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The Regulation of Cell Survival by the p75 Neurotrophin Receptor

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Abstract

During the development of the mammalian nervous system, the p75 neurotrophin receptor ($p75^{NTR}$) can fulfill dual functions. Through the activation of the stress-activated kinase JNK or by stimulation of $p75^{NTR}$-associated factors, the receptor can induce pro-apoptotic pathways. In other contexts, $p75^{NTR}$ can promote cell survival by associating with tropomyosin-related-kinase (Trk) receptors or by independently promoting activation of the transcription factor NFκB. Though these signaling processes are not fully understood, recent studies have indicated that the regulated proteolytic cleavage of $p75^{NTR}$ may play a particularly important role. Moreover, analyses of $p75^{NTR}$-associated receptors and cytoplasmic interactors have provided new $p75^{NTR}$ into the mechanisms by which $p75^{NTR}$ mediates these functions. This review discusses the signaling events associated with the regulation of cell survival by $p75^{NTR}$, highlighting how these activities may contribute not only to neurodevelopment, but also to cellular responses to stressful or injurious conditions.

Keywords: *p75ntr, neurotrophins, NGF, BDNF, TRAF6, NRIF, NRAGE, apoptosis, sortilin*

Introduction

The neurotrophin family, which consists of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4), is a group of secreted proteins which mediate a wide range of biological functions, including the regulation of cell survival, myelin formation, neurite outgrowth, synaptic plasticity, neuronal differentiation, and cell migration[1,2]. Neurotrophins perform these many functions by acting through two classes of receptors: the Trk family of receptor tyrosine kinases (TrkA, TrkB, and TrkC), and the p75 neurotrophin receptor ($p75^{NTR}$), a member of the Tumor Necrosis Factor (TNF) superfamily[1,2]. Trk receptors preferentially bind to particular neurotrophins, with TrkA selectively associating with NGF, TrkB with BDNF and NT-4, and TrkC with NT-3[3,4]. Depending upon the cellular context, these interactions can activate well-studied phosphatidylinositol-3-kinase (PI-3 kinase)/Akt, Ras/extracellular signal–regulated kinase (ERK), and phospholipase C-γ (PLC-γ) signaling pathways, as well as other signaling cascades, and thereby regulate a diversity of physiological activities[4]. In contrast to Trk receptors, $p75^{NTR}$ has a similar affinity for all four neurotrophins, and the signaling events associated with its activation are less well characterized[2,3]. The established functional roles of $p75^{NTR}$ are quite diverse, due largely to abundance of ligands and co-receptors that can associate with $p75^{NTR}$ and regulate its signaling. For example, $p75^{NTR}$ can form a high-affinity complex with Trk receptors and thereby enhance Trk signaling[1,5]. By associating with the Nogo receptor and Lingo-1 in the presence of myelin-based ligands, $p75^{NTR}$ can also inhibit the axonal regeneration of injured neurons[1,6,7]. Numerous other functional roles for $p75^{NTR}$ have been established, including modulation of the cell cycle[8], synaptic plasticity[9], and tumor cell migration[10]. This review discusses the mechanisms by which $p75^{NTR}$ regulates cell survival and how these events relate to neurodevelopment and to physiological responses to cellular injury.

P75NTR Activates Programmed Cell Death

Programmed cell death is an essential aspect of mammalian neurodevelopment, as approximately 50% of neurons generated during development undergo an apoptotic program[11]. Analyses from *p75ntr*$^{-/-}$ mice have revealed that $p75^{NTR}$ is vital to this process and induces the developmental loss of neurons within the retina[12,13], basal forebrain[14], spinal cord[13], and superior cervical ganglia[15]. Additionally, *in vitro* studies have shown that neurotrophin binding, or neurotrophin withdrawal, induces $p75^{NTR}$-mediated apoptosis in a plethora of cell types, including Schwann cells[16,17], oligodendrocytes[18], hippocampal neurons[19], motor neurons[20], photoreceptor cells[21], sympathetic neurons[22], and several others[23-25]. The signaling cascades induced by $p75^{NTR}$-mediated apoptosis are not completely understood, but are known to involve the phosphorylation of c-Jun N-terminal kinase (JNK)[26-28], as well as the downstream activation of p53[29] and BH3-domain-only family members Bad[27] and BimEL[26], the accumulation of cytochrome c within the cytosol[27], and the activation caspases-3, -6, and -9[27,28]. This is in contrast to other members of the TNF superfamily, which activate apoptosis through a caspase-8-dependent pathway[30]. Exactly how activation of $p75^{NTR}$ leads to these downstream activities is incompletely understood, but many studies have recently identified critical early signaling events. One such important early event is proteolytic processing of the receptor. In a manner similar to that of the transmembrane proteins Notch and amyloid precursor protein (APP), $p75^{NTR}$ is subject to proteolytic cleavage in its extracellular domain (ECD) by the metalloproteinase[A] TNF-α converting enzyme (TACE, also known as ADAM17), thereby producing a membrane-bound c-terminal fragment (CTF). Following release of the ECD, the $p75^{NTR}$-CTF is cleaved in its transmembrane region by γ-secretase, thus releasing into the cytoplasm the intracellular domain (ICD) of $p75^{NTR}$ [2,31,32]. This type of proteolytic processing of $p75^{NTR}$ has been demonstrated to occur in a ligand-dependent manner in 3T3-$p75^{NTR}$ over-expressing cells[33], glial cells[34], and sympathetic neurons[2,35]. Cleavage of $p75^{NTR}$ in response to phorbol ester[B] treatment has been revealed in HEK-293 cells expressing $p75^{NTR}$ [32], SN56 cells[32], and RNF22 Schwannoma cells[31]. In other contexts, $p75^{NTR}$ cleavage has been demonstrated to occur in PC12 cells[36], dorsal root ganglion (DRG) neurons[37], cerebellar granular neurons (CGNs)[38] and in a transgenic photoreceptor cell line[39]. The functional significance of these proteolytic events is, in many aspects, not well understood and likely varies depending upon the cellular context. One possibility is that γ-secretase-mediated cleavage of the $p75^{NTR}$-CTF allows for the translocation of the $p75^{NTR}$-ICD into the nucleus, where it may alter transcriptional events that contribute to apoptotic signaling. Indeed, the soluble $p75^{NTR}$-ICD has been detected in the

[A] **Metalloproteinases**: a group of peptidases which require metals such as zinc or calcium for catalytic function.
[B] **Phorbol esters**: poly-cyclic compounds commonly used as diacylglycerol analogues which bind and activate protein kinase C.

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nucleus of both 3T3-cells over-expressing p75^{NTR} [33] and Schwann cells[34] in a ligand-dependent manner. In PC12 cells, NGF stimulation induced nuclear localization of endogenous p75^{NTR}-ICD and association of p75^{NTR} with the cyclin E promoter[40]. Altogether, this evidence suggests that proteolytic cleavage of p75^{NTR} may promote regulation of transcriptional activity by facilitating nuclear entry of the p75^{NTR}-ICD.

Another function of p75^{NTR} cleavage is to allow proteins associated with the p75^{NTR}-ICD to be released into the cytoplasm, thus allowing these interactors to undergo nuclear translocation or to associate with other cytoplasmic proteins. Numerous p75^{NTR} interacting factors have been reported, including NRIF[41], NADE[42], NRAGE[43], RIP-2[17], Rac[44], Rho-GDI[45], SC-1[46], MAGE-H1[47], Necdin[47], ARMS[48], and TRAF2, 4, and 6[49]. Many of these have been shown to mediate apoptotic signaling, including NRIF[41], TRAF6[50], NRAGE[51], and NADE[42]. Among these p75^{NTR}-associated proteins, the E3 ubiquitin ligase TRAF6 (TNF receptor-associated factor 6) plays a particularly important role. TRAF6 is recruited to the cytoplasmic domain of p75^{NTR} in a ligand-dependent fashion and is required for p75^{NTR}-mediated activation of JNK and subsequent neuronal death[50,52-54]. Recently, it was reported that following treatment of PC12 cells with NGF, TRAF6 associates with presenilin-1, the primary catalytic component of the γ-secretase complex, and this association enhanced ubiquitylation of p75^{NTR}, cleavage of p75^{NTR}, and autoubiquitylation of TRAF6[54]. While the functional significance of p75^{NTR} ubiquitylation is still unclear, this evidence suggests that TRAF6 may enhance p75^{NTR} cleavage by binding both p75^{NTR} and γ-secretase in response to stimulation by neurotrophins. The widely expressed DNA-binding protein NRIF (neurotrophin receptor-interacting factor) is another cytoplasmic interactor that facilitates p75^{NTR}-mediated apoptosis[35]. NRIF is required for p75^{NTR}-mediated JNK activation and apoptosis in cultured sympathetic neurons[55], and NRIF was recently shown to be necessary for p75^{NTR}-mediated apoptosis in hippocampal neurons both *in vivo* and *in vitro*[19]. In sympathetic neurons, pro-apoptotic ligands stimulate proteolytic cleavage of p75^{NTR}, which in turn induces the ubiquitylation and nuclear translocation of NRIF[35]. Inhibition of p75^{NTR} proteolysis by a γ-secretase inhibitor or by expression of a mutant, non-cleavable form of p75^{NTR} blocked nuclear translocation of NRIF and prevented neuronal death. Ubiquitylation of NRIF, which is required for its nuclear localization, as well as for p75^{NTR}-mediated apoptosis, also depends upon TRAF6[56]. Thus, in a current model of p75^{NTR}-mediated apoptosis, neurotrophin-dependent activation of p75^{NTR} induces cleavage of the receptor by TACE and γ-secretase, with a potential enhancement of this cleavage occurring through an interaction between presenilin-1 and TRAF6. Cleavage of p75^{NTR} then results in the release of a complex containing the p75^{NTR}-ICD, NRIF, and TRAF6 into the cytoplasm. In turn, this facilitates the TRAF6-dependent ubiquitylation and nuclear localization of NRIF, as well as the activation of JNK, thereby triggering downstream signaling events that induce neuronal death (Fig. 1).

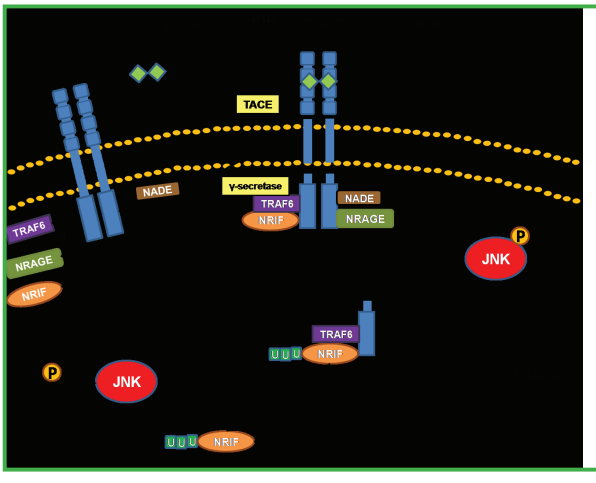

Figure 1: Activation of p75NTR by mature neurotrophins(NTs) or proNTs induces recruitment of p75NTR –associated factors and short-term JNK activation. JNK promotes cleavage of p75NTR by TACE and γ-secretase, thereby facilitating the release of a complex containing the p75NTR –ICD, TRAF6, and NRIF. This complex promotes the TRAF6-dependent ubiquitylation and nuclear translocation of NRIF, as well as the long-term activation of JNK, both of which lead to apoptosis. NRAGE, NADE, and other interactors may also contribute to this process, though the details of their interactions are currently unknown.

While this represents a plausible model of p75^{NTR}-mediated apoptosis, the roles of NRIF and TRAF6 in cell types other than sympathetic and hippocampal neurons are less well understood, and thus further investigation of potential cell-specific differences is needed. Additionally, other p75^{NTR}-associated factors are known to contribute to apoptotic signaling. NRAGE (neurotrophin receptor-interacting MAGE homolog), a member of the MAGE family, is a p75^{NTR}-associated protein that potently induces p75^{NTR}-dependent cell death when over-expressed in MAH cells treated with neurotrophins[43]. Recently, it was discovered that NRAGE knockout mice have a defect in the developmental apoptosis of sympathetic neurons similar to that observed in p75^{NTR} knockout mice, suggesting that NRAGE may be required for p75^{NTR}-mediated developmental apoptosis *in vivo*. Sympathetic neurons from these mice were resistant to BDNF-induced apoptosis and showed reduced BDNF-dependent JNK activation[51]. Thus, NRAGE appears to be an important component of p75^{NTR}-mediated apoptotic signaling. Interestingly, NRAGE knockout animals have a severe motor neuron defect not seen in p75^{NTR} knockout mice, indicating that NRAGE may also regulate apoptosis through pathways not involving p75^{NTR} [51]. NADE (p75^{NTR}-associated cell death executor) is another p75^{NTR}-associated protein that is thought to contribute to apoptotic signaling. When co-expressed in HEK293 cells, NADE associates with p75^{NTR} in response to NGF treatment and activates p75^{NTR}-dependent cell death, and these results were replicated in PC12 cells, nnr5 cells, and oligodendrocytes[42]. Whether NADE and NRAGE function within the same pathway as NRIF and TRAF6 or instead act in parallel to promote p75^{NTR}-mediated apoptosis is not well understood, and thus further analyses of these signaling events in similar cell types is needed.

p75^{NTR}-mediated Apoptosis in Response to Cellular Injury – Role of Proneurotrophins

In addition to regulating developmental apoptosis, it is well established that p75^{NTR} induces programmed cell death in response to different types of cellular injury. For example, p75^{NTR} facilitates cell death in corticospinal neurons following axotomy[57], in hippocampal neurons in response to seizures[19], in oligodendrocytes after spinal cord injury[58], and in motor neurons following lesion of the facial nerve[59,60]. Recently, a study conducted using cultured sympathetic neurons revealed that the neurotrophin-dependent induction of p75^{NTR} cleavage requires the activity of JNK. Interestingly, activation of JNK by over-expression of the upstream kinase MEK kinase-1 (MEKK1) was sufficient to induce p75^{NTR} cleavage and subsequent cell death[61]. Many types of cellular insults, including oxidative stress and ultraviolet irradiation, can activate JNK[62], and thus the activation of JNK by these different types of cellular stressors may stimulate p75^{NTR} cleavage and initiate subsequent apoptotic signaling. The precursor forms of neurotrophins also play an especially important role in stimulating p75^{NTR}-mediated cell death in response to neuronal injury. Like many secreted proteins, neurotrophins are synthesized as precursors (proneurotrophins), which can be proteolytically cleaved to produce mature proteins[9]. Proneurotrophins can be cleaved intracellularly by furin and other proconvertases or secreted in their precursor form and proteolytically cleaved by enzymes within the extracellular matrix[63,64]. The serine protease plasmin, which is activated through the proteolysis of plasminogen by tissue plasminogen activator (tPA),

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is one such enzyme capable of cleaving proneurotrophins within the extracellular environment[30,64]. Additionally, proneurotrophins can be converted by extracellular matrix metalloproteinases (MMPs), and, in particular, it has been demonstrated that proBDNF can be cleaved by MMP-3 and MMP-7, while proNGF is cleaved by MMP-7, but not MMP-2, -3, or -9[30,64]. Accumulating evidence has revealed that secreted proneurotrophins serve as potent endogenous ligands for $p75^{NTR}$. Proneurotrophins can activate $p75^{NTR}$ at low nanomolar concentrations by binding to a protein complex containing $p75^{NTR}$ and its co-receptor sortilin, a member of the Vps10p-domain family of receptors[65]. Proneurotrophins are thought to bind to sortilin via their pro-domain and to $p75^{NTR}$ through their mature domain, thus serving as a crosslinker that brings the three proteins together and initiates $p75^{NTR}$-mediated apoptotic signaling[65]. The death-promoting activity of proneurotrophins has been demonstrated in a variety of cell types, including oligodendrocytes[58], basal forebrain neurons[23], sympathetic neurons[22,65], Schwann cells[65], photoreceptor cells[21], corticospinal neurons[57], smooth muscle cells[64], and hippocampal neurons[19]. In several contexts, proneurotrophins have been demonstrated to promote programmed cell death in response to cellular injury *in vivo*. Exogenous proBDNF was shown to enhance the apoptosis of axotomized sensory neurons *in vivo*, and neutralizing antibodies which specifically bind the pro-domain of proBDNF reduced cell death following sciatic nerve lesion[66]. In hippocampal neurons, proNGF and proBDNF were upregulated after pilocarpine-induced seizures, particularly within astrocytes, and secretion of these proneurotrophins was detected in cerebrospinal fluid. Infusion of neutralizing proNGF antibodies into the hippocampal region reduced seizure-induced neuronal loss[19]. Following internal capsule lesion, an increase in the production and secretion of proNGF was detected, and infusion of neutralizing proNGF antibodies rescued corticospinal neurons from axotomy-induced cell death[57]. Because proneurotrophins have a greater affinity for $p75^{NTR}$/sortilin complexes and lower affinity for Trk receptors[65], proneurotrophins can selectively stimulate apoptosis in cellular systems in which mature neurotrophins promote Trk-mediated survival. Indeed, in cultured basal forebrain neurons, proNGF and proBDNF both induced $p75^{NTR}$-mediated programmed cell death, while the mature forms of these proteins instead activated pro-survival signaling pathways, presumably by stimulating TrkA and TrkB[23]. Apart from the differences in affinity for Trk receptors and $p75^{NTR}$, how the $p75^{NTR}$-mediated apoptotic signaling pathways stimulated by proneurotrophins differ from those induced by mature neurotrophins remains to be fully established. At least in some cellular contexts, the signaling mechanisms appear to be similar. For example, in sympathetic neurons, the induction of $p75^{NTR}$ cleavage and NRIF nuclear translocation by mature BDNF could also be invoked by lower concentrations of proBDNF[35,56]. Proteolysis of $p75^{NTR}$ and nuclear localization of NRIF were also required for the cell death of hippocampal neurons treated with proneurotrophins in culture[19]. Therefore, these signaling events appear facilitate $p75^{NTR}$-mediated cell death induced by both proneurotrophins and mature neurotrophins. However, sortilin may also contribute to $p75^{NTR}$-mediated apoptotic signaling in a manner that has yet to be revealed, and the involvement of other $p75^{NTR}$ interactors has not been thoroughly studied.

$p75^{NTR}$ Regulates Pro-survival Signaling

In contrast to the aforementioned role of $p75^{NTR}$, in some cellular contexts $p75^{NTR}$ can promote cell survival. Neurotrophin-dependent activation of $p75^{NTR}$ has been demonstrated to inhibit the death of neuroblastoma cells[67], of hippocampal neurons treated with NMDA[68], and of both sensory neurons[69] and cortical subplate neurons deprived of trophic support[70]. Mice lacking expression of $p75^{NTR}$ exhibit a dramatic loss of sensory neurons, thus indicating that the receptor is required for the survival of these neurons *in vivo*[71]. Additionally, a recent study of $p75^{NTR}$ knockout mice revealed an increased loss of primary auditory neurons following acoustic trauma, demonstrating that $p75^{NTR}$ may play a protective role following certain types of cellular injury[72]. As one mechanism of promoting cell survival, $p75^{NTR}$ can form a high affinity complex with Trk receptors, thereby increasing their specificity for particular neurotrophins[5,73]. Alternatively, stimulation of $p75^{NTR}$ can promote the activation of nuclear factor kappaB (NFκB), a pro-survival transcription factor that is also activated by other members of the TNF receptor family[60]. Neurotrophin binding to $p75^{NTR}$ has been shown to activate pro-survival signaling by NFκB in a number of cell types, including RN22 cells[74], primary Schwann cells[17], trigeminal neurons[75], and hippocampal neurons[76]. Activation of NFκB can, in turn, promote the expression of neuroprotective NFκB target genes such as Bcl-2 and Bcl-xl[76]. Recently, it was demonstrated that proteolytic cleavage of $p75^{NTR}$ might contribute to pro-survival signaling as well. Interestingly, activation of Trk receptors in PC12 cells, as well as in cerebellar granular neurons, was shown to induce cleavage of $p75^{NTR}$, which subsequently enhanced Trk signaling[36,38]. This function of $p75^{NTR}$ cleavage, however, is likely specific to particular cell types, since cleavage of $p75^{NTR}$ is not stimulated by Trk receptor activation in sympathetic neurons and expression of the $p75^{NTR}$-ICD in these cells promotes apoptosis[35].

Conclusion

Substantial progress has been made in uncovering the mechanisms by which $p75^{NTR}$ regulates cell survival during neurodevelopment and in response to cellular injury. Elucidating these processes is challenging due to cell-specific differences in $p75^{NTR}$ signaling and due to the complexity of the interactions of the receptor with multiple functionally specific signaling pathways. Despite these challenges, within many cellular contexts, the mechanisms of $p75^{NTR}$ signaling are becoming better understood. The association of $p75^{NTR}$ with sortilin or Trk receptors, the proteolytic cleavage of $p75^{NTR}$, and the stimulation of $p75^{NTR}$-associated factors represent key events in the regulation of cell survival by the receptor. Further analyses of $p75^{NTR}$ interacting factors and their activities within different cell types are needed, and the relationship of these activities to signaling events modulated by Trk receptors remains to be fully elucidated. Investigations along these lines will significantly enhance our understanding of the molecular processes through which $p75^{NTR}$ regulates cell survival.

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References

1. Nykjaer A, Willnow TE and Petersen CM (2005). p75NTR--live or let die. *Curr Opin Neurobiol*. **15** (1): 49-57.
2. Bronfman FC (2007). Metalloproteases and gamma-secretase: new membrane partners regulating p75 neurotrophin receptor signaling? *J Neurochem*. **103 Suppl 1**: 91-100.
3. Huang EJ and Reichardt LF (2001). Neurotrophins: roles in neuronal development and function. *Annu Rev Neurosci*. **24**: 677-736.
4. Huang EJ and Reichardt LF (2003). Trk receptors: roles in neuronal signal transduction. *Annu Rev Biochem*. **72**: 609-642.
5. Chao MV (2003). Neurotrophins and their receptors: a convergence point for many signalling pathways. *Nat Rev Neurosci*. **4** (4): 299-309.
6. Schwab ME (2004). Nogo and axon regeneration. *Curr Opin Neurobiol*. **14** (1): 118-124.
7. Wang KC, Kim JA, Sivasankaran R, Segal R and He Z (2002). P75 interacts with the Nogo receptor as a co-receptor for Nogo, MAG and OMgp. *Nature*. **420** (6911): 74-78.
8. Jin H, Pan Y, Zhao L, Zhai H, Li X, Sun L, He L, Chen Y, Hong L, Du Y and Fan D (2007). p75 neurotrophin receptor suppresses the proliferation of human gastric cancer cells. *Neoplasia*. **9** (6): 471-478.
9. Lu B, Pang PT and Woo NH (2005). The yin and yang of neurotrophin action. *Nat Rev Neurosci*. **6** (8): 603-614.
10. Johnston AL, Lun X, Rahn JJ, Liacini A, Wang L, Hamilton MG, Parney IF, Hempstead BL, Robbins SM, Forsyth PA and Senger DL (2007). The p75 neurotrophin receptor is a central regulator of glioma invasion. *PLoS Biol*. **5** (8): e212.
11. Oppenheim RW (1991). Cell death during development of the nervous system. *Annu Rev Neurosci*. **14**: 453-501.
12. Frade JM, Rodriguez-Tebar A and Barde YA (1996). Induction of cell death by endogenous nerve growth factor through its p75 receptor. *Nature*. **383** (6596): 166-168.
13. Frade JM and Barde YA (1999). Genetic evidence for cell death mediated by nerve growth factor and the neurotrophin receptor p75 in the developing mouse retina and spinal cord. *Development*. **126** (4): 683-690.
14. Naumann T, Casademunt E, Hollerbach E, Hofmann J, Dechant G, Frotscher M and Barde YA (2002). Complete deletion of the neurotrophin receptor p75NTR leads to long-lasting increases in the number of basal forebrain cholinergic neurons. *J Neurosci*. **22** (7): 2409-2418.
15. Bamji SX, Majdan M, Pozniak CD, Belliveau DJ, Aloyz R, Kohn J, Causing CG and Miller FD (1998). The p75 neurotrophin receptor mediates neuronal apoptosis and is essential for naturally occurring sympathetic neuron death. *J Cell Biol*. **140** (4): 911-923.
16. Syroid DE, Maycox PJ, Soilu-Hanninen M, Petratos S, Bucci T, Burrola P, Murray S, Cheema S, Lee KF, Lemke G and Kilpatrick TJ (2000). Induction of postnatal schwann cell death by the low-affinity neurotrophin receptor in vitro and after axotomy. *J Neurosci*. **20** (15): 5741-5747.
17. Khursigara G, Bertin J, Yano H, Moffett H, DiStefano PS and Chao MV (2001). A prosurvival function for the p75 receptor death domain mediated via the caspase recruitment domain receptor-interacting protein 2. *J Neurosci*. **21** (16): 5854-5863.
18. Casaccia-Bonnefil P, Carter BD, Dobrowsky RT and Chao MV (1996). Death of oligodendrocytes mediated by the interaction of nerve growth factor with its receptor p75. *Nature*. **383** (6602): 716-719.
19. Volosin M, Trotter C, Cragnolini A, Kenchappa RS, Light M, Hempstead BL, Carter BD and Friedman WJ (2008). Induction of proneurotrophins and activation of p75NTR-mediated apoptosis via neurotrophin receptor-interacting factor in hippocampal neurons after seizures. *J Neurosci*. **28** (39): 9870-9879.
20. Sedel F, Bechade C and Triller A (1999). Nerve growth factor (NGF) induces motoneuron apoptosis in rat embryonic spinal cord in vitro. *Eur J Neurosci*. **11** (11): 3904-3912.
21. Srinivasan B, Roque CH, Hempstead BL, Al-Ubaidi MR and Roque RS (2004). Microglia-derived pronerve growth factor promotes photoreceptor cell death via p75 neurotrophin receptor. *J Biol Chem*. **279** (40): 41839-41845.
22. Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen ZY, Lee FS, Kraemer RT, Nykjaer A and Hempstead BL (2005). ProBDNF induces neuronal apoptosis via activation of a receptor complex of p75NTR and sortilin. *J Neurosci*. **25** (22): 5455-5463.
23. Volosin M, Song W, Almeida RD, Kaplan DR, Hempstead BL and Friedman WJ (2006). Interaction of survival and death signaling in basal forebrain neurons: roles of neurotrophins and proneurotrophins. *J Neurosci*. 26 (29): 7756-7766.
    This study demonstrates the upregulation of proneurotrophins in the basal forebrain *in vivo* following kainic-acid-induced seizures and the activation of $p75^{NTR}$-mediated apoptosis of cultured basal forebrain neurons treated with proneurotrophins. The relationship between $p75^{NTR}$ activity and Trk receptor signaling is also examined.
24. Wang S, Bray P, McCaffrey T, March K, Hempstead BL and Kraemer R (2000). p75(NTR) mediates neurotrophin-induced apoptosis of vascular smooth muscle cells. *Am J Pathol*. **157** (4): 1247-1258.
25. Bunone G, Mariotti A, Compagni A, Morandi E and Della Valle G (1997). Induction of apoptosis by p75 neurotrophin receptor in human neuroblastoma cells. *Oncogene*. **14** (12): 1463-1470.
26. Becker EB, Howell J, Kodama Y, Barker PA and Bonni A (2004). Characterization of the c-Jun N-terminal kinase-BimEL signaling pathway in neuronal apoptosis. *J Neurosci*. **24** (40): 8762-8770.
27. Bhakar AL, Howell JL, Paul CE, Salehi AH, Becker EB, Said F, Bonni A and Barker PA (2003). Apoptosis induced by p75NTR overexpression requires Jun kinase-dependent phosphorylation of Bad. *J Neurosci*. **23** (36): 11373-11381.
28. Friedman WJ (2000). Neurotrophins induce death of hippocampal neurons via the p75 receptor. *J Neurosci*. **20** (17): 6340-6346.
29. Aloyz RS, Bamji SX, Pozniak CD, Toma JG, Atwal J, Kaplan DR and Miller FD (1998). p53 is essential for developmental neuron death as regulated by the TrkA and p75 neurotrophin receptors. *J Cell Biol*. **143** (6): 1691-1703.
30. Friedman WJ (2010). Proneurotrophins, seizures, and neuronal apoptosis. *Neuroscientist*. **16** (3): 244-252.
31. Kanning KC, Hudson M, Amieux PS, Wiley JC, Bothwell M and Schecterson LC (2003). Proteolytic processing of the p75 neurotrophin receptor and two homologs generates C-terminal fragments with signaling capability. *J Neurosci*. **23** (13): 5425-5436.
32. Jung KM, Tan S, Landman N, Petrova K, Murray S, Lewis R, Kim PK, Kim DS, Ryu SH, Chao MV and Kim TW (2003). Regulated intramembrane proteolysis of the p75 neurotrophin receptor modulates its association with the TrkA receptor. *J Biol Chem*. **278** (43): 42161-42169.
33. Podlesniy P, Kichev A, Pedraza C, Saurat J, Encinas M, Perez B, Ferrer I and Espinet C (2006). Pro-NGF from Alzheimer's disease and normal human brain displays distinctive abilities to induce processing and nuclear translocation of intracellular domain of p75NTR and apoptosis. *Am J Pathol*. **169** (1): 119-131.
34. Frade JM (2005). Nuclear translocation of the p75 neurotrophin receptor cytoplasmic domain in response to neurotrophin binding. *J Neurosci*. **25** (6): 1407-1411.
35. Kenchappa RS, Zampieri N, Chao MV, Barker PA, Teng HK, Hempstead BL and Carter BD (2006). Ligand-dependent cleavage of the P75 neurotrophin receptor is necessary for NRIF nuclear translocation and apoptosis in sympathetic neurons. *Neuron*. 50 (2): 219-232.
    This study establishes that ligand-dependent cleavage of $p75^{NTR}$ and nuclear translocation of NRIF are required for $p75^{NTR}$-mediated apoptosis of sympathetic neurons *in vitro*. Additionally, these signaling events are observed during the natural period of developmental apoptosis *in vivo*.
36. Urra S, Escudero CA, Ramos P, Lisbona F, Allende E, Covarrubias P, Parraguez JI, Zampieri N, Chao MV, Annaert W and Bronfman FC (2007). TrkA receptor activation by nerve growth factor induces shedding of the p75 neurotrophin receptor followed by endosomal gamma-secretase-mediated release of the p75 intracellular domain. *J Biol Chem*. **282** (10): 7606-7615.
37. Underwood CK, Reid K, May LM, Bartlett PF and Coulson EJ (2008). Palmitoylation of the C-terminal fragment of p75(NTR) regulates death signaling and is required for subsequent cleavage by gamma-secretase. *Mol Cell Neurosci*. **37** (2): 346-358.
38. Ceni C, Kommaddi RP, Thomas R, Vereker E, Liu X, McPherson PS, Ritter B and Barker PA (2010). The p75NTR intracellular domain generated by neurotrophin-induced receptor cleavage potentiates Trk signaling. *J Cell Sci*. **123** (Pt 13): 2299-2307.
39. Srinivasan B, Wang Z, Brun-Zinkernagel AM, Collier RJ, Black RA, Frank SJ, Barker PA and Roque RS (2007). Photic injury promotes cleavage of p75NTR by TACE and nuclear trafficking of the p75 intracellular domain. *Mol Cell Neurosci*. **36** (4): 449-461.
40. Parkhurst CN, Zampieri N and Chao MV (2010). Nuclear localization of the p75 neurotrophin receptor intracellular domain. *J Biol Chem*. **285** (8): 5361-5368.
41. Casademunt E, Carter BD, Benzel I, Frade JM, Dechant G and Barde YA (1999). The zinc finger protein NRIF interacts with the neurotrophin receptor p75(NTR) and participates in programmed cell death. *EMBO J*. **18** (21): 6050-6061.
42. Mukai J, Hachiya T, Shoji-Hoshino S, Kimura MT, Nadano D, Suvanto P, Hanaoka T, Li Y, Irie S, Greene LA and Sato TA (2000). NADE, a p75NTR-associated cell death executor, is involved in signal transduction mediated by the common neurotrophin receptor p75NTR. *J Biol Chem*. **275** (23): 17566-17570.
43. Salehi AH, Roux PP, Kubu CJ, Zeindler C, Bhakar A, Tannis LL, Verdi JM and Barker PA (2000). NRAGE, a novel MAGE protein, interacts with the p75 neurotrophin receptor and facilitates nerve growth factor-dependent apoptosis. *Neuron*. **27** (2): 279-288.
44. Harrington AW, Kim JY and Yoon SO (2002). Activation of Rac GTPase by p75 is necessary for c-jun N-terminal kinase-mediated apoptosis. *J Neurosci*. **22** (1): 156-166.
45. Yamashita T and Tohyama M (2003). The p75 receptor acts as a displacement factor that releases Rho from Rho-GDI. *Nat Neurosci*. **6** (5): 461-467.
46. Chittka A and Chao MV (1999). Identification of a zinc finger protein whose subcellular distribution is regulated by serum and nerve growth factor. *Proc Natl Acad Sci U S A*. **96** (19): 10705-10710.
47. Tcherpakov M, Bronfman FC, Conticello SG, Vaskovsky A, Levy Z, Niinobe M, Yoshikawa K, Arenas E and Fainzilber M (2002). The p75 neurotrophin receptor interacts with multiple MAGE proteins. *J Biol Chem*. **277** (51): 49101-49104.
48. Kong H, Boulter J, Weber JL, Lai C and Chao MV (2001). An evolutionarily conserved transmembrane protein that is a novel downstream target of neurotrophin and ephrin receptors. *J Neurosci*. **21** (1): 176-185.
49. Ye X, Mehlen P, Rabizadeh S, VanArsdale T, Zhang H, Shin H, Wang JJ, Leo E, Zapata J, Hauser CA, Reed JC and Bredesen DE (1999). TRAF family proteins interact with the common neurotrophin receptor and modulate apoptosis induction. *J Biol Chem*. **274** (42): 30202-30208.
50. Yeiser EC, Rutkoski NJ, Naito A, Inoue J and Carter BD (2004). Neurotrophin signaling through the p75 receptor is deficient in traf6-/- mice. *J Neurosci*. **24** (46): 10521-10529.
51. Bertrand MJ, Kenchappa RS, Andrieu D, Leclercq-Smekens M, Nguyen HN, Carter BD, Muscatelli F, Barker PA and De Backer O (2008). NRAGE, a p75NTR adaptor protein, is required for developmental apoptosis in vivo. *Cell Death Differ*. **15** (12): 1921-1929.
52. Inoue J, Gohda J and Akiyama T (2007). Characteristics and biological functions of TRAF6. *Adv Exp Med Biol*. **597**: 72-79.
53. Pineda G, Ea CK and Chen ZJ (2007). Ubiquitination and TRAF signaling. *Adv Exp Med Biol*. **597**: 80-92.
54. Powell JC, Twomey C, Jain R and McCarthy JV (2009). Association between Presenilin-1 and TRAF6 modulates regulated intramembrane proteolysis of the p75NTR neurotrophin receptor. *J Neurochem*. **108** (1): 216-230.
55. Linggi MS, Burke TL, Williams BB, Harrington A, Kraemer R, Hempstead BL, Yoon SO and Carter BD (2005). Neurotrophin receptor interacting factor (NRIF) is an essential mediator of apoptotic signaling by the p75 neurotrophin receptor. *J Biol Chem*. **280** (14): 13801-13808.
56. Geetha T, Kenchappa RS, Wooten MW and Carter BD (2005). TRAF6-mediated ubiquitination regulates nuclear translocation of NRIF, the p75 receptor interactor. *EMBO J*. **24** (22): 3859-3868.
57. Harrington AW, Leiner B, Blechschmitt C, Arevalo JC, Lee R, Morl K, Meyer M, Hempstead BL, Yoon SO and Giehl KM (2004). Secreted proNGF is a pathophysiological death-inducing ligand after adult CNS injury. *Proc Natl Acad Sci U S A*. 101 (16): 6226-6230.
    This is one of the initial studies demonstrating that endogenous proneurotrophins bind to $p75^{NTR}$ and stimulate programmed cell death in response to cellular injury *in vivo*. Specifically, the role of proNGF in inducing $p75^{NTR}$-mediated apoptotic signaling in lesioned corticospinal neurons is revealed.

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58. Beattie MS, Harrington AW, Lee R, Kim JY, Boyce SL, Longo FM, Bresnahan JC, Hempstead BL and Yoon SO (2002). ProNGF induces p75-mediated death of oligodendrocytes following spinal cord injury. *Neuron*. **36** (3): 375-386.
59. Ferri CC, Moore FA and Bisby MA (1998). Effects of facial nerve injury on mouse motoneurons lacking the p75 low-affinity neurotrophin receptor. *J Neurobiol*. **34** (1): 1-9.
60. Gentry JJ, Barker PA and Carter BD (2004). The p75 neurotrophin receptor: multiple interactors and numerous functions. *Prog Brain Res*. **146**: 25-39.
61. Kenchappa RS, Tep C, Korade Z, Urra S, Bronfman FC, Yoon SO and Carter BD (2010). p75 neurotrophin receptor-mediated apoptosis in sympathetic neurons involves a biphasic activation of JNK and up-regulation of tumor necrosis factor-alpha-converting enzyme/ADAM17. *J Biol Chem*. **285** (26): 20358-20368.
62. Maroney AC, Finn JP, Bozyczko-Coyne D, O'Kane TM, Neff NT, Tolkovsky AM, Park DS, Yan CY, Troy CM and Greene LA (1999). CEP-1347 (KT7515), an inhibitor of JNK activation, rescues sympathetic neurons and neuronally differentiated PC12 cells from death evoked by three distinct insults. *J Neurochem*. **73** (5): 1901-1912.
63. Seidah NG, Benjannet S, Pareek S, Chretien M and Murphy RA (1996). Cellular processing of the neurotrophin precursors of NT3 and BDNF by the mammalian proprotein convertases. *FEBS Lett*. **379** (3): 247-250.
64. Lee R, Kermani P, Teng KK and Hempstead BL (2001). Regulation of cell survival by secreted proneurotrophins. *Science*. **294** (5548): 1945-1948.
65. Nykjaer A, Lee R, Teng KK, Jansen P, Madsen P, Nielsen MS, Jacobsen C, Kliemannel M, Schwarz E, Willnow TE, Hempstead BL and Petersen CM (2004). Sortilin is essential for proNGF-induced neuronal cell death. *Nature*. **427** (6977): 843-848.
66. Fan YJ, Wu LL, Li HY, Wang YJ and Zhou XF (2008). Differential effects of pro-BDNF on sensory neurons after sciatic nerve transection in neonatal rats. *Eur J Neurosci*. **27** (9): 2380-2390.
67. Cortazzo MH, Kassis ES, Sproul KA and Schor NF (1996). Nerve growth factor (NGF)-mediated protection of neural crest cells from antimitotic agent-induced apoptosis: the role of the low-affinity NGF receptor. *J Neurosci*. **16** (12): 3895-3899.
68. Bui NT, Konig HG, Culmsee C, Bauerbach E, Poppe M, Krieglstein J and Prehn JH (2002). p75 neurotrophin receptor is required for constitutive and NGF-induced survival signalling in PC12 cells and rat hippocampal neurones. *J Neurochem*. **81** (3): 594-605.
69. Longo FM, Manthorpe M, Xie YM and Varon S (1997). Synthetic NGF peptide derivatives prevent neuronal death via a p75 receptor-dependent mechanism. *J Neurosci Res*. **48** (1): 1-17.
70. DeFreitas MF, McQuillen PS and Shatz CJ (2001). A novel p75NTR signaling pathway promotes survival, not death, of immunopurified neocortical subplate neurons. *J Neurosci*. **21** (14): 5121-5129.
71. Lee KF, Li E, Huber LJ, Landis SC, Sharpe AH, Chao MV and Jaenisch R (1992). Targeted mutation of the gene encoding the low affinity NGF receptor p75 leads to deficits in the peripheral sensory nervous system. *Cell*. **69** (5): 737-749.
72. Tan J, Clarke M, Barrett G and Millard R (2010). The p75 neurotrophin receptor protects primary auditory neurons against acoustic trauma in mice. *Hear Res*.
73. Hempstead BL, Martin-Zanca D, Kaplan DR, Parada LF and Chao MV (1991). High-affinity NGF binding requires coexpression of the trk proto-oncogene and the low-affinity NGF receptor. *Nature*. **350** (6320): 678-683.
74. Gentry JJ, Casaccia-Bonnefil P and Carter BD (2000). Nerve growth factor activation of nuclear factor kappaB through its p75 receptor is an anti-apoptotic signal in RN22 schwannoma cells. *J Biol Chem*. **275** (11): 7558-7565.
75. Hamanoue M, Middleton G, Wyatt S, Jaffray E, Hay RT and Davies AM (1999). p75-mediated NF-kappaB activation enhances the survival response of developing sensory neurons to nerve growth factor. *Mol Cell Neurosci*. 14 (1): 28-40.
This study reveals that p75^{NTR} promotes the survival of cultured trigeminal neurons through the ligand-dependent activation of NFkappaB. Moreover, analyses of p65-/- animals suggest that this function may contribute to developmental survival signaling *in vivo*.
76. Culmsee C, Gerling N, Lehmann M, Nikolova-Karakashian M, Prehn JH, Mattson MP and 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** (4): 1089-1108.

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