., Chen, Z., Lv, X., Zhu, Y. et al. (2013). Activation of Smurf E3 ligase promoted by smoothened regulates hedgehog signaling through targeting patched turnover. *PLoS Biol.*, *11*, e1001721. ↗

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Editions

2014-10-20	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

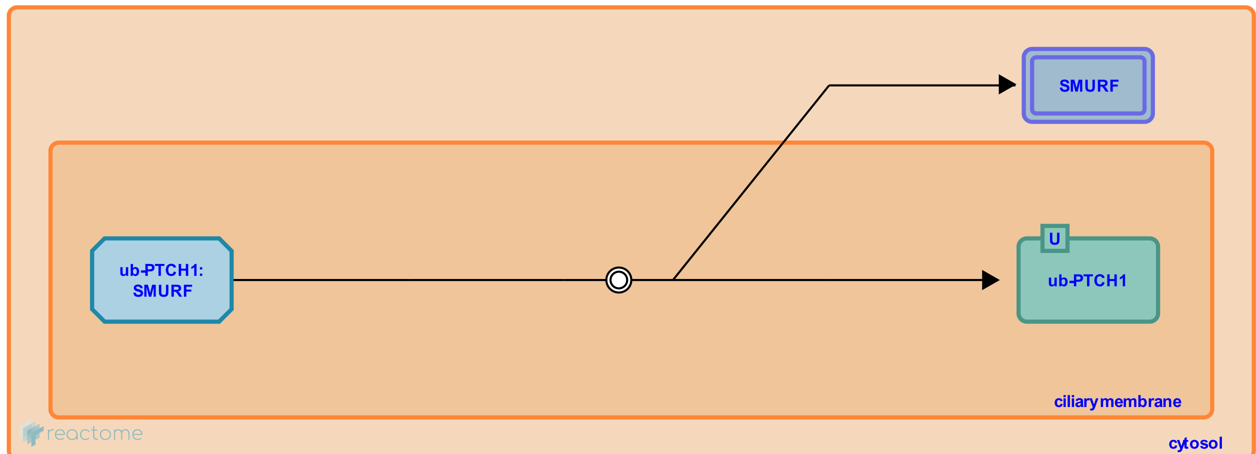
SMURF1/2 dissociates from ub-PTCH1 ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635865

Type: dissociation

Compartments: ciliary membrane



After ubiquitinating PTCH1, the SMURF E3 ligase presumably dissociates, although this has not been studied in detail (Huang et al, 2013; Yue et al, 2014).

Preceded by: SMURF1/2 ubiquitinates PTCH1

Followed by: PTCH is internalized

Literature references

Zhang, YE., Shen, QH., Tang, LY., Chen, Y., Yue, S., Zhang, Z. et al. (2014). Requirement of Smurf-mediated endocytosis of Patched1 in Sonic Hedgehog signal reception. *Elife*, e02555. ↗

Wang, H., Liu, F., Sun, L., Chen, Z., Lv, X., Zhu, Y. et al. (2013). Activation of Smurf E3 ligase promoted by smoothened regulates hedgehog signaling through targeting patched turnover. *PLoS Biol., 11*, e1001721. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

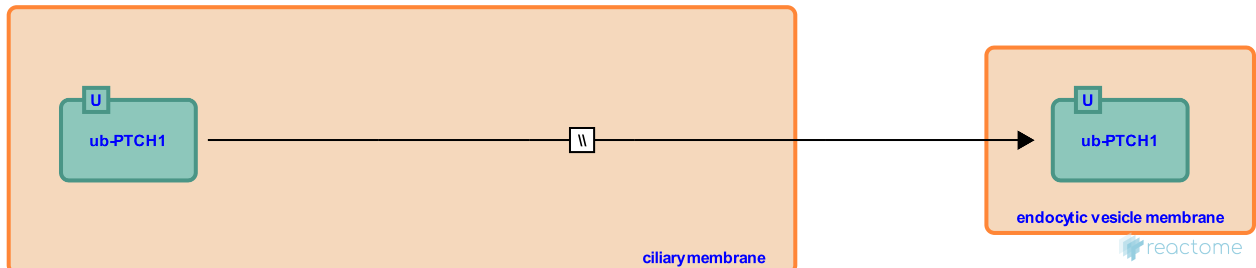
PTCH is internalized ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5632677

Type: omitted

Compartments: ciliary membrane



After SMURF-dependent ubiquitination, PTCH1 is internalized to endocytic vesicles for degradation (Rohatgi et al, 2007; Huang et al, 2013; Yue et al, 2014). PTCH1 and SMO show reciprocal changes in localization upon Hh pathway activation, with PTCH moving from the primary cilium to internal vesicles while SMO becomes enriched in the primary cilium after ligand binding (Denef et al, 2000; Rohatgi et al, 2007; Corbit et al, 2005; Kovacs et al, 2008; reviewed in Goetz and Anderson). In mice, internalization of PTCH1 appears to be independent of SMO, while in flies, activated SMO is required to promote the SMURF-dependent downregulation of PTCH (Yue et al, 2014; Huang et al, 2013).

Preceded by: SMURF1/2 dissociates from ub-PTCH1

Literature references

Stainier, DY., Singla, V., Norman, AR., Reiter, JF., Aanstad, P., Corbit, KC. (2005). Vertebrate Smoothened functions at the primary cilium. *Nature, 437*, 1018-21. ↗

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Chen, W., Liu, R., Kim, J., Wang, J., Chen, M., Whalen, EJ. et al. (2008). Beta-arrestin-mediated localization of smoothened to the primary cilium. *Science, 320*, 1777-81. ↗

Wang, H., Liu, F., Sun, L., Chen, Z., Lv, X., Zhu, Y. et al. (2013). Activation of Smurf E3 ligase promoted by smoothened regulates hedgehog signaling through targeting patched turnover. *PLoS Biol., 11*, e1001721. ↗

Cohen, SM., Denef, N., Neubüser, D., Perez, L. (2000). Hedgehog induces opposite changes in turnover and subcellular localization of patched and smoothened. *Cell, 102*, 521-31. ↗

Editions

2014-10-20	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

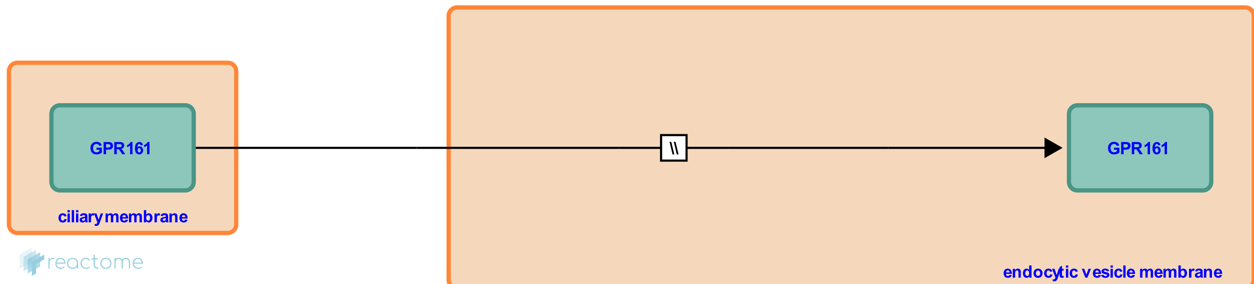
GPR161 is internalized ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635102

Type: omitted

Compartments: endocytic vesicle membrane, ciliary membrane



Hh signaling promotes the removal of the orphan G protein coupled receptor GPR161 from the cilium (Rohatgi et al, 2007). GPR161 is a negative regulator of Hh signaling that is recruited to the cilium through interaction with TULP3 (Mukhopadhyay et al, 2010; Mukhopadhyay et al, 2013). GPR161 thought to act by locally increasing the cAMP levels, promoting PKA activity and thereby favouring the production of the repressor form of the GLI proteins in the absence of Hh ligand. Consistent with this, deletion of GPR161 results in ectopic pathway activation (Mukhopadhyay et al, 2013). The decrease in PKA activity in the cilium after clearance of GPR161 from the ciliary membrane may contribute to the dissociation of the GLI:SUFU complex upon pathway activation, although this remains to formally demonstrated (Humke et al, 2010; Tukachinsky et al, 2010; reviewed in Mukhopadhyay et al, 2014).

Literature references

Scales, SJ., Wen, X., Rangell, L., Jackson, PK., Loktev, A., Mukhopadhyay, S. et al. (2013). The ciliary G-protein-coupled receptor Gpr161 negatively regulates the Sonic hedgehog pathway via cAMP signaling. *Cell, 152*, 210-23. ↗

Lane, WS., Scales, SJ., Wen, X., Chih, B., Jackson, PK., Nelson, CD. et al. (2010). TULP3 bridges the IFT-A complex and membrane phosphoinositides to promote trafficking of G protein-coupled receptors into primary cilia. *Genes Dev., 24*, 2180-93. ↗

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Salic, A., Lopez, LV., Tukachinsky, H. (2010). A mechanism for vertebrate Hedgehog signaling: recruitment to cilia and dissociation of SuFu-Gli protein complexes. *J. Cell Biol., 191*, 415-28. ↗

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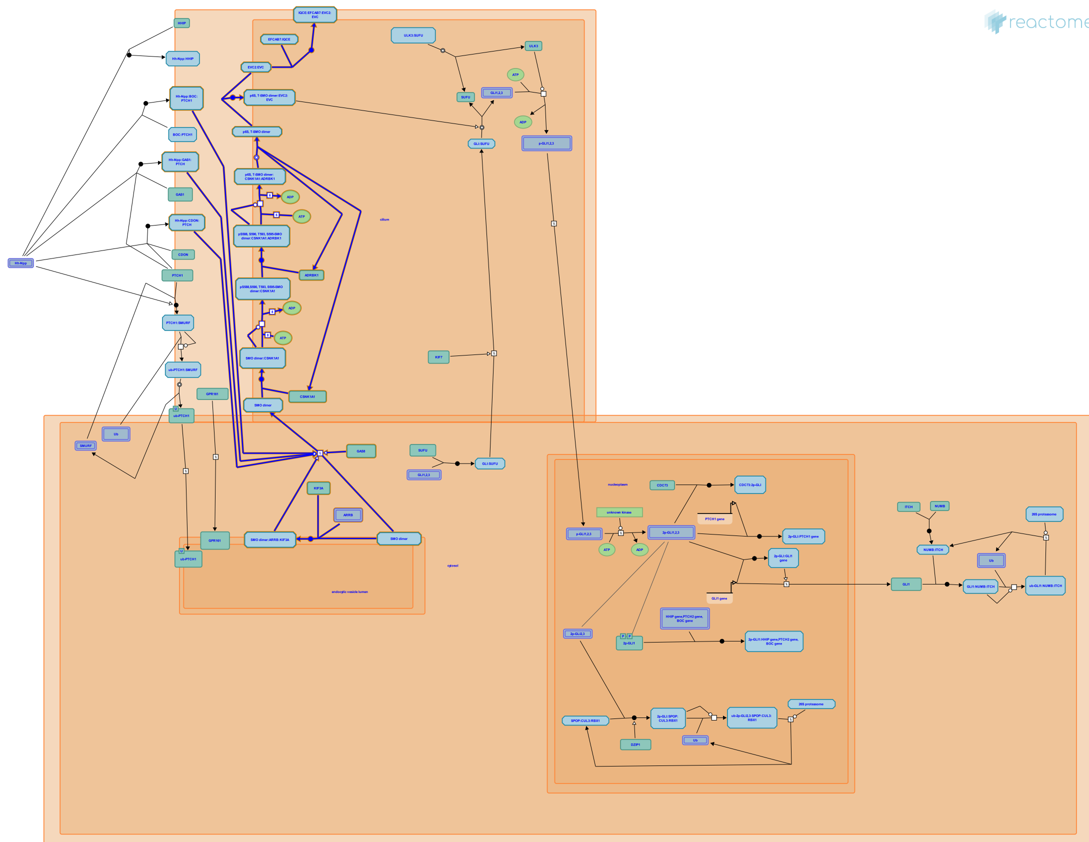
Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

Activation of SMO ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635838



Activation of the transmembrane protein SMO in response to Hh stimulation is a major control point in the Hh signaling pathway (reviewed in Ayers and Therond, 2010; Jiang and Hui, 2008). In the absence of ligand, SMO is inhibited in an unknown manner by the Hh receptor PTCH. PTCH regulates SMO in a non-stoichiometric manner and there is little evidence that endogenous PTCH and SMO interact directly (Taipale et al, 2002; reviewed in Huangfu and Anderson, 2006). PTCH may regulate SMO activity by controlling the flux of sterol-related SMO agonists and/or antagonists, although this has not been fully substantiated (Khaliullina et al, 2009; reviewed in Rohatgi and Scott, 2007; Briscoe and Therond, 2013).

PTCH-mediated inhibition of SMO is relieved upon ligand stimulation of PTCH, but the mechanisms for this relief are again unknown. SMO and PTCH appear to have opposing localizations in both the 'off' and 'on' state, with PTCH exiting and SMO entering the cilium upon Hh pathway activation (Denef et al, 2000; Rohatgi et al, 2007; reviewed in Goetz and Anderson, 2010; Hui and Angers, 2011). Activation of SMO involves a conserved phosphorylation-mediated conformational change in the C-terminal tails that destabilizes an intramolecular interaction and promotes the interaction between adjacent tails in the SMO dimer. In Drosophila, this phosphorylation is mediated by PKA and CK1, while in vertebrates it appears to involve ADRBK1/GRK2 and CSNK1A1. Sequential phosphorylations along multiple serine and threonine motifs in the SMO C-terminal tail appear to allow a graded response to Hh ligand concentration in both flies and vertebrates (Zhao et al, 2007; Chen et al, 2010; Chen et al, 2011). In flies, Smo C-terminal tail phosphorylation promotes an association with the Hedgehog signaling complex (HSC) through interaction with the scaffolding kinesin-2 like protein Cos2, activating the Fu kinase and ultimately releasing uncleaved Ci from the complex (Zhang et al, 2005; Ogden et al, 2003; Lum et al, 2003; reviewed in Mukhopadhyay and Rohatgi, 2014). In vertebrates, SMO C-terminal tail phosphorylation and conformational change is linked to its KIF7-dependent ciliary accumulation (Chen et al, 2011; Zhao et al, 2007; Chen et al, 2010). In the cilium, SMO is restricted to a transition-zone proximal region known as the EvC zone (Yang et al, 2012; Blair et al, 2011; Pusapati et al, 2014; reviewed in Eggenschwiler 2012). Both SMO phosphorylation and its ciliary localization are required to promote the Hh-dependent dissociation of the GLI:SUFU complex, ultimately allowing full-length GLI transcription factors to translocate to the nucleus to activate Hh-responsive genes (reviewed in Briscoe and Therond, 2013).

Literature references

Yang, C., Chen, W., Jiang, J., Chen, Y. (2012). Smoothened transduces Hedgehog signal by forming a complex with Evc/Evc2. *Cell Res., 22*, 1593-604. ↗

Cooper, MK., Maiti, T., Beachy, PA., Taipale, J. (2002). Patched acts catalytically to suppress the activity of Smoothened. *Nature, 418*, 892-7. ↗

Yue, T., Jia, J., Ma, G., Sasai, N., Briscoe, J., Jiang, J. et al. (2011). Sonic Hedgehog dependent phosphorylation by CK1? and GRK2 is required for ciliary accumulation and activation of smoothened. *PLoS Biol., 9*, e1001083. ↗

Tong, C., Wang, G., Zhang, W., Zhao, Y., Wang, B., Jiang, J. et al. (2005). Hedgehog-regulated Costal2-kinase complexes control phosphorylation and proteolytic processing of Cubitus interruptus. *Dev Cell, 8*, 267-78. ↗

Hui, CC., Angers, S. (2011). Gli proteins in development and disease. *Annu. Rev. Cell Dev. Biol., 27*, 513-37. ↗

Editions

2014-10-30	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

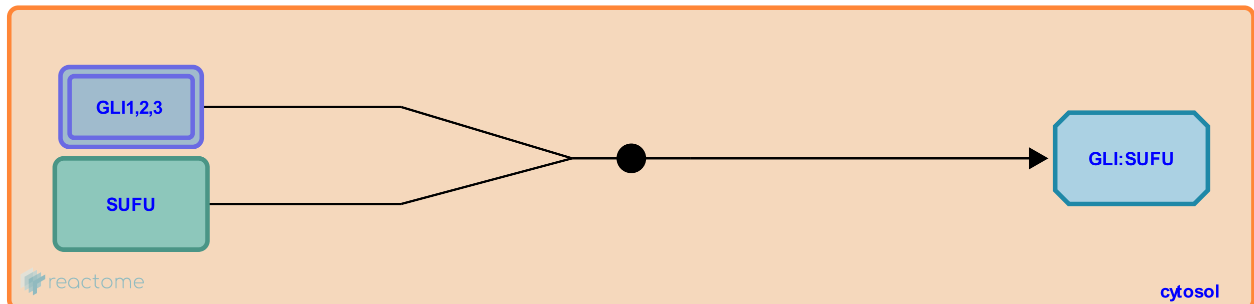
GLI proteins bind SUFU ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5610723

Type: binding

Compartments: cytosol



Vertebrate SUFU plays a critical role in the negative regulation of Hh signaling in the absence of ligand. Disruption of SUFU causes constitutive activation of the pathway, and is associated with the development of medulloblastoma in humans (Cooper et al, 2005; Svard et al, 2006; Taylor et al, 2002; Pastorino et al, 2009). SUFU binds directly to all three GLI proteins (Pearse et al, 1999; Stone et al, 1999; Jia et al, 2009; Svard et al, 2006). Formation of a SUFU:GLI complex is required for the processing of GLI3 to the GLI3R repressor form, and the processing depends on transit through the primary cilia (Kise et al, 2009; Humke et al, 2010; Huangfu and Anderson, 2005). Despite this, primary cilia are not required for SUFU to inhibit GLI activity; SUFU may also serve in a cilia-independent manner to sequester the full-length protein in the cytoplasm in the absence of Hh signal (Chen et al, 2009; Humke et al, 2010; Jia et al, 2009; Tukachinsky et al, 2010). After processing, GLI3R dissociates from SUFU and its activity is SUFU-independent (Humke et al, 2010; Tukachinsky et al, 2010). Nuclear SUFU may also play a direct role as a transcriptional co-repressor through interaction with the N-terminal DNA-binding domain of GLI proteins, though this remains to be fully elaborated (Monnier et al, 1998; Pearse et al, 1999; Cheng and Bishop, 2002; Paces-Fessy et al, 2004; Dunaeva et al, 2003; Szczepny et al, 2014).

Followed by: GLI:SUFU translocates to the ciliary tip in response to Hh signaling

Literature references

Gajewska, K., Kaur, G., Wagstaff, KM., Wang, C., Loveland, KL., Ly-Huynh, J. et al. (2014). Overlapping binding sites for importin ?1 and suppressor of fused (SuFu) on glioma-associated oncogene homologue 1 (Gli1) regulate its nuclear localization. *Biochem. J., 461*, 469-76. ↗

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Zeng, H., Liu, A., Kolterud, A., Toftgård, R., Hoover, A., Jia, J. et al. (2009). Suppressor of Fused inhibits mammalian Hedgehog signaling in the absence of cilia. *Dev. Biol., 330*, 452-60. ↗

Bishop, JM., Cheng, SY. (2002). Suppressor of Fused represses Gli-mediated transcription by recruiting the SAP18-mSin3 corepressor complex. *Proc. Natl. Acad. Sci. U.S.A., 99*, 5442-7. ↗

Kogerman, P., Toftgard, R., Dunaeva, M., Michelson, P. (2003). Characterization of the physical interaction of Gli proteins with SUFU proteins. *J. Biol. Chem., 278*, 5116-22. ↗

Editions

2014-05-07	Authored	Rothfels, K.
2014-07-25	Edited	Gillespie, ME.
2014-08-01	Reviewed	Liu, Y C.

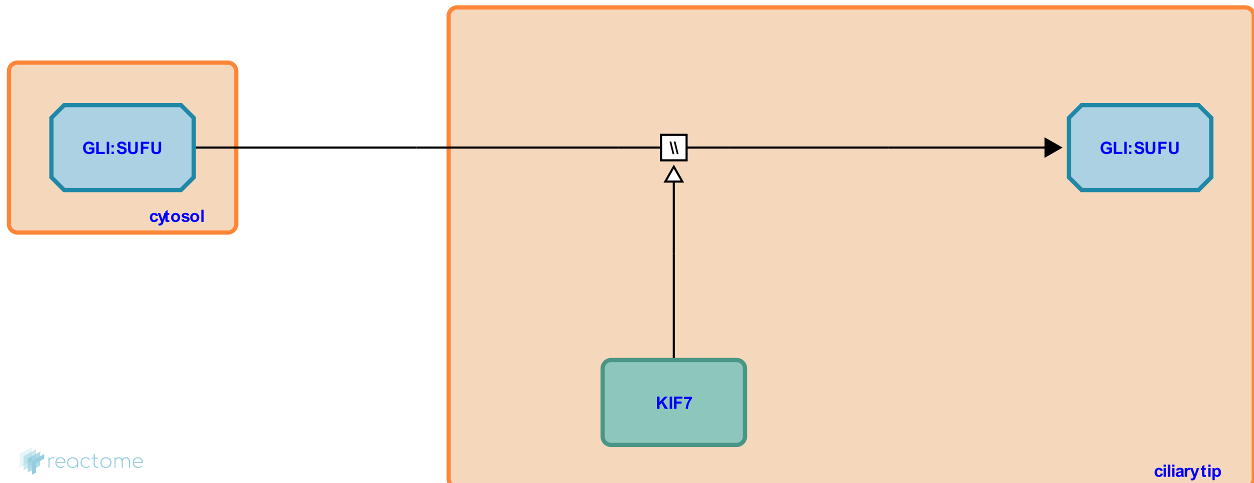
GLI:SUFU translocates to the ciliary tip in response to Hh signaling ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635860

Type: omitted

Compartments: ciliary tip



Activation of the Hh pathway causes the GLI:SUFU complex to concentrate in the primary cilium (Humke et al, 2010; Tukachinsky et al, 2010; Kim et al, 2009). The net movement of the GLI:SUFU complex into the cilium occurs downstream of SMO phosphorylation and activation, and requires the Cos2 homologue KIF7, but how the signal is transmitted from the SMO:EVC complex is not clear (Chen et al, 2009; Chen et al, 2010; Pusapati et al, 2013; Endoh-Yamagami et al, 2009; Liem et al, 2009; Cheung et al, 2009). SUFU appears to be a major regulator of the ratio of full length:repressor forms of GLI proteins in vertebrate cells, and the GLI:SUFU interaction is required for the production of GLIR. Dissociation of the GLI:SUFU complex after ligand stimulation diverts GLI from the degradation pathway and allows the full-length form to be activated (Humke et al, 2010; Tukachinsky et al, 2010; Pan et al, 2006; Kim et al, 209; Wen et al, 2010; Chen et al, 2009; reviewed in Briscoe and Therond, 2013). This represents another major point of divergence between the fly and the vertebrate Hh pathways. In Drosophila, absence of SUFU has no effect on Hh signaling, and the scaffolding protein Cos2 may play the key inhibitory role (Varjosalo et al, 2006; reviewed in Briscoe and Therond, 2013).

Preceded by: GLI proteins bind SUFU

Followed by: GLI:SUFU dissociates

Literature references

Yue, T., Jia, J., Ma, G., Sasai, N., Briscoe, J., Jiang, J. et al. (2011). Sonic Hedgehog dependent phosphorylation by CK1? and GRK2 is required for ciliary accumulation and activation of smoothened. *PLoS Biol.*, *9*, e1001083. ↗

Theunissen, JW., Scales, SJ., Phamluong, K., Endoh-Yamagami, S., Wen, X., Wilson, D. et al. (2009). The mammalian Cos2 homolog Kif7 plays an essential role in modulating Hh signal transduction during development. *Curr. Biol.*, *19*, 1320-6. ↗

Kim, J., Kato, M., Beachy, PA. (2009). Gli2 trafficking links Hedgehog-dependent activation of Smoothened in the primary cilium to transcriptional activation in the nucleus. *Proc. Natl. Acad. Sci. U.S.A.*, *106*, 21666-71. ↗

Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol.*, *30*, 1910-22. ↗

Li, SP., Varjosalo, M., Taipale, J. (2006). Divergence of hedgehog signal transduction mechanism between Drosophila and mammals. *Dev. Cell*, *10*, 177-86. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

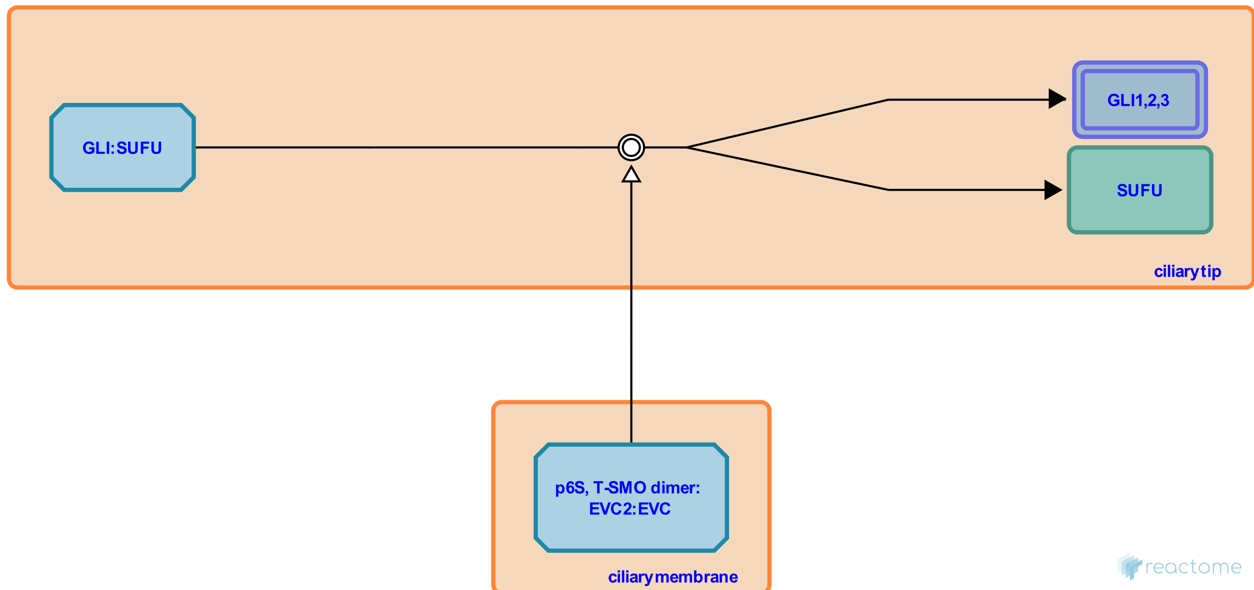
GLI:SUFU dissociates ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635859

Type: dissociation

Compartments: ciliary tip



Hh signaling promotes the dissociation of the GLI:SUFU complex in the cilium downstream of SMO activation (Humke et al, 2010; Tukachinsky et al, 2010). This appears to divert the transcription factors away from the partial processing/degradation pathway and allow the full-length forms to translocate to the nucleus where they are converted to labile transcriptional activators (Humke et al, 2010; Tukachinsky et al, 2010; Pan et al, 2006; Kim et al, 2009). How the Hh signal is transmited from SMO to promote the dissociation of the GLI:SUFU complex is not clear, however it may involve changes in PKA activity as a result of lowered cAMP levels upon pathway stimulation. (Tukachinsky et al, 2010; Wen et al, 2010; Tuson et al, 2011; Barzi et al, 2010; reviewed in Briscoe and Therond, 2013). GPR161, which localizes to the cilium in a TULP3-dependent manner and which increases cAMP levels in the absence of ligand, is cleared from the cilium upon pathway activation, and deletion of GPR161 increases Hh-dependent signaling (Mukhopadhyay et al, 2010; Mukhopadhyay et al, 2013). These data suggest that removal of ciliary GPR161 upon Hh stimulation may contribute to pathway activity by downregulating PKA activity through cAMP levels (reviewed in Mukhopadhyay and Rohatgi, 2014).

Preceded by: GLI:SUFU translocates to the ciliary tip in response to Hh signaling

Followed by: ULK3 phosphorylates GLI

Literature references

Kim, J., Kato, M., Beachy, PA. (2009). Gli2 trafficking links Hedgehog-dependent activation of Smoothened in the primary cilium to transcriptional activation in the nucleus. *Proc. Natl. Acad. Sci. U.S.A., 106*, 21666-71. ↗

Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol., 30*, 1910-22. ↗

Tuson, M., He, M., Anderson, KV. (2011). Protein kinase A acts at the basal body of the primary cilium to prevent Gli2 activation and ventralization of the mouse neural tube. *Development, 138*, 4921-30. ↗

Scales, SJ., Wen, X., Rangell, L., Jackson, PK., Loktev, A., Mukhopadhyay, S. et al. (2013). The ciliary G-protein-coupled receptor Gpr161 negatively regulates the Sonic hedgehog pathway via cAMP signaling. *Cell, 152*, 210-23. ↗

Pan, Y., Bai, CB., Wang, B., Joyner, AL. (2006). Sonic hedgehog signaling regulates Gli2 transcriptional activity by suppressing its processing and degradation. *Mol. Cell. Biol., 26*, 3365-77. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

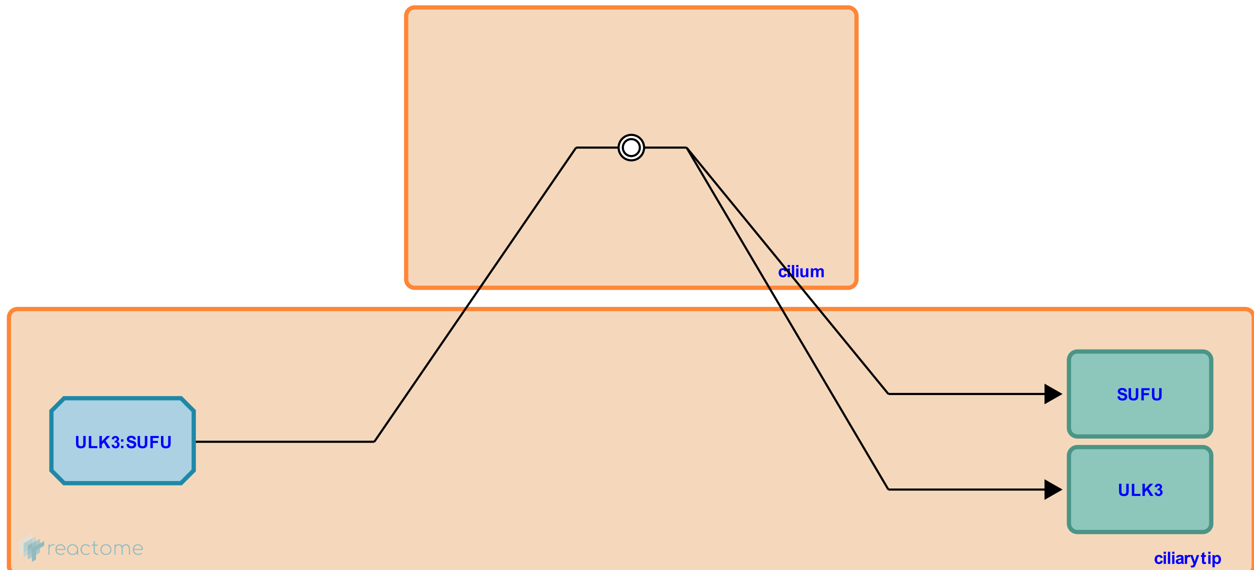
ULK3:SUFU dissociates ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635839

Type: dissociation

Compartments: cilium



ULK3 is a serine-threonine kinase that was identified as a positive regulator of Hh signaling that regulates GLI activity by phosphorylating the full-length form (Maloverjan et al, 2010a). In the absence of Hh ligand, ULK3 forms a complex with SUFU that restricts its kinase activity (Maloverjan et al, 2010b). Upon Hh stimulation, the ULK3:SUFU complex dissociates, allowing ULK3 to phosphorylate the full-length GLI proteins and promoting their activation and nuclear localization (Maloverjan et al, 2010a; Maloverjan et al, 2010b). ULK3 is related by sequence to the vertebrate kinase STK36, homologue to Drosophila Fused (Fu). While Fu plays a critical role in propagating Hh signal and is part of the Hedgehog signaling complex (HSC), STK36 is not required for Hh signaling in vertebrate cells but instead contributes to the formation of motile cilia (Wilson et al, 2009; reviewed in Briscoe and Therond, 2013; Maloverjan and Piirsoo, 2012).

Followed by: ULK3 phosphorylates GLI

Literature references

Piirsoo, M., Maloverjan, A. (2012). Mammalian homologues of Drosophila fused kinase. *Vitam. Horm.*, *88*, 91-113. ↗

Huang, J., Chen, JN., Chuang, PT., Gacayan, R., Yang, JH., Nguyen, CT. et al. (2009). Fused has evolved divergent roles in vertebrate Hedgehog signalling and motile ciliogenesis. *Nature*, *459*, 98-102. ↗

Kogerman, P., Kasak, L., Piirsoo, M., Maloverjan, A., Østerlund, T., Peil, L. (2010). Dual function of UNC-51-like kinase 3 (Ulk3) in the Sonic hedgehog signaling pathway. *J. Biol. Chem.*, *285*, 30079-90. ↗

Thérond, PP., Briscoe, J. (2013). The mechanisms of Hedgehog signalling and its roles in development and disease. *Nat. Rev. Mol. Cell Biol.*, *14*, 416-29. ↗

Kogerman, P., Osterlund, T., Piirsoo, M., Maloverjan, A., Michelson, P. (2010). Identification of a novel serine/threonine kinase ULK3 as a positive regulator of Hedgehog pathway. *Exp. Cell Res.*, *316*, 627-37. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

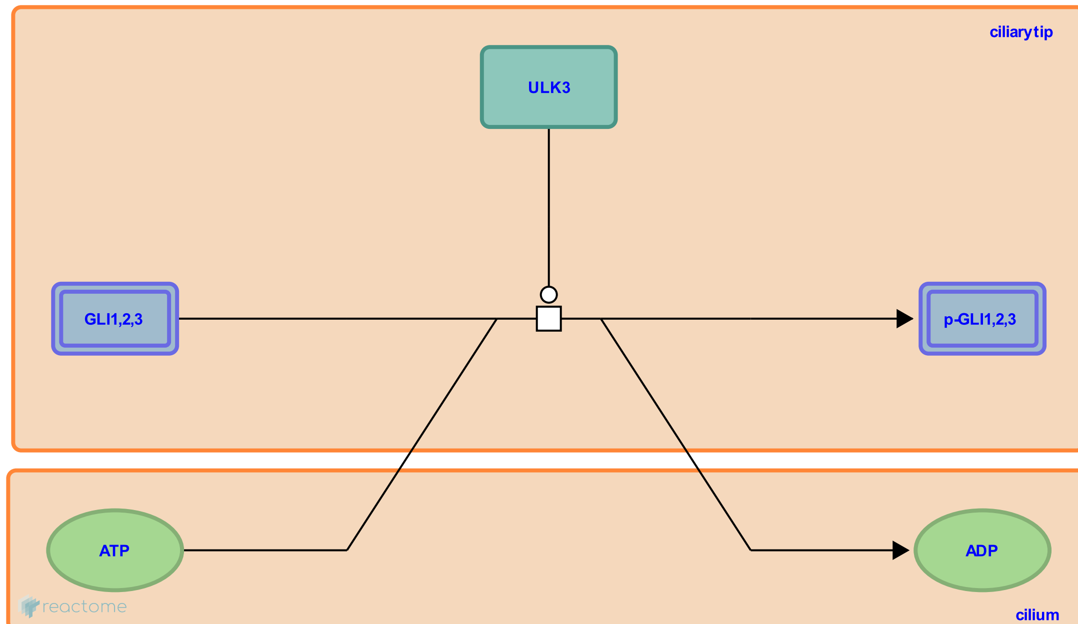
ULK3 phosphorylates GLI ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635842

Type: transition

Compartments: ciliary tip



Dissociation from SUFU allows the STK36/dFu homologue ULK3 to phosphorylate full-length GLI proteins. Phosphorylation promotes the nuclear translocation of the proteins and stimulates the transcription factor activity as assessed by a GLI-responsive reporter gene. In vitro, ULK3 phosphorylates GLI2 with the highest efficiency, but the kinase is also able to phosphorylate GLI1 and GLI3 (Maloverjan et al, 2010a; Maloverjan et al, 2010b). ULK3 is only one of a number of kinases that have been implicated in the regulation of GLI proteins in response to pathway stimulation, and how all the putative regulators interact to control GLI transcriptional activity remains to be elucidated (Evangelista et al, 2008; Mao et al, 2002; Varjosalo et al, 2008; reviewed in Marjosalo and Piirsoo, 2012).

Preceded by: ULK3:SUFU dissociates, GLI:SUFU dissociates

Followed by: GLI translocates to the nucleus

Literature references

Davis, DP., Ye, W., Ashique, A., Parker, L., Lee, J., Evangelista, M. et al. (2008). Kinome siRNA screen identifies regulators of ciliogenesis and hedgehog signal transduction. *Sci Signal, 1*, ra7. ↗

Wu, G., Kogerman, P., Maye, P., Tejedor, FJ., Xie, W., Mao, J. et al. (2002). Regulation of Gli1 transcriptional activity in the nucleus by Dyrk1. *J. Biol. Chem., 277*, 35156-61. ↗

Piirsoo, M., Maloverjan, A. (2012). Mammalian homologues of Drosophila fused kinase. *Vitam. Horm., 88*, 91-113. ↗

Kogerman, P., Kasak, L., Piirsoo, M., Maloverjan, A., Østerlund, T., Peil, L. (2010). Dual function of UNC-51-like kinase 3 (Ulk3) in the Sonic hedgehog signaling pathway. *J. Biol. Chem., 285*, 30079-90. ↗

Mechler, BM., Wu, W., Li, M., Marhold, J., Niehrs, C., Stannek, P. et al. (2002). Kremen proteins are Dickkopf receptors that regulate Wnt/beta-catenin signalling. *Nature, 417*, 664-7. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

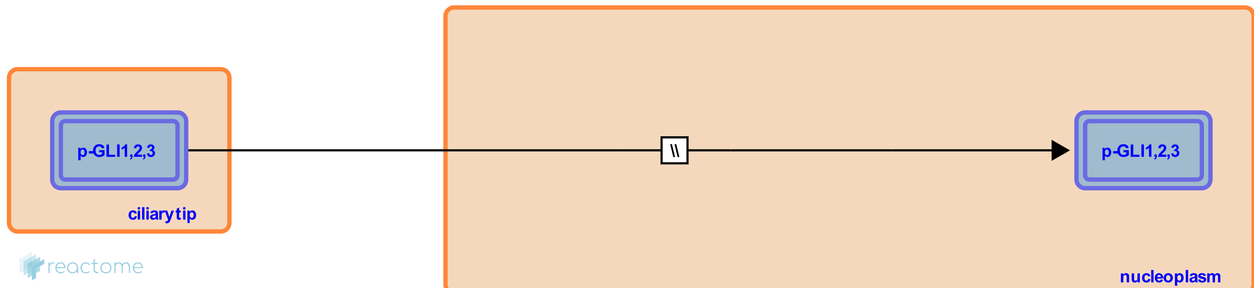
GLI translocates to the nucleus ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635843

Type: omitted

Compartments: nucleoplasm, ciliary tip



Activation of SMO downstream of Hh ligand binding results in the dissociation of the SUFU:GLI complex and the translocation of the full-length GLI proteins to the nucleus where it is converted to a short-lived transcriptionally active form (Pan et al, 2006; Kim et al, 2009; Wen et al, 2010; Humke et al, 2010; Tukachinsky et al, 2010; reviewed in Briscoe and Therond, 2013).

Preceded by: ULK3 phosphorylates GLI

Followed by: GLI proteins are phosphorylated

Literature references

Kim, J., Kato, M., Beachy, PA. (2009). Gli2 trafficking links Hedgehog-dependent activation of Smoothened in the primary cilium to transcriptional activation in the nucleus. *Proc. Natl. Acad. Sci. U.S.A., 106*, 21666-71. ↗

Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol., 30*, 1910-22. ↗

Pan, Y., Bai, CB., Wang, B., Joyner, AL. (2006). Sonic hedgehog signaling regulates Gli2 transcriptional activity by suppressing its processing and degradation. *Mol. Cell. Biol., 26*, 3365-77. ↗

Thérond, PP., Briscoe, J. (2013). The mechanisms of Hedgehog signalling and its roles in development and disease. *Nat. Rev. Mol. Cell Biol., 14*, 416-29. ↗

Milenkovic, L., Rohatgi, R., Scott, MP., Humke, EW., Dorn, KV. (2010). The output of Hedgehog signaling is controlled by the dynamic association between Suppressor of Fused and the Gli proteins. *Genes Dev., 24*, 670-82. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

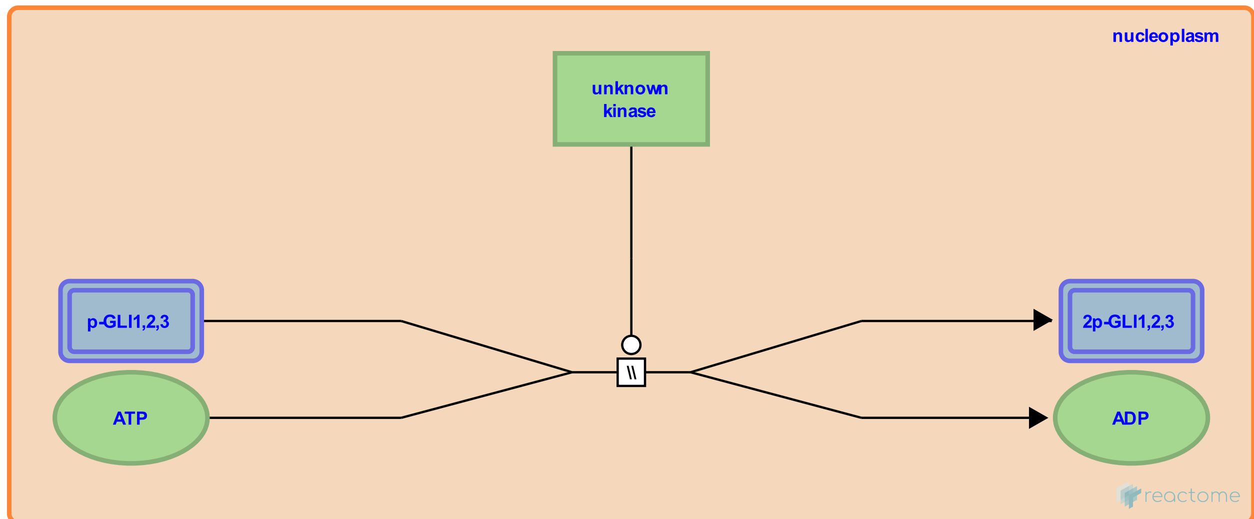
GLI proteins are phosphorylated ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635841

Type: omitted

Compartments: nucleoplasm



Hh signaling induces phosphorylation of full-length GLI that coincides with its nuclear localization and transcription factor activity (Humke et al, 2010; reviewed in Hui and Angers, 2011). Although this is depicted as occuring in the nucleus, the identity and location of the kinase(s) is not definitively known, nor is the ordering of the phosphorylation and translocation events (Wen et al, 2010; Humke et al, 2010; reviewed in Hui and Angers, 2011). Both cytoplasmic/ciliary and nuclear full-length GLI proteins are likely subject to phosphorylation, and the interaction between the numerous regulatory events is not clear. CDC2L1 was identified as a kinase that positively regulates Hh pathway activity, and it was shown to bind SUFU and promote the dissociation of the GLI1:SUFU complex in a kinase-dependent manner in mouse, but it has not been implicated in the phosphorylation of the GLI transcription factors themselves (Evangelista et al, 2008). ULK3 is another kinase that positively regulates Hh signaling and has been proposed to phosphorylate GLI proteins to promote their transcriptional activity (Maloverjan et al, 2010a; Maloverjan et al, 2010b; reviewed in Maloverjan and Piirsoo, 2012). DYRK family kinases are also implicated in the post-transcriptional regulation of the GLI proteins in both a positive and a negative manner (Mao et al, 2002; Lauth et al, 2010; Varjosalo et al, 2008).
Once in the nucleus, phosphorylated GLI transcription factors bind to promoters of Hh-responsive genes such as PTCH1, PTCH2, GLI1 and HHIP to activate transcription (Vokes et al, 2007; Vokes et al 2007; Lee et al, 2010; reviewed in Briscoe and Therond, 2013). The full-length transcriptionally active GLI proteins are labile and subject to SPOP-dependent proteolysis (Chen et al, 2009; Zhang et al, 2009; Wen et al, 2010).

Preceded by: GLI translocates to the nucleus

Followed by: GLI proteins bind CDC73, phosphorylated GLI proteins bind SPOP:CUL3:RBX1

Literature references

Davis, DP., Ye, W., Ashique, A., Parker, L., Lee, J., Evangelista, M. et al. (2008). Kinome siRNA screen identifies regulators of ciliogenesis and hedgehog signal transduction. *Sci Signal, 1*, ra7. ↗

Hui, CC., Angers, S. (2011). Gli proteins in development and disease. *Annu. Rev. Cell Dev. Biol., 27*, 513-37. ↗

Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol., 30*, 1910-22. ↗

Piirsoo, M., Maloverjan, A. (2012). Mammalian homologues of Drosophila fused kinase. *Vitam. Horm., 88*, 91-113. ↗

Kogerman, P., Osterlund, T., Piirsoo, M., Maloverjan, A., Michelson, P. (2010). Identification of a novel serine/threonine kinase ULK3 as a positive regulator of Hedgehog pathway. *Exp. Cell Res., 316*, 627-37. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

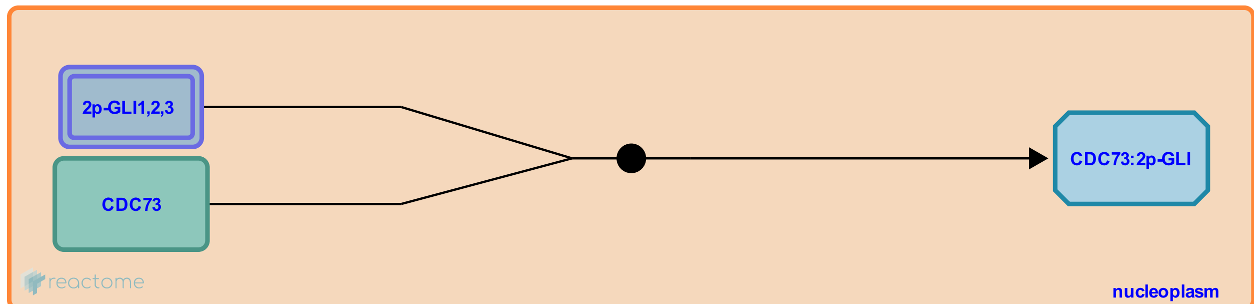
GLI proteins bind CDC73 ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635845

Type: binding

Compartments: nucleoplasm



Each of the GLI proteins can form a complex in the nucleus with CDC73, also known as Parafibromin, a component of the PAF complex (Mosimann et al, 2009). PAF1 is a conserved protein complex that affects aspects of RNA polymerase II transcription including histone modification, transcription elongation and RNA 3' end formation, among others. In humans, the PAF1 complex consists of CDC73, PAF1, LEO1, CTR9, RTF1 and WDR61 (reviewed in Tomson and Arndt, 2013). Knockdown of CDC73 in mammalian cell culture compromises GLI1- and GLI2-dependent transcriptional activation and has been shown to abrogate expression of endogenous targets in Drosophila. CDC73 interacts with the GLI proteins through the SUFU-interacting domain in region 1 of the N-terminal (Mosimann et al, 2009). Direct binding of a CDC73:GLI complex on an endogenous human target gene has not yet been demonstrated.

Preceded by: GLI proteins are phosphorylated

Literature references

Arndt, KM., Tomson, BN. (2013). The many roles of the conserved eukaryotic Paf1 complex in regulating transcription, histone modifications, and disease states. *Biochim. Biophys. Acta, 1829*, 116-26. ↗

Mosimann, C., Hausmann, G., Basler, K. (2009). The role of Parafibromin/Hyrax as a nuclear Gli/Ci-interacting protein in Hedgehog target gene control. *Mech. Dev., 126*, 394-405. ↗

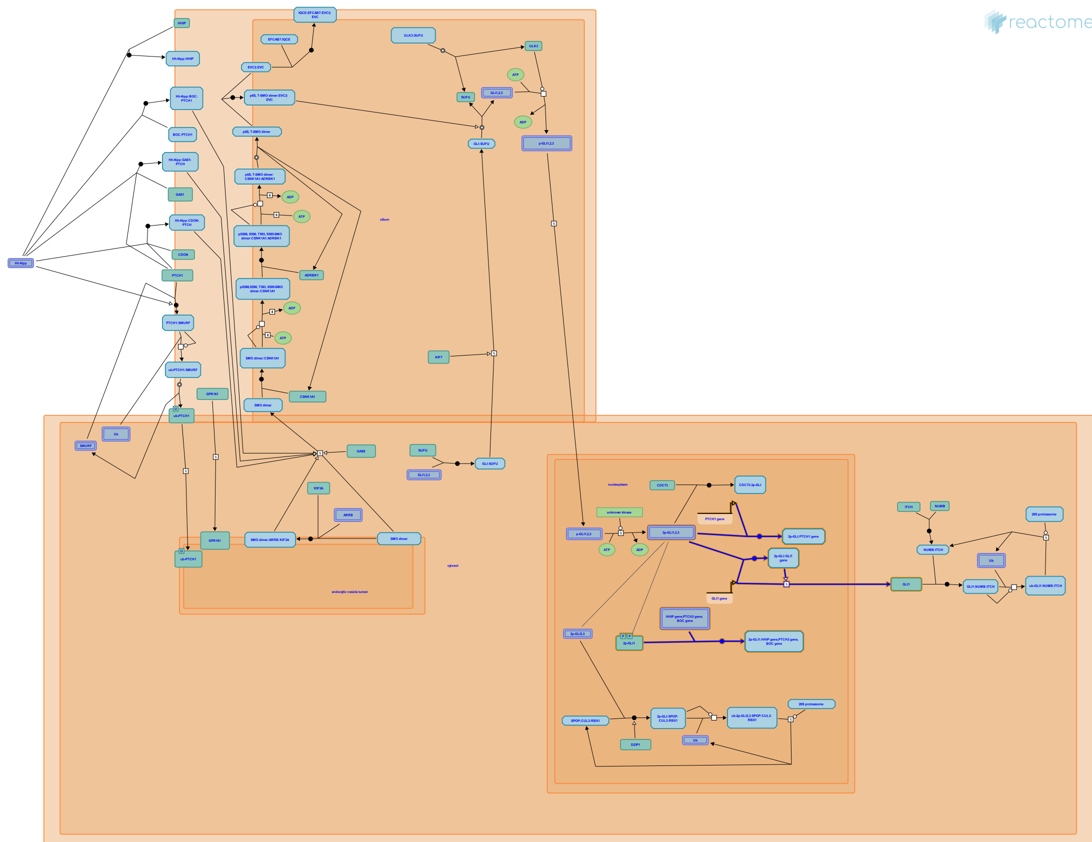
Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

GLI proteins bind promoters of Hh responsive genes to promote transcription ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635851



GLI proteins are bifunctional DNA-binding proteins that recognize consensus GLI sites 5'-GACCACCC-3' in the promoters of target genes (Kinzler and Vogelstein, 1990). Pathway induction upon ligand-binding diverts the GLI proteins from the processing/degradation pathway that generates the truncated repressor form and promotes the formation of the full-length transcriptional activator (reviewed in Hui and Angers, 2011; Briscoe and Therond, 2013). GLI-dependent target genes have been identified by a number of ChIP based screens, and well-established, direct targets include a number of Hh pathway members including PTCH1, PTCH2, GLI1, HHIP and BOC (Lee et al, 2010; Vokes et al, 2007; Vokes et al, 2008; Agren et al, 2004; Bai et al, 2004; Bai et al, 2002; Dai et al, 1999). Full-length GLI proteins nucleate the assembly of a transcriptional activation complex at target gene promoters, but the details of interacting partners are not well known. The C-terminus of GLI3 has been shown to interact with a number of transcriptional activators including the histone acetyltransferase CBP, the Mediator component Med12 and the TATA-box recognition protein TAF31, but the detail of how and when these binding partners interact is not known (Dai et al, 1999; Zhou et al, 2006; Yoon et al, 1998; reviewed in Hui and Angers, 2011). Each of the GLI proteins has been shown to bind to CDC 73, a component of the PAF complex that has roles in RNA polymerase II-mediated transcription (Mosimann et al, 2009; reviewed in Tomson and Arndt, 2013).

Literature references

Hui, CC., Angers, S. (2011). Gli proteins in development and disease. *Annu. Rev. Cell Dev. Biol., 27*, 513-37. ↗

Stephen, D., Joyner, AL., Bai, CB. (2004). All mouse ventral spinal cord patterning by hedgehog is Gli dependent and involves an activator function of Gli3. *Dev. Cell, 6*, 103-15. ↗

Ishii, S., Dai, P., Nakafuku, M., Maekawa, T., Akimaru, H., Tanaka, Y. (1999). Sonic Hedgehog-induced activation of the Gli1 promoter is mediated by GLI3. *J. Biol. Chem., 274*, 8143-52. ↗

Davidson, EH., Giles, S., Wong, WH., Longabaugh, WJ., McCuine, S., McMahon, AP. et al. (2007). Genomic characterization of Gli-activator targets in sonic hedgehog-mediated neural patterning. *Development, 134*, 1977-89. ↗

Kinzler, KW., Vogelstein, B. (1990). The GLI gene encodes a nuclear protein which binds specific sequences in the human genome. *Mol. Cell. Biol., 10*, 634-42. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

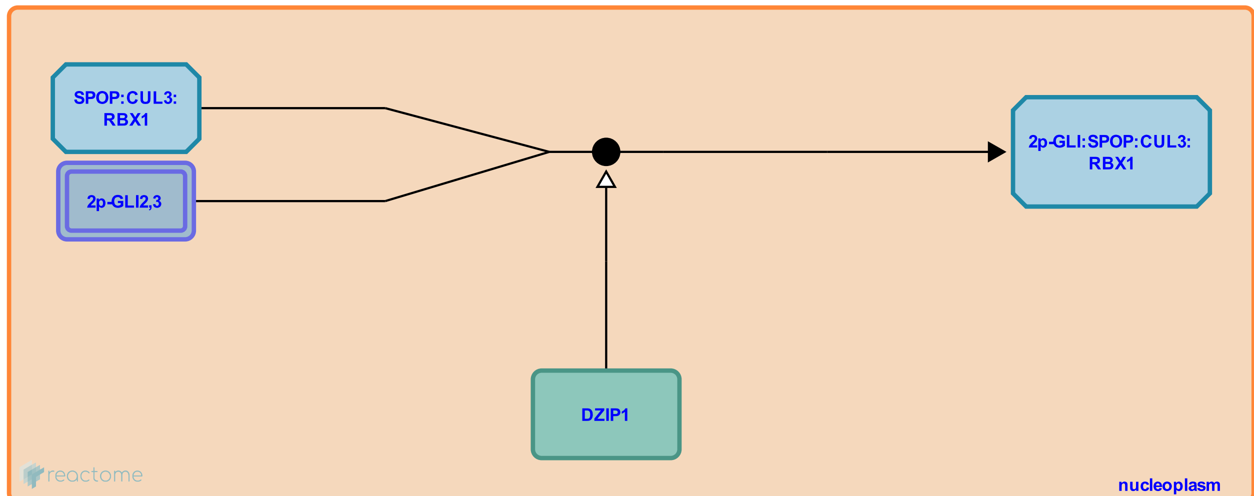
phosphorylated GLI proteins bind SPOP:CUL3:RBX1 ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635855

Type: binding

Compartments: nucleoplasm



Full-length GLI proteins are labile transcription factors that are rapidly degraded after ubiquitination by the SPOP:CUL3:RBX1 E3 ligase (Ohlmeyer et al, 1998; Humke et al, 2010; Tukachinsky et al, 2010; Chen et al, 2009; Zhang et al, 2009; Wen et al, 2010). SPOP (Speckle-type POZ protein) is the vertebrate homologue of Drosophila Hib/Roadkill, which was identified as a negative regulator of Hh signaling (Ohlmeyer et al, 1998; Zhang et al, 2006; Kent et al, 2006). SPOP/Hib proteins contain BTB and MATH domains and function as the substrate-binding component of the E3 ligase complex, where they promote oligomerization (Zhang et al, 2009; Furukawa et al, 2003; Zhuang et al, 2009). SPOP has been shown to bind to GLI2 and GLI3 through multiple serine and threonine rich motifs in the transcription factors, but direct binding to GLI1 has not been demonstrated (Cheng et al, 2009; Zhang et al, 2009).
The stability of SPOP itself is regulated in an unknown manner by DZIP1, a regulator of Hh signaling best characterized in zebrafish for its positive role in promoting ciliogenesis (Sekimizu et al, 2004; Wolff et al, 2004; Glazer et al, 2010; Kim et al, 2010; Tay et al, 2010; Wang et al, 2013). More recently, DZIP1 has also been shown to act as a negative regulator of Hh signaling by preventing the ubiquitin- and proteasome-dependent degradation of SPOP, and in this way increasing the turnover of activated GLI proteins (Jin et al, 2011; Schwend et al, 2013).

Preceded by: GLI proteins are phosphorylated

Followed by: SPOP:CUL3:RBX1 ubiquitinates GLI2,3

Literature references

Tay, SY., Wong, KN., Yu, X., Ng, CP., Roy, S., Panse, P. (2010). The iguana/DZIP1 protein is a novel component of the ciliogenic pathway essential for axonemal biogenesis. *Dev. Dyn., 239*, 527-34. ↗

Yang, J., Jia, J., Mei, W., Jin, Z., Strack, S. (2011). The antagonistic action of B56-containing protein phosphatase 2As and casein kinase 2 controls the phosphorylation and Gli turnover function of Daz interacting protein 1. *J. Biol. Chem., 286*, 36171-9. ↗

Hooper, JE., Bush, EW., Kent, D. (2006). Roadkill attenuates Hedgehog responses through degradation of Cubitus interruptus. *Development, 133*, 2001-10. ↗

Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol., 30*, 1910-22. ↗

Wang, C., Liu, A., Low, WC., Wang, B. (2013). Centrosomal protein DZIP1 regulates Hedgehog signaling by promoting cytoplasmic retention of transcription factor GLI3 and affecting ciliogenesis. *J. Biol. Chem., 288*, 29518-29. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

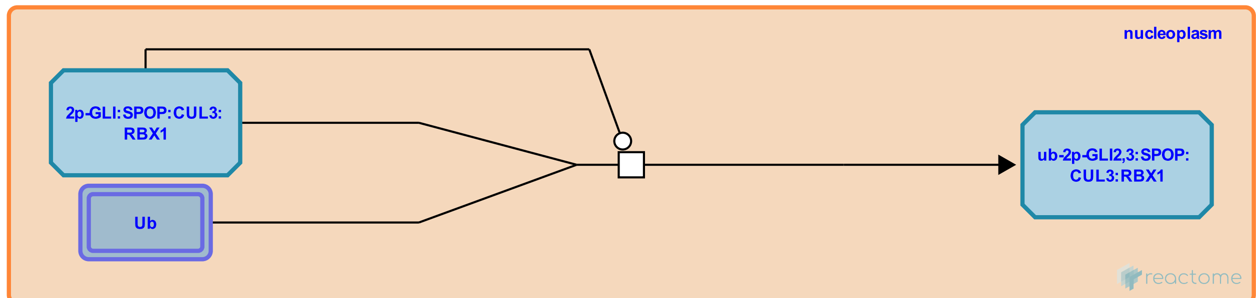
SPOP:CUL3:RBX1 ubiquitinates GLI2,3 ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635856

Type: transition

Compartments: nucleoplasm



The transcriptional activity of full-length activated Ci/GLI proteins is restricted by their rapid ubiquitin-mediated degradation after initiation of Hh signaling (Ohlmeyer et al, 1998; Humke et al, 2010; Tukachinsky et al, 2010; Wen et al, 2010). Ubiquitination of Ci, GLI2 and GLI3 is mediated by the E3 ligase complex SPOP:CUL3:RBX1, which ubiquitinates the transcription factors in a Hh-dependent manner (Zhang et al, 2006; Kent et al, 2006; Zhang et al, 2009; Chen et al, 2009).

Preceded by: phosphorylated GLI proteins bind SPOP:CUL3:RBX1

Followed by: GLI2,3 are degraded by the proteasome

Literature references

Yue, T., Li, S., Zhang, Q., Wang, B., Shi, Q., Jiang, J. et al. (2009). Multiple Ser/Thr-rich degrons mediate the degradation of Ci/Gli by the Cul3-HIB/SPOP E3 ubiquitin ligase. *Proc. Natl. Acad. Sci. U.S.A., 106*, 21191-6. ↗

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Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol., 30*, 1910-22. ↗

Ou, CY., Wang, B., Jiang, J., Chien, CT., Zhang, L., Zhang, Q. (2006). A hedgehog-induced BTB protein modulates hedgehog signaling by degrading Ci/Gli transcription factor. *Dev Cell, 10*, 719-29. ↗

Editions

2014-10-31	Edited	Gillespie, ME.
2014-10-31	Authored	Rothfels, K.
2014-11-09	Reviewed	Liu, Y C.

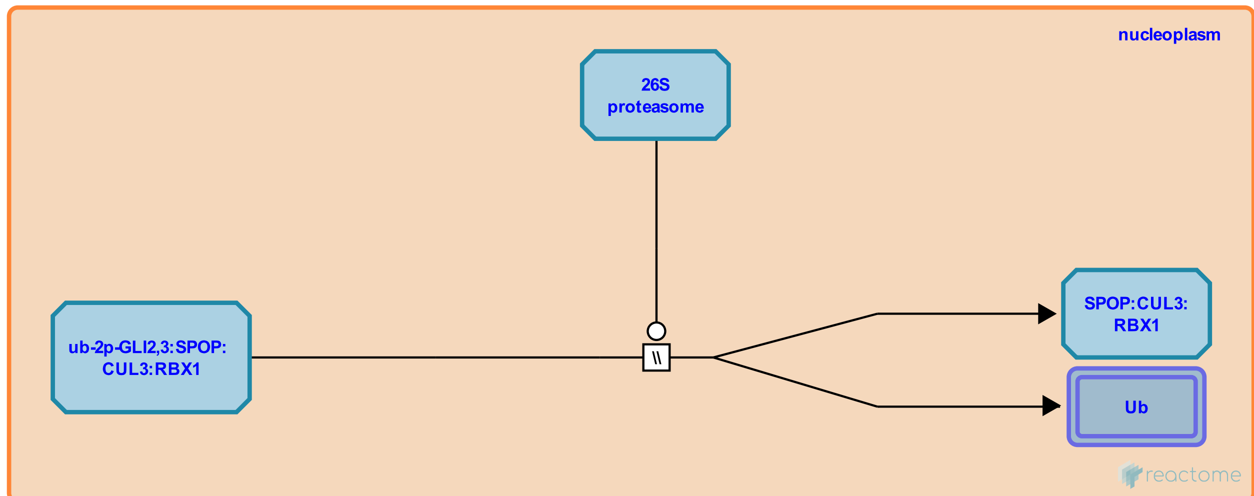
GLI2,3 are degraded by the proteasome ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635854

Type: omitted

Compartments: nucleoplasm



SPOP:CUL3:RBX1-mediated ubiquitination of the transcriptionally active GLI proteins attenuates Hh-dependent signaling by promoting their degradation by the proteasome (Zhang et al, 2009; Chen et al, 2009; Humke et al, 2010; Tukachinsky et al, 2010; Wen et al, 2010).

Preceded by: SPOP:CUL3:RBX1 ubiquitinates GLI2,3

Literature references

Yue, T., Li, S., Zhang, Q., Wang, B., Shi, Q., Jiang, J. et al. (2009). Multiple Ser/Thr-rich degrons mediate the degradation of Ci/Gli by the Cul3-HIB/SPOP E3 ubiquitin ligase. *Proc. Natl. Acad. Sci. U.S.A., 106*, 21191-6. ↗

Scales, SJ., Hongo, JA., Wen, X., Evangelista, M., Lai, CK., de Sauvage, FJ. (2010). Kinetics of hedgehog-dependent full-length Gli3 accumulation in primary cilia and subsequent degradation. *Mol. Cell. Biol., 30*, 1910-22. ↗

Li, YJ., Zhang, X., Hui, CC., Chuang, PT., Gacayan, R., Law, KK. et al. (2009). Cilium-independent regulation of Gli protein function by Sufu in Hedgehog signaling is evolutionarily conserved. *Genes Dev., 23*, 1910-28. ↗

Milenkovic, L., Rohatgi, R., Scott, MP., Humke, EW., Dorn, KV. (2010). The output of Hedgehog signaling is controlled by the dynamic association between Suppressor of Fused and the Gli proteins. *Genes Dev., 24*, 670-82. ↗

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Editions

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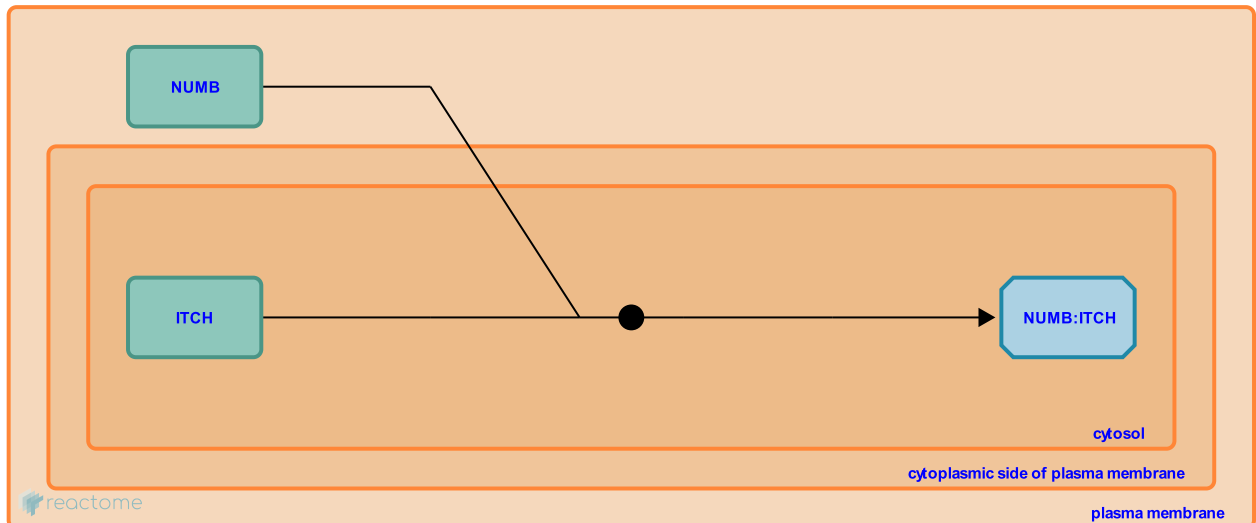
NUMB binds ITCH ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5610735

Type: binding

Compartments: cytosol



NUMB is a negative regulator of Hh signaling that acts by promoting the ITCH-dependent ubiquitination of GLI1. ITCH is an E3 ligase that is kept in an inactive conformation by an intramolecular interaction between the HECT domain and a WW motif. Binding of the adaptor protein NUMB to the WW region of ITCH displaces the HECT domain and promotes the catalytic activity of the E3 ligase (di Marcotullio et al, 2006; 2011).

Followed by: NUMB:ITCH binds GLI1

Literature references

De Smaele, E., Gulino, A., Sico, MA., Screpanti, I., Ferretti, E., Maroder, M. et al. (2006). Numb is a suppressor of Hedgehog signalling and targets Gli1 for Itch-dependent ubiquitination. *Nat. Cell Biol., 8*, 1415-23. ↗

Canettieri, G., Pietrosanti, L., Mazzà, D., Screpanti, I., Greco, A., Coni, S. et al. (2011). Numb activates the E3 ligase Itch to control Gli1 function through a novel degradation signal. *Oncogene, 30*, 65-76. ↗

Editions

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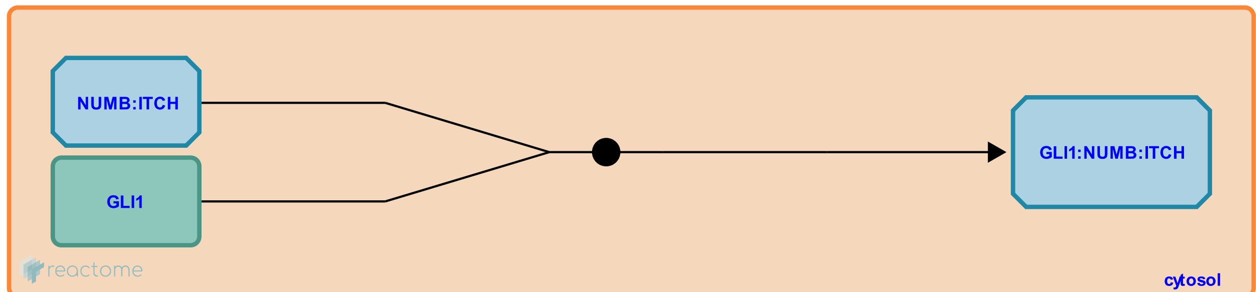
NUMB:ITCH binds GLI1 ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635861

Type: binding

Compartments: cytosol



GLI1 is recruited to the NUMB:ITCH complex through a direct interaction with both proteins. Once recruited, GLI1 is ubiquitinated by ITCH and subsequently degraded by the proteasome. ITCH-mediated degradation of GLI1 does not depend on the Dc or Dn degrons required for interaction with beta-TrCP, but instead relies on a novel PPXYs/pSP degron of GLI1 (di Marcotullio et al, 2006, 2011; Huntzicker et al, 2006).

Preceded by: NUMB binds ITCH

Followed by: NUMB:ITCH ubiquitinates GLI1

Literature references

Huntzicker, EG., Oro, AE., Estay, IS., Jackson, PK., Zhen, H., Lokteva, LA. (2006). Dual degradation signals control Gli protein stability and tumor formation. *Genes Dev., 20*, 276-81. ↗

De Smaele, E., Gulino, A., Sico, MA., Screpanti, I., Ferretti, E., Maroder, M. et al. (2006). Numb is a suppressor of Hedgehog signalling and targets Gli1 for Itch-dependent ubiquitination. *Nat. Cell Biol., 8*, 1415-23. ↗

Canettieri, G., Pietrosanti, L., Mazzà, D., Screpanti, I., Greco, A., Coni, S. et al. (2011). Numb activates the E3 ligase Itch to control Gli1 function through a novel degradation signal. *Oncogene, 30*, 65-76. ↗

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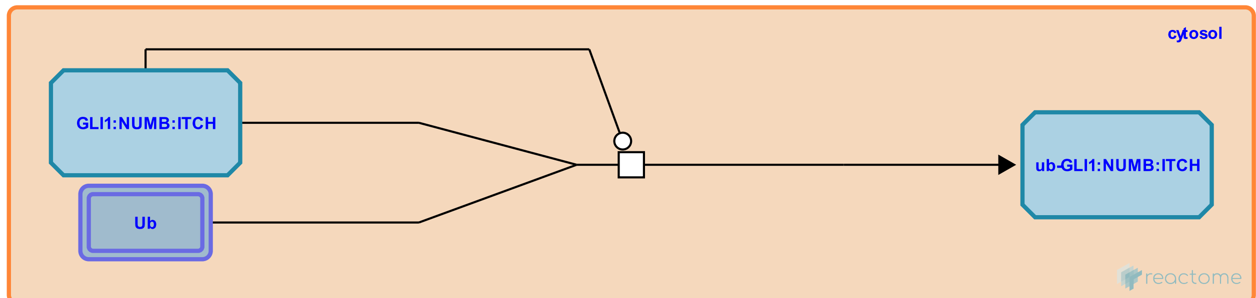
NUMB:ITCH ubiquitinates GLI1 ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635864

Type: transition

Compartments: cytosol



GLI1 is ubiquitinated by ITCH and subsequently degraded by the proteasome. ITCH-mediated degradation of GLI1 does not depend on the Dc or Dn degrons required for interaction with beta-TrCP, but instead relies on a novel PPXYs/pSP degron of GLI1 (di Marcotullio et al, 2006, 2011; Huntzicker et al, 2006).

Preceded by: NUMB:ITCH binds GLI1

Followed by: ub-GLI is degraded by the proteasome

Literature references

Huntzicker, EG., Oro, AE., Estay, IS., Jackson, PK., Zhen, H., Lokteva, LA. (2006). Dual degradation signals control Gli protein stability and tumor formation. *Genes Dev., 20*, 276-81. ↗

De Smaele, E., Gulino, A., Sico, MA., Screpanti, I., Ferretti, E., Maroder, M. et al. (2006). Numb is a suppressor of Hedgehog signalling and targets Gli1 for Itch-dependent ubiquitination. *Nat. Cell Biol., 8*, 1415-23. ↗

Canettieri, G., Pietrosanti, L., Mazzà, D., Screpanti, I., Greco, A., Coni, S. et al. (2011). Numb activates the E3 ligase Itch to control Gli1 function through a novel degradation signal. *Oncogene, 30*, 65-76. ↗

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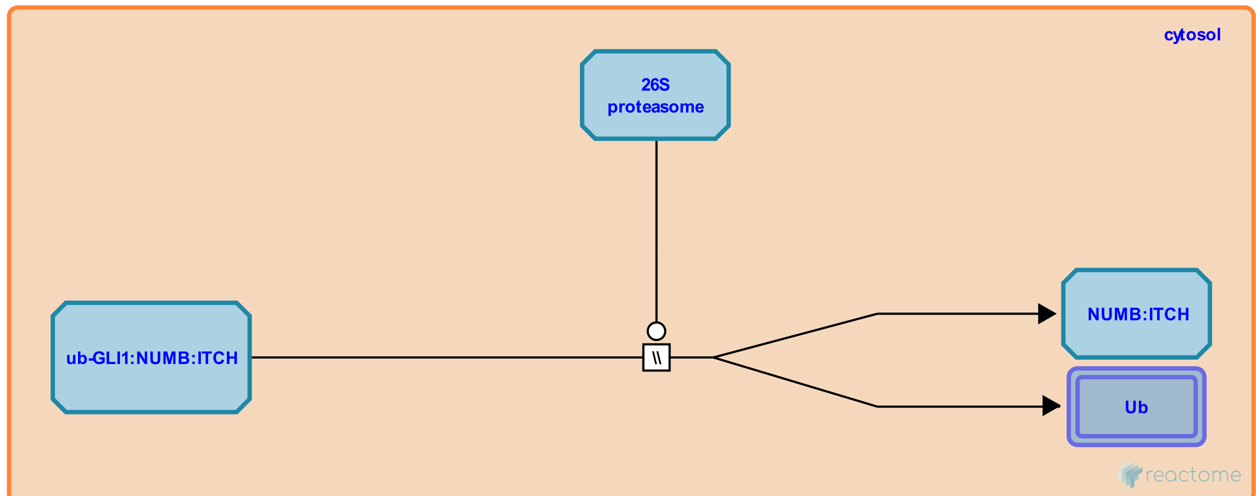
ub-GLI is degraded by the proteasome ↗

Location: Hedgehog 'on' state

Stable identifier: R-HSA-5635868

Type: omitted

Compartments: cytosol



After NUMB:ITCH-mediated ubiquitination, GLI1 is degraded by the proteasome. This degradation limits the extent and duration of the response to Hh signaling (di Marcotullio et al, 2006; Huntzicker et al, 2006; di Marcotullio et al, 2011).

Preceded by: NUMB:ITCH ubiquitinates GLI1

Literature references

Huntzicker, EG., Oro, AE., Estay, IS., Jackson, PK., Zhen, H., Lokteva, LA. (2006). Dual degradation signals control Gli protein stability and tumor formation. *Genes Dev., 20*, 276-81. ↗

De Smaele, E., Gulino, A., Sico, MA., Screpanti, I., Ferretti, E., Maroder, M. et al. (2006). Numb is a suppressor of Hedgehog signalling and targets Gli1 for Itch-dependent ubiquitination. *Nat. Cell Biol., 8*, 1415-23. ↗

Canettieri, G., Pietrosanti, L., Mazzà, D., Screpanti, I., Greco, A., Coni, S. et al. (2011). Numb activates the E3 ligase Itch to control Gli1 function through a novel degradation signal. *Oncogene, 30*, 65-76. ↗

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