
The Biological Functions and Signaling Mechanisms of the p75 Neurotrophin Receptor

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Abstract

The p75 neurotrophin receptor (p75^{NTR}) regulates a wide range of cellular functions, including programmed cell death, axonal growth and degeneration, cell proliferation, myelination, and synaptic plasticity. The multiplicity of cellular functions governed by the receptor arises from the variety of ligands and co-receptors which associate with p75^{NTR} and regulate its signaling. P75^{NTR} promotes survival through interactions with Trk receptors, inhibits axonal regeneration via partnerships with Nogo receptor (Nogo-R) and Lingo-1, and promotes apoptosis through association with Sortilin. Signals downstream of these interactions are further modulated through regulated intramembrane proteolysis (RIP) of p75^{NTR} and by interactions with numerous cytosolic partners. In this chapter, we discuss the intricate signaling mechanisms of p75^{NTR}, emphasizing how these signals are differentially regulated to mediate these diverse cellular functions.

Keywords

NGF • BDNF • NT3 • NRIF • TRAF • NRAGE • NADE • Nectin • Trk • Sortilin • Nogo • p75NTR

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1 Introduction

The discovery of nerve growth factor (NGF) as the factor released by the target to promote survival and differentiation quickly led to the hunt for the receptor involved in mediating its actions. Early studies characterizing radiolabeled NGF binding to peripheral neurons revealed that NGF bound its receptors in a complex manner that likely involved multiple sites (Frazier et al. 1974a, b). Subsequently, two distinct NGF binding sites, one with high affinity and one with low affinity, were demonstrated on sensory neurons (Sutter et al. 1979). Cross-linking studies confirmed two receptor components in sympathetic neurons (Massague et al. 1981) and PC12 cells (Grob et al. 1983; Massague et al. 1982) of approximately 140–200 kDa and 70–100 kDa, with the lower molecular weight species being most abundant. These binding studies set the stage for the expression cloning of the NGF receptor by Chao et al. (1986) and, independently, by the Shooter lab (Radeke et al. 1987). Both groups identified the cDNA for the lower molecular weight species; it was termed the p75 receptor, which proved to be the low affinity binding site. Eventually, the proto-oncogene tropomyosin-related kinase A, or TrkA, was recognized as another NGF receptor accounting for the higher molecular weight component (Kaplan et al. 1991; Klein et al. 1991), and a complex of both p75 and TrkA was shown to comprise the high affinity binding site (Hempstead et al. 1991).

The cloning of the p75 receptor was a major achievement in the field; however, it opened a Pandora's box of puzzles and paradoxes. Prior to the cloning of p75, it had been suggested that only the high-affinity binding component was able to mediate the neurite growth-promoting effects of NGF (Sonnenfeld and Ishii 1982; Stach and Wagner 1982), raising the question of the role of the low affinity component. Once TrkA was identified as another receptor for NGF, it was quickly established as the primary mediator of NGF's survival and differentiation effects, being a tyrosine kinase with potent signaling capability (Ibanez et al. 1992; Loeb et al. 1991). For several years the p75 receptor was thought to simply function as a binding partner for TrkA or acting to increase the local concentration of NGF to facilitate activation of TrkA (Chao and Hempstead 1995). However, there were a number of observations that piqued the interest of researchers in the field, causing them to further explore the role of p75; for example, the receptor is expressed widely in the developing nervous system, with expression in peripheral neurons, within the spinal cord, and throughout the brain (Ernfors et al. 1991). It is expressed by many neuronal cell types, as well as neural stem cells, some astrocytes, oligodendrocyte precursors, Schwann cells, and olfactory ensheathing glia (Cragolini and Friedman 2008). Several nonneural tissues also express the receptor during some stage of development, such as kidney and muscle (Ernfors et al. 1991; Wheeler and Bothwell 1992). In contrast, the Trk receptors exhibit a much more restricted expression pattern. In addition, the p75 receptor is strongly upregulated in many neurons and glial cells following injury, suggesting that it has a functional role in such conditions (discussed below). Finally, there are portions of the intracellular domain, where signaling would initiate, that are highly conserved across species, from chicken to human. These findings prompted further study of the p75 receptor,

and in the 25 years since its initial cloning, it has been shown to regulate an amazing array of cellular responses, including cell survival, cell cycle, neurite outgrowth, synaptic function, and myelination. This chapter will discuss our current understanding of the molecular mechanisms by which the p75 receptor mediates these diverse signals.

2 Structure

After the cloning of p75 it was quickly recognized that it not only bound NGF but also brain-derived neurotrophic factor (BDNF) (Rodriguez-Tebar et al. 1990), neurotrophin-3 (NT3) (Rodriguez-Tebar et al. 1992), and neurotrophin-4 (NT4) (Ryden et al. 1995), with similar affinity, although with somewhat different kinetics (Rodriguez-Tebar et al. 1992). The ability of the receptor to bind all neurotrophins led to its designation as the p75 neurotrophin receptor (p75^{NTR}) as opposed to the p75 NGF receptor. The p75^{NTR} interacts with the neurotrophins through the four cysteine-rich domains in its extracellular domain (Baldwin and Shooter 1995). The initial X-ray crystallography structural analysis of the extracellular domain of p75^{NTR} bound to NGF indicated that the receptor monomer binds NGF in an asymmetrical fashion, resulting in a 1:2 ratio (He and Garcia 2004). However, considerable biochemical data indicated that p75^{NTR} associates with neurotrophins in a 2:2 ratio. Binding analyses using cross-linkers to attach neurotrophins to the receptor indicated a dimer of p75^{NTR} bound to a neurotrophin dimer (Grob et al. 1985). Further crystallographic analyses support a 2:2 complex between neurotrophins and p75^{NTR} (Feng et al. 2010; Gong et al. 2008), and it has been suggested that the 1:2 asymmetrical binding may represent an intermediate in the formation of the 2:2 complex (Feng et al. 2010).

At least a fraction of p75^{NTR} has been shown to preexist as a disulfide-linked dimer (Grob et al. 1985; Ross et al. 1984), and a highly conserved cysteine (257) in the transmembrane domain responsible for linking the monomers was recently identified, although non-covalent dimerization still occurred even when cysteine 257 was mutated (Vilar et al. 2009). Further analysis revealed that a conserved AxxxG²⁶⁶ sequence in the transmembrane region, which is often found in self-associating transmembrane proteins, is required for the formation of dimers. Through their studies, the authors elucidated an interesting aspect of the receptor's structural dynamics that provided a mechanism by which p75^{NTR} transduces its signal upon ligand binding: the disulfide in the transmembrane domain acts as a pivot point, such that when the extracellular domain clamps down on a neurotrophin, the intracellular domains separate. The parting of the dimerized intracellular portions of the receptor facilitates binding of signaling molecules necessary for p75^{NTR}-mediated cell death (Vilar et al. 2009).

The intracellular domain (ICD) of p75^{NTR} contains a region similar to the Tumor necrosis factor receptor (TNFR) and the Fas antigen (Chapman 1995; Chapman and Kuntz 1995; Feinstein et al. 1995). Since TNFR and Fas mediate apoptotic signals, this portion of their ICD was termed the "death domain." The 3-D structure of

p75^{NTR}'s death domain was determined by NMR and was similar to the structure of the Fas death domain, although there were a few differences. In particular, the death domain of Fas and TNFR self-assemble, while that of p75^{NTR} does not (Liepinsh et al. 1997). This result is in agreement with the ability of TNFR and Fas to signal by recruiting other death domain-containing proteins while the intracellular interactors of p75^{NTR} so far identified do not contain a death domain.

In addition to the full length form of p75^{NTR}, a splice variant was reported lacking exon III, which encodes the cysteine-rich domains 2, 3, and 4 that are required for neurotrophin binding (von Schack et al. 2001). The original p75^{NTR} knockout mouse was created by deleting exon III (Lee et al. 1992); thus the short form of p75^{NTR} (s-p75^{NTR}) could still be detected in these mice, in principle. The existence of s-p75^{NTR}, however, remains rather controversial, and its function is not known. Nevertheless, an alternative mutant mouse was created lacking exon IV, such that both splice isoforms of p75^{NTR} are deleted (von Schack et al. 2001). These mice exhibit a number of neurological and vascular defects similar to the exon III knockout mice, but with a more severe phenotype. However, understanding the phenotype of the exon IV mutants is complicated by the fact that the targeting strategy created a cryptic truncated protein encoding an extracellular stalk with the entire transmembrane and intracellular domains of the receptor (Paul et al. 2004). Since expression of the intracellular domain of the receptor can initiate signaling independent of ligand (Majdan et al. 1997), some phenotypic characteristics of this mouse may be due to the expression of this fragment. Clearly, results from using either of these genetically altered mice need to be interpreted with caution, and further study is needed to understand the role of s-p75^{NTR}.

3 Apoptotic Signaling

Although p75^{NTR} was first discovered for its ability to bind NGF, which promotes neuronal survival, the most investigated function of the receptor is, ironically, its ability to induce programmed cell death. One of the earliest indications of this function was revealed in a study by Bredesen's group demonstrating that ectopic expression of p75^{NTR} in an immortalized neural cell line increased apoptosis after serum withdrawal (Rabizadeh et al. 1993). These results proved challenging to reproduce in primary cells with the endogenous receptor; however, the groups of Barde and Chao found that activation of endogenous p75^{NTR} by NGF could induce apoptosis in early retinal neurons in the chick (Frade et al. 1996) and oligodendrocytes in rat (Casaccia-Bonnet et al. 1996), respectively. The ability of p75^{NTR} to induce programmed cell death in response to ligand binding has now been observed in a wide variety of neuronal and non-neuronal cell types, including sympathetic (Bamji et al. 1998; Linggi et al. 2005; Teng et al. 2005), motor (Sedel et al. 1999), and hippocampal neurons (Volosin et al. 2008); photoreceptor cells (Srinivasan et al. 2004); oligodendrocytes (Casaccia-Bonnet et al. 1996); Schwann cells (Khursigara et al. 2001; Syroid et al. 2000); and other cells (Bunone et al. 1997; Volosin et al. 2006; Wang et al. 2000). These *in vitro* studies together

with the analysis of $p75^{NTR} -/-$ mice have established this receptor as a critical regulator of developmental apoptosis, promoting the naturally occurring elimination of neurons within the developing basal forebrain (Naumann et al. 2002), trigeminal ganglia (Agerman et al. 2000), retina (Frade et al. 1996), superior cervical ganglion (Bamji et al. 1998), and spinal cord (Frade and Barde 1999). This developmental role of $p75^{NTR}$ has been particularly well characterized in sympathetic neurons. These neurons express TrkA and $p75^{NTR}$, which together mediate a survival signal in response to NGF (discussed below); however, Miller and colleagues demonstrated that selective activation of $p75^{NTR}$ by BDNF led to apoptosis (Bamji et al. 1998). Furthermore, deletion of the receptor resulted in an increase in the number of neurons during the development of the superior cervical ganglia, suggesting that $p75^{NTR}$ mediates normal developmental death in this population. Ginty's group later demonstrated that these neurons produce BDNF in response to NGF and suggested a model in which neurons receiving robust trophic support through NGF-induced activation of TrkA produce BDNF, thereby promoting $p75^{NTR}$ -dependent death of neighboring neurons receiving insufficient NGF signal (Deppmann et al. 2008). Their computer simulations based on this model quite accurately predicted the normal developmental kinetics of cell death in the superior cervical ganglia.

3.1 Activation of the Mitochondrial Cascade

Over the past decade, significant progress has been made in understanding the cellular mechanisms through which $p75^{NTR}$ promotes apoptosis, although many facets of the receptor's signaling remain enigmatic. Members of the TNF receptor superfamily can activate two pathways that regulate cell survival. Through their death domain, they recruit other death domain-containing adaptors, such as TRADD and FADD, leading to caspase-8 activation and induction of a terminal caspase cascade (Dempsey et al. 2003). Despite attempts to detect activation of caspase-8 (Gu et al. 1999; Troy et al. 2002), no evidence supports $p75^{NTR}$ utilizing this pathway, which agrees with the structural divergence of $p75^{NTR}$'s death domain from that of TNFR and Fas. The second pathway initiated by many members of the TNF receptor family involves stimulation of the stress kinase c-Jun N-terminal kinase (JNK) and of the transcription factor NF- κ B (Dempsey et al. 2003). JNK activation causes cell death by inducing phosphorylation of the transcription factor c-Jun and the tumor suppressors p53 and p73 (Dhanasekaran and Reddy 2008), resulting in transcriptional upregulation of an array of pro-apoptotic genes, including Bax (Miyashita and Reed 1995), PUMA (Nakano and Vousden 2001), Bak (Bogoyevitch and Kobe 2006), and Caspase-6 (MacLachlan and El-Deiry 2002), among others (Wu 2004). In addition, JNK directly phosphorylates several Bcl-2 family proteins, causing inhibition of pro-survival members such as Bcl-2 (Yamamoto et al. 1999) and activation of pro-death members such as Bim (Lei and Davis 2003) and Bad (Donovan

et al. 2002). These events ultimately lead to the release of cytochrome c from mitochondria and caspase-dependent apoptosis (Bogoyevitch and Kobe 2006).

An accumulation of evidence has indicated that p75^{NTR}-induced apoptosis occurs via this mitochondrial cascade. Activation of JNK in response to ligand binding to endogenous p75^{NTR} has been demonstrated in oligodendrocytes (Casaccia-Bonnel et al. 1996), sympathetic neurons (Bamji et al. 1998), and hippocampal neurons (Friedman 2000), and inhibition of the kinase prevented the induction of apoptosis (Friedman 2000; Harrington et al. 2002; Kenchappa et al. 2010; Yeiser et al. 2004; Yoon et al. 1998). Overexpressing p75^{NTR} in cortical neurons also resulted in activation of JNK (Bhakar et al. 2003). In mammals, there are three genes encoding the JNK family, JNK1–3. While JNK1 and JNK2 are ubiquitously expressed, JNK3 is selectively expressed in the nervous system and heart (Gupta et al. 1996; Kuan et al. 2003; Mohit et al. 1995) and has been suggested to be the primary isoform mediating neuronal death in response to a variety of ligands and insults (Dhanasekaran and Reddy 2008). Of these three JNK isoforms, JNK3 was selectively activated following ligand binding to p75^{NTR} in oligodendrocytes (Harrington et al. 2002) and sympathetic neurons (Kenchappa et al. 2010), and gene deletion of JNK3 prevented receptor-mediated apoptosis both *in vitro* and *in vivo* (Kenchappa et al. 2010; Li et al. 2007).

Further support for p75^{NTR} activating a JNK-p53 apoptotic pathway comes from the fact that cell death mediated by the receptor is associated with upregulation of p53 (Aloyz et al. 1998; Linggi et al. 2005). Induction of apoptosis by p75^{NTR} has also been linked to phosphorylation of Bim (Becker et al. 2004) and Bad (Bhakar et al. 2003), cytochrome c release (Bhakar et al. 2003), and cleavage of procaspase-3, -6, -7, or -9 (Bhakar et al. 2003; Tabassum et al. 2003). Curiously, however, the receptor does not require c-Jun for killing sympathetic neurons (Palmada et al. 2002).

3.2 Cytosolic Factors Linking p75^{NTR} to JNK

Like many other receptors of the tumor necrosis factor (TNF) receptor superfamily, p75^{NTR} promotes downstream signaling via association with a number of cytosolic interactors (Fig. 1). One group of p75^{NTR} interactors that contributes to activation of JNK is the family of TNF receptor-associated factors (TRAFs). TRAF family proteins are distinguished by a conserved C-terminal domain that is responsible for their oligomerization and interactions with the cytoplasmic domains of TNF receptor family members (Zotti et al. 2012). With the exception of TRAF1, all TRAF family members also feature an N-terminal domain containing RING and zinc finger structures that are critical for their signaling function. The RING finger domain in the TRAFs acts as an E3 ubiquitin ligase, but instead of targeting proteins for proteasomal degradation, the TRAFs form a ubiquitin chain through Lys 63 linkages, which serve as protein–protein interaction motifs (Ha et al. 2009; Hacker et al. 2011). TRAF1–6 have been reported to associate with p75^{NTR}, with TRAF2, 4, and 6 shown to modulate p75^{NTR}-induced cell death via interactions

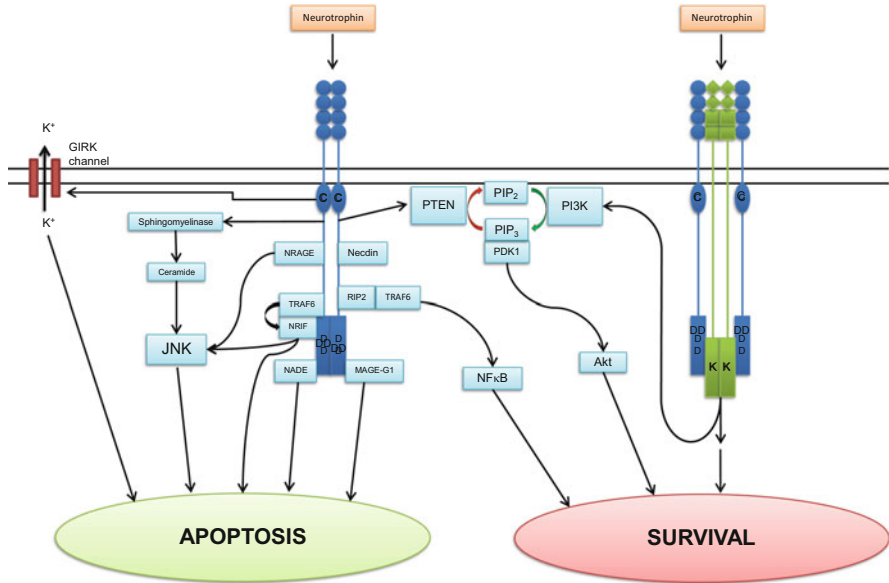


Fig. 1 Signaling pathways mediated by p75^{NTR} that regulate cell survival and apoptosis. In response to neurotrophin binding, p75^{NTR} promotes JNK activation via interactions with NRAGE, TRAF6, and NRIF, thus leading to apoptosis. Activation of JNK by p75^{NTR} also occurs through induction of sphingomyelinases. The chopper domain of p75^{NTR} promotes apoptosis by facilitating depletion of internal K⁺ through GIRK channels. Other cytosolic interactors contribute to p75^{NTR}-mediated cell death, including NADE, MAGE-G1, and Nectin. In response to pro-neurotrophins, p75^{NTR} inhibits Trk-mediated survival signaling via induction of PTEN and the resultant inhibition of PI3K-Akt survival signaling. Promotion of cell survival by p75^{NTR} is facilitated by its interactions with Trk receptors which enhance Trk-mediated PI3K-Akt survival signaling, as well as other Trk-mediated survival pathways. P75^{NTR} may also promote survival via activation of NFκB, possibly through associations between RIP2 and TRAF6 (abbreviations: DD p75^{NTR} death domain, C p75^{NTR} chopper domain, K Trk receptor tyrosine kinase domain)

with the ICD of the receptor (Khursigara et al. 1999; Ye et al. 1999). However, the role of TRAF6 in p75^{NTR} signaling has been the most thoroughly studied. TRAF6 associates with p75^{NTR} in a ligand-dependent manner (Khursigara et al. 1999) and mediates signaling from the receptor to both JNK and NF-κB (Khursigara et al. 1999; Yeiser et al. 2004). Sympathetic neurons from *traf6*^{-/-} mice fail to activate JNK in response to BDNF binding to p75^{NTR} and fail to undergo apoptosis (Yeiser et al. 2004). Furthermore, there is reduced developmental cell death in the superior cervical ganglia in *traf6*^{-/-} mice relative to the wild type, indicating that TRAF6 is essential for p75^{NTR}-mediated apoptotic signaling in vivo.

TRAF6 also associates with the neurotrophin receptor-interacting factor (NRIF) to promote JNK activation (Gentry et al. 2004; Linggi et al. 2005). NRIF is a zinc-finger protein that was first identified in a yeast 2-hybrid screen for proteins interacting with the ICD of p75^{NTR} (Casademunt et al. 1999). NRIF and TRAF6 can directly interact, and overexpression of NRIF together with TRAF6 enhanced

TRAF6-mediated JNK activation (Gentry et al. 2004). Furthermore, BDNF-induced JNK activation and cell death were significantly attenuated in *nrif*^{-/-} sympathetic neurons (Linggi et al. 2005). Gene deletion revealed that NRIF was required for developmental apoptosis in the retina (Casademunt et al. 1999), which is a p75^{NTR}-dependent process (Frade et al. 1996). Thus, interaction of NRIF with TRAF6 and p75^{NTR} appears to be critical for p75^{NTR}-mediated JNK activation and apoptosis. However, expression of NRIF alone in mouse embryonic fibroblasts was not sufficient to activate the kinase, although it did induce cell death (Linggi et al. 2005). Exactly how NRIF contributes to the activation of JNK is not clear, but it may facilitate oligomerization of TRAF6, which is necessary for it to mediate its biological actions (Yin et al. 2009).

Another intracellular binding partner of p75^{NTR} that is linked to JNK activation is the neurotrophin receptor-interacting MAGE homolog, NRAGE (also known as Maged1 and dlxin) (Salehi et al. 2002). NRAGE contains a melanoma-associated antigen (MAGE) domain, which is a region of homology defining the MAGE family of proteins. The function of the MAGE proteins is poorly understood, but many have been implicated in the regulation of cell cycle and apoptosis (Sang et al. 2011). Ectopic expression of NRAGE along with p75^{NTR} in a sympathetic precursor cell line enabled NGF-dependent cell death, thereby implicating this interactor in the apoptotic pathway activated by p75^{NTR} (Salehi et al. 2000). Overexpression of NRAGE in PC12 cells led to potent activation of JNK, release of cytochrome c from mitochondria, and the induction of caspases -3, -6, and -9, ultimately resulting in cell death (Salehi et al. 2002). These results suggested that NRAGE could be involved in p75^{NTR}-mediated stimulation of JNK. Corroborating evidence came from analysis of *nrage*^{-/-} mice: p75^{NTR}-induced JNK activation in *nrage*^{-/-} sympathetic neurons was significantly reduced compared to wild-type neurons (Bertrand et al. 2008). Furthermore, the null animals have an increased number of neurons in their superior cervical ganglia, like *p75^{NTR}*^{-/-} mice, and sympathetic neurons isolated from *nrage*^{-/-} mice were resistant to p75^{NTR}-mediated apoptosis (Bertrand et al. 2008). These results suggest a function for NRAGE as an adaptor protein, linking the receptor to JNK activation and apoptosis. Whether NRAGE, TRAF6, and NRIF form a complex or function independently to regulate the kinase remains an open question; however, they may function at different stages of the cascade to affect the kinetics of JNK activity (discussed below). It should be noted that sequestering the anti-apoptotic factor XIAP (Jordan et al. 2001; Kendall et al. 2005) and promoting degradation of the anti-apoptotic transcription factor Che1 (Di Certo et al. 2007) have also been suggested as mechanisms through which NRAGE affects cell survival, though these interactions have not been studied in the context of p75^{NTR} signaling.

Another mechanism through which p75^{NTR} has been suggested to regulate JNK involves production of the lipid signaling molecule ceramide (Fig. 1). When the field was searching for evidence of signaling by p75^{NTR}, a NGF-mediated increase in ceramide levels through activation of neutral sphingomyelinase in T9 glioma cells was one of the first signals detected (Dobrowsky et al. 1994). Multiple reports have since confirmed the ability of p75^{NTR} to stimulate ceramide production in

other cell types, including in oligodendrocytes (Casaccia-Bonnet et al. 1996), hippocampal neurons (Brann et al. 2002), Schwann cells (Hirata et al. 2001), and mesencephalic neurons (Blochl and Sirrenberg 1996). One known downstream effect of elevated ceramide is activation of JNK (Westwick et al. 1995), and thus ceramide may couple p75^{NTR} to JNK phosphorylation. Indeed, in cultured hippocampal neurons activation of p75^{NTR} resulted in upregulation of ceramide, stimulation of JNK, and cell death (Brann et al. 2002). Furthermore, inhibition of sphingomyelinase in these neurons prevented ceramide accumulation, JNK activation, and the induction of apoptosis. However, increasing ceramide levels does not always result in cell death. In fact, p75^{NTR}-mediated ceramide production has also been linked to promotion of cell survival (DeFreitas et al. 2001; McCollum and Estus 2004). Understanding this lipid signaling pathway is complicated by the fact that ceramide is a central intermediate in sphingolipid metabolism and can have a variety of effects depending on the specific fatty acid chain attached and its cellular concentration and localization (Horres and Hannun 2012). Further studies are needed to elucidate the mechanisms by which p75^{NTR} activates sphingomyelinase and to reveal how ceramide elicits its effects in various cellular contexts.

3.3 Other Factors Involved in p75^{NTR} Mediated Apoptosis

Apart from TRAF6, NRIF, and NUAGE, several other cytosolic proteins have been shown to associate with p75^{NTR} and suggested to regulate its apoptotic signaling. For example, p75^{NTR}-associated cell death executor (NADE), a novel protein isolated in a two-hybrid screening for proteins binding to the ICD of the receptor, was reported to associate with endogenous p75^{NTR} in PC12 cells (Mukai et al. 2000). Overexpression of NADE together with p75^{NTR} in HEK 293 cells induced apoptosis (Mukai et al. 2000) and expression of a fragment of NADE lacking the region identified as necessary for promoting apoptosis blocked receptor-mediated cell death in oligodendrocytes (Mukai et al. 2002). Currently, though, how NADE contributes to p75^{NTR}-mediated apoptotic signaling is unknown. In addition, MAGE-G1, MAGE-H1 and the MAGE-related protein, Necdin, have also been shown to interact with p75^{NTR} (Kuwako et al. 2004; Tcherpakov et al. 2002). Both Necdin and MAGE-G1 associate with E2F1, a transcription factor that is important for G1/S transition in the cell cycle and that can induce apoptosis in postmitotic cells (Ginsberg 2002). When the ICD of p75^{NTR} was overexpressed in a neuroblastoma cell line, Necdin and MAGE-G1 bound to the receptor ICD, thereby releasing E2F1 and triggering apoptosis (Kuwako et al. 2004; Lopez-Sanchez et al. 2007). Additional studies are needed to determine whether Necdin and MAGE-G1 regulate ligand-mediated cell death in primary cells. The p75^{NTR} has also been reported to promote apoptosis through upregulation of the sugar binding protein Galectin-1 (Plachta et al. 2007). Embryonic stem (ES) cells engineered to express p75^{NTR} degenerated when they were induced to differentiate into neurons. This degeneration correlated with expression of Galectin-1, which promoted death of the ES cells as well as cortical neurons (Plachta et al. 2007). Furthermore, mice

lacking Galectin-1 were resistant to neuronal apoptosis caused by pilocarpine-induced seizures (Bischoff et al. 2012), which was demonstrated to be a p75^{NTR}-dependent process (Roux et al. 1999; Volosin et al. 2008). The mechanisms by which this lectin causes cell death remain to be determined.

3.4 Regulated Intramembrane Proteolysis of p75^{NTR}

In a manner similar to Notch and amyloid precursor protein (APP), p75^{NTR} undergoes regulated intramembrane proteolysis (RIP). Proteolysis of p75^{NTR} was first described as a response to phorbol esters in HEK293 cells transfected with the receptor (Jung et al. 2003; Kanning et al. 2003). The extracellular region of p75^{NTR} is first cleaved by the metalloproteinase TNF α -converting enzyme (TACE, also known as ADAM17), thereby producing a 24 kDa membrane-bound C-terminal fragment (p75^{NTR}-CTF) (Weskamp et al. 2004). This cleavage event appears to be quite promiscuous in terms of the amino acid sequence; however, deletion analysis revealed that at least 15 residues extracellular to the transmembrane domain are required (Zampieri et al. 2005). Following release of the soluble ectodomain, the p75^{NTR}-CTF is then further cleaved within its transmembrane region by the γ -secretase complex, thereby releasing the 19 kDa intracellular domain of the receptor (p75^{NTR}-ICD). Similar to proteolysis by TACE, cleavage by γ -secretase is quite permissive for various amino acids; nevertheless, there must be some sequence specificity for both enzymes since substituting the transmembrane domain of Fas for that of p75^{NTR} blocked cutting by γ -secretase and replacing the 15 amino acid juxtamembrane sequence with the Fas sequence blocked p75^{NTR} proteolysis by TACE (Zampieri et al. 2005). The order of the two cleavage reactions is also invariant, with TACE acting on the receptor prior to γ -secretase. This was determined by studies in which cleavage of p75^{NTR} by γ -secretase was prevented by TACE inhibition, but inhibition of γ -secretase did not affect TACE activity, thus indicating that release of the extracellular domain is required for further proteolysis of the receptor within the transmembrane domain (Kenchappa et al. 2010; Zampieri et al. 2005). Since the initial finding of RIP of p75^{NTR} in response to phorbol esters, a number of reports have demonstrated that proteolysis of p75^{NTR} occurs through a ligand-dependent mechanism; for example, treatment of sympathetic neurons with BDNF (Kenchappa et al. 2006, 2010), Schwann cells with NGF (Frade 2005), and cerebellar neurons with myelin-associated glycoprotein (Domeniconi et al. 2005) (this ligand is discussed below) resulted in RIP. It is unclear, however, whether ligand activated p75^{NTR} always results in RIP.

One functional role of p75^{NTR} cleavage, like for many γ -secretase substrates, is to facilitate signaling to the nucleus. Release of the p75^{NTR}-ICD may facilitate nuclear translocation of associated factors such as NRIF. Although NRIF was shown to be required for p75^{NTR}-mediated apoptotic signaling based on analyses of *nrif*^{-/-} mice (Casademunt et al. 1999; Linggi et al. 2005), exactly how it contributed to the cell death was not clear. NRIF contains a classic C2H2 zinc-finger motif (Casademunt et al. 1999), which is typically found among DNA

binding transcription factors (Wolfe et al. 2000), suggesting that in addition to facilitating JNK activation, NRIF could bind DNA and regulate transcription. The recognition of p75^{NTR} proteolysis by γ -secretase revealed a possible mechanism by which NRIF could be translocated from the surface-bound ICD of the receptor to the nucleus. Indeed, it was demonstrated that BDNF-induced cleavage of the receptor in sympathetic neurons facilitated nuclear localization of NRIF and, subsequently, apoptosis (Kenchappa et al. 2006). Blocking receptor cleavage prevented both localization of NRIF to the nucleus and cell death. A similar signaling cascade has been detected in hippocampal neurons, where neuronal death due to pilocarpine-induced seizures was associated with p75^{NTR} proteolysis and NRIF nuclear translocation. Moreover, the number of apoptotic neurons after seizure was significantly reduced in p75^{NTR}^{-/-} (Troy et al. 2002) and in *nrf1*^{-/-} mice (Volosin et al. 2008).

The mechanism of NRIF nuclear translocation also depends on TRAF6-mediated ubiquitylation. TRAF6 was shown to ubiquitylate NRIF following ligand binding to p75^{NTR}, and blocking this event by mutating the ubiquitin-attachment site of NRIF prevented its nuclear translocation and inhibited p75^{NTR}-mediated apoptosis (Geetha et al. 2005). The ubiquitylation of NRIF required p75^{NTR} cleavage (Kenchappa et al. 2006), suggesting that receptor proteolysis facilitates an interaction between NRIF and TRAF6, enabling ubiquitylation of NRIF, which is needed for it to enter the nucleus, and oligomerization of TRAF6, which promotes the activation of JNK (Fig. 2).

The cleavage of p75^{NTR} and the activation of JNK were recently shown to occur through interdependent pathways. In sympathetic neurons, JNK activation was required for ligand-induced proteolysis of the receptor by both TACE and γ -secretase (Kenchappa et al. 2010), as blocking JNK activity or deleting JNK3 prevented receptor cleavage by both proteases. The activation of JNK facilitated the transcriptional upregulation of TACE and, through an unknown mechanism, stimulated both TACE and γ -secretase, thereby inducing p75^{NTR} processing. Interestingly, the release of the receptor's ICD, along with NRIF and TRAF6, was necessary for prolonged JNK stimulation by the receptor. Expression of a non-cleavable mutant p75^{NTR} prevented JNK activation at 24 h, yet the kinase was still activated for the first hour after ligand binding (Kenchappa et al. 2010). Hence, there appears to be a biphasic activation of JNK by p75^{NTR}, with an early signal, perhaps initiated through NRAGE, inducing proteolytic processing of the receptor, which allows NRIF and TRAF6 to promote long-term stimulation of the kinase as well as nuclear signaling, ultimately resulting in cell death (Fig. 2).

In contrast to the evidence that proteolytic processing of p75^{NTR} induces apoptosis by releasing the p75^{NTR}-ICD, in certain cellular contexts programmed cell death may be activated by the p75^{NTR}-CTF alone. Coulson et al. found that overexpression of the p75^{NTR}-CTF was sufficient to promote the apoptosis of dorsal root ganglion (DRG) neurons and that the death domain was not necessary (Coulson et al. 2000; Underwood et al. 2008). This function of the p75^{NTR}-CTF required a 29 amino acid sequence in the cytoplasmic juxtamembrane region of the receptor termed the "chopper domain" (Coulson et al. 2000). Coulson and

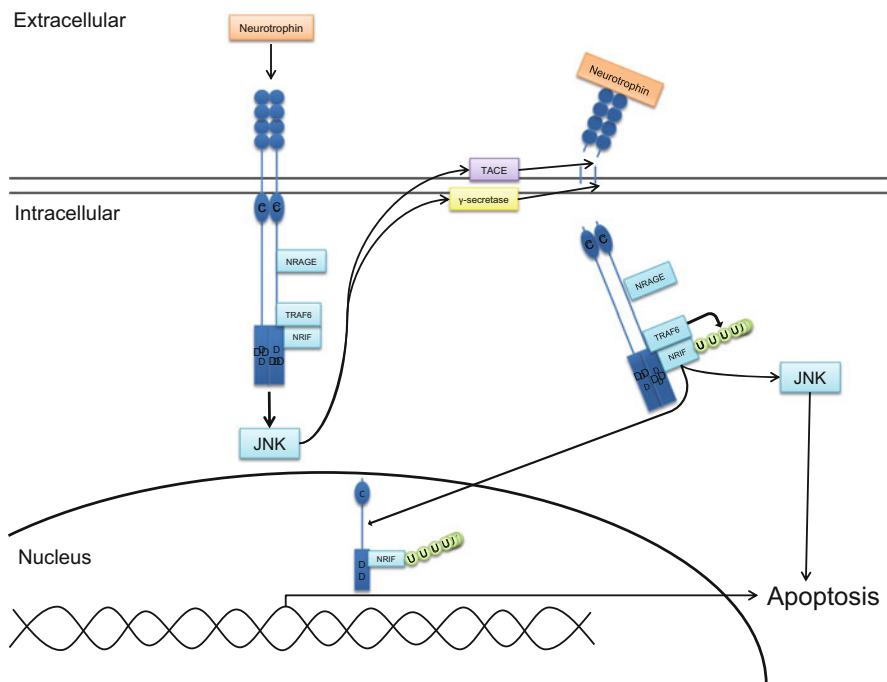


Fig. 2 Cell death signaling initiated by regulated intramembrane proteolysis (RIP) of p75^{NTR}. Stimulation of p75^{NTR} by neurotrophins promotes an early phase of JNK activation, occurring within 30 min of ligand binding. Through a mechanism currently unknown, JNK induces sequential proteolytic cleavage of p75^{NTR} by TACE and γ -secretase. Release of the p75^{NTR} intracellular domain promotes TRAF6-dependent ubiquitylation and nuclear translocation of NRIF, as well as persistent JNK activation, ultimately leading to induction of programmed cell death (abbreviations: *DD* death domain, *C* chopper domain, *U* ubiquitin)

colleagues demonstrated that ectopic expression of membrane-associated fragments of p75^{NTR} containing the chopper domain promoted apoptosis by inducing a Rac-dependent increase in phosphatidylinositol 4,5-bisphosphate (PIP₂). In turn, PIP₂ stimulated G-protein-coupled inwardly rectifying potassium (GIRK) channels, causing a depletion of internal potassium that ultimately activated an apoptotic protease activating factor 1 (APAF-1)-dependent cell death pathway (Coulson et al. 2004, 2008; Skeldal et al. 2011). It should be cautioned, however, that these studies relied on overexpression of the CTF; thus, further studies are needed to determine how the various fragments of the receptor regulate cell death under different physiological conditions.

3.5 Proneurotrophins and Sortilin

The initial discovery that p75^{NTR} can induce programmed cell death was somewhat puzzling, as *in vitro* studies indicated that relatively high concentrations of

neurotrophins were needed to induce apoptosis, and in certain cell types, cross-reactivity of neurotrophins with Trk receptors could potentially promote an opposing, pro-survival signal. An answer was found, at least in part, by Hempstead's group, who discovered that precursor forms of neurotrophins are biologically active, selective ligands for p75^{NTR}. Like most secreted proteins, neurotrophins are initially synthesized as larger precursors, which are enzymatically cleaved to generate the mature form of the protein (Edwards et al. 1988; Suter et al. 1991). Proneurotrophins have an amino-terminal pro-domain that assists in their proper folding and dimerization (Heymach and Shooter 1995; Rattenholl et al. 2001a, b). The pro-domain can be proteolytically removed by furin and pro-protein convertases in the endoplasmic reticulum and Golgi apparatus (Seidah et al. 1996). Alternatively, the cleavage of the pro-domain can also be mediated by plasmin and matrix metalloproteases following secretion of the proneurotrophin into the extracellular milieu (Lee et al. 2001). While it was originally thought that mature neurotrophins are the only physiologically active ligands for p75^{NTR}, it is now well established that endogenous proneurotrophins can be secreted to function as potent activators of p75^{NTR} signaling (Beattie et al. 2002; Harrington et al. 2004; Lebrun-Julien et al. 2010; Lee et al. 2001; Teng et al. 2005).

Proneurotrophins do not activate Trk receptors (Boutillier et al. 2008; Lee et al. 2001) and have been demonstrated to induce significant p75^{NTR}-mediated cell death at sub-nanomolar concentrations (Lee et al. 2001). Thus, proteolytic processing determines the functional fate of nascent neurotrophins, with uncleaved forms selectively triggering p75^{NTR}-mediated cell death and mature forms activating either p75^{NTR} or Trk receptors, depending upon the cellular context. Proneurotrophins induce programmed cell death by binding to a high affinity protein complex containing p75^{NTR} and its co-receptor Sortilin, a member of the Vps10p-domain receptor family (Nykjaer et al. 2004; Teng et al. 2005). Mammalian members of the Vps10p family, which consists of Sortilin, SorLA, and SorCS-1, -2, and -3, are type I transmembrane receptors with multifunctional roles that include the modulation of protein sorting and trafficking, as well as regulation of signal transduction (Willnow et al. 2008). Proneurotrophins bind to Sortilin via their pro-domain and to p75^{NTR} by their mature domain, thus facilitating the association of these two receptors to initiate programmed cell death (Nykjaer et al. 2004, 2005; Teng et al. 2005). Following initial reports that Sortilin mediates neurotrophin-induced cell death in vitro (Nykjaer et al. 2004; Teng et al. 2005), studies have indicated that Sortilin is required for developmental p75^{NTR}-mediated cell death in vivo. For example, mice lacking Sortilin have a reduction in the developmental apoptosis of retinal ganglion cells that is indistinguishable from that of p75^{NTR}-deficient mice (Jansen et al. 2007). However, Sortilin may not be required for all p75^{NTR}-mediated cell death, as these mice did not have defects in the apoptosis of sympathetic neurons during the developmental time period in which p75^{NTR}-mediated death is known to occur (Jansen et al. 2007). Loss of Sortilin did, however, impair age-related degeneration of these neurons, suggesting that proneurotrophins may not have been involved in the early development of the sympathetic neurons, but do have a role in their loss during aging.

3.6 Apoptotic Role of p75^{NTR} in Pathology

In addition to its critical role during neurodevelopment, p75^{NTR} is a stress-activated receptor that stimulates the death of cells within injured tissue. Though the receptor is downregulated in most regions of the nervous system after early postnatal development, reexpression of p75^{NTR} occurs in response to many forms of cellular damage. For example, increases in p75^{NTR} expression have been reported following neuronal axotomy (Ernfors et al. 1989; Giehl et al. 2001; Harrington et al. 2004; Koliatsos et al. 1991; Taniuchi et al. 1986), mechanical damage (Beattie et al. 2002; Brunello et al. 1990; Rende et al. 1993), elevated intraocular pressure (Wei et al. 2007), seizures (Roux et al. 1999; Volosin et al. 2008), and focal ischemia (Kokaia et al. 1998). Beyond measuring increases in expression of the receptor, multiple studies have more definitively demonstrated that p75^{NTR} signaling is responsible for injury-induced cell death in vivo. In one such study, unilateral administration of kainic acid to the basal forebrain resulted in reexpression of p75^{NTR} in the degenerating cholinergic neurons, which correlated with their apoptosis. Administration of a function-blocking p75^{NTR} antibody prevented this cell death, thereby indicating that p75^{NTR} signaling contributes to excitotoxin-induced death of basal forebrain neurons (Oh et al. 2000). Similarly, expression of p75^{NTR} was induced and associated with programmed cell death caused by axotomy of corticospinal neurons, and antibodies to p75^{NTR} prevented this apoptosis (Giehl et al. 2001). Although these two studies indicated that p75^{NTR} promotes neuronal death after injury, whether proneurotrophins contribute to the death caused by these injuries was not known. In a later report, injury to the spinal cord was found to induce production of proNGF and to stimulate p75^{NTR}-dependent apoptosis of spinal cord oligodendrocytes (Beattie et al. 2002). ProNGF extracted from the injured region elicited apoptosis of cultured oligodendrocytes expressing p75^{NTR} but not of p75^{NTR}-/- oligodendrocytes. Thus, this work suggested that proNGF functions to promote the elimination of damaged cells by activating p75^{NTR} after spinal cord injury (Beattie et al. 2002). A subsequent study by Yoon and colleagues demonstrated that axotomy of corticospinal neurons also resulted in apoptosis of the neurons through a proNGF-p75^{NTR}-dependent mechanism (Harrington et al. 2004). Following lesion of the internal capsule, proNGF was detected in cerebral spinal fluid, indicating that proNGF is produced and secreted in vivo after brain injury. In the cortex of lesioned animals, an interaction between proNGF and p75^{NTR} was detected in vivo, and disruption of this interaction by infusion of an antibody specific for proNGF prevented the apoptosis caused by the injury (Harrington et al. 2004). These experiments provided the first conclusive evidence that proNGF is a pathophysiological ligand that induces apoptosis in response to neuronal damage. Since then, a growing body of evidence has linked proneurotrophins to cell death induced by various types of injury. For example, hippocampal seizures stimulated the upregulation and secretion of proNGF in vivo, and antibodies specific for proNGF prevented seizure-induced apoptosis of neurons within the dentate gyrus (Volosin et al. 2008). In another study, increases in proNGF, along with p75^{NTR} and Sortilin, were reported in the retina after exposure

of albino mice to intense light, and blockade of Sortilin with the pro-domain of proNGF attenuated light-induced retinal cell death (Santos et al. 2012). The ability of proneurotrophins to induce cell death in response to cellular damage is likely not specific to proNGF, as proBDNF has also been demonstrated to promote apoptosis in a number of cell culture models (Fan et al. 2008; Taylor et al. 2012; Teng et al. 2005), and upregulation of proBDNF has been detected in *in vivo* injury models, such as in an animal model of cochlear damage (Tan and Shepherd 2006). ProBDNF has also been implicated in apoptosis occurring due to neuronal axotomy, as infusion of a proBDNF antibody prevented the death of sensory neurons induced by lesion of the sciatic nerve *in vivo* (Fan et al. 2008).

While the signaling mechanisms responsible for the induction of p75^{NTR} and the proneurotrophins after injury are not well understood, several studies have provided some clues. One possibility is that cellular damage prevents the proteolytic processing of neurotrophins, thus increasing the release of death inducing proneurotrophins. A recent study by Friedman and colleagues has revealed that following kainic acid-induced seizures, the proneurotrophin-processing enzyme matrix metalloproteinase-7 (MMP-7) and its inhibitor tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) were regulated in a manner that would hinder cleavage of proneurotrophins and lead to increased release of proNGF (Le and Friedman 2012). Decreased MMP-7 production has also been observed in samples from human patients and animal models with diabetic retinopathy (Ali et al. 2011). These findings suggest that regulation of proteolytic processing of proneurotrophins is one mechanism by which the levels of these factors are modulated, though a greater understanding of the pathways regulating their release in the unprocessed versus the mature form is needed. Along with increases in the levels of proneurotrophins, upregulation of p75^{NTR} after injury may occur due to inflammatory signals released in response to tissue damage. The inflammatory cytokines interleukin-12 (IL-12), tumor necrosis factor alpha (TNF α), and interleukin-1 β have been demonstrated to increase p75^{NTR} expression in a variety of *in vitro* systems, such as in cultured hippocampal neurons (Choi and Friedman 2009), natural killer cells (Rogers et al. 2010), or astrocytes (Choi and Friedman 2009). Interestingly, a recent report indicated that trauma-induced upregulation of p75^{NTR} could also result from calcium influx. Within axotomized hippocampal neurons, cellular responses to GABA change from hyperpolarizing to depolarizing, leading to increased intracellular calcium and the subsequent activation of Rho kinase (ROCK). The activation of ROCK resulted in upregulation of p75^{NTR}, ultimately leading to neuronal death (Shulga et al. 2012). Thus, multiple signals may contribute to trauma-induced upregulation of the receptor. However, the mechanisms by which these signals increase p75^{NTR} transcription are still poorly understood. The ubiquitous transcription factor Sp1 has been linked to p75^{NTR} basal expression (Poukka et al. 1996) and upregulation following hypo-osmotic stress (Kommaddi et al. 2011a; Ramos et al. 2007), but whether this factor is involved in other forms of injury is not known. It should also be added that long-term treatment of SH-SY5Y

cell lines with IGF1 resulted in a significant upregulation of p75^{NTR} levels (Costantini et al. 2006), suggesting that a factor that responds to IGF1 signaling may also be involved.

In addition to regulating cell death following injury, p75^{NTR} signaling has been suggested to contribute to neurodegeneration caused by a number of diseases. Among these disorders, the link between p75^{NTR} and Alzheimer's disease (AD) has been most studied. Besides Purkinje neurons in the cerebellum, p75^{NTR} is expressed at high levels in cholinergic neurons of the adult basal forebrain, a population of neurons that undergoes severe degeneration early in the progression of AD pathology. Additionally, several in vitro studies have indicated that amyloid beta 1–42 (A β), the main component of plaques commonly found within brains of AD patients, is a pro-apoptotic ligand for p75^{NTR} (Costantini et al. 2005; Hashimoto et al. 2004; Yaar et al. 1997). These findings have led to the hypothesis that activation of p75^{NTR} by A β contributes to neurodegeneration caused by AD. This idea has remained controversial, however, due to other reports indicating that expression of p75^{NTR} is protective against A β -induced toxicity (Bengoechea et al. 2009; Zhang et al. 2003). Nonetheless, a role for p75^{NTR} in A β -induced neurotoxicity was recently strengthened by an in vivo finding that deletion of p75^{NTR} prevented the degeneration of cholinergic basal forebrain neurons in vivo following A β injection into the hippocampus (Sotthibundhu et al. 2008). Furthermore, when p75^{NTR} $-/-$ mice were crossed with the Thy1-hAPP^{Lond/Swe} mouse model of AD, the degeneration of hippocampal and forebrain cholinergic fibers was dramatically rescued (Knowles et al. 2009). Just as for the in vitro studies, however, these in vivo studies were also challenged by a recent study by Wang et al, which indicated that p75^{NTR} signaling induces production of A β , since deletion of the p75^{NTR} gene in the APP^{swe}/PS1^{dE} mouse model of AD resulted in decreased production of A β within cortical neurons (Wang et al. 2011). Despite some differences, these findings together suggest that p75^{NTR} signaling by A β peptides contributes to overall AD pathology. Apart from A β -induced apoptosis, studies have also implicated proNGF in AD pathology. Increased expression of proNGF has been detected in human brains affected by AD (Pedraza et al. 2005; Peng et al. 2004), and proNGF isolated from these brain samples induced p75^{NTR}-mediated death of cultured sympathetic neurons (Pedraza et al. 2005; Podlesniy et al. 2006). Thus, in addition to activation of p75^{NTR} by A β , enhanced production of proNGF may contribute to neurodegeneration within the AD brain. While these studies provide multiple links between p75^{NTR} signaling and AD-induced neurodegeneration, collective evidence suggests that the degeneration of neurons in AD occurs near the end-stages of the disease (Jack et al. 2010). Hence, understanding whether p75^{NTR} plays a critical role in the onset and early progression of AD remains essential.

While the majority of studies related to p75^{NTR} and neurodegenerative disease have focused on the contributions of the receptor to AD, it is perhaps not surprising that p75^{NTR} has been linked to a number of other disorders. For example, p75^{NTR} may contribute to degeneration of motor neurons during the progression of amyotrophic lateral sclerosis (ALS). Though p75^{NTR} is downregulated in motor

neurons of the spinal cord during the perinatal period, reexpression of the receptor was detected in spinal motorneurons of an ALS mouse model (Coprav et al. 2003; Lowry et al. 2001), as well as in spinal cord samples from human patients with ALS (Lowry et al. 2001; Seeburger et al. 1993). Furthermore, the receptor was implicated in ALS-associated motoneuron death by a study in which knockdown of p75^{NTR} delayed locomotor impairment and mortality in the SOD1G93A mouse model of ALS (Turner et al. 2003). However, when the SOD1G93A mice were crossed with the p75^{NTR}-/- mice, prolonged survival was only detected in the female mice, and this improvement did not correlate with increased motorneuron survival, but with reduced astrocytosis (Kust et al. 2003). Nevertheless, the SOD mutation represents a very small fraction of ALS patients, thus further study into the role of the receptor in this disease is warranted.

Degeneration of dopaminergic neurons in Parkinson's disease (PD) could also involve p75^{NTR}. A study by Simon and colleagues demonstrated that loss of the *Engrailed* transcription factors results in increased expression of p75^{NTR} in the ventral midbrain (Alavian et al. 2009). This finding has implications for Parkinson's disease because mice deficient in *Engrailed-1* and *Engrailed-2* exhibit progressive loss of mesencephalic dopaminergic neurons and have PD-like motor deficiencies (Alavian et al. 2009). Importantly, knocking down p75^{NTR} or addition of a receptor-blocking antibody prevented the apoptosis of mesencephalic dopaminergic neurons in cultures from the *engrailed 1, 2* double knockout mice. Upregulation of p75^{NTR} in dopaminergic nigro-striatal neurons has also been reported following kainic-acid treatment (Wang et al. 2008). However, direct evidence for p75^{NTR} expression in nigral dopaminergic neurons in PD and causal evidence linking expression of p75^{NTR} to PD-associated nigral neurodegeneration in vivo is still missing.

In addition to these neurodegenerative conditions, evidence continues to grow implicating p75^{NTR} in the pathology of other neurological diseases. For example, p75^{NTR} has been suggested as having a role in spongiform encephalomyelopathy (Stoica et al. 2008), diabetes-related impairment of neovascularization (Caporali et al. 2008), and psoriasis (Truzzi et al. 2011), among others. The abundance of links between p75^{NTR} and such a variety of diseases indicates that the receptor may function in a broader sense as a stress-induced apoptotic signal that is activated by a mechanism common to all of these pathological conditions. Thus, further elucidation of the mechanisms by which p75^{NTR} is upregulated and activated during these pathological conditions and of the contributions of the receptor to the resulting neurodegeneration may be of critical therapeutic importance.

4 Promotion of Cell Survival

Despite its currently known role in eliciting programmed cell death, early studies of p75^{NTR} demonstrated that in a variety of cellular contexts the receptor has the opposite function: to promote cell survival. Though p75^{NTR}-induced apoptosis has been more widely studied, the receptor has been demonstrated to promote cell survival in a wide variety of cell types. One of the first indications that the receptor

can promote neuronal survival came from analysis of $p75^{NTR-/-}$ mice, which revealed significant loss of sensory innervation of limbs (Lee et al. 1992). Subsequently, the number of neurons in the dorsal root ganglia (DRG) was reported to be reduced by 50–75 % in the knockout mice (Murray et al. 1999). Although the DRG is a very heterogeneous population of neurons, a decrease in virtually all types of neurons was detected, based on morphological criteria (Bergmann et al. 1997; Gjerstad et al. 2002) or expression of various markers (Jiang et al. 2004). Since then, numerous reports have suggested that $p75^{NTR}$ promotes survival in a wide range of cell types, with the majority suggesting that this is through cooperation with the Trk family, leading to a high affinity receptor complex or enhanced Trk signaling.

4.1 $p75^{NTR}$ Interactions with the Trks

Shortly after TrkA was identified as a receptor for NGF, Chao and colleagues demonstrated that $p75^{NTR}$ interacts with TrkA to form a high-affinity binding complex (Hempstead et al. 1991). While TrkA alone was found to bind NGF with nanomolar affinity, co-expression with $p75^{NTR}$ was discovered to increase this interaction by 100-fold (Esposito et al. 2001; Hempstead et al. 1991). Thus, $p75^{NTR}$ can augment Trk-mediated survival by increasing its interaction with neurotrophins. Given that neurotrophins are typically present in limiting amounts in the target tissues, the presence of high-affinity receptors is an obvious advantage. The requirement for $p75^{NTR}$ in forming the high-affinity complex was initially offered as an explanation for the sensory neuron loss in the animals lacking the receptor. Indeed, neurotrophin dose–response curves revealed that higher doses of NGF were needed to promote survival of sensory and sympathetic neurons from $p75^{NTR-/-}$ mice (Davies et al. 1993; Lee et al. 1992). However, a critical element unanswered by this interpretation of the data relates to the fact that, unlike the loss of neurons in the DRG, $p75^{NTR-/-}$ mice actually have excess sympathetic neurons (Bamji et al. 1998; Deppmann et al. 2008; Jansen et al. 2007). As discussed above, $p75^{NTR}$ contributes to normal, developmental apoptosis of sympathetic neurons, which could explain the increased neuronal number in the knockout mice, yet why the receptor functions differently in sensory neurons has yet to be resolved.

Although functional interaction between $p75^{NTR}$ and Trk receptors is clear, the molecular details are not fully understood. Surprisingly, the transmembrane and intracellular domains of $p75^{NTR}$, but not the neurotrophin-binding portion of the extracellular domain, are required for the high-affinity complex (Esposito et al. 2001). Furthermore, structure analysis by X-ray crystallography and complementation assays (using fragments of beta-galactosidase) indicated that complexes of each receptor bind NGF independently and that there is no direct interaction between $p75^{NTR}$ and TrkA (Wehrman et al. 2007). The structural analysis disagrees with many early cross-linking experiments (discussed above) and co-immunoprecipitation studies in HEK293 cells (e.g., Bibel et al. 1999) that

indicate the presence of a complex of both receptors. Clearly, further study is required to resolve the nature of the high affinity complex.

It is also important to note that a p75^{NTR} homolog, neurotrophin receptor homolog 2 (NRH2), was recently identified (Kanning et al. 2003). Like p75^{NTR}, NRH2 can also undergo cleavage by TACE and γ -secretase (Kanning et al. 2003), associate with Sortilin (Kim and Hempstead 2009), and form a high-affinity NGF receptor with TrkA (Murray et al. 2004). NRH2 is co-expressed with p75^{NTR} in multiple neuronal subtypes. Thus, understanding how NRH2 and p75^{NTR} function together with their co-receptors is necessary to interpret the phenotype of p75^{NTR} $-/-$ mice.

Remarkably, Trk-p75^{NTR} interactions not only facilitate the formation of a high-affinity receptor complex but also regulate the neurotrophin selectivity of the tyrosine kinase receptor. For example, in the absence of p75^{NTR}, TrkA can respond to both NT3 and NGF; however, the Trk-p75^{NTR} complex is highly selective for NGF (Benedetti et al. 1993; Clary and Reichardt 1994). During the development of sympathetic neurons, NT3-TrkA interaction is necessary for neuronal survival (Ernfors et al. 1994; Farinas et al. 1994; Francis et al. 1999). Ginty and colleagues demonstrated that intermediate targets, such as blood vessels, produce NT3 and promote axon growth, but not survival, through TrkA. However, as the neurons innervate their NGF-secreting targets, p75^{NTR} is upregulated, causing TrkA to become selective for NGF over NT3. The NGF-Trk-p75^{NTR} complex is then retrogradely transported to promote survival (Kuruvilla et al. 2004). Hence, p75^{NTR} can function as a switch factor, allowing differential TrkA responses. Similar selectivity is observed with TrkB ligands; co-expression of p75^{NTR} with TrkB increased its selectivity for BDNF over NT3 and NT4 (Bibel et al. 1999).

Beyond regulating the affinity and selectivity of Trks for neurotrophins, p75^{NTR} also potentiates Trk survival signaling. Prevention of neurotrophin binding to p75^{NTR} attenuated TrkA signaling in several in vitro systems (Barker and Shooter 1994; Lachance et al. 1997; Ryden et al. 1997; Verdi et al. 1994). The mechanism by which p75^{NTR} enhances Trk signaling remains poorly understood. Barker and colleagues demonstrated that co-expression of p75^{NTR} with TrkA attenuated TrkA ubiquitylation and delayed the NGF-dependent internalization and degradation of the receptor (Makkerh et al. 2005). Therefore, one mechanism utilized by p75^{NTR} to augment Trk-mediated survival signaling is prolonging cell surface expression of the Trk receptor. Chao and colleagues identified a large transmembrane protein, Ankyrin repeat-rich membrane spanning (ARMS/Kidins220), that interacts with both p75^{NTR} and Trk (Kong et al. 2001). ARMS is tyrosine phosphorylated following neurotrophin treatment and is expressed in many of the neuronal populations that receive neurotrophin stimulation (Kong et al. 2001). While these data suggest that ARMS may serve as a link between p75^{NTR} and Trk receptors, expression of ARMS was discovered to decrease association of TrkA with p75^{NTR} (Chang et al. 2004), and the functional role of the protein has yet to be determined. Recently, however, analysis of mice lacking ARMS revealed substantial apoptosis of sensory neurons (Cesca et al. 2011), a phenotype similar to that observed in p75^{NTR} $-/-$ animals (Murray et al. 1999), thus further highlighting the potential

importance of this interactor in regulation of cell survival through p75^{NTR}-Trk interaction.

In addition to p75^{NTR} regulating Trk function at the cell surface, there is evidence that intracellular signaling pathways are modulated by co-activation of the receptors. One such signaling event particularly affected by this interaction is activation of the pro-survival kinase Akt. Treatment of PC12 cells with NGF in the presence of an antibody that blocked binding to p75^{NTR} inhibited the activation of Akt (Bui et al. 2002). Similarly, silencing of P75^{NTR} in PC12 cells or cerebellar granule neurons reduced neurotrophin-induced activation of the kinase (Ceni et al. 2010). These authors also reported that activation of Akt required proteolysis of p75^{NTR}. In contrast to what was observed for p75^{NTR} in sympathetic neurons (Kenchappa et al. 2006), Ceni et al. reported that the cleavage of p75^{NTR} was induced by Trk activation. They have since extended these findings, demonstrating that Trk activation promoted phosphorylation of TACE, which activated the protease and lead to cleavage of p75^{NTR}, which was necessary for potentiation of neurotrophin-induced survival signaling (Kommaddi et al. 2011b).

Although p75^{NTR} can function in cooperation with Trks to promote survival signals, Friedman and colleagues found that in basal forebrain neurons, p75^{NTR} reduced Akt signaling by increasing the levels of active PTEN (phosphatase and tensin homolog deleted on chromosome 10), an inhibitor of the PI3 kinase-Akt pathway (Song et al. 2010). ProNGF binding to p75^{NTR} upregulated PTEN, which resulted in apoptosis of the neurons, even if TrkB was activated by BDNF. Since proNGF signals through binding a complex of p75^{NTR} and Sortilin, the effects of p75^{NTR} on Akt activity appears to depend on its co-receptor.

4.2 P75^{NTR} Activation of NFκB

Apart from enhancing Trk survival signaling, there is evidence that p75^{NTR} can activate an independent pro-survival signal; for example, selective activation of p75^{NTR} prevented the death of certain neuroblastoma (Cortazzo et al. 1996) and breast cancer cells (Verbeke et al. 2010), of hippocampal neurons treated with NMDA (Bui et al. 2002), and of both sensory neurons (Longo et al. 1997) and cortical subplate neurons deprived of trophic support (DeFreitas et al. 2001). In addition, the receptor appears to play a protective role after certain injuries; e.g., p75^{NTR}-/- mice have increased death of primary auditory neurons following acoustic trauma (Tan et al. 2010). The pro-survival effects of p75^{NTR} appear to be more of a modulatory signal, as they are not as potent as the effects of tyrosine kinases like the Trks. The molecular mechanisms by which p75^{NTR} promotes survival independent of the Trk receptors are not fully understood; however, one downstream pathway that has been identified involves the transcription factor nuclear factor kappa B (NFκB). NFκB is best characterized for its role in the immune system, where it is activated by many cytokine and Toll-like receptors, leading to upregulation of other cytokines and pro-survival genes (Baldwin 2012). The activation of NFκB by p75^{NTR} was first reported in Schwann cells

(Carter et al. 1996) and has since been demonstrated in a variety of cell types, including Schwannoma cells (Gentry et al. 2000), primary Schwann cells (Khursigara et al. 2001), trigeminal neurons (Hamanoue et al. 1999), and hippocampal neurons (Culmsee et al. 2002). NF κ B exists as a dimer, held in the cytosol through binding to its inhibitor I κ B. The transcription factor is activated through phosphorylation of I κ B by the I κ B kinase (IKK) complex, leading to proteasomal degradation of the inhibitor and release of the NF κ B dimer to translocate into the nucleus (Baldwin 2012). As mentioned above, neurotrophin binding to p75^{NTR} can recruit members of the TRAF family, which activate the IKK complex (Ha et al. 2009; Hacker et al. 2011); specifically, TRAF6 was shown to mediate activation of NF κ B, as Schwann cells from *traf6*^{-/-} mice did not respond to p75^{NTR} activation (Yeiser et al. 2004). Since TRAF6 promotes both NF κ B and JNK activation, it was recognized as a potential nodal point for determining survival vs. apoptotic signaling. How TRAF6 selectively promotes one pathway over the other remains to be fully elucidated; however, the finding that the adaptor protein receptor-interacting protein 2 (RIP2) directly associates with the death domain of p75^{NTR} provided an important clue. Chao and colleagues demonstrated that expression of RIP2 in Schwann cells conferred NGF-dependent activation of NF κ B through interaction with TRAF6. Expression of RIP2 in these cells also reduced JNK activation and the subsequent apoptosis (Khursigara et al. 2001). Thus, RIP2 expression may serve as the key toggle, switching TRAF6 signaling to NF κ B from JNK (Fig. 1).

Another well-established activator of NF κ B is Akt. Although evidence suggests that p75^{NTR} enhances Trk activation of Akt, as discussed above, p75^{NTR} has also been reported to promote Akt activation in a manner that was independent of Trk signaling in hippocampal neurons (Arevalo and Rodriguez-Tebar 2006), melanoma cells, and mutant PC12 cells lacking TrkA (Roux et al. 2001). Therefore, NF κ B may be among the downstream pro-survival signals activated by p75^{NTR} in some contexts.

It is also notable that the p75^{NTR} was recently shown to regulate the stability of HIF1 α , a transcription factor induced by oxidative stress that controls the expression of a wide variety of genes involved in protection from reactive oxygen species and, importantly, promoting cell survival (Hu et al. 2003). Le Moan et al. (2011) reported that the ICD of the receptor can bind the E3 ubiquitin ligase Siah2, which targets HIF1 α for degradation. The interaction between p75^{NTR}-ICD and Siah2 lead to upregulation of HIF1 α and increased expression of vascular endothelial growth factor, which promoted angiogenesis after retinal hypoxia. While the authors did not address a potential role in regulating survival, given that many target genes of HIF1 α are pro-survival, it will be interesting to determine whether this pathway has a role in promoting neuronal survival in response to activation of the receptor.

Because of the ability of p75^{NTR} to augment Trk-mediated survival signaling and ligand selectivity, the overall effect of p75^{NTR} on cell survival is quite variable by cell type and highly dependent upon the presence or absence of the Trk receptor. In general, though not always, simultaneous activation of both Trk receptors and p75^{NTR} by mature neurotrophins results in cell survival. However, selective activation of p75^{NTR} by neurotrophins in the absence of Trk-receptor activation more

often promotes cell death than survival. For example, NGF treatment of sympathetic neurons, which express both p75^{NTR} and TrkA, promotes neuronal survival. Stimulation of these neurons with BDNF, however, results in apoptosis, as these neurons do not express TrkB (Bamji et al. 1998). The proliferative state of the cell also may influence the effects of p75^{NTR} signaling, as the majority of reports describing p75^{NTR} mediated cell death have involved post-mitotic neurons, while studies of p75^{NTR} in proliferative cells have revealed more variable survival outcomes (Skeldal et al. 2011).

5 Regulation of the Cell Cycle

One of the first effects described for selective activation of p75^{NTR} in the absence of Trks was cell cycle arrest in a glioma cell line treated with NGF (Dobrowsky et al. 1994). The effects of p75^{NTR} on cell cycle have since been linked to several receptor-interacting proteins, including SC-1 (Chittka et al. 2004), NRIF (Benzel et al. 2001), and NRAGE (Salehi et al. 2000). Like NRIF, SC-1 is a C2H2 zinc finger-containing protein, and translocation of SC-1 to the nucleus was demonstrated in response to NGF binding to p75^{NTR} in transfected COS cells (Chittka and Chao 1999). Expression of SC-1 in these cells blocked cell proliferation through a mechanism involving repression of cyclin E transcription (Chittka et al. 2004). Chao and colleagues have also demonstrated that expression of p75^{NTR}-ICD inhibited cyclin E mRNA production in HeLa cells, and the endogenous p75^{NTR}-ICD in PC12 cells could be localized to the cyclin E promoter by chromatin immunoprecipitation following NGF treatment (Parkhurst et al. 2010). These results suggest that the ICD of p75^{NTR} translocates to the nucleus along with SC-1 to modulate genes involved in the cell cycle. Whether SC-1 has a role in the receptor's apoptotic signal remains an open question.

NRIF (Benzel et al. 2001) and NRAGE (Salehi et al. 2000) have also been implicated in the regulation of cell cycle based on the observation that ectopic expression of either factor in HEK 293 cells induced cell cycle arrest. It is interesting that these two proteins inhibit proliferation in immortalized fibroblasts but cause apoptosis when expressed in neurons, Schwann cells (Linggi et al. 2005), or neural precursors (Salehi et al. 2000, 2002). Perhaps the differential effects relate to the presence of the tumor suppressor p53, which is mutated or inhibited in many immortalized cells, including HEK 293s. Cell death induced by ectopic expression of NRIF is dependent on p53 (Linggi et al. 2005) and over-expression of NRAGE in breast cancer cells upregulated p53 (Du et al. 2009). One interpretation of these findings is that in response to p75^{NTR} activation, NRIF and NRAGE may alter expression of key cell cycle genes, thereby triggering an increase in p53 expression, ultimately resulting in cell death, but in cells with p53 mutated or blocked, the effects are limited to inhibiting proliferation.

6 Regulation of Synaptic Plasticity

In addition to regulating neuronal survival, the balance of signaling between the Trks and p75^{NTR} plays an important role in modulating synaptic efficacy. BDNF, acting through TrkB, is essential for the strengthening of synaptic function, referred to as long-term potentiation (LTP) (Figurov et al. 1996; Kang et al. 1997; Korte et al. 1998; Patterson et al. 2001). In contrast, p75^{NTR} has a critical role in the weakening of synaptic connections, a process called long-term depression (LTD). Analysis of p75^{NTR} knockout mice revealed a deficiency in the ability to induce LTD in hippocampal slices, although LTP was not impaired (Rosch et al. 2005; Woo et al. 2005). The mechanism by which p75^{NTR} regulates synaptic function has yet to be fully resolved; however, glutamate receptor expression appears to be altered in the null animals. Lu and colleagues found reduced levels of the NMDA receptor subunit NR2B in p75^{NTR}-/- hippocampal lysates, and NMDA currents measured in slices from the null mice were not affected by the NR2B antagonist ifenprodil, while in wild types they were blocked (Woo et al. 2005). In addition, Korte's group found impaired AMPA receptor function and decreased levels of the AMPA receptor subunits GluR2 and 3 in the hippocampus of p75^{NTR}-/- mice (Rosch et al. 2005). Glutamatergic signaling is essential for the development of LTD, and both NMDA and AMPA receptors have been implicated as contributing to the synaptic changes, depending on the mechanism of induction (Hunt and Castillo 2012). Therefore, the altered expression of these receptors in p75^{NTR}-/- mice likely contributes to their inability to induce LTD. Furthermore, these changes in glutamatergic signaling may underlie the impairments in learning, inhibitory avoidance, and habituation that have been observed in the p75^{NTR} null mice (Peterson et al. 1999).

p75^{NTR} may also regulate synaptic plasticity through modulating dendritic structure. No gross morphological changes in the structure of the hippocampus have been detected in the p75^{NTR}-/- animals; however, careful measurements of dendritic spines revealed an increase in their density and complexity (Zagrebelsky et al. 2005). Moreover, immunoelectron microscopy revealed that p75^{NTR} is expressed on dendritic shafts and spines in the hippocampus (Woo et al. 2005). These results suggest that the receptor may be important for normal pruning and refining of these postsynaptic structures. Correspondingly, overexpression of p75^{NTR} in hippocampal slices resulted in reduced spine density and complexity. Decreases in spine size and number are associated with LTD (Okamoto et al. 2004; Zhou et al. 2004) and increases in size and number correlate with LTP (Desmond and Levy 1986; Fifkova and Anderson 1981; Van Harrevelde and Fifkova 1975); therefore, it is interesting to speculate that during LTD induction, p75^{NTR} may cause retraction of dendritic spines. As described below, the receptor can activate the Rho family of GTPases, which regulate the actin-cytoskeleton (Yamashita et al. 1999). Thus, local dendritic activation of the receptor may result in collapse or shrinkage of a spine through activation of Rho or inhibition of Rac, ultimately resulting in reduced synaptic efficacy. However, how morphological changes in dendritic spines affect synaptic plasticity remains an open question.

The ligand responsible for activating p75^{NTR} during LTD has been suggested to be proBDNF; however, this remains somewhat controversial. Pang et al. (2004) reported that proBDNF cleavage by the extracellular protease plasmin to produce mature BDNF was required for the induction of LTP. Previous studies demonstrated that tissue plasminogen activator (tPA), which activates plasmin from plasminogen, is secreted from axon terminals (Krystosek and Seeds 1981) and is required for LTP (Baranes et al. 1998; Frey et al. 1996; Huang et al. 1996), but what role the protease played in the process was not clear. The finding that tPA targets proBDNF provided a relevant substrate. Moreover, the fact that tPA/plasmin is acting extracellularly suggested that proBDNF is released into the synaptic cleft, where it could activate p75^{NTR} if it's not cleaved. Indeed, Woo et al. (2005) found that perfusion of hippocampal slices with proBDNF enhanced LTD, but slices from p75^{NTR}−/− mice were insensitive. More recently, this group also demonstrated that synaptic competition is regulated by a balance between pro- and mature-BDNF. Using cocultures of *Xenopus* myocytes and motor neurons, they demonstrated that when two neurons innervate one myocyte, the active terminal promotes cleavage of proBDNF to mature BDNF, which stabilizes the synapse through activation of TrkB. In contrast, at the less active terminal proBDNF is not cleaved and causes axon retraction through binding to p75^{NTR} (Je et al. 2012). Such activity-dependent synaptic competition is a common principle in many areas of the developing nervous system, although the underlying molecular mechanisms are not known. The finding that pro-/mature BDNF levels can be dynamically regulated to act as the punishment and reward signal provides some important clues as to the mechanisms that could underlie this competition. Nevertheless, despite these elegant studies, results from the Barde group cast doubt on a role for proBDNF in synaptic plasticity. They reported that proBDNF was not secreted by hippocampal neurons in culture and that the induction of LTD was unaffected by conditional deletion of BDNF (both the pro- and mature-form of the neurotrophin) in neurons (Matsumoto et al. 2008). Clearly, additional studies are needed to fully understand the role of p75^{NTR} in synaptic plasticity.

7 Promotion of Peripheral Myelination

All cells of the neural crest lineage express p75^{NTR} during development, including those that become Schwann cells in the sciatic nerve. Schwann cells continue to express p75^{NTR} until myelination, at which time it is downregulated. This reduction in its expression was attributed to axonal signals, whose identity still remains unknown (Lemke and Chao 1988). Due to its regulated expression in the sciatic nerve, questions have persisted as to whether p75^{NTR} plays a role in some aspects of the myelination process by Schwann cells. Anton et al. (1994) first reported that p75^{NTR} is involved in migration of Schwann cells: Schwann cell migration out of DRGs onto sciatic nerve explants was enhanced by NGF treatment, but REX, a p75^{NTR} antibody, blocked its effect. The effect was, however, observed only with explants from denervated sciatic nerves and not with intact sciatic nerves,

suggesting that p75^{NTR} may play a role only after injury. When Schwann cell migration was examined during embryogenesis in trigeminal ganglia, however, p75^{NTR} did have an effect: the extent of Schwann cell migration to the axon tips was significantly reduced in p75^{NTR} knockout mice compared to littermates (Bentley and Lee 2000). Since trigeminal ganglion neurons also express p75^{NTR}, Bentley and Lee examined Schwann cell migration *in vitro* using sciatic nerve explants. The extent of Schwann cell migration was reduced in cultures from p75^{NTR} knockout mice compared to that in the wild-type counterparts, although NGF addition had no effect. These results suggest that p75^{NTR} expression specifically in Schwann cells regulates their migration both during development and after injury.

Schwann cells have to migrate along the axon before they form myelin sheaths around axons. The fact that p75^{NTR} plays a role in Schwann cell migration suggests that the receptor could regulate the myelination process. This question was first addressed by Eric Shooter's group in 2002. Cosgaya et al. (2002) reported that blocking p75^{NTR} signaling resulted in inhibition of myelin formation both in DRG-Schwann cell cocultures as well as in developing sciatic nerves. In particular, EM analysis of sciatic nerves that were injected with REX antibody at P0, before the onset of myelination, revealed that the myelin sheath became thinner 4 days later, without affecting the number of myelinated axons, suggesting that p75^{NTR} promotes Schwann cell myelination *in vivo*. As for the ligand that activates p75^{NTR} in Schwann cells, BDNF, which the group had previously reported to promote Schwann cell myelination (Chan et al. 2001), was shown to be responsible. Attributing the effect of BDNF to p75^{NTR} in Schwann cells was indirect, however, because p75^{NTR} is expressed both in axons and Schwann cells at the neonate stage in the sciatic nerve. For instance, Cosgaya et al. (2002) illustrated that while the full-length TrkB levels were barely detectable, p75^{NTR} levels were very high in Schwann cells. While modulating BDNF signaling by either injecting excess BDNF or scavenging the neurotrophin with TrkB-Fc affected myelination in wild type mice, no effect on myelination was observed in p75^{NTR} knockout mice. Since p75^{NTR} is the only receptor in Schwann cells that could elicit downstream signaling to promote myelination, the lack of effect was attributed to BDNF acting through p75^{NTR} in Schwann cells.

The idea that BDNF promotes myelination through p75^{NTR} in Schwann cells was challenged by the Murray group (Xiao et al. 2009). In their study, a DRG-Schwann cell coculture system was utilized, wherein p75^{NTR} expression was regulated both in DRG and Schwann cells independently. To delete p75^{NTR} from DRG neurons, DRG neurons were isolated from p75^{NTR} knockout mice, maintained in NGF, and subsequently seeded with rat Schwann cells. To knock-down p75^{NTR} in Schwann cells, they transduced rat Schwann cells with p75^{NTR}-shRNA prior to seeding them onto NGF-dependent DRG neurons. Surprisingly, adding BDNF to the NGF-dependent DRG neurons from p75^{NTR} knockout mice failed to promote myelination, while in wild-type counterparts BDNF increased myelin protein levels by 1.5–2-fold. When p75^{NTR} expression was knocked down in Schwann cells before they were seeded onto NGF-dependent DRG neurons, however, there was little effect, regardless of whether BDNF was present or not.

This study thus demonstrated that it is p75^{NTR} in DRG neurons and not in Schwann cells that influences Schwann cell myelination.

Tep et al., on the other hand, reported opposite results by using the same DRG-Schwann cell coculture system, wherein p75^{NTR} expression was knocked down only in Schwann cells before they were seeded onto NGF-dependent DRG neurons (Tep et al. 2012): the number of myelinated nerves were reduced by ≥ 50 %. As for the reason why the two studies differ, Tep et al. stated that while Xiao et al. isolated DRG neurons at P2 and cultured them in the presence of NGF for 2–3 weeks, Tep et al. cultured DRG neurons from embryonic day 15 animals and cultured them for a week before Schwann cells were seeded. It is not clear whether the age of DRG neurons subjected to myelination in culture is responsible for the opposite outcome, since the studies were conducted independently. Since p75^{NTR} was shown to affect the extent of remyelination after injury (Song et al. 2006), it is possible that under injury conditions in the adult PNS, p75^{NTR} expressed in DRG neurons controls aspects of remyelination. What now awaits is the analysis of conditional p75^{NTR} knockout mice in Schwann cells and neurons, individually, to resolve the issue.

Regardless of where p75^{NTR} exerts its effect, the question remained as to what signaling pathway p75^{NTR} employs to promote myelination in Schwann cells. p75^{NTR} was shown to regulate small GTPases that are critical for cytoskeletal reorganization, such as RhoA (Domeniconi et al. 2005; Harrington et al. 2008; Passino et al. 2007; Wang et al. 2002; Yamashita et al. 1999, 2002; Yamashita and Tohyama 2003; Yamauchi et al. 2004) and Rac1 (Deinhardt et al. 2011; Harrington et al. 2002; Tep et al. 2012) in a variety of tissues both in and outside of the nervous system. During Schwann cell myelination, p75^{NTR}-mediated Rac1 activation appears to be important, as partitioning-defective 3 (Par3) was shown to bind p75^{NTR} through its PDZ-binding tri-peptide motifs in Schwann cells (Chan et al. 2006). Par3 is a member of the polarization complex that includes Par6 and protein kinase C, regulating activation of Rac1 and Cdc42 (Goldstein and Macara 2007). In Schwann cells, Par3 was colocalized with p75^{NTR} at axon–glial interfaces in response to BDNF (Chan et al. 2006) and was shown to mediate Rac1 activation by BDNF (Tep et al. 2012). Rac1 activation was also significantly reduced in neonate sciatic nerves from p75^{NTR} knockout mice, supporting the notion that p75^{NTR} activates Rac1 as it forms a complex with Par3 at the axon–glial interface (Tep et al. 2012). Thus, Rac1 activation appears to be a pathway induced by p75^{NTR} that regulates Schwann cell myelination.

8 Regulation of Neurite Growth and Axonal Degeneration

Although p75^{NTR} was shown to activate members of the Rac/Rho family in Schwann cells, thereby affecting myelination, the role of p75^{NTR}-dependent RhoA activation has been best studied in the context of neurite outgrowth. The regulation of RhoA by p75^{NTR} was first demonstrated by Yamashita et al, who identified RhoA as a receptor-interacting factor in a yeast two-hybrid screen. They

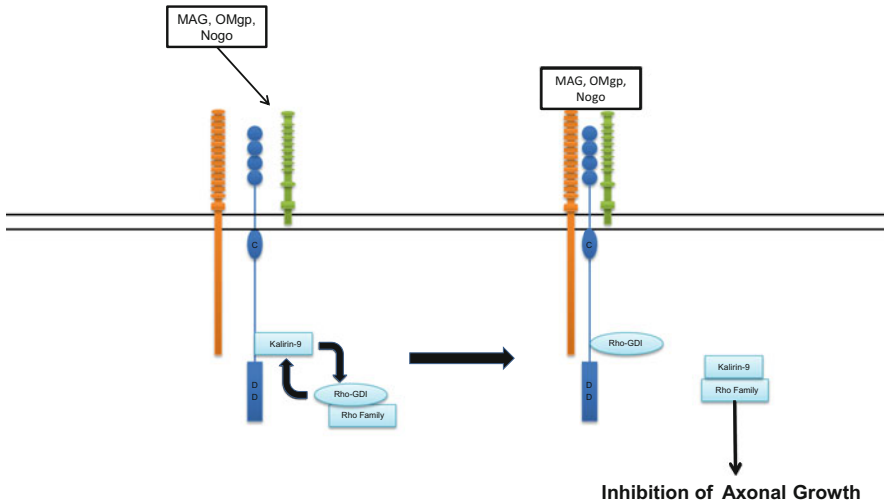


Fig. 3 Regulation of axonal growth by p75^{NTR}. A complex comprised of p75^{NTR}, NogoR, and Lingo-1 is formed in response to myelin-derived inhibitors such as MAG, OMgp, and Nogo. In response to stimulation by these ligands, Rho-GDI is recruited to the intracellular domain of p75^{NTR}. Concurrently, association of Kalirin-9 with the p75^{NTR} intracellular domain is decreased, thus resulting in enhanced activation of Rho family members by Kalirin-9 and inhibition of axonal growth

found that unliganded p75^{NTR} promoted RhoA activation and neurotrophin binding prevented this activation, thereby promoting neurite outgrowth (Yamashita et al. 1999). Soon after this finding, p75^{NTR} was shown to regulate RhoA in response to a group of myelin proteins, including myelin associated glycoprotein (MAG), Oligodendrocyte myelin glycoprotein (OMgp), and Nogo (Wang et al. 2002; Wong et al. 2002; Yamashita et al. 2002). These myelin proteins are expressed by oligodendrocytes and are known to inhibit neurite outgrowth, which has made them a major focus for studies aimed at axonal regeneration after spinal cord injury (Akbik et al. 2012). All three of these inhibitors bind to a glycosylphosphatidylinositol (gpi)-linked receptor, the Nogo receptor (NgR). The NgR lacks an intracellular domain, but it can associate with p75^{NTR} and another transmembrane protein, Lingo-1, to regulate RhoA (Mi et al. 2004) (Fig. 3).

The ability of p75^{NTR} to regulate Rho family members depends on a number of intracellular interacting factors. The activation of RhoA by myelin proteins occurs through the recruitment of the Rho inhibitor RhoGDI to p75^{NTR}, thereby releasing RhoA (Yamashita and Tohyama 2003). RhoGDI competes with the guanine nucleotide exchange factor (GEF), Kalirin 9, for p75^{NTR} binding (Harrington et al. 2008), such that upon receptor activation, Kalirin 9 is released, allowing binding of RhoGDI. Once RhoA is freed from RhoGDI, it is then activated by Kalirin 9 (Fig. 3). It should be added that RhoA activation by MAG in cerebellar granule neurons required cleavage of p75^{NTR} (Domeniconi et al. 2005). It is not known

how receptor cleavage facilitates the stimulation of Rho or whether other myelin inhibitory molecules that bind the NgR-p75^{NTR}-Lingo-1 complex also induce p75^{NTR} cleavage. In addition to regulating RhoA, Hempstead's group recently demonstrated that proneurotrophin binding to p75^{NTR} caused a decrease in Rac activity. Rac typically counterbalances Rho, such that decreasing Rac has a similar effect to activating Rho. The reduction in Rac activation after proneurotrophin binding was linked to dissociation of the Rac GEF Trio from a complex of p75^{NTR} with another Sortilin family member, SorCS2, suggesting that the release of Trio reduces basal Rac activity (Deinhardt et al. 2011). Hence, there may be multiple mechanisms by which p75^{NTR} regulates members of the Rho family, depending on the ligand and the co-receptors present.

As might be expected, evidence suggests that p75^{NTR} can regulate axonal growth and retraction at the tip of the growing axon in the growth cone. Treatment of *Xenopus* spinal neurons with MAG caused p75^{NTR}-dependent repulsion of the growth cone (Wong et al. 2002). Similarly, proneurotrophins were recently reported to induce growth cone collapse in cortical neurons (Sun et al. 2012) and in hippocampal neurons (Deinhardt et al. 2011). In contrast to the inhibitory effects of proneurotrophins and myelin proteins on growth cones, mature neurotrophin binding to p75^{NTR} increased filopodial length in the growth cone of subplate neurons (McQuillen et al. 2002), as well as in retinal ganglion and dorsal root ganglion cells, where it was demonstrated that the receptor promoted filopodia growth through inhibition of RhoA (Gehler et al. 2004).

The recognition of p75^{NTR} as a signal transducer for MAG, OMgp and Nogo created a considerable amount of interest in targeting the receptor as a means of promoting regeneration following CNS injury; however, the regulation of axonal regeneration is very complex, and the role of p75^{NTR} is not well understood. Despite the fact that p75^{NTR} null neurons failed to activate RhoA and respond to myelin inhibitors in culture (Wang et al. 2002; Yamashita et al. 2002; Yamashita and Tohyama 2003; Zheng et al. 2005) and after spinal cord injury (Dubreuil et al. 2003), there was no effect on regeneration of corticospinal tract after spinal cord injury in the p75^{NTR} knockout mice (Song et al. 2004; Zheng et al. 2005). The reason why p75^{NTR} does not appear to regulate regeneration after spinal cord injury is not clear, but this may be due to the fact that p75^{NTR} expression is upregulated in oligodendrocytes as well as denervated axons following spinal cord injury (Beattie et al. 2002; Tep et al. 2013), potentially confounding its effect on regeneration. It is also possible that the NgR can partner with other receptors in addition to p75^{NTR}; for example, another member of the TNF receptor superfamily, Troy, was shown to function as a signal transducer for the NgR (Park et al. 2005; Shao et al. 2005). In addition, another receptor, PirB, was identified that also binds myelin inhibitory molecules (Atwal et al. 2008), and Fujita et al. (2011b) reported that myelin inhibitory molecules induced interaction between the PirB and p75^{NTR} in cerebellar granule neurons. In that study, the authors demonstrated that optic nerve regeneration was significantly improved after injury in p75^{NTR} knockout mice, suggesting that p75^{NTR} does play a role in regeneration at least in the optic system, which is less complex than spinal cord injury in terms of affected cell types and the cellular

responses to injury. The question remains, however, whether this effect is mediated through the interaction of p75^{NTR} with PirB, since PirB knockout mice had no effect on optic nerve regeneration (Fujita et al. 2011a). The ultimate outcome of whether p75^{NTR} promotes axon regrowth or retraction after an injury may depend, in part, on the type of injury and the different ligands produced that bind to p75^{NTR} and its signaling partners: p75^{NTR} interacts with Lingo-1 and NgR or PirB in response to myelin inhibitory molecules (Mi et al. 2004; Wang et al. 2002), Sortilin in response to proNGF (Nykjaer et al. 2004), EphA in response to Ephrin-As (Lim et al. 2008), in addition to TrkA, TrkB, and TrkC in response to NGF, BDNF, and NT3.

Does myelin play a similarly inhibitory role in intact brains in the absence of any injury? Freda Miller's group addressed this question by examining axonal sprouting of p75^{NTR}-expressing cholinergic septal neurons into the corpus callosum in the adult brain (Park et al. 2010). Surprisingly, there were many more cholinergic fibers entering the corpus callosum in p75^{NTR} knockout than in the wild type mice, suggesting that p75^{NTR} normally prevents misrouting of these fibers in vivo. P75^{NTR} appeared to have induced degeneration of the fibers that entered the white matter tract, since cholinergic axons degenerated when plated on myelin. Similar axonal breakdown was observed in cultured sympathetic neurons when BDNF was applied selectively to axons while the soma was maintained in NGF (Singh et al. 2008). The axonal degeneration induced by p75^{NTR} in vitro and in vivo extended beyond the collapse of growth cones, as there was overt breakdown of axonal fibers; however, there was no apoptosis of the neurons. The signaling mechanisms involved in the degeneration appear to involve both Rho and caspase-6, as activation of both enzymes was detected in axons following stimulation of p75^{NTR}, and inhibition of either Rho or caspase-6 blocked the axonal breakdown (Park et al. 2010). Local activation of caspases in distal axons during axonal degeneration has been increasingly reported; for example, degeneration due to withdrawal of NGF selectively from distal axons of DRG neurons grown in compartmentalized chambers was dependent on both caspase-3 and -6 (Simon et al. 2012). These caspases were not activated in the soma; thus the neurons did not undergo apoptosis. How such degenerative/apoptotic signaling is restricted to the axon is not known. The caspase inhibitor XIAP is also upregulated in mature sympathetic neurons, making them resistant to injection of cytochrome c (Potts et al. 2003). Thus, NGF acting at the soma may prevent the spread of caspase activation through upregulation of such inhibitors. Additional studies are needed to understand the spatial control of such signaling pathways.

Conclusion

Since the initial cloning of p75^{NTR}, the field has undergone a remarkable transformation in its understanding of this puzzling receptor. Initially, p75^{NTR} was viewed as a non-signaling, auxiliary binding component for members of the Trk family that simply enabled neurotrophins to bind with high affinity to the Trks. Now, p75^{NTR} is considered a key signaling component for multiple ligands through the formation of a variety of receptor complexes that regulate a wide

array of biological responses, from cell survival to neurite growth, axon degeneration, or myelin formation. Many questions remain to be answered regarding the mechanisms utilized by p75^{NTR} to mediate its responses, such as how the receptor can selectively activate one pathway over another, some of which can be in direct opposition (e.g., survival vs. apoptosis). The genes regulated by receptor proteolysis and the ICD-binding proteins that translocate to the nucleus are also yet to be identified. What role Sortilin and other Vps10p family members play in p75^{NTR} signaling beyond binding to the pro-domain of proneurotrophins remains to be determined. Even the molecular nature of the high affinity complex between p75^{NTR} and the Trks is still poorly understood. Beyond these questions regarding receptor signaling, it will be equally important to explore the role of the receptor in the many injuries and diseases where it is upregulated. Given that p75^{NTR} has the potential to signal both survival and degeneration/apoptosis, it is enticing to consider the possibility of developing novel therapeutics that switch the receptor's degeneration signal to one promoting survival. Certainly, further understanding of how the receptor functions will provide additional insights for developing novel therapeutics for many neuropathologies.

In this chapter, we attempted to cover the many aspects of signaling through the p75^{NTR} receptor and the biological outcomes; nevertheless, we could not fully encompass the many contributions made by the large number of researchers who have studied this complex system. We apologize for those omissions.

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