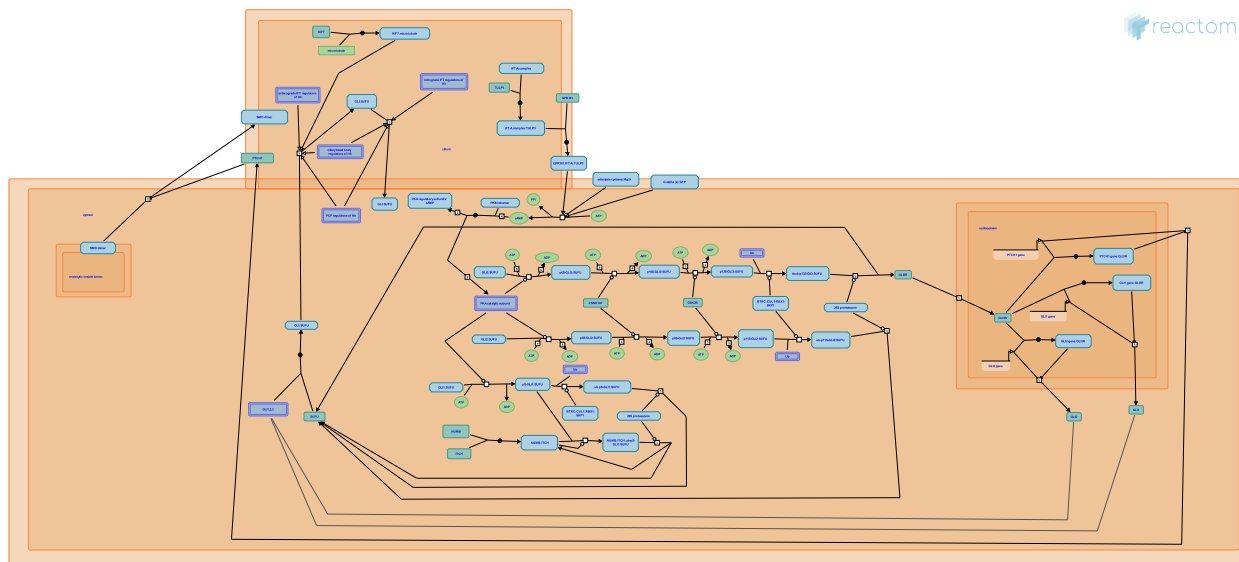


Hedgehog 'off' state



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

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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](https://reactome.org/about/reactome-textbook/).

02/05/2024

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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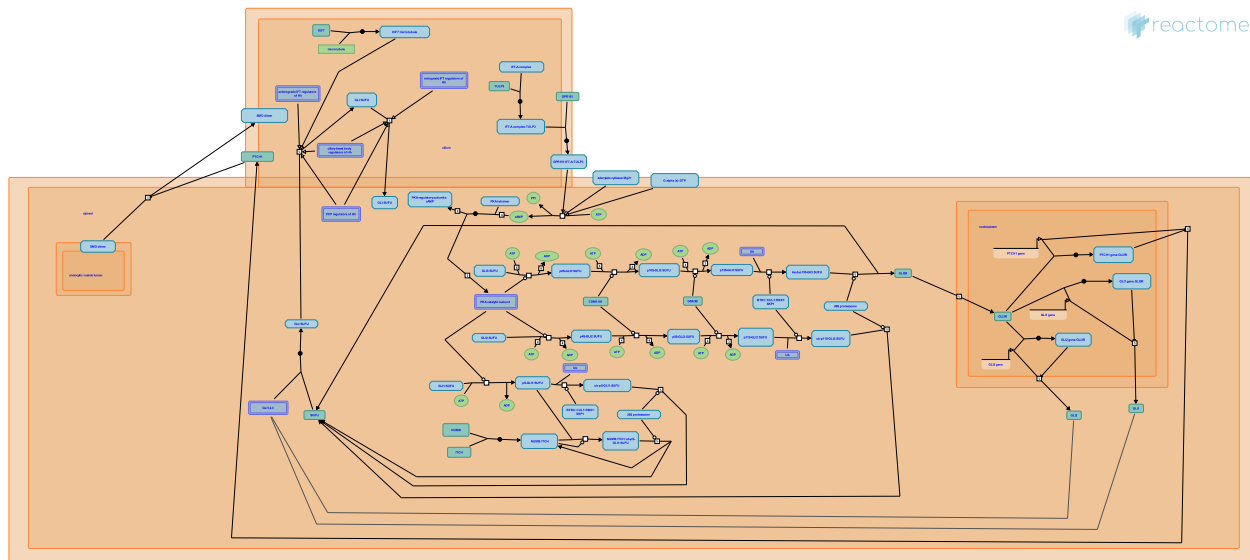
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 4 pathways and 16 reactions ([see Table of Contents](#))

Hedgehog 'off' state ↗

Stable identifier: R-HSA-5610787



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 repress 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).

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2014-08-01	Reviewed	Liu, Y C.

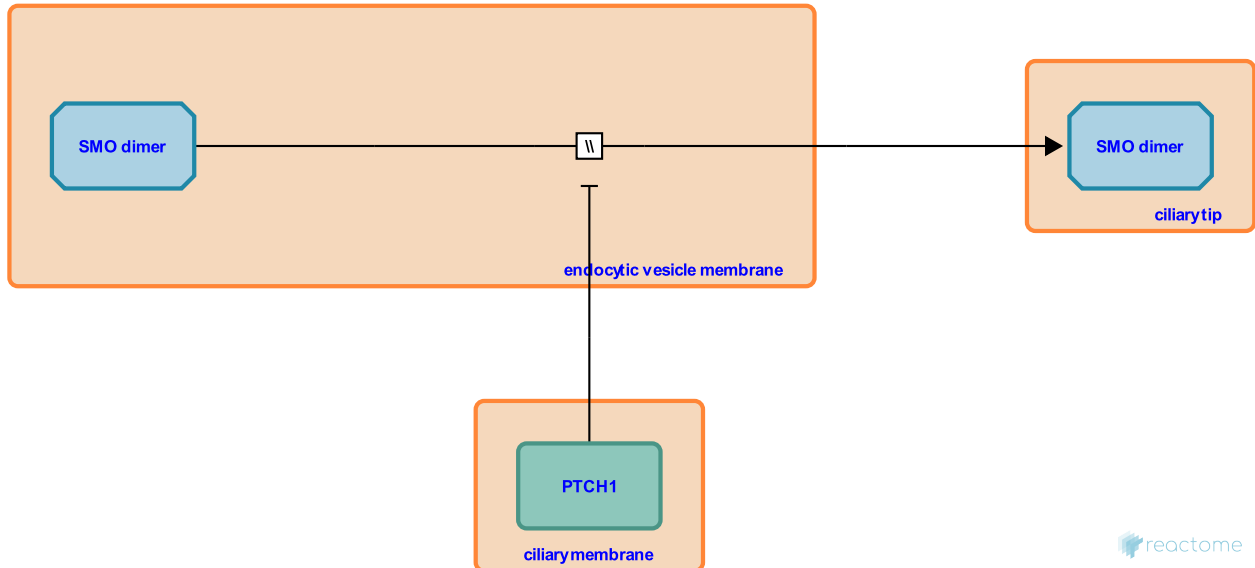
PTCH1 inhibits accumulation of SMO in the primary cilium in the absence of Hh signal ↗

Location: Hedgehog 'off' state

Stable identifier: R-HSA-5610763

Type: omitted

Compartments: endocytic vesicle membrane



In the absence of Hh ligand, the Hh receptor PTCH inhibits signaling by negatively regulating the activity of SMO, a candidate member of the GPCR superfamily that transduces the Hh signal to downstream pathway components (reviewed in Ayers and Therond, 2010; Briscoe and Therond, 2013). Neither the mechanism by which SMO activates Hh signaling nor the manner in which PTCH represses this activity are fully elucidated, but these may involve regulation of putative SMO ligand(s) or changes in cellular localization, protein conformation and phosphorylation status, among other possibilities (reviewed in Briscoe and Therond, 2013; Ayers and Therond, 2010).

PTCH is a 7 transmembrane protein that is localized to the primary cilium in the absence of Hh ligand (Rohatgi et al, 2007). 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 has a sterol sensing domain (SSD) and structural similarity to bacterial RND transporters. Mutation in conserved motifs in the RND domain abrogate the ability of PTCH to negatively regulate SMO activity (Taipale et al, 2002). The transmembrane heptahelical domain of SMO has been shown to bind to a number of natural and synthetic molecules, many of which are structurally related to sterols, and this binding can activate or repress SMO activity (Mas et al, 2010; Dwyer et al, 2007; Nachtergaele et al, 2012; Corcoran et al, 2006). Together, these data suggest a speculative model where PTCH regulates 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).

In the absence of Hh signal, SMO is largely found in intracellular vesicles, with a fraction localized to the plasma membrane (Milenkovic et al, 2009; Huangfu et al, 2006; Corbit et al, 2005; Rohatgi et al, 2007; Wang et al, 2009; Wilson et al, 2009). Like GLI2, 3 and SUFU, however, SMO may traffic through the cilium in the absence of ligand (Wilson et al, 2009; Kim et al, 2009). 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). Clearance of PTCH from the ciliary membrane in the presence of Hh is promoted by its ubiquitination by the E3 ligase SMURF (Huang et al, 2013; Yue et al, 2014).

Like the *Drosophila* homologue, vertebrate SMO appears to exist as a constitutive dimer. Dimerization is mediated by the N-terminal Cys-rich domain (CRD) and is required for function (Zhao et al, 2007). The C-terminal tail of SMO has arginine-rich clusters that appear to regulate the conformation of the tails in the dimer, maintaining the SMO dimer in an inactive state. In *Drosophila*, the inhibitory effect of the arginine-rich region is counteracted upon Hh pathway activation by PKA-mediated phosphorylation of adjacent serine residues. This promotes an open tail conformation that is required for cell surface accumulation and signaling (Zhao et al, 2007; Chen et al, 2010). These consensus PKA motifs are not conserved in the vertebrate SMO C-terminal tail, and a role for PKA-mediated phosphorylation and direct activation of SMO appears not to hold true in mammalian cells (Zhao et al, 2007; Tuson

et al, 2011). A similar activating phosphorylation of vertebrate SMO may be CK1 or GRK2-dependent (Chen et al, 2011).

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Editions

2014-07-17	Authored	Rothfels, K.
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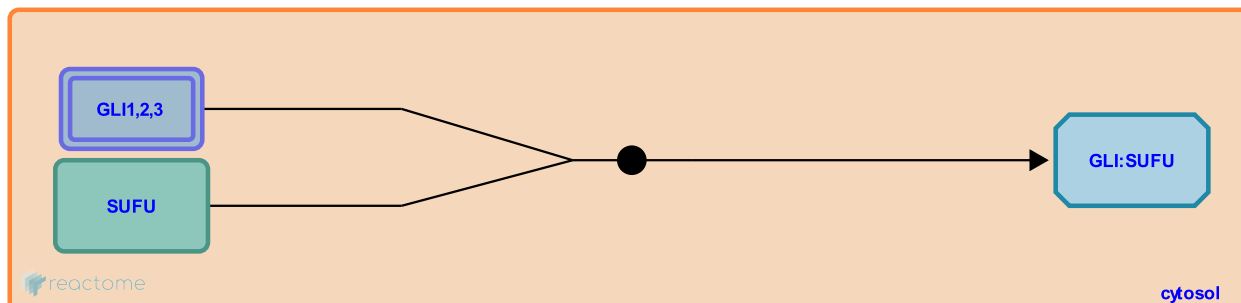
GLI proteins bind SUFU ↗

Location: [Hedgehog 'off' 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).

Preceded by: [Expression of GLI1 is repressed by GLI3R in the absence of Hh signaling](#), [Expression of GLI2 is repressed by GLI3R in the absence of Hh signaling](#)

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2014-05-07	Authored	Rothfels, K.
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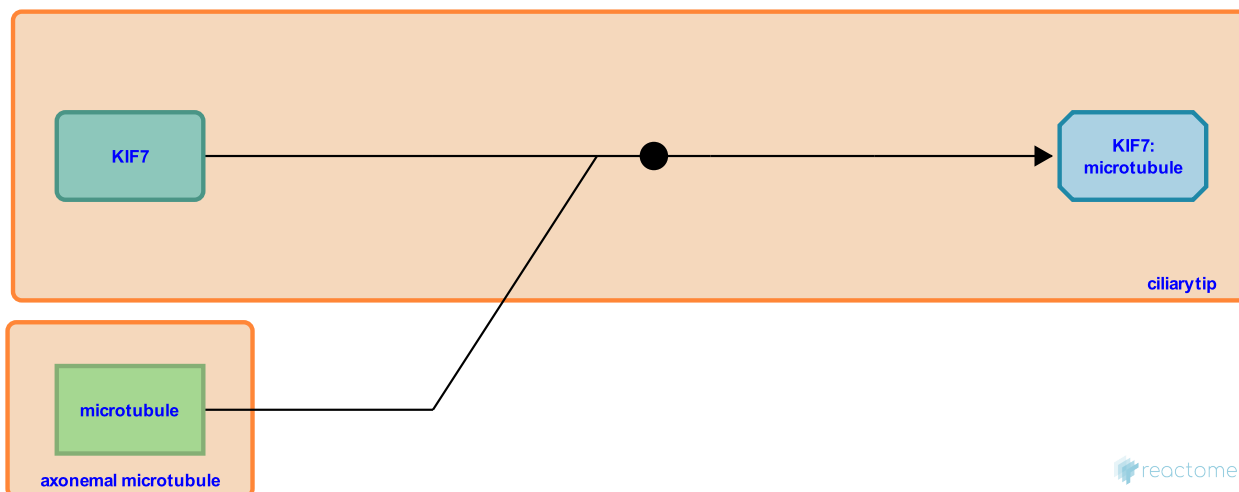
KIF7 is recruited to the ciliary tip through interaction with axonemal microtubules ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610733

Type: binding

Compartments: ciliary tip



KIF7, the human ortholog of *Drosophila* COS2, is a kinesin-4 motor protein that binds directly to the plus ends of axonemal microtubules and inhibits their growth in an ATP-dependent manner (He et al, 2014). KIF7 is required for the processing and activity of GLI in the absence of Hh signal, and KIF7 function depends on the primary cilium (Liem et al, 2009; Cheung et al, 2009; Endoh-Yamagami et al, 2009). KIF7 has been shown to bind to GLI3 and to SUFU and may act in part by promoting the transit of the GLI:SUFU complex through the primary cilium, which is required for GLI processing (Endoh-Yamagami et al, 2009; Maurya et al, 2013). How KIF7 itself is localized to the cilia tip is unknown, although localization depends on the KIF7 motor domain (Liem et al, 2009; He et al, 2014). KIF7 localization is further enhanced at the primary cilia tip in response to Hh signaling, as is also the case for GLI2, GLI3 and SUFU (He et al, 2014; Varjosalo et al, 2008; Haycraft et al, 2005; Wen et al, 2010; Qin et al, 2011; Tukachinsky et al, 2010).

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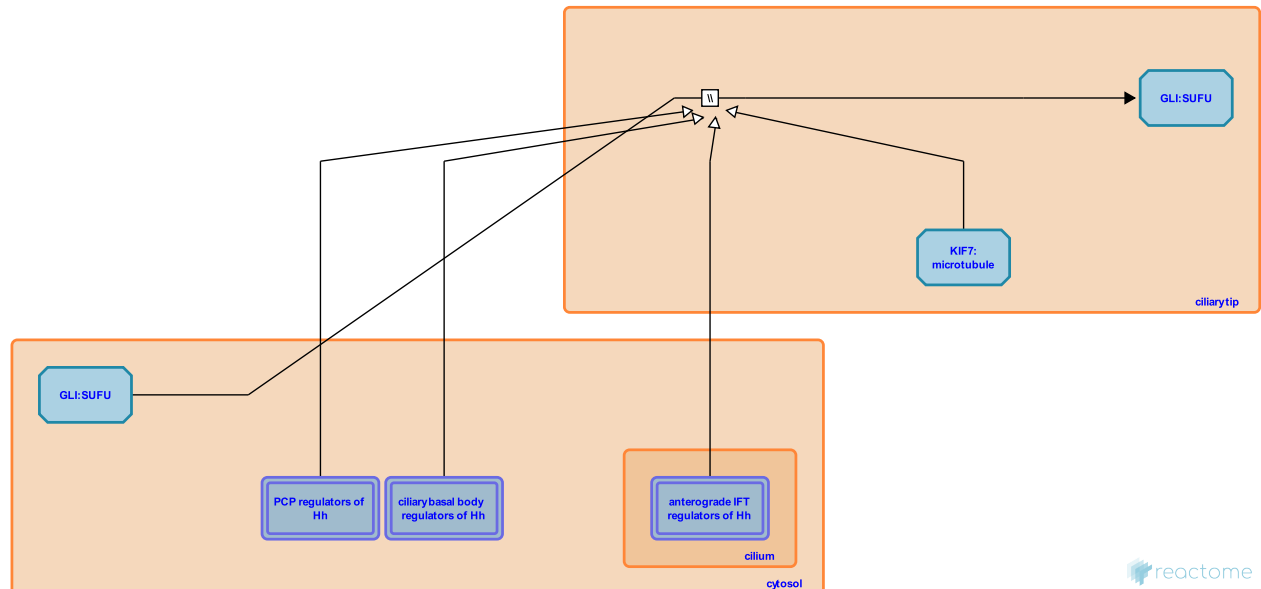
The intraflagellar transport B (IFT-B) complex is required for the transit of GLI:SUFU complexes to the ciliary tip ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610767

Type: omitted

Compartments: ciliary tip



Vertebrate hedgehog signaling depends on the passage and/or localization of many of the pathway components through the primary cilium (reviewed in Goetz and Anderson, 2010). Although GLI and SUFU proteins are not concentrated in the cilium in the absence of Hh signaling, processing and/or degradation of the transcription factors requires transit through the cilium and basal levels of these proteins can be detected there (Wen et al, 2010; Tukachinsky et al, 2010; Kim et al, 2006; Liu et al, 2005; Haycraft et al 2005). Consistent with this, members of both the IFT-B and IFT-A complex, as well as components of the ciliary basal body and the kinesin-2 and dynein motor proteins have been identified as regulators of Hh signaling (Huangfu et al, 2003; Tran et al, 2008; Liu et al, 2005; Houde et al, 2006; Huangfu et al, 2005; May et al, 2005; Cortellino et al, 2009; Vierkotten et al, 2007; Ferrante et al, 2006; Weatherbee et al, 2009; Liem et al, 2012; Qin et al 2011). KIF7, a microtubule-associated kinesin-type motor that negatively regulates the length of axonemal microtubules, is also required for correct localization of GLI:SUFU (He et al, 2014). Finally, a number of PCP pathway effectors have recently been shown to be required for ciliogenesis, and mutations in these genes disrupt GLI processing (Zeng et al, 2010; Gray et al, 2009; Heydeck et al, 2009; Park et al, 2006).

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- Liu, KJ., Weiss, GS., Wlodarczyk, BJ., Blanchard, O., Abitua, PB., Lee, I. et al. (2009). The planar cell polarity effector Fuz is essential for targeted membrane trafficking, ciliogenesis and mouse embryonic development. *Nat. Cell Biol.*, 11, 1225-32. ↗
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Bassi, MR., Champeval, D., Calmont, A., Wang, C., Zaret, KS., Cortellino, S. et al. (2009). Defective ciliogenesis, embryonic lethality and severe impairment of the Sonic Hedgehog pathway caused by inactivation of the mouse complex A intraflagellar transport gene Ift122/Wdr10, partially overlapping with the DNA repair gene Med1/Mbd4. *Dev. Biol.*, 325, 225-37. [↗](#)

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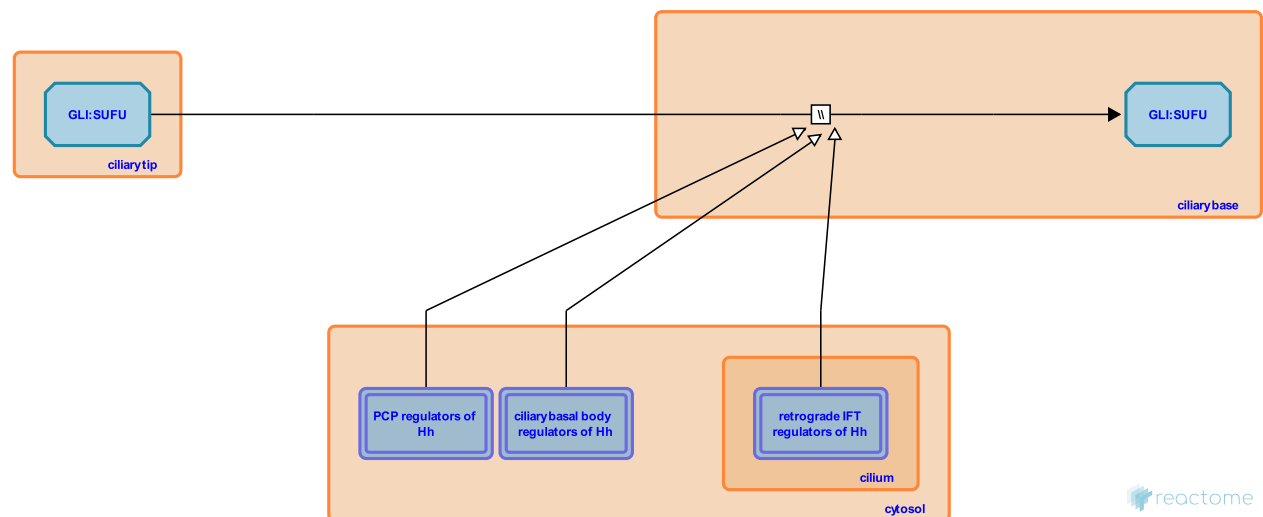
The intraflagellar transport A (IFT-A) complex is required for the transit of GLI:SUFU complexes to the ciliary base ↗

Location: Hedgehog 'off' state

Stable identifier: R-HSA-5610766

Type: omitted

Compartments: ciliary base



Vertebrate hedgehog signaling depends on the passage and/or localization of many of the pathway components through the primary cilium (reviewed in Goetz and Anderson, 2010). Although GLI and SUFU proteins are not concentrated in the cilium in the absence of Hh signaling, processing and/or degradation of the transcription factors requires transit through the cilium and basal levels of these proteins can be detected there (Wen et al, 2010; Tukachinsky et al, 2010; Kim et al, 2006; Liu et al, 2005; Haycraft et al, 2005). Consistent with this, members of both the IFT-B and IFT-A complex, as well as components of the ciliary basal body and the kinesin-2 and dynein motor proteins have been identified as regulators of Hh signaling (Huangfu et al, 2003; Tran et al, 2008; Liu et al, 2005; Houde et al, 2006; Huangfu et al, 2005; May et al, 2005; Cortellino et al, 2009; Vierkotten et al, 2007; Ferrante et al, 2006; Weatherbee et al, 2009; Liem et al, 2012; Qin et al, 2011). KIF7, a microtubule-associated kinesin-type motor that negatively regulates the length of axonemal microtubules, is also required for correct localization of GLI:SUFU (He et al, 2014). Finally, a number of PCP pathway effectors have recently been shown to be required for ciliogenesis, and mutations in these genes disrupt GLI processing (Zeng et al, 2010; Gray et al, 2009; Heydeck et al, 2009; Park et al, 2006).

Literature references

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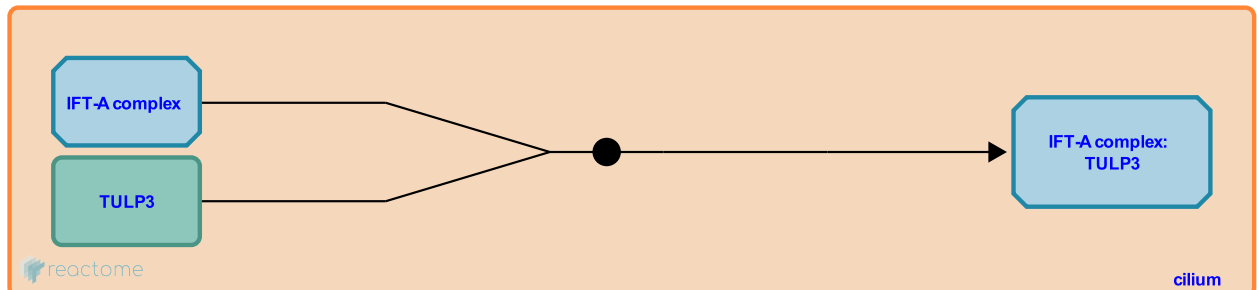
The IFT-A complex recruits TULP3 ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610726

Type: binding

Compartments: cilium



TULP3 is recruited to the primary cilium through a direct interaction with the retrograde transport IFT-A complex and with membrane phosphoinositides (Santagata et al, 2001; Mukhopadhyay et al, 2010; Qin et al, 2011; reviewed in Mukhopadhyay and Rohatgi, 2014). TULP3 facilitates GLI processing by recruiting the GPCR GPR161, which in turn activates PKA by increasing cAMP levels in a G alpha s-dependent manner (Mukhopadhyay et al, 2013, reviewed in Hwang and Mukhopadhyay, 2014; Pal and Mukhopadhyay, 2014).

Followed by: [TULP3 is required for GPR161 localization in the cilium](#)

Literature references

- Ko, HW., Lin, Y., Qin, J., Eggenschwiler, JT., Norman, RX. (2011). Intraflagellar transport protein 122 antagonizes Sonic Hedgehog signaling and controls ciliary localization of pathway components. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 1456-61. ↗
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- 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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Editions

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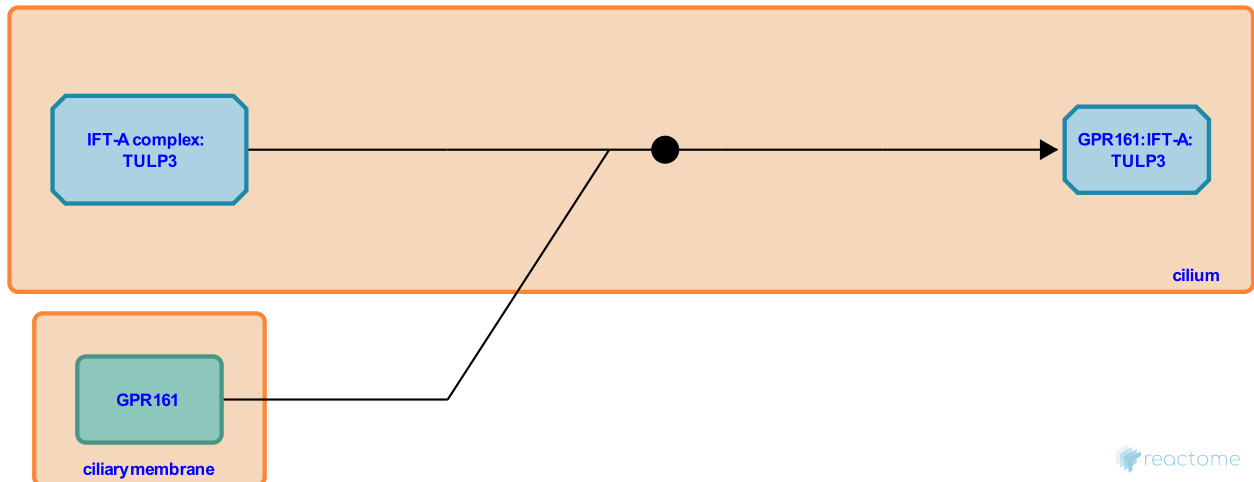
TULP3 is required for GPR161 localization in the cilium ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610725

Type: binding

Compartments: cilium



TULP3 and the retrograde complex IFT-A are required to recruit GPR161 to the cilium in the absence of Hh ligand (Mukhopadhyay et al, 2010; Mukhopadhyay et al, 2013; reviewed in Mukhopadhyay and Rohtagi, 2014). TULP3 is a negative regulator of Hh signaling and siRNA depletion of TULP3 reduces the ciliary accumulation of GPR161 (Norman et al, 2009; Patterson et al, 2009; Mukhopadhyay et al, 2010; Mukhopadhyay et al, 2013).

Preceded by: [The IFT-A complex recruits TULP3](#)

Followed by: [GPR161 promotes cAMP production in a G alpha\(s\)-dependent manner](#)

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. ↗
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Editions

2014-07-17	Authored	Rothfels, K.
2014-07-25	Edited	Gillespie, ME.
2014-08-01	Reviewed	Liu, Y C.

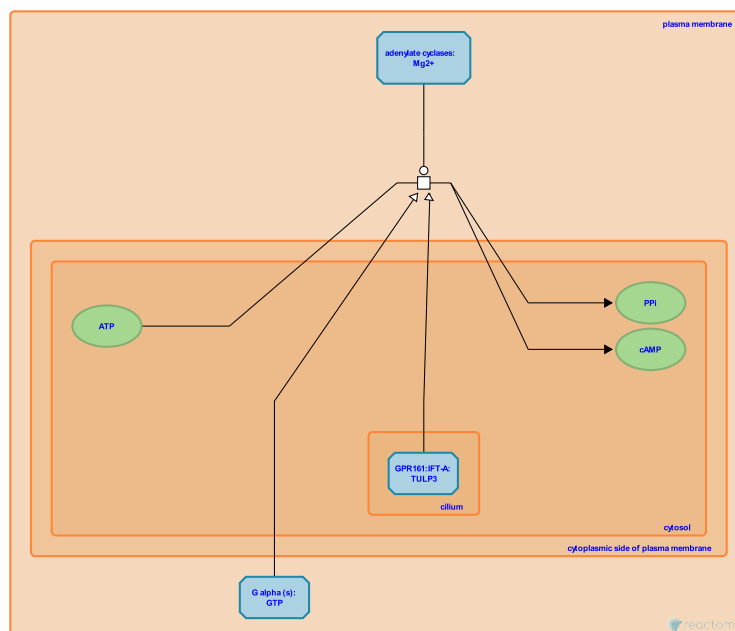
GPR161 promotes cAMP production in a G alpha(s)-dependent manner ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610727

Type: transition

Compartments: plasma membrane



cAMP is generated by the action of adenylyl cyclases (reviewed in Sassone-Corsi, 2012). GPR161 is an orphan GPCR that has recently been identified as a negative regulator of Hh signaling that acts by increasing cellular cAMP levels in the absence of ligand. Overexpression of GPR161 increases cellular cAMP levels in a manner that depends on the G alpha s subunit, and depletion of GPR161 results in aberrant Hh signaling and a decrease in the ratio of processed GLI3R (Mukhopadhyay et al, 2013). These data suggest that GPR161 negatively regulates GLI processing in the absence of Hh signal by modulating PKA activity through cAMP levels (Mukhopadhyay et al, 2013; reviewed in Mukhopadhyay and Rohatgi, 2014).

Preceded by: [TULP3 is required for GPR161 localization in the cilium](#)

Followed by: [cAMP dissociates PKA, promoting GLI processing](#)

Literature references

Sassone-Corsi, P. (2012). The cyclic AMP pathway. *Cold Spring Harb Perspect Biol*, 4. ↗

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. ↗

Rohatgi, R., Mukhopadhyay, S. (2014). G-protein-coupled receptors, Hedgehog signaling and primary cilia. *Semin. Cell Dev. Biol.*.. ↗

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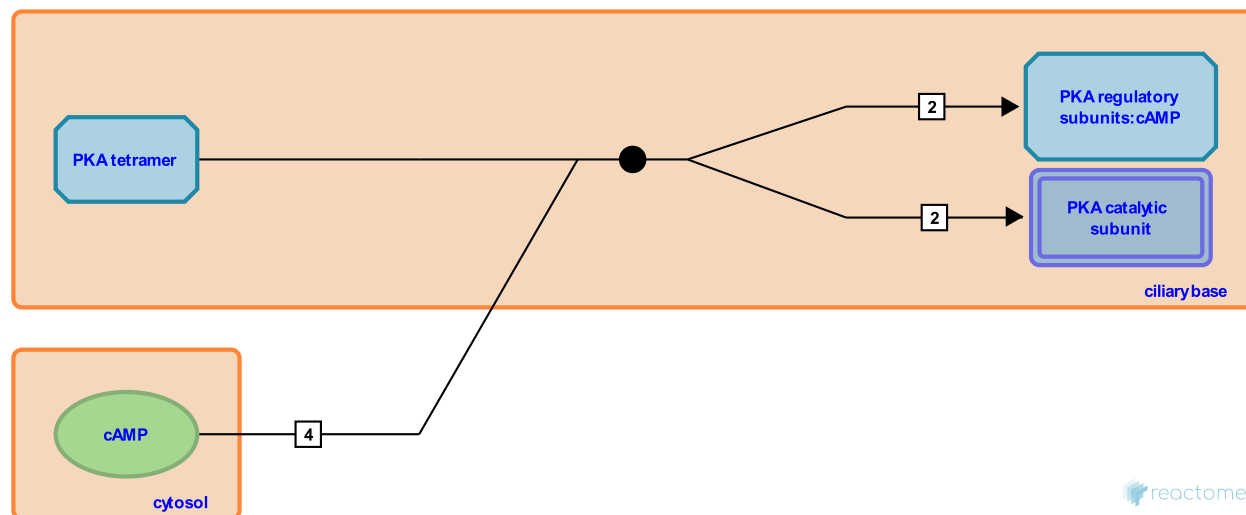
cAMP dissociates PKA, promoting GLI processing [↗](#)

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610749

Type: binding

Compartments: ciliary base



cAMP is a known regulator of PKA activity and works by binding to the regulatory subunits and promoting dissociation of the tetramer, freeing the active catalytic subunits (reviewed in Sassone-Corsi, 2012). In the Hh pathway in the absence of ligand, cAMP levels increase in response to the recruitment of GPR161 to the ciliary base by TULP3 and the IFT-A retrograde complex (Mukhopadhyay et al, 2010; Mukhopadhyay et al, 2013). Activated PKA then initiates the phosphorylation cascade that regulates processing and/or degradation of the GLI proteins (reviewed in Briscoe and Therond, 2013; Mukhopadhyay and Rohatgi, 2014).

Preceded by: [GPR161 promotes cAMP production in a G alpha\(s\)-dependent manner](#)

Literature references

Sassone-Corsi, P. (2012). The cyclic AMP pathway. *Cold Spring Harb Perspect Biol*, 4. [↗](#)

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. [↗](#)

Rohatgi, R., Mukhopadhyay, S. (2014). G-protein-coupled receptors, Hedgehog signaling and primary cilia. *Semin. Cell Dev. Biol.* [↗](#)

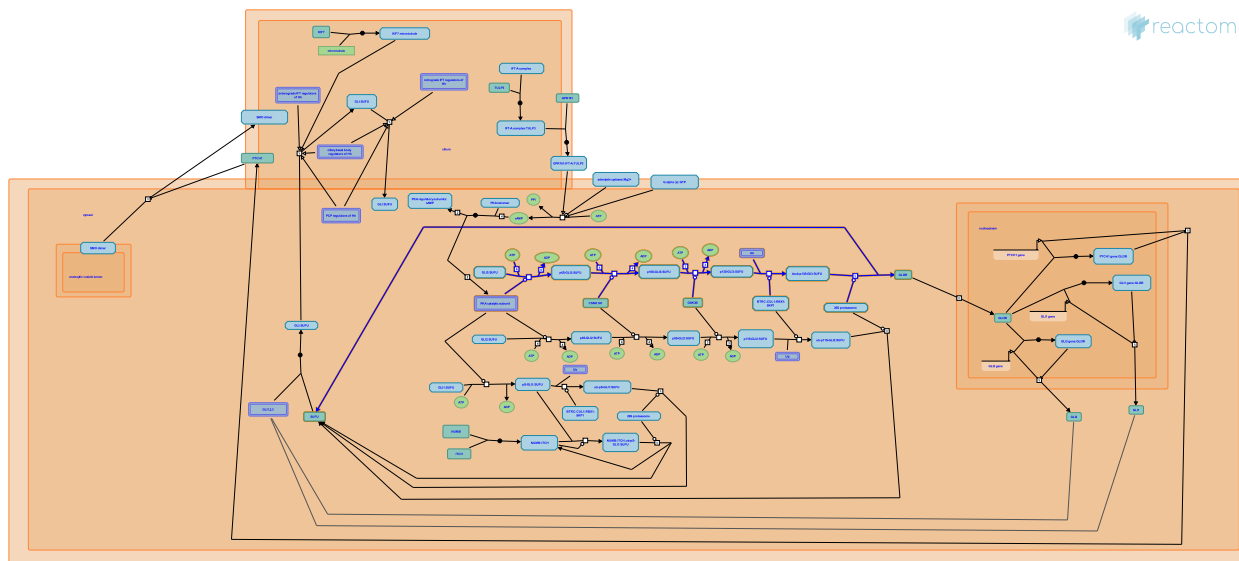
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GLI3 is processed to GLI3R by the proteasome ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610785



In the absence of Hh signaling, the majority of full-length GLI3 is partially processed by the proteasome to a shorter form that serves as the principal repressor of Hh target genes (Wang et al, 2000). Processing depends on phosphorylation at 6 sites by PKA, which primes the protein for subsequent phosphorylation at adjacent sites by CK1 and GSK3. The hyperphosphorylated protein is then a direct target for β TrCP-dependent ubiquitination and proteasome-dependent processing (Wang and Li, 2006; Tempe et al, 2006; Wen et al, 2010; Schrader et al, 2011; Pan and Wang, 2007).

Literature references

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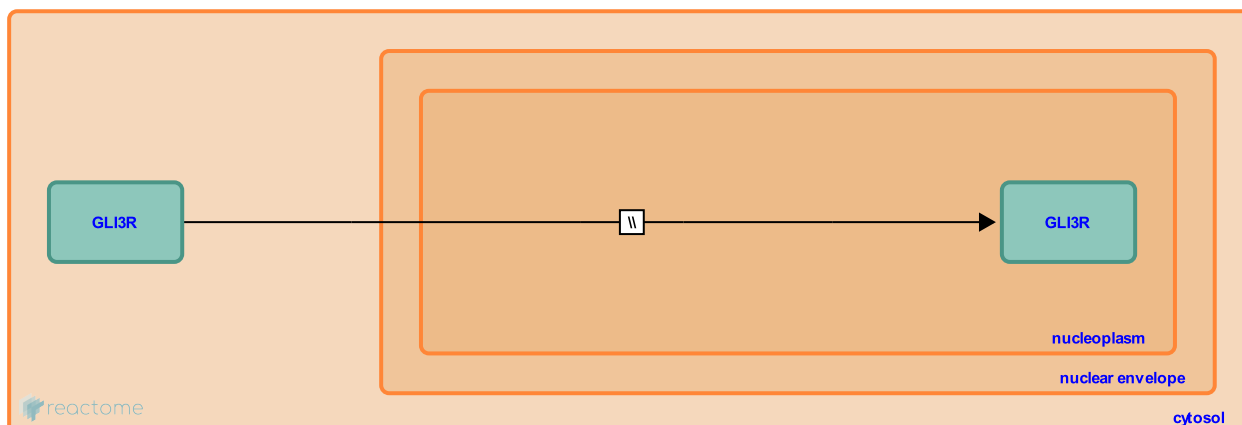
GLI3R translocates to the nucleus ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610752

Type: omitted

Compartments: nucleoplasm, cytosol



After processing by the proteasome, the truncated GLI3 translocates into the nucleus where it acts as the primary repressor for Hh-responsive genes (reviewed in Briscoe and Therond, 2013). Based on sequence comparisons with Ci and GLI1, GLI3 is predicted to have a bipartite NLS signal near the zinc finger domain, and import to the nucleus may be mediated by Importin alpha3, although the details remain to be worked out (reviewed in Hatayama and Aruga, 2012).

Followed by: [GLI3R binds the PTCH1 promoter](#), [GLI3R binds the GLI1 promoter](#), [GLI3R binds the GLI2 promoter](#)

Literature references

Aruga, J., Hatayama, M. (2012). Gli protein nuclear localization signal. *Vitam. Horm.*, 88, 73-89. ↗

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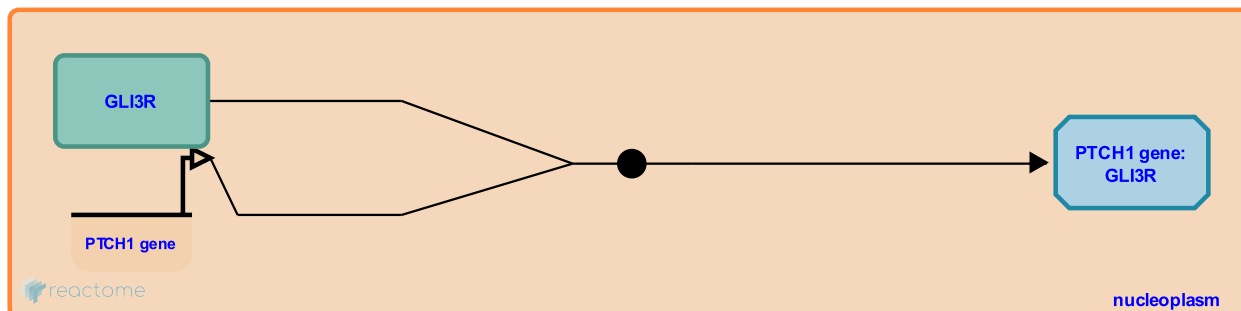
GLI3R binds the PTCH1 promoter ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5612508

Type: binding

Compartments: nucleoplasm



GLI3R is a DNA-binding transcriptional repressor that recognizes consensus GLI sites 5'-GACCACCC-3' in the promoters of target genes (Kinzler and Vogelstein, 1990). DNA-binding is mediated through 5 C2H2 Kruppel zinc fingers in the N-terminal region of the protein, which remains intact after proteasome-mediated processing (reviewed in Hui and Angers, 2011). GLI-dependent target genes have been identified by a number of ChIP based screens, and one well established target of GLI3R is the Hh receptor, PTCH1 (Lee et al, 2010; Vokes et al, 2007; Vokes et al, 2008). GLI3R has been shown to bind to a GLI-consensus sequence in the PTCH1 promoter as assessed by electrophoretic mobility shift assay and the protein is able to repress expression of a reporter gene driven by this element (Agren et al, 2004). GLI3R may promote repressive complexes at the PTCH1 promoter by the SKI1-dependent recruitment of HDAC complexes (Dai et al, 2002). Other GLI3R transcriptional targets include GLI1 and GLI2 (Hu et al, 2006).

Preceded by: [GLI3R translocates to the nucleus](#)

Followed by: [Expression of PTCH1 is repressed by GLI3R in the absence of Hh signaling](#)

Literature references

- Mo, R., Hui, CC., Hu, MC., Bhella, S., Chuang, PT., Rosenblum, ND. et al. (2006). GLI3-dependent transcriptional repression of Gli1, Gli2 and kidney patterning genes disrupts renal morphogenesis. *Development*, 133, 569-78. ↗
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Editions

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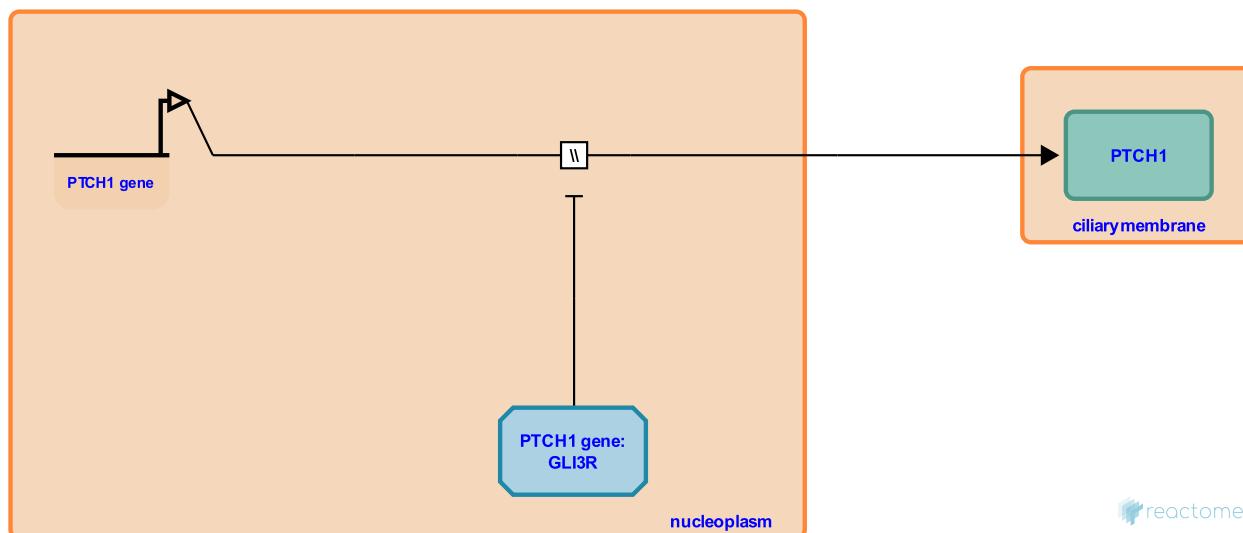
Expression of PTCH1 is repressed by GLI3R in the absence of Hh signaling ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5612510

Type: omitted

Compartments: nucleoplasm, ciliary membrane



Expression of the PTCH1 gene is repressed in the absence of Hh signaling by GLI3R (Agren et al, 2004; Lee et al, 2010; Vokes et al, 2007; Vokes et al, 2008). GLI3R may exert its repression activity through the SKI-dependent recruitment of HDACs (Dai et al, 2002).

Preceded by: [GLI3R binds the PTCH1 promoter](#)

Literature references

- Akimaru, H., Sasaki, H., Khan, MM., Kaul, SC., Shinagawa, T., Colmenares, C. et al. (2002). Ski is involved in transcriptional regulation by the repressor and full-length forms of Gli3. *Genes Dev.*, 16, 2843-8. ↗
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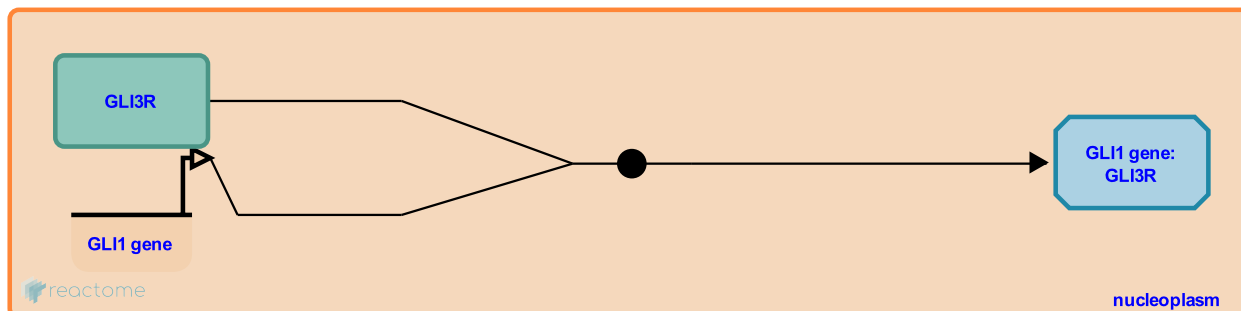
GLI3R binds the GLI1 promoter ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5617408

Type: binding

Compartments: nucleoplasm



GLI3R is a DNA-binding transcriptional repressor that recognizes consensus GLI sites 5'-GACCACCC-3' in the promoters of target genes (Kinzler and Vogelstein, 1990). DNA-binding is mediated through 5 C2H2 Kruppel zinc fingers in the N-terminal region of the protein, which remains intact after proteasome-mediated processing (reviewed in Hui and Angers, 2011). In the absence of Hh signaling, GLI3R has been shown to bind to the promoters of the GLI1 and GLI2 genes as assessed by ChIP and to repress gene expression (Hu et al, 2006).

Preceded by: [GLI3R translocates to the nucleus](#)

Followed by: [Expression of GLI1 is repressed by GLI3R in the absence of Hh signaling](#)

Literature references

Mo, R., Hui, CC., Hu, MC., Bhella, S., Chuang, PT., Rosenblum, ND. et al. (2006). GLI3-dependent transcriptional repression of Gli1, Gli2 and kidney patterning genes disrupts renal morphogenesis. *Development*, 133, 569-78. ↗

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

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. ↗

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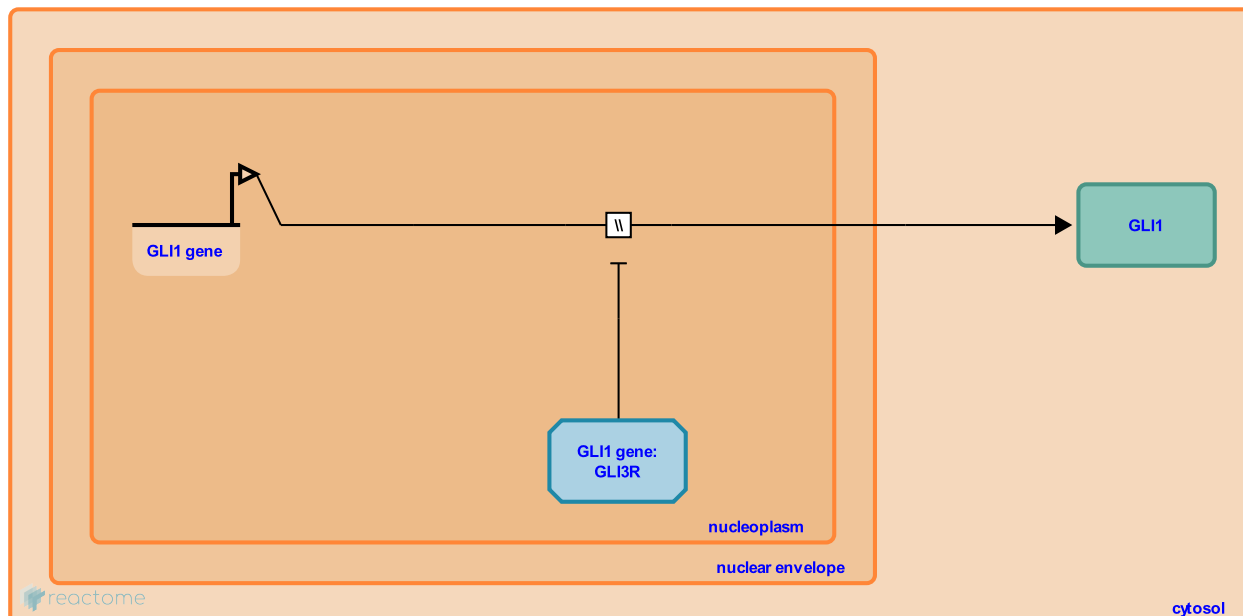
Expression of GLI1 is repressed by GLI3R in the absence of Hh signaling ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5617412

Type: omitted

Compartments: nucleoplasm, cytosol



Expression of the GLI1 gene is repressed in the absence of Hh signaling by GLI3R (Hu et al, 2006). GLI3R may exert its repression activity through the SKI-dependent recruitment of HDACs (Dai et al, 2002).

Preceded by: [GLI3R binds the GLI1 promoter](#)

Followed by: [GLI proteins bind SUFU](#)

Literature references

Mo, R., Hui, CC., Hu, MC., Bhella, S., Chuang, PT., Rosenblum, ND. et al. (2006). GLI3-dependent transcriptional repression of Gli1, Gli2 and kidney patterning genes disrupts renal morphogenesis. *Development*, 133, 569-78. ↗

Akimaru, H., Sasaki, H., Khan, MM., Kaul, SC., Shinagawa, T., Colmenares, C. et al. (2002). Ski is involved in transcriptional regulation by the repressor and full-length forms of Gli3. *Genes Dev.*, 16, 2843-8. ↗

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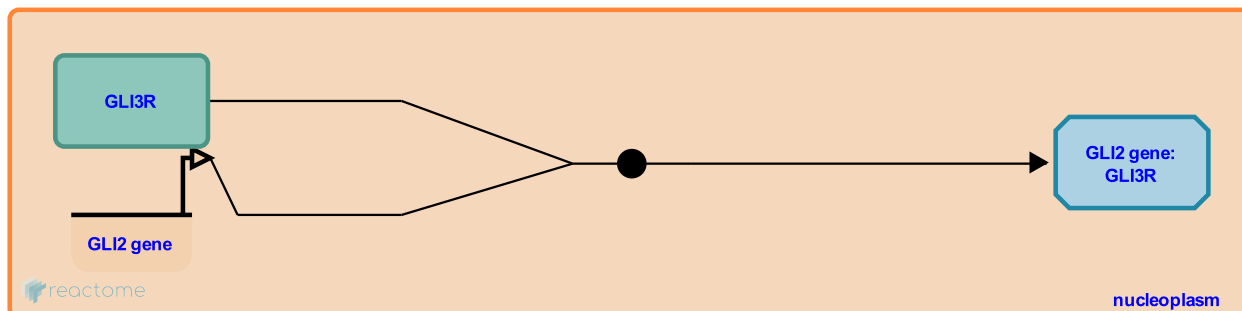
GLI3R binds the GLI2 promoter ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5617410

Type: binding

Compartments: nucleoplasm



GLI3R is a DNA-binding transcriptional repressor that recognizes consensus GLI sites 5'-GACCACCC-3' in the promoters of target genes (Kinzler and Vogelstein, 1990). DNA-binding is mediated through 5 C2H2 Kruppel zinc fingers in the N-terminal region of the protein, which remains intact after proteasome-mediated processing (reviewed in Hui and Angers, 2011). In the absence of Hh signaling, GLI3R has been shown to bind to the promoters of the GLI1 and GLI2 genes as assessed by ChIP and to repress gene expression (Hu et al, 2006).

Preceded by: [GLI3R translocates to the nucleus](#)

Followed by: [Expression of GLI2 is repressed by GLI3R in the absence of Hh signaling](#)

Literature references

Mo, R., Hui, CC., Hu, MC., Bhella, S., Chuang, PT., Rosenblum, ND. et al. (2006). GLI3-dependent transcriptional repression of Gli1, Gli2 and kidney patterning genes disrupts renal morphogenesis. *Development*, 133, 569-78. ↗

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

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. ↗

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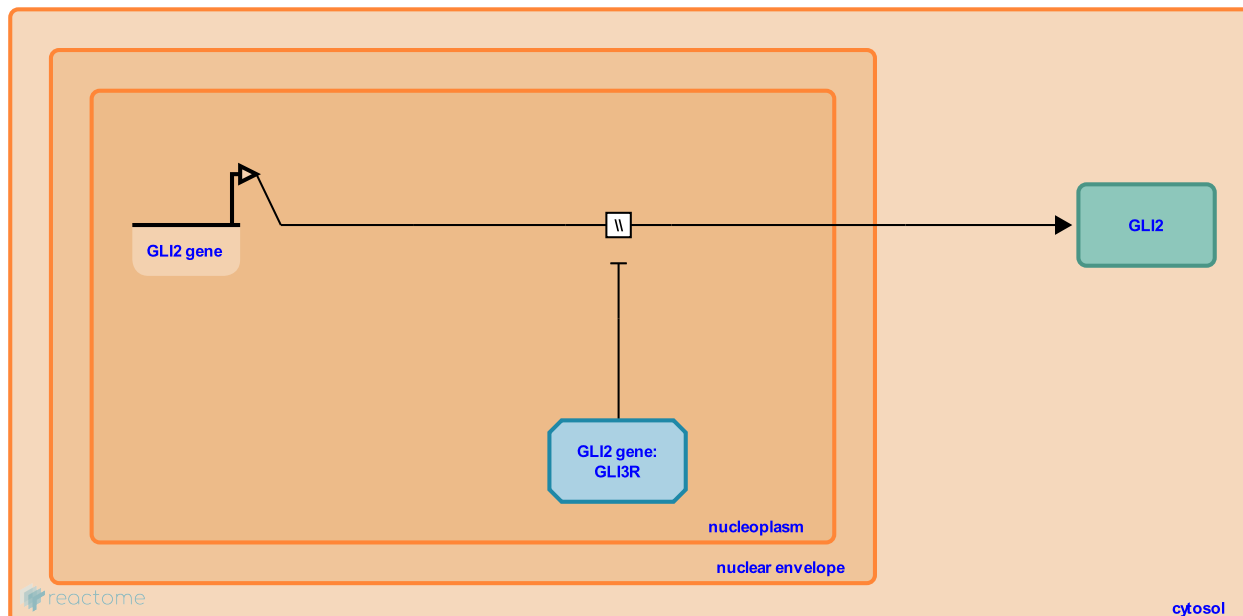
Expression of GLI2 is repressed by GLI3R in the absence of Hh signaling ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5617413

Type: omitted

Compartments: nucleoplasm, cytosol



Expression of the GLI2 gene is repressed in the absence of Hh signaling by GLI3R (Hu et al, 2006). GLI3R may exert its repression activity through the SKI-dependent recruitment of HDACs (Dai et al, 2002).

Preceded by: [GLI3R binds the GLI2 promoter](#)

Followed by: [GLI proteins bind SUFU](#)

Literature references

Mo, R., Hui, CC., Hu, MC., Bhella, S., Chuang, PT., Rosenblum, ND. et al. (2006). GLI3-dependent transcriptional repression of Gli1, Gli2 and kidney patterning genes disrupts renal morphogenesis. *Development*, 133, 569-78. ↗

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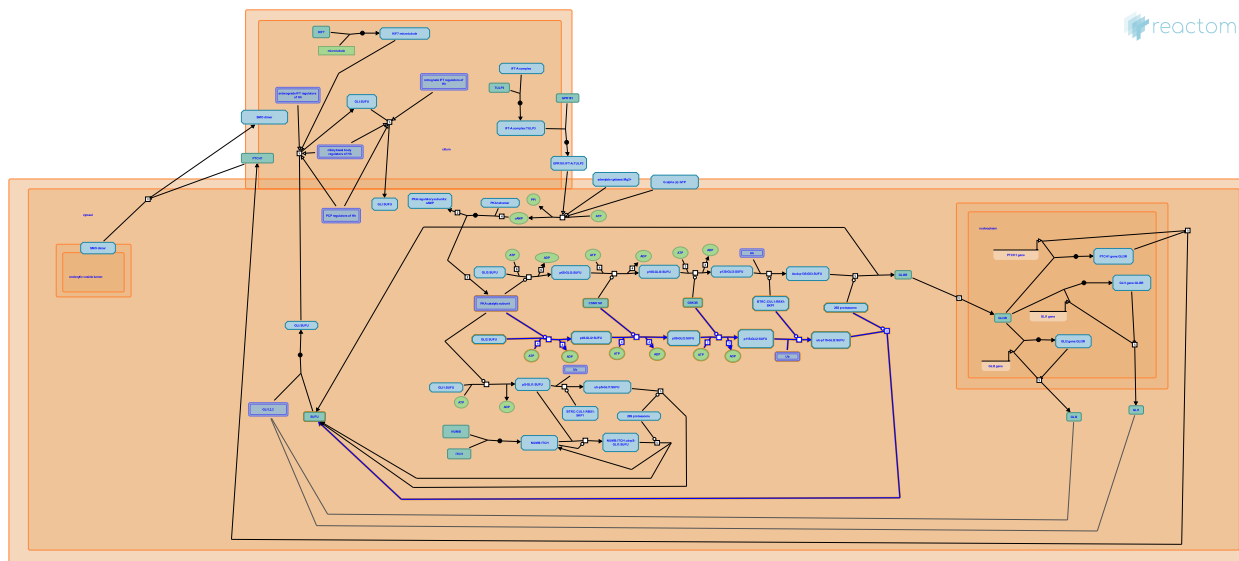
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Degradation of GLI2 by the proteasome ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610783



The primary role of the GLI2 protein is as an activator of Hh-dependent signaling upon pathway stimulation; in the absence of Hh ligand, a small fraction of GLI2 appears to be processed to a repressor form, but the bulk of the protein is completely degraded by the proteasome (reviewed in Briscoe and Therond, 2013). Both the processing and the degradation of GLI2 is dependent upon sequential phosphorylation of multiple serine residues by PKA, CK1 and GSK3, analogous to the requirement for these kinases in the processing of GLI3 (Pan et al, 2009; Pan et al, 2006; Pan and Wang, 2007). The differential processing of GLI2 and GLI3 depends on the processing determinant domain (PDD) in the C-terminal of the proteins, which directs the partial proteolysis of GLI3 in the absence of Hh signal. Substitution of 2 amino-acids from GLI3 into the GLI2 protein is sufficient to promote efficient processing of GLI2 to the repressor form (Pan and Wang, 2007).

Literature references

- Pan, Y., Wang, B. (2007). A novel protein-processing domain in Gli2 and Gli3 differentially blocks complete protein degradation by the proteasome. *J. Biol. Chem.*, 282, 10846-52. ↗
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- 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. ↗

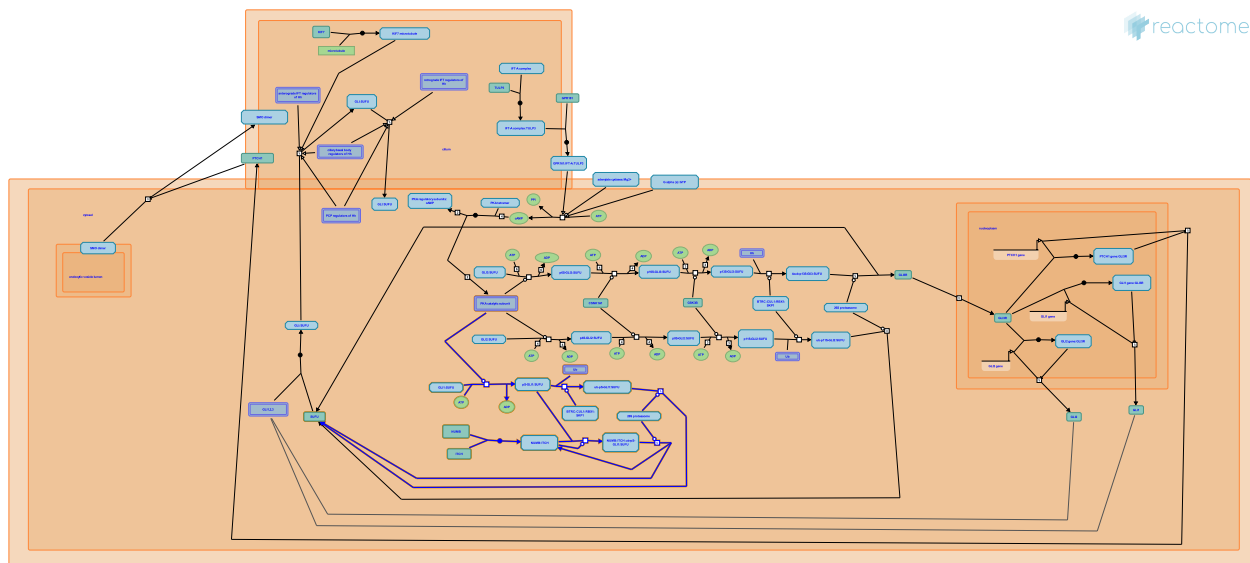
Editions

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Degradation of GLI1 by the proteasome ↗

Location: [Hedgehog 'off' state](#)

Stable identifier: R-HSA-5610780



GLI1 is the most divergent of the 3 mammalian GLI transcription factors and lacks a transcriptional repressor domain. Although GLI1 is dispensible for development, the gene is an early transcriptional target of Hh signaling and the protein contributes a minor activation function in mammals (Dai et al, 1999; Bai et al, 2002; Park et al, 2000).

In the absence of Hh signaling, GLI1 is completely degraded by the proteasome, in contrast to the partial processing that occurs with GLI3. This differential response reflects the absence in GLI1 of two of the three elements identified in GLI3 that promote partial proteolysis; these are the zinc finger region, present in all GLI proteins, and an adjacent linker sequence and the degron, neither of which are found in the GLI1 protein (Schrader et al, 2011; Pan and Wang, 2007).

Literature references

Pan, Y., Wang, B. (2007). A novel protein-processing domain in Gli2 and Gli3 differentially blocks complete protein degradation by the proteasome. *J. Biol. Chem.*, 282, 10846-52. ↗

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