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INVITED REVIEW

The p75 neurotrophin receptor: at the crossroad of neural repair and death

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Abstract

The strong repair and pro-survival functions of neurotrophins at their primary receptors, TrkA, TrkB and TrkC, have made them attractive candidates for treatment of nervous system injury and disease. However, difficulties with the clinical implementation of neurotrophin therapies have prompted the search for treatments that are stable, easier to deliver and allow more precise regulation of neurotrophin actions. Recently, the p75 neurotrophin receptor ($p75^{NTR}$) has emerged as a potential target for pharmacological control of neurotrophin activity, supported in part by studies demonstrating 1) regulation of neural plasticity in the mature nervous system, 2) promotion of adult neurogenesis and 3) increased expression in neurons, macrophages, microglia, astrocytes and/or Schwann cells in response to injury and neurodegenerative diseases. Although the receptor has no intrinsic catalytic activity it interacts with and modulates the function of TrkA, TrkB, and TrkC, as well as sortilin and the Nogo receptor. This provides substantial cellular and molecular diversity for regulation of neuron survival, neurogenesis, immune responses and processes that support neural function. Upregulation of the $p75^{NTR}$ under pathological conditions places the receptor in a key position to control numerous processes necessary for nervous system recovery. Support for this possibility has come from recent studies showing that small, non-peptide $p75^{NTR}$ ligands can selectively modify pro-survival and repair functions. While a great deal remains to be discovered about the wide ranging functions of the $p75^{NTR}$, studies summarized in this review highlight the immense potential for development of novel neuroprotective and neurorestorative therapies.

***Key Words:** injury; plasticity; neurodegenerative disease; brain; therapy; neuron; microglia; neural progenitor*

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Introduction

Neurotrophins and their receptors have the potential to contribute enormously to the restoration of the central nervous system (CNS) and peripheral nervous system (PNS) following injury. Considerable effort has been expended to take therapeutic advantage of their strong survival and growth promoting properties but such efforts have faced significant hurdles due to technical difficulties associated with peptide delivery and the complexity of neurotrophin signaling. Efforts to circumvent these hurdles continue and include the use of better delivery strategies and the development of novel neurotrophin receptor ligands. Each member of the neurotrophin family, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4) interacts with specific tropomyosin regulated kinase (Trk) receptors which regulate growth and survival *via* activation of PI3K-Akt, extracellular signal-regulated kinase (Erk) and phospholipase C-γ (PLCγ) pathways. In addition to the Trk receptors, both the mature neurotrophins and their pro-neurotrophin precursors can bind to the p75 neurotrophin receptor ($p75^{NTR}$), a single membrane spanning protein in the tumor necrosis factor (TNF) receptor family. Unlike the Trk receptors which autophosphorylate after ligand engagement, the $p75^{NTR}$ does not have intrinsic catalytic activity. Instead, it partners with the three neurotrophin receptors, TrkA, TrkB, TrkC, as well as non-neurotrophin receptors, sortilin and Nogo. These various interactions, summarized in **Figure 1**, provide the opportunity for the $p75^{NTR}$ to influence a wide range of cellular functions.

When complexed with Trk receptors, the $p75^{NTR}$ increases the affinity of the mature neurotrophins and supports pro-survival and pro-growth signaling (Hempstead et al., 1991). In contrast to the mature neurotrophins, pro-neurotrophins bind with high affinity to the $p75^{NTR}$/sortilin complex, which often leads to the activation of apoptotic pathways and death (Friedman, 2000; Beattie et al., 2002; Nykjaer et al., 2004). In complex with Nogo receptor and Lingo-1, the $p75^{NTR}$ supports growth cone retraction in response to myelin-derived proteins (Wang et al., 2002; Wong et al., 2002; Mi et al., 2004). Each of these $p75^{NTR}$ mediated processes contributes in different ways to the development, maturation and maintenance of the nervous system (Kraemer et al., 2014).

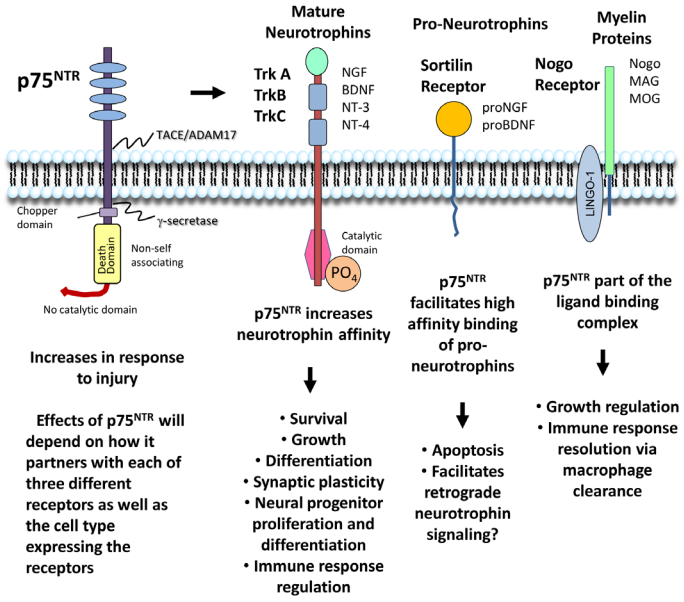

Figure 1 Potential signaling partners of the p75 neurotrophin receptor (p75^{NTR}) following nervous system injury.
The p75^{NTR} is a single membrane-spanning receptor in the tumor necrosis factor (TNF) death domain containing receptor family. Four cysteine-rich extracellular domains bind each of the 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 does not contain a catalytic domain to autoactivate the receptor. Thus, the receptor functions largely *via* interactions with other effector proteins. The p75^{NTR} can interact with at least three different receptor classes which mediate different outcomes: Trk receptors, sortilin and Nogo receptor. 1) The p75^{NTR}-Trk receptor complex increases the affinity of the mature neurotrophin/Trk interaction and enhances pro-survival and growth signaling *via* PI3K-Akt, ERK or PLCγ pathways. In addition, expression on neural progenitors supports proliferation and differentiation. 2) Interactions of p75^{NTR} with sortilin allow high affinity binding of the pro-neurotrophins to the p75^{NTR}/sortilin complex leading to apoptosis. However, the role of sortilin may be diverse as it also supports neuron survival *via* its prominent sorting functions which include anterograde trafficking of neurotrophin receptors. 3) Interactions of the p75^{NTR} with the Nogo receptor and Lingo-1 play a role in the control of growth. Binding of myelin proteins to the complex activates RhoA by displacement of Rho-GDI and concurrently suppress Rac leading to collapse of growth cones, neurite retraction and decreases in spine density. These various interactions afford 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. The role of the p75^{NTR} in response to injury is largely unknown and is a potential source of new strategies to facilitate recovery of the damaged nervous system.
NGF: Nerve growth factor; BDNF: brain-derived neurotrophic factor; NT-3: neurotrophin-3; NT-4: neurotrophin-4; Trk: tropomyosin regulated kinase; ERK: extracellular signal-regulated kinase; PLCγ: phospholipase C-γ.

During development, the p75^{NTR} plays a well-defined role in synapse strengthening and neuron selection. With the notable exception of cholinergic cells of the basal forebrain, the p75^{NTR} is highly down regulated as the nervous system matures. While the low level of expression suggested that the p75^{NTR} may have limited function in the adult nervous system, several new studies have identified important functions of the p75^{NTR} such as hippocampal synapse modification (Rosch et al., 2005; Woo et al., 2005; Zagrebelsky et al., 2005) and the regulation of neurogenesis (Bernabeu and Longo, 2010). In addition, many studies have now shown that the p75^{NTR} can increase dramatically in response to injury or disease in both the PNS and CNS. These observations highlight the expanding role of the p75^{NTR} in the regulation of nervous system function in both normal and pathological states.

As recently reviewed (Ibanez and Simi, 2012; Kraemer et al., 2014; Meeker and Williams, 2014), increased neuronal expression of the p75^{NTR} has been documented in response to axotomy (Zhou et al., 1996; Johnson et al., 1999), neural damage, intraocular pressure (Wei et al., 2007), seizures (Roux et al., 1999; Ozbas-Gerceker et al., 2004) and ischemia (Kokaia et al., 1998). In addition to neurons, injury-induced increases in p75^{NTR} expression may occur in Schwann cells (Taniuchi et al., 1986; Gschwendtner et al., 2003; Zhou and Li, 2007; Provenzano et al., 2008), astrocytes (Choi and Friedman, 2009), oligodendrocytes (Beattie et al., 2002) or microglia/macrophages (Dowling et al., 1999; Wong et al., 2010). Why does expression of the p75^{NTR} increase in response to damage? This is still an emerging area of research but there are several notable possibilities. The p75^{NTR} may 1) enhance survival of injured neurons by increasing the efficiency of Trk activation, 2) trigger apoptosis to eliminate damaged cells while minimizing inflammatory responses, 3) provide a supportive environment for appropriate re-growth and/or 4) control inflammation.

Survival versus Apoptosis: the Decision to Live or Die

The ability of the p75^{NTR} to support either the pro-survival actions of the Trk receptors or the induction of apoptosis with sortilin, places it in a position to make major life and death decisions for the cell. Given this diversity, it is not too surprising that many studies have been published in support of either death or survival functions of the p75^{NTR} following injury (Meeker and Williams, 2014) .

In p75^{NTR} deficient mice, less cell death is seen after axotomy (Sorensen et al., 2003), seizures (Troy et al., 2002) or ligation by proneurotrophins (Teng et al., 2005). Similar effects are seen in sortilin knockout mice suggesting that the p75^{NTR}/sortilin interaction underlies the loss of the cells (Nykjaer and Willnow, 2012). An increased capacity for interactions of the p75^{NTR} with sortilin following injury may recapitulate its functions in the developing nervous system where apoptosis plays an important role in eliminating neurons that make weak connections in a “survival of the fittest” strategy. After injury, a similar strategy may be essential for effective resolution of injury while minimizing inflammation.

Knockdown of the p75^{NTR} also reduces damage in neurodegenerative disease models (Underwood and Coulson, 2008). In the superoxide dismutase 1 (SOD1) mutant mouse, an amyotrophic lateral sclerosis (ALS) model which develops severe neurodegeneration, the expression of p75^{NTR} correlated with the extent of degeneration (Shepheard et al., 2014) and p75^{NTR} knockdown delayed disease progression (Turner et al., 2003). In animal models of Alzheimer's disease (AD), the p75^{NTR} contributes to amyloid β (Aβ)-induced neural damage (Yang et al., 2008). In humans with AD, increases in p75^{NTR} expression relative to TrkA have been suggested to be responsible for the loss of cholinergic neurons (Counts et al., 2004; Costantini et al., 2006). Increases in proNGF in AD (Fahnestock et al., 2001) indicate that the neurotrophin environment is favorable for p75^{NTR}/sortilin signaling and supports the theory that age-related neural damage is facilitated by a shift toward proNGF-mediated signaling. A similar shift to p75^{NTR} expression in response to injury has been suggested to foster damage and loss of neurons.

While the above findings implicate p75^{NTR} involvement in the loss of neural cells, many other studies support the idea that the p75^{NTR} plays an essential role in protection and recovery of the nervous system (Meeker and Williams, 2014). For example, expression of the p75^{NTR} in proliferating satellite glia in the injured dorsal root ganglion (DRG) correlates with the appearance of sympathetic sprouting which is attenuated in p75^{NTR} null mice (Hannila and Kawaja, 2005). In studies of motor neuron injury, less motor neuron survival was seen after the introduction of grafted Schwann cells deficient in p75^{NTR} (Tomita et al., 2007). BDNF, a positive modulator of myelination during peripheral nerve recovery, is dependent on the p75^{NTR} and knockout of the p75^{NTR} impairs re-myelination of injured sciatic nerve (Song et al., 2006). Chu et al. (2007) observed that the p75^{NTR} was essential for functional recovery after spinal cord injury. In cultured hippocampal neurons subjected to excitotoxic concentrations of glutamate, the p75^{NTR} was necessary to see protective NGF/TrkA signaling (Culmsee et al., 2002). Thus, in many studies, the p75^{NTR} appears to play a pivotal role in support of neuron survival and regrowth.

The seemingly contradictory observations noted above reflect the complex and diverse roles of the p75^{NTR}, where some conditions may support repair while other conditions facilitate neural damage and apoptosis. The pivotal role of the p75^{NTR} in crucial decisions regarding cell fate and efforts to support nervous system recovery following injury provides opportunities to therapeutically influence the recovery process. However, the implementation of new therapies will require a better understanding of how opposing effects of the p75^{NTR} are regulated.

Neural Plasticity and Re-growth

The regulation of proper growth and synaptic plasticity also depends on p75^{NTR} functions. Depending on the context, the p75^{NTR} may either support or restrict new growth. Restrictions to axonal growth in the damaged nervous system are thought to be due, in part, to the growth inhibiting effects of myelin proteins (Nogo, MAG, MOG) that bind to the p75^{NTR}/Nogo receptor complex. Since excess activity of this pathway is thought to restrict neural recovery after injury, many therapeutic efforts to overcome these restrictions have focused on suppression of p75^{NTR}/Nogo receptor activity (Fry et al., 2007). However, the p75^{NTR} may also play a positive role in recovery by suppressing inappropriate growth and therefore restricting new growth and re-innervation to appropriate targets. Thus, efforts to prevent growth restrictions post-injury have to be balanced with appropriate guidance of axonal outgrowth and development of synaptic connections.

The role of the p75^{NTR} in synapse modification is still emerging, and there is a need to better understand how the synapse is regulated by the p75^{NTR} under normal conditions as well as in response to injury. In rat hippocampal slices, proBDNF enhanced long-term depression in a p75^{NTR}-dependent fashion, indicating that the p75^{NTR} plays a normal role in the regulation of synaptic plasticity (Woo et al., 2005) perhaps by modifying AMPA glutamate receptor subunit expression (Rosch et al., 2005) and/or regulation of spine density (Zagrebelsky et al., 2005). The impact of increases in p75^{NTR} expression in response to injury on synaptic function remains to be determined and is fertile ground for studies of nervous system recovery.

The role of the p75^{NTR} in neurogenesis of adult neural progenitors may also play a role in recovery of function following injury. Neurospheres generated from p75^{NTR}-positive cells have been shown to be selectively neurogenic, possibly *via* a synergistic effect with BDNF or NGF stimulation (Young et al., 2007). Adult mice deficient in p75^{NTR} show reduced proliferation/maturation of hippocampal dentate progenitors (Bernabeu and Longo, 2010). The functional implications of these observations are still being explored but are likely to impact the extensive efforts to develop neuroregenerative therapies designed to enhance production of new neurons from progenitors.

Immune Cell Activity and Clearance

Finally, a new and relatively unexplored area that may ultimately have a significant impact on nervous system recovery is revealed by the increased expression of the p75^{NTR} on macrophages and microglia under different pathological conditions (Meeker and Williams 2014). Exploration of the functions of the p75^{NTR} in macrophages and microglia has been limited but the expression of Trk receptors, sortilin and Nogo receptors indicate that the same signaling pathways are present that exist in neurons. Several studies suggest that neurotrophins may regulate monocyte/macrophage chemotaxis and retention at sites of injury (Fry et al., 2007; David et al., 2008; Yan et al., 2012) and promote recovery from spinal cord injury (Zhu et al., 2010). The p75^{NTR}/Nogo receptor complex may play a role in resolution of inflammation by facilitating macrophage clearance. In Nogo receptor deficient mice with sciatic nerve crush injury, macrophages fail to leave the area following myelin regeneration (Fry et al., 2007). The repulsive interactions of myelin proteins with Nogo appear to be necessary for migration from the site of injury and ultimate resolution of the inflammation. Actions

of neurotrophins may also participate in the functional differentiation of macrophages/microglia and this may provide new avenues for regulation of the wide range of supportive or deleterious actions of these cells in the injured nervous system.

The p75^{NTR} as a Therapeutic Target

While the diverse and often opposing roles of the p75^{NTR} pose significant challenges for attempts to develop therapies, recent studies have clearly demonstrated the feasibility of efforts to pharmacologically modify p75^{NTR} function (Longo and Massa, 2013). 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 Aβ induced damage in mouse and culture models of AD (Yang et al., 2008; Nguyen et al., 2014), spinal cord injury (Tep et al., 2013), traumatic brain injury (Shi et al., 2013), virus-induced inflammation (Meeker et al., 2012) and chemotherapeutic toxicity (James et al., 2008) in the absence of pro-apoptotic effects. This therapeutic approach was based, in part, on the concept that small molecules might regulate neurotrophin receptor dimerization, activation and/or interactions with co-receptors in ways that do not necessarily recapitulate the full actions of the naturally occurring peptides. Because the binding may be unconventional, the compounds were identified through functional screens designed to reveal neurotrophic, pro-survival activity. Therapeutic efficacy has now been evaluated in a variety of *in vitro* and *in vivo* models. LM11A-31 inhibits neuritic dystrophy and impairments in long-term potentiation (LTP) induced in neural cultures treated with Aβ; a protective effect not recapitulated by NGF (Yang et al., 2008). In a mouse model of AD, 3 months of oral administration decreased CNS pathology and suppressed the development of behavioral deficits (Nguyen et al., 2014). In a model of spinal cord injury with robust upregulation of p75^{NTR} expression, LM11A-31 promoted recovery in tests of motor function in the absence of effects on pain sensitivity (Tep et al., 2013). Protection from RhoA-dependent degeneration of DRG cultures exposed to chemotherapeutic agents (James et al., 2008) and the dendritic beading, pruning and calcium dysregulation associated with viral inflammation (Meeker et al., 2012) suggest that prevention of cytoskeletal damage may be a common effect that confers protection in a variety of pathological circumstances. The precise pharmacological mechanisms of protection are under investigation but may include facilitation of Akt signaling and inhibition of proNGF binding. The ability to selectively modify specific neurotrophin actions with small ligands is also seen with the experimental TrkA ligand, MT2, which has been shown to influence the TrkA tyrosine phosphorylation pattern, resulting in NGF-like pro-survival activity with significantly less effect on differentiation (Scarpi et al., 2012). Although these efforts are still in relatively early stages of development they provide strong proof of concept that small molecules targeted to specific domains of the p75^{NTR} can exert fine control over neurotrophin receptor signaling. Thus, the p75^{NTR} is a novel and versatile target for the development of neurotrophin based therapies.

Conclusion

As evidenced in the above studies, the p75^{NTR} supports a wide range of activity throughout the CNS. The ability to interact with all Trk receptors, sortilin, and the NOGO receptor affords the p75^{NTR} with the opportunity to control many different signaling pathways. Established roles for p75^{NTR} in neurogenesis, regulation of sprouting, synaptogenesis and pruning of unwanted synapses puts it in the center of major efforts to promote recovery of the nervous system. The many functions of the p75^{NTR} 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. The challenge of future studies will be to determine the role of the various p75^{NTR}-dependent pathways in response to injury as well as to determine the appropriate balance of activity that maximally supports recovery. The pivotal role of the p75^{NTR} in so many processes necessary for nervous system recovery and the promising results from p75^{NTR}-targeted interventions makes the receptor an attractive target for the development of novel neuroprotective and neurorestorative therapies.

References

Beattie MS, Harrington AW, Lee R, Kim JY, Boyce SL, Longo FM, Bresnahan JC, Hempstead BL, Yoon SO (2002) ProNGF induces p75-mediated death of oligodendrocytes following spinal cord injury. Neuron 36:375-386.

Bernabeu RO, Longo FM (2010) The p75 neurotrophin receptor is expressed by adult mouse dentate progenitor cells and regulates neuronal and non-neuronal cell genesis. BMC Neurosci 11:136.

Choi S, Friedman WJ (2009) Inflammatory cytokines IL-1beta and TNF-alpha regulate p75^{NTR} expression in CNS neurons and astrocytes by distinct cell-type-specific signalling mechanisms. ASN Neuro 1.

Chu GK, Yu W, Fehlings MG (2007) The p75 neurotrophin receptor is essential for neuronal cell survival and improvement of functional recovery after spinal cord injury. Neuroscience 148:668-682.

Costantini C, Scrable H, Puglielli L (2006) An aging pathway controls the TrkA to p75NTR receptor switch and amyloid beta-peptide generation. Embo J 25:1997-2006.

Counts SE, Nadeem M, Wuu J, Ginsberg SD, Saragovi HU, Mufson EJ (2004) Reduction of cortical TrkA but not p75(NTR) protein in early-stage Alzheimer's disease. Ann Neurol 56:520-531.

Culmsee C, Gerling N, Lehmann M, Nikolova-Karakashian M, Prehn JH, Mattson MP, Krieglstein J (2002) Nerve growth factor survival signaling in cultured hippocampal neurons is mediated through TrkA and requires the common neurotrophin receptor P75. Neuroscience 115:1089-1108.

David S, Fry EJ, Lopez-Vales R (2008) Novel roles for Nogo receptor in inflammation and disease. Trends Neurosci 31:221-226.

Dowling P, Ming X, Raval S, Husar W, Casaccia-Bonnefil P, Chao M, Cook S, Blumberg B (1999) Up-regulated p75^{NTR} neurotrophin receptor on glial cells in MS plaques. Neurology 53:1676-1682.

Fahnestock M, Michalski B, Xu B, Coughlin MD (2001) The precursor pro-nerve growth factor is the predominant form of nerve growth factor in brain and is increased in Alzheimer's disease. Mol Cell Neurosci 18:210-220.

Friedman WJ (2000) Neurotrophins induce death of hippocampal neurons via the p75 receptor. J Neurosci 20:6340-6346.

Fry EJ, Ho C, David S (2007) A role for Nogo receptor in macrophage clearance from injured peripheral nerve. Neuron 53:649-662.

Gschwendtner A, Liu Z, Hucho T, Bohatschek M, Kalla R, Dechant G, Raivich G (2003) Regulation, cellular localization, and function of the p75 neurotrophin receptor (p75^{NTR}) during the regeneration of facial motoneurons. Mol Cell Neurosci 24:307-322.

Hannila SS, Kawaja MD (2005) Nerve growth factor-mediated collateral sprouting of central sensory axons into deafferentated regions of the dorsal horn is enhanced in the absence of the p75 neurotrophin receptor. J Comp Neurol 486:331-343.

Hempstead BL, Martin-Zanca D, Kaplan DR, Parada LF, Chao MV (1991) High-affinity NGF binding requires coexpression of the trk proto-oncogene and the low-affinity NGF receptor. Nature 350:678-683.

Ibanez CF, Simi A (2012) p75 neurotrophin receptor signaling in nervous system injury and degeneration: paradox and opportunity. Trends Neurosci 35:431-440.

James SE, Burden H, Burgess R, Xie Y, Yang T, Massa SM, Longo FM, Lu Q (2008) Anti-cancer drug induced neurotoxicity and identification of Rho pathway signaling modulators as potential neuroprotectants. Neurotoxicology 29:605-612.

Johnson H, Hokfelt T, Ulfhake B (1999) Expression of p75(NTR), trkB and trkC in nonmanipulated and axotomized motoneurons of aged rats. Brain Res Mol Brain Res 69:21-34.

Kokaia Z, Andsberg G, Martinez-Serrano A, Lindvall O (1998) Focal cerebral ischemia in rats induces expression of P75 neurotrophin receptor in resistant striatal cholinergic neurons. Neuroscience 84:1113-1125.

Kraemer BR, Yoon SO, Carter BD (2014) The biological functions and signaling mechanisms of the p75 neurotrophin receptor. Handb Exp Pharmacol 220:121-164.

Longo FM, Massa SM (2013) Small-molecule modulation of neurotrophin receptors: a strategy for the treatment of neurological disease. Nat Rev Drug Discov 12:507-525.

Meeker R, Williams K (2014) Dynamic nature of the p75 neurotrophin receptor in response to injury and disease. J Neuroimmune Pharmacol 9:615-628.

Meeker RB, Poulton W, Feng WH, Hudson L, Longo FM (2012) Suppression of immunodeficiency virus-associated neural damage by the p75 neurotrophin receptor ligand, LM11A-31, in an in vitro feline model. J Neuroimmune Pharmacol 7:388-400.

Mi S, Lee X, Shao Z, Thill G, Ji B, Relton J, Levesque M, Allaire N, Perrin S, Sands B, Crowell T, Cate RL, McCoy JM, Pepinsky RB (2004) LINGO-1 is a component of the Nogo-66 receptor/p75 signaling complex. Nat Neurosci 7:221-228.

Nguyen TV, Shen L, Vander Griend L, Quach LN, Belichenko NP, Saw N, Yang T, Shamloo M, Wyss-Coray T, Massa SM, Longo FM (2014) Small molecule p75NTR ligands reduce pathological phosphorylation and misfolding of tau, inflammatory changes, cholinergic degeneration, and cognitive deficits in AβPP(L/S) transgenic mice. J Alzheimers Dis 42:459-483.

Nykjaer A, Willnow TE (2012) Sortilin: a receptor to regulate neuronal viability and function. Trends Neurosci 35:261-270.

Nykjaer A, Lee R, Teng KK, Jansen P, Madsen P, Nielsen MS, Jacobsen C, Kliemannel M, Schwarz E, Willnow TE, Hempstead BL, Petersen CM (2004) Sortilin is essential for proNGF-induced neuronal cell death. Nature 427:843-848.

Ozbas-Gerceker F, Gorter JA, Redeker S, Ramkema M, van der Valk P, Baayen JC, Ozguc M, Saygi S, Soylemezoglu F, Akalin N, Troost D, Aronica E (2004) Neurotrophin receptor immunoreactivity in the hippocampus of patients with mesial temporal lobe epilepsy. Neuropathol Appl Neurobiol 30:651-664.

Provenzano MJ, Xu N, Ver Meer MR, Clark JJ, Hansen MR (2008) p75NTR and sortilin increase after facial nerve injury. Laryngoscope 118:87-93.

Rosch H, Schweigreiter R, Bonhoeffer T, Barde YA, Korte M (2005) The neurotrophin receptor p75NTR modulates long-term depression and regulates the expression of AMPA receptor subunits in the hippocampus. Proc Natl Acad Sci U S A 102:7362-7367.

Roux PP, Colicos MA, Barker PA, Kennedy TE (1999) p75 neurotrophin receptor expression is induced in apoptotic neurons after seizure. J Neurosci 19:6887-6896.

Scarpi D, Cirelli D, Matrone C, Castronovo G, Rosini P, Occhiato EG, Romano F, Bartali L, Clemente AM, Bottegoni G, Cavalli A, De Chiara G, Bonini P, Calissano P, Palamara AT, Garaci E, Torcia MG, Guarna A, Cozzolino F (2012) Low molecular weight, non-peptidic agonists of TrkA receptor with NGF-mimetic activity. Cell Death Dis 3:e339.

Shepheard SR, Chataway T, Schultz DW, Rush RA, Rogers ML (2014) The extracellular domain of neurotrophin receptor p75 as a candidate biomarker for amyotrophic lateral sclerosis. PLoS One 9:e87398.

Shi J, Longo FM, Massa SM (2013) A small molecule p75(NTR) ligand protects neurogenesis after traumatic brain injury. Stem Cells 31:2561-2574.

Song XY, Zhou FH, Zhong JH, Wu LL, Zhou XF (2006) Knockout of p75(NTR) impairs re-myelination of injured sciatic nerve in mice. J Neurochem 96:833-842.

Sorensen B, Tandrup T, Koltzenburg M, Jakobsen J (2003) No further loss of dorsal root ganglion cells after axotomy in p75 neurotrophin receptor knockout mice. J Comp Neurol 459:242-250.

Taniuchi M, Clark HB, Johnson EM, Jr. (1986) Induction of nerve growth factor receptor in Schwann cells after axotomy. Proc Natl Acad Sci U S A 83:4094-4098.

Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen ZY, Lee FS, Kraemer RT, Nykjaer A, Hempstead BL (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of $p75^{NTR}$ and sortilin. J Neurosci 25:5455-5463.

Tep C, Lim TH, Ko PO, Getahun S, Ryu JC, Goettl VM, Massa SM, Basso M, Longo FM, Yoon SO (2013) Oral administration of a small molecule targeted to block proNGF binding to p75 promotes myelin sparing and functional recovery after spinal cord injury. J Neurosci 33:397-410.

Tomita K, Kubo T, Matsuda K, Fujiwara T, Yano K, Winograd JM, Tohyama M, Hosokawa K (2007) The neurotrophin receptor p75NTR in Schwann cells is implicated in remyelination and motor recovery after peripheral nerve injury. Glia 55:1199-1208.

Troy CM, Friedman JE, Friedman WJ (2002) Mechanisms of p75-mediated death of hippocampal neurons. Role of caspases. J Biol Chem 277:34295-34302.

Turner BJ, Cheah IK, Macfarlane KJ, Lopes EC, Petratos S, Langford SJ, Cheema SS (2003) Antisense peptide nucleic acid-mediated knockdown of the p75 neurotrophin receptor delays motor neuron disease in mutant SOD1 transgenic mice. J Neurochem 87:752-763.

Underwood CK, Coulson EJ (2008) The p75 neurotrophin receptor. Int J Biochem Cell Biol 40:1664-1668.

Wang KC, Kim JA, Sivasankaran R, Segal R, He Z (2002) P75 interacts with the Nogo receptor as a co-receptor for Nogo, MAG and OMgp. Nature 420:74-78.

Wei Y, Wang N, Lu Q, Zhang N, Zheng D, Li J (2007) Enhanced protein expressions of sortilin and $p75^{NTR}$ in retina of rat following elevated intraocular pressure-induced retinal ischemia. Neurosci Lett 429:169-174.

Wong I, Liao H, Bai X, Zaknic A, Zhong J, Guan Y, Li HY, Wang YJ, Zhou XF (2010) ProBDNF inhibits infiltration of ED1+ macrophages after spinal cord injury. Brain Behav Immun 24:585-597.

Wong ST, Henley JR, Kanning KC, Huang KH, Bothwell M, Poo MM (2002) A p75(NTR) and Nogo receptor complex mediates repulsive signaling by myelin-associated glycoprotein. Nat Neurosci 5:1302-1308.

Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA, Hempstead BL, Lu B (2005) Activation of $p75^{NTR}$ by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 8:1069-1077.

Yan J, Zhou X, Guo JJ, Mao L, Wang YJ, Sun J, Sun LX, Zhang LY, Zhou XF, Liao H (2012) Nogo-66 inhibits adhesion and migration of microglia via GTPase Rho pathway in vitro. J Neurochem 120:721-731.

Yang T, Knowles JK, Lu Q, Zhang H, Arancio O, Moore LA, Chang T, Wang Q, Andreasson K, Rajadas J, Fuller GG, Xie Y, Massa SM, Longo FM (2008) Small molecule, non-peptide p75 ligands inhibit Abeta-induced neurodegeneration and synaptic impairment. PLoS One 3:e3604.

Young KM, Merson TD, Sotthibundhu A, Coulson EJ, Bartlett PF (2007) p75 neurotrophin receptor expression defines a population of BDNF-responsive neurogenic precursor cells. J Neurosci 27:5146-5155.

Zagrebelsky M, Holz A, Dechant G, Barde YA, Bonhoeffer T, Korte M (2005) The p75 neurotrophin receptor negatively modulates dendrite complexity and spine density in hippocampal neurons. J Neurosci 25:9989-9999.

Zhou XF, Li HY (2007) Roles of glial p75NTR in axonal regeneration. J Neurosci Res 85:1601-1605.

Zhou XF, Rush RA, McLachlan EM (1996) Differential expression of the p75 nerve growth factor receptor in glia and neurons of the rat dorsal root ganglia after peripheral nerve transection. J Neurosci 16:2901-2911.

Zhu Z, Ni B, Yin G, Zhou F, Liu J, Guo Q, Guo X (2010) NgR expression in macrophages promotes nerve regeneration after spinal cord injury in rats. Arch Orthop Trauma Surg 130:945-951.