



## 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

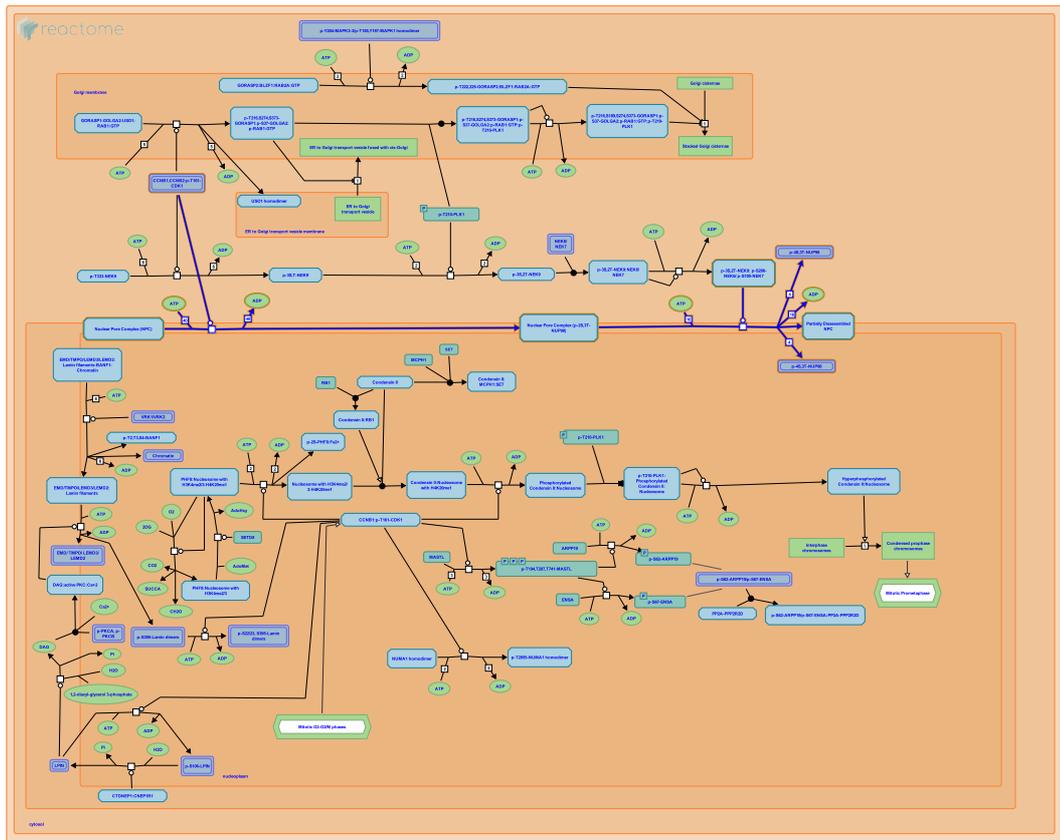
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Reactome database release: 69

This document contains 1 pathway and 2 reactions ([see Table of Contents](#))

# Nuclear Pore Complex (NPC) Disassembly ↗

Stable identifier: R-HSA-3301854



Nuclear envelope breakdown in mitosis involves permeabilization of the nuclear envelope through disassembly of the nuclear pore complex (NPC) (reviewed by Guttinger et al. 2009). Nucleoporin NUP98, located at both the cytoplasmic and the nucleoplasmic side of the NPC (Griffis et al. 2003), and involved in the formation of the transport barrier through its FG (phenylalanine glycine) repeats that protrude into the central cavity of the NPC (Hulsmann et al. 2012), is probably the first nucleoporin that dissociates from the NPC at the start of mitotic NPC disassembly (Dultz et al. 2008). NUP98 dissociation is triggered by phosphorylation. Phosphorylation of NUP98 by CDK1 and NIMA family kinases NEK6 and/or NEK7 is needed for NUP98 dissociation from the NPC (Laurell et al. 2011). While the phosphorylation of NUP98 by CDK1 and NEK6/7 is likely to occur simultaneously, CDK1 and NEK6/7-mediated phosphorylations are shown as separate events, for clarity purposes.

## Literature references

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## Editions

2013-01-18	Authored	Orlic-Milacic, M.
2013-01-23	Edited	Gillespie, ME.
2013-05-17	Reviewed	Antonin, W.

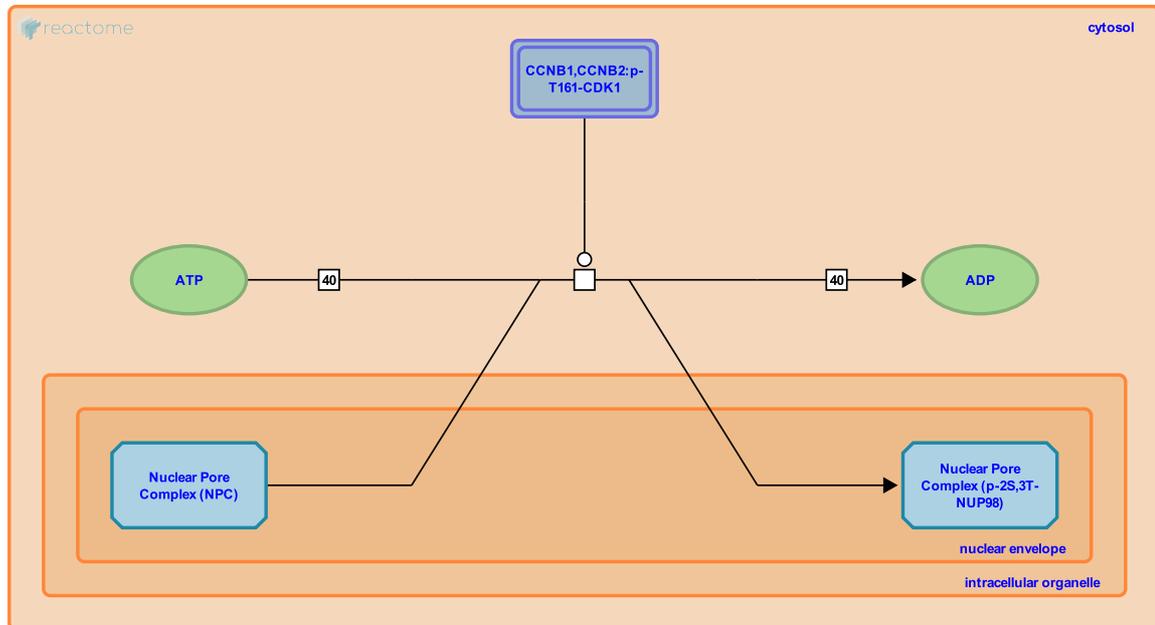
## CDK1 phosphorylates NUP98 ↗

**Location:** [Nuclear Pore Complex \(NPC\) Disassembly](#)

**Stable identifier:** R-HSA-2990882

**Type:** transition

**Compartments:** cytosol, nuclear envelope



CDK1 activity promotes the nuclear pore complex (NPC) disassembly in mitosis (Mühlhäusser and Kutay 2007). While NUP98 is probably not the only nucleoporin phosphorylated by CDK1 at mitotic entry, NUP98 is the best characterized CDK1 target among nuclear pore complex components. NUP98 threonine residues T529, T536, and T653, as well as serine residues S595 and S606 were found to be phosphorylated when NUP98 was isolated from mitotic HeLa cells (human cervical carcinoma cell line); these five sites match the CDK1 target site consensus and are phosphorylated by CDK1:CCNB in vitro (Laurell et al. 2011). The NUP98 splicing isoform NUP98-4 was used in the study by Laurell et al. 2011 and the indicated positions of phosphorylated amino acid residues refer to this isoform. An additional splicing isoform NUP98-3, the product of an alternative splicing site in exon10 of the NUP98 gene, which is 17 amino acids longer than NUP98-4, could also be a part of the NPC. CDK1-phosphorylated residues in NUP98-3 would be threonines T546, T553 and T670, and serines S612 and S623.

**Followed by:** [NEK6/NEK7 phosphorylates NUP98](#)

### Literature references

Laurell, E., Beck, K., Krupina, K., Theerthagiri, G., Bodenmiller, B., Horvath, P. et al. (2011). Phosphorylation of Nup98 by multiple kinases is crucial for NPC disassembly during mitotic entry. *Cell*, 144, 539-50. ↗

Mühlhäusser, P., Kutay, U. (2007). An in vitro nuclear disassembly system reveals a role for the RanGTPase system and microtubule-dependent steps in nuclear envelope breakdown. *J. Cell Biol.*, 178, 595-610. ↗

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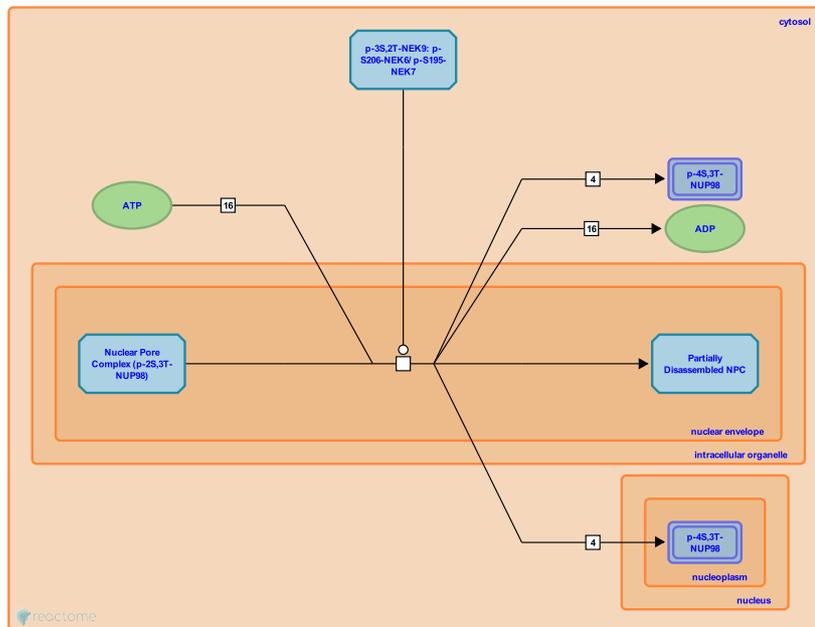
## NEK6/NEK7 phosphorylates NUP98 ↗

**Location:** Nuclear Pore Complex (NPC) Disassembly

**Stable identifier:** R-HSA-2990880

**Type:** transition

**Compartments:** nuclear envelope, cytosol, nucleoplasm



Phosphorylation of NUP98 by NEK6 (and/or NEK7) promotes nuclear envelope permeabilization by initiating nuclear pore complex (NPC) disassembly. Two NUP98 serine residues, S591 and S822 (referring to NUP98 splice variant NUP98-4; these residues correspond to S608 and S839 of NUP98 splice variant NUP98-3), are phosphorylated on NUP98 isolated from mitotic HeLa cells (human cervical cancer cell line). These serine residues match the NEK6 target site consensus and are phosphorylated by NEK6 in vitro. Both sites can also be phosphorylated in vitro by NEK7 and weakly by NEK2. As NEK7 but not NEK2 was shown to be involved, with NEK6, in nuclear envelope permeabilization, NEK2 is not shown as the NUP98 kinase. Phosphorylated NUP98 dissociates from the NPC (Laurell et al. 2011). As NUP98 localizes to both sides of the NPC, cytosolic and nucleoplasmic (Griffis et al. 2003), the reaction shows a portion of NUP98 being released to the cytosol, and a portion of NUP98 dissociating into the nucleus, similar to what is observed by immunocytochemistry (Laurell et al. 2011).

**Preceded by:** CDK1 phosphorylates NUP98

### Literature references

Laurell, E., Beck, K., Krupina, K., Theerthagiri, G., Bodenmiller, B., Horvath, P. et al. (2011). Phosphorylation of Nup98 by multiple kinases is crucial for NPC disassembly during mitotic entry. *Cell*, 144, 539-50. ↗

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