Degradation of GLI1 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 6 reactions (see Table of Contents)
**Degradation of GLI1 by the proteasome**

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**


**Editions**

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PKA phosphorylates GLI1

Location: Degradation of GLI1 by the proteasome

Stable identifier: R-HSA-5610741

Type: transition

Compartments: ciliary base

Inferred from: Pka phosphorylates GLI1 (Mus musculus)

Although direct phosphorylation of GLI1 by PKA has not been demonstrated, deletion of the putative PKA sites abrogates the interaction of GLI1 with beta-TrCP and stabilizes GLI1 protein levels; similarly, treatment of GLI1-expressing cells with PKA inhibitors delays the kinetics of GLI1 degradation (Huntzicker et al, 2006). These data are consistent with a role for PKA-mediated phosphorylation in promoting the proteasome-dependent degradation of GLI1 in the absence of Hh signal, as is the case for GLI2 and GLI3 (Huntzicker et al, 2006; Tempe et al, 2006; Pan and Wang, 2007; Pan et al, 2009). Potential roles for CK2 and GSK3 in promoting the phosphorylation-dependent degradation of GLI1 have not been investigated.

Followed by: SCF(beta-TrCP) ubiquitinates p-GLI1, NUMB:ITCH bind and ubiquitin GLI1

Literature references


## Editions

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SCF(beta-TrCP) ubiquitinates p-GLI1

Location: Degradation of GLI1 by the proteasome

Stable identifier: R-HSA-5610742

Type: transition

Compartments: ciliary base

GLI1 protein is degraded by the proteasome in the absence of Hh signal. GLI1 levels are stabilized by treatment of cells with the proteasome inhibitor MG312, and GLI1 and beta-TrCP1 co-precipitate when expressed in NIH 3T3 cells.

Two SCF(beta-TrCP)-dependent degradation sites, Dn and Dc, have been identified in human GLI1. Removal of these sites abrogates the interaction with beta-TrCP, reduces the beta-TrCP-dependent ubiquitination of GLI1 and stabilizes the GLI1 protein levels. As is the case for GLI2 and GLI3, ubiquitination of GLI1 depends on the its prior phosphorylation by PKA, as GLI1 degradation is sensitive to PKA inhibitors and removal of the putative PKA sites abrogates the interaction with beta-TrCP and delays the kinetics of degradation (Huntzicker et al, 2006).

Preceded by: PKA phosphorylates GLI1

Followed by: GLI1 is degraded by the proteasome after ubiquitination by beta-TrCP

Literature references


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GLI1 is degraded by the proteasome after ubiquitination by beta-TrCP

Location: Degradation of GLI1 by the proteasome

Stable identifier: R-HSA-5610758

Type: omitted

Compartments: cytosol

In the absence of Hh signal, GLI1 is degraded by the proteasome. Degradation depends on GLI1 ubiquitination by SCF(beta-TrCP) and by the E3 ligase ITCH (Huntzicker et al, 2006; di Marcotullio et al, 2006, 2011).

Preceded by: SCF(beta-TrCP) ubiquitinates p-GLI1

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NUMB binds ITCH

Location: Degradation of GLI1 by the proteasome

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 bind and ubiquitnate GLI1

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NUMB:ITCH bind and ubiquitnate GLI1

Location: Degradation of GLI1 by the proteasome

Stable identifier: R-HSA-5610737

Type: transition

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). How these two apparently parallel systems of GLI1 ubiquitination and degradation are coordinated is not yet clear.

Preceded by: NUMB binds ITCH, PKA phosphorylates GLI1

Followed by: GLI1 is degraded by the proteasome after ubiquitination by ITCH

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GLI1 is degraded by the proteasome after ubiquitination by ITCH

**Location:** Degradation of GLI1 by the proteasome

**Stable identifier:** R-HSA-5610760

**Type:** omitted

**Compartments:** cytosol

In the absence of Hh signal, GLI1 is degraded by the proteasome. Degradation depends on GLI1 ubiquitination by SCF(beta-TrCP) and by the E3 ligase ITCH (Huntzicker et al, 2006; di Marcotullio et al, 2006, 2011).

**Preceded by:** NUMB:ITCH bind and ubiquitnate GLI1

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