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Neurotrophin signalling pathways regulating neuronal apoptosis

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Abstract. Recent evidence indicates that naturally occurring neuronal death in mammals is regulated by the interplay between receptor-mediated prosurvival and proapoptotic signals. The neurotrophins, a family of growth factors best known for their positive effects on neuronal biology, have now been shown to mediate both positive and negative survival signals, by signalling through the Trk and p75 neurotrophin receptors, respectively. The mechanisms whereby these two neurotrophin receptors interact to determine neuronal survival have been difficult to decipher, largely because both can signal independently or coincidentally, depending upon the cell or developmental context. Nonetheless, the past several years have seen significant advances in our understanding of this receptor signalling system. In this review, we focus on the proapoptotic actions of the p75 neurotrophin receptor ($p75^{NTR}$), and on the interplay between Trk and $p75^{NTR}$ that determines neuronal survival.

Key words. Neurotrophin; Trk receptor; p75 neurotrophin receptor; neuronal apoptosis; p53; p73; JNK; sympathetic neuron; neuronal signal transduction; neuronal cell cycle.

Introduction

During development of the nervous system, both progenitor cells and postmitotic neurons are overproduced, and the nervous system then chooses, through a process of elimination, those cells that have differentiated and made appropriate connections. This cell selection process takes place during two major periods of apoptosis. The first occurs in the ventricular and subventricular zones of the developing nervous system, where neural stem and progenitor cells differentiate to produce the neurons and glial cells that will migrate and populate the brain and spinal cord. This period of apoptosis likely serves two functions: to eliminate those progenitors that do not differentiate appropriately, and to ensure that the appropriate cell number is generated in rapidly growing tissues such as the cerebral cortex. The existence of this period of apoptotic death has only recently been appreciated [1], and the mechanisms that control the life versus death of any given cell are still only poorly understood.

The second period of apoptotic death in the nervous system occurs once newly born neurons have migrated to their final destinations, have extended their axons, and have attempted to establish appropriate connections. This period of naturally occurring neuronal death eliminates approximately half the neurons in any given population [2]. In the peripheral nervous system, where this process has been extensively studied, recent work indicates that the ultimate survival of any given neuron during this period is dependent upon the interplay between receptor mediated prosurvival and proapoptotic signals. One family of growth factors that have been implicated both as positive survival signals and negative proapoptotic signals are the neurotrophins, the subject of this review.

Neurotrophins mediate the survival, differentiation, growth, and apoptosis of neurons by binding to two types of cell surface receptors, the Trk tyrosine kinases [3, 4], and the p75 neurotrophin receptor ($p75^{NTR}$) [5, 6]. These receptors, often present on the same cell, coordinate and modulate the responses of neurons to neurotrophins. The functions of the neurotrophin receptors vary markedly, from sculpting the developing nervous system to regulation of the survival and regeneration of injured neurons [7, 8]. Strikingly, while Trk receptors largely transmit positive signals that promote neuronal survival, $p75^{NTR}$ transmits both positive and negative signals and, in part-

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icular, can cause neuronal apoptosis. Research is just now elucidating the intracellular mechanisms that allow the same family of growth factors to be both prosurvival and proapoptotic. In this review, we will focus on the mechanisms underlying the proapoptotic function of $p75^{NTR}$.

$p75^{NTR}$ as an apoptotic receptor

$p75^{NTR}$ [5, 6] was the first-discovered member of the Fas/tumor necrosis factor (TNF) receptor family of receptors, which mediate cellular differentiation and apoptosis [9]. $p75^{NTR}$ can interact with all of the mammalian members of the neurotrophin family with approximately equivalent affinities [10, 11]. $p75^{NTR}$ was originally reported to function as a positive regulator of TrkA activity in a number of neural cell lines [12–15]. Compared to cells that express each receptor individually, coexpression of the $p75^{NTR}$ and TrkA receptors in transformed cells led to an increase in both high-affinity nerve growth factor (NGF)-binding sites [16, 17] and NGF-mediated TrkA activation [12, 14, 17]. The decrease in sensory neurons in the dorsal root ganglion (DRG) observed in the $p75^{NTR}$–/– mouse was consistent with this hypothesis [18]; however, other defects have since been observed in these mice that are not consistent with this idea (reviewed below).

More recent evidence indicates that, like other members of this family of receptors, $p75^{NTR}$ signals on its own and that, in certain cellular contexts, this signalling leads to apoptosis. Neurotrophin binding to $p75^{NTR}$ stimulates the generation of ceramide [19–21], regulates its association with a number of proteins, including the TRAFs [22, 23], NRIF [24], NRAGE [25], SC-1 [26], NADE [27] and Rho [28], leads to the activation and translocation of NF-κB [29–31], and activates the JNK pathway [19, 32–34]. As for apoptosis, the original finding that $p75^{NTR}$ could mediate apoptosis of a neural cell line [35] has been extended to a large number of primary neural cells in culture. In particular, $p75^{NTR}$ has been implicated in the apoptosis of cultured neonatal sympathetic neurons [32, 33], motor neurons [36, 37], sensory neurons [38–40], hippocampal neurons [34], oligodendrocytes [19], and postnatal Schwann cells [41, 42]. A number of studies indicate that this proapoptotic function of $p75^{NTR}$ is essential for rapid and appropriate apoptosis during developmental cell death. In particular, apoptosis is significantly reduced in certain neuronal populations in mice lacking $p75^{NTR}$ or its neurotrophin ligands. For example, apoptosis is decreased in embryonic retinae of NGF–/– and $p75^{NTR}$–/– mice [43, 44], the period of naturally occurring sympathetic neuron death is attenuated in brain-derived neurotrophic factor (BDNF)–/– mice and greatly delayed in the $p75^{NTR}$–/– mice [32], apoptosis of trigeminal ganglion neurons is attenuated in both neurotrophin (NT)-4–/– and $p75^{NTR}$–/– mice [40], and more basal forebrain cholinergic neurons are present in the early postnatal $p75^{NTR}$–/– brain [45]. Moreover, $p75^{NTR}$ is essential for maintaining the specificity of neuronal survival responses to different neurotrophins during development: sympathetic neurons of $p75^{NTR}$–/– but not $p75^{NTR}$+/+ mice utilized NT-3 as a survival ligand both in vivo [46] and in culture [47]. Thus, $p75^{NTR}$ and its neurotrophin ligands are essential negative regulators of neuronal survival during developmental neuron death.

The proapoptotic function of $p75^{NTR}$ has also been implicated in injury-induced apoptosis. The first study to support this idea involved the neuron-specific expression of the $p75^{NTR}$ intracellular domain, which led to the death of injured facial motor neurons in transgenic mice [48]. Endogenous $p75^{NTR}$ was subsequently shown to play a role in the death of injured neonatal facial motor neurons [36], and Schwann cell apoptosis was greatly reduced in the distal stump of the axotomized neonatal sciatic nerve of $p75^{NTR}$–/– animals [42]. Moreover, in the adult central nervous system (CNS), excitotoxin-induced neuronal apoptosis was accompanied by induction of $p75^{NTR}$ in the dying neurons [49], suggesting that $p75^{NTR}$ might represent a general stress-induced apoptotic mechanism in the damaged or degenerating nervous system.

All of these studies indicate that $p75^{NTR}$ is a signalling receptor that is important for neuronal apoptosis during development and in the injured nervous system. However, it is important to recognize that, like other members of the TNF receptor family, $p75^{NTR}$ regulates a number of other biological responses, including cell migration [50] and neuronal growth and target innervation [28, 31, 45, 51–54] and that it can, paradoxically, enhance Trk-mediated survival (discussed below). At least part of this pleiotropy is simply a function of cellular context. However, additional complexity derives from the fact that $p75^{NTR}$ can interact directly with Trk [55, 56], and by the finding that its signalling capacity within a given cell is modified by the coincident activation of Trk receptors (discussed below). Nonetheless, the past several years have seen the elucidation of several of the apoptotic pathways that are activated by $p75^{NTR}$, and of the mechanisms whereby interactions with Trk modify its biological potential.

$p75^{NTR}$ as an apoptotic receptor independent of Trk

The mechanisms whereby $p75^{NTR}$ mediates neuronal apoptosis have been difficult to decipher, largely because of the interplay between $p75^{NTR}$ and the Trk receptors that are present on many of the primary cells that have been studied. However, a number of major conclusions can be derived from the many studies described above. First, in most of the cell culture studies, the apoptotic actions of

p75^{NTR} were ligand mediated, indicating that ligand binding to p75^{NTR} does not abolish its ability to mediate apoptosis, as previously suggested [57]. Second, a number of these studies indicate that p75^{NTR} can signal apoptosis in a Trk-independent fashion. For example, p75^{NTR} activation caused apoptosis when sympathetic neurons were maintained in KCl [32, 33], when sensory neurons were maintained in ciliary neurotrophic factor (CNTF) [39], and when Schwann cells were maintained in insulin-like growth factor (IGF) plus neuregulin [41], all Trk-independent survival signals. Third, in most of these studies, p75^{NTR} only mediated apoptosis when Trk was inactive or suboptimally activated, leading to the conclusion that Trk activation can silence p75^{NTR} apoptotic signalling. For example, robust Trk activation blocked p75^{NTR}-mediated death of sympathetic [32] and trigeminal mesencephalic sensory neurons [39], and expression of exogenous TrkA in oligodendrocytes [58] or TrkB in sympathetic neurons [59] inhibited NGF- and BDNF-induced apoptosis, respectively. Thus, the outcome of neurotrophin-mediated p75^{NTR} signalling depends on the expression of Trk receptors; NGF has the potential to be proapoptotic for cells that do not express TrkA [such as oligodendrocytes; ref. 58], while BDNF would be proapoptotic for those cells that do not express TrkB [such as sympathetic neurons; ref. 32].

A fourth and somewhat surprising conclusion is that, for at least some developing neurons, p75^{NTR} mediates a constitutive death signal, and that one of the primary ways that Trk receptors mediate neuronal survival is by silencing this constitutive signal (fig. 1). The first line of evidence supporting this conclusion derives from studies showing that p75^{NTR} is essential for apoptosis of some cells following growth factor withdrawal. Barrett and Bartlett [38] first showed that sensory neuron survival following neurotrophin withdrawal was enhanced when p75^{NTR} levels were decreased. More recent work extended this finding to other primary cells; apoptosis of p75^{NTR}–/– sympathetic neurons was greatly delayed following NGF withdrawal [32], even when Trk receptor signalling was completely eliminated [M. Majdan, R. Aloyz and F. D. Miller, unpublished data], and p75^{NTR}–/– Schwann cells showed enhanced survival in the absence of survival factors [41, 42]. Interestingly, as no exogenous p75^{NTR} ligand is present following growth factor withdrawal, these data may suggest that p75^{NTR} can signal apoptosis in a ligand-independent fashion [57]. However, as both sympathetic neurons and Schwann cells make endogenous p75^{NTR} ligands, these data raise the equally interesting possibility of an autocrine p75^{NTR}-driven apoptosis loop that is suppressed by survival factors.

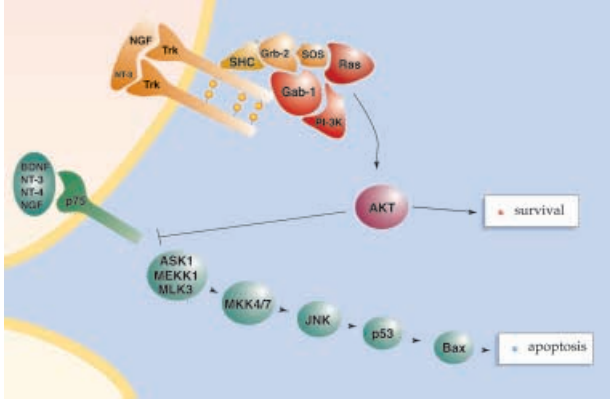

Figure 1. TrkA mediates sympathetic neuron survival during naturally occurring neuronal death by blocking p75NTR-mediated apoptotic signals. NGF signals robustly through TrkA, thereby silencing any p75^{NTR}-mediated signalling. In contrast, NT-3 signals only weakly through TrkA, and robustly through p75^{NTR}, thereby 'tipping the balance' toward apoptosis. TrkA likely overrides a p75^{NTR}-JNK-p53 apoptotic pathway via Ras, PI3-kinase and Akt, acting upstream of JNK. TrkA must also signal neuronal survival via at least one other, p75^{NTR}-independent pathway, since sympathetic neuron apoptosis is greatly delayed but not eliminated in the absence of p75^{NTR}. This latter survival pathway may involve regulation of the cell cycle machinery. For references, see text.

Perhaps the most compelling evidence for the model presented in figure 1 derives from a second set of studies examining p75^{NTR}–/– and TrkA–/– mice. During the postnatal period of naturally occurring sympathetic neuron death, absence of the TrkA receptor leads to death of virtually all sympathetic neurons [60], while absence of p75^{NTR} has the reverse effect, dramatically decreasing apoptosis [32]. When these two animals are crossed, the coincident loss of p75^{NTR} in TrkA–/– mice leads to the rescue of most of the neurons that would have died, at least during the first postnatal week (the double knockouts die by P7) [M. Majdan and F. Miller, unpublished data]. Thus, sympathetic neurons are 'destined to die' as a consequence of an ongoing, p75^{NTR}-mediated apoptotic signal, and survive only if they sequester sufficient NGF to robustly activate TrkA, supporting the idea that developmental neuron death is partially due to constitutive receptor-mediated death signals that must be silenced by sequestration of the appropriate prosurvival factor (fig. 1). However, the fact that sympathetic neuron rescue is not complete in the p75^{NTR}–/–, TrkA–/– mice [M. Majdan and F. Miller, unpublished data], and that p75^{NTR}–/– sympathetic neurons still die, albeit at a reduced rate, when NGF is withdrawn [32] or when all Trk function is pharmacologically inhibited [M. Majdan and F. Miller, unpublished data], indicates that TrkA also partially mediates neuronal survival in a p75^{NTR}-independent fashion (fig. 1).

What is the biological rationale for having two neurotrophin receptors, one of which, TrkA, mediates neuronal survival, and one of which, p75^{NTR}, mediates apoptosis? The data for sympathetic neurons suggest that p75^{NTR} provides a molecular mechanism for ensuring rapid and active apoptosis when a neuron is unsuccessful in competing for adequate amounts of the appropriate neurotrophin [61]. If a sympathetic neuron reaches the appro-

priate target and sequesters NGF, TrkA is robustly activated and any coincident activation of p75^{NTR} is insufficient to override this survival signal [32]. Conversely, when a neuron arrives late and/or reaches an inappropriate target, TrkA is only weakly induced (if at all) due to lack of NGF, whereas p75^{NTR} can still be robustly activated by non-TrkA-binding neurotrophins such as BDNF [32] that are encountered in the target environment [53] and/or made by sympathetic neurons themselves [62]. The net outcome of such a scenario would be the rapid apoptotic elimination of that neuron, thereby ensuring that the subsequent period of target innervation occurs appropriately. Interestingly, a similar model has recently been proposed for developmental apoptosis of trigeminal ganglion neurons where NT-4 signals apoptosis via p75^{NTR} [40].

What if a developing sympathetic neuron encounters a neurotrophin such as NT-3, which has the capacity to weakly activate TrkA [63]? Recent evidence indicates that p75^{NTR} is also essential for sympathetic neurons to select 'appropriate' (NGF) versus 'inappropriate' (NT-3) neurotrophins for survival; the absence of p75^{NTR} converts NT-3 to a survival factor for sympathetic neurons both in culture [47] and in vivo [46]. How does p75^{NTR} subserve this function? Since NT-3 activates TrkA on p75^{NTR}+/+ and –/– neurons to a similar extent [Majdan et al., unpublished data], but maintains survival only for the p75^{NTR}–/– neurons [46, 47], and since coincident p75^{NTR} activation does not affect the levels of sympathetic neuron TrkA activation [32, 33], then p75^{NTR} likely 'selects' survival ligands by antagonistically signalling neuronal apoptosis. Thus, a weak TrkA survival signal deriving from NT-3 would normally be overriden by a strong apoptotic signal deriving from p75^{NTR}, but in the absence of p75^{NTR}, this weak TrkA signal is sufficient for survival (fig. 1).

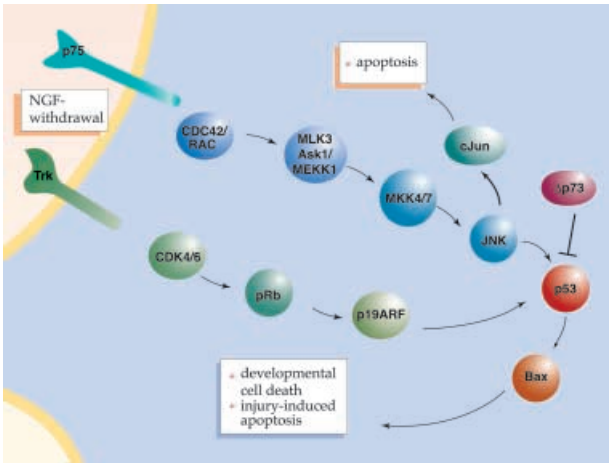

Figure 2. Apoptotic signalling pathways in sympathetic neurons activated by NGF withdrawal or selective p75NTR activation. Two pathways are activated by withdrawal of NGF from sympathetic neurons. The first consists of cdc42/Rac, Ask1, and, possibly, MEKK1or MLK3 [64], MKK4/7, JNK, and p53. JNK isoforms induce cell death through c-Jun and/or by increases in p53 and Bax levels or activity [65]. This pathway is also activated when p75^{NTR} is selectively activated under conditions that cause apoptosis. A second pathway involves the activation of cell cycle regulatory molecules such as CDK4/6, which results in increased pRb phosphorylation, and possibly the subsequent activation of p53 through p19ARF. ΔNp73 blocks the apoptosis caused by NGF withdrawal. We hypothesize that each pathway converges upon and activates the p53 family to cause cell death. For references, see text.

p75^{NTR} apoptotic signal transduction

How does p75^{NTR} signal apoptosis? One recently elucidated pathway involves JNK-p53-Bax, which is activated in sympathetic neurons both by p75^{NTR} activation and by NGF withdrawal [33] (fig. 2). The JNK family of stress-activated kinases [66] has been shown to be downstream of p75^{NTR} in oligodendrocytes [19], sympathetic neurons [32, 33], and hippocampal neurons [34], and JNK-mediated activation of c-jun has been demonstrated to be essential for NGF withdrawal induced death of sympathetic neurons [66–69]. A number of studies indicate that p53 is also essential for both p75^{NTR}-mediated and NGF withdrawal-induced sympathetic neuron death. First, overexpression of p53 is sufficient to cause the death of sympathetic neurons in the presence of NGF [70]. Second, Vogel and Parada [71] demonstrated that embryonic p53–/– sympathetic neurons showed enhanced survival in culture in the absence of NGF, their obligate survival factor. Third, Aloyz et al. [33] demonstrated that p53 levels increased when sympathetic neurons underwent apoptosis in response to either NGF withdrawal or activation of p75^{NTR}, and that apoptosis could be inhibited if this increase in p53 levels was prevented. Moreover, developmental sympathetic neuron death was delayed (but not prevented) in the p53–/– mice.

The link between JNK and p53 was established by studies showing that activation of the JNK pathway using a constitutively activated form of MEKK (a kinase upstream of JNK), increased p53 levels and caused p53-dependent sympathetic-neuron apoptosis [33]. What is upstream of JNK? Although this is still unclear with regard to p75^{NTR}, cdc42/Rac1 [72] and Ask1 [73] have both been shown to act upstream of JNK in NGF withdrawal-induced apoptosis of sympathetic neurons. The presence of apoptotic proteins common to both p75^{NTR}- and NGF withdrawal-induced cell death pathways, and the observation that p75^{NTR}–/– sympathetic neurons are delayed in their death in the absence of TrkA activation both in vitro and in vivo (reviewed above) suggest that a major component of NGF withdrawal-induced apoptosis involves p75^{NTR}-driven activation of the JNK-p53-Bax pathway. Although the importance of this pathway for apoptosis in other cells is not yet known, it is intriguing that p75^{NTR} is induced in dying cells following seizure [49] and that seizure-induc-

ed apoptosis requires JNK3 [74] and p53 [75]. Also intriguing is the finding that $p75^{NTR}$-mediated apoptosis of oligodendrocytes involves the same pattern of caspase activation as radiation-induced oligodendrocyte apoptosis [76], which is known to require p53 [77]. Thus, although the mechanism by which $p75^{NTR}$ activates the JNK-p53-Bax cell death pathway is still unclear, this pathway may well play a key role in a variety of $p75^{NTR}$-driven apoptotic events.

Given the parallels between NGF withdrawal and $p75^{NTR}$-driven sympathetic neuron apoptosis, a second pathway that is important for NGF withdrawal is also worth considering (fig. 2). This pathway involves activation of the cell cycle regulatory molecules CDK4/6, which activate the retinoblastoma tumor suppressor protein (pRb) by phosphorylation, and subsequently participate in causing sympathetic neuron apoptosis after NGF withdrawal [78–80]. No link has yet been made between $p75^{NTR}$ activation and stimulation of this cell cycle pathway in sympathetic neurons, although NGF-induced apoptosis of retinal ganglion cells is correlated with cell cycle reentry [81]. Moreover, a number of new $p75^{NTR}$-interacting proteins, including SC-1 [26] and NRAGE [25], appear to regulate cell cycle function and, at least in the case of NRAGE, apoptosis. However, the cell cycle pathway possibly represents a $p75^{NTR}$-independent pathway that is responsible for the delayed apoptosis of $p75^{NTR}$–/– sympathetic neurons. Such a model implies that TrkA would suppress this pathway independent of its effects on $p75^{NTR}$; TrkA is known to lock PC12 cells out of the cell cycle [82], and a number of Trk family members are thought to play key roles in regulating the progenitor-to-postmitotic neuron transition [83, 84], presumably at least partially via cell cycle regulation. Interestingly, since pRb dysregulation is (i) known to cause p53 activation via p19ARF in nonneuronal cells [85] and (ii) leads to p53-dependent apoptosis in the embryonic nervous system [1], it follows that this cell cycle pathway might also converge on p53. If this were the case, then p53 would play a pivotal role in integrating neuronal apoptotic stimuli, perhaps thereby ensuring that apoptosis ensues only when these stimuli reach a certain critical threshold (fig. 2).

In addition to a role for p53 in sympathetic neuron apoptosis, recent work indicates that the related p53 family member, p73 [86, 87], also plays an essential role, but whereas p53 is proapoptotic, p73 is antiapoptotic. A recent study by Pozniak et al. [88] indicates that the predominant isoform of p73 in the developing brain and sympathetic ganglia is truncated at the amino-terminus (ΔNp73) and lacks the transactivation domain. Levels of $\Delta Np73\beta$ are high in sympathetic neurons when they are maintained in NGF, but decrease dramatically when NGF is withdrawn; if this decrease is prevented by ectopic expression of ΔNp73, neurons are rescued from apoptosis. Moreover, in p73–/– mice [88], developmental sympathetic neuron death is enhanced, indicating an essential antiapoptotic role for p73 in these neurons.

How does ΔNp73 inhibit sympathetic neuron apoptosis? ΔNp73 can directly bind to p53, at least in vitro, and can rescue p53-mediated death of sympathetic neurons [88]. Thus, one of the potential mechanisms whereby ΔNp73 might inhibit apoptosis is by binding to p53 and inhibiting its proapoptotic actions (fig. 2). Does p73 play a similar antiapoptotic role in other populations of developing or mature neurons? Although this question has not yet been answered, the phenotype of the p73–/– mice indicates that p73 is essential for normal neural development [89]. These mice display hippocampal dysgenesis, absence of certain neuronal subtypes in both the central and peripheral nervous systems, and many die showing greatly enlarged ventricles and decreased cortical tissue. Although there are several potential explanations for these phenotypes, they could all be explained by the absence of an antiapoptotic activity in selected populations of CNS neurons and/or progenitors. Moreover, the truncated form of $p73\beta$ that is predominantly observed in the developing brain is generated from the same gene as the full-length, proapoptotic form of p73 by alternative promoter usage [89], providing a mechanism for rapidly altering the ratios of the pro- versus anti-apopotic isoforms of p73 in the nervous system. One potential explanation for the partial penetrance of the neural phenotype observed in p53–/– embryos [1] is that p73 may be able to compensate for the absence of p53 in the nervous system, at least with regard to developmental apoptosis.

Other potential $p75^{NTR}$-dependent apoptotic pathways involve the recently reported $p75^{NTR}$ interactors, NRIF [24], NRAGE [25], and NADE [27]. NRIF is a ubiquitously expressed zinc finger protein that interacts with $p75^{NTR}$ in glutathione-s-transferase (GST) pulldown assays. Intriguingly, analysis of NRIF–/– mice revealed a deficit in apoptosis in the embryonic retina similar to that seen in the NGF–/– and $p75^{NTR}$–/– mice [43, 44], raising the possibility that $p75^{NTR}$ signals apoptosis in some cells via NRIF. NRAGE promotes cell cycle exit and enhances NGF-mediated apoptosis of MAH cells, a sympathetic progenitor cell line [25]. The third interactor, NADE, interacts with $p75^{NTR}$ in a ligand-dependent fashion and can, when cotransfected with $p75^{NTR}$, lead to cellular apoptosis. A number of other $p75^{NTR}$-interacting proteins have also recently been described, but their potential role in apoptotic neuronal signalling is less clear. In particular, TRAF6 and other TRAF family members can interact with $p75^{NTR}$ [22, 23], as can SC-1, a zinc finger protein that, like NRIF, associates with $p75^{NTR}$ in GST pulldown assays [26]. Interestingly, NGF-mediated activation of $p75^{NTR}$ led to translocation of SC-1 from the cytoplasm to the nucleus and inhibited cellular proliferation, an activity similar to that seen for NRAGE [25]. Are any of

these proteins upstream in the p75^{NTR}-JNK-p53 apoptotic pathway? Although none of the novel interactors have been demonstrated to couple to this pathway, a number of the TRAFs have previously been shown to activate JNK [90], and elevations in ceramide can also lead to activation of the JNK pathway [91].

The Interplay between p75^{NTR} and TrkA signalling

One of the major conclusions that can be derived from recent studies on the neurotrophin receptors is that the signalling capacity and biological role of p75^{NTR} is a function of cellular Trk activation status. In particular, as discussed above, in most situations, p75^{NTR} only mediates neuronal apoptosis when the cognate Trk receptor is not, or is only weakly, activated. Moreover, ectopic expression of the appropriate Trk receptor can convert a proapoptotic neurotrophin (which binds only to p75^{NTR}) into a prosurvival neurotrophin (by binding to both Trk and p75^{NTR}) [58, 59]. How does Trk silence the p75^{NTR}-mediated apoptotic pathway? A number of studies suggest that it does so by inhibiting JNK activation. Specifically, in sympathetic neurons, TrkA activation silenced the JNK-p53 death pathway via Ras [92], while in oligodendrocytes and PC12 cells, exogenous TrkA silenced JNK activation [58] and elevations in ceramide [21], respectively. Although the precise mechanism by which Ras inhibits JNK activation has not yet been determined, it likely involves the PI3-kinase-Akt pathway, which is a major Trk-mediated survival pathway in many cells, including sympathetic neurons [93].

But does coincident Trk activation convert p75^{NTR} to a 'silent' receptor? An increasing number of studies indicate not, and suggest that while the proapoptotic signals are silenced, other signals remain intact. For example, in basal forebrain cholinergic neurons [45], sympathetic neurons [52, 53], and sensory neurons [31], p75^{NTR} activation negatively regulates axonal growth and neuronal hypertrophy. In one dramatic example of this effect, adult p75^{NTR}–/– but not p75^{NTR}+/+ sympathetic neurons grow robustly over CNS myelin when stimulated with NGF in a transgenic mouse [52]. Similarly, sympathetic neurons hyperinnervate their target organs when BDNF levels are decreased even by half in the BDNF+/- mice [53]. Thus, even when neuronal survival is maintained by Trk signalling, antagonistic signalling between TrkA and p75^{NTR} can regulate neuronal growth.

Recent evidence also indicates that, when p75^{NTR} and Trk are coincidentally activated, p75^{NTR}-mediated NF-κB signalling may, paradoxically, enhance the ability of Trk to promote neuronal survival. The finding that p75^{NTR} caused activation of the transcription factor NF-κB in Schwann cells [29] has recently been extended to oligodendrocytes [30] and sensory neurons [31]. Unlike the JNK-p53 pathway, p75^{NTR}-mediated activation of NFκB is not silenced by coincident TrkA activation [58]. Two recent studies suggest that this NF-κB activation represents a p75^{NTR}-mediated prosurvival pathway that collaborates with Trk. Specifically, Maggirwar et al. [94] demonstrated that NGF treatment of sympathetic neurons led to NF-κB activation, and that this activation was important for NGF-mediated survival. Although this study did not examine the relative roles of TrkA versus p75^{NTR}, Hamanoue et al. [95] demonstrated that NGF-induced NF-κB activation in sensory neurons required p75^{NTR} and that this pathway was important for survival. Thus, p75^{NTR} may act as a 'switch' in neurons. In the absence of Trk signalling, JNK-p53 would be activated, providing a constitutive death pathway, as seen in sympathetic neurons. Conversely, coincident, optimal activation of Trk signalling would silence the JNK-p53 pathway selectively, and p75^{NTR}-mediated activation of the NF-κB pathway would now collaborate with Trk to maintain neuronal survival.

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