GLI3 is processed to GLI3R by the proteasome

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


Reactome database release: 69

This document contains 1 pathway and 5 reactions (see Table of Contents)
GLI3 is processed to GLI3R by the proteasome

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 betaTrCP-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


Editions

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https://reactome.org
Phosphorylation of GLI3 by PKA on up to six sites in the C-terminal region primes the protein for subsequent phosphorylation by CK1 and GSK3 and is required for the ubiquitin-mediated processing by the proteasome to yield the truncated repressor form (Tempe et al, 2006; Pan et al, 2006; Pan and Wang, 2007; Wang and Li, 2006). Processing of GLI3 is regulated in part by movement through the primary cilia, and disruption of intraflagellar transport abrogates processing (Wen et al, 2010).

Followed by: CK1 phosphorylates p-GLI3

Literature references


**CK1 phosphorylates p-GLI3**

**Location:** GLI3 is processed to GLI3R by the proteasome

**Stable identifier:** R-HSA-5610722

**Type:** transition

**Compartments:** cytosol

Phosphorylation by PKA primes GLI3 for subsequent phosphorylation by CK1 at four or more sites. These serial phosphorylations are required for the recruitment of beta-TrCP and subsequent ubiquitination and processing of GLI3 (Tempe et al, 2006; Wang and Li, 2006; Wen et al, 2010; Schrader et al, 2011)

**Preceded by:** PKA phosphorylates GLI3

**Followed by:** GSK3 phosphorylates p-GLI3

**Literature references**


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GSK3 phosphorylates p-GLI3

Location: GLI3 is processed to GLI3R by the proteasome

Stable identifier: R-HSA-5610732

Type: transition

Compartments: cytosol

GSK3-mediated phosphorylation of GLI3 is primed by earlier phosphorylations by PKA and CK1 and is required for the subsequent recruitment of beta-TrCP (Tempe et al, 2006; Wang and Li, 2006).

Preceded by: CK1 phosphorylates p-GLI3

Followed by: SCF(beta-TrCP) ubiquitinates p-GLI3

Literature references


SCF(beta-TrCP) ubiquinates p-GLI3

**Location:** GLI3 is processed to GLI3R by the proteasome

**Stable identifier:** R-HSA-5610746

**Type:** transition

**Compartments:** cytosol

Hyperphosphorylated GLI3 binds directly with beta-TrCP though at least three independent domains and is polyubiquitinatated at lysines 773, 778, 784 and 800 (Tempe et al, 2006). After ubiquitination, GLI3 is processed to the truncated repressor form by the proteasome (Tempe et al, 2006; Wang and Li, 2006)

**Preceded by:** GSK3 phosphorylates p-GLI3

**Followed by:** GLI3 is partially degraded by the proteasome to yield the GLI3 repressor

**Literature references**


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GLI3 is partially degraded by the proteasome to yield the GLI3 repressor

**Location:** GLI3 is processed to GLI3R by the proteasome

**Stable identifier:** R-HSA-5610754

**Type:** omitted

**Compartments:** cytosol

After phosphorylation and ubiquitination, GLI3 is processed by the proteasome to an 83-kDa repressor form that lacks the C-terminal activation domain (Wang et al, 2000; Tempe et al, 2006; Wang and Li, 2006). Partial processing appears to rely on at least three features of the GLI3 protein: the folded N-terminal zinc finger domain, an adjacent simple linker sequence, and the degron in the C-terminus that contains the phosphorylation and ubiquitination target residues (Pan and Wang, 2007; Schrader et al, 2011). The C-terminal end of the processed repressor form is not precisely defined.

**Preceded by:** SCF(beta-TrCP) ubiquitinates p-GLI3

**Literature references**


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