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Understanding Proneurotrophin Actions: Recent Advances and Challenges

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Abstract

Neurotrophins are initially synthesized as larger precursors (proneurotrophins), which undergo proteolytic cleavage to yield mature forms. Although the functions of the mature neurotrophins have been well established during neural development and in the adult nervous system, roles for the proneurotrophins in developmental and injury-induced cell death, as well as in synaptic plasticity, have only recently been appreciated. Interestingly, both mature neurotrophins and proneurotrophins utilize dual-receptor complexes to mediate their actions. The mature neurotrophin coreceptors consist of the Trk receptor tyrosine kinases and $p75^{NTR}$, wherein Trk transduces survival and differentiative signaling, and $p75^{NTR}$ modulates the affinity and selectivity of Trk activation. On the other hand, proneurotrophins engage $p75^{NTR}$ and the structurally distinct coreceptor sortilin, to initiate $p75^{NTR}$-dependent signal transduction cascade. Although the specificity of mature neurotrophins vs. proneurotrophins actions is due in part to the formation of distinct coreceptor complexes, a number of recent studies highlight how different $p75^{NTR}$-mediated cellular actions are modulated. Here, we review emerging evidence for a novel transmembrane mechanism for ligand-specific $p75^{NTR}$ activation and several mechanisms by which $p75^{NTR}$-dependent apoptotic and nonapoptotic responses can be selective activated.

Keywords

ProNGF; ProBDNF; neurodegenerative diseases; neural development; neuronal apoptosis

INTRODUCTION

The neurotrophins are a four-member peptide growth factor family that includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4), which exhibit well-described actions in the nervous system (Snider, 1994; Lewin and Barde, 1996). Classically defined as target-derived survival factors for developing neuronal populations, roles of the neurotrophins now include growth cone guidance, synaptic modulation, injury protection, and influence on memory and behavior (Glebova and Ginty, 2005; Lu et al., 2005; Zweifel et al., 2005; Schecterson and Bothwell, 2008; Lessmann and Brigadski, 2009). Indeed one of the most intriguing aspects of neurotrophin physiology is that only four neurotrophin genes are found in mammals and yet they appear to modulate a diverse repertoire of critical functions both in and outside of the nervous system.

All neurotrophins, translated from single coding exons, are synthesized as larger precursors (proneurotrophins) of ~30–34 kDa that rapidly associate as noncovalent homodimers (Suter

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et al., 1991; Kolbeck et al., 1994; Heymach and Shooter, 1995; Ibanez, 2002). Proneurotrophins can be cleaved by furin and proconvertases in the ER and Golgi to produce C-terminal mature neurotrophins (~13 kDa). The prodomains of neurotrophins have been demonstrated to play a critical role in ensuring proper protein folding and dimerization of the nascent molecules(Suter et al., 1991; Heymach and Shooter, 1995), while the mature domains are traditionally viewed as the secreted ligands responsible for neurotrophins' diverse biological effects. At the molecular level, mature neurotrophins interact with two distinct receptors: $p75^{NTR}$ and Trk (Kaplan and Miller, 2000; Huang and Reichardt, 2003; Segal, 2003; Teng and Hempstead, 2004; Reichardt, 2006). Indeed most neurotrophin actions on neuronal differentiation and survival can be ascribed to this coreceptor system; with Trk receptor tyrosine kinase being the signaling entity and $p75^{NTR}$ serving to restrict and augment ligand recognition specificity.

Unexpectedly, NGF or BDNF activation of $p75^{NTR}$ has been found to induce apoptosis when Trk signaling is absent (Casaccia-Bonnefil et al., 1996; Frade et al., 1996; Bamji et al., 1998). Despite these elegant studies, the ability of neurotrophins to act both as pro-survival and pro-death ligands was perplexing; high concentrations of ligands were required to induce modest levels of cell death in *in vitro* paradigms (see Casaccia-Bonnefil et al., 1996; Friedman, 2000 for examples), leading to the hypothesis of additional $p75^{NTR}$ ligands that selectively trigger apoptosis. The findings that proNGF and proBDNF selectively bind $p75^{NTR}$ but not Trk receptors to elicit cell killing provided a mechanism by which different forms of neurotrophins can initiate diverse actions (Lee et al., 2001; Ibanez, 2002; Teng et al., 2005). Interestingly a third structurally unrelated receptor, sortilin, specifically recognizes the pro-domains of proNGF and proBDNF, and forms a high affinity coreceptor complex with $p75^{NTR}$ to convey proneurotrophin-induced apoptotic signaling (Nykjaer et al., 2004; Teng et al., 2005; Jansen et al., 2007; Willnow et al., 2008). Thus, the opposing effects of neurotrophins on neuronal survival/death depend on whether proneurotrophins or mature neurotrophins are released, and bind to Trk receptors or $p75^{NTR}$:sortilin receptor complex to elicit distinct cellular responses (see Fig. 1).

ROLES OF PRONEUROTROPHINS IN NERVOUS SYSTEM DEVELOPMENT AND FOLLOWING INJURY

Following the initial description of proNGF induced $p75^{NTR}$-mediated apoptosis *in vitro*, multiple *in vivo* models have validated the role of proNGF during periods of naturally occurring developmental cell death and in injury and disease progression (Hempstead, 2009). Building upon the observation that proNGF binds to sortilin in biochemical analysis (Nykjaer et al., 2004), as well as $p75^{NTR}$ and sortilin colocalization in the developing retina by immuno-histological study (Nakamura et al., 2007), genetic ablation of sortilin was found to result in a significant reduction of retinal ganglion cell apoptosis in embryos (Jansen et al., 2007), comparable to that observed in $p75^{NTR}$- and NGF-null animals (Frade and Barde, 1998, 1999). Somewhat surprisingly, no reduction in sympathetic neuron death in sortilin-deficient mice was observed at early postnatal time points when $p75^{NTR}$ has been shown to be critical for sympathetic neuron elimination (Bamji et al., 1998). Instead, an increase in sympathetic neuron survival in aged (>1-year-old) animals was demonstrated (Jansen et al., 2007), suggesting a causal role for sortilin, and potentially proneurotrophins, in neuronal loss with aging (Bierl and Isaacson, 2007). These findings are intriguing because proNGF levels are elevated in Alzheimer's Disease patients (Fahnestock et al., 2001; Peng et al., 2004; Pedraza et al., 2005) and more recently, implicated in spongiform encephalomyelopathy (Stoica et al., 2008) and Parkinson's disease progression (Chen et al., 2008). Better understanding of a mechanistic role for proNGF in slow onset neurodegenerative diseases awaits further experimental validation and identification of pharmacological agents that selectively block proNGF actions. Both $p75^{NTR}$ and proNGF

have been clearly implicated in acute neural tissue damage resulting from spinal cord injury (Beattie et al., 2002; Harrington et al., 2004) and seizure models (Volosin et al., 2006, 2008). Significantly, infusion of anti-proNGF antibody improves neuronal survival in these studies. Future studies will be required to determine whether blockade of proNGF:sortilin interactions might be a means to prevent age-associated neuronal loss, as has been proposed for proNGF:p75^{NTR} antagonists (Massa et al., 2006; Hempstead, 2009).

Mature BDNF is well documented to modulate synaptic efficacy in the hippocampus, and neurotransmitter release at the neuromuscular junction (Nagappan and Lu, 2005; Cohen and Greenberg, 2008; Lu et al., 2009; Waterhouse and Xu, 2009). Like NGF, the unprocessed pro-form of BDNF was originally thought to be a precursor with no biological function of its own. However, multiple reports suggest that both proNGF and proBDNF can escape intracellular processing and be secreted from neurons (Lee et al., 2001; Pang et al., 2004; Woo et al., 2005; Bruno and Cuello, 2006; Yang et al., 2009b), although the efficiency of intracellular processing remains a point of controversy (Matsumoto et al., 2008; Yang et al., 2009b). Following secretion, cleavage of proNGF or proBDNF by enzymes in the extracellular milieu, such as matrix metalloproteases or plasmin, can occur, allowing for highly localized activation of receptors on adjacent cells (Pang et al., 2004; Bruno and Cuello, 2006). In contrast to proNGF that induces neuronal apoptosis upon injury, a primary role of proBDNF may be to modulate synaptic efficacy during development (Woo et al., 2005; Yang et al., 2009a). Thus, extracellular conversion of proBDNF to mature BDNF by the tPA/plasmin protease cascade promotes TrkB-dependent late phase-long term potentiation (L-LTP) (Pang et al., 2004). In contrast, application of proBDNF to p75^{NTR}-expressing hippocampal slices enhanced long-term depression (LTD) (Woo et al., 2005), suggesting that proBDNF can also act as an endogenous ligand to directly regulate LTD. Since p75^{NTR} expression is developmentally regulated, with highest expression in early postnatal stages that decreases at later times (Rosch et al., 2005; Woo et al., 2005; Yang et al., 2009b), these studies suggest that different forms of synaptic plasticity may be modulated by BDNF isoforms; with proBDNF enhancing LTD in the p75^{NTR}-expressing neonatal and juvenile hippocampus, whereas intracellular or extracellular conversion to mature BDNF may enhance hippocampal L-LTP in the adult (Lu et al., 2005). More recently, a cleavage-resistant BDNF (CR-proBDNF), encoded by two rare single nucleotide polymorphisms in humans, has been shown to promote cerebellar granule neuron apoptosis and to reduce dendritic spine density in hippocampal neurons *in vitro* (Koshimizu et al., 2009), suggesting that even among CNS neuron classes, proneurotrophins can elicit cell type-specific responses.

At present, it is unclear how p75^{NTR} can distinguish between proNGF and proBDNF to execute downstream signaling events unique to a given proneurotrophin. In addition, although both secreted proNGF and proBDNF can be internalized by the glia and rereleased as mature neurotrophins (Althaus and Kloppner, 2006; Bergami et al., 2008; Boutilier et al., 2008), the physiological significance of this novel neuron-glia interplay is currently unknown.

RECENT ADVANCES IN UNDERSTANDING p75^{NTR} ACTIVATION

Historically, p75^{NTR} was the first neurotrophin receptor identified (Johnson et al., 1986; Radeke et al., 1987); however, its biological actions and signaling mechanisms remain incompletely defined due in part to the ability of p75^{NTR} to act as a coreceptor for diverse ligands that exhibit distinct biological activities (Dechant and Barde, 2002; Hempstead, 2002; Roux and Barker, 2002; Chao, 2003; Barker, 2004; Gentry et al., 2004; Teng and Hempstead, 2004). p75^{NTR} can interact with Trk receptor kinases to enhance the binding specificity and affinity of mature neurotrophins (Esposito et al., 2001), with NogoR and

Lingo-1 to mediate the axonal growth inhibitory effects of CNS myelin (Wang et al., 2002; Mi et al., 2004), with Neuropilin-1 to modulate Semaphorin3A-mediated axonal growth inhibition (Ben-Zvi et al., 2007) and with Ephrin-A for reverse signaling upon Eph receptor activation (Lim et al., 2008). In addition to being the "bridesmaid" to these receptors, $p75^{NTR}$ also acts to trigger apoptosis during development and following injury (Bamji et al., 1998; Majdan et al., 2001; Beattie et al., 2002; Harrington et al., 2004; Pedraza et al., 2005; Volosin et al., 2006, 2008; Jansen et al., 2007), to promote myelination of DRG axons (Chan et al., 2006; Xiao et al., 2009), to induce axonal retraction (Singh et al., 2008) and to modulate synaptic plasticity (Woo et al., 2005; Yang et al., 2009a). How does $p75^{NTR}$ mediate these distinct biological outcomes? A unifying theory has yet to emerge; however, a number of significant advances, summarized below, have begun to shed light on the mechanisms of $p75^{NTR}$ activation.

Structural Insights

Structurally, $p75^{NTR}$ belongs to the tumor necrosis factor receptor (TNFR) superfamily and like other members of this family, does not possess intrinsic catalytic activity (Hempstead, 2002; Bandtlow and Dechant, 2004; Gentry et al., 2004; Hasegawa et al., 2004). Thus, upon activation, $p75^{NTR}$ relies on the recruitment of adaptor protein complexes for downstream actions. However, $p75^{NTR}$ differs from other TNF receptor members in two aspects, the most notable of which is that $p75^{NTR}$ binds dimeric neurotrophins whereas receptors for TNF and Fas-L exist as preformed homotrimers that bind cognate trimeric ligands. Second, the globular intracellular "death domain" of $p75^{NTR}$ does not self-associate in solution (Liepinsh et al., 1997), consistent with the hypothesis that $p75^{NTR}$ is distinct from other TNFRs in its recruitment of downstream effector molecules not shared by the other family members (Schutze et al., 2008; Guicciardi and Gores, 2009).

Although $p75^{NTR}$ can bind to all four neurotrophins, both kinetic and mutagenesis studies have demonstrated that NGF and NT-3 interact with $p75^{NTR}$ distinctively (Rodriguez-Tebar et al., 1992; Urfer et al., 1994; Ryden et al., 1995). To date, the cocrystal structures for $p75^{NTR}$:NGF and $p75^{NTR}$:NT-3 have been solved (He and Garcia, 2004; Gong et al., 2008). Surprisingly while the former represents a single $p75^{NTR}$ in complex with dimeric NGF (He and Garcia, 2004), $p75^{NTR}$ binds to NT-3 in a 2:2 stoichiometry (Gong et al., 2008). Biochemical analysis to resolve this discrepancy has suggested that the glycosylation state of $p75^{NTR}$ can influence the stoichiometry of $p75^{NTR}$:neurotrophin complex (Gong et al., 2008); however, a direct structural comparison of glycosylated vs. nonglycosylated $p75^{NTR}$ in complex with NGF is not yet available for evaluation. The co-crystal structure of NGF with TrkA (Wehrman et al., 2007) reveals a 2:2 stoichiometry; however, the NGF dimer is oriented in an opposite direction as compared to the NGF dimer bound to $p75^{NTR}$. Thus while $p75^{NTR}$ enhances the affinity of NGF binding to TrkA (Mahadeo et al., 1994), the mechanism by which this occurs is not apparent from the crystal structure data (Barker, 2007), and may reflect interactions between the transmembrane domains of Trk and $p75^{NTR}$ (Esposito et al., 2001).

In addition to the structural analyses, a recent study highlights the dynamic nature of $p75^{NTR}$ clustering and offers intriguing insights into how $p75^{NTR}$ might be activated upon ligand binding. Vilar et al. (2009) have identified an intermolecular disulfide bond utilizing a conserved cysteine residue (Cys^{257}) in the transmembrane domain of $p75^{NTR}$, as well as additional amino acids ($AxxxG^{266}$) in the transmembrane domain that maintain a proportion of $p75^{NTR}$ as preformed dimers. Mutagenesis of the G^{266} to isoleucine results in monomeric $p75^{NTR}$, while mutation of Cys^{257} to alanine renders $p75^{NTR}$ incapable of neurotrophin signaling without affecting its dimerization status. Thus, the authors propose a "snail-tong" mechanism for $p75^{NTR}$ activation whereby dimeric ligand binding to predimerized $p75^{NTR}$, brings about a Cys^{257}-dependent conformational change in the intracellular regions

(including the death domain) that permits effector molecule recruitment. Interestingly, the $p75^{NTR}$ Cys^{257} mutant is still functional in RhoA activation in response to MAG, suggesting that $p75^{NTR}$ may signal through dimeric or monomeric modes of activation. In addition, the dependence of neurotrophin signaling on Cys^{257} raises the possibility that $p75^{NTR}$ activation can be modulated by "cysteine modifying" cellular redox pathways such as protein S-nitrosylation (Hess et al., 2005; Forrester and Stamler, 2007).

Roles of the Coreceptor Sortilin

Although $p75^{NTR}$ was the first proneurotrophin receptor to be identified (Lee et al., 2001), subsequent studies revealed that proneurotrophins also bind to sortilin via their pro-domains (Nykjaer et al., 2004; Teng et al., 2005). Indeed, interactions of proNGF with a coreceptor complex of $p75^{NTR}$ and sortilin initiate apoptosis in cultured sympathetic neurons and genetic deletion of either sortilin or $p75^{NTR}$, or inclusion of a sortilin antagonist, neurotensin, impairs proNGF-induced apoptosis (Nykjaer et al., 2004).

Sortilin is a member of the Vps10p domain containing family of proteins that includes sorLA and sorCS1-3 (Petersen et al., 1997; Willnow et al., 2008). It is dynamically regulated in the CNS during development, with expression observed in neuronal precursors beginning at E9.5 and high levels in the cortex, hippocampus, and neural retinal at E14.5. Expression persists in these areas in adulthood and is particularly high in the pyramidal cells of the hippocampus (Hermans-Borgmeyer et al., 1999; Sarret et al., 2003).

Recent elucidation of the crystal structure of the sortilin ectodomain in complex with neurotensin provides some insight into its interactions with diverse binding partners. Quistgaard et al. (2009) observed that sortilin is folded into a novel 10 bladed β propeller and identified neurotensin binding in the tunnel formed by the blades. The structure also reveals two cysteine-rich regions (10CC) that interact extensively with the propeller and two protruding hydrophobic loops, providing possible interactions with hydrophobic patches of receptors, ligands, or with membranes.

Although neurotensin blocks proneurotrophin-induced apoptosis (Nykjaer et al., 2004; Teng et al., 2005), competition assays suggest that the binding site for the proneurotrophins may not precisely overlap that of neurotensin (Quistgaard et al., 2009). This is in agreement with the observation that 10,000-fold molar excess of neurotensin is required to effectively inhibit proNGF-induced apoptosis. The authors suggest that the narrow tunnel restricts access to binding sites such that sortilin interaction with one ligand precludes binding of another. Although the resolution of a sortilin crystal improves our understanding of the sortilin structure and possible functional relationships, several questions are unanswered. These include the possibility that ligand binding alters the conformation of the extracellular domain, and to this end, the structure of the proneurotrophins in a complex with sortilin and $p75^{NTR}$ would be highly desirable. In addition, the Quistgaard model needs to be reconciled with the studies published by Westergaard et al. (2004), which demonstrated that the 10CC domain dictates ligand specificity.

NRH2: Modulator of Proneurotrophin Actions

Prior studies have identified a gene structurally related to $p75^{NTR}$ in mammals, named NRH2 (*n*eurotrophin *r*eceptor *h*omolog 2, also termed PLAIDD and NRADD) (Frankowski et al., 2002; Kanning et al., 2003). NRH2 shares sequence homology to $p75^{NTR}$ in the transmembrane and cytoplasmic domains, but contains a unique truncated extracellular domain that does not bind to neurotrophin ligands (Kanning et al., 2003). Although NRH2 lacks a neurotrophin binding domain, it can associate with TrkA receptor and enhances NGF binding to TrkA receptor (Murray et al., 2004). This action is similar to that observed when

p75^{NTR} is coexpressed with TrkA to form a high-affinity NGF binding site (Hempstead et al., 1991), suggesting that NRH2 may function in some regards like p75^{NTR}.

Interestingly, NRH2 is expressed in subpopulations of cells in the developing spinal cord, retina, dorsal root ganglion, or by sympathetic neurons (Kanning et al., 2003; Murray et al., 2004), regions where p75^{NTR} and sortilin are coexpressed, and where proneurotrophin-induced cell death has been reported (Sarret et al., 2003; Nykjaer et al., 2004; Domeniconi et al., 2007; Jansen et al., 2007; Nakamura et al., 2007). Recently a novel mechanism for NRH2 in regulating proneurotrophin-induced neuronal death has been described (Kim and Hempstead, 2009), which is selective for NRH2 and is not mediated by p75^{NTR}. In this study, NRH2 was found to interact with sortilin through its intracellular juxtamembrane region, and specifically retargets sortilin to the cell surface (Kim and Hempstead, 2009).

Unlike the other neurotrophin receptors, p75^{NTR} and Trks, which are highly expressed on the cell membrane, sortilin is predominantly intracellular in location, particularly in the trans-Golgi network, endosomes and lysosomes, and less than 10% of the total sortilin pool is localized on the plasma membrane (Willnow et al., 2008). These observations raised the question of whether a cell intrinsic mechanism regulates sortilin localization to the cell surface and thus controls cellular responsiveness to proneurotrophins. Upon expression of NRH2, sortilin relocalizes to the cell surface, and promotes the formation of a dual receptor complex of p75^{NTR} and sortilin, which renders neurons sensitive to the apoptotic actions of proneurotrophins (Kim and Hempstead, 2009). NRH2 expression is also dynamically regulated during development, with increased expression during periods when proneurotrophin-induced apoptosis is robust. Thus, NRH2 may act as a developmentally regulated component that co-opts sortilin from an intracellular trafficking chaperone to become a part of the death receptor complex. In the future, it will be interesting to determine whether NRH2 is upregulated under pathological conditions, similar to the induced expression of p75^{NTR} and proNGF (Beattie et al., 2002; Harrington et al., 2004; Volosin et al., 2006) and how NRH2 expression is regulated during neural development.

Negative Modulator of Nerve Growth

In a series of elegant analyses, Miller and coworkers have previously demonstrated that excess sympathetic neurons in newborn animals are eliminated by BDNF via a p75^{NTR}-dependent mechanism (Bamji et al., 1998; Majdan et al., 2001). In addition to inducing apoptosis, p75^{NTR} activation by neurotrophins can also inhibit axonal growth and induces dendritic retraction (Yamashita et al., 1999, 2002; Zagrebelsky et al., 2005). In a recent study, activity-dependent synthesis and release of BDNF was found to induce p75^{NTR}-dependent axon pruning that occurs in postnatal life, unless TrkA was concomitantly activated by NGF (Singh and Miller, 2005; Singh et al., 2008). These studies provide a model of how the fidelity of neural circuitry can be established by a coordinated mechanism that involves (i) target-derived neurotrophic support to the winning axons and (ii) active elimination of strayed nascent axons. Although the authors did not distinguish whether the *in vivo* effects on p75^{NTR}-dependent axon pruning were due to secreted mature BDNF or proBDNF, the possible role for proBDNF as the p75^{NTR} ligand that causes axonal retraction was investigated in another recent study. Using the neuromuscular synapse to probe proBDNF actions and function blocking antibody against proBDNF, the work identified target-derived proBDNF as a critical ligand to induce presynaptic terminal retraction (Yang et al., 2009a).

Since mature BDNF does not bind sortilin (Teng et al., 2005) and high concentrations of BDNF are required to observe axonal degeneration *in vitro* (Singh et al., 2008), it is unclear how mature BDNF triggers p75^{NTR} signaling *in vivo* to promote pruning. Nevertheless, the dissociation of BDNF from p75^{NTR} is the slowest among the neurotrophins (Rodriguez-

Tebar et al., 1992), and it interacts distinctively with $p75^{NTR}$, based on mutagenesis studies (Ryden et al., 1995); which may provide a mechanism by which mature BDNF signals without a $p75^{NTR}$ coreceptor. Interestingly, BDNF is retrogradedly transported along with $p75^{NTR}$ in sympathetic neurons (Hibbert et al., 2006) where it triggers apoptosis (Bamji et al., 1998; Majdan et al., 2001). Further studies are necessary to understand how BDNF, presented at the axons, selectively activates retrograde $p75^{NTR}$-dependent transport or mediates localized pruning actions (Glebova and Ginty, 2005; Zweifel et al., 2005; Ibanez, 2007; Deppmann et al., 2008).

It is likely that activation of specific $p75^{NTR}$ effector pathways is modulated by both the coreceptor with which it partners, and by the ligand to which it binds (Dechant and Barde, 2002; Hempstead, 2002; Roux and Barker, 2002; Chao, 2003; Teng and Hempstead, 2004). Prior studies have identified a number of downstream pathways that play critical roles in $p75^{NTR}$-mediated apoptosis (Gentry et al., 2004), including the stress-induced MAP kinase member JNK (Harrington et al., 2002; Bhakar et al., 2003; Becker et al., 2004), which can be activated by either high concentrations of mature BDNF or lesser amount of proneurotrophins. More recent findings suggest that proneurotrophins and mature BDNF activate γ-secretase mediated cleavage of $p75^{NTR}$ to release its intracellular domain, resulting in the ubiquitination and nuclear translocation of NRIF, a zinc finger transcription factor that binds $p75^{NTR}$ (Linggi et al., 2005; Kenchappa et al., 2006; Volosin et al., 2006, 2008). Although $p75^{NTR}$ cleavage and NRIF nuclear translocation may be required for $p75^{NTR}$-dependent apoptosis, it is not known whether NRIF transcriptionally activates “pro-apoptotic genes” upon nuclear translocation. In addition, Bertrand et al. (2008) has provided genetic evidence that another $p75^{NTR}$ binding protein NRAGE participates in developmental cell death of the sympathetic ganglia and in neurotrophin-induced JNK activation. However, NRAGE null animals do not fully phenocopy the defects in embryonic development exhibited by the $p75^{NTR}$ and NRIF knockout mice (Casademunt et al., 1999; Bertrand et al., 2008), perhaps reflecting the diverse actions of different $p75^{NTR}$ ligands, or possible interactions of NRAGE with other receptors.

FUTURE CHALLENGES AND PROMISES

Since the discovery of NGF as a growth promoting factor some 50 years ago (Levi-Montalcini and Angeletti, 1968), there have been many advancements in the field including the identification of other neurotrophin family members, their individual roles in neural development and in adulthood, as well as the underlying mechanisms of how neurotrophins signal through different receptors. The unexpected finding that neurotrophins can elicit both pro-survival and pro-death pathways offers new possibilities for therapeutic intervention of acute neuronal injuries and slow onset neurodegenerative diseases. Central to this endeavor will be determining whether apoptotic signaling induced by the proneurotrophins can be selectively attenuated. To this end, the finding that $p75^{NTR}$ can differentiate between different ligands (e.g., BDNF vs. MAG) (Vilar et al., 2009) suggests that a better structural understanding of $p75^{NTR}$ bound to individual ligands, and in complex with sortilin, may lead to promising venues for drug discovery. Thus, an emerging challenge is to identify the *in vivo* triggers that activate $p75^{NTR}$-mediated apoptosis under pathological conditions and to differentiate these apoptotic signaling events from those that modulate axonal growth and synaptic plasticity.

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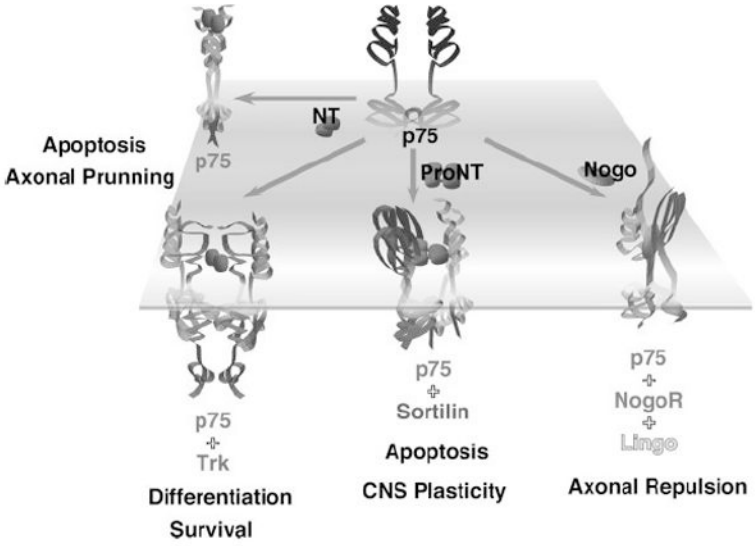

Figure 1.
Schematic representation of mature neurotrophins (NT) and proneurotrophin (proNT) actions as well as the diversity of coreceptor interactions. See text for detail discussion.