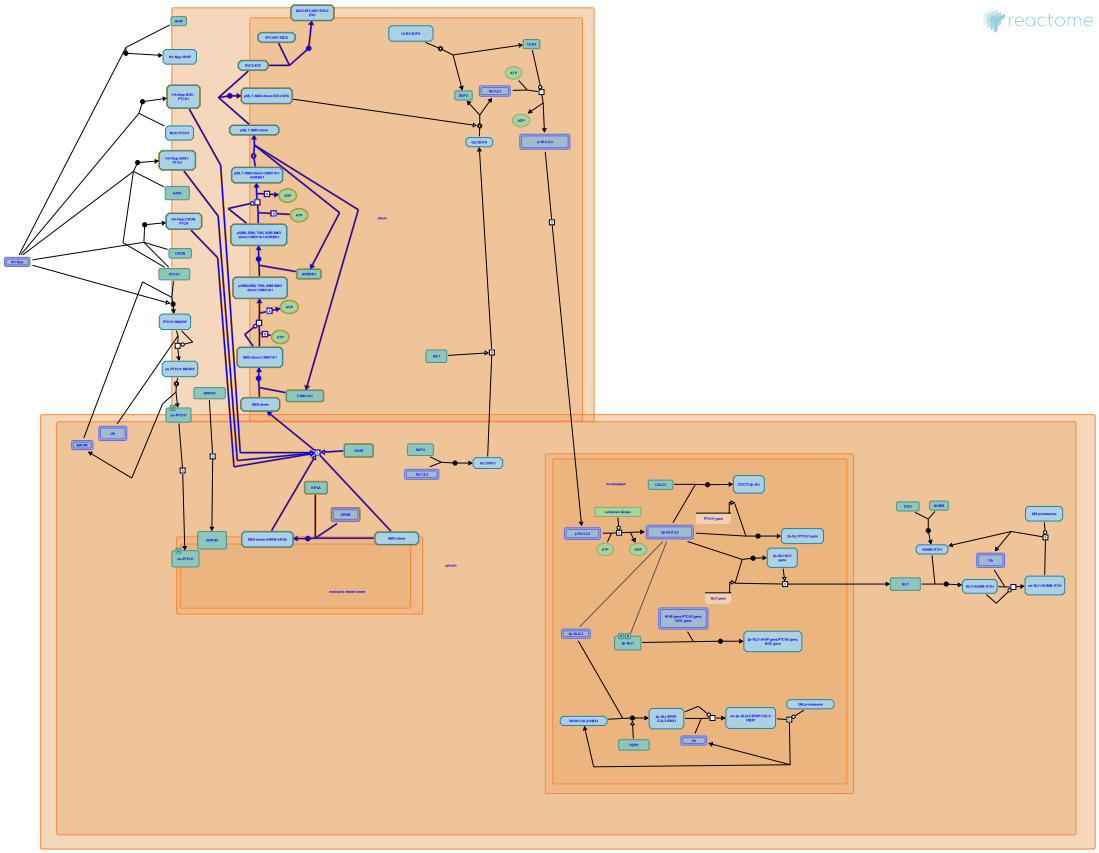
Activation of SMO



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20/04/2021

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. ↗

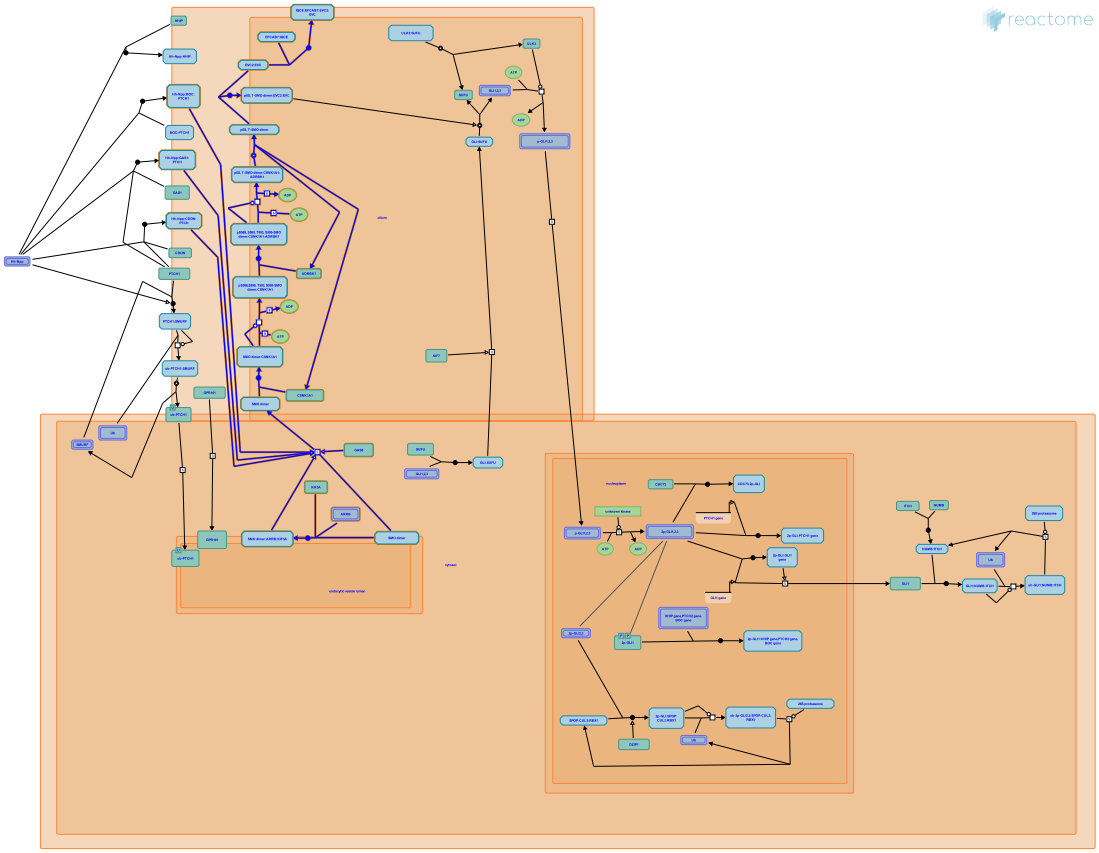
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

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. ↗

Activation of SMO ↗

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

Rohatgi, R., Milenkovic, L., Scott, MP. (2007). Patched1 regulates hedgehog signaling at the primary cilium. *Science, 317*, 372-6. ↗

Jiang, J., Hui, CC. (2008). Hedgehog signaling in development and cancer. *Dev. Cell, 15*, 801-12. ↗

Blair, HJ., Tompson, S., Liu, YN., Campbell, J., MacArthur, K., Ponting, CP. et al. (2011). Evc2 is a positive modulator of Hedgehog signalling that interacts with Evc at the cilia membrane and is also found in the nucleus. *BMC Biol., 9*, 14. ↗

Zhao, Y., Tong, C., Jiang, J. (2007). Hedgehog regulates smoothened activity by inducing a conformational switch. *Nature, 450*, 252-8. ↗

Pusapati, GV., Hughes, CE., Dorn, KV., Zhang, D., Sugianto, P., Aravind, L. et al. (2014). EFCAB7 and IQCE regulate hedgehog signaling by tethering the EVC-EVC2 complex to the base of primary cilia. *Dev. Cell, 28*, 483-96. ↗

Editions

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

SMO dimer binds ARRB and KIF3A ↗

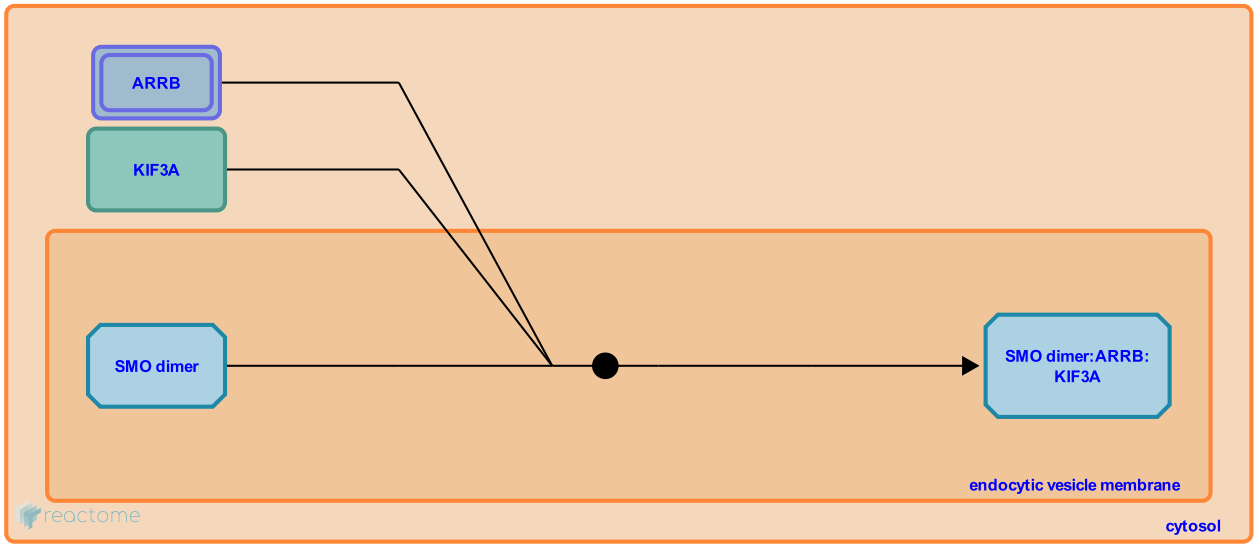
Location: Activation of SMO

Stable identifier: R-HSA-5632667

Type: binding

Compartments: endocytic vesicle membrane

Inferred from: Smo dimer binds Arrb and Kif3a (Mus musculus)



Beta-arrestin 1 and 2 (ARRB1 and 2) and the anterograde motor protein KIF3A bind to SMO and may be required for its ciliary accumulation after Hh stimulation (Kovacs et al, 2008; Barakat et al, 2013).

Followed by: SMO translocates to the cilium

Literature references

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

Barakat, B., Yu, L., Lo, C., Vu, D., De Luca, E., Cain, JE. et al. (2013). Interaction of smoothened with integrin-linked kinase in primary cilia mediates Hedgehog signalling. *EMBO Rep., 14*, 837-44. ↗

Editions

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

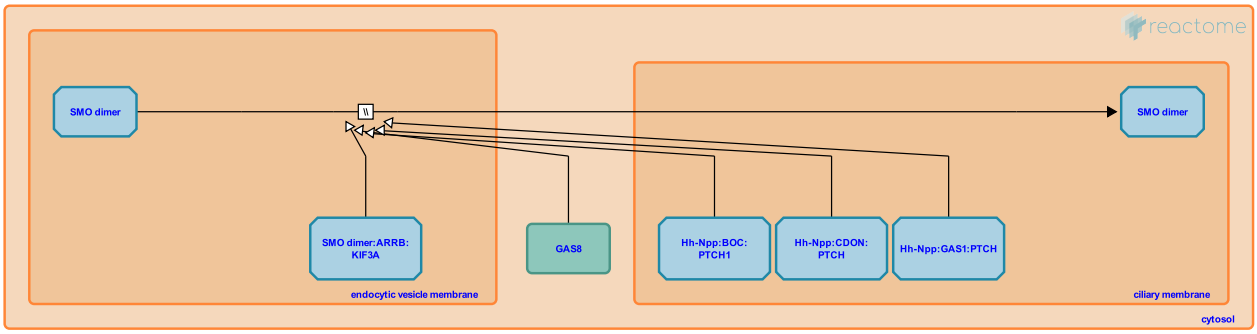
SMO translocates to the cilium ↗

Location: Activation of SMO

Stable identifier: R-HSA-5632668

Type: omitted

Compartments: endocytic vesicle membrane, ciliary membrane



Binding of ligand to the PTCH receptor activates the Hh signaling pathway and results in the accumulation of SMO in the primary cilium (Denef et al, 2000; Corbit et al, 2005; Rohatgi et al, 2007; Milenkovic et al, 2009; Wang et al, 2009; Wilson et al, 2009; reviewed in Briscoe and Therond, 2013). Neither the mechanism for how PTCH represses SMO in the absence of ligand nor how this relief is lifted upon pathway activation are fully understood, however SMO translocation to the cilium appears to depend upon complex formation with beta-arrestin proteins and the anterograde motor protein KIF3A (Chen et al, 2004; Kovacs et al, 2008). GAS8, a SMO- and microtubule-binding protein, is also required for the ciliary localization of SMO, although the mechanism is not clear (Evron et al, 2011; reviewed in Evron et al, 2012). In response to pathway activation, SMO is phosphorylated in a CKI- and ADRBK1/GRK2-dependent fashion and undergoes a conformational change, both of which are required for downstream pathway activation; accumulation of SMO in the cilium is in itself not sufficient (Chen et al, 2011; Zhao et al, 2007; Chen et al, 2010; Rohatgi et al, 2009). In the primary cilium, SMO interacts with the Ellis-van Creveld syndrome proteins 1 and 2 (EVC1 and 2) in a SMO phosphorylation-dependent manner, and the interaction with EVC1 and 2 is required for downstream signal propagation (Yang et al, 2012; Dorn et al, 2012; Capparos-Martin et al, 2013; Pusapati et al, 2014; Yang et al, 2012). SMO activation results in the concentration of SUFU and the GLI proteins in the cilium, the dissociation of the SUFU:GLI complex and the nuclear accumulation of the full length activator form of the GLI proteins (reviewed in Briscoe and Therond, 2013).

Preceded by: SMO dimer binds ARRB and KIF3A

Followed by: CSNK1A1 binds SMO dimer

Literature references

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

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

Rohatgi, R., Milenkovic, L., Scott, MP. (2007). Patched1 regulates hedgehog signaling at the primary cilium. *Science, 317*, 372-6. ↗

Milenkovic, L., Scott, MP., Rohatgi, R. (2009). Lateral transport of Smoothened from the plasma membrane to the membrane of the cilium. *J. Cell Biol., 187*, 365-74. ↗

Wang, Y., Zhou, Z., Walsh, CT., McMahon, AP. (2009). Selective translocation of intracellular Smoothened to the primary cilium in response to Hedgehog pathway modulation. *Proc. Natl. Acad. Sci. U.S.A., 106*, 2623-8. ↗

Editions

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

CSNK1A1 binds SMO dimer ↗

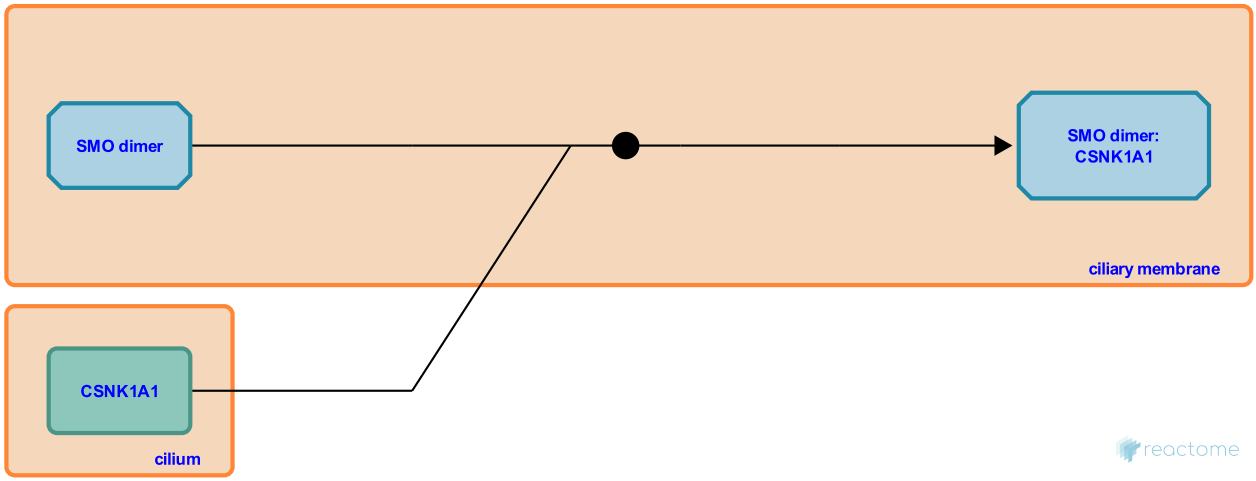
Location: Activation of SMO

Stable identifier: R-HSA-5632671

Type: binding

Compartments: ciliary membrane

Inferred from: Csnk1a1 binds Smo dimer (Mus musculus)



Activation of SMO in vertebrate cells depends upon its sequential phosphorylation by CSNK1A1/CK1alpha and ADRBK1/GRK2 kinases. Phosphorylation is thought to promote a conformational change in the SMO C-terminal tails, destabilizing an intramolecular interaction within the tail and promoting a more open conformation that brings the two tails of the SMO dimer into closer proximity (Chen et al, 2010; Chen et al, 2011; Wilson et al, 2009). This mechanism parallels the activation of Smo in Drosophila, where phosphorylation of consensus PKA and CK1 sites in the C-terminus promotes conformational change (Zhao et al, 2007). In both Drosophila and vertebrates, the kinases interact with SMO as assessed by co-precipitation (Zhao et al, 2007; Chen et al, 2010; Chen et al, 2011). In vertebrate cells, SHH stimulation appears to promote a 2-step activation of SMO. In the first step, CSNK1A1 binds to the C-terminal tails in the closed conformation. Initial CSNK1A1-mediated phosphorylation promotes the open conformation and increases the binding affinity of both CSNK1A1 and ADRBK1/GRK2 for the SMO tail, establishing a positive feedback loop to enhance SMO phosphorylation (Chen et al, 2010; Chen et al, 2011; Meloni et al 2006; Philipp et al, 2008). CSNK1A1 accumulates in the primary cilium in an SHH-dependent manner, and the kinetics of SMO phosphorylation are faster there than in the whole cell. Phosphorylation also depends on the kinesin II ciliary motor KIF3A, and promotes the ciliary accumulation of SMO, possibly in a ARRB-dependent manner (Chen et al, 2011; Meloni et al, 2006).

Preceded by: SMO translocates to the cilium

Followed by: CSNK1A1 phosphorylates SMO dimer

Literature references

Chen, Y., Li, S., Tong, C., Zhao, Y., Wang, B., Liu, Y. et al. (2010). G protein-coupled receptor kinase 2 promotes high-level Hedgehog signaling by regulating the active state of Smo through kinase-dependent and kinase-independent mechanisms in Drosophila. *Genes Dev., 24*, 2054-67. ↗

Chen, Y., Sasai, N., Ma, G., Yue, T., Jia, J., Briscoe, 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. ↗

Wilson, CW., Chen, MH., Chuang, PT. (2009). Smoothened adopts multiple active and inactive conformations capable of trafficking to the primary cilium. *PLoS ONE, 4*, e5182. ↗

Zhao, Y., Tong, C., Jiang, J. (2007). Hedgehog regulates smoothened activity by inducing a conformational switch. *Nature, 450*, 252-8. ↗

Philipp, M., Fralish, GB., Meloni, AR., Chen, W., MacInnes, AW., Barak, LS. et al. (2008). Smoothened signaling in vertebrates is facilitated by a G protein-coupled receptor kinase. *Mol. Biol. Cell, 19*, 5478-89. ↗

Editions

2014-10-24	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

CSNK1A1 phosphorylates SMO dimer ↗

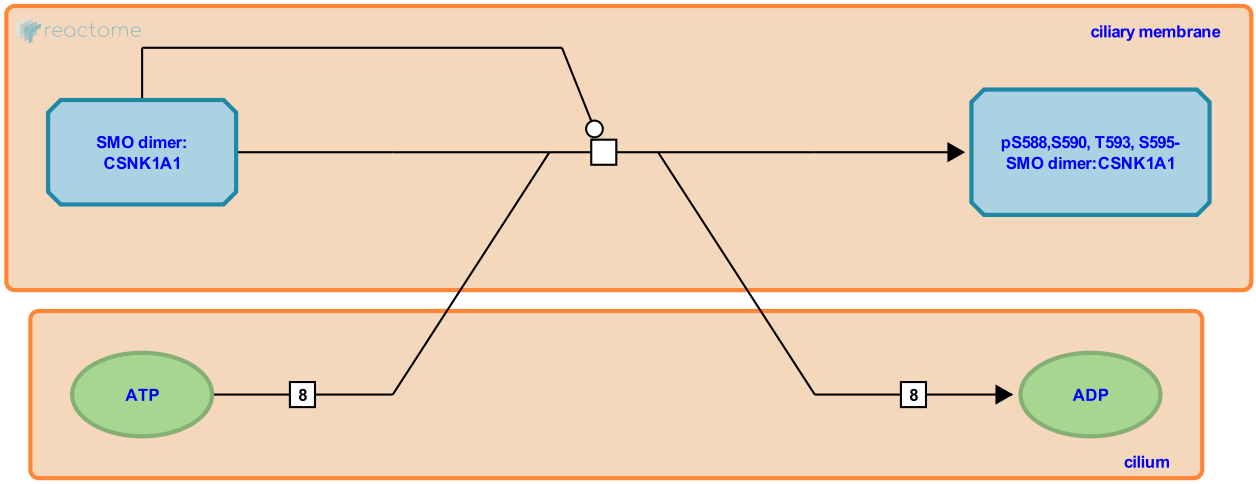
Location: Activation of SMO

Stable identifier: R-HSA-5632670

Type: transition

Compartments: ciliary membrane

Inferred from: Csnk1a1 phosphorylates Smo dimer (Mus musculus)



Initial activation of SMO in response to HH occurs with the CSNK1A1-mediated phosphorylation of serine and threonine residues in the C-terminal tail. While many potential CSNK1A1 target residues have been identified in in vitro assays, residues S588, S590, T593 and S595 in the S0 region appear to be the most critical for function (Chen et al, 2011). Initial phosphorylation increases the affinity of the C-terminal tail for both CSNK1A1 and ADRBK1/GRK2, establishing a positive feedback mechanism that promotes further phosphorylation. CSNK1A1 and ADRBK1-mediated phosphorylation is thought to promote an open, activated conformation of the C-terminal tails, analogous to that in Drosophila Smo upon pathway activation (Chen et al, 2011; Chen et al, 2010; Zhao et al, 2007).

Preceded by: CSNK1A1 binds SMO dimer

Followed by: ADRBK1 binds phosphorylated SMO dimer

Literature references

Chen, Y., Sasai, N., Ma, G., Yue, T., Jia, J., Briscoe, 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. ↗

Chen, Y., Li, S., Tong, C., Zhao, Y., Wang, B., Liu, Y. et al. (2010). G protein-coupled receptor kinase 2 promotes high-level Hedgehog signaling by regulating the active state of Smo through kinase-dependent and kinase-independent mechanisms in Drosophila. *Genes Dev., 24*, 2054-67. ↗

Zhao, Y., Tong, C., Jiang, J. (2007). Hedgehog regulates smoothened activity by inducing a conformational switch. *Nature, 450*, 252-8. ↗

Editions

2014-10-24	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

ADRBK1 binds phosphorylated SMO dimer ↗

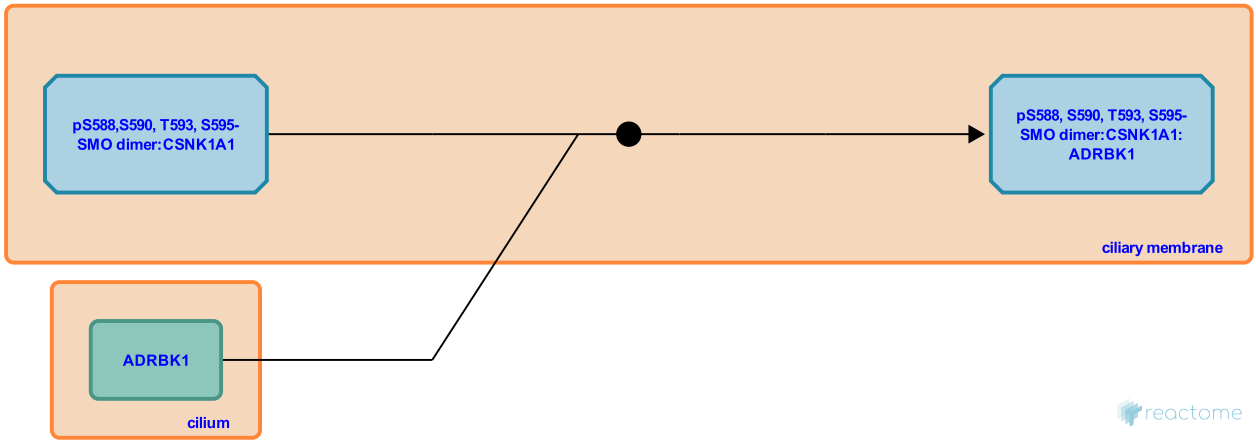
Location: Activation of SMO

Stable identifier: R-HSA-5632674

Type: binding

Compartments: ciliary membrane

Inferred from: Adrbk1 binds pS592, S594, T597, S599 Smo dimer:Csnk1a1 (Mus musculus)



Initial binding and phosphorylation of the SMO C-terminal tail by CSNK1A1 increases the affinity of the tail for ADRBK1/GRK2. Like CSNK1A1, ADRBK1 phosphorylates multiple sites in the SMO tail in a Hh-dependent manner, and this phosphorylation is required for a conformational change that promotes closer association of the two tails in the SMO dimer, analogous to what is seen in Drosophila (Chen et al, 2011; Chen et al, 2010; Zhao et al, 2007; Meloni et al, 2006; Philipp et al, 2008).

Preceded by: CSNK1A1 phosphorylates SMO dimer

Followed by: ADRBK1 phosphorylates SMO dimer

Literature references

Chen, Y., Sasai, N., Ma, G., Yue, T., Jia, J., Briscoe, 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. ↗

Chen, Y., Li, S., Tong, C., Zhao, Y., Wang, B., Liu, Y. et al. (2010). G protein-coupled receptor kinase 2 promotes high-level Hedgehog signaling by regulating the active state of Smo through kinase-dependent and kinase-independent mechanisms in Drosophila. *Genes Dev., 24*, 2054-67. ↗

Zhao, Y., Tong, C., Jiang, J. (2007). Hedgehog regulates smoothened activity by inducing a conformational switch. *Nature, 450*, 252-8. ↗

Meloni, AR., Fralish, GB., Kelly, P., Salahpour, A., Chen, JK., Wechsler-Reya, RJ. et al. (2006). Smoothened signal transduction is promoted by G protein-coupled receptor kinase 2. *Mol. Cell. Biol., 26*, 7550-60. ↗

Philipp, M., Fralish, GB., Meloni, AR., Chen, W., MacInnes, AW., Barak, LS. et al. (2008). Smoothened signaling in vertebrates is facilitated by a G protein-coupled receptor kinase. *Mol. Biol. Cell, 19*, 5478-89. ↗

Editions

2014-10-28	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

ADRBK1 phosphorylates SMO dimer ↗

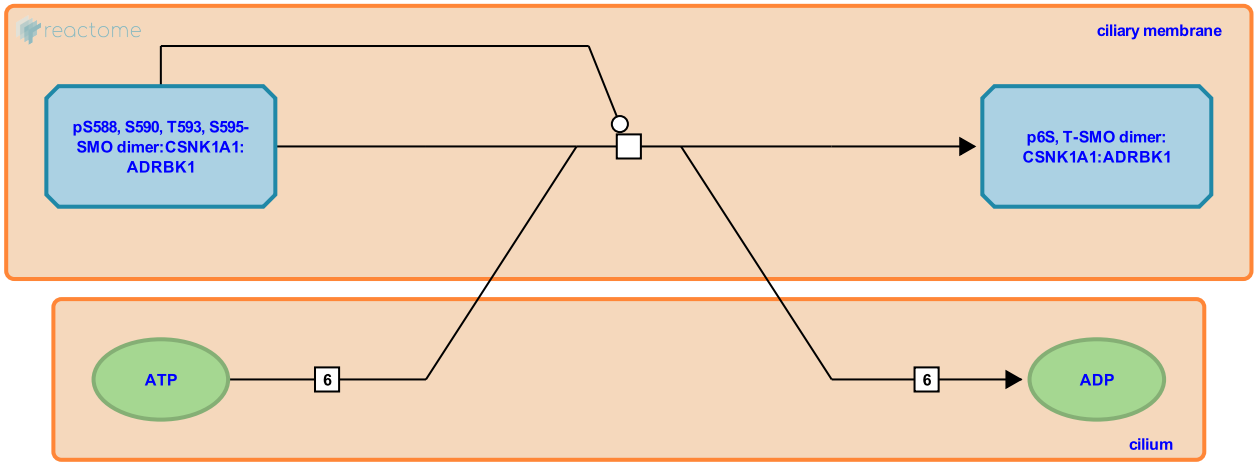
Location: Activation of SMO

Stable identifier: R-HSA-5632672

Type: transition

Compartments: ciliary membrane

Inferred from: Adrbk1 phosphorylates Smo dimer (Mus musculus)



ADRBK1 phosphorylates the SMO C-terminal tail after initial phosphorylation by CSNK1A1. Phosphorylation promotes an open, activated conformation of the C-terminal tails, allowing an intramolecular interaction between tails of adjacent monomers in the SMO dimer. This Hh-dependent conformational change is required for downstream signal propagation (Chen et al, 2011; Chen et al, 2010; Zhao et al, 2007; Meloni et al, 2006; Philipp et al, 2008; reviewed in Briscoe and Therond, 2013). In Drosophila, Smo C-terminal tail phosphorylation promotes an association with the Hedgehog signaling complex (HSC) through interaction with the scaffolding kinesin-2 like protein Cos2, and ultimately results in the release of full-length Ci from the complex (Zhang et al, 2005; Ogden et al, 2003; Lum et al, 2003; reviewed in Mukhopadhyay and Rohatgi, 2014). How Hh signal is transmitted from activated SMO to downstream components in vertebrate cells is not fully established

Preceded by: ADRBK1 binds phosphorylated SMO dimer

Followed by: CSNK1A1 and ADRBK1 dissociate from p-SMO dimer

Literature references

Chen, Y., Sasai, N., Ma, G., Yue, T., Jia, J., Briscoe, 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. ↗

Chen, Y., Li, S., Tong, C., Zhao, Y., Wang, B., Liu, Y. et al. (2010). G protein-coupled receptor kinase 2 promotes high-level Hedgehog signaling by regulating the active state of Smo through kinase-dependent and kinase-independent mechanisms in Drosophila. *Genes Dev., 24*, 2054-67. ↗

Zhao, Y., Tong, C., Jiang, J. (2007). Hedgehog regulates smoothened activity by inducing a conformational switch. *Nature, 450*, 252-8. ↗

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

Meloni, AR., Fralish, GB., Kelly, P., Salahpour, A., Chen, JK., Wechsler-Reya, RJ. et al. (2006). Smoothened signal transduction is promoted by G protein-coupled receptor kinase 2. *Mol. Cell. Biol., 26*, 7550-60. ↗

Editions

2014-10-24	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

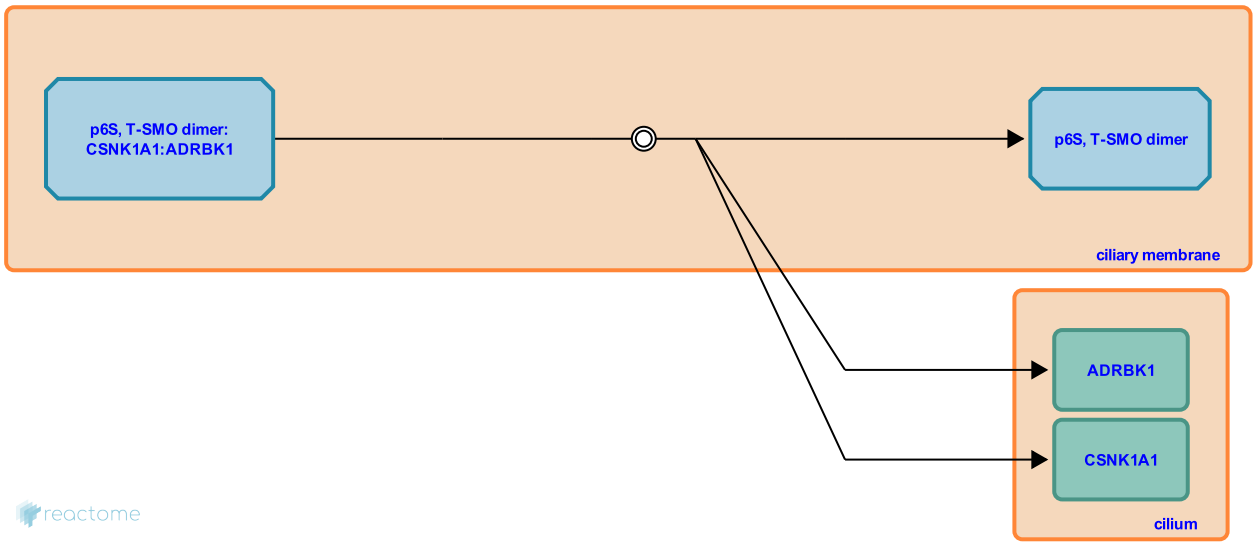
CSNK1A1 and ADRBK1 dissociate from p-SMO dimer ↗

Location: Activation of SMO

Stable identifier: R-HSA-5633040

Type: dissociation

Compartments: ciliary membrane



After phosphorylating the SMO dimer, CSNK1A1 and ADRBK1 presumably dissociate, although this has not been demonstrated explicitly (Chen et al, 2011).

Preceded by: ADRBK1 phosphorylates SMO dimer

Followed by: EVC2:EVC binds p-SMO

Literature references

Chen, Y., Sasai, N., Ma, G., Yue, T., Jia, J., Briscoe, 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. ↗

Editions

2014-10-28	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

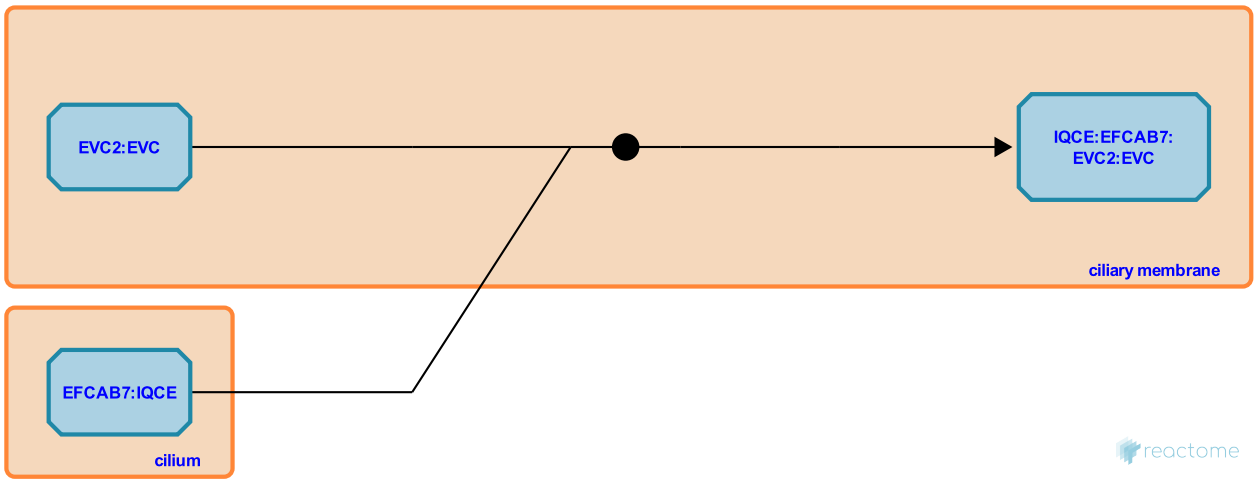
EFCAB7:IQCE binds EVC2:EVC ↗

Location: Activation of SMO

Stable identifier: R-HSA-5633051

Type: binding

Compartments: ciliary membrane



IQCE and EFCAB7 are ciliary proteins that are required to restrict the EVC2:EVC complex to the 'EVC region' at the base of the cilium, just distal to the transition zone (Pusapati et al, 2014). EVC2 and EVC are transmembrane proteins that form a ciliary-localized complex that is a positive regulator of Hh signal transduction. The EVC2:EVC complex appears to act downstream of both SMO ciliary localization and its activation by CSNK1A1 and ADRBK1, and is required for the dissociation of the GLI:SUFU complex at the ciliary tip, although the mechanism for this is not known (Blair et al, 2011; Dorn et al, 2012; Capparos-Martin et al, 2013; Pusapati et al, 2014). EVC2 interacts with the IQCE:EFCAB7 subcomplex through the so called 'W-peptide', a stretch of amino acids in the intracellular tail that is deleted in the ciliopathy Weyers Acrofacial Dysostosis. Deletion of the W-peptide results in mislocalization of EVC2 throughout the length of the cilium, rather than being concentrated in the 'EVC zone' (Pusapati et al, 2014; Dorn et al, 2012; Capparos-Martin et al, 2011). EVC2:EVC localization to the EVC region, mediated by the IQCE:EFCAB7 complex and the W-peptide, is required for the Hh-dependent activation of full-length GLI2, but does not appear to critical for the regulation of GLI3R levels, suggesting a bifurcation of the pathway (Pusapati et al, 2014).

Literature references

Pusapati, GV., Hughes, CE., Dorn, KV., Zhang, D., Sugianto, P., Aravind, L. et al. (2014). EFCAB7 and IQCE regulate hedgehog signaling by tethering the EVC-EVC2 complex to the base of primary cilia. *Dev. Cell, 28*, 483-96. ↗

Dorn, KV., Hughes, CE., Rohatgi, R. (2012). A Smoothened-Evc2 complex transduces the Hedgehog signal at primary cilia. *Dev. Cell, 23*, 823-35. ↗

Caparrós-Martín, JA., Valencia, M., Reytor, E., Pacheco, M., Fernandez, M., Perez-Aytes, A. et al. (2013). The ciliary Evc/Evc2 complex interacts with Smo and controls Hedgehog pathway activity in chondrocytes by regulating Sufu/Gli3 dissociation and Gli3 trafficking in primary cilia. *Hum. Mol. Genet., 22*, 124-39. ↗

Blair, HJ., Tompson, S., Liu, YN., Campbell, J., MacArthur, K., Ponting, CP. et al. (2011). Evc2 is a positive modulator of Hedgehog signalling that interacts with Evc at the cilia membrane and is also found in the nucleus. *BMC Biol., 9*, 14. ↗

Editions

2014-10-28	Authored	Rothfels, K.
2014-10-31	Edited	Gillespie, ME.
2014-11-09	Reviewed	Liu, Y C.

EVC2:EVC binds p-SMO ↗

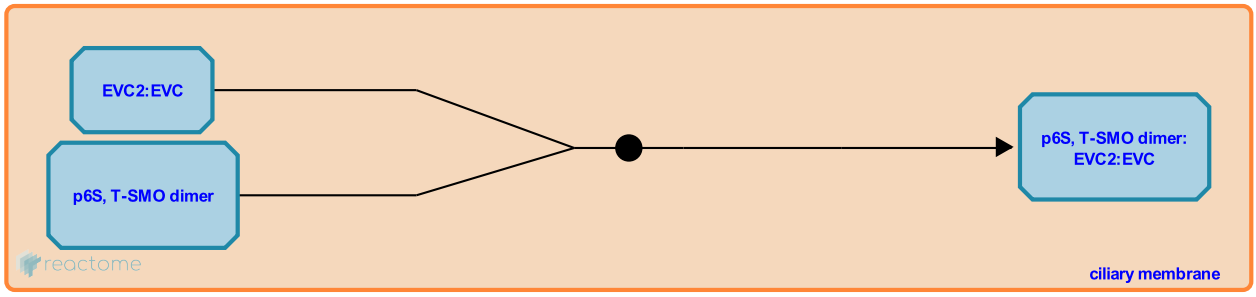
Location: Activation of SMO

Stable identifier: R-HSA-5632679

Type: binding

Compartments: ciliary membrane

Inferred from: Evc2:Evc binds Smo (Mus musculus)



EVC2 and EVC are components of a complex that localizes to the base of the cilium in a so-called EvC zone just distal to the transition zone. Mutations in the genes for EVC2 and EVC are associated with the ciliopathy Ellis van Creveld syndrome and result in an abrogated response to stimulation by Hh, making EVC2 and EVC positive regulators of Hh signaling (Blair et al, 2011; Dorn et al, 2012; Caparros-Martin et al, 2013). The EVC2:EVC complex interacts with SMO in the cilium after Hh stimulation and restricts SMO localization to the EvC zone (Dorn et al, 2012; Yang et al, 2012; Caparros-Martin et al, 2013). Disruption of the EVC2:EVC complex does not interfere with SMO ciliary localization or its activation by CSNK1A1 and ADRBK1, but prevents the Hh-dependent localization of the GLI transcription factors to the tip of the cilium and abrogates the dissociation of the GLI:SUFU complex (Dorn et al, 2012; Yang et al, 2012; Caparros-Martin et al, 2013). These events are required for the activation of the GLI transcription factors in response to ligand stimulation. Localization of the EVC2:EVC complex to the EVC zone depends on an interaction between the EVC2 W peptide (a stretch of 43 amino-acids in the C-terminal tail that is missing in a disease associated EVC2-variant), and the IQCE:EFCAB7 complex. Abrogation of this interaction causes the EVC2:EVC complex to localize along the length of the cilium and disrupts production and nuclear translocation of the full length GLI2 transcriptional activator (Pusapati et al, 2014). How the Hh signal is transmitted from the SMO:EVC2:EVC complex to downstream components is not known.

Preceded by: CSNK1A1 and ADRBK1 dissociate from p-SMO dimer

Literature references

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Editions

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