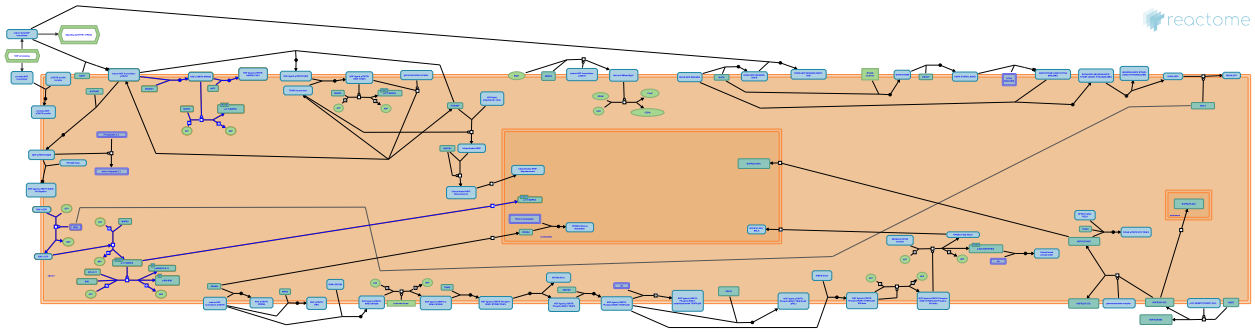
NRAGE signals death through JNK



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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

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. ↗

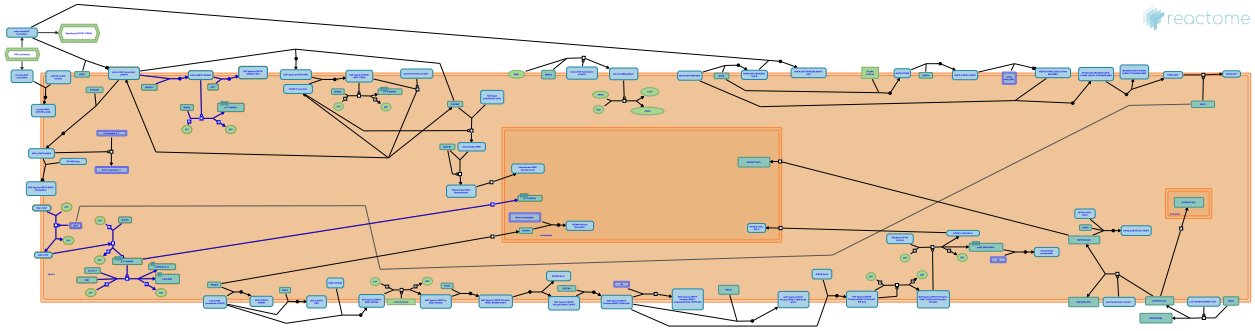
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

NRAGE signals death through JNK ↗

Stable identifier: R-HSA-193648



Once bound by either NGF or proNGF, p75NTR interacts with NRAGE, thus leading to phosphorylation and activation of JUN Kinase (JNK). JNK controls apoptosis in two ways: it induces transcription of pro-apoptotic genes, and directly activates the cell death machinery. Only NGF-bound p75NTR is shown here.

Literature references

Xanthoudakis, S., Salehi, AH., Barker, PA. (2002). NRAGE, a p75 neurotrophin receptor-interacting protein, induces caspase activation and cell death through a JNK-dependent mitochondrial pathway. *J Biol Chem, 277*, 48043-50. ↗

Editions

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NGF:p75NTR complex binds to NRAGE ↗

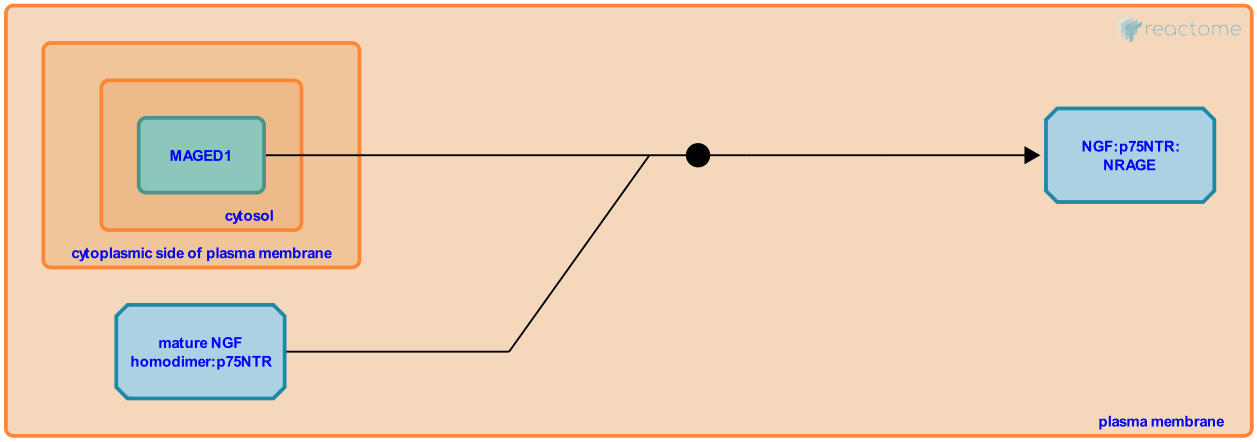
Location: NRAGE signals death through JNK

Stable identifier: R-HSA-205115

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: NGF:p75NTR complex binds to Nrage (Mus musculus)



NRAGE (neurotrophin receptor-interacting MAGE homolog), a member of the MAGE family of proteins, is a cytoplasmic protein that mediates neurotrophin-induced cell death. NRAGE binding is stimulated following NGF (or proNGF) binding to p75NTR. Some studies indicate that NRAGE expression is limited to proliferative neural populations, whereas others indicate its presence in differentiated neurons in hippocampus. Another MAGE protein, Necdin, was reported to interact with p75NTR and affect cell death.

Followed by: NRAGE sequesters CHE1 in the cytoplasm, NRAGE activates JNK

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NRAGE sequesters CHE1 in the cytoplasm ↗

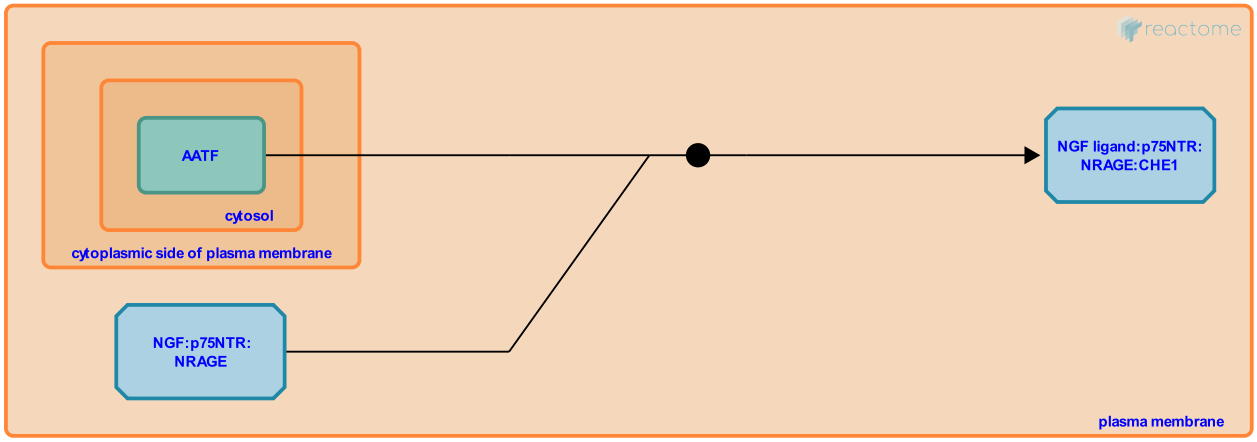
Location: NRAGE signals death through JNK

Stable identifier: R-HSA-204958

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Nrage sequesters Che1 in the cytoplasm (Mus musculus)



CHE1, also named AATF, is an Apoptosis Antagonizing Transcription Factor in cortical neurons. NRAGE binds to CHE1, inhibiting its nuclear localization by sequestering it in the cytoplasm, and, consequently, antagonizes its anti-apoptotic function.

Preceded by: NGF:p75NTR complex binds to NRAGE

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NRAGE activates JNK ↗

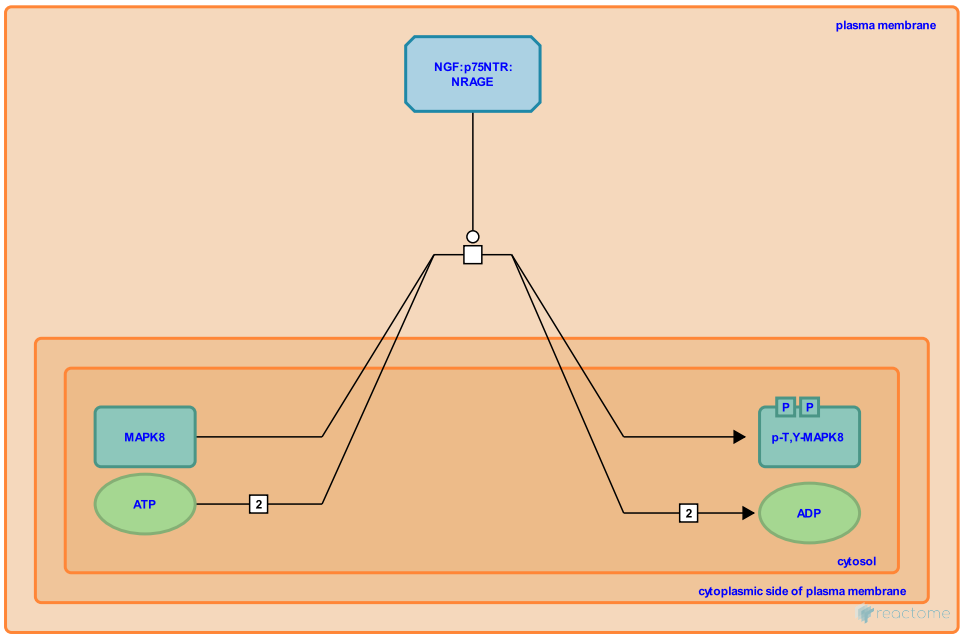
Location: NRAGE signals death through JNK

Stable identifier: R-HSA-205132

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Nrage activates Jnk1 (Rattus norvegicus)



The NGF:p75:NRAGE complex promotes threonine and tyrosine phosphorylation, and activation of JNK, by an unknown mechanism.

Preceded by: NGF:p75NTR complex binds to NRAGE

Followed by: JNK phosphorylates BIM, BAD and other targets

Editions

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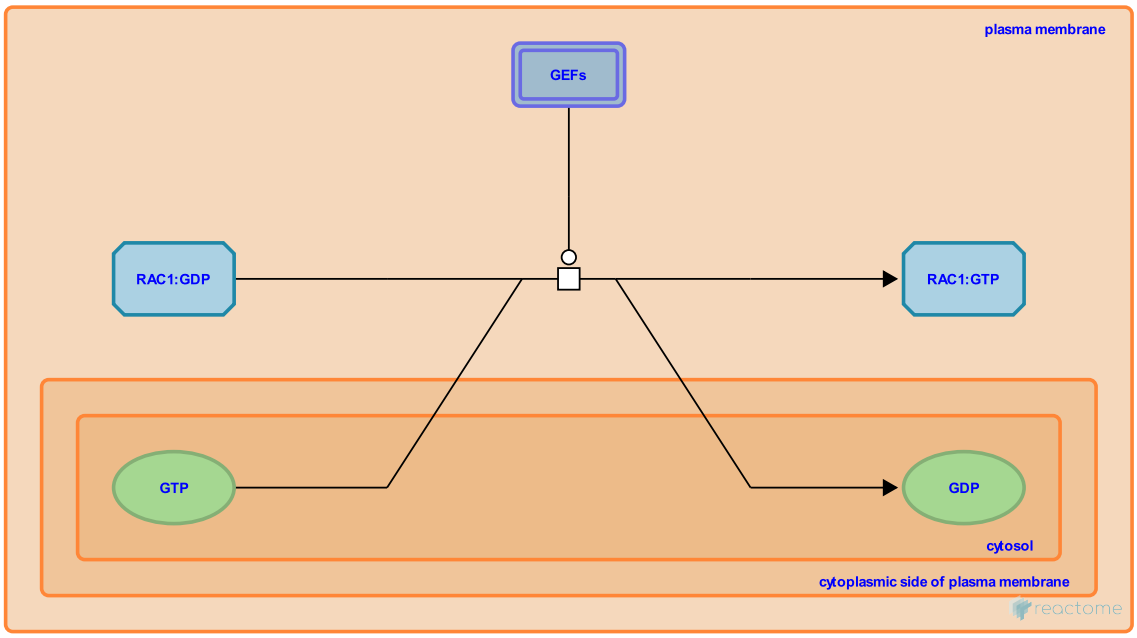
p75NTR indirectly activates RAC and Cdc42 via a guanyl-nucleotide exchange factor ↗

Location: NRAGE signals death through JNK

Stable identifier: R-HSA-205039

Type: transition

Compartments: plasma membrane, cytosol



Following NGF binding, p75NTR activates the RAC (Ras-related C3 botulinum toxin substrate) GTPase.

Literature references

Yoon, SO., Kim, JY., Harrington, AW. (2002). Activation of Rac GTPase by p75 is necessary for c-jun N-terminal kinase-mediated apoptosis. *J Neurosci, 22*, 156-66. ↗

Editions

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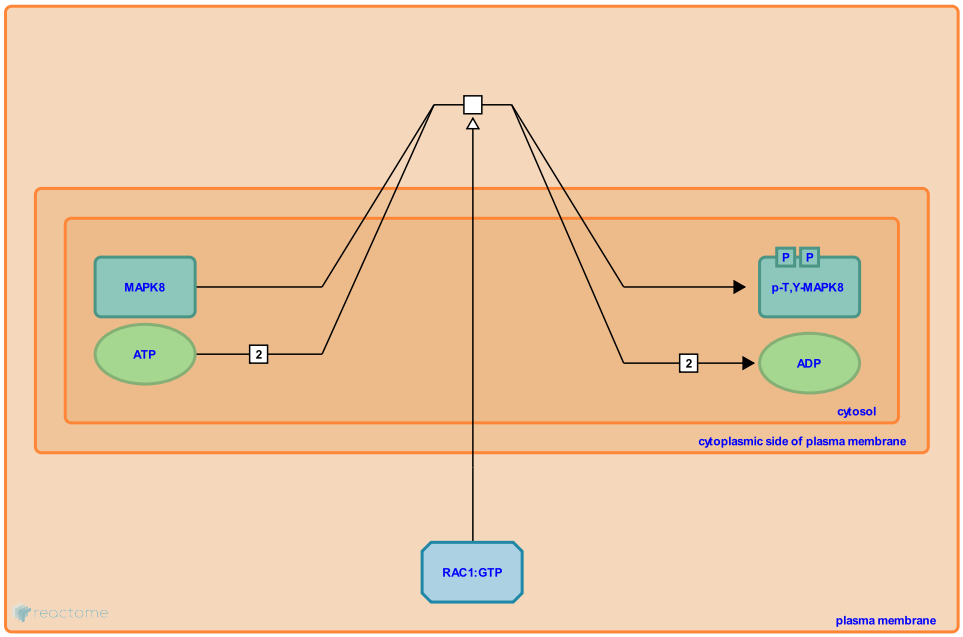
GTP-bound RAC contributes to JNK activation ↗

Location: NRAGE signals death through JNK

Stable identifier: R-HSA-205136

Type: transition

Compartments: plasma membrane, cytosol



Ras-related C3 botulinum toxin substrate 1 (RAC1) activation was described as essential for p75NTR to induce MAPK8 (aka JNK) and apoptosis in cortical oligodendrocytes (Bazenet et al. 1998). The simultaneous activation of TRKA counteracts the apoptotic action of p75, by modulating the kinetics of p75-mediated RAC activation.

Followed by: JNK phosphorylates BIM, BAD and other targets

Literature references

Bazenet, CE., Mota, MA., Rubin, LL. (1998). The small GTP-binding protein Cdc42 is required for nerve growth factor withdrawal-induced neuronal death. *Proc Natl Acad Sci U S A, 95*, 3984-9. ↗

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2006-10-10	Authored	Annibali, D., Nasi, S.
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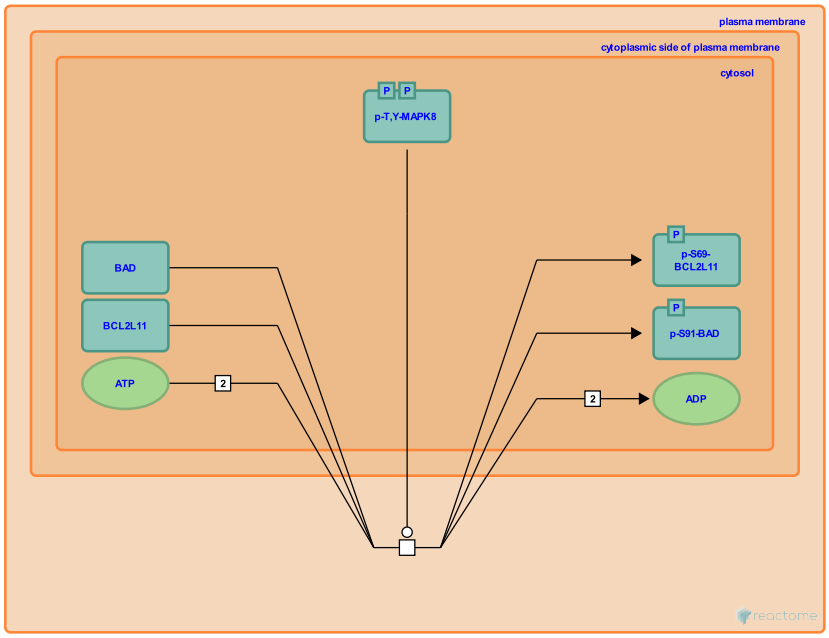
JNK phosphorylates BIM, BAD and other targets ↗

Location: NRAGE signals death through JNK

Stable identifier: R-HSA-205075

Type: transition

Compartments: plasma membrane, cytosol



Once activated, JNK phosphorylates targets in cytoplasm, including BIM and BAD that promote the release of cytochrome c and activation of caspases 9, 6 and 3.

Preceded by: NRAGE activates JNK, GTP-bound RAC contributes to JNK activation

Literature references

Becker, EB., Bonni, A., Said, F., Bhakar, AL., Salehi, AH., Howell, JL. et al. (2003). Apoptosis induced by p75NTR overexpression requires Jun kinase-dependent phosphorylation of Bad. *J Neurosci, 23*, 11373-81. ↗

Howell, J., Kodama, Y., Becker, EB., Bonni, A., Barker, PA. (2004). Characterization of the c-Jun N-terminal kinase-BimEL signaling pathway in neuronal apoptosis. *J Neurosci, 24*, 8762-70. ↗

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Active JNK moves to the nucleus and phosphorylates different transcription factors

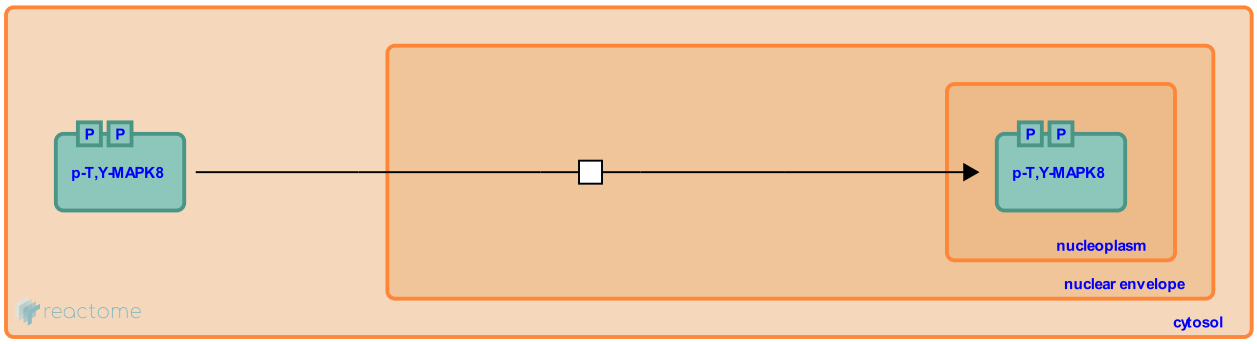
↗

Location: NRAGE signals death through JNK

Stable identifier: R-HSA-193666

Type: transition

Compartments: nuclear envelope



The different molecules listed (NRAGE, NRIF, NADE, TRAF6) mediate, through unclear mechanisms, JNK activation by threonine and tyrosine phosphorylation. While active JNK does move to the nucleus and phosphorylates and activate transcription factors such as c-JUN and ATF2, these have not been implicated in p75-mediated cell death, but rather the direct activation of the cell death machinery by JNK has been implicated. p75 activates the intrinsic caspase pathway (involving mitochondrial release of cytochrome c, Apaf-1, and caspases-9) rather than the extrinsic (caspase-8) pathway activated by most other death receptors.

Literature references

Friedman, JE., Friedman, WJ., Troy, CM. (2002). Mechanisms of p75-mediated death of hippocampal neurons. Role of caspases. *J Biol Chem, 277*, 34295-302. ↗

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2006-10-10	Authored	Annibali, D., Nasi, S.
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