Editorial

Life and death decisions: a biological role for the p75 neurotrophin receptor

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The cellular mechanisms that regulate neuronal survival either during naturally-occurring cell death or in the traumatized mature nervous system are still not well-understood. However, over the past several years, evidence has emerged to support the somewhat surprising conclusion that the neurotrophins, perhaps the best-characterized neuronal survival factors, mediate cellular apoptosis via the p75 neurotrophin receptor. These findings are discussed in three separate reviews in this issue of *Cell Death and Differentiation* and, although all three agree that p75^{NTR} can mediate apoptosis, none of them agree on the underlying mechanism. In this editorial, we will discuss some of the differences between these models, and will discuss the biological rationale for having a proapoptotic neurotrophin receptor.

Ligand-dependent or independent?

As discussed in the review by Bredesen *et al.* (1998, this issue), a number of papers have demonstrated that simply altering the level of p75^{NTR} in cells is sufficient to regulate cellular survival; high levels of p75^{NTR} caused apoptosis, and decreasing these levels allowed cells to survive (for example, see Rabizadeh *et al.*, 1993). On the basis of these findings, Bredesen and colleagues suggest that p75^{NTR} mediates apoptosis in a ligand-independent fashion. In apparent contradiction, p75^{NTR} in nontransformed cells such as neurons (Bamji *et al.*, 1998) and oligodendrocytes (Casaccia-Bonnel *et al.*, 1996) must bind neurotrophins to mediate an apoptotic signal, as discussed in the reviews by Barker (1998, this issue) and Casaccia-Bonnel *et al.* (1998, this issue).

Are these two groups of findings really contradictory? Perhaps not. The term 'ligand-independent' in these studies refers to the absence of exogenous neurotrophins. However, since p75^{NTR} binds to all of the neurotrophins (Rodriguez-Tebar *et al.*, 1990; 1992), and since virtually all cells make one neurotrophin or another, then it is almost inevitable that autocrine or paracrine neurotrophin:p75^{NTR} loops occur. In the absence of evidence eliminating this possibility, it is not possible to state that p75^{NTR} signals in a ligand-independent fashion. Instead, the difference between these two sets of findings may well be an exogenous

versus endogenous source of neurotrophins. This is not to state that p75^{NTR} never signals death in a ligand-independent fashion; only that it has not yet been conclusively demonstrated. One test of the 'ligand-independent' hypothesis would be to assess whether p75^{NTR} could still induce apoptosis in the presence of function-blocking neurotrophin antibodies.

Trk-dependent or independent?

The second major difference between the models presented in these reviews involves the role of the Trk family of tyrosine kinase receptors. Barker (1998, this issue) proposes that p75^{NTR} mediates cellular apoptosis primarily by suppressing Trk-mediated survival signals, while Casaccia-Bonnel *et al.* (1998, this issue), propose that p75^{NTR} directly activates apoptotic signalling cascades. In fact, evidence supports both of these mechanisms, and suggests that they are not mutually-exclusive. With regard to a Trk-dependent mechanism, it is clear that there are multiple interactions between Trk and p75^{NTR} that affect cell survival, and that cross-talk between them is bi-directional. TrkA can suppress p75^{NTR}-mediated ceramide fluxes (Dobrowsky *et al.*, 1995) and apoptosis of sympathetic neurons (Bamji *et al.*, 1998), while p75^{NTR}-activation leads to serine-threonine phosphorylation of TrkA (MacPhee and Barker, 1997), and overrides suboptimal TrkA survival signals (Bamji *et al.*, 1998). The most compelling argument that p75^{NTR} mediates apoptosis in a Trk-independent fashion derives from two sets of experiments with primary cells. NGF-mediated activation of p75^{NTR} causes rapid apoptosis of primary oligodendrocytes, where Trk is not active (Casaccia-Bonnel *et al.*, 1996), and BDNF-mediated activation of p75^{NTR} causes apoptosis of sympathetic neurons maintained in KCl (Bamji *et al.*, 1998), a survival agent that does not activate Trk. These data therefore indicate that p75^{NTR} elicits cell death by both Trk-dependent and Trk-independent mechanisms, and that the relative importance of the two is likely a function of cellular context.

With respect to direct p75^{NTR}-mediated signalling cascades, the proapoptotic signals mediated by this receptor have not yet been defined. While a number of studies demonstrate that p75^{NTR} can activate ceramide fluxes (Dobrowsky *et al.*, 1994), and activation of JNK (Casaccia-Bonnel *et al.*, 1996; Bamji *et al.*, 1998) and NF- κ B (Carter *et al.*, 1996), none of these have been demonstrated to be necessary for p75^{NTR}-mediated apoptosis. We do know, however, that it is the intracellular domain (ICD) of p75^{NTR} that signals apoptosis, since expression of the p75^{NTR} ICD in developing or injured

neurons of transgenic mice was sufficient to cause apoptosis of selective populations of neurons (Majdan *et al*, 1997). Whether or not it is the 'death domain' homology found in the ICD (discussed in detail in all three reviews) that is responsible for these effects is still not known.

Is NGF the only apoptotic p75^{NTR} ligand?

With regard to interactions between Trk and p75^{NTR} it is also worth revisiting the question of the neurotrophin ligands that act through p75^{NTR} to cause apoptosis. Although the original reports indicated that perhaps NGF was the only apoptotic ligand for p75^{NTR} (Frade *et al*, 1996; Casaccia-Bonofil *et al*, 1996), it is now clear that BDNF can function in a similar fashion (Bamji *et al*, 1998). The confusion in this regard derives from the fact that neurotrophins differentially activate p75^{NTR} on any given cell. What is responsible for these differences? Since Trk signaling can silence p75^{NTR} signaling, it is likely that the cellular repertoire of Trk receptors determines whether or not a given neurotrophin activates p75^{NTR} and/or is an apoptotic ligand. For example, in the case of sympathetic neurons, the only non-Trk p75^{NTR} ligand is BDNF, and only BDNF can mediate apoptosis (Bamji *et al*, 1998), whereas with oligodendrocytes that express the TrkB/BDNF receptor and TrkC/NT-3 receptor, NGF is the only proapoptotic p75^{NTR} ligand (Casaccia-Bonofil *et al*, 1996). Thus, all neurotrophins likely can signal survival or apoptosis through Trk or p75^{NTR}, respectively, and the ultimate outcome is therefore a function of the precise neurotrophin receptor repertoire and/or cellular context.

A role for p75^{NTR}-mediated apoptosis during naturally-occurring neuronal death

What is the biological rationale for having two neurotrophin receptors, one of which, TrkA, mediates survival, and one of which, p75^{NTR}, mediates apoptosis? We have recently demonstrated that sympathetic neuron survival during the period of naturally-occurring cell death is determined by the relative levels of activation of TrkA *versus* p75^{NTR} with TrkA mediating survival, and p75^{NTR} mediating neuronal apoptosis (Bamji *et al*, 1998). Specifically, when sympathetic neuron survival was maintained with low quantities of NGF or KCl, BDNF-mediated activation of p75^{NTR} caused neuronal apoptosis and led to increased phosphorylation of *c-jun*. A physiological role for these observations was demonstrated by examination of BDNF^{-/-} (Ernfors *et al*, 1996) and p75^{NTR}^{-/-} mice (Lee *et al*, 1992). In BDNF^{-/-} mice, sympathetic neuron number was increased, and in p75^{NTR}^{-/-} mice, the normal period of sympathetic neuron death was greatly delayed (Bamji *et al*, 1998). This deficit in apoptosis was intrinsic to sympathetic neurons, since cultured p75^{NTR}^{-/-} neurons died much more slowly than their wild-type counterparts in the absence of NGF.

On the basis of these findings, we propose that p75^{NTR} provides a molecular mechanism for ensuring rapid and active apoptosis when a neuron is unsuccessful in competing for adequate amounts of appropriate neurotrophin. If a sympathetic neuron reaches the appropriate target and sequesters NGF, TrkA is robustly activated, and

any coincidental activation of p75^{NTR} is insufficient to override this survival signal. Conversely, if a neuron is late-arriving and/or reaches an inappropriate target, then TrkA would be only weakly induced as a consequence of the lack of NGF, and p75^{NTR} would be robustly activated by neurotrophins such as BDNF. Our data indicate that the net outcome of such a scenario would be the rapid apoptotic elimination of that neuron.

Does such a mechanism generalize to neurons other than sympathetic neurons? The most compelling case that it does, to at least some degree, derives from recent studies on basal forebrain cholinergic neurons; in the p75^{NTR}^{-/-} mice, the number of basal forebrain cholinergic neurons is increased (Van der Zee *et al*, 1996), and the innervation is perturbed (Yeo *et al*, 1997), phenotypes reminiscent of those observed for p75^{NTR}^{-/-} sympathetic neurons. Moreover, a p75^{NTR}-mediated death signal may become important in situations of neuronal stress and/or injury. For example, in the p75^{NTR} ICD-expressing transgenic mice, expression of the ICD had no apparent effect on motor neuron development, but induced expression of the p75^{NTR} ICD following axonal injury led to the death of injured adult facial motoneurons (Majdan *et al*, 1997).

The neurotrophins are traditionally thought to regulate neuronal survival positively via the Trk family of tyrosine kinase receptors (reviewed in Snider, 1994). Recent findings reviewed in this issue of *Cell Death and Differentiation* demonstrate that neurotrophins can act both via Trk to promote neuronal survival, and via p75^{NTR} to promote neuronal apoptosis, and define an unexpected apoptotic role for the neurotrophins during naturally-occurring neuronal death. Such a mechanism, whereby the precise cohort of neurotrophins to which a neuron is exposed determines life *versus* death provides a level of sophistication that was previously unsuspected. This additional level of complexity provides a mechanism whereby neurons can recognize not only whether they are exposed to the 'right' neurotrophins, but whether or not they are seeing the 'wrong' neurotrophin. Such functional antagonism, mediated by Trk and p75^{NTR} is essential for appropriate sympathetic neuron target innervation, and may well turn out to play an essential role in the matching of neurons with their targets throughout the nervous system.

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