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Review

Neurotrophin signaling: many exciting surprises!

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Abstract. Neurotrophins are growth factors implicated in the development and maintenance of different neuronal populations in the nervous system. Neurotrophins bind to two sets of receptors, Trk receptor tyrosine kinases and the $p75^{NTR}$ receptor, to activate several different signaling pathways that mediate various biological functions. While Trk receptor activation has been well-studied and triggers the well-characterized Ras/Rap-MAPK, PI3K-Akt, and PLCγ-PKC cascades, $p75^{NTR}$ signaling is more complex, and its *in vivo* significance has not yet been completely determined. In the last few years, $p75^{NTR}$ has received much attention mainly due to recent findings describing pro-neurotrophins as new ligands for the receptor and the ability of the receptor to form different complexes with other transmembrane proteins. This review will update the neurotrophin signaling pathways known for Trk receptors to include newly identified Trk-interacting molecules and will address surprising new findings that suggest a role for $p75^{NTR}$ in different receptor complexes and functions.

Keywords. Neurotrophin, Trk, $p75^{NTR}$, signaling, neuron, survival.

Introduction

Neurotrophins are growth factors implicated in several different functions in the nervous system, including survival, proliferation, differentiation, myelination, apoptosis, axonal growth, and synaptic plasticity. The history of neurotrophins started 50 years ago when Levi-Montalcini, Cohen, and Hamburger discovered nerve growth factor (NGF), the prototypical neurotrophin, as a factor required for axonal growth from explants. The other neurotrophins, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4), were identified 30 years later. Neurotrophins mediate their effects through binding to two different receptors – tropomyosin-related kinase (Trk) receptors and the p75 neurotrophin receptor ($p75^{NTR}$). The $p75^{NTR}$ receptor belongs to the tumor necrosis factor (TNF) superfamily and was the first identified receptor for NGF [1, 2]. The first Trk receptor was originally discovered as a rearrangement of non-muscle tropomyosin and a then unknown tyrosine kinase. This tyrosine kinase was referred to as TrkA and subsequently identified as a receptor for NGF [3–6]. The identification of TrkB and TrkC, based on their similarity to TrkA, followed thereafter [7–10].

For a long time, neurotrophins were believed to bind preferentially to specific Trk receptors: NGF to TrkA, BDNF and NT-4 to TrkB, and NT-3 to TrkC. However, some promiscuity exists, as NT-3 can also bind to TrkA and TrkB receptors that contain an additional short insert in the extracellular domain [11, 12]. All neurotrophins bind to $p75^{NTR}$ with equal affinity. Recently, the precursors of the neurotrophins, the pro-neurotrophins, have been identified as high-affinity ligands for $p75^{NTR}$ in complex with a co-receptor, sortilin [13–15].

In this review, we will first update the signaling pathways mediated by the Trk neurotrophin receptors to integrate new players that have been recently described. Then, we will focus on the pan-neurotrophin $p75^{NTR}$ receptor and its interacting molecules. We will conclude by addressing different modes of regulation of Trk signaling.

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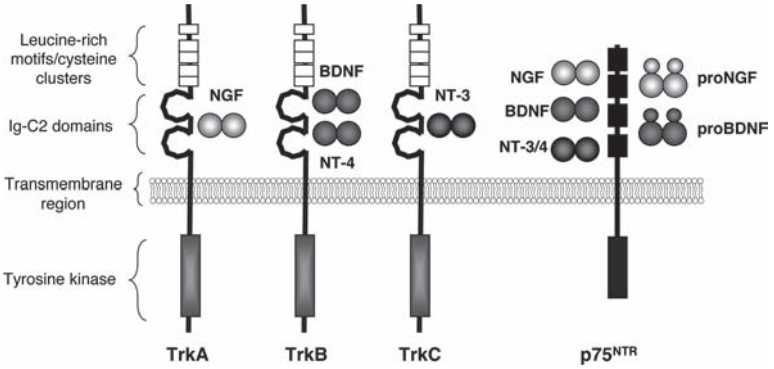

Figure 1. Neurotrophins and their receptors: Trk and p75 ^{NTR} receptors. Neurotrophins are dimers that bind with equal affinity to p75 ^{NTR} and preferentially to specific Trk receptors. Neurotrophins are synthesized as pro-proteins that bind exclusively to p75^{NTR}. Trk receptors are prototypical receptor tyrosine kinases that dimerize and become active upon neurotrophin ligand binding. p75 ^{NTR} belongs to the TNF receptor superfamily.

Trk receptor structure and neurotrophin binding

Trk receptors are prototypical receptor tyrosine kinases that contain an extracellular domain composed of three leucine-rich motifs flanked by two cysteine clusters, two immunoglobulin-like C2 type domains (Ig-C2), a single transmembrane domain, and a cytoplasmic region with a kinase domain (Fig. 1). Binding of neurotrophins to Trk receptors occurs mainly through the Ig-C2 domains, as described using chimeras between different Trk receptors, deletions, and point mutation analyses, with the domain closer to the transmembrane region playing a more prominent role [16–20]. The leucine-rich motifs and the cysteine clusters may also be involved [21].

In addition to ligand binding, the Ig-C2 domains can also stabilize the monomeric form of the Trk receptor to prevent spontaneous dimerization and activation in the absence of neurotrophins (Fig. 2). Deletions, chimeric receptors, or point mutations that disrupt the structure of the first or second Ig-C2 domains allow receptor activation independent of ligand [18, 19]. Also, a TrkA receptor isoform that lacks the first Ig-C2 domain in neuroblastoma SH-SY5Y cells has the potential to signal and transform fibroblasts in the absence of ligand [20].

The structures of NGF alone and in complex with the second Ig-C2 have been resolved [22, 23]. Future resolution of the structure of NGF in complex with the entire extracellular domain of the TrkA receptor will provide important data about the involvement of other domains in the binding as well as the conformational changes which may occur upon binding of NGF to TrkA.

The affinity of neurotrophins to TrkA and TrkB receptors is modulated by the presence of p75^{NTR}, which enhances specificity for their primary ligands NGF and BDNF, respectively [24]. Formation of high-affinity binding sites for NGF requires the presence of a correct ratio of full p75^{NTR} and Trk receptors, as mutations of the cytoplasmic or transmembrane domains of either TrkA or p75^{NTR} abolish the configuration of high-affinity binding sites [25, 26]. At the same time, p75^{NTR} reduces the ability of NT-3 to activate TrkA, and NT-3 and NT-4 to activate TrkB [11, 27, 28]. This effect has been recently demonstrated

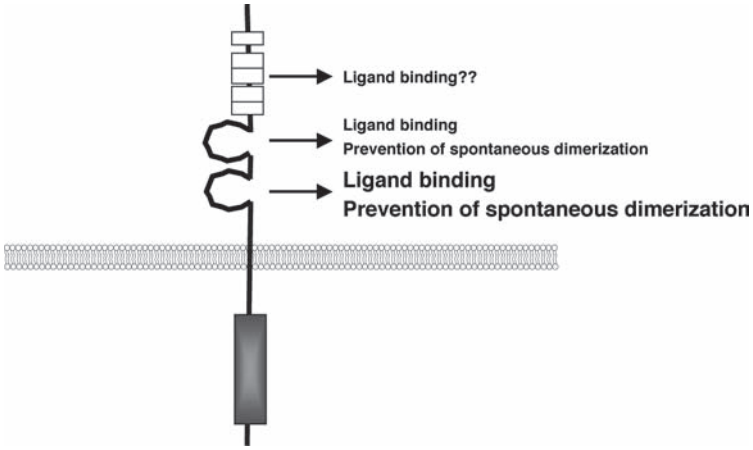

Figure 2. Functions of Trk receptor extracellular domains. The extracellular domains of Trk receptors are implicated in ligand binding and also in the prevention of the spontaneous dimerization of the receptor in the absence of ligand. The second Ig-C2 domain plays a prominent role for both processes. Size of the font indicates relative contribution to the designated function.

in vivo in sympathetic neurons, where NT-3 can signal locally via TrkA receptors in the absence of $p75^{NTR}$. Once axons reach their final target and receive NGF, TrkA retrograde signaling upregulates $p75^{NTR}$, and the cells no longer respond to NT-3 [29].

Recently, a $p75^{NTR}$ neurotrophin-related homolog-2, NRH2, has been identified, which contains a transmembrane and intracellular domains similar to that of $p75^{NTR}$ but lacks the cysteine-rich repeats in the extracellular domain [30]. NRH2 is expressed in neuronal populations that also express $p75^{NTR}$ and Trk receptors and, like $p75^{NTR}$, can interact with TrkA receptors to form high-affinity binding sites for NGF [31].

Neurotrophin signaling mediated by Trk receptors

The signaling pathways activated by neurotrophins through Trk receptors result in many neuronal functions, such as cell survival, differentiation, dendritic arborization, synapse formation, plasticity, axonal growth, and axonal guidance. Binding of neurotrophins to Trk receptors leads to dimerization, phosphorylation in trans of the receptors, recruitment of different adaptors and enzymes, and activation of several signaling pathways. These events are shared by other receptor tyrosine kinases, but the unique combination of Trk receptor docking sites, recruitment of different adaptors and enzymes, and regulated receptor trafficking elicits specific responses for neurotrophins.

Two tyrosines in Trk receptors, Y490 and Y785 in the human TrkA receptor and their corresponding tyrosines in TrkB and TrkC receptors, are phosphorylated in response to neurotrophins and serve as the major docking sites for binding of adaptor proteins and enzymes. Y490 and Y785 primarily recruit Shc and phospholipase C-γ(PLC-γ), respectively [32]. The phosphorylated tyrosines located at the kinase domain, Y670, Y674, and Y675, can also engage adaptor proteins, including SH2B, APS, and Grb2 [33, 34].

Among the signaling pathways activated by Trk receptors in response to neurotrophins, the Shc-Ras-MAPK, Rap-MAPK, PI3K-Akt, and PLCγ-protein kinase C (PKC) pathways are the most studied (Fig. 3). Most of the work describing these signaling pathways has been performed in PC12 cells, a rat adrenal pheochromocytoma cell line that responds to NGF and resembles sympathetic neurons, but also differs from neurons in many aspects. These pathways have also been studied largely in the context of NGF activation of TrkA and extrapolated to the other Trk receptors. In the last few years, several new proteins downstream of Trk receptors have been described that may contribute to the biological functions elicited by neurotrophins. Due to space constraints, these new proteins are summarized in Table 1. Some of these molecules have been linked to specific pathways and will be described later on.

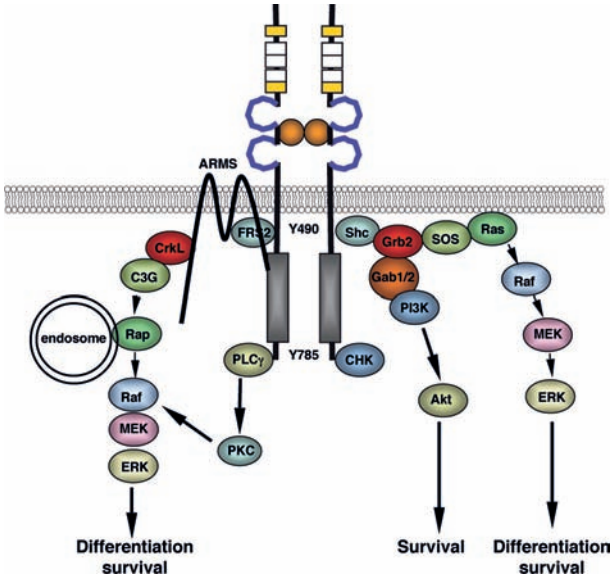

Figure 3. Trk receptor-mediated signaling pathways. Neurotrophin binding to Trk receptors leads to their activation and to the recruitment of different proteins that associate with specific phosphotyrosine residues in the cytoplasmic domain of Trk receptors. These interactions trigger the activation of various signaling pathways, such as the Ras, Rap, PI3K, and PLCγ pathways, which result in survival, neurite outgrowth, gene expression, and synaptic plasticity. Tyrosine residue nomenclature is based on the human sequence of TrkA. Additional proteins implicated in neurotrophin signaling are documented in Table 1.

Ras-MAPK

Activation of the small GTPase Ras in response to neurotrophins has been linked to signaling and transcriptional regulation implicated in neuronal survival and differentiation. The first evidence that Ras is important for neurotrophin signaling came from microinjection of antibodies against Ras in PC12 cells, which inhibited neurite formation and resulted in temporary regression of partially extended neurites after NGF treatment [35]. Expression of mutant Ras proteins also showed a marked inhibition of morphological differentiation induced by NGF [36].

Ras is induced rapidly, but transiently, by NGF in PC12 cells [37]. Since Ras proteins cycle between active GTP-bound and inactive GDP-bound states, the biological activity of these GTPases is controlled by guanine nucleotide exchange factors (GEFs) and guanosine triphosphatase-activating proteins (GAPs). TrkA receptor stimulation by NGF engages Shc and Grb2 to activate the GEF SOS, which then activates Ras [32] (Fig. 3). Raf-1 and B-Raf activation downstream of Ras subsequently triggers the activation of extracellular signal-regulated kinases/mitogen-activated protein kinases (ERK/MAPK, referred hereafter

Table 1. New Trk-interacting/signaling molecules.

Protein	Trk interaction	Signaling pathway	Function	Reference
rAPS	yes	Grb2-Ras-MAPK	neurite outgrowth	33, 166
SH2-B	yes	Grb2-Ras-MAPK	neurite outgrowth	33, 166, 167
FRS2	yes	CrkII-Rap-MAPK	neurite outgrowth	46
CHK	yes	MAPK	neurite outgrowth	168
TRPC3		intracellular Ca^{2+} release	growth-cone turning	143, 145
Neurofibromin	no	Ras-MAPK		42
Calmodulin	yes	Raf-1	Trk intracellular location/cleavage	169, 170
Abl	yes			171, 172
TRPV1	yes		channel sensitization	73, 144
ARMS/Kidins220	yes	CrkL-Rap-MAPK	neurite outgrowth	49, 51, 52, 173
GIPC	yes			174
Erk5	no		retrograde signaling	155
Pincher	no		macroendocytosis/retrograde signaling	175, 176
Grit	yes		neurite outgrowth	177
Rin	no	MAPK/p38	neurite outgrowth	178, 179
Rit	no	MAPK	neurite outgrowth/survival	180, 181
GSK-3β	no	PI3K-Akt	axonal growth	67
Nesca	no		neurite outgrowth	182
FAIM	yes	Ras-MAPK/NF-kB	neurite outgrowth	183
TID1	yes		neurite outgrowth	184
STAT5			transcription	185
SAP	yes		negative regulator/signaling	186
RasGrf1	yes		neurite outgrowth	187, 188
PPARγ	no		transcriptional activity	189
Dbs	yes	Cdc42	Schwann cell migration	190
Tiam	no	Ras-Rac1	Schwann cell migration	191

as MAPK) [38, 39]. Stimulation of Ras through this pathway promotes only transient activation of MAPK [40].
Modulation of Ras signaling can be achieved by a negative feedback loop, as activation of MAPK can stop the signaling of this pathway by phosphorylating SOS to disrupt the Grb2-SOS complex [41]. Moreover, neurofibromin, a GAP for Ras, negatively regulates Ras signaling in developing neurons that depend on neurotrophins for their survival [42]. Whether neurofibromin activity is modulated by neurotrophins remains to be addressed.

Rap-MAPK

Neurotrophins stimulate two different phases of MAPK activation. A transient one, described above, involves Shc-Grb2-SOS-Ras-B-Raf/Raf1-MAPK, while a prolonged MAPK activation requires the adaptor CrkII/CrkL, the GEF C3G, the small GTPase Rap1, and B-Raf [43, 44] (Fig. 3). NGF activation of TrkA leads to activation of C3G by CrkII/CrkL. C3G then activates Rap1 to signal further downstream through B-Raf, resulting in the sustained activation of MAPK. This pathway requires internalization of the Trk receptor into the endosomal compartment [44, 45].
Although the NGF-mediated activation of Rap1 by C3G is generally accepted, how the TrkA receptor signals to CrkII/CrkL remains controversial. Under one proposed model, the adaptor fibroblast receptor substrate-2 (FRS2) can serve as the link. *In vitro,* FRS2 can bind to residue Y490 of TrkA upon phosphorylation to compete with Shc binding and can also interact with the SH2 domain of CrkII [41, 46]. However, signaling through the Y490 site does not fully account for the MAPK activation of neurotrophin action *in vivo*. Mice bearing Y490F mutations in TrkB and TrkC receptors retain the ability to induce sustained MAPK activation, suggesting the presence of Y490-independent mechanisms [47, 48].
Recently, an ankyrin repeat-rich membrane-spanning protein (ARMS/Kidins220, referred hereafter as ARMS),

a new substrate of Trk receptors and protein kinase D, has been identified that may provide another possible link between TrkA and CrkII/CrkL [49, 50]. ARMS becomes rapidly tyrosine phosphorylated in response to neurotrophins, remains active for a long time, and associates with Trk receptors using transmembrane-transmembrane regions [49, 51]. Additionally, an interaction between ARMS, CrkL, and C3G increases upon NGF treatment and modulates the activation of Rap1. Disruption of ARMS expression, or its interaction with either Trk or CrkL, impairs Rap1 activation and prolonged MAPK [51, 52]. Furthermore, ARMS phosphorylation at Y1096 in response to neurotrophins modulates CrkL binding, to work as a switch to trigger prolonged MAPK activation [52]. The involvement of ARMS in the Rap1-MAPK pathway is compatible with the previous *in vivo* results from the TrkB/TrkC knock-ins that eliminate signaling from the Y490 site and binding of Shc/FRS2 but maintain a certain level of MAPK activation [47, 48]. Further experiments with these adaptor proteins *in vivo* will be required to provide new insights into the sustained MAPK activation elicited by neurotrophins.

Phosphorylation of MAPK leads to activation of several downstream targets that mediate gene transcription, such as Rsk and MSK1. These two kinases can phosphorylate and activate the cyclic adenosine monophosphate response element-binding protein (CREB), which controls expression of genes essential for the survival and differentiation of neurons [53–55]. The regulation of BDNF expression by CREB suggests that a positive feedback loop may potentiate neurotrophin actions [56]. For additional information about CREB targets and functions see the review by West et al. [57].

PI3K-Akt

Neurotrophins play an important role in the survival of several neuronal populations during development, and signaling through the PI3K-Akt pathway is critical for this function. Active Trk receptors engage Shc, which associates with Grb2 and Gab1 to activate PI3K and, subsequently, Akt (Fig. 3). PI3K binding to Gab1 is required for PI3K activation, as disruption of this association decreases the NGF-dependent survival of PC12 cells [58]. The role of PI3K-Akt signaling in survival has also been shown in primary neurons and in the neuroblatoma cell line SH-SY5Y [59, 60].

Several different pro-apoptotic and pro-survival effectors downstream of Akt can mediate the survival actions of neurotrophins. For example, Bad phosphorylation by Akt leads to additional phosphorylation of Bad by other kinases, which prevents the pro-apoptotic effects of the protein [61]. Similarly, the forkhead transcription factor, FKHRL1, which regulates the expression of several pro-apoptotic proteins, is phosphorylated by Akt in response to neurotrophins, preventing its transcriptional activity [62]. Moreover, the NF-κB pro-survival pathway is activated via Akt phosphorylation of the inhibitor IκB, targeting it for degradation [63, 64]. PI3K-Akt can also exert a positive effect on the retrograde signaling that modulates neuronal survival [65].

Signaling through PI3K-Akt mediates functions other than survival. Active Akt at the growth cone causes axonal growth and increases axon caliber and branching in sensory neurons by phosphorylating and inactivating GSK-3β locally, leading to microtubule assembly that promotes axonal growth [59, 66, 67]. These mechanistic data support the activation of PI3K downstream of neurotrophins in growth cone chemotropism reported in *Xenopus* spinal neurons [68].

PLCγ

The first reports indicating that neurotrophin actions result in activation of PLCγ showed serine, threonine, and tyrosine phosphorylation of PLCγ, directly mediated by the Trk receptor kinase [69, 70]. Trk receptor phosphorylation at Y785 leads to PLCγ recruitment and activation, which results in the hydrolysis of PtdIns(4,5)P_2 to generate inositol tris-phosphate (IP3) and diacylglycerol (DAG) [71]. IP3 and DAG cause the activation of different PKC isoforms. The effect of IP3 is mediated by release of Ca^{2+} from internal stores that additionally stimulate Ca^{2+}-calmodulin-regulated protein kinases (CaM kinases). PKC subsequently activates the Erk1 signaling pathway via Raf [72]. PLCγ activation in response to neurotrophins has been implicated in growth cone chemotropism and in the potentiation of thermal sensitivity by VR1, a heat-activated ion channel on sensory neurons [68, 73]. Moreover, the prolonged activation of PLCγ by a brief pulse of NGF induces transcription of a sodium channel gene [74, 75].

PLCγ signaling may be important for TrkB signaling in response to BDNF that is involved in synaptic plasticity in the hippocampus [76–78]. TrkB-targeted mice with a mutation at the PLCγ-binding site Y816 show an impairment of hippocampal long-term potentiation (LTP) in response to BDNF, probably mediated by decreased activation of CaM kinase and CREB [79]. Whether additional proteins which bind to the same tyrosine residue as PLCγ, such as Csk homologous kinase, contribute to the LTP mediated by TrkB remains to be addressed.

p75^{NTR} receptor structure and neurotrophin binding

The p75^{NTR} integral membrane protein is the founding member of the TNF family of receptors, and contains a cys-

teine-rich domain and a cytoplasmic death domain (Fig. 1). The nuclear magnetic resonance structure of the intracellular p75^{NTR} region shows a flexible juxtamembrane region and a death domain that consists of two perpendicular sets of three helices packed into a globular structure [80]. Surprisingly, unlike the TNF receptor, p75^{NTR} does not exhibit trimerization [81]. The lack of self-association of the intracellular region of p75^{NTR} differentiates the activation of this receptor from that of TNF and Fas receptors, which require aggregation for proper signaling.

The crystal structure of NGF in complex with the extracellular domain of p75^{NTR} has been recently solved, revealing a surprising 2:1 NGF:p75^{NTR} stoichiometry that is unlike the trimeric ligand-receptor complexes of the other TNF receptor family members [82]. Binding of an NGF dimer to one molecule of p75^{NTR} induces conformational changes in the NGF protein that prevents the association of a second p75^{NTR} molecule [82]. The observed 2:1 NGF: p75^{NTR} ratio may allow other receptors to be recruited to form higher-order complexes. Indeed, p75^{NTR} can form high-affinity sites with Trk receptors [7]. Additional crystal structures, including that of a Trk-NGF-p75^{NTR} ternary complex, would provide further insights into the stoichiometry and the conformational changes that modulate neurotrophin receptor function.

Neurotrophin signaling mediated by the p75^{NTR} receptor

Functions ascribed to the p75^{NTR} receptor are diverse, complex, and sometimes contradictory. p75^{NTR} has been implicated in both promoting survival and inducing apoptosis, enhancing neurite outgrowth and facilitating growth-cone collapse, and mediating differentiation and enhancing proliferation. Moreover, p75^{NTR} may also play a role in myelination [83–85].

Several of the functions previously described for p75^{NTR} were originally observed *in vivo* using a knock-out mouse in which exon III was targeted (p75^{NTR} exon III –/–) [86]. Another genetic mouse model in which exon IV was targeted (p75^{NTR} exon IV –/–) was developed by von Schack et al. in an attempt to eliminate an alternatively spliced protein that was generated in the p75^{NTR} exon III –/– animals [87]. The p75^{NTR} exon IV –/– mice displayed several nervous system defects similar to exon III –/– mice as well as an unexpected abnormality in the formation of blood vessels. However, a p75^{NTR}-truncated protein was found to be expressed in the p75^{NTR} exon IV –/– mice which was not observed in the p75^{NTR} exon III –/– animals and which exhibits pro-apoptotic activities *in vitro* due to c-Jun N-terminal kinase (JNK) and caspase activation [88]. Therefore, the p75^{NTR} exon IV –/– mouse phenotypes may reflect a gain-of-function mutation rather than loss of p75^{NTR} function [88]. To clarify these discrepancies, additional studies should be performed with both targeted mice.

Neurotrophins are synthesized as precursor proteins that undergo proteolytic cleavage to generate mature neurotrophins. Recently, a milestone was achieved with the discovery of pro-NGF as a ligand for p75^{NTR}, which provided several answers to many long-standing questions [13]. Compared to mature NGF, pro-NGF binds with higher affinity to p75^{NTR} in A875 cells and triggers cell death at much lower concentrations [13]. *In vivo,* pro-NGF causes oligodendrocyte cell death through p75^{NTR} in a spinal injury model and apoptosis of adult corticospinal neurons in a brain injury model [89, 90]. These discoveries have shed light on the inconsistent data obtained from experiments investigating the apoptotic function of neurotrophins, as reagents used in previous studies contained variable amounts of pro-neurotrophins. Additionally, the pro-region of the NGF precursor protein contains two novel bioactive peptides that may induce the rapid phosphorylation of the Trk receptor protein [91]. Thus, pro-NGF may also activate TrkA receptor in a weaker way than mature NGF does [92].

Another important advance in the field of p75^{NTR} signaling has been the discovery that sortilin, a member of the Vps10p-domain receptor family, binds to pro-NGF and works as a co-receptor with p75^{NTR} to mediate apoptosis [14]. The apoptotic effect mediated by p75^{NTR} and sortilin is not exclusive to pro-NGF, as pro-BDNF has similar consequences in cells expressing both receptors [15]. Thus, the presence or absence of sortilin at the cell surface will affect the way p75^{NTR}-expressing cells will ultimately respond to pro-neurotrophin molecules.

p75^{NTR}-interacting molecules

The lack of catalytic activity in the cytoplasmic domain of p75^{NTR} suggests that the signaling of this receptor is carried out by interacting proteins that are either constitutively associated with or are recruited to the receptor in response to neurotrophins (Fig. 4). One of the first indications that p75^{NTR} signals independently of Trk receptors was the demonstration that neurotrophin binding to p75^{NTR} causes sphingomyelin hydrolysis and ceramide production [93, 94]. In mature oligodendrocytes, NGF binding of p75^{NTR} leads to the activation of JNK and to apoptosis, which can be counteracted by the presence of TrkA [95, 96]. JNK activation may occur through interaction of the TNF receptor-associated factor-6 (TRAF6) with p75^{NTR} [97, 98].

The apoptotic effects mediated by p75^{NTR} may depend on the orchestration of several downstream molecules of neurotrophins in addition to TRAF6. Several other p75^{NTR}-interacting proteins – NRIF, NRAGE, NADE, and SC-1 – will be described individually.

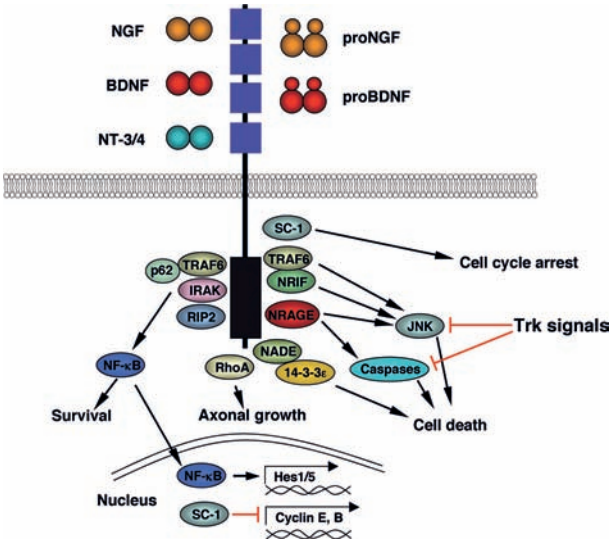

Figure 4. p75 ^{NTR} receptor-mediated signaling pathways. Binding of mature neurotrophins or pro-neurotrophins to p75^{NTR} triggers the activation of different signaling pathways through different adaptors that result in diverse and at times opposite outcomes like survival, apoptosis, axonal growth, axonal collapse, and cell cycle arrest.

NRIF

Efforts to find p75^{NTR} signaling molecules using yeast two-hybrid screens identified a p75^{NTR} intracellular domain-interacting protein called neurotrophin receptor interacting factor (NRIF) [99]. 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 [99, 100]. NRIF-induced cell death through p75^{NTR} requires p53 and NRIF nuclear translocation, which is modulated by TRAF6-mediated polyubiquitination of NRIF at lysine 63 [101, 102].

NRAGE

Neurotrophin receptor-interacting MAGE homolog (NRAGE) also interacts with p75^{NTR} to mediate neurotrophin-induced cell death through a mechanism that involves cell cycle arrest, JNK activation, cytosolic cytochrome c accumulation, and activation of caspases-3, -7, and -9 [103]. The NGF-dependent apoptosis mediated by NRAGE is blocked by the expression of TrkA, which competes with NRAGE for binding to p75^{NTR} [103]. Other proteins of the MAGE family, like necdin, also interact with p75 ^{NTR} and TrkA to promote growth arrest and differentiation of PC12 cells and survival of sympathetic neurons in response to NGF [104–106]. Studies of NRAGE protein expression in the nervous system have led to contradictory results, with some data indicating NRAGE protein expression limited to proliferative neural subpopulations and others indicating its presence in differentiated neurons in the dentate gyrus and stratum oriens of the rat hippocampus [107, 108].

NADE

The p75^{NTR}-associated cell death executor (NADE) protein may induce cell death upon NGF binding to p75^{NTR}, but not BDNF, NT-3, or NT-4/5 binding [109]. Expression of p75^{NTR}, NADE, and NGF is upregulated in response to zinc, and NGF secretion leads to a p75^{NTR}/NADE-dependent apoptosis that may be modulated by an interaction between NADE and 14-3-3ε protein [110, 111].

SC-1

A yeast two-hybrid screen using the cytoplasmic domain of p75^{NTR} as bait identified Schwann cell-1 (SC-1), a protein with an SET domain and six Kruppel-type zinc fingers that was originally implicated in growth arrest [112]. Subsequent studies defined SC-1 as a transcriptional repressor which may function by forming a complex with histone deacyetylases (HDACs) to regulate the levels of cyclins E and B in response to NGF [113].

p75^{NTR} function

Depending on the cellular context, the p75^{NTR} protein can promote pro-survival as well as pro-apototic effects in response to neurotrophins. An important pro-survival signaling pathway activated by NGF, but not BDNF or NT-3, through p75^{NTR} is the NF-κB pathway [114]. The activation of NF-κB requires several proteins, including TRAF6, p62, interleukin-1 receptor-associated kinase (IRAK), and receptor-interacting protein-2 (RIP2) [65, 97, 98, 115, 116]. Production of reactive oxygen intermediates may also be important for NF-κB activation [117]. Upon activation in response to neurotrophins, NF-κB translocates to the nucleus and triggers the expression of Hes1/5 to modulate dendritic growth [118]. This pro-survival pathway, unlike JNK activation, is not abolished by the expression of TrkA and is more likely to be activated when the cells have been previously exposed to stress conditions, as with addition of TNF or serum deprivation [95, 119, 120].

Among other functions, p75^{NTR} can also modulate axonal growth with different outcomes depending on the molecule that binds to the receptor. Neurotrophin binding leads to axonal growth whereas myelin-derived growth inhibitors (MDGIs) evoke growth-cone collapse. These opposite effects are obtained by the regulation of the small GTPase RhoA, a member of the Rho family of proteins that have been shown to control the organization of the actin cytoskeleton in many cell types [for an extensive review see ref. 121]. In the absence of neurotrophins, a constitutive interaction between p75^{NTR} and RhoA maintains RhoA activation and inhibition of axonal growth. Neurotrophin binding to p75^{NTR} causes dissociation of RhoA from the receptor, blocking RhoA activity and leading to axonal growth [122]. Neurotrophins can also promote lengthen-

ing of filopodia through p75^{NTR} by decreasing local RhoA activity in retina and dorsal root ganglion neurons [123, 124].

Modulation of axonal growth through p75^{NTR}-RhoA pathways is not exclusive to neurotrophins. In the last few years several reports have implicated p75^{NTR} as a part of a receptor complex with the Nogo receptor (NgR) that mediates the axonal outgrowth inhibitory signals of MDGI, such as Nogo66, myelin-associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp) [125, 126]. LINGO-1, a nervous system-specific transmembrane protein, also binds NgR1 and p75^{NTR} and is a functional component of the NgR1/p75^{NTR} signaling complex. In non-neuronal cells, co-expression of human NgR, p75^{NTR}, and LINGO-1 conferred responsiveness to OMgp, as measured by RhoA activation [127]. The signal transduction mechanism may involve the displacement of Rho-GDI from RhoA, resulting in its activation and the consequent axonal growth inhibition [128]. Additionally, a positive feedback loop occurs upon spinal cord injury where p75^{NTR} expression is upregulated through a RhoA-dependent mechanism, with a subsequent further increase in RhoA activation [129]. All the above data indicate a convergence point in MDGI signaling to p75^{NTR} to modulate RhoA activity. It will be interesting to investigate the putative therapeutic potential of p75^{NTR} inhibition in injury models to promote axonal regeneration.

p75^{NTR} cleavage

Proteolytic shedding of the p75^{NTR} extracellular domain was reported a long time ago, but not much attention has been paid to this phenomenon until recently, when the proteolytic processing of p75^{NTR} was related to the process of regulated intramembrane proteolysis (RIP) described for other proteins [130, 131]. RIP is a new way of receptor processing that has been recently described for Notch, β-amyloid precursor protein (APP), and ErbB4, which involves two sequential cleavages of a given transmembrane protein. The first cleavage occurs in the extracellular part of the protein and is mediated by the metalloproteinase α-secretase, while the second cleavage occurs in the intramembrane region and is mediated by γ-secretase. The final result is the release of the intracellular domain (ICD), which often traffics to the nucleus and acts as a transcriptional regulator [for a review see ref. 132]. Additionally, intramembrane p75^{NTR} proteolysis may play a role in the assembly/disassembly of a receptor complex containing p75^{NTR} and Trk receptors [131].

The TNF-α-converting enzyme (TACE/ADAM17) is responsible for the α-secretase activity that sheds the extracellular region of p75^{NTR} [133]. Chimeric receptors containing swapped extracellular regions of the p75^{NTR} receptor and the RIP-resistant Fas receptor showed that the p75^{NTR} stalk domain plays a critical role in the α-secretase processing [134]. The biological function of p75^{NTR} cleavage has been addressed in a growth inhibition paradigm in response to myelin inhibitor molecules. The p75^{NTR} ICD is produced in response to MAG in cerebellar granule neurons [135]. Additionally, p75^{NTR}/Fas chimeras resistant to cleavage by α- and γ-secretase act as dominant-negatives that block MAG-induced growth inhibition when expressed in NG108 cells and in dorsal root ganglia sensory neurons [135].

The exciting discovery that p75^{NTR} undergoes sequential cleavage through α- and γ-secretase activities has opened a surprising new area of investigation for the function of this receptor. p75^{NTR} cleavage has been postulated to generate an ICD fragment that might translocate into the cell nucleus [136]. Whether neurotrophins can modulate the proteolytic cleavage of the receptor and whether the p75^{NTR} ICD does translocate to the nucleus to regulate gene expression in a way similar to the Notch receptor remains to be seen.

Although many functions have been described for p75^{NTR}, the verification of the signaling pathways has been a difficult enterprise due to the weakness of signaling transduction and the lack of genetic systems to verify protein-protein interactions. With the recent findings that (i) pro-neurotrophins are more potent effectors than mature neurotrophins for p75^{NTR} activation, (ii) sortilin forms a co-receptor complex with p75^{NTR} to promote apoptosis, (iii) p75^{NTR} undergoes α- and γ-secretase cleavage, and (iv) p75 ^{NTR} acts as a signaling co-receptor with NgR for MDGI, p75^{NTR} now has a new and more promiscuous life than anybody would have predicted a few years ago.

Neurotrophin cross-talk with other signaling pathways

Receptor tyrosine kinases are usually activated upon binding of their cognate ligands, but they can also be transactivated in response to G protein-coupled receptor (GPCR) signaling. This type of activation has been previously described for the receptors for epidermal growth factor, platelet-derived growth factor, and insulin-like growth factor 1 [137–139]. Transactivation of TrkA receptors in PC12 cells and TrkB in hippocampal neurons has been observed after treatment with adenosine or PACAP neuromodulators, both of which act through GPCRs [140, 141]. Interestingly, in contrast to other receptor transactivation events, Trk receptor transactivation by adenosine or PACAP requires a longer time course. The increase in Trk activity can be inhibited by the use of K252a, a Trk receptor inhibitor, and PP1, a Src family-specific inhibitor [140, 141]. Transactivated Trk receptors lead to activation of the PI3K-Akt pathway, which results in increased cell survival after NGF or BDNF withdrawal in PC12 cells and

hippocampal neurons, respectively. Surprisingly, most of the transactivated Trk receptors are found in intracellular locations, particularly associated with Golgi membranes [142]. The effects of adenosine- and PACAP-dependent activation of Trk receptors raise the possibility that small molecules may be used to elicit neurotrophic effects for the treatment of neurodegenerative diseases.

Just as Trk receptors are activated by GPCRs, other receptors and channels can be activated as a result of Trk receptor stimulation by neurotrophins. For example, members of the TRP family of cation channels, like TRPC3 and TRPV1, are stimulated through Trk receptors [73, 143]. TRPV1 sensitization in response to NGF may involve PLCγ activity for those channels already present in the membrane, as well as phosphorylation and new insertion of intracellular channels mediated by Src and PI3K activities, respectively [73, 144]. Additionally, TRPC channels may contribute to the BDNF-induced elevation of Ca^{2+} at the growth-cone and are required for BDNF-induced chemo-attractive turning [145]. Similarly, N-methyl-D-aspartic acid (NMDA) receptor open-probability and glutamate-evoked currents are augmented by BDNF-activated TrkB receptor, which phosphorylates the specific NMDA receptor subunit NR2B [146, 147]. Trk receptors also have the capacity to activate the Ret51 receptor tyrosine kinase in postnatal superior cervical ganglion (SCG) neurons [148]. The mechanism of Ret activation does not depend upon PI3K or MAPK pathways and occurs with a very slow kinetics, similar to GPCR activation of Trk receptors. Interestingly, cultures from *ret–/–* neurons have a smaller soma size in the presence of NGF compared with wild-type neurons [148]. The previous data indicate that cross-talk between neurotrophins and other signaling pathways may play an important role in the modulation of different molecules required for proper functioning of the nervous system.

Regulation of neurotrophin signaling by retrograde transport

The signals of activated Trk receptors by neurotrophins at the growth-cone are sent to the cell body to trigger the transcriptional programs that mediate the neurotrophin-dependent survival of the neuron. The identification of a transported retrograde signal from the distal part of the neurons in response to neurotrophins has been the focus of many studies performed in the last few years. Knowing that NGF treatment evoked a massive endocytosis of the activated receptors, Grimes et al. proposed that the retrograde transport of activated receptors in endocytic vesicles could be the way to transmit this signal [149]. Support for this hypothesis has been provided by several reports. An active complex of NGF-TrkA transported to the cell body of sympathetic neurons mediated a regulated phosphorylation of the transcription factor CREB, which elicited the expression of the pro-survival molecule Bcl-2 [150, 151]. The internalization and transport of a ligand-receptor complex are required to initiate cell body responses to target-derived neurotrophins, as demonstrated by dynamin mutants that block the internalization of the receptor and the involvement of dynein motor machinery to retrogradely transport Trk receptors [152–154]. Additionally, the neurotrophin-retrograde signaling activates Erk5, but not Erk1/2, to phosphorylate CREB [155]. The identity of the endosomes implicated in the retrograde transport of active Trk receptors has been addressed by several other studies [156–158].

Another possibility that has been postulated to mediate the neuronal survival by neurotrophins is a mechanism of propagation of the signaling that does not require the internalization or transport of the active receptor, as reported for EGF [159, 160]. However, there is no doubt that TrkA together with NGF is transported to elicit a signal in the cell body of the neuron. Extensive information about neurotrophin retrograde signaling can be found in several reviews [161–163].

Regulation of neurotrophin receptors by ubiquitination

Neurotrophin signaling should be tightly regulated to elicit the correct cellular response, and once neurotrophin receptors are activated, they should signal in the proper location and to the proper extent to avoid undesirable effects for the cells. Downregulation of the neurotrophin signal can be achieved by degradation of the receptors, as occurs with other transmembrane proteins. Recently, two reports have suggested that Trk receptors undergo ligand-dependent ubiquitination which may be modulated by the presence of $p75^{NTR}$ [164, 165]. However, there are big discrepancies between the two reports. Makkerh et al. [164] suggest that co-expression of $p75^{NTR}$ negatively regulates the ubiquitination of Trk receptors, impairing their internalization and degradation, while Geetha et al. [165] suggest that $p75^{NTR}$ positively regulates the ubiquitination of TrkA. Future experiments should address the controversy about the role of $p75^{NTR}$ in the ubiquitination of Trk receptors as understanding how neurotrophin receptor activation is downregulated will be an important step in the comprehension of neurotrophin signaling and biology.

Perspectives

Neurotrophins not only mediate several different functions in the nervous system during development and adulthood but have also been implicated in different hu-

man pathologies, such as depression, eating disorders, Huntington's, Parkinson's, and Alzheimer's diseases. In the last 15 years, much effort has been invested to try to understand the signaling pathways elicited by these versatile and pleiotropic molecules. The recent identification of several new proteins downstream of Trk and $p75^{NTR}$ receptors has provided many more insights into the intricate functions and mechanisms of neurotrophin actions. Future studies should attempt to (i) address the role of these new proteins in the neurotrophin signaling not only in PC12 cells, but also in different neuronal populations, (ii) use genetically modified animals to verify their function related to neurotrophins, (iii) identify new signaling molecules, mechanisms, and regulators of $p75^{NTR}$ that can explain such a diversity of functions, and (iv) investigate further the role of neurotrophins in human pathologies. In conclusion, neurotrophins remain mysterious growth factors that can provide many exciting surprises for years to come.

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