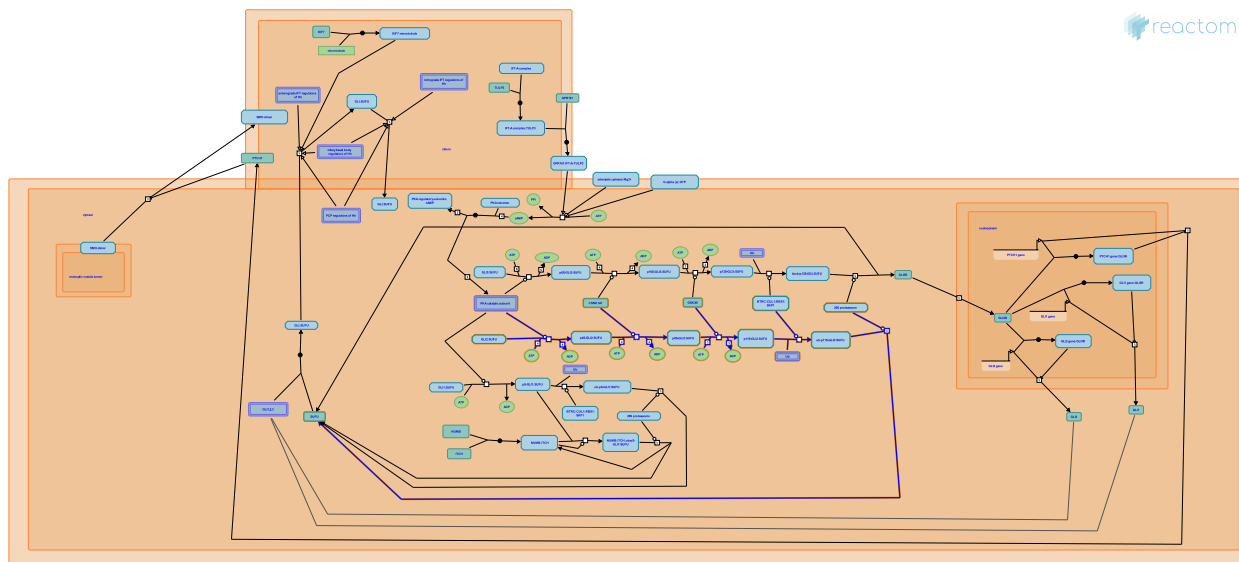


Degradation of GLI2 by the proteasome



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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/).

17/05/2024

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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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. [↗](#)

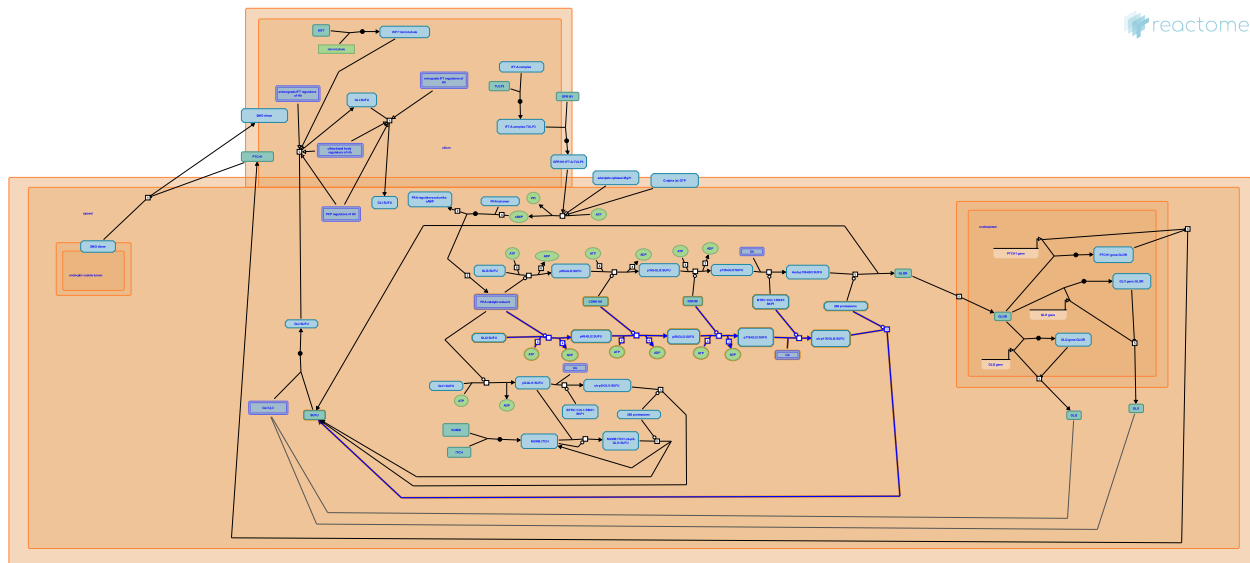
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 5 reactions ([see Table of Contents](#))

Degradation of GLI2 by the proteasome ↗

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. ↗

Wang, C., Pan, Y., Wang, B. (2009). Phosphorylation of Gli2 by protein kinase A is required for Gli2 processing and degradation and the Sonic Hedgehog-regulated mouse development. *Dev. Biol.*, 326, 177-89. ↗

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. ↗

Editions

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

PKA phosphorylates GLI2 ↗

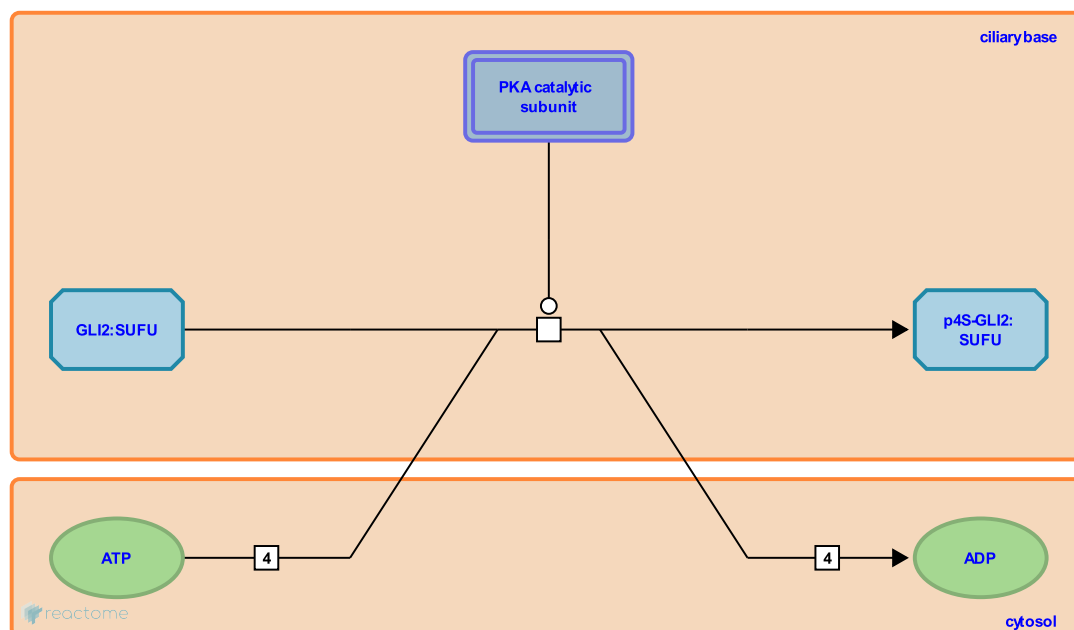
Location: [Degradation of GLI2 by the proteasome](#)

Stable identifier: R-HSA-5610717

Type: transition

Compartments: ciliary base

Inferred from: [Pka phosphorylates Gli2 \(Mus musculus\)](#)



Despite sharing 44% amino acid identity with GLI3, only a small fraction of GLI2 appears to be processed to a repressor form in the absence of Hh signaling; the bulk of the protein is completely degraded in a phosphorylation- and proteasome-dependent manner (Pan et al, 2007; Pan et al, 2009; Pan and Wang, 2007). Degradation of GLI2 depends on phosphorylation of four consensus PKA sites in the C-terminal region. This phosphorylation primes GLI2 for subsequent phosphorylation by CK1 and GSK3, creating a binding site for betaTrCP and promoting its subsequent ubiquitination and degradation (Pan et al, 2006; Pan and Wang, 2007; Pan et al, 2009).

Followed by: [CK1 phosphorylates p-GLI2](#)

Literature references

- Wang, C., Pan, Y., Wang, B. (2009). Phosphorylation of Gli2 by protein kinase A is required for Gli2 processing and degradation and the Sonic Hedgehog-regulated mouse development. *Dev. Biol.*, 326, 177-89. ↗
- 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. ↗
- 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. ↗

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CK1 phosphorylates p-GLI2 ↗

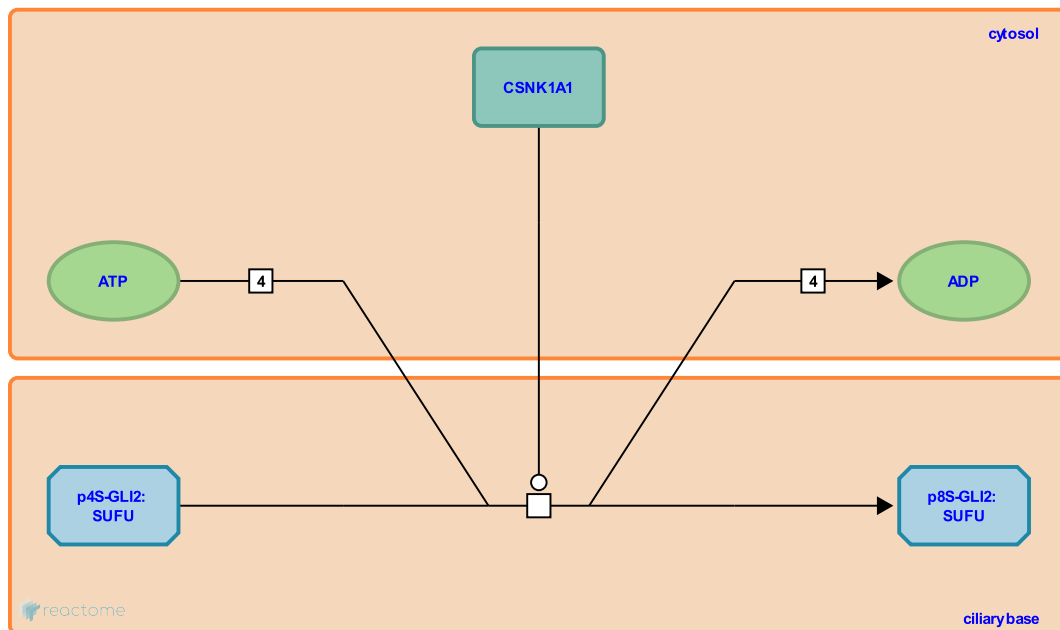
Location: [Degradation of GLI2 by the proteasome](#)

Stable identifier: R-HSA-5610718

Type: transition

Compartments: ciliary base

Inferred from: [CK1 phosphorylates p-Gli2 \(Mus musculus\)](#)



Phosphorylation by PKA primes GLI2 for subsequent phosphorylation at adjacent CK sites (Pan et al, 2006; Pan and Wang, 2007).

Preceded by: [PKA phosphorylates GLI2](#)

Followed by: [GSK3 phosphorylates p-GLI2](#)

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. ↗

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. ↗

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GSK3 phosphorylates p-GLI2 ↗

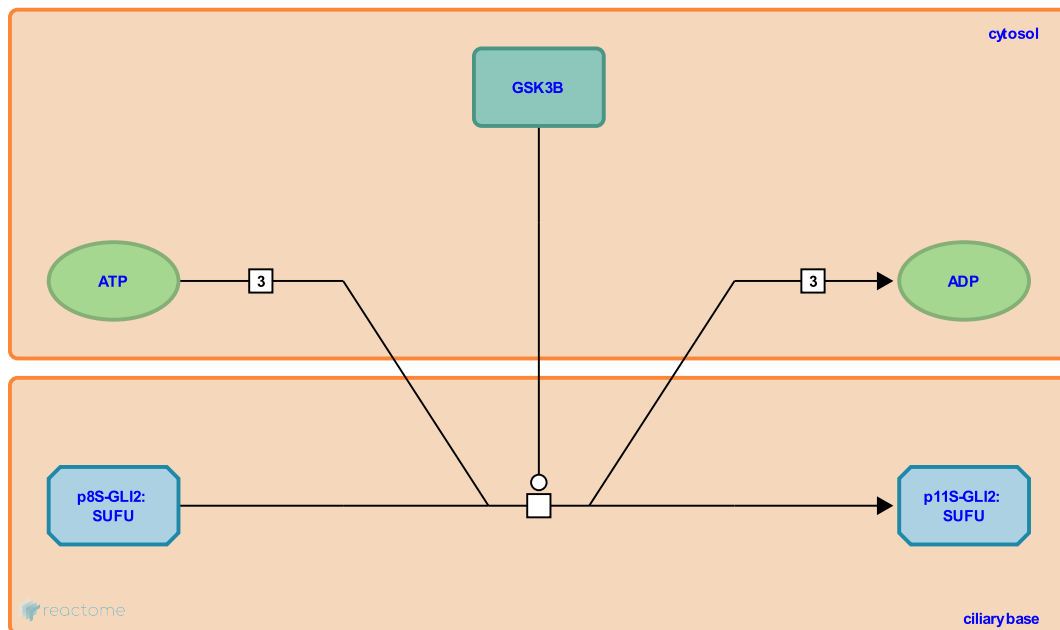
Location: [Degradation of GLI2 by the proteasome](#)

Stable identifier: R-HSA-5610730

Type: transition

Compartments: ciliary base

Inferred from: [GSK3 phosphorylates p-Gli2 \(Mus musculus\)](#)



Like GLI3, GLI2 has putative GSK3 sites that contribute to the proteasome-dependent degradation of the protein in the absence of Hh signal. Deletion of the GSK3 phosphorylation sites abrogates the interaction with beta-TrCP, stabilizes GLI2 protein and increases the expression of a GLI-dependent reporter, consistent with a role for GSK3 in promoting GLI2 degradation (Pan et al, 2006).

Preceded by: [CK1 phosphorylates p-GLI2](#)

Followed by: [SCF\(beta-TrCP\) ubiquitinates p-GLI2](#)

Literature references

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. ↗

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SCF(beta-TrCP) ubiquitinates p-GLI2 ↗

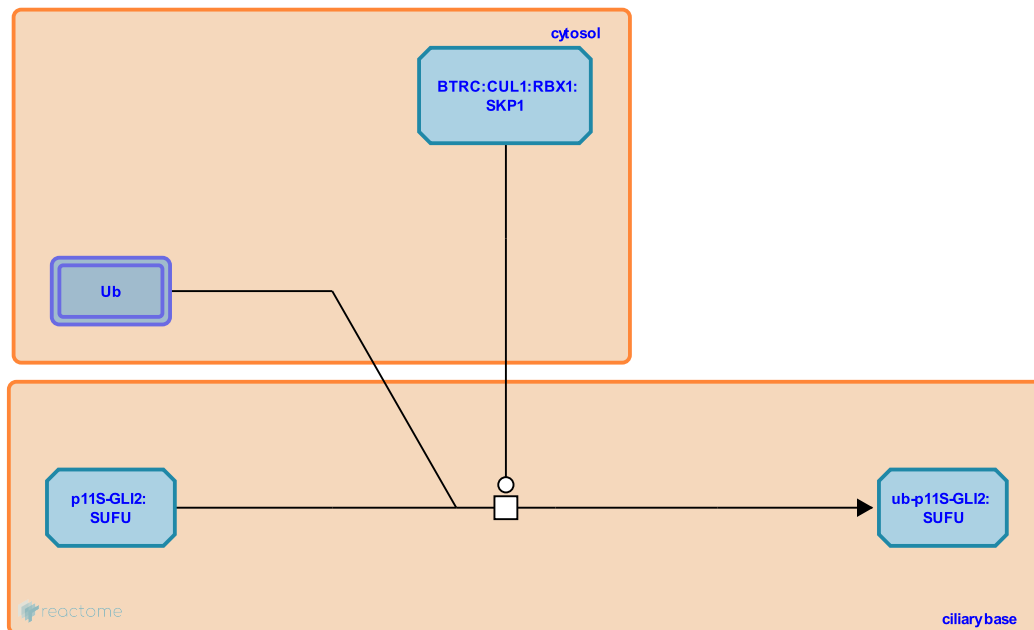
Location: [Degradation of GLI2 by the proteasome](#)

Stable identifier: R-HSA-5610745

Type: transition

Compartments: ciliary base

Inferred from: [SCF\(beta-TrCP\) ubiquitinates p-Gli2 \(Homo sapiens\)](#)



GLI2 interacts directly with beta-TrCP and is polyubiquitinated in a phosphorylation-dependent manner. Binding and ubiquitination by beta-TrCP depends on 2 motifs located in the region of GLI2 phosphorylated by PKA, CK1 and GSK3 (Pan et al, 2006).

Preceded by: [GSK3 phosphorylates p-GLI2](#)

Followed by: [GLI2 is degraded by the proteasome](#)

Literature references

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

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2014-08-01	Reviewed	Liu, Y C.

GLI2 is degraded by the proteasome ↗

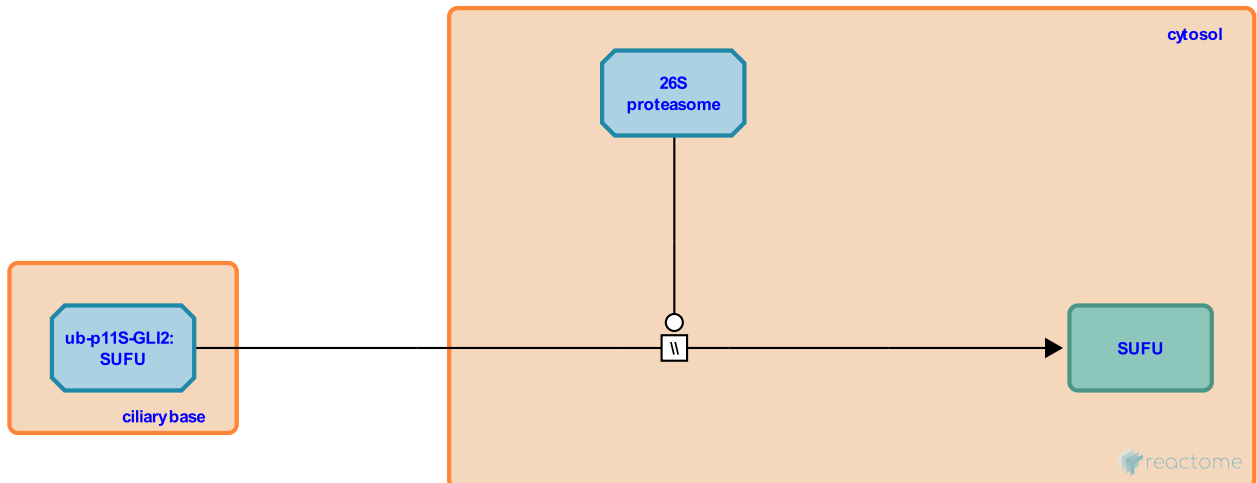
Location: [Degradation of GLI2 by the proteasome](#)

Stable identifier: R-HSA-5610757

Type: omitted

Compartments: cytosol

Inferred from: [Gli2is degraded by the proteasome \(Homo sapiens\)](#)



After being ubiquitinated, the bulk of GLI2 is fully degraded by the proteasome; a small fraction of GLI2 may be converted to the repressor form after ubiquitination (Pan et al, 2006; Pan and Wang, 2007).

Preceded by: [SCF\(beta-TrCP\) ubiquitinates p-GLI2](#)

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. ↗

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. ↗

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