

Review

Neurotrophins and their receptors: signaling trios in complex biological systems

K. K. Teng and B. L. Hempstead *

Department of Medicine, Weill Medical College of Cornell University, Room C-606, 1300 York Ave., New York, New York 10021 (USA), Fax: +1 212 746 8647, e-mail: blhempst@med.cornell.edu

Received 10 March 2003; received after revision 3 June 2003; accepted 23 June 2003

Abstract. The neurotrophins, a class of four related growth factors, utilize a dual receptor system consisting of Trk receptor tyrosine kinases and the structurally unrelated p75^{NTR} to modulate diverse and sometimes opposing biological actions. The identification of novel ligands for p75^{NTR}, unconventional mechanisms for Trk activation and unique signaling intermediates further under-

scores the complex nature of neurotrophin: receptor interactions, as well as their functions within and outside of the nervous systems. This review summarizes recent surprises of how ligand-receptor pairing may affect diverse developmental events, regulate response to injury and extend their influence on memory and learning.

Key words. NGF; BDNF; NT-3; NT-4; p75^{NTR}; Trk; nervous system; vascular biology.

Introduction

Neurotrophins, including nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin (NT) 3–4, are a family of highly conserved polypeptide growth factors that regulate the generation and maintenance of diverse neuronal populations [1, 2]. More recent studies have revealed additional actions in mediating axonal guidance [3], synaptic plasticity [4] and injury protection [5]. Although initially characterized as a soluble survival factor for peripheral neurons [6], NGF has emerged as an important player with diverse roles in the fields of glial biology [7, 8], vascular biology [9, 10] and tumor biology [11, 12]. Likewise, following their identification as NGF homologues with neurotrophic activities, BDNF, NT-3 and NT-4 have all been implicated in a variety of biological processes in neuronal and nonneuronal populations [1, 13].

Similar to many other secreted growth factors, neurotrophins are synthesized as preproteins, which are

subsequently cleaved to smaller, mature forms that homodimerize. At the molecular level, mature neurotrophins exert their effects by interacting with two structurally unrelated receptors: p75^{NTR}, a member of the tumor necrosis factor (TNF) receptor superfamily, and the Trk receptor tyrosine kinases. The two receptors for neurotrophins also differ in terms of ligand binding specificity. While p75^{NTR} is capable of binding to all mature neurotrophins with equivalent affinity but unique kinetics [14, 15], Trk family members exhibit ligand selectivity. Thus NGF is the preferred ligand for Trk A, BDNF and NT-4 for Trk B and NT-3 for Trk C [16]. The extracellular motifs of p75^{NTR} and Trk receptors are unrelated, with neurotrophins interacting with the immunoglobulin-like C2 (IgGC2) domains of the Trk receptors, but with the cysteine-rich domains of the p75^{NTR} receptor [17–19]. The intracellular portions of the two receptors also share no homology. Unlike full-length Trk receptors that possess signature tyrosine kinase motifs, the intracellular domain of p75^{NTR} does not exhibit intrinsic ligand-inducible enzymatic activity [20–22].

* Corresponding author.

Historically p75^{NTR} was the first neurotrophin receptor to be identified as a NGF-binding transmembrane protein [23, 24]. However, the lack of readily identifiable signal-transducing modules within its cytoplasmic sequence led to the hypothesis that p75^{NTR} functions primarily to augment Trk signaling by enhancing the affinity and the specificity of neurotrophin-Trk interactions [20, 21]. Expression of p75^{NTR} can promote the survival of Trk A-expressing neurons to limiting concentrations of endogenous neurotrophins, best exemplified in studies using p75^{NTR} gene targeted mice where decreased responsiveness to NGF was observed in p75^{NTR}-null sympathetic neurons [25]. As other members of the TNF receptors were demonstrated to modulate apoptotic responses [26], a potential role for p75^{NTR} as a mediator of cell death has rekindled interest in this receptor [27–30]. Indeed, large number of studies now establish neurotrophin-p75^{NTR} interactions as a critical biological event that governs life and death decisions in neuronal and nonneuronal cells alike [20–22, 31] (table 1).

In contrast, survival signaling predominantly reflects Trk activation. Tyrosine phosphorylation of activated Trk recruits downstream signaling enzymes and adaptor proteins that contain protein interacting domains. The formation of receptor-adaptor-enzyme complexes ultimately mediates the trophic responses ascribed to the neurotrophins. Classic signaling modules, such as the Ras-mitogen-activated protein (MAP) kinase cascade and the phosphatidylinositol-3 (PI-3)-kinase-Akt pathway, have been identified as downstream cellular events induced by Trk activation. The latter in particular is considered pro-survival, as Akt-mediated phosphorylation of a number of proapoptotic proteins results in their inactivation [32, 33].

In numerous neuronal and nonneuronal cells, ligand activation of p75^{NTR} can initiate apoptosis when p75^{NTR} is expressed independently of Trk. When p75^{NTR} and Trk are expressed in the same cell, however, survival signaling dominates following addition of mature neurotrophins. This is due in part to enhanced affinity of neurotrophins to their cognate Trk receptor (a function of p75^{NTR}) and in part to the ability of Akt to suppress the apoptotic signal-

ing cascade initiated by neurotrophin binding to p75^{NTR}. The ‘Jekyll and Hyde’ nature of p75^{NTR} is perplexing, given the diametrically opposite roles this receptor plays in promoting death and augmenting survival. A recent study has shed light on this issue by identifying a high-affinity proapoptotic ligand for p75^{NTR} as pro-NGF [34]. Surprisingly, pro-NGF neither binds to nor activates Trk A. Accordingly, pro-NGF and pro-BDNF can be differentially released as soluble proneurotrophins or processed as mature neurotrophins, each with distinct ligand-receptor interactions and biological consequences. Recent studies have revealed additional levels of complexity within the neurotrophin-receptor trios. A number of p75^{NTR} ligands, including β -amyloid and prion peptides can induce receptor clustering and signaling, leading to cell death. Novel actions for p75^{NTR} in regulating glial differentiation and myelination have also been uncovered [35]. In exciting recent studies p75^{NTR} appears to act as a signal-transducing component of the Nogo receptor complex to limit neuronal process extension by selective glial proteins [36, 37]. Lastly, a point mutation in the pro-domain of BDNF has been linked to memory loss in human [38]. The purpose of this review is to highlight the unusual modulation of neurotrophins and their receptors by diverse cellular mechanisms. In addition, we integrate the newly found identities for this ligand-receptor system with its traditional roles in neuronal differentiation and survival promotion.

Distinct domains and processing of neurotrophins

The neurotrophins are phylogenetically one of the oldest families of polypeptide growth factors, with members expressed in zebrafish and the lamprey. Despite divergence of NGF and BDNF more than 600 million years ago [39], neurotrophins remain remarkably well conserved across species, as exhibited by the finding that zebrafish BDNF can provide trophic support to rodent Trk B-expressing neurons [40, 41]. Indeed, from lamprey to humans, each neurotrophin is translated from a single coding exon to generate a preproneurotrophin of approximately 30 kDa,

Table 1. Selected examples of p75^{NTR}-modulated survival and death in the nervous system.

p75 ^{NTR} -dependent survival (Trk-independent)			p75 ^{NTR} -induced apoptosis		
Cell types	Ligand	Ref.	Cell types	Ligand	Ref.
Neocortical subplate neurons	BDNF, NT-3	[153]	oligodendrocytes	NGF	[28]
Sensory neurons	NGF	[154]	retinal ganglion cells	NGF	[27]
Schwann cells	NGF	[73]	sympathetic neurons	BDNF	[29–30]
			hippocampal neurons	all	[155–156]
			sympathetic neurons	pro-NGF	[34]
			oligodendrocytes	pro-NGF	[56]

which can be glycosylated in the N-terminal pro-domain. Proneurotrophins dimerize to yield approximately 60-kDa species [42]. They are cleaved intracellularly by furin and proconvertases to yield C-terminal mature proteins of 13.5 kDa that exist as 28-kDa dimers and have been considered the biologically active forms [2, 43, 44]. In comparing neurotrophin sequences, two regions are highly conserved across species: the distal 35 amino acids of the pro-domain of the neurotrophin as well as the amino acids within the mature portion of the protein. The degree of conservation in these regions is striking. For example, zebrafish and mammalian BDNF are 94% conserved in the distal 43 residues of the pro-region and 91% identical in the mature BDNF sequence. Past work has also established that one function for the highly conserved pro-domain of the neurotrophins is to enable proper folding of the mature neurotrophins [45]. Another is that the pro-domain is required for correctly sorting the mature neurotrophins to constitutive or regulated secretory pathways [46, 47].

Recently, Egan et al. [38] reported that a single nucleotide polymorphism (SNP) within the human BDNF gene results in an amino acid substitution (valine to methionine at position 66) within the pro-domain of BDNF. Consistent with the interpretations that the pro-domains of the neurotrophins are important for the processing and release of the mature isoforms, human met⁶⁶-BDNF appears mislocalized, and perhaps as a consequence is less efficiently processed for stimulated release when assessed in cultured rat hippocampal neurons [38]. The most intriguing aspect of this study, however, is the strong correlation between (i) episodic memory deficiency in humans with one or both copies of the val → met substitution, (ii) functional magnetic resonance imaging (MRI) evidence of decreased hippocampal activity and (iii) reduced activity-dependent release of mature BDNF from neurons. Thus, for the first time, neuronal functions in humans have been linked to the neurotrophins in a manner that is largely consistent with the role of BDNF in modulating synaptic plasticity [4], an area well described in animal models.

Analysis of adult tissue lysates reveals the presence of multiple NGF and BDNF isoforms with molecular masses that range from 13.5 kDa (mature neurotrophins) to 30 kDa (proneurotrophins) of the reduced proteins. The intermediate-size peptides correspond to a number of the predicted cleavage products by selective metalloproteases (MMPs) and plasmin within the pro-domain of NGF and BDNF [34]. These potential cleavage sites, some of which contain dibasic motifs, are conserved phylogenetically. While this study does not directly address whether the intermediate neurotrophin isoforms are released, it raises the possibility that mature neurotrophins may not be the only biologically active peptides from this growth factor family and that higher molecular isoforms

of neurotrophins may exist with distinct functions. Indeed, proneurotrophins as well as mature neurotrophins are released from heterologous recipient cells in culture [46, 48, 49]. Although met⁶⁶-BDNF is processed and released, albeit less efficiently, as mature BDNF, currently available information does not indicate whether additional alternative isoforms might be concomitantly produced, and if so, whether these isoforms contribute to altered neuronal function.

Pro-NGF as an apoptotic ligand for p75^{NTR}

Several lines of evidence suggest that the mature neurotrophins are potent and selective ligands for Trk receptors. In nonneuronal paradigms, mature NGF is a more effective Trk ligand than the pro-domain of NGF in mediating cell survival [11, 50]. Comparable results have also been observed with BDNF and Trk B activation [48]. In addition, the mature NGF dimer and the portion of the Trk A extracellular domain which binds NGF (i.e. the IgGC₂ domain) have been cocrystallized [51], as have mature NT-4 and the Trk B IgGC₂ domain [52]. The crystallographic structure confirms that the ligand:receptor interface is composed of two extended patches, but does not predict whether Trk A dimers can accommodate and effectively interact with the larger pro-NGF dimeric ligand.

Far less is known about the interaction of neurotrophins with the p75^{NTR} receptor. Structural/functional analysis of the p75^{NTR} receptor suggests that multiple regions of the extracellular domain contribute to NGF binding, with the second and third cysteine loop in the extracellular domain being most critical [17, 18]. Point mutagenesis of the four neurotrophins suggests that the variable loops are important for interaction with p75^{NTR} [53]. This is an unexpected finding, as these loops exhibit the highest degree of variation between neurotrophins, yet all neurotrophins bind specifically to p75^{NTR}. The kinetic analysis of NGF:p75^{NTR} binding is also unusual in that NGF binds and dissociates very rapidly, whereas most ligand:receptor interactions exhibit slow dissociation rates that reflect the close apposition of ligand and receptor binding domains [54]. Lastly, mature neurotrophins are relatively ineffective in inducing an apoptotic response via p75^{NTR}; high concentrations of neurotrophins (2–4 nM), significantly above the 1-nM binding constant, are required for apoptosis to be initiated (see [9, 28] for example). In contrast, activation of other proapoptotic TNF receptor family members occurs following receptor occupancy of 10–20% of the total binding sites [55].

Given these inconsistencies, the activity of pro-forms of neurotrophins as p75^{NTR} ligands was investigated. Indeed, recombinant pro-NGF, in which the conserved furin cleavage site has been mutated to impair proteolytic pro-

cessing to the mature form, is five times as effective as mature NGF in dissociating radiolabeled NGF from p75^{NTR} but is ineffective in competing for Trk A binding. These results strongly suggest that pro-NGF is a high-affinity, specific ligand for p75^{NTR} but that, unlike mature NGF, lacks the ability to activate Trk A. Results from *in vivo* comparison of the biological actions of pro-NGF and mature NGF are consistent with the receptor binding studies. In p75^{NTR}-expressing vascular smooth cells where Trk A is absent, pro-NGF is approximately 10 times as effective as mature NGF in inducing apoptosis. In cultured sympathetic neurons where Trk A is present, pro-NGF induces neuronal death where mature NGF promotes cell survival [34].

Further support for pro-NGF as a high-affinity apoptotic ligand comes from a recent study in which upregulation of pro-NGF is causally linked to p75^{NTR}-mediated oligodendrocyte death following spinal cord injury [56]. In this study, expression of pro-NGF, but not other proneurotrophins, was detected within 1–2 days of traumatic spinal cord injury in rodents. Pro-NGF was likely responsible in part for oligodendroglial apoptosis via p75^{NTR}, as cell death was significantly reduced in p75^{NTR} gene-targeted animals, and the apoptotic actions of neurotrophins upon p75^{NTR}-expressing oligodendrocytes could be blocked by pro-NGF-specific antibody. As p75^{NTR} is induced in other cell populations in the injured

spinal cord, including motor and corticospinal neurons, future studies will be needed to assess the potential actions of proneurotrophins in these cells.

Modulating the role of p75^{NTR} as a death receptor

The above studies are consistent with the limited extent of apoptosis observed in normal tissues that express both neurotrophins and p75^{NTR}, as they predict that pro-NGF actions are not only regulated by its secretion, but also governed by tissue-specific regulation of proteases such as plasmin and MMPs. These results further suggest that different neurotrophin isoforms can discriminate among distinct components of multimeric Trk-p75^{NTR} receptor complexes: mature neurotrophins selectively bind Trk, whether it is expressed alone or complexed with p75^{NTR} (fig. 1), while proneurotrophins bind selectively to p75^{NTR} but not to Trk. Proteolytic processing of pro-NGF thus releases the molecule in its mature form, capable of activating Trk A for prosurvival signaling. In contrast, apoptotic events are triggered when pro-NGF is released as a result of protease inhibition. Clearly, this hypothesis will require the reevaluation of prior studies of neurotrophins and p75^{NTR}, which are highly expressed during development and reinduced post injury, to assess the ratio of proneurotrophin vs. mature neurotrophin that is re-

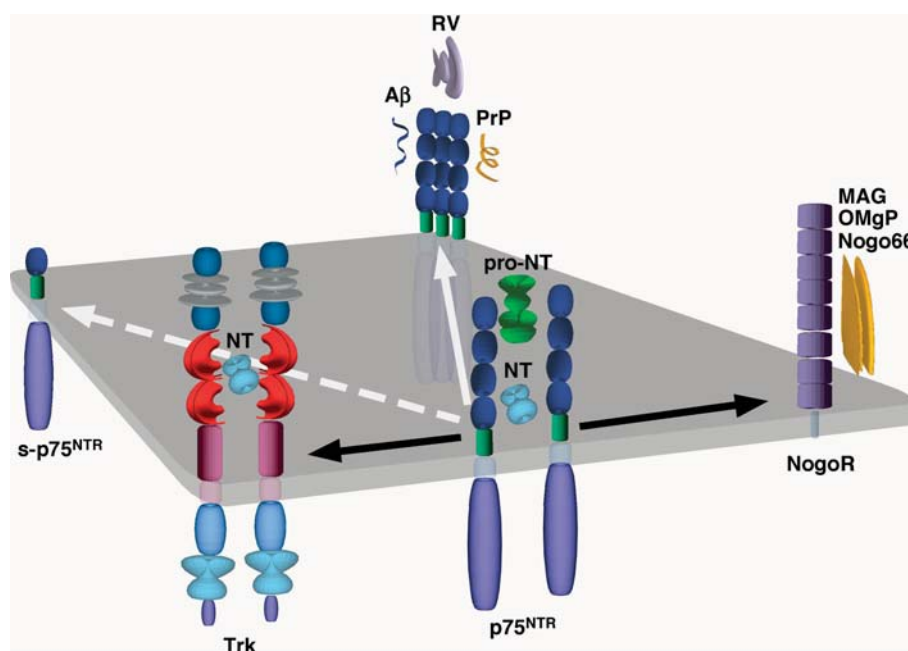


Figure 1. Distinct interactions of p75^{NTR} with proneurotrophins, mature neurotrophins and other ligands. Dimeric P75^{NTR} is depicted here to bind either mature neurotrophin (NT) or proneurotrophin (pro-NT), resulting in apoptosis. It also interacts with dimeric Trk receptor tyrosine kinase and modulates the specificity of mature neurotrophin actions. In addition, p75^{NTR} interacts with the Nogo receptor (NogoR) for axonal growth inhibition mediated by MAG, OMgp and Nogo66. The binding of rabies virus (RV), prion protein (PrP) or a β -amyloid to p75^{NTR} appears to induce receptor trimerization. Finally, the potential interaction between full length p75^{NTR} and its naturally occurring short isoform s-p75^{NTR} is denoted by dashed arrow. The signaling mechanisms and biological actions of p75^{NTR} activation were recently reviewed [20–22].

leased from cells for differential receptor activation. In addition, a better understanding of the potential pathobiology of proneurotrophins requires the use of pro-domain-specific antisera to distinguish pro- from mature isoforms as well as in vivo approaches to misexpress cleavage-resistant proneurotrophins in models of neuronal and nonneuronal injury.

Although pro-NGF may bind p75^{NTR} with higher affinity than mature NGF, the molecular mechanisms utilized by these two related ligands to trigger apoptosis have not yet been characterized in detail. Whether p75^{NTR} activation by pro-NGF results in recruitment of novel adaptors to more efficiently induce cell death remains an open question. Towards this end, it is interesting to note that a truncated isoform of p75^{NTR} (s-p75^{NTR}) has been reported to negatively regulate neuronal survival, but may promote the survival of vascular cells [10]. In addition, a gene related to p75^{NTR}, named *NRH* (neurotrophin receptor homolog), has been identified in lower vertebrates, and consists of a short extracellular domain, as well as transmembrane and cytoplasmic regions that are highly homologous to p75^{NTR} [57]. As both s-p75^{NTR} and NRH encode transmembrane and intracellular domains, signaling actions are possible through the binding of apoptotic adaptor proteins. It is interesting to note that other members of the tumor necrosis factor (TNF) receptor family exist as preformed trimeric receptor complexes and are activated by trimeric ligands [26]. Thus, one could postulate that an efficient means for dimeric pro-NGF to induce apoptosis is to induce complex formation between s-p75^{NTR} or NRH with a dimeric p75^{NTR}, thereby enabling dimeric ligand:receptor interaction to induce trimeric p75^{NTR} cytoplasmic complexes. In addition, full-length p75^{NTR} can be cleaved by matrix metalloproteinases within the extracellular domain to yield a product that does not bind ligand, but could signal via the transmembrane and cytoplasmic domains [58]. Overexpression of recombinant p75^{NTR} proteins that similarly lack the extracellular domain can promote apoptotic signaling in vivo [59]. Adding complexity, the generation of p75^{NTR} (or p75^{NTR}-like) forms lacking most of the extracellular domain could potentially enhance Trk-mediated survival. As the transmembrane and cytoplasmic domain interactions between p75^{NTR} and Trk A receptors appear important in dictating the formation of Trk A high-affinity sites [60], it is tempting to consider whether these 'short' forms of p75^{NTR} or p75^{NTR} homologs could modulate responsiveness of Trk A, B or C. Evidence suggests that this may occur in vivo, as gene-targeted animals that lack both s-p75^{NTR} and full-length p75^{NTR} exhibit impaired survival of vascular cell populations [10] known to express Trk B receptor and respond to BDNF [61]. In addition, overexpression of a short form of p75^{NTR} that lacks a ligand binding domain can promote survival via activation of PI-3 kinase in in vitro systems [62]. Spatial and

temporal regulation of these naturally occurring p75^{NTR} related isoforms as well as the relevant proteases may clarify the roles of p75^{NTR} in postnatal life and in pathologic states.

Novel biological actions of neurotrophin:p75^{NTR}-mediated induction of glial differentiation have recently been uncovered [35]. Although prior studies utilizing p75^{NTR} null mice had described impaired Schwann cell migration and defective coverage of dorsal root ganglia axons [7], more recent evaluations implicate BDNF-mediated p75^{NTR} activation as an important regulator of myelin formation by Schwann cells [35, 63]. These studies underscore the emerging, diverse biological responses observed upon p75^{NTR} activation. Like other TNF receptors, p75^{NTR} appears capable of mediating a range of responses from apoptosis, to migration, to differentiation. Consistent with this interpretation is the finding that pro-NGF activation of p75^{NTR} in A875 melanoma cells results not in apoptosis but rather in enhanced chemotactic response via an interaction with the actin-bundling protein fascin [64]. Further characterization will be required to determine whether the spectrum of p75^{NTR}-dependent cellular responses reflects differences mediated by distinct ligands, or by recruitment and activation of cell-type-specific intracellular mediators.

Distinct signaling intermediates for p75^{NTR}

Structurally, p75^{NTR} belongs to TNF-receptor superfamily, and like other members contains a death domain consisting of six α helices in a packed antiparallel conformation within its intracellular region [65]. Fas and TNFR1 encode a type I death domain, whereas p75^{NTR} encodes a related domain that differs in reduced ability to self-associate in vitro. This domain is critical to recruit scaffolding proteins and additional mediators to promote the proapoptotic functions of the TNF receptors [26]. In contrast, although p75^{NTR} has also been established to induce cell death in neuronal and nonneuronal paradigms, the molecular mechanism by which this occurs is less clear [20–22, 31]. In particular, one study reports that mature neurotrophin-induced p75^{NTR}-dependent apoptosis of an immortalized striatal neuron cell line requires the p75^{NTR} death domain but not the apoptotic adaptor molecules FADD and TRADD, which are utilized by Fas or TNFR [66]; however, more recent studies in breast cancer cell lines suggest that TRADD/p75^{NTR} interaction can occur [67]. The structural distinction between p75^{NTR} and TNFR1 intracellular domains suggest a potential mechanistic divergence between p75^{NTR} and other apoptotic receptors. Consistent with this possibility is the observation that of the many p75^{NTR} interacting proapoptotic proteins thus far identified, including NRIF [68], NADE [69], members of the MAGE protein family [70, 71] and

TRAF-2 [72], only NADE interacts with the death domain of p75^{NTR}. Interestingly, RIP-2 also interacts with the p75^{NTR} death domain, but its engagement with the receptor is antiapoptotic [73]. The identification of prosurvival p75^{NTR} interacting proteins such as RIP-2 [73], IRAK [74] and TRAF-6 [75] suggests that the equilibrium between apoptotic and survival signaling cascades ultimately determines the cellular consequence of p75^{NTR} activation. This equilibrium may be dictated by cell-type-specific expression of critical signaling proteins, as has been proposed for other TNF receptor family members [76].

Other p75^{NTR}-binding molecules identified by biochemical means and by yeast two-hybrid analysis reveal potential functions of p75^{NTR} in cell cycle control and in cytoskeleton rearrangement. The former includes SC-1 [77], NRAGE [70] and NRIF [78], while the latter pathway is specified by an interaction between RhoA [79] and Rho-GDI [80]. Very recently, Higuchi et al. [81] reported that the β -catalytic subunit of protein kinase A (PKA) directly phosphorylates p75^{NTR} to induce p75^{NTR} migration into lipid rafts, events that support prior findings of an interaction between p75^{NTR} and caveolin [82]. Although serine/threonine phosphorylation of p75^{NTR} has been noted previously, this is the first study that integrates ligand-induced phosphorylation of p75^{NTR} with PKA-dependent inactivation of RhoA and axonal outgrowth.

The lack of ligand-induced enzymatic activity and the dual capability of p75^{NTR} to signal independently and together with Trk have made the study of this receptor a challenging endeavor. However, the identification of novel interacting proteins, newly described selective ligands and cell types in which p75^{NTR} activation, independent of Trk, can be probed should provide welcome tools to dissect this multifaceted receptor.

Novel ligands for p75^{NTR}

Recently a number of nonneurotrophin ligands for p75^{NTR} have been described. Two of these are the aggregated β -amyloid [83] and the aggregated prion peptide [84]. Both appear to bind p75^{NTR} with relatively low affinity, in the nanomolar ranges, and both are reported to induce apoptosis. Interestingly, β -amyloid binds monomeric p75^{NTR} and may induce its trimerization to activate c-jun transcription and c-jun N-terminal kinase (JNK) activity [83, 85]. Likewise, an aggregated prion protein fragment implicated in mediating neuronal apoptosis has also been proposed as a p75^{NTR} ligand [84]. This protein fragment competes poorly with mature NGF in kinetic analysis, suggesting that p75^{NTR} may have distinct binding domains for mature NGF or aggregated prion peptides. These aggregated prion peptides initiate apoptosis in a neural crest line, with concomitant caspase-8 activation. Although the

concentrations of β -amyloid or aggregated prion peptide required for p75^{NTR} activation are as high or higher than those of mature neurotrophins, such local concentrations may be attained in pathologic states.

Two rabies/rabies-related viral encoded glycoproteins that form a trimeric transmembrane protein complex have also been reported to selectively bind p75^{NTR} in vitro [86, 87]. Again, this interaction utilizes regions of the p75^{NTR} extracellular domains that are distinct from those mediating mature neurotrophin binding. These extracellular sequences of p75^{NTR} are encoded in the alternatively spliced s-p75^{NTR} product, and evidence suggests that both full-length and s-p75^{NTR} bind to rabies virus. The biological consequence does not appear to involve apoptosis regulation but rather facilitation of viral entry in a p75^{NTR}-dependent manner [87].

Exciting new studies also suggest that p75^{NTR} may inhibit the elongation of axons that is mediated by specific myelin proteins. In a rapidly unfolding field, p75^{NTR} was initially identified as a coreceptor with the ganglioside GT1b to mediate the inhibitory actions of myelin-associated glycoprotein (MAG) on the migration of growth cones. Although MAG does not appear to bind directly to p75^{NTR}, it interacts with a GT1b: p75^{NTR} receptor complex, and can activate Rho in a p75^{NTR}-dependent manner, to inhibit process extension [88]. These actions contrast with mature neurotrophins, which impair p75^{NTR}-mediated Rho activation to promote axonal elongation [89]. These observations have been extended in mouse studies by the use of animals that lack expression of the full-length p75^{NTR}. Aberrant axonal elongation is detected in these gene-targeted animals into myelin-rich regions where these processes would otherwise not grow [90].

In addition to MAG, emerging evidence suggests that other myelin glycoproteins utilize multicomponent receptor complexes that include p75^{NTR} to mediate repulsive axonal signaling. The extracellular domains of Nogo-A, oligodendrocyte myelin glycoprotein (OMgp) and MAG can interact with the Nogo receptor present on axons to limit elongation [91]. Because the Nogo receptor is a glycosylphosphatidylinositol (GPI)-anchored protein and thus lacks an intracellular domain capable of signal transduction, additional members of a receptor complex had been sought to provide a molecular mechanism. In recent studies, p75^{NTR} has been identified as a component of the Nogo receptor complex, as Nogo and p75^{NTR} biochemically interact [36, 37] and as misexpression of p75^{NTR} lacking an intracellular domain permits extensive process outgrowth on inhibitory myelin substrates [36]. Interestingly, mature neurotrophins do not appear to compete with Nogo in biochemical assays of p75^{NTR} binding [36]. However, antibodies that induce clustering of the extracellular domain of p75^{NTR} can overcome the axonal repulsion mediated by MAG [37]. These surprising studies together illustrate the unique abilities of p75^{NTR} to

partner with numerous receptors to mediate diverse biological actions (fig. 1).

Neurotrophin signaling via Trk receptors

Amongst the neurotrophin-Trk interactions thus far characterized, that between NGF and Trk A remains the best-studied paradigm of how neurotrophins signal through their cognate receptors. NGF-induced Trk A activation in PC12 cells and BDNF-induced activation of Trk B in neurons is accompanied by a cascade of well-defined cellular events (recently reviewed in [32, 92]). In particular, activation of the small GTPases Ras and Rap1 has been linked to the Raf-1/B-Raf $\rightarrow$ MAPK/ERK kinase (MEK) $\rightarrow$ extracellular signal-related kinase (ERK) pathway for transcriptional regulation and differentiative signaling [93, 94], while the PI-3 kinase $\rightarrow$ PDK $\rightarrow$ Akt cassette targets and inactivates proapoptotic substrates [95–98]. Unlike the lipid enzyme phospholipase C- γ 1 (PLC- γ) which binds directly to activated Trk A at Tyr⁷⁸⁵ residue [32, 33], both of these pathways interact indirectly with the autophosphorylated receptor on Tyr⁴⁹⁰ [99–101]. Indeed, both genetic and biochemical evidence indicates that adaptor proteins, including Grb-2 [102], Shc [101], FRS-2/SNT [99] and Gab-1 [103], link Trk A to the Ras pathway for Erk activation, and to the PI 3-kinase pathway for Akt activation. Perhaps paradoxically, a number of cytoplasmic SH2 domain-containing tyrosine phosphatases have been shown to positively regulate neuronal differentiation and survival [104–106]. Although the precise cellular mechanisms for these observations are unknown, they appear to involve interaction with the adaptor proteins FRS-2 and Gab-1 [107].

Unlike many other receptor tyrosine kinases which utilize multiple tyrosine-containing motifs to define distinct interaction sites for downstream signaling components [108], only two of the seven conserved (among Trk A, B and C) tyrosine residues that lie outside of the Trk kinase domain have been established to play critical roles in functional reconstitution studies (i.e. Y⁴⁹⁰ and Y⁷⁸⁵; reviewed in [32, 92]). Thus the adaptor proteins FRS-2 and Shc, each of which has been associated with differentiative and survival signaling, compete for phosphorylated Y⁴⁹⁰ on activated Trk A [100]. Similarly, at least two molecules have been shown to interact with phosphorylated Y⁷⁸⁵: PLC- γ , whose activation has been linked to intracellular Ca²⁺ mobilization, PKC δ activation and transcriptional regulation [32, 109–111], and a C-terminal SRC kinase (CSK) homolog kinase (CHK), implicated to modulate neurite outgrowth in PC12 cells via an as yet undefined mechanism [112].

A number of independent studies have also demonstrated that upon Trk activation, the activation loop tyrosine residues (Y⁶⁷⁰, Y⁶⁷⁴ and Y⁶⁷⁵) constitute binding sites

for several SH2 domain-containing adaptor proteins. These include rAPS and the closely related SH2-B [113]; the latter has been characterized in terms of growth hormone signaling via JAK2 [114]. In neuronal cells, however, SH2-B has been implicated in the survival signaling of NGF-dependent sympathetic neurons [113] and differentiation of PC12 cells [115, 116]. This appears to occur, in part, via the MAP kinase cascade initiated by Grb-2 binding to tyrosine-phosphorylated SH-2B [113]. In addition, a direct SH2-B-independent interaction between the activation loop tyrosines of Trk A with Grb-2 has been reported [102]. As Grb-2 also interacts with FRS-2 and Shc, these studies suggest a highly redundant mechanism for modulating Grb-2-associated signaling events. Finally, an interaction between the cytoplasmic tyrosine kinase c-Abl with Y⁶⁷⁴ and Y⁶⁷⁵ of activated Trk A has been proposed based on in vitro binding analysis [117], while another study has proposed that the c-Abl interaction occurs within the juxtamembrane region of Trk A [118]. Although the precise mode of c-Abl:Trk interaction remains to be clarified, c-Abl and the c-Abl related gene product (Arg) have been implicated in early neurulation [119] and regulation of growth cone dynamics [120], cellular events in which Trk might potentially participate.

In addition to direct interactions with Trk as summarized above, a number of signaling proteins have been indirectly linked to neurotrophin responsiveness with only partially defined signal transduction pathways. Most notable is the Rap 1 $\rightarrow$ B-Raf-mediated prolonged MAP kinase activation cascade, which has been correlated with differentiative signaling in PC12 cells [93, 94]. Although it is generally recognized that upon NGF treatment, the small GTPase Rap1 is activated by the guanine exchange factor C3G via the adaptor c-Crk II (or the related CrkL) [121], direct interaction to connect ligand-activated Trk A to c-Crk II or CrkL remains to be delineated. However, an in vitro interaction between the SH2 domain of c-Crk II with FRS-2 has been reported [100]. Alternatively, the identification of additional Rap 1 exchange factors [122] might afford a C3G-independent means for modulating the B-Raf-directed MAP kinase activation. Members of the Src kinase family may also modulate distinct aspects of neurotrophin-induced cellular responses, but the molecular mechanisms await clarification [92]. In contrast to other growth factor receptors such as the PDGF receptor, which contains distinct SH2 domain binding motifs for c-Crk II/CrkL and c-Src [123], direct binding of these signaling modules to Trk has not been established. Although future analysis should identify whether these (and other) ‘orphan’ signaling proteins interact directly with Trk, it is interesting to note that in addition to Y⁴⁹⁰ and Y⁷⁸⁵, other conserved tyrosine residues of Trk A have been posited to play synergistic roles in mediating NGF-induced neurite outgrowth [124].

Novel Trk substrates and modes of activation

Many of the downstream effectors of Trk are not unique to the neurotrophins, but are activated by other receptor tyrosine kinases to yield distinct biological endpoints. Although the duration (i.e. sustained vs. transient) of MAP kinase activation remains an important parameter in defining growth factor specificity [93, 94], recent advances suggest that additional mechanisms orchestrate the diversity and specificity of neurotrophin actions. Initially described by Campenot more than 20 years ago, compartmentalized cultures of peripheral neurons can be used to evaluate the differential effects of Trk A activation in the cell body and in distal processes [125]. In these highly polarized cells, where sustained delivery of NGF at the axon *in vivo* is required for cell survival, the mechanisms that facilitate retrograde transport of distal Trk signaling are highly relevant [126]. Creative application of this tissue culture system by a number of investigators has begun to dissect the cellular consequences of distal Trk receptor activation. Although many of the molecular details remain unresolved (recently reviewed by [127, 128]), retrograde transport of activated Trk receptor itself [129–131] is a critical event in promoting CREB-mediated gene transcription [132] and neuronal survival [129]. Other studies also demonstrate that both PI-3 kinase and a member of the Erk family (ERK 5) are integral components of the retrograde neurotrophic signal [133–135]. In addition to its role in activating Akt [97], PI-3 kinase activity is required for the internalization of Trk-containing signaling endosomes [136, 137]. Equally intriguing, however, is the finding that direct application of NGF to the proximal cell body compartments results in local activation of both ERK1/2 and ERK5, while axonal exposure to NGF (confined within the distal compartment) leads to retrograde transport of only activated ERK5 [135]. Since ERK1/2 and ERK5 can mediate distinct transcriptional events, these results strongly suggest that unique signaling pathways can be generated by spatially limiting the exposure of neurotrophins in highly polarized neurons.

Interestingly, intrinsic mechanisms also exist to define spatially specific signals. Using fluorescent resonance energy transfer to detect activated Ras and Rap1, Mochizuki et al. have reported distinct cellular localization of these two GTPases [138]. Surprisingly, active Ras was detectable along the neurites of NGF-differentiated PC12 cells, while activated Rap1 remained only within the perinuclear region of the cells [138, 139], suggesting that even on cells that are uniformly exposed to NGF, biochemically redundant pathways for MAP kinase activation need not cross paths. Given the number of known downstream effectors that could modulate neurotrophin signaling, systematic analysis of localized activation of these molecules would be extremely informative.

Recent reports on the crosstalk between Trk and G-protein-coupled receptors (GPCRs) provide yet another mechanism by which activation of Trk results in selective utilization of downstream signaling pathways. In these studies, adenosine and the neuropeptide PACAP were shown to promote neuronal survival in a Trk-dependent manner [140, 141]. In contrast to similar observations with the EGF receptor, transactivation of Trk occurs with delayed kinetics, suggesting an alternative mechanism of activation than that which occurs on the plasma membrane. Interestingly, and unlike that reported for the EGF receptor, transactivated Trk A engages only the PI-3 kinase pathway to promote neuronal survival without concomitant activation of the MAP kinase cascade [140]. Although transactivation of Trk A (and Trk B) by GPCRs is still an emerging theme in receptor crosstalk, the preferential activation of PI-3 kinase but not of MAP kinase suggests the mode of Trk activation (i.e. ligand-induced vs. transactivated) may play a critical role in dictating downstream biological outcomes.

Of potential relevance with regard to specificity of Trk signaling, several novel Trk interacting proteins have been identified. These include Tctex-1, a 14-kDa cytoplasmic dynein light chain that might play an important role in retrograde transport of activated Trk [142], and GIPC, a PDZ domain-containing protein that modulates GPCR functions [143]. Interestingly, both of these proteins interact with Trk within the juxtamembrane portion but not the signal-transducing tyrosine Y⁴⁹⁰ or Y⁷⁸⁵, a region which has previously been implicated in NGF-dependent neuritogenesis [144]. In the search of p75^{NTR}-interacting protein, an ankyrin rich membrane spanning protein (ARMS) was identified. Further characterization revealed that ARMS also interacts with Trk and that it is tyrosine phosphorylated in response to NGF and BDNF but not the mitogenic growth factor EGF [145]. A GTPase-activating protein (Grit) for Rho and CDC42 has also been reported to bind Trk A [146]. Although the region of interaction has not been clearly defined, Grit appears to complex with Trk A but not Trk B or C in *in vitro* analysis. This is a potentially important finding, as distinct Trk family members have been known to exhibit biological responses unique to the corresponding neurotrophins [147–149], and little is known of the molecular mechanism that might exist to account for such selectivity at the postreceptor level. Finally, the transcription cofactor MafK has been identified from serial analysis of gene expression (SAGE) of NGF-treated PC12 cells [150]. Its expression profile belongs to those of the immediate early genes (IEGs), but unlike other IEGs, MafK appears to be specifically induced by NGF. The additional finding that MafK expression is required for the differentiation of telencephalic neurons and PC12 cells [150] suggests that Trk-specific signaling is coupled to transcription responses unique for neuronal functions.

An additional level of complexity is encountered in cells which coexpress both p75^{NTR} and Trk receptors. Although coexpression of both receptors can modulate the affinity of ligand binding, there is increasing evidence that crosstalk between p75^{NTR} and Trk receptors occurs via modulation of intracellular signaling pathway (recently reviewed by [20]). For example, prior studies have suggested that p75^{NTR} increases serine phosphorylation of Trk A via an unknown kinase [151]. Further study will be required to determine whether this results in attenuation or augmentation of specific signaling pathways downstream of Trk. In addition, Trk activation of PI-3 kinase can suppress p75^{NTR}-mediated ceramide production and may serve as a mechanism to impair p75^{NTR}-elicited apoptosis [152]. Thus, future studies that clarify the biologically relevant p75^{NTR}-signaling cascade will provide important targets that additionally may be regulated by Trk-induced intermediates to balance and modulate neurotrophin responsiveness (fig. 2).

Perspectives

Since the identification of NGF as a soluble factor with axonal growth-promoting activity more than 50 years ago [6], this small family of polypeptides has continued to fascinate the neuroscience community. This is due not only to

the critical roles of the neurotrophins in maintaining neuronal survival, but also to an expanding list of equally important functions governed by the neurotrophins [1, 2]. At the molecular level, a dual-receptor system with unique and redundant signal transduction networks appears to have evolved to account for the complexity of neurotrophin actions. Recent findings of proneurotrophin-specific effects, alternative p75^{NTR} ligands and spatially regulated Trk signaling have addressed some outstanding issues and uncovered new ones in terms of how neurotrophins and their receptors modulate basic cellular functions (e.g. survival/death and differentiation) and extending those influences to higher order mental activities (e.g. memory and behavior). On the other hand, these studies also hold promise for rational therapeutic approaches for diseases within and outside of the nervous systems. For example, once the molecular mechanism is better characterized, the apparently 'promiscuous' interaction of p75^{NTR} with mature and proneurotrophins, myelin components and β -amyloid might be pivotal for selective blockade of one ligand-induced event over another. In summary, it appears that neurotrophin:receptor trios have expanded to include additional players, as has the repertoire of associated biological effects. Perhaps future studies will determine whether other growth factor:receptor systems are equal diverse in terms of ligand specificity, receptor signaling and functions.

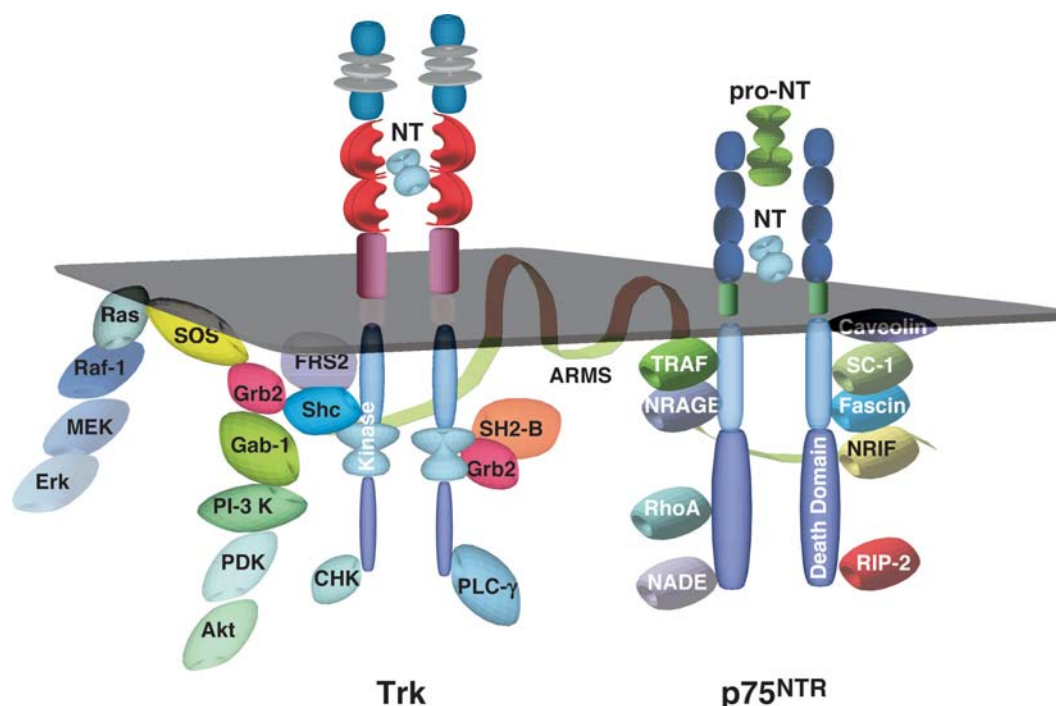


Figure 2. Schematic representation of p75^{NTR} and Trk interacting proteins and selected downstream signaling cascades. The final biological outcomes of (pro)neurotrophin binding to p75^{NTR} and/or Trk are ultimately determined by the equilibrium between downstream signaling components that maintain survival (i.e. Akt, TRAFs, FAP-1 and RIP2), or induce death (i.e. NRIF, NADE and NRAGE), or modulate cell cycle progression (i.e. NRAGE and SC-1) or promote neuronal differentiation (i.e. Erk, and RhoA). See main text for a detailed discussion.

Acknowledgements. B. L. Hempstead is supported by the NINDS, NHLBI and the Burroughs Wellcome Fund.

- 1 Huang E. J. and Reichardt L. F. (2001) Neurotrophins: roles in neuronal development and function. *Annu. Rev. Neurosci.* **24**: 677–736
- 2 Lewin G. R. and Barde Y. A. (1996) Physiology of the neurotrophins. *Ann. Rev. Neurosci.* **19**: 289–317
- 3 Tucker, K. L. (2002) Neurotrophins and the control of axonal outgrowth. *Panminerva Med.* **44**: 325–333
- 4 Schinder A. F. and Poo M. (2000) The neurotrophin hypothesis for synaptic plasticity. *Trends Neurosci.* **23**: 639–645
- 5 Blesch A., Grill R. J. and Tuszynski M. H. (1998) Neurotrophin gene therapy in CNS models of trauma and degeneration. *Prog. Brain Res.* **117**: 473–484
- 6 Levi-Montalcini R. (1987) The nerve growth factor: thirty-five years later. *Science* **237**: 1154–1164
- 7 Bentley C. A. and Lee K. F. (2000) p75 is important for axon growth and schwann cell migration during development. *J. Neurosci.* **20**: 7706–7715
- 8 Syroid D. E., Maycox P. J., Soilu-Hanninen M., Petratos S., Bucci T., Burrola P. et al. (2000) Induction of postnatal schwann cell death by the low-affinity neurotrophin receptor in vitro and after axotomy. *J. Neurosci.* **20**: 5741–5747
- 9 Wang S., Bray P., McCaffrey T., March K., Hempstead B. L. and Kraemer R. (2000) p75(NTR) mediates neurotrophin-induced apoptosis of vascular smooth muscle cells. *Am. J. Pathol.* **157**: 1247–1258
- 10 von Schack D., Casademunt E., Schweigreiter R., Meyer M., Bibel M. and Dechant G. (2001) Complete ablation of the neurotrophin receptor p75^{NTR} causes defects both in the nervous and the vascular system. *Nat. Neurosci.* **4**: 977–978
- 11 Delsite R. and Djakiew D. (1999) Characterization of nerve growth factor precursor protein expression by human prostate stromal cells: a role in selective neurotrophin stimulation of prostate epithelial cell growth. *Prostate* **41**: 39–48
- 12 Descamps S., Toillon R. A., Adriaenssens E., Pawlowski V., Cool S. M., Nurcombe V. et al. (2001) Nerve growth factor stimulates proliferation and survival of human breast cancer cells through two distinct signaling pathways. *J. Biol. Chem.* **276**: 17864–17870
- 13 Sofroniew M. V., Howe C. L. and Mobley W. C. (2001) Nerve growth factor signaling, neuroprotection and neural repair. *Annu. Rev. Neurosci.* **24**: 1217–1281
- 14 Rodriguez-Tebar A., Dechant G. and Barde Y.-A. (1990) Binding of brain-derived neurotrophic factor to the nerve growth factor receptor. *Neuron* **4**: 487–492
- 15 Rodriguez-Tebar A., Dechant G., Gotz R. and Barde Y. A. (1992) Binding of neurotrophin-3 to its neuronal receptors and interactions with nerve growth-factor and brain-derived neurotrophic factor. *EMBO J.* **11**: 917–922
- 16 Ip N. Y., Stitt T. N., Tapley P., Klein R., Glass D. J., Fandl J. et al. (1993) Similarities and differences in the way neurotrophins interact with the trk receptors in neuronal and non-neuronal cells. *Neuron* **10**: 137–149
- 17 Yan H. and Chao M. V. (1991) Disruption of cysteine-rich repeats of the p75 nerve growth factor receptor leads to loss of ligand binding. *J. Biol. Chem.* **266**: 12099–12104
- 18 Baldwin A. N., Bitler C. M., Welcher A. A. and Shooter E. M. (1992) Studies on the structure and binding-properties of the cysteine-rich domain of rat low affinity nerve growth-factor receptor (p75^{ngfr}). *J. Biol. Chem.* **267**: 8352–8359
- 19 Wiesmann C. and de Vos A. M. (2001) Nerve growth factor: structure and function. *Cell. Mol. Life Sci.* **58**: 748–759
- 20 Roux P. P. and Barker P. A. (2002) Neurotrophin signaling through the p75 neurotrophin receptor. *Prog. Neurobiol.* **67**: 203–233
- 21 Hempstead B. L. (2002) The many faces of p75^{NTR}. *Curr. Opin. Neurobiol.* **12**: 260–267
- 22 Dechant G. and Barde Y. A. (2002) The neurotrophin receptor p75(NTR): novel functions and implications for diseases of the nervous system. *Nat. Neurosci.* **5**: 1131–1136
- 23 Radeke M. J., Misko T. P., Hsu C., Herzenberg L. A. and Shooter E. M. (1987) Gene transfer and molecular cloning of the rat NGF receptor. *Nature* **325**: 593–597
- 24 Johnson D., Lanahan A., Buck C. R., Sehgal A., Morgan C., Mercer E. et al. (1986) Expression and structure of the human NGF receptor. *Cell* **47**: 545–554
- 25 Lee K. F., Davies A. M. and Jaenisch R. (1994) p75-deficient embryonic dorsal root sensory and neonatal sympathetic neurons display a decreased sensitivity to NGF. *Development* **120**: 1027–1033
- 26 Ashkenazi A. (2002) Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nat. Rev. Cancer* **2**: 420–430
- 27 Frade J. M., Rodriguez-Tebar A. and Barde Y. A. (1996) Induction of cell death by endogenous nerve growth factor through its p75 receptor. *Nature* **383**: 166–168
- 28 Casaccia-Bonnel P., Carter B. D., Dobrowsky R. T. and Chao M. V. (1996) Death of oligodendrocytes mediated by the interaction of nerve growth factor with its receptor p75. *Nature* **383**: 716–719
- 29 Bamji S. X., Majdan M., Pozniak C. D., Belliveau D. J., Aloyz R., Kohn J. et al. (1998) The p75 neurotrophin receptor mediates neuronal apoptosis and is essential for naturally occurring sympathetic neuron death. *J. Cell Biol.* **140**: 911–923
- 30 Palmada M., Kanwal S., Rutkowski N. J., Gustafson-Brown C., Johnson R. S., Wisdom R. et al. (2002) c-jun is essential for sympathetic neuronal death induced by NGF withdrawal but not by p75 activation. *J. Cell Biol.* **158**: 453–461
- 31 Chao M. V. (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat. Rev. Neurosci.* **4**: 299–309
- 32 Patapoutian A. and Reichardt L. F. (2001) Trk receptors: mediators of neurotrophin action. *Curr. Opin. Neurobiol.* **11**: 272–280
- 33 Miller F. D. and Kaplan D. R. (2001) Neurotrophin signalling pathways regulating neuronal apoptosis. *Cell. Mol. Life Sci.* **58**: 1045–1053
- 34 Lee R., Kermani P., Teng K. K. and Hempstead B. L. (2001) Regulation of cell survival by secreted proneurotrophins. *Science* **294**: 1945–1948
- 35 Cosgaya J. M., Chan J. R. and Shooter E. M. (2002) The neurotrophin receptor p75^{NTR} as a positive modulator of myelination. *Science* **298**: 1245–1248
- 36 Wang K. C., Kim J. A., Sivasankaran R., Segal R. and He Z. (2002) P75 interacts with the Nogo receptor as a co-receptor for Nogo, MAG and OMgp. *Nature* **420**: 74–78
- 37 Wong S. T., Henley J. R., Kanning K. C., Huang K. H., Bothwell M. and Poo M. M. (2002) A p75(NTR) and Nogo receptor complex mediates repulsive signaling by myelin-associated glycoprotein. *Nat. Neurosci.* **5**: 1302–1308
- 38 Egan M. F., Kojima M., Callicott J. H., Goldberg T. E., Kolachana B. S., Bertolino A. et al. (2003) The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* **112**: 257–269
- 39 Ebendal T. (1992) Function and evolution in the NGF family and its receptors. *J. Neurosci. Res.* **32**: 461–470
- 40 Heinrich G. and Lum T. (2000) Fish neurotrophins and trk receptors. *Int. J. Devl. Neurosci.* **18**: 1–27
- 41 Ibanez C. F. (1996) Neurotrophin-4: the odd one out in the neurotrophin family. *Neurochem. Res.* **21**: 787–793
- 42 Kolbeck R., Jungbluth S. and Barde Y. A. (1994) Characterisation of neurotrophin dimers and monomers. *Eur. J. Biochem.* **225**: 995–1003

- 43 Edwards R. H., Selby M. J., Garcia P. D. and Rutter W. J. (1988) Processing of the native nerve growth factor precursor to form biologically active nerve growth factor. *J. Biol. Chem.* **263**: 6810–6815
- 44 Seidah N. G., Benjannet S., Pareek S., Savaria D., Hamelin J., Goulet B. et al. (1996) Cellular processing of the nerve growth factor precursor by the mammalian pro-protein convertases. *Biochem. J.* **314**: 951–960
- 45 Suter U., Heymach J. V. Jr and Shooter E. M. (1991) Two conserved domains in the NGF propeptide are necessary and sufficient for the biosynthesis of correctly processed and biologically active NGF. *EMBO J.* **10**: 2395–2400
- 46 Farhadi H. F., Mowla S. J., Petrecca K., Morris S. J., Seidah N. G. and Murphy R. A. (2000) Neurotrophin-3 sorts to the constitutive secretory pathway of hippocampal neurons and is diverted to the regulated secretory pathway by coexpression with brain-derived neurotrophic factor. *J. Neurosci.* **20**: 4059–4068
- 47 Mowla S. J., Pareek S., Farhadi H. F., Petrecca K., Fawcett J. P., Seidah N. G. et al. (1999) Differential sorting of nerve growth factor and brain-derived neurotrophic factor in hippocampal neurons. *J. Neurosci.* **19**: 2069–2080
- 48 Mowla S. J., Farhadi H. F., Pareek S., Atwal J. K., Morris S. J., Seidah N. G. et al. (2001) Biosynthesis and post-translational processing of the precursor to brain-derived neurotrophic factor. *J. Biol. Chem.* **276**: 12660–12666
- 49 Heymach J. V. Jr and Shooter E. M. (1995) The biosynthesis of neurotrophin heterodimers by transfected mammalian cells. *J. Biol. Chem.* **270**: 12297–12304
- 50 Dicou E., Pflug B., Magazin M., Lehy T., Djakiew D., Ferrara P. et al. (1997) Two peptides derived from the nerve growth factor precursor are biologically active. *J. Cell Biol.* **136**: 389–398
- 51 Wiesmann C., Ultsch M. H., Bass S. H. and de Vos A. M. (1999) Crystal structure of nerve growth factor in complex with the ligand-binding domain of the TrkA receptor. *Nature* **401**: 184–188
- 52 Banfield M. J., Naylor R. L., Robertson A. G., Allen S. J., Dawbarn D. and Brady R. L. (2001) Specificity in Trk receptor:neurotrophin interactions: the crystal structure of TrkB-d5 in complex with neurotrophin-4/5. *Structure* **9**: 1191–1199
- 53 Ryden M., Murray-Rust J., Glass D., Ilag L. L., Trupp M., Yancopoulos G. D. et al. (1995) Functional analysis of mutant neurotrophins deficient in low-affinity binding reveals a role for p75^{LNGFR} in NT-4 signalling. *EMBO J.* **14**: 1979–1990
- 54 Moscatelli D. (1992) Basic fibroblast growth factor (bFGF) dissociates rapidly from heparan sulfates but slowly from receptors. Implications for mechanisms of bFGF release from pericellular matrix. *J. Biol. Chem.* **267**: 25803–25809
- 55 Locksley R. M., Killeen N. and Lenardo M. J. (2001) The TNF and TNF receptor superfamilies: integrating mammalian biology. *Cell* **104**: 487–501
- 56 Beattie M. S., Harrington A. W., Lee R., Kim J. Y., Boyce S. L., Longo F. M. et al. (2002) ProNGF induces p75-mediated death of oligodendrocytes following spinal cord injury. *Neuron* **36**: 375–386
- 57 Hutson L. D. and Bothwell M. (2001) Expression and function of *Xenopus laevis* p75^(NTR) suggest evolution of developmental regulatory mechanisms. *J. Neurobiol.* **49**: 79–98
- 58 DiStefano P. S., Chelsea D. M., Schick C. M. and McKelvey J. F. (1993) Involvement of a metalloprotease in low-affinity nerve growth factor receptor truncation: inhibition of truncation in vitro and in vivo. *J. Neurosci.* **13**: 2405–2414
- 59 Majdan M., Lachance C., Gloster A., Aloyz R., Zeindler C., Bamji S. et al. (1997) Transgenic mice expressing the intracellular domain of the p75 neurotrophin receptor undergo neuronal apoptosis. *J. Neurosci.* **17**: 6988–6998
- 60 Esposito D., Patel P., Stephens R. M., Perez P., Chao M. V., Kaplan D. R. et al. (2001) The cytoplasmic and transmembrane domains of the p75 and Trk A receptors regulate high affinity binding to nerve growth factor. *J. Biol. Chem.* **276**: 32687–32695
- 61 Donovan M. J., Lin M. I., Wiegand P., Ringstedt T., Kraemer R., Hahn R. et al. (2000) Brain derived neurotrophic factor is an endothelial cell survival factor required for intramyocardial vessel stabilization. *Development* **127**: 4531–4540
- 62 Roux P. P., Bhakar A. L., Kennedy T. E. and Barker P. A. (2001) The p75 neurotrophin receptor activates Akt (protein kinase B) through a phosphatidylinositol 3-kinase-dependent pathway. *J. Biol. Chem.* **276**: 23097–23104
- 63 Chan J. R., Cosgaya J. M., Wu Y. J. and Shooter E. M. (2001) Neurotrophins are key mediators of the myelination program in the peripheral nervous system. *Proc. Natl. Acad. Sci. USA* **98**: 14661–14668
- 64 Shonukan T., Bagayogo I., McCrea P., Chao M. V. and Hempstead B. L. (2003) The p75^{NTR} interacts with the actin-bundling protein fascin-putative role in cell migration. *Oncogene* **22**: 3616–3623
- 65 Liepinsh E., Ilag L. L., Otting G. and Ibanez C. F. (1997) NMR structure of the death domain of the p75 neurotrophin receptor. *EMBO J.* **16**: 4999–5005
- 66 Wang X., Bauer J. H., Li Y., Shao Z., Zetoun F. S., Cattaneo E. et al. (2001) Characterization of a p75^(NTR) apoptotic signaling pathway using a novel cellular model. *J. Biol. Chem.* **276**: 33812–33820
- 67 El Yazidi-Belkoura I., Adriaenssens E., Dolle L., Descamps S. and Hondermarck H. (2003) Tumor necrosis factor receptor-associated death domain protein (TRADD) is involved in the neurotrophin receptor (p75^{NTR})-mediated anti-apoptotic activity of nerve growth factor in breast cancer cells. *J. Biol. Chem.* **278**: 16952–16956
- 68 Casademunt E., Carter B. D., Benzel I., Frade J. M., Dechant G. and Barde Y. A. (1999) The zinc finger protein NRIF interacts with the neurotrophin receptor p75^(NTR) and participates in programmed cell death. *EMBO J.* **18**: 6050–6061
- 69 Mukai J., Hachiya T., Shoji-Hoshino S., Kimura M. T., Nadano D., Suvanto P. et al. (2000) NADE, a p75^{NTR}-associated cell death executor, is involved in signal transduction mediated by the common neurotrophin receptor p75^{NTR}. *J. Biol. Chem.* **275**: 17566–17570
- 70 Salehi A. H., Roux P. P., Kubu C. J., Zeindler C., Bhakar A., Tannis L. L. et al. (2000) NRAGE, a novel MAGE protein, interacts with the p75 neurotrophin receptor and facilitates nerve growth factor-dependent apoptosis. *Neuron* **27**: 279–288
- 71 Jordan B. W., Dinev D., LeMellay V., Troppmair J., Gotz R., Wixler L. et al. (2001) Neurotrophin receptor-interacting mage homologue is an inducible inhibitor of apoptosis protein-interacting protein that augments cell death. *J. Biol. Chem.* **276**: 39985–39989
- 72 Ye X., Mehlen P., Rabizadeh S., VanArsdale T., Zhang H., Shin H. et al. (1999) TRAF family proteins interact with the common neurotrophin receptor and modulate apoptosis induction. *J. Biol. Chem.* **274**: 30202–30208
- 73 Khursigara G., Bertin J., Yano H., Moffett H., DiStefano P. S. and Chao M. V. (2001) A prosurvival function for the p75 receptor death domain mediated via the caspase recruitment domain receptor-interacting protein 2. *J. Neurosci.* **21**: 5854–5863
- 74 Mamidipudi V., Li X. and Wooten M. W. (2002) Identification of interleukin 1 receptor-associated kinase as a conserved component in the p75-neurotrophin receptor activation of nuclear factor-kappa B. *J. Biol. Chem.* **277**: 28010–28018
- 75 Khursigara G., Orlinick J. R. and Chao M. V. (1999) Association of the p75 neurotrophin receptor with TRAF6. *J. Biol. Chem.* **274**: 2597–2600
- 76 Baud V. and Karin M. (2001) Signal transduction by tumor necrosis factor and its relatives. *Trends Cell Biol.* **11**: 372–377

- 77 Chittka A. and Chao M. V. (1999) Identification of a zinc finger protein whose subcellular distribution is regulated by serum and nerve growth factor. *Proc. Natl. Acad. Sci. USA* **96**: 10705–10710
- 78 Benzel I., Barde Y. A. and Casademunt E. (2001) Strain-specific complementation between NRIF1 and NRIF2, two zinc finger proteins sharing structural and biochemical properties. *Gene* **281**: 19–30
- 79 Yamashita T., Tucker K. L. and Barde Y.-A. (1999) Neurotrophin binding to the p75 receptor modulates Rho activity and axonal outgrowth. *Neuron* **24**: 585–593
- 80 Yamashita T. and Tohyama M. (2003) The p75 receptor acts as a displacement factor that releases Rho from Rho-GDI. *Nat. Neurosci.* **6**: 461–467
- 81 Higuchi H., Yamashita T., Yoshikawa H. and Tohyama M. (2003) PKA phosphorylates the p75 receptor and regulates its localization to lipid rafts. *EMBO J.* **22**: 1790–1800
- 82 Bilderback T. R., Grigsby R. J. and Dobrowsky R. T. (1997) Association of p75(NTR) with caveolin and localization of neurotrophin-induced sphingomyelin hydrolysis to caveolae. *J. Biol. Chem.* **272**: 10922–10927
- 83 Yaar M., Zhai S., Fine R. E., Eisenhauer P. B., Arble B. L., Stewart K. B. et al. (2002) Amyloid beta binds trimers as well as monomers of the 75-kDa neurotrophin receptor and activates receptor signaling. *J. Biol. Chem.* **277**: 7720–7725
- 84 Della-Bianca V., Rossi F., Armato U., Dal-Pra I., Costantini C., Perini G. et al. (2001) Neurotrophin p75 receptor is involved in neuronal damage by prion peptide-(106-126). *J. Biol. Chem.* **276**: 38929–38933
- 85 Troy C. M., Rabacchi S. A., Xu Z., Maroney A. C., Connors T. J., Shelanski M. L. et al. (2001) beta-Amyloid-induced neuronal apoptosis requires c-Jun N-terminal kinase activation. *J. Neurochem.* **77**: 157–164
- 86 Tuffereau C., Benejean J., Blondel D., Kieffer B. and Flamand A. (1998) Low-affinity nerve-growth factor receptor (P75NTR) can serve as a receptor for rabies virus. *EMBO J.* **17**: 7250–7259
- 87 Langevin C., Jaaro H., Bressanelli S., Fainzilber M. and Tuffereau C. (2002) Rabies virus glycoprotein (RVG) is a trimeric ligand for the N-terminal cysteine-rich domain of the mammalian p75 neurotrophin receptor. *J. Biol. Chem.* **277**: 37655–37662
- 88 Yamashita T., Higuchi H. and Tohyama M. (2002) The p75 receptor transduces the signal from myelin-associated glycoprotein to Rho. *J. Cell. Biol.* **157**: 565–570
- 89 Yamashita T., Tucker K. L. and Barde Y. A. (1999) Neurotrophin binding to the p75 receptor modulates Rho activity and axonal outgrowth. *Neuron* **24**: 585–593
- 90 Walsh G. S., Krol K. M., Crutcher K. A. and Kawaja M. D. (1999) Enhanced neurotrophin-induced axon growth in myelinated portions of the CNS in mice lacking the p75 neurotrophin receptor. *J. Neurosci.* **19**: 4155–4168
- 91 McKerracher L. and Winton M. J. (2002) Nogo on the go. *Neuron* **36**: 345–348
- 92 Segal R. A. and Greenberg M. E. (1996) Intracellular signaling pathways activated by neurotrophic factors. *Annu. Rev. Neurosci.* **19**: 463–489
- 93 York R. D., Yao H., Dillon T., Ellig C. L., Eckert S. P., McCleskey E. W. et al. (1998) Rap1 mediates sustained MAP kinase activation induced by nerve growth factor. *Nature* **392**: 622–626
- 94 Qui M. S. and Green S. H. (1992) PC12 cell neuronal differentiation is associated with prolonged p21ras activity and consequent prolonged ERK activity. *Neuron* **9**: 705–717
- 95 Yao R. and Cooper G. M. (1995) Requirement for phosphatidylinositol-3 kinase in the prevention of apoptosis by nerve growth factor. *Science* **267**: 2003–2006
- 96 Cardone M. H., Roy N., Stennicke H. R., Salvesen G. S., Franke T. F., Stanbridge E. et al. (1998) Regulation of cell death protease caspase-9 by phosphorylation. *Science* **282**: 1318–1321
- 97 Dudek H., Datta S. R., Franke T. F., Birnbaum M. J., Yao R., Cooper G. M. et al. (1997) Regulation of neuronal survival by the serine-threonine protein kinase Akt. *Science* **275**: 661–665
- 98 Brunet A., Bonni A., Zigmond M. J., Lin M. Z., Juo P., Hu L. S. et al. (1999) Akt promotes cell survival by phosphorylating and inhibiting a Forkhead transcription factor. *Cell* **96**: 857–868
- 99 Koushara H., Hadari Y. R., Spivak-Kroizman T., Schilling J., Bar-Sagi D., Lax I. et al. (1997) A lipid-anchored Grb2-binding protein that links FGF-receptor activation to the Ras/MAPK signaling pathway. *Cell* **89**: 693–702
- 100 Meakin S. O., MacDonald J. I., Gryz E. A., Kubu C. J. and Verdi J. M. (1999) The signaling adapter FRS-2 competes with Shc for binding to the nerve growth factor receptor TrkA. A model for discriminating proliferation and differentiation. *J. Biol. Chem.* **274**: 9861–9870
- 101 Stephens R. M., Loeb D. M., Copeland T. D., Pawson T., Greene L. A. and Kaplan D. R. (1994) Trk receptors use redundant signal transduction pathways involving SHC and PLC-gamma 1 to mediate NGF responses. *Neuron* **12**: 691–705
- 102 MacDonald J. I., Gryz E. A., Kubu C. J., Verdi J. M. and Meakin S. O. (2000) Direct binding of the signaling adapter protein Grb2 to the activation loop tyrosines on the nerve growth factor receptor tyrosine kinase, TrkA. *J. Biol. Chem.* **275**: 18225–18233
- 103 Korhonen J. M., Said F. A., Wong A. J. and Kaplan D. R. (1999) Gab1 mediates neurite outgrowth, DNA synthesis, and survival in PC12 cells. *J. Biol. Chem.* **274**: 37307–37314
- 104 Vambutas V., Kaplan D. R., Sells M. A. and Chernoff J. (1995) Nerve growth factor stimulates tyrosine phosphorylation and activation of Src homology-containing protein-tyrosine phosphatase 1 in PC12 cells. *J. Biol. Chem.* **270**: 25629–25633
- 105 Chen B., Hammonds-Odie L., Perron J., Masters B. A. and Bixby J. L. (2002) SHP-2 mediates target-regulated axonal termination and NGF-dependent neurite growth in sympathetic neurons. *Dev. Biol.* **252**: 170–187
- 106 Wright J. H., Drueckes P., Bartoe J., Zhao Z., Shen S. H. and Krebs E. G. (1997) A role for the SHP-2 tyrosine phosphatase in nerve growth-induced PC12 cell differentiation. *Mol. Biol. Cell* **8**: 1575–1585
- 107 Ong S. H., Guy G. R., Hadari Y. R., Laks S., Gotoh N., Schlessinger J. et al. (2000) FRS2 proteins recruit intracellular signaling pathways by binding to diverse targets on fibroblast growth factor and nerve growth factor receptors. *Mol. Cell. Biol.* **20**: 979–989
- 108 Madhani H. D. (2001) Accounting for specificity in receptor tyrosine kinase signaling. *Cell* **106**: 9–11
- 109 Choi D. Y., Toledo-Aral J. J., Segal R. and Halegoua S. (2001) Sustained signaling by phospholipase C-gamma mediates nerve growth factor-triggered gene expression. *Mol. Cell. Biol.* **21**: 2695–2705
- 110 Rhee S. G. (2001) Regulation of phosphoinositide-specific phospholipase C. *Annu. Rev. Biochem.* **70**: 281–312
- 111 Ye K., Aghdasi B., Luo H. R., Moriarity J. L., Wu F. Y., Hong J. J. et al. (2002) Phospholipase C gamma 1 is a physiological guanine nucleotide exchange factor for the nuclear GTPase PIKE. *Nature* **415**: 541–544
- 112 Yamashita H., Avraham S., Jiang S., Dikic I. and Avraham H. (1999) The Csk homologous kinase associates with TrkA receptors and is involved in neurite outgrowth of PC12 cells. *J. Biol. Chem.* **274**: 15059–15065
- 113 Qian X., Riccio A., Zhang Y. and Ginty D. D. (1998) Identification and characterization of novel substrates of Trk receptors in developing neurons. *Neuron* **21**: 1017–1029

- 114 Rui L. and Carter-Su C. (1999) Identification of SH2-beta as a potent cytoplasmic activator of the tyrosine kinase Janus kinase 2. *Proc. Natl. Acad. Sci. USA* **96**: 7172–7177
- 115 Rui L., Herrington J. and Carter-Su C. (1999) SH2-B, a membrane-associated adapter, is phosphorylated on multiple serines/threonines in response to nerve growth factor by kinases within the MEK/ERK cascade. *J. Biol. Chem.* **274**: 26485–26492
- 116 Rui L., Herrington J. and Carter-Su C. (1999) SH2-B is required for nerve growth factor-induced neuronal differentiation. *J. Biol. Chem.* **274**: 10590–10594
- 117 Koch A., Mancini A., Stefan M., Niedenthal R., Niemann H. and Tamura T. (2000) Direct interaction of nerve growth factor receptor, TrkA, with non-receptor tyrosine kinase, c-Abl, through the activation loop. *FEBS Lett.* **469**: 72–76
- 118 Yano H., Cong F., Birge R. B., Goff S. P. and Chao M. V. (2000) Association of the Abl tyrosine kinase with the Trk nerve growth factor receptor. *J. Neurosci. Res.* **59**: 356–364
- 119 Koleske A. J., Gifford A. M., Scott M. L., Nee M., Bronson R. T., Miczek K. A. et al. (1998) Essential roles for the Abl and Arg tyrosine kinases in neurulation. *Neuron* **21**: 1259–1272
- 120 Yu H. H., Zisch A. H., Dodelet V. C. and Pasquale E. B. (2001) Multiple signaling interactions of Abl and Arg kinases with the EphB2 receptor. *Oncogene* **20**: 3995–4006
- 121 Feller S. M., Posern G., Voss J., Kardinal C., Sakrab D., Zheng J. et al. (1998) Physiological signals and oncogenesis mediated through Crk family adapter proteins. *J. Cell. Physiol.* **177**: 535–552
- 122 de Rooij J., Zwartkruis F. J., Verheijen M. H., Cool R. H., Nijman S. M., Wittinghofer A. et al. (1998) Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. *Nature* **396**: 474–477
- 123 Heldin C. H., Ostman A. and Ronnstrand L. (1998) Signal transduction via platelet-derived growth factor receptors. *Biochim. Biophys. Acta* **1378**: F79–113
- 124 Inagaki N., Thoenen H. and Lindholm D. (1995) TrkA tyrosine residues involved in NGF-induced neurite outgrowth of PC12 cells. *Eur. J. Neurosci.* **7**: 1125–1133
- 125 Campenot R. B. (1982) Development of sympathetic neurons in compartmentalized cultures. II. Local control of neurite survival by nerve growth factor. *Dev. Biol.* **93**: 13–21
- 126 Neet K. E. and Campenot R. B. (2001) Receptor binding, internalization, and retrograde transport of neurotrophic factors. *Cell. Mol. Life Sci.* **58**: 1021–1035
- 127 Ginty D. D. and Segal R. A. (2002) Retrograde neurotrophin signaling: Trk-ing along the axon. *Curr. Opin. Neurobiol.* **12**: 268–274
- 128 Miller F. D. and Kaplan D. R. (2001) On Trk for retrograde signaling. *Neuron* **32**: 767–770
- 129 Riccio A., Ahn S., Davenport C. M., Blendy J. A. and Ginty D. D. (1999) Mediation by a CREB family transcription factor of NGF-dependent survival of sympathetic neurons. *Science* **286**: 2358–2361
- 130 Watson F. L., Heerssen H. M., Moheban D. B., Lin M. Z., Sauvageot C. M., Bhattacharyya A. et al. (1999) Rapid nuclear responses to target-derived neurotrophins require retrograde transport of ligand-receptor complex. *J. Neurosci.* **19**: 7889–7900
- 131 MacInnis B. L. and Campenot R. B. (2002) Retrograde support of neuronal survival without retrograde transport of nerve growth factor. *Science* **295**: 1536–1539
- 132 Riccio A., Pierchala B. A., Ciarallo C. L. and Ginty D. D. (1997) An NGF-TrkA-mediated retrograde signal to transcription factor CREB in sympathetic neurons. *Science* **277**: 1097–1100
- 133 Atwal J. K., Massie B., Miller F. D. and Kaplan D. R. (2000) The TrkB-Shc site signals neuronal survival and local axon growth via MEK and P13-kinase. *Neuron* **27**: 265–277
- 134 Kuruvilla R., Ye H. and Ginty D. D. (2000) Spatially and functionally distinct roles of the PI3-K effector pathway during NGF signaling in sympathetic neurons. *Neuron* **27**: 499–512
- 135 Watson F. L., Heerssen H. M., Bhattacharyya A., Klesse L., Lin M. Z. and Segal R. A. (2001) Neurotrophins use the Erk5 pathway to mediate a retrograde survival response. *Nat. Neurosci.* **4**: 981–988
- 136 York R. D., Molliver D. C., Grewal S. S., Stenberg P. E., McCleskey E. W. and Stork P. J. (2000) Role of phosphoinositide 3-kinase and endocytosis in nerve growth factor-induced extracellular signal-regulated kinase activation via Ras and Rap1. *Mol. Cell. Biol.* **20**: 8069–8083
- 137 Howe C. L., Valletta J. S., Rusnak A. S. and Mobley W. C. (2001) NGF signaling from clathrin-coated vesicles: evidence that signaling endosomes serve as a platform for the Ras-MAPK pathway. *Neuron* **32**: 801–814
- 138 Mochizuki N., Yamashita S., Kurokawa K., Ohba Y., Nagai T., Miyawaki A. et al. (2001) Spatio-temporal images of growth-factor-induced activation of Ras and Rap1. *Nature* **411**: 1065–1068
- 139 Wu C., Lai C. F. and Mobley W. C. (2001) Nerve growth factor activates persistent Rap1 signaling in endosomes. *J. Neurosci.* **21**: 5406–5416
- 140 Lee F. S. and Chao M. V. (2001) Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc. Natl. Acad. Sci. USA* **98**: 3555–3560
- 141 Lee F. S., Rajagopal R., Kim A. H., Chang P. C. and Chao M. V. (2002) Activation of Trk neurotrophin receptor signaling by pituitary adenylate cyclase-activating polypeptides. *J. Biol. Chem.* **277**: 9096–9102
- 142 Yano H., Lee F. S., Kong H., Chuang J., Arevalo J., Perez P. et al. (2001) Association of Trk neurotrophin receptors with components of the cytoplasmic dynein motor. *J. Neurosci.* **21**: RC125
- 143 Lou X., Yano H., Lee F., Chao M. V. and Farquhar M. G. (2001) GIPC and GAIP form a complex with TrkA: a putative link between G protein and receptor tyrosine kinase pathways. *Mol. Biol. Cell* **12**: 615–627
- 144 Peng X., Greene L. A., Kaplan D. R. and Stephens R. M. (1995) Deletion of a conserved juxtamembrane sequence in Trk abolishes NGF-promoted neurogenesis. *Neuron* **15**: 395–406
- 145 Kong H., Boulter J., Weber J. L., Lai C. and Chao M. V. (2001) An evolutionarily conserved transmembrane protein that is a novel downstream target of neurotrophin and ephrin receptors. *J. Neurosci.* **21**: 176–185
- 146 Nakamura T., Komiya M., Sone K., Hirose E., Gotoh N., Morii H. et al. (2002) Grit, a GTPase-activating protein for the Rho family, regulates neurite extension through association with the TrkA receptor and N-Shc and CrkL/Crk adapter molecules. *Mol. Cell. Biol.* **22**: 8721–8734
- 147 McAllister A. K., Katz L. C. and Lo D. C. (1997) Opposing roles for endogenous BDNF and NT-3 in regulating cortical dendritic growth. *Neuron* **18**: 767–778
- 148 Postigo A., Calella A. M., Fritzsche B., Knipper M., Katz D., Eilers A. et al. (2002) Distinct requirements for TrkB and TrkC signaling in target innervation by sensory neurons. *Genes Dev.* **16**: 633–645
- 149 Markus A., Zhong J. and Snider W. D. (2002) Raf and akt mediate distinct aspects of sensory axon growth. *Neuron* **35**: 65–76
- 150 Torocsik B., Angelastro J. M. and Greene L. A. (2002) The basic region and leucine zipper transcription factor MafK is a new nerve growth factor-responsive immediate early gene that regulates neurite outgrowth. *J. Neurosci.* **22**: 8971–8980
- 151 MacPhee I. J. and Barker P. A. (1997) Brain-derived neurotrophic factor binding to the p75 neurotrophin receptor reduces TrkA signaling while increasing serine phosphorylation

- in the TrkA intracellular domain. *J. Biol. Chem.* **272**: 23547–23551
- 152 Yoon S. O., Casaccia-Bonofil P., Carter B. and Chao M. V. (1998) Competitive signaling between TrkA and p75 nerve growth factor receptors determines cell survival. *J. Neurosci.* **18**: 3273–3281
- 153 DeFreitas M. F., McQuillen P. S. and Shatz C. J. (2001) A novel p75NTR signaling pathway promotes survival, not death, of immunopurified neocortical subplate neurons. *J. Neurosci.* **21**: 5121–5129
- 154 Hamanoue M., Middleton G., Wyatt S., Jaffray E., Hay R. T. and Davies A. M. (1999) p75-mediated NF-kappaB activation enhances the survival response of developing sensory neurons to nerve growth factor. *Mol. Cell. Neurosci.* **14**: 28–40
- 155 Freidman W. J. (2000) Neurotrophins induce death of hippocampal neurons via the p75 receptor. *J. Neurosci.* **20**: 6340–6346
- 156 Brann A. B., Tcherpakov M., Williams I. M., Futerma A. H. and Fainzilber M. (2002) Nerve growth factor-induced p75-mediated death of cultured hippocampal neurons is age-dependent and transduced through ceramide generated by neutral sphingomyelinase. *J. Biol. Chem.* **277**: 9812–9818



To access this journal online:
<http://www.birkhauser.ch>
