

Trk

Key References

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Overview

The neurotrophins are a family of proteins that regulate cell survival, differentiation and growth in the vertebrate nervous system. Nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5) are produced as precursor proteins (pro-neurotrophins) that are cleaved to mature proteins of 118-120 amino acids that associate as non-covalent homodimers. Two classes of cell surface proteins function as receptors for the neurotrophins, the *Trk* family of receptor tyrosine kinases and the p75 neurotrophin receptor (p75NTR), a member of the TNF receptor superfamily. There are three vertebrate *trk* genes, which generate full-length and truncated receptors. NGF binds most specifically to TrkA; BDNF and NT-4 to TrkB; and NT-3 to TrkC. On their own, Trk and p75NTR, in most cases, bind their ligands with an affinity in the 0.1-1 nM range. Expression of p75NTR enhances the binding affinity of NGF for TrkA by increasing the on-rate, resulting in high-affinity binding sites of K_d 0.01 nM. Co-expression of p75NTR and Trk also provides more specificity for neurotrophin binding to Trk receptors. In addition to activation by neurotrophins, Trk can be activated by ligands of G-protein coupled receptors, including pituitary adenylate cyclase-activating protein (PACAP) and adenosine A_{2A} . The major domains in Trk that determine specificity of binding are the immunoglobulin-C2 domains. For p75NTR, binding is facilitated through the four negatively charged cysteine-rich repeats. Binding of two NGF molecules induces dimerization of Trk receptors. In contrast, NGF binds to p75NTR in a 1:2 ratio. Neurotrophins induce very different effects depending upon the cell type they bind to, as well as which receptor or complex of receptors are engaged. In general, the Trks mediate neuronal survival, axon and dendrite growth, the elaboration of the differentiated neuronal

phenotype, chemoattraction, growth cone guidance and maintenance, neurotransmitter release, and synaptic plasticity. In tumor cells, TrkA activation induces the neuronal differentiation of neuroblastoma cells and the apoptosis of medulloblastoma cells, while TrkB activation mediates metastasis in breast cancer cells, and migration, survival, and resistance to chemotherapy in neuroblastoma cells. In contrast, the p75NTR induces developmental and injury-induced apoptosis, and inhibits the growth of axons during development and regeneration. p75NTR has been shown to act with TrkA to stimulate survival, or alone to regulate survival and differentiation in some neurons. Recently, the p75NTR was found to associate with several receptors involved in suppressing axonal growth in the central nervous system, and with the neurotensin receptor sortilin. p75NTR mediates signaling of the myelin-associated and growth inhibitory molecules MAG, Nogo-66 and OMgp though association with the Nogo-receptor and the transmembrane protein LINGO-1. In this context, p75NTR binds and sequesters Rho-GDI, a Rho GTP dissociation inhibitor, thereby activating RhoA and inhibiting axonal growth. The sortilin-p75NTR complex binds the pro-neurotrophin pro-NGF with high affinity, inducing potent apoptotic responses. Proteolytic processing of p75NTR by extracellular metalloproteases results in shedding of the extracellular domain, while intramembrane proteolysis of p75NTR by α - and γ -secretases generate C-terminal fragments with potential signaling capability. The transmembrane and intracellular domain of the p75NTR resembles the mammalian p75-homolog NRH2, the latter that can, like p75NTR, modulate ligand binding to TrkA. Upon neurotrophin binding, Trk associates in neurons with a number of signaling proteins including the Shc, SNT/FRS-2, and

AP5/SH2-B adapter proteins and regulators of Ras function, the calcium and PKC regulator phospholipase C- γ 1, and the phosphotyrosine phosphatase SHP-1. These proteins link Trk to the Ras/Raf/MEK/MAP kinase, Rap1/Braf, PI3-kinase/Akt/GSK3- β /ILK, Δ Np73 (p53 family member) and PKC signaling pathways. In peripheral neurons, survival is mediated through Akt, MEK5, and Δ Np73, while growth is induced by the MEK1/2/MAPK1/2 and PI3-kinase/GSK3- β /ILK signaling pathways. Binding of neurotrophins to TrkB can also result in rapid depolarization through the TTX-insensitive Na(V)1.9 channel. p75NTR can stimulate ceramide production and the activities of the NF κ B, RhoA, Rac1/JNK, and JNK/p53 tumor suppressor pathways. The cytoplasmic portion of p75NTR contains a death domain sequence similar to those in the Fas and p55TNF receptors. Since p75NTR lacks intrinsic catalytic activity, its signal transduction depends on the cell-type specific interaction with adaptor proteins such as NRAGE, NRIF, NADE and various members of the TRAF family. These proteins likely couple p75NTR to intracellular signaling pathways that regulate growth suppression such as RhoA, or cell death such as Rac1, JNK, and p53. The positive effects of Trk and the negative effects of p75NTR on growth and survival likely depend upon their relative activities and their ability to regulate each other's signaling potential both directly at the level of the receptors, and indirectly at the level of their downstream signaling pathways. In addition to their critical roles during nervous system development, neurotrophins and their receptors mediate important functions in the adult, including neurotransmitter release, hyperalgesia and synaptic efficacy. Neurotrophins have been proposed as therapeutic agents for the treatment of a variety of neurodegenerative disorders and nerve injury.

Trk

FAMILY MEMBERS	Trk A	Trk B	Trk C	p75
OTHER NAMES	gp140 Trk, TrkA1; neurotrophic tyrosine kinase receptor type 1, NTRK1	Neurotrophic tyrosine kinase receptor type 2, NTRK2	Neurotrophic tyrosine kinase receptor type 3, NTRK3	p75NTR
MOLECULAR WEIGHT/ STRUCTURAL DATA	140 kDa 796 aa	140 kDa 822 aa	140 kDa 839 aa	75 kDa 427 aa
ISOFORMS	TrkAII, TrkAIII	TrkB.T1, TrkB.T2	C14, C25, C39; truncated forms	s-p75NTR
SPECIES	All vertebrates	All vertebrates	All vertebrates	All vertebrates
DOMAIN ORGANIZATION	2 leucine-rich repeats, 2 Ig-like C2-type domains, 1 protein kinase domain	2 leucine-rich repeats, 2 Ig-like C2-type domains, 1 protein kinase domain	2 leucine-rich repeats, 2 Ig-like C2-type domains, 1 protein kinase domain	4 TNFR-Cys repeats, 1 death domain
PHOSPHORYLATION SITES	Tyr ⁴⁹⁶ , Tyr ⁶⁷⁶ , Tyr ⁶⁸⁰ , Tyr ⁶⁸¹ , Tyr ⁷⁹¹	Tyr ⁵¹⁶ , Tyr ⁷⁰² , Tyr ⁷⁰⁶ , Tyr ⁷⁰⁷ , Tyr ⁸¹⁷	Tyr ⁵¹⁶ , Tyr ⁷⁰⁵ , Tyr ⁷⁰⁹ , Tyr ⁷¹⁰ , Tyr ⁸³⁴	Not known
TISSUE DISTRIBUTION	Central and peripheral nervous system, muscle, kidney, lung and immune system	Central and peripheral nervous system, muscle, kidney, lung and immune system	Central and peripheral nervous system, muscle, kidney, lung and immune system	Broad pattern of expression
SUBCELLULAR LOCALIZATION	Plasma membrane	Plasma membrane	Plasma membranes	Plasma membrane
BINDING PARTNERS/ ASSOCIATED PROTEINS	Shc, PLC-γ1, Grb2, FRS2, SH2-B, APS, CHK, GIPC, Csk, SHP-1, GRIT, TID1, Ras-GRF1, Kalirin, Dynein light chain, ARMS, c-Abl, SAP	Shc, PLC-γ1, FRS2, SH2-B, APS, Fyn, SAP, Dynein light chain	Shc, PLC-γ1, FRS2, SH2-B, APS, SAP, Dynein light chain	Rho GDI, NRAGE, TRAFs, NRIF, NADE, RIP-2, SC-1, Fascin, FAP-1
UPSTREAM ACTIVATORS	NGF, NT3, NT4/5, adenosine, PACAP	BDNF, NT4/5, NT3, adenosine, PACAP	NT3, adenosine, PACAP	NGF, NT3, BDNF, NT4/5, pro-NGF, pro-BDNF
DOWNSTREAM ACTIVATION	ERK1/2, ERK5, PI 3-kinase, Akt, PLC-γ1, GSK-3β, ILK, Rac1, PKCi	ERK1/2, ERK5, PI 3-kinase, Akt, PLC-γ1	ERK1/2, PI 3-kinase, Akt, PLC-γ1	NFκB, JNK, Ceramide, Rho A, Rac1
ACTIVATORS	Not known	Not known	Not known	Not known
INHIBITORS	K252a (K1639), CEP-701, CEP-751	K252a (K1639), CEP-701, CEP-751	K252a (K1639), CEP-701, CEP-751	Not known
SELECTIVE ACTIVATORS	Not known	Not known	Not known	Not known
PHYSIOLOGICAL FUNCTION	Critical role in development and function of nociceptive reception system	Receptor for BDNF, NT-3 and NT4/5; involved in development and/or maintenance of nervous system	Receptor for NT-3	Receptor for NGF, BDNF, NT3, NT4/5 and unprocessed pro-forms of neurotrophins; modulates survival, death, differentiation, migration and growth of axons and dendrites of neural cells
DISEASE RELEVANCE	Mutations cause congenital insensitivity to pain with anhidrosis; good prognostic marker in neuroblastoma	Val66Met mutation in the prodomain of BDNF correlated with depression, bipolar disorders and schizophrenia; Trk B is a poor prognostic marker in neuroblastoma	Good prognostic marker in medulloblastoma	Not identified as a direct cause of a disease state but modulation of p75 levels has been observed in spinal cord injury, ischemia/stroke, epilepsy, ALS and Alzheimer's disease