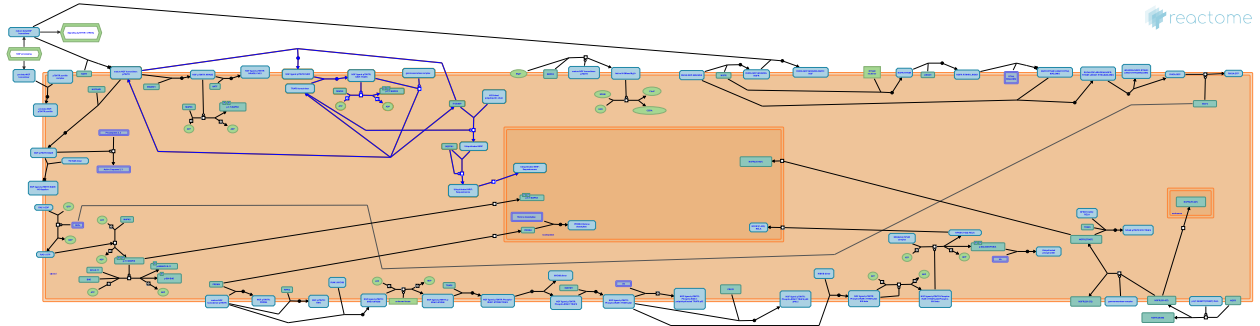


NRIF signals cell death from the nucleus



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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/textbook).

27/04/2024

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

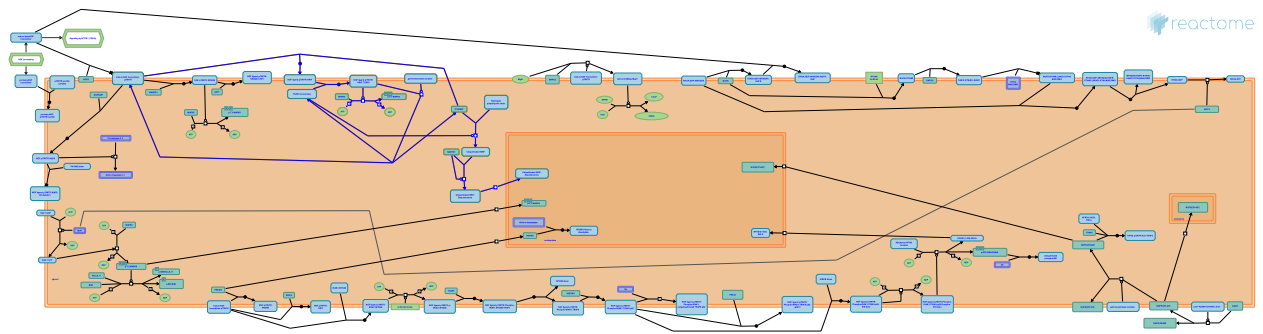
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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, 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 7 reactions ([see Table of Contents](#))

NRIF signals cell death from the nucleus [↗](#)

Stable identifier: R-HSA-205043



NRIF (nuclear receptor-interacting factor) is a DNA binding protein that is essential for p75-mediated apoptosis in retina and sympathetic neurons. Neurotrophin or proneurotrophin binding to p75TR induces nuclear translocation of NRIF, which involves gamma-secretase cleavage of p75NTR ICD (Intra Cellular Domain). Once in the nucleus, NRIF mediates apoptosis, probably by acting as transcription factor.

Literature references

Nykjaer, A., Petersen, CM., Willnow, TE. (2005). p75NTR--live or let die. *Curr Opin Neurobiol*, 15, 49-57. [↗](#)

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2008-05-20	Reviewed	Friedman, WJ.
2008-05-20	Edited	Jassal, B.
2008-05-28	Reviewed	Chao, MV.

NRIF binds to p75NTR ↗

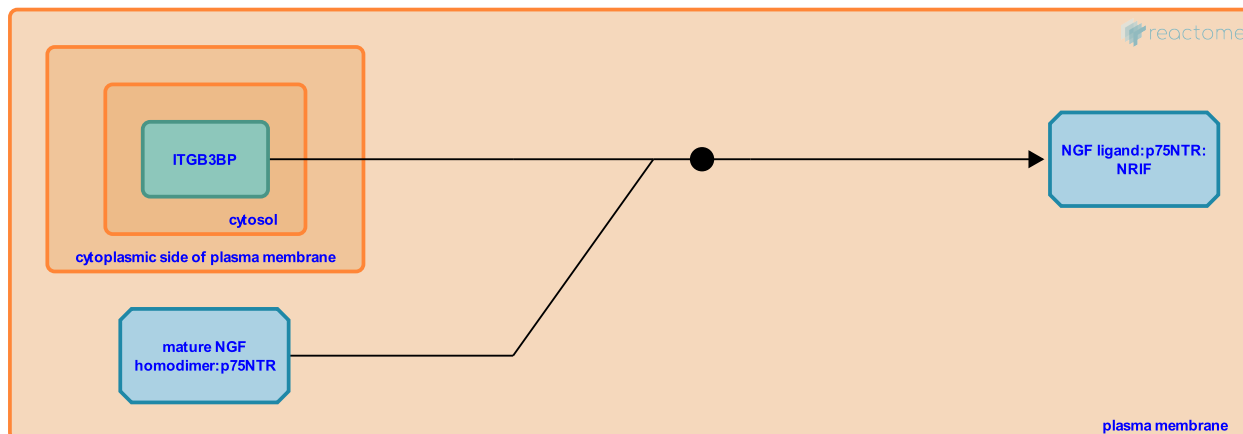
Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-193677

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: NRIF binds to p75NTR (Mus musculus)



NRIF is a ubiquitously expressed zinc finger protein of the Kruppel family that may transduce cell death signals during development and functions in association with TRAF6 to induce activation of JNK. NRIF-induced cell death through p75NTR requires p53 and NRIF nuclear translocation, which is modulated by TRAF6-mediated polyubiquitination of NRIF at lysine 63.

Followed by: TRAF6 binds to p75NTR:NRIF

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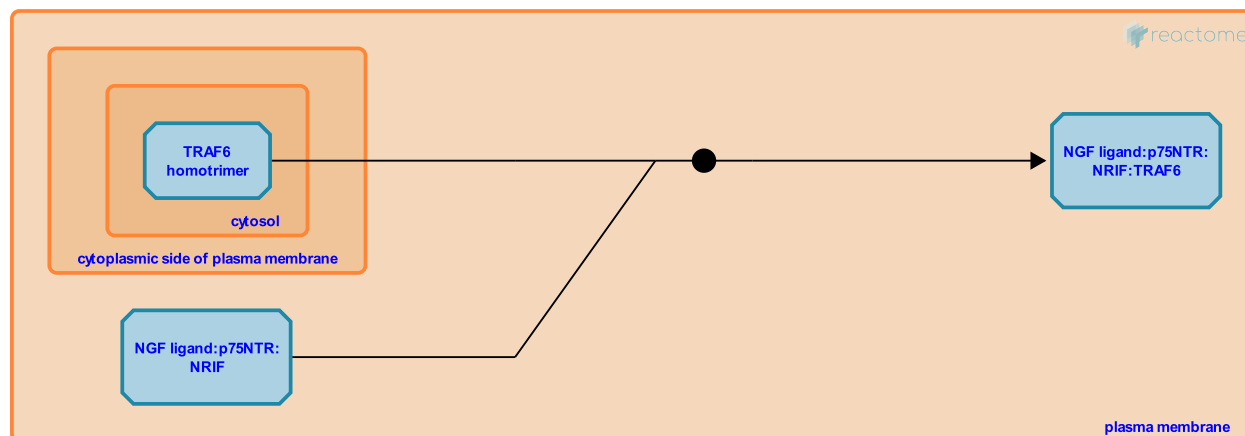
TRAF6 binds to p75NTR:NRIF [↗](#)

Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-193669

Type: binding

Compartments: plasma membrane, cytosol



Upon neurotrophin stimulation, p75NTR interacts with the ubiquitin 3 ligase TRAF6 (TNF receptor-associated factor 6). It is unclear whether TRAF6 binds to p75NTR directly, or whether it needs to be recruited through an adaptor protein such as MyD88. Recruitment of NRIF and TRAF6 to p75NTR is followed by an interaction between the two cytoplasmic proteins. It is possible that the NRIF:TRAF6 interaction promotes formation of a multimeric signalling complex. TRAF6 appears to promote NRIF release from p75NTR

Preceded by: NRIF binds to p75NTR

Followed by: NRIF and TRAF6 may activate JNK, gamma-secretase cleaves p75NTR, releasing NRIF and TRAF6

Literature references

Burke, TL., Carter, BD., Rutkoski, NJ., Gentry, JJ. (2004). A functional interaction between the p75 neurotrophin receptor interacting factors, TRAF6 and NRIF. *J Biol Chem*, 279, 16646-56. [↗](#)

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NRIF and TRAF6 may activate JNK ↗

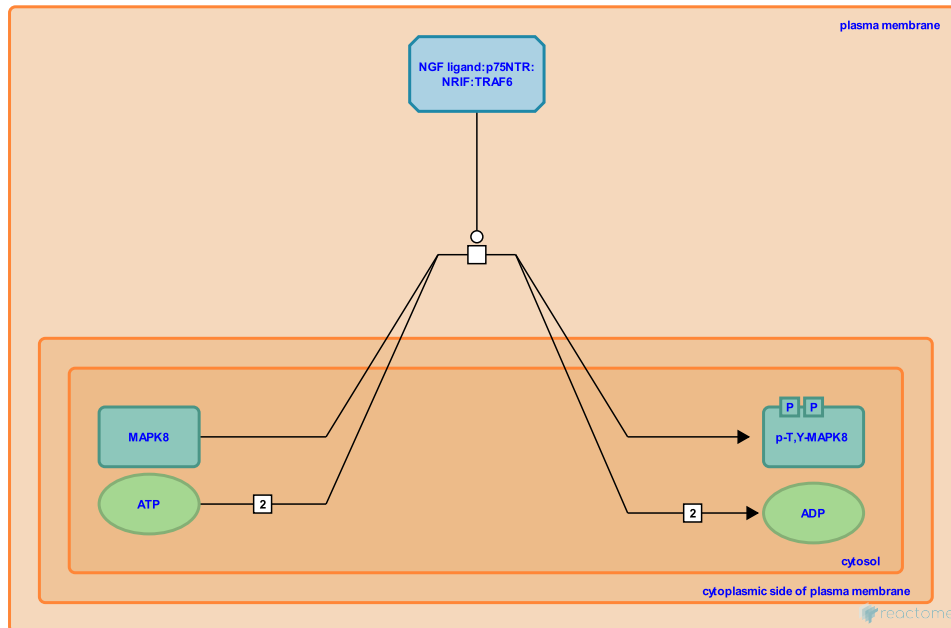
Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-204949

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: NRIF and TRAF6 may activate JNK (Mus musculus)



NRIF and TRAF6 appear to cooperate in JNK activation. TRAF6 is involved both in JNK activation and in NF- κ B activation. Although the NRIF:TRAF6 interaction enhances by threefold the TRAF6-mediated activation of JNK, it only modestly affects TRAF6-mediated activation of NF- κ B.

Preceded by: TRAF6 binds to p75NTR:NRIF

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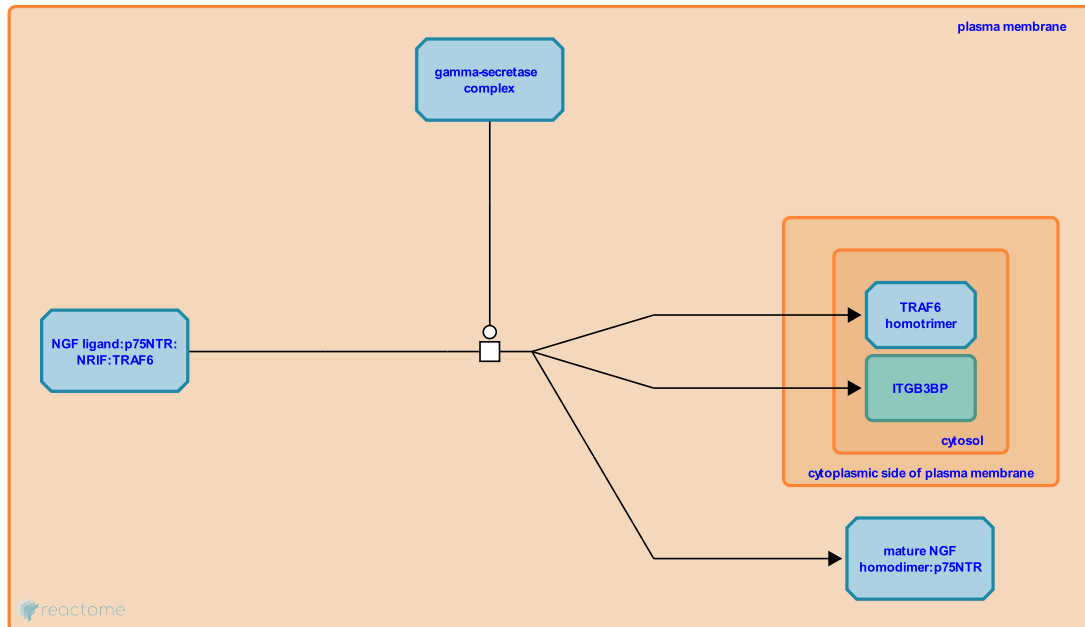
gamma-secretase cleaves p75NTR, releasing NRIF and TRAF6 ↗

Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-205112

Type: transition

Compartments: plasma membrane, cytosol



Neurotrophin or proneurotrophin signalling promotes p75NTR cleavage by gamma-secretase, allowing the release of p75 ICD and NRIF. This mechanism was shown in sympathetic neurons.

Gamma-secretase can be activated in a number of ways, including signalling via p75NTR. The phorbol ester PMA induces p75 cleavage, followed by NRIF nuclear translocation, after 30 min. Neurotrophin binding to p75, instead, triggers the same events only after 12 h.

Preceded by: TRAF6 binds to p75NTR:NRIF

Followed by: TRAF6 polyubiquitinates NRIF

Literature references

Kenchappa, RS., Carter, BD., Zampieri, N., Hempstead, BL., Barker, PA., Teng, HK. et al. (2006). Ligand-dependent cleavage of the P75 neurotrophin receptor is necessary for NRIF nuclear translocation and apoptosis in sympathetic neurons. *Neuron*, 50, 219-32. ↗

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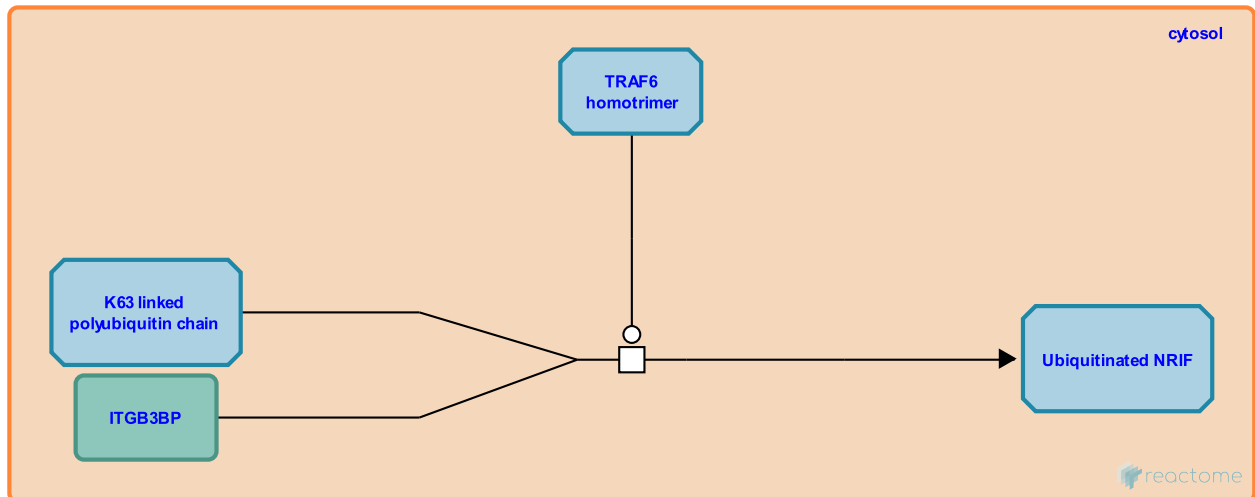
TRAF6 polyubiquitinates NRIF ↗

Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-205118

Type: transition

Compartments: cytosol



TRAF6 attaches a lysine 63-linked polyubiquitin chain to lysine 19 of NRIF. Mutation of NRIF lysine 19 prevents p75-mediated apoptosis. p75NTR cleavage by gamma-secretase is required for NRIF ubiquitination.

Preceded by: gamma-secretase cleaves p75NTR, releasing NRIF and TRAF6

Followed by: Polyubiquitinated NRIF binds to p62 (Sequestosome), Polyubiquitinated NRIF migrates to the nucleus

Literature references

Kenchappa, RS., Carter, BD., Wooten, MW., Geetha, T. (2005). TRAF6-mediated ubiquitination regulates nuclear translocation of NRIF, the p75 receptor interactor. *EMBO J*, 24, 3859-68. ↗

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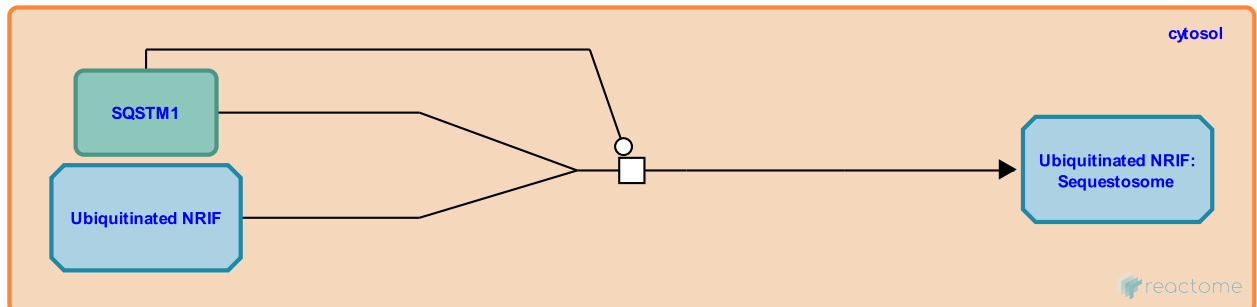
Polyubiquitinated NRIF binds to p62 (Sequestosome) [↗](#)

Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-205008

Type: transition

Compartments: cytosol



Binding of NRIF to p62 (Sequestosome) is suspected to modulate NRIF transcriptional activity.

Preceded by: TRAF6 polyubiquitinates NRIF

Literature references

Kenchappa, RS., Carter, BD., Wooten, MW., Geetha, T. (2005). TRAF6-mediated ubiquitination regulates nuclear translocation of NRIF, the p75 receptor interactor. *EMBO J*, 24, 3859-68. [↗](#)

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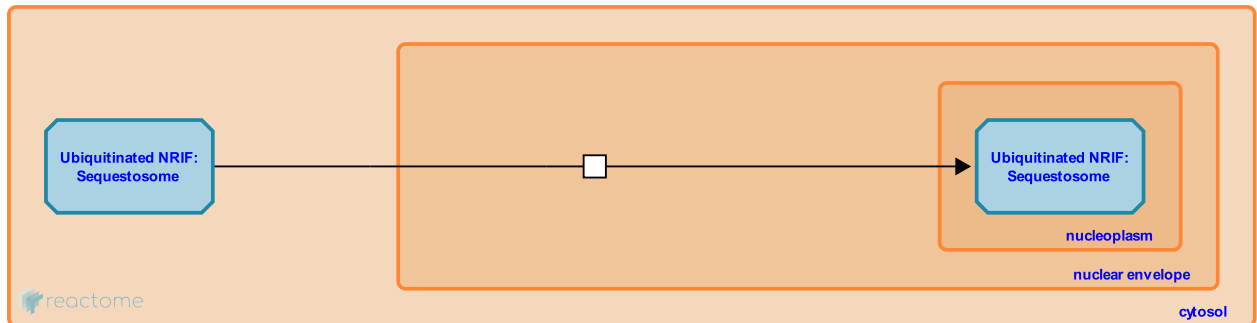
Polyubiquitinated NRIF migrates to the nucleus ↗

Location: NRIF signals cell death from the nucleus

Stable identifier: R-HSA-204947

Type: transition

Compartments: nuclear envelope



NRIF polyubiquitination is necessary for nuclear translocation. The carboxyl terminus of NRIF mediates nuclear localization, whereas the amino terminus prevents it. Once in the nucleus, NRIF regulates gene expression, acting as a transcriptional repressor.

Preceded by: TRAF6 polyubiquitinates NRIF

Literature references

Kenchappa, RS., Carter, BD., Zampieri, N., Hempstead, BL., Barker, PA., Teng, HK. et al. (2006). Ligand-dependent cleavage of the P75 neurotrophin receptor is necessary for NRIF nuclear translocation and apoptosis in sympathetic neurons. *Neuron*, 50, 219-32. ↗

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