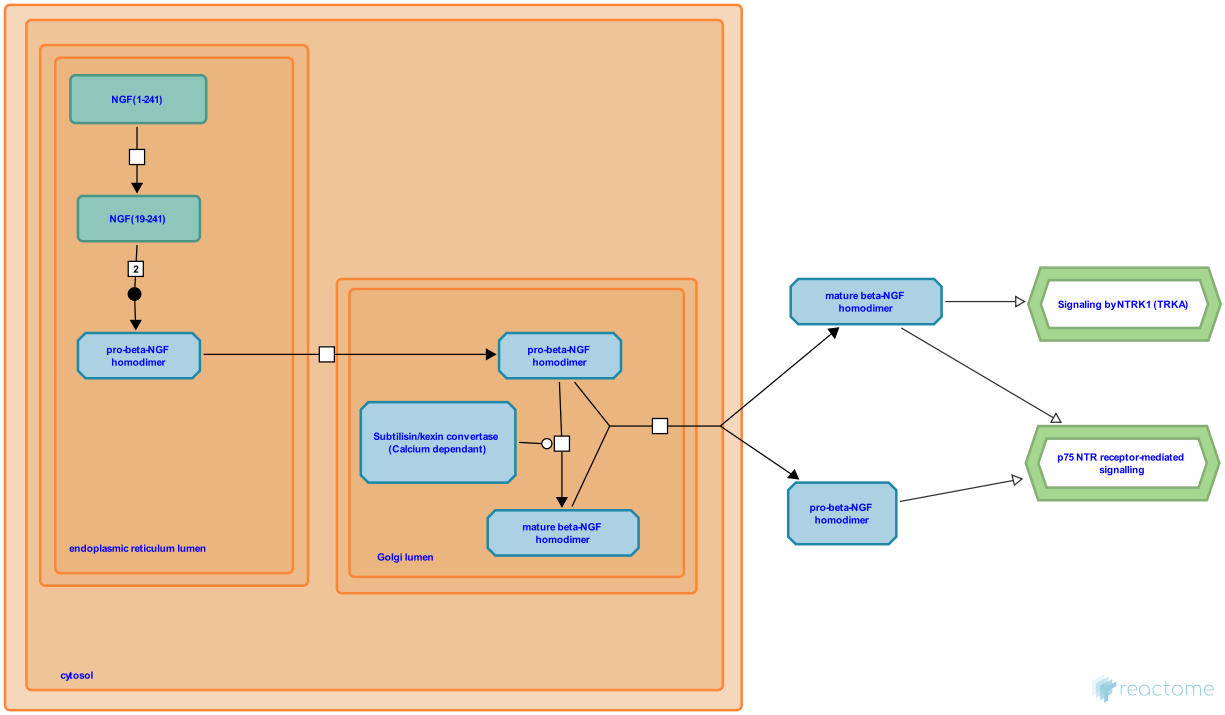
NGF processing



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18/05/2024

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

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. ↗

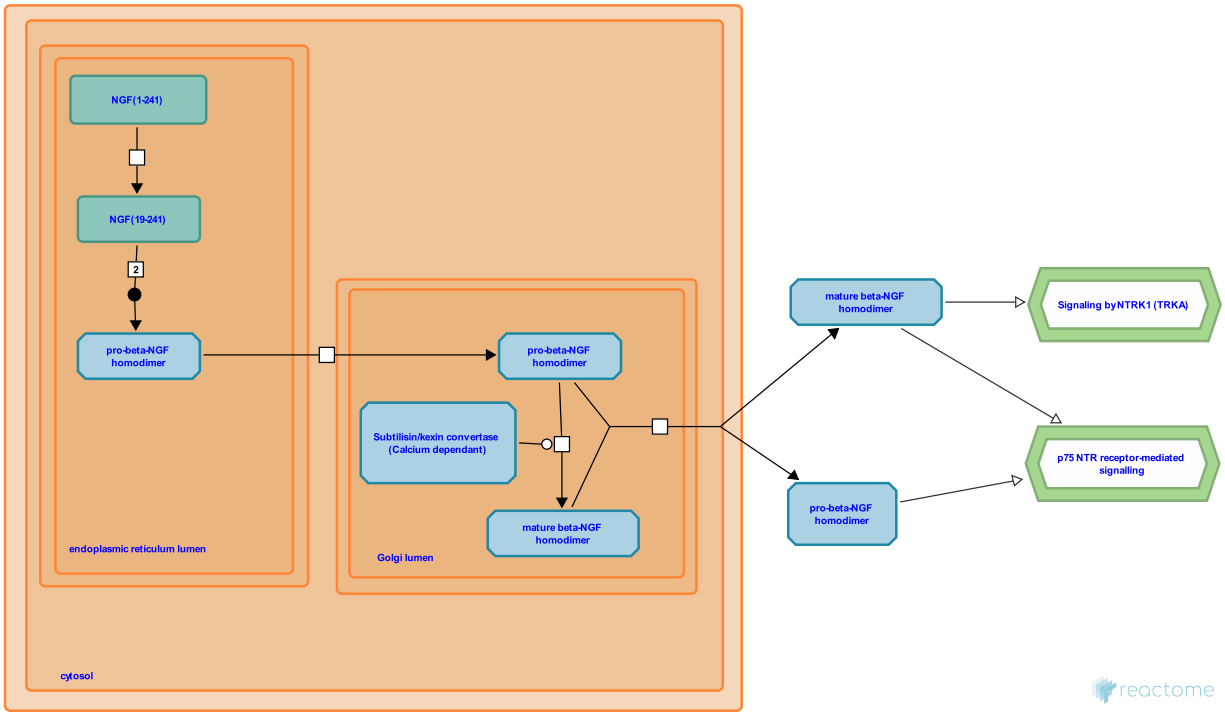
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

NGF processing ↗

Stable identifier: R-HSA-167060



All neurotrophins (NTs) are generated as pre-pro-neurotrophin precursors. The signal peptide is cleaved off as NT is associated with the endoplasmic reticulum (ER). The resulting pro-NT can form a homodimer spontaneously which then transits to the Golgi apparatus and then onto the trans-Golgi network (TGN). Resident protein convertases (PCs) can cleave off the pro-sequence and mature NT is is targeted to constitutively released vesicles. The pro-NT form can also be released to the extracellular region.

Literature references

Lessmann, V., Gottmann, K., Malcangio, M. (2003). Neurotrophin secretion: current facts and future prospects. *Prog Neurobiol, 69*, 341-74. ↗

Editions

2006-10-10	Edited	Jassal, B.
2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

The signal peptide is excised from beta-NGF pre-pro-precursor ↗

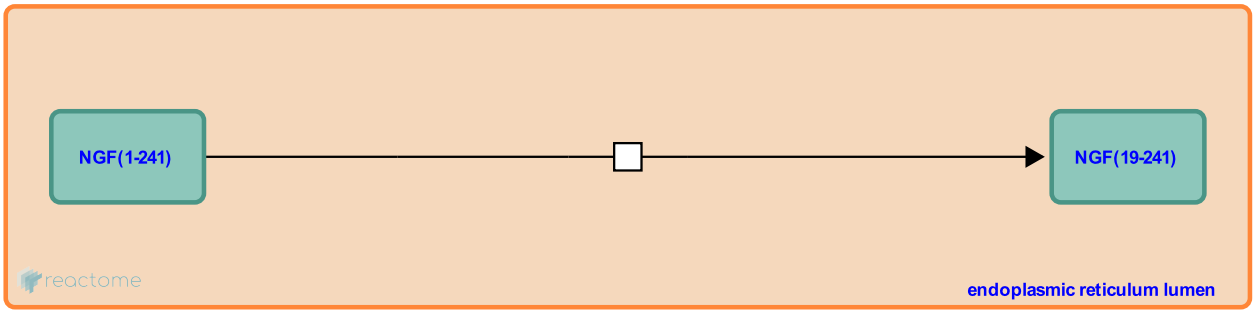
Location: NGF processing

Stable identifier: R-HSA-187045

Type: transition

Compartments: endoplasmic reticulum lumen

Inferred from: The signal peptide is excised from pre-pro-NGF (Mus musculus)



Pre-pro- precursors of the neurotrophins NGF, BDNF, NT-3, NT-4/5 are synthesized in various cell types by endoplasmic reticulum (ER) attached ribosomes, leading to sequestration of the newly formed polypeptide chain into the ER. The mouse NGF gene gives rise to two major transcripts that contain NGF (12.5 kDa) at the C-terminus and differ by alternative splicing of an N-terminal exon, so that the large precursor (34 kDa) has 67 amino acids upstream of an internal signal peptide and the smaller precursor (27 kDa) has this signal peptide at its N-terminus. The transcript for the large precursor predominates in the submaxillary gland, whereas the transcript for the smaller precursor predominates in virtually all other tissues.
The signal peptide is cleaved off immediately after sequestration into the ER. Therefore, expression of either NGF transcript gives rise to an apparently identical intracellular glycosylated precursor formed by cleavage of the primary gene product after the signal peptide.

Followed by: pro-beta-NGF dimerizes

Editions

2006-10-10	Edited	Jassal, B.
2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

pro-beta-NGF dimerizes ↗

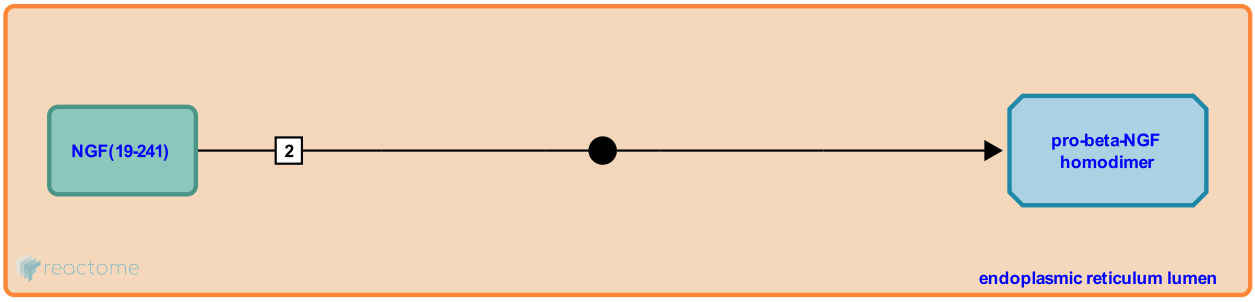
Location: NGF processing

Stable identifier: R-HSA-167047

Type: binding

Compartments: endoplasmic reticulum lumen

Inferred from: pro-NGF dimerizes (Mus musculus)



The pro-neurotrophin (pro-NGF: 27 kDa) spontaneously forms stable, non-covalent dimers directly in the ER. The homodimer is associated by noncovalent forces, with an equilibrium dissociation constant of 10 pM. The neurotrophin pro- domain is important for proper folding and intracellular sorting. Heterodimers of different neurotrophin monomers can also be generated at the ER.

Preceded by: The signal peptide is excised from beta-NGF pre-pro-precursor

Followed by: pro-beta-NGF homodimer transits to the golgi apparatus

Editions

2006-10-10	Edited	Jassal, B.
2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

pro-beta-NGF homodimer transits to the golgi apparatus ↗

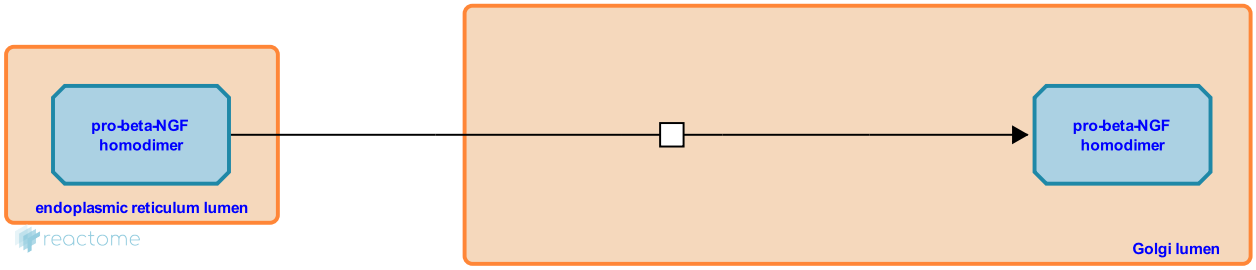
Location: NGF processing

Stable identifier: R-HSA-167014

Type: transition

Compartments: Golgi lumen, endoplasmic reticulum lumen

Inferred from: pro-beta-NGF homodimer transits to the golgi apparatus (Rattus norvegicus)



From the endoplasmic reticulum, the pro-neurotrophins transit to the golgi apparatus, most likely via intermediate non-clathrin-coated transport vesicles, and finally accumulate in the trans-golgi network (TGN). In the TGN, two different types of secretory vesicles can be generated and filled with neurotrophins: regulated and constitutive secretory vesicles.

Preceded by: pro-beta-NGF dimerizes

Followed by: Part of pro-beta-NGF is processed to mature beta-NGF

Editions

2006-10-10	Edited	Jassal, B.
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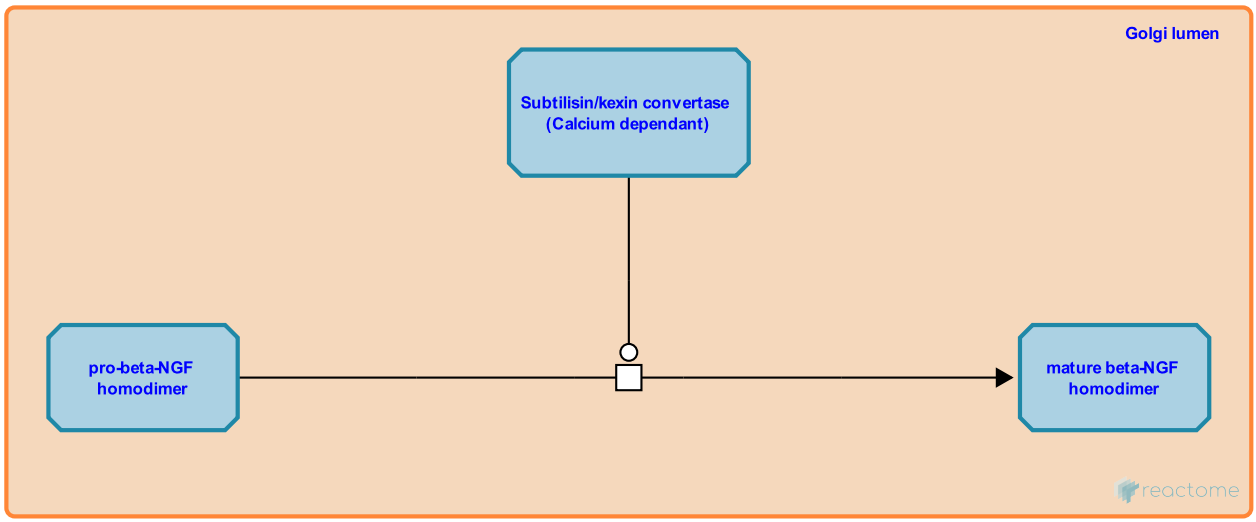
Part of pro-beta-NGF is processed to mature beta-NGF ↗

Location: NGF processing

Stable identifier: R-HSA-187020

Type: transition

Compartments: Golgi lumen



The pro-neurotrophins are rapidly cleaved intra-cellularly by furin or the pro-protein convertases at a highly conserved site, to produce the mature protein of 12-14 kDa in size (mature NGF or beta-NGF: 12.5 kDa). Furin, PACE4 and PC7 belong to the constitutive secretory pathway; NEC1/PC1, NEC2/PC2, PC4 and PC5 are instead targeted to regulated secretory granules. Furin is expressed ubiquitously in all tissues, whereas NEC1 and NEC2 are the dominant pro-protein convertases in neurons. The mature neurotrophins can be stored within neurons and released extra-cellularly upon stimulation.
Cells, however, appear to have a limited capacity to process pro-neurotrophins, a capacity that may be exhausted when they are produced in excess (Matsumoto T et al, 2008). In this case, the proforms of NGF and BDNF are secreted and cleaved extracellularly by the serine protease plasmin and by selective matrix metalloproteinases (MMPs). The signalling capacities of pro-neurotrophins and mature neurotrophins are markedly different. The pro-neurotrophins are high affinity ligands for p75NTR and can induce p75NTR dependent apoptosis in cultured neurons with minimal activation of TRK receptor mediated differentiation or survival. The biological action of neurotrophins may thus be regulated by proteolytic cleavage, with proforms preferentially activating p75NTR to mediate apoptosis and mature forms activating TRK receptors to promote survival.
It is possible that pro-neurotrophins may somehow be released during development and eliminate neurons in a p75NTR dependent fashion. Substantial quantities of proNGF are found in the cerebrospinal fluid of adult rodents after brain injury, perhaps following NGF expression by inflammatory cells that may not efficiently process pro-neurotrophins. When proBDNF is added as recombinant protein, activation of p75NTR by proBDNF facilitates hippocampal long-term depression (LTD; Woo NH et al, 2005). However, it is unclear whether proBDNF plays any role in LTD under physiological conditions.

Preceded by: pro-beta-NGF homodimer transits to the golgi apparatus

Followed by: Pro-beta-NGF and mature beta-NGF are secreted

Literature references

Lazure, C., Savaria, D., Goulet, B., Chretien, M., Seidah, NG., Murphy, RA. et al. (1996). Cellular processing of the nerve growth factor precursor by the mammalian pro-protein convertases. *Biochem J, 314*, 951-60. ↗

Editions

2006-10-10	Edited	Jassal, B.
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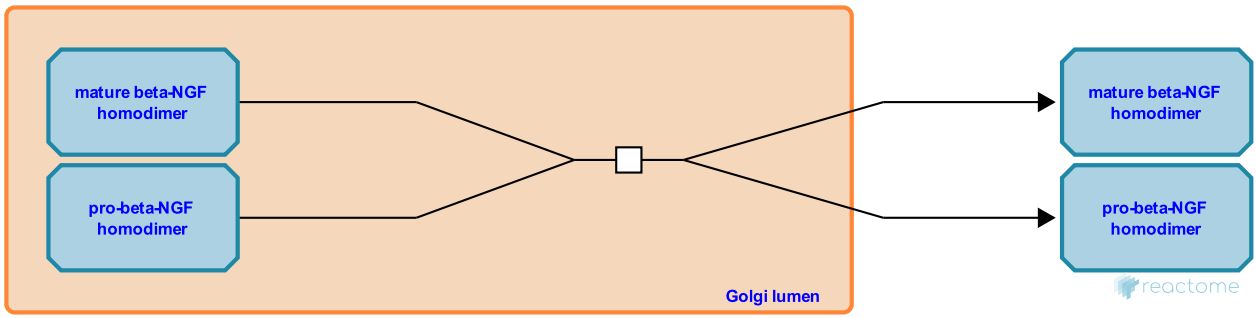
Pro-beta-NGF and mature beta-NGF are secreted ↗

Location: NGF processing

Stable identifier: R-HSA-187035

Type: transition

Compartments: Golgi lumen, extracellular region



Both mature neurotrophin and pro-neurotrophin are released extracellularly and are biologically active. The precursor proNGF, instead of mNGF (mature NGF), is the molecular form preferentially released by neurons in an activity-dependent manner. Neurotrophins are secreted in low amounts from several tissues, mainly from target tissues of innervating neurons. In the nervous system, they are secreted by neurons, astrocytes and microglia. Neurotrophin secretion can be both constitutive and regulated. Constitutive release is observed in cells lacking a regulated pathway, and additional stimulus-dependent regulated secretion is evident in those cells where this route is available. Secretion is regulated by a number of stimuli, including neurotrophins themselves. In neurons, regulated secretion appears to be the prevalent pathway. NGF is secreted from the cell soma and the dendrites, while it is unclear whether it can also be secreted by axons. Constitutive secretion of NGF is observed only from the soma and the most proximal dendrites. Similar considerations hold for the other neurotrophins as well.

Preceded by: Part of pro-beta-NGF is processed to mature beta-NGF

Literature references

Lessmann, V., Gottmann, K., Malcangio, M. (2003). Neurotrophin secretion: current facts and future prospects. *Prog Neurobiol, 69*, 341-74. ↗

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