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Dynamic nature of the p75 neurotrophin receptor in response to injury and disease

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Neurotrophins and their receptors play a fundamental role in the development and maintenance of neurons throughout the nervous system. They have a wide range of well documented functions within both the central nervous system (CNS) and peripheral nervous system (PNS) including established roles in neuronal differentiation, regulation of neurite outgrowth, synaptic regulation, cell survival and death. Many of the functions are context and tissue specific providing a highly versatile system for the development and maintenance of proper brain function (Dechant and Barde, 2002; Roux and Barker, 2002; Reichardt, 2006; Kraemer et al., 2014). The neurotrophin family is comprised of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). Each neurotrophin exerts unique actions via interactions with specific high affinity tropomyosin regulated kinase (Trk) receptors. NGF interacts with TrkA, BDNF with TrkB, NT-3 with TrkC and to a lesser extent with TrkA and TrkB and NT-4 with TrkB. In addition to the Trk receptors, both the mature neurotrophins and their pro-neurotrophin precursors can bind to the p75 neurotrophin receptor (p75^{NTR}) with low and high affinity, respectively. Signaling via the p75^{NTR} is complex and many aspects are still poorly understood. The complexity is due, in part, to the many ways in which the receptor signals. At least four different processes may contribute to signaling specificity: 1) different heterodimeric neurotrophin receptor pairings, 2) activation by mature versus pro-neurotrophin, 3) post-activation proteolytic processing and trafficking and 4) transactivation. Each process contributes in different ways to the development, maturation and maintenance of the nervous system. Excellent reviews are available that discuss, in greater detail, the diverse functions of the p75^{NTR} (Dechant and Barde, 2002; Roux and Barker, 2002; Kraemer et al., 2014) and its association with other co-receptors (Underwood and Coulson, 2008; Skeldal et al., 2011; Ibanez and Simi, 2012; Kraemer et al., 2014).

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The authors declare that they have no conflict of interest.

In addition to these functions, the p75^{NTR} plays a less understood role in response to disease and injury. In this brief review we discuss the potential role of p75^{NTR} expression in the adult nervous system and in response to nervous system injury and disease.

p75^{NTR} signaling partners

To understand the functions of the p75^{NTR}, one must also understand the nature of its interactions with various co-receptors. The neurotrophin receptors can function as homodimers or heterodimers. The specific receptor interactions determine a wide range of signaling events and allow a few receptors to exert many different responses. The p75^{NTR}, in particular, plays a pivotal role in neurotrophin receptor signaling through its interactions with three major signaling partners: Trk receptors (A, B and C), sortilin or Nogo receptors. A summary of p75^{NTR} interactions with these receptors is illustrated in Figure 1.

Trk receptor-p75^{NTR} interactions

The p75^{NTR} is a single membrane spanning protein in the tumor necrosis factor (TNF) receptor family with four cysteine rich regions in the extracellular domain that are important for neurotrophin binding and receptor-receptor interactions. In contrast to the Trk receptors, the p75^{NTR} does not have a catalytic domain for autophosphorylation, but instead contains a death domain similar in some ways to other TNF associated death domains. However, a major difference between the p75^{NTR} and other death receptors is the inability of p75^{NTR} to autoactivate. Because the p75^{NTR} does not auto-phosphorylate or auto-activate, it exerts its functions by interacting with other receptors. Heterodimerization of p75^{NTR} with Trk receptors increases the affinity of the mature neurotrophin/Trk interaction by about 100-fold and enhances pro-survival and growth signaling (Hempstead et al., 1991; Bibel et al., 1999). During development, the increased efficacy of p75^{NTR}-TrkA signaling plays an important role in initiating NGF dependent growth and neuronal survival. Trk receptor signaling is typically mediated via downstream activation of pro-survival pathways such as PI3K-Akt, extracellular signal-regulated kinases (Erk) or phospholipase C- γ (PLC γ). In the absence of p75^{NTR} signaling there is a reduced ability to activate Akt signaling via TrkA in PC12 cells (Bui et al., 2002; Ceni et al., 2010). *In vivo*, DRG neurons are highly dependent on the trophic effects of NGF and in mice lacking functional p75^{NTR} there is decreased survival of these neurons (Hannila and Kawaja, 2003). The ability to interact with all Trk receptors affords the p75^{NTR} with the opportunity to control many different aspects of neurotrophin signaling. This includes a growing appreciation for effects in the mature nervous system and responses to injury and disease. The functional consequences of these interactions are still being defined but should yield major insights into the processes that regulate neuronal growth, survival and plasticity under both normal and pathological conditions.

Sortilin-p75^{NTR} interactions

The most widely studied non-Trk co-receptor with p75^{NTR} is sortilin. Sortilin is a sorting protein with many functions (Nykjaer and Willnow, 2012). However, its interaction with p75^{NTR} has received a great deal of attention due to two important discoveries; 1) p75^{NTR}-sortilin heterodimers activate apoptotic pathways in neurons and other cells, a process often used for cell selection during development (Hempstead, 2006; Kraemer et al., 2014) and 2)

pro-neurotrophins bind with high affinity to the sortilin-p75^{NTR} complex and initiate cell death signaling (Lee et al., 2001) via the transcription factor JNK-3 and activation of c-Jun. The p75^{NTR} has been shown to be important for initiation of apoptotic cell death in developing neurons (Huang and Reichardt, 2001; Teng et al., 2005; Jansen et al., 2007; Nykjaer and Willnow, 2012), retinal neurons (Frade and Barde, 1998; Roberti et al., 2014) sympathetic neurons (Kenchappa et al., 2010) and oligodendrocytes (Beattie et al., 2002). However, while sortilin's role in cell death has received a great deal of attention, it is important to note that it is one of many functions. Sortilin functions principally as a sorting protein and most is found within late endosomes derived from the trans-Golgi network. In this context an important role of sortilin is to assist in anterograde trafficking of neurotrophin receptors and control of proBDNF secretion, important for neuronal function and survival (Vaegter et al., 2011). The potential role of sortilin in the trafficking of p75^{NTR} is not known but could provide alternative signaling pathways that warrant further investigation.

Nogo receptor-p75^{NTR} interactions

Interactions of p75^{NTR} with the Nogo receptor provide additional mechanisms for control of growth. The myelin proteins Nogo, MAG or MOG bind to the Nogo receptor and suppress axonal growth via interactions with the p75^{NTR}/Nogo receptor complex. The ligand-receptor complex activates the release of Rho-GDI from RhoA (Yamashita et al., 1999) via an interaction with LINGO-1 (Mi et al., 2004) which triggers growth cone collapse. At the same time Rac is inhibited, further reducing the stimulus for growth cone formation (Deinhardt et al., 2011). These processes are important not only in development but also during recovery from injury and have been the focus of studies to develop therapies that restore neural growth (McDonald et al., 2011).

Interaction of p75^{NTR} with truncated Trks

In addition to the classical Trk signaling, each Trk receptor has splice variants that lack the catalytic domain. The best characterized is truncated TrkB which is prominently expressed in the adult CNS and is thought to modify full length TrkB signaling. These splice variants work in concert with the p75^{NTR} to control the formation of dendritic filopodia (Hartmann et al., 2004) and spines (Michaelsen et al., 2010). Transgenic mice overexpressing a truncated form of TrkB showed impaired maintenance of both long-term potentiation (LTP) and long-term depression (LTD). Concomitant expression of p75^{NTR} rescued these phenotypes suggesting that truncated TrkB may have a dominant negative relationship with the p75^{NTR} (Michaelsen et al., 2010) which limits interactions with full length TrkB.

Receptor activation by mature versus pro-neurotrophin

Neurotrophins are synthesized as a pro-neurotrophin which is then proteolytically processed to the mature neurotrophin. Initially, the pro-neurotrophins were thought to be inactive precursors of the active mature peptides. With the later recognition that the pro-neurotrophins are physiologically active came numerous studies showing that the pro-neurotrophins were ligands for the p75^{NTR}. It is now well recognized that neurotrophin signaling is dependent on the balance between mature vs. pro-neurotrophins as well as the

nature of the target receptor complex. The availability of high affinity targets for pro versus mature neurotrophins is highly regulated by the interactions of p75^{NTR} with its receptor partner. In the case of Trk signaling, heterodimerization with p75^{NTR} enhances mature neurotrophin signaling by increasing the binding affinity (Chao, 1994; Esposito et al., 2001; Hempstead, 2006) leading to increased cell survival, differentiation and growth. In contrast, interactions of p75^{NTR} with sortilin promotes high affinity binding of pro-neurotrophins which activates pathways that lead to apoptotic cell death. The best studied of the pro-neurotrophins is proNGF. ProNGF is synthesized and secreted by a variety of different cell types providing a rich source of cell-cell interactions (Hasan et al., 2003; Bruno and Cuello, 2006; Domeniconi et al., 2007; Yang et al., 2009). Cleavage of proNGF can take place intracellularly by convertases or extracellularly by the enzymes, furin, plasmin and matrix metalloprotease-7 (MMP-7) (Lee et al., 2001; Teng et al., 2010). ProNGF and proBDNF have both been shown to trigger a p75^{NTR}-dependent apoptotic cascade (Beattie et al., 2002; Harrington et al., 2004; Teng et al., 2005; Lebrun-Julien et al., 2010; Nykjaer and Willnow, 2012). Confirmation of the role of each pro-neurotrophin was provided by demonstrating protection using specific antibodies to block the binding of proNGF (Harrington et al., 2004; Volosin et al., 2008) or proBDNF (Fan et al., 2008). The apoptotic cascade induced by proNGF and proBDNF was dependent on the interaction of p75^{NTR} with the co-receptor sortilin since addition of a fusion molecule containing the extracellular domain of sortilin prevented the apoptotic effects of proBDNF. In p75^{NTR} deficient mice, less cell death is seen after axotomy (Ferri et al., 1998; Syroid et al., 2000), seizures (Volosin et al., 2008) or ligation by proNGF (Beattie et al., 2002). Similar effects are seen after sortilin knockout (Jansen et al., 2007). Activation of the p75^{NTR}/sortilin complex is thought to induce cell death through extended activation of c-Jun N-terminal protein kinase-3 (JNK-3) which in turn induces the synthesis of pro-apoptotic factors while also phosphorylating and inactivating anti-apoptotic factors (Kraemer et al., 2014). Induction of the apoptotic cascade may depend in part on proteolytic processing of the p75^{NTR} (discussed below).

The dichotomy between the actions of mature neurotrophins versus pro-neurotrophins has led to the hypothesis that an imbalance may facilitate the progression of many neurodegenerative diseases including aging. The potential significance of proNGF signaling was further elevated by the observation that proNGF was the predominant form in human brain and was increased by two-fold in the parietal cortex of patients with Alzheimer disease (AD) (Fahnestock et al., 2001). A corresponding loss of TrkA in patients with AD (Counts et al., 2004; Ginsberg et al., 2006) and preservation of p75^{NTR} and sortilin expression (Counts et al., 2004; Mufson et al., 2010) provided further support for a shift in pro versus mature neurotrophin signaling (Clewes et al., 2008; Mufson et al., 2008). Excess pro-neurotrophin signaling has also been implicated in the pathology associated with other neurodegenerative conditions. For example, the loss of MMP-7 activity in response to kainic acid induced seizures (Le and Friedman, 2012) and in diabetic retinopathy (Ali et al., 2011) is thought to contribute to the disease pathology by reducing the conversion of proNGF to NGF. However, other studies in HIV infected patients have shown that increases in MMP-7 activity are associated with a decline in neurological function (Ragin et al., 2011). Further studies are needed to resolve the precise role of pro-neurotrophin processing in response to damage and disease. Nevertheless, these studies indicate that interventions designed to

restore a more favorable balance of mature neurotrophin-Trk protective signaling have the potential to slow neurodegenerative processes.

Post-activation proteolytic processing and trafficking of p75^{NTR}

The contribution of p75^{NTR} to neurotrophin signaling also depends on post-activation processing of the receptor. Following activation, p75^{NTR} is proteolytically cleaved into fragments that possess specific signaling capacities. The proteolytic processing of the receptor termed regulated intra-membrane proteolysis (RIP) gives rise to receptor fragments compartmentalized within endosomes which can be transported to various sites for signaling, recycling or lysosomal destruction. As illustrated in Figure 1, initial cleavage of the p75^{NTR} by TACE/ADAM17 gives rise to an extracellular N-terminal fragment and a C-terminal fragment that is subsequently cleaved by the actions of γ -secretase to give the intracellular domain (ICD) that is responsible for signaling. Cytosolic trafficking of the endosome may divert the fragment to different proteins where it can have effects as diverse as survival signaling via interactions with a Trk receptor or apoptotic death via interactions with neurotrophin receptor interacting factor (NRIF)(Skeldal et al., 2011). Interactions with NRIF appear to cooperate with sortilin signaling by sustaining JNK activity. Other studies have suggested that the chopper domain of the ICD (Figure 1) may also function independently to induce cell death(Coulson et al., 2004). Although the p75^{NTR} interacts with Trks in the membrane it may be processed separately since, with the exception of a small number of vesicles, it tends to be localized to distinctively different endosomes than Trks(McCaffrey et al., 2009). Endosomal trafficking of Trk receptors to the nucleus and subsequent transcriptional activation are known to mediate many of the long-term effects of neurotrophins. The significance of endosomal trafficking of the p75^{NTR} ICD is less clear but associations with multiple processes including cell death, growth, differentiation and cell survival (Skeldal et al., 2011) suggest that sorting/trafficking mechanisms target the p75^{NTR}-ICD containing endosomes to specific effector proteins.

Transactivation of Trk receptors

An additional, although less explored area of receptor interactions is the potential for transactivation within the membrane. Several receptors have been reported to catalyze the phosphorylation of the Trk receptors. This transactivation increases Akt activity and promotes survival signaling(Chao et al., 2006). The known transactivation events are accomplished through interactions with G-protein coupled receptors, such as the adenosine receptor. Because of the abundance of drugs within this class, efforts have been directed to the identification of pharmaceutical agents that may influence neurotrophin activity(Skaper, 2008). Currently, no such relationships have been identified for the p75^{NTR}. Nevertheless, since the p75^{NTR} is a multifunctional protein that works in concert with other proteins, such interactions should not be ruled out.

P75^{NTR} in the adult nervous system

In contrast to TrkA, B and C which are expressed in the adult nervous system and fulfill a variety of trophic functions, the expression of p75^{NTR} is widely down regulated as the nervous system matures. Since only a few types of neurons retain relatively high levels of

expression into adulthood (e.g. sympathetic neurons, basal forebrain cholinergic neurons) the p75^{NTR} has been viewed as having little role in the functions of the adult nervous system. However, this view is gradually being revised by studies that show low levels of endogenous expression and/or induced expression of p75^{NTR} throughout the nervous system.

In an early study of the developmental expression of p75^{NTR} in rat nervous system, expression of p75^{NTR} mRNA in cerebellum, striatum, septum, medulla and pons persisted at low levels into adulthood (Ernfors et al., 1988). In the spinal cord, p75^{NTR} expression decreased to undetectable levels from E8 to P1 but increased again in adults albeit at reduced levels relative to the high expression seen at E8. An *in situ* hybridization study of p75^{NTR} mRNA expression in adult mouse brain showed expression in the hippocampus, cerebellum and septum at postnatal day 21 (Zagrebelsky et al., 2005). P75^{NTR} RNA was particularly high in the hippocampal dentate gyrus, CA1 and CA3 regions. Woo, et al. (Woo et al., 2005) also demonstrated expression of p75^{NTR} protein in the juvenile (P14) and adult (P60) mouse hippocampus. Staining was seen in post-synaptic dendrites and spines indicating that the expression was synaptic and not restricted to presynaptic cholinergic fibers. These expression studies were supported by studies showing that p75^{NTR} signaling played a role in the regulation of synaptic plasticity in the adult brain. An increase in dendrite complexity and spine density was seen in organotypic hippocampal explants from p75 exon IV null mice at P5 relative to age matched wild type mice, suggesting a normal role for the p75^{NTR} in the negative modulation of dendrite and spine density (Zagrebelsky et al., 2005). Importantly, stimulation of hippocampal slices with proBDNF enhanced long-term depression in a p75^{NTR}-dependent fashion indicating that p75^{NTR} plays a normal role in the regulation of synaptic plasticity, possibly via increased expression of NR2B (Woo et al., 2005) or shifts in the AMPA receptor GluR2/3 balance (Rosch et al., 2005). *In vivo* studies supported these observations by showing that p75^{NTR} expression in adult hippocampal neurons was increased in aged rats with cognitive impairment (VanGuilder Starkey et al., 2013). Thus, qualitative shifts in plastic neural responses based on receptor availability may influence the efficiency of learning and memory processes. Synaptic spine modifications that restrict growth may underlie these changes in plasticity through p75^{NTR}-dependent mechanisms that activate RhoA and suppress Rac signaling (Yamashita and Tohyama, 2003; Gehler et al., 2004; Deinhardt et al., 2011; Sun et al., 2012).

The number of regions showing p75^{NTR} expression and function in adult tissues is growing steadily and include motor axons, post-synaptic muscle and Schwann cells (Garcia et al., 2010), retina (Hu et al., 1998), Muller glia (Lebrun-Julien et al., 2010), cochlea (Liu et al., 2012), adult sensory neurons (Skoff and Adler, 2006) and neural progenitors (Young et al., 2007). Expression of the p75^{NTR} on adult neural progenitors may be particularly important for neurogenesis as only neurospheres generated from p75^{NTR}-positive cells were neurogenic, possibly via a synergistic effect on neuron production in response to BDNF or NGF stimulation (Young et al., 2007). The functional implications of these observations are still being explored but the findings clearly establish actions of p75^{NTR} and pro-neurotrophin signaling that contribute to neuronal plasticity in the adult nervous system.

P75^{NTR} expression in response to injury and disease

The above studies reflect a growing body of evidence suggesting that p75^{NTR} may be expressed at low but functional levels in the adult nervous system. Alternatively, it is possible that p75^{NTR} expression is induced as needed. In particular, many studies have demonstrated rapid upregulation of p75^{NTR} in the nervous system under a variety of pathological conditions (Dechant and Barde, 2002; Chao et al., 2006; Ibanez and Simi, 2012; Kraemer et al., 2014). Such increases have been documented throughout the nervous system (Ibanez and Simi, 2012) and may be due to re-activation of developmental processes that support survival of the cell.

Injury

Increased expression of p75^{NTR} in response to injury or stress has been seen in response to axotomy (Ernfors et al., 1989; Harrington et al., 2004), neural damage (Brunello et al., 1990; Beattie et al., 2002), intraocular pressure (Wei et al., 2007), seizures (Roux et al., 1999; Volosin et al., 2008) and ischemia (Kokaia et al., 1998). In addition to neurons, the increases in p75^{NTR} may reflect expression in Schwann cells (Gai et al., 1996; Kobayashi et al., 2012; Richner et al., 2014), astrocytes (Cragnolini and Friedman, 2008; Cragnolini et al., 2009), oligodendrocytes (Dowling et al., 1999; Althaus and Richter-Landsberg, 2000; Casha et al., 2001; Beattie et al., 2002; Petratos et al., 2004; Guo et al., 2013) and microglia/macrophages (Dowling et al., 1999; Ozbas-Gerceker et al., 2004).

Much of the early work documenting changes in p75^{NTR} expression was in studies of peripheral nerve damage. Nerve damage in the adult PNS induces mechanisms normally seen in development and has been termed a “regrowth mode” by Richner et al. (2014). Repair is mediated in part by Schwann cells which show a robust up-regulation of p75^{NTR} (Taniuchi et al., 1986). Migration of Schwann cells is inhibited by BDNF (Yamauchi et al., 2004) and increased by NGF (Anton et al., 1994), both in a p75^{NTR}-dependent fashion. Thus, the p75^{NTR} may help to regulate the movement of Schwann cells to injured areas. Increases in p75^{NTR} are also seen in peripheral neurons where there is a strong relationship between expression and the induction of apoptosis. This observation suggests that the induction of p75^{NTR} is part of a process designed to promote apoptosis in damaged cells. However, although p75^{NTR} function is associated with induction of apoptosis under many conditions, not all neurons co-expressing p75^{NTR} with sortilin are affected by apoptosis-inducing injury (Arnett et al., 2007). This implies that there may be other roles of p75^{NTR} yet to be explored.

In the CNS, increased expression of p75^{NTR} has been demonstrated in spinal cord, brainstem, cerebellum, substantia nigra, cerebral cortex, hippocampus, basal forebrain and caudate-putamen (Ibanez and Simi, 2012). Expression is increased in substantia nigra dopamine neurons after kainic acid (Wang et al., 2008) and in the cortex and hippocampus after pilocarpine-induced seizures (Roux et al., 1999; Volosin et al., 2008). The p75^{NTR} was dramatically upregulated in damaged cells within one day following cerebellar lesions (Martinez-Murillo et al., 1993) and within the striatum 20 min after cerebral ischemia (Kokaia et al., 1998), highlighting the capacity of adult neurons to rapidly induce the expression of the receptor. The expression after ischemia was transient and both functional and p75^{NTR} recovery were seen at one week suggesting a close relationship between

p75^{NTR} expression and the damage. Similarly, in retinal ischemia induced by elevated intraocular pressure, p75^{NTR} was expressed in ganglion cells and the inner plexiform and nuclear layers (Wei et al., 2007). In contrast, no p75^{NTR} expression was seen in normal retina. Overall, these studies indicate that p75^{NTR} expression is a relatively common response to damage in both the PNS and CNS.

Neurodegenerative diseases

Increased expression of the p75^{NTR} is also seen in a variety of neurodegenerative diseases. In aging and related neurodegeneration, studies have shown that p75^{NTR} and sortilin expression in neurons increases while TrkA decreases (Harrington et al., 2004; Jansen et al., 2007; Al-Shawi et al., 2008; Mufson et al., 2008; Terry et al., 2011) leading to the hypothesis that the p75^{NTR}/TrkA ratio correlates with cell fate. In human AD, a detailed study of p75^{NTR} expression in the membranes of hippocampal neurons showed a 2-fold increase (Chakravarthy et al., 2012) indicating that changes were not due to modifications to afferent cholinergic fibers. Increased expression of both p75^{NTR} and TrkB has also been seen in the spinal cord of amyotrophic lateral sclerosis (ALS) patients (Seeburger et al., 1993; Lowry et al., 2001) and ALS mouse models (Lowry et al., 2001). Using a temperature-sensitive mutant of Moloney murine leukemia virus (MoMuLV-ts1) to induce experimental progressive spongiform encephalomyelopathy, Stoica, et al. (Stoica et al., 2008) observed intense immunoreactivity for proNGF, p75^{NTR} and sortilin in regions with spongiform pathology. Expression of p75^{NTR} under neurodegenerative conditions is not restricted to neurons as increases have been seen in all cell types within the nervous system. In multiple sclerosis plaques, oligodendrocytes and macrophage/microglia expressed increased levels of p75^{NTR} (Dowling et al., 1999). Notably, only a fraction of these cells were apoptotic. The signals that drive the upregulation of p75^{NTR} are not known but may include inflammatory influences. For example, a study of cellular p75^{NTR} expression *in vitro* by Choi and Friedman (Choi and Friedman, 2009) demonstrated that expression could be induced by IL-1 or TNF α in hippocampal neurons and astrocytes. As with injury, an increase in p75^{NTR} is a common response to neurodegenerative diseases reinforcing the view that it is a general response to a variety of stressors.

Effects of p75^{NTR} upregulation

The above studies clearly illustrate that the capacity for rapid expression of p75^{NTR} is widespread throughout the adult nervous system but why do these cells increase expression of p75^{NTR} in response to damage? Is it to promote apoptotic death of cells and limit inflammation or to support survival and functional recovery of damaged cells? Evidence exists in support of both possibilities. In the majority of studies showing p75^{NTR} upregulation, the increases correlated with the presence of apoptotic cells (Kraemer et al., 2014) and p75^{NTR} knockdown is widely protective in a variety of models (Underwood and Coulson, 2008). For example, ALS disease progression is delayed by p75^{NTR} knockdown (Turner et al., 2003). In the mutant SOD1 mouse, an ALS model which develops severe neurodegeneration, an increase in the expression of p75^{NTR} (little to no expression detected in control mice) and RIP fragments correlated with the extent of degeneration (Perlson et al., 2009). In animal models of AD, experimental studies showed

that p75^{NTR} contributed to amyloid β (A β)-induced neural damage(Perini et al., 2002; Knowles et al., 2009; Sotthibundhu et al., 2009). The contribution of the p75^{NTR} may be mediated in part by the binding of A β to the receptor(Yaar et al., 1997; Perini et al., 2002).

Interactions of A β with the p75^{NTR} has become a focus of recent studies of AD pathogenesis and may reveal yet another functional role for the p75^{NTR}. Increases in proNGF in AD and Parkinson disease(Fahnestock et al., 2001; Peng et al., 2004; Pedraza et al., 2005; Chen et al., 2008) indicate that the environment is favorable for p75^{NTR} signaling and supports the theory that age-related damage is due to a shift toward proNGF/p75^{NTR} signaling versus beneficial NGF/TrkA signaling.

While the above studies paint an ominous picture of p75^{NTR} upregulation in the nervous system, the role of p75^{NTR} may be far from deadly. Many other studies also support the idea that p75^{NTR} plays an essential role in protection and recovery of the nervous system. For example, proliferating satellite glia in the injured DRG express p75^{NTR} and are found where sympathetic sprouting is seen(Zhou et al., 1996). The sprouting is attenuated in p75^{NTR} null mice indicating an essential role for p75^{NTR} in re-growth(Ramer and Bisby, 1997). In studies of motor neuron injury, the introduction of grafted Schwann cells deficient in p75^{NTR} resulted in less motor neuron survival(Tomita et al., 2007). Also, BDNF is a positive modulator of myelination via p75^{NTR} (Cosgaya et al., 2002; Song et al., 2006; Tomita et al., 2007) during peripheral nerve recovery, and p75^{NTR} knockout impairs re-myelination of injured sciatic nerve(Song et al., 2006). Thus p75^{NTR} appears to play a pivotal role in Schwann cell support of neuron survival and regrowth. These positive effects of p75^{NTR} may be mediated via pro-growth interactions with TrkB. Beneficial effects of p75^{NTR} may also extend to its interactions with sortilin since the lack of sortilin function in knockout mice synergizes with a loss of p75^{NTR} to produce a severe late-onset sensory neuropathy (Vaegter et al., 2011). Positive effects of p75^{NTR} are also seen in the adult CNS where several studies have demonstrated that p75^{NTR} has protective effects in AD(Bengoechea et al., 2009; Sotthibundhu et al., 2009; Wang et al., 2011).

The above observations highlight the complex and diverse roles of the p75^{NTR} that range from apoptotic death to neuroprotection and plasticity. Rapid expression in response to various challenges indicate that the receptor is dynamically regulated. Some theories have suggested that the increase in p75^{NTR} in response to injury or disease is a major factor contributing to neurodegeneration and there is strong evidence to support this view. On the other hand, studies also clearly demonstrate the beneficial role of the p75^{NTR}. Thus, the p75^{NTR} should be viewed as a flexible modulator of neurotrophin actions with the functional impact depending on specific interactions with co-receptors, availability of ligands, proteolytic processing and selection of signaling pathways. We have only begun to understand these actions and considerable work is needed to appreciate how p75^{NTR} regulates nervous system functions in both normal and disease states.

p75^{NTR} in the immune system

Our understanding of the role of p75^{NTR} in the damaged nervous system would not be complete without mention of an additional target for neurotrophin interactions that may play

an important role in pathogenesis: p75^{NTR} expression on immune cells. As early as 1996 Levi-Montalcini (Levi-Montalcini et al., 1996) introduced the idea that neurotrophins may regulate the immune response. Since this early observation, a handful of studies have explored neurotrophin receptor gene transcript expression and immunoreactivity in immune cells in blood and various tissues. These studies have shown that the p75^{NTR} is constitutively expressed on many types of immune cells and can be upregulated in response to injury. This provides considerable opportunity for neurotrophin regulation of immune cell function, particularly in the nervous system where neurotrophins are abundant. However, this aspect of neuroimmune interactions has received little attention. Table 1 summarizes studies that have documented expression of p75^{NTR} in various immune cells.

Lymphocytes

Although TrkA receptors have been reported on CD3⁺ T lymphocytes, p75^{NTR} expression was absent or negligible in T lymphocytes from blood, tonsil, and inflamed muscle, (Sariola, 2001; Rogers et al., 2010; Raychaudhuri et al., 2011; Colombo et al., 2012). Expression of p75^{NTR}, however, has been found at moderate levels in CD20⁺ B cells under some circumstances. Although expression of the p75^{NTR} was negligible on the surface of B cells in blood from healthy patients (Rogers et al., 2010) it was identified at very low levels in inflamed muscle tissue (Colombo et al., 2012) and relatively high levels in thymus explants from myasthenia gravis patients (Berzi et al., 2008). Flow cytometry of cells isolated from involuted and hyperplastic thymus tissue found that 25% of B lymphocytes expressed p75^{NTR}, whereas only 3% of the B cells were p75^{NTR}-positive in neoplastic thymoma tissue samples illustrating selectivity in the induction of the receptor. In hyperplastic thymus samples, p75^{NTR} overlapped with proliferating marker, ki-67, implicating its involvement in B cell proliferation (Berzi et al., 2008). Natural killer (NK) cells isolated from human blood also expressed low levels of p75^{NTR} intracellularly but not extracellularly. Stimulation of the NK cells with IL-2 or IL-12 increased p75^{NTR} expression by up to 10-fold (Rogers et al., 2010). Induction of p75^{NTR} expression by IL-2 was also seen in NK cells isolated from mouse spleen with low levels of endogenous p75^{NTR} expression (Ralaivirina et al., 2010) indicating that the receptors are robustly mobilized in response to inflammatory cytokines.

Granulocytes

Expression of the p75^{NTR} has been documented in human skin mast cells (Fischer et al., 2008) and eosinophils isolated from blood of atopic dermatitis patients (Raap et al., 2005). p75^{NTR} expression in eosinophils was increased about 2-fold and lesional mast cells about 5-fold in the atopic dermatitis patients compared to control patients (Raap et al., 2005). Basophils isolated from healthy donor blood were reported to have negligible p75^{NTR} expression by flow cytometry yet were positive for p75^{NTR} mRNA (Burgi et al., 1996). The increases in p75^{NTR} expression seen in the eosinophils and mast cells again illustrate that the upregulation is a response shared by different cell types during injury.

Macrophages/microglia

p75^{NTR} expression has been identified in cells of the monocytic lineage in various tissues. Low to moderate p75^{NTR} expression was seen in macrophages in inflamed muscle tissue (Colombo et al., 2012) and in human monocyte derived macrophages (hMDM) from

blood (Caroleo et al., 2001; Aronica et al., 2004). In contrast, p75^{NTR} expression was absent in macrophages in the thymus and tonsils (Labouyrie et al., 1997) suggesting that expression may be tissue or context specific. Microglia cells, the resident macrophages of the brain, showed weak p75^{NTR} expression in white matter regions of normal brain but expression was increased in glial cell bodies and large patches of macrophages/microglia in white matter MS plaques, as well as in glioblastoma, ALS or HIV encephalopathy (Dowling et al., 1999). Garaci et al. found 15% of HIV-infected macrophages were immunoreactive for p75^{NTR} in culture. P75^{NTR} expression was increased to 35% with NGF starvation and was accompanied by an initiation of apoptosis in approximately 45% of HIV-infected cultured macrophages (Garaci et al., 1999). In a similar fashion, p75^{NTR} expression was moderate to strong in microglial-like cells positive for tal1b5 and CD68 surrounding blood vessels and neurons in frontal cortical dysplasia, glioneuronal tumors and dysplastic neuronal tissue (Aronica et al., 2004). There were no Trk receptors found in these samples suggesting a primary role for p75^{NTR} in these disease states. Moderate to strong p75^{NTR} expression was also found in microglia in hippocampal sclerosis samples from temporal lobe epilepsy patients (Ozbas-Gerceker et al 2004). Immune interactions between neurons and microglia may also be regulated by the p75^{NTR}. When neural activity in rat hippocampus was blocked with tetrodotoxin (TTX), the induction of major histocompatibility complex (MHC) class II in microglia by interferon- γ was increased. This immune activation of microglia was blocked by NGF via a mechanism dependent on microglial p75^{NTR} signaling (Neumann et al., 1998). In some studies, the p75^{NTR} was co-expressed in microglia positive for Trk receptors, indicating potential receptor interactions in these cells (Nakajima et al 1998). On close examination of the expression of p75^{NTR} and TrkA on hMDM *in vitro*, we have seen that the two receptors are enriched in small domains on membrane ruffles (Fig 2). The intensity of stain can vary greatly with morphological phenotype suggesting a link between p75^{NTR} expression and structural modifications. The functional significance of these receptors is only now beginning to be explored.

In addition to the expression of neurotrophin receptors, activated microglia/macrophages can release neurotrophins (Heese et al., 1998; Srinivasan et al., 2004; Ulmann et al., 2008) providing the capacity for autocrine feedback. Thus, the expression of p75^{NTR} on immune cells and macrophages/microglia, in particular, raises the possibility of a host of neuro-immune interactions that have not yet been investigated.

Therapeutic approaches targeted to p75^{NTR}

The potential protective effects of neurotrophins have been the focus of a long history of efforts to develop therapies that take advantage of their beneficial effects (Aloe et al., 2012; Longo and Massa, 2013; Steiner and Nath, 2014). These efforts include clinical trials with neurotrophins directly delivered to neural tissue and the implantation of vectors and cells engineered to release neurotrophins. More recently, efforts have been directed to the potential use of non-peptide drugs that directly influence neurotrophin receptor function (Longo and Massa, 2013) or have indirect effects on neurotrophin signaling via transactivation or induction of neurotrophin secretion (Tanis et al., 2007; Obianyo and Ye, 2013; Steiner and Nath, 2014). The potential role of the p75^{NTR} as a therapeutic target for

the treatment of neurodegenerative diseases has been recognized in recent reviews(Chen et al., 2008; Ibanez and Simi, 2012; Longo and Massa, 2013).

The upregulation of p75^{NTR} in neurons and other cells in response to injury or stress makes it possible to selectively target changes directly associated with the disease processes with minimal impact on normal tissues. This selectivity makes the p75^{NTR} an attractive candidate for therapy and has encouraged the development of research strategies to better understand the role of p75^{NTR} in response to damage. Additional features that make the p75^{NTR} an excellent candidate for therapeutic modulation include its ability to exert a wide range of actions. Small non-peptide ligands in particular may be attractive since they have the potential to interact selectively with the many different binding/interacting domains on neurotrophin receptor monomers or dimers(Longo and Massa, 2013). Because the small molecule ligands are incapable of recapitulating the multi-domain binding of the naturally occurring proteins, they do not function as “agonists” or “antagonists” but most likely exert selective modulatory influences capable of “steering” a response in particular directions. For example, the experimental TrkA ligand, MT2, influences the TrkA tyrosine phosphorylation pattern resulting in NGF-like pro-survival activity with significantly less effect on differentiation(Scarpi et al., 2012). Such modulatory effects may minimize adverse effects resulting from excessive neurotrophin stimulation or blockade via potent agonists or antagonists. Promising results have recently been published that demonstrate the therapeutic utility of compounds that target the p75^{NTR}. Nanomolar concentrations of the experimental compound, LM11A-31, a non-peptide structural mimetic of loop1 of NGF, have been shown to have neurotropic properties and to offer potent neuroprotection from A β induced damage in mouse and culture models of AD(Yang et al., 2008; Knowles et al., 2009; Nguyen et al., 2014), spinal cord injury(Tep et al., 2013), traumatic brain injury(Shi et al., 2013), virus-induced inflammation(Meeker et al., 2011), chemotherapeutic toxicity(James et al., 2008) as well as protection against apoptotic effects normally induced in oligodendrocytes by p75^{NTR} ligation(Massa et al., 2006). A structurally unrelated compound similarly modeled after loop 1 of NGF and targeted to the p75^{NTR}, LM11A-24, also protected against motor neuron degeneration(Pehar et al., 2006). Although these efforts are still in early stages of development they provide strong proof of concept that p75^{NTR} is an important target for the development of therapies designed to influence neurotrophin signaling.

Conclusions

The p75^{NTR} is a multifunctional receptor that can heterodimerize with TrkA, TrkB, TrkC, sortilin or the Nogo receptor to regulate a wide array of functions. In addition to the variety of receptor partners, signaling is modified by proteolytic processing of the receptor, trafficking to different targets and differential interactions with mature versus pro-neurotrophins. The functional consequences of activation of p75^{NTR} complexes and the various signaling pathways can range from growth and survival to cell death depending on the molecular and cellular context. Increasing evidence for expression and function in the mature nervous system is exemplified by the demonstrated role of the p75^{NTR} in synaptic plasticity. Widespread upregulation in response to injury or disease underscores a prominent although poorly understood role for the p75^{NTR}. Evidence exists for both pro-apoptotic and protective effects of the p75^{NTR} in the damaged nervous system emphasizing the need to

fully understand the context of p75^{NTR} expression. In addition, expression of the p75^{NTR} on immune cells, particularly macrophages and microglia, indicate that the effects of the p75^{NTR} may extend beyond neurons and glia and will likely encompass a range of neuroimmune interactions. Recent studies of small non-peptide p75^{NTR} ligands have demonstrated potent neuroprotective effects in models of injury and neurodegenerative diseases that highlight the importance of the p75^{NTR} as a therapeutic target. The functions of the p75^{NTR} in the adult nervous system are still poorly understood and future studies in this area hold the promise of revealing a wealth of information on the multifaceted actions of neurotrophins in the context of normal and disease states.

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Neurotrophins and their respective tropomyosin related kinase (Trk) receptors (TrkA, TrkB, and TrkC) and the p75 neurotrophin receptor (p75^{NTR}) play a fundamental role in the development and maintenance of the nervous system making them important targets for treatment of neurodegenerative diseases. Whereas Trk receptors are directly activated by specific neurotrophins, the p75^{NTR} is a multifunctional receptor that exerts its effects via heterodimeric interactions with TrkA, TrkB, TrkC, sortilin or the Nogo receptor to regulate a wide array of cellular functions. By partnering with different receptors the p75^{NTR} regulates binding of mature versus pro-neurotrophins and access to numerous signaling pathways with outcomes ranging from growth and survival to cell death. While the developmental downregulation of the p75^{NTR} has raised questions regarding its role in the mature nervous system, recent data have revealed widespread expression of low levels, a role in synaptic plasticity and adult neurogenesis and upregulation in response to injury or disease. Studies are needed to better understand these processes, particularly in the damaged nervous system, but will be complicated by expression of p75^{NTR} on immune cells including macrophages and microglia that are intimately involved in disease and repair processes. Recent approaches that regulate p75^{NTR} function with small non-peptide ligands have demonstrated potent neuroprotection in models of injury and neurodegenerative diseases that highlight the importance of the p75^{NTR} as a therapeutic target. Future studies hold the promise of revealing a wealth of information on the multifaceted actions of the p75^{NTR} that will inform the design of new neurotrophin-based therapies.

Figure 1.

Signaling partners of the p75^{NTR}. The p75^{NTR} is a single membrane-spanning receptor in the tumor necrosis factor (TNF) receptor family with four cysteine-rich extracellular domains that bind each of the four neurotrophins: NGF, BDNF, NT-3 or NT-4 with low affinity and their respective pro-forms with high affinity. The intracellular portion of the receptor contains a death domain that does not self activate thereby requiring interactions with other effector proteins. The intracellular domain also includes a chopper domain that may independently interact with APAF-1 to induce apoptosis. The p75^{NTR} can interact with at least three different receptor classes which mediate different outcomes: Trk receptors, sortilin and Nogo receptor. 1) Heterodimerization with Trk receptors increases the affinity of the mature neurotrophin/Trk interaction and enhances pro-survival and growth signaling via PI3K-Akt, ERK or PLCγ pathways and downstream effectors such as TRAF6 and NFκB. Activated Trk receptors phosphorylate TACE/ADAM17 which initiates p75^{NTR} cleavage. The receptor is further cleaved by γ-secretase which generates the intracellular domain (ICD) within endosomes. The ICD subserves a variety of functions depending on the fate of the endosome. Selective endosomal trafficking to sites of interaction with other proteins may determine to a large degree the outcome of p75^{NTR} activation. Interactions of the ICD with

neurotrophin receptor interacting factor (NRIF) may support apoptosis whereas interactions with Trk receptors may promote survival. 2) Interactions of p75^{NTR} with sortilin allow high affinity binding of the pro-neurotrophins to the p75^{NTR}/sortilin complex. Subsequent activation of the Ras/MAPK pathway and activation of JNK3 lead to apoptosis. However, most sortilin is found within late endosomes derived from the trans-Golgi network and may function independently to support neuron survival via anterograde trafficking of neurotrophin receptors and control of proBDNF secretion. 3) Interactions of the p75^{NTR} with the Nogo receptor and Lingo-1 play a role in the control of growth. Activation of RhoA by displacement of Rho-GDI and a concurrent suppression of Rac leads to collapse of growth cones, neurite retraction and decreases in spine density. An additional source of signaling is suggested by the transactivation (phosphorylation) of Trk receptors by G-protein coupled receptors. Although there are currently no known G-protein interactions with the p75^{NTR} efforts are underway to identify potential trans-acting ligands that modify neurotrophin signaling. These various interactions affords the p75^{NTR} the capacity to play a pivotal role in the regulation of numerous processes that determine the fate and functions of the cell.

Figure 2.

P75^{NTR} and TrkA expression on cultured human monocyte-derived macrophages. Example of a highly ruffled macrophage (middle) in culture flanked by more ameboid macrophages (upper left and right). The expression of both p75^{NTR} (green) and TrkA (red) is highly enriched on ruffled membranes and finger-like folds. Discrete foci where the two receptors overlap are occasionally seen (yellow regions) but receptors were more typically localized to adjacent, non-overlapping domains. Inset: Highly magnified view of the ruffled membrane showing the focal expression of TrkA relative to the more widely distributed p75^{NTR} stain.

Table 1Expression of p75^{NTR} in cells of the immune system.

Cell type	Tissue	Stain intensity or % of cells	Disease-Associated Increase	Reference
B Cells	Blood Muscle Thymus	Negligible Low 25%		Rogers et al. 2010 Colombo et al. 2012 Berzi et al. 2008
T Cells	Blood Tonsil Muscle	Absent Absent Negligible		Rogers et al. 2010 Sariola 2001 Raychaudhuri et al 2011 Colombo et al. 2012
Natural Killer Cells	Spleen Bone Marrow Blood Lung	3% 3% Absent to low 3%	IL-12 induced IL-12, IL-2 induced	Ralainirina et al. 2010 Rogers et al. 2010
Basophils	Blood	Negligible (detectable mRNA)		Burgi et al. 1996
Eosinophils	Blood	10%	Atopic dermatitis	Raap et al. 2005
Mast Cells	Skin	0.5%	Atopic dermatitis	Fischer et al. 2008
Monocytes/ Macrophages/ Microglia	Muscle Spleen Thymus Tonsil Blood	Low to moderate Moderate Absent Absent Low to moderate		Colombo et al. 2012 Labouyrie et al. 1997 Caroleo et al. 2001
	Brain	Low to moderate	HIV encephalopathy Glioblastoma ALS Multiple Sclerosis Frontal cortical dysplasia Temporal Lobe Epilepsy	Dowling et al. 1999 Neumann et al. 1998 Aronica et al. 2004 Ozbas-Gerceker et al. 2004
	Macrophages/ Microglia in vitro	Moderate to strong		Garaci et al. 1999 Nakakima et al. 1998 Heese et al. 1998