Neurotrophins: Neurotrophic modulation of neurite growth

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As well as regulating neuronal survival, neurotrophins control the growth of axons and dendrites. New light has been shed on the mechanism of this latter control process by the discovery that the common neurotrophin receptor p75NTR interacts in a ligand-dependent manner with RhoA, a known regulator of actin assembly.

The neurotrophins are a family of structurally related, secreted proteins that have a profound influence on the development and functioning of the nervous system [1]. Four members of this family have been identified in birds and mammals: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4 (NT-4). Experimental manipulation of the availability of neurotrophins within the developing nervous system has shown that these proteins play a key role in regulating the size of certain populations of neurons [2,3]. The recent demonstration that the common neurotrophin receptor p75NTR selectively modulates the Trk-mediated survival response of neurons to neurotrophins [6] has shed light on the mechanism of this latter control process by the discovery that p75NTR interacts in a ligand-dependent manner with RhoA, known regulator of actin assembly.

The functions of p75NTR are more diverse and complex than those of the Trks. In vitro studies of neurons obtained from p75NTR null mice, and studies using mutated neurotrophins that have altered binding affinity for p75NTR, have shown that p75NTR selectively modulates the Trk-mediated survival response of neurons to neurotrophins [6]. For example, p75NTR enhances the sensitivity of TrkA-expressing neurons to the survival-promoting effects of NGF, whilst decreasing their sensitivity to the survival-promoting effects of NT-3, NT-4, and TrkC is a receptor for NT-3. NT-3 can also bind and signal, albeit less efficiently, via TrkA and TrkB [5].

The finding that the distinctive neuronal deficiencies in mice with null mutations in the p75NTR, trkA, trkB and trkC genes are similar to those observed in mice with null mutations in the NGF, BDNF and NT-3 genes, respectively, suggests that the Trks mediate the survival-promoting actions of neurotrophins on developing neurons.

neurons are dependent on a supply of one or more neurotrophins for survival, whereas in a few well-substantiated cases, NGF promotes cell death.

Numerous studies in recent years have revealed that neurotrophins also influence synaptic function. But one of the most striking actions of neurotrophins — the feature for which NGF was originally named — is the promotion of neurite growth. The most extensive data on this have come from studies of the effects of NGF on the morphology of NGF-dependent neurons of the developing and adult peripheral nervous system. Numerous studies of sensory and sympathetic neurons have shown that the local availability of NGF influences the extent of terminal axonal branching and dendritic complexity or neurite extension in vitro [2,3]. The recent demonstration of an interaction between the common neurotrophin receptor p75NTR and RhoA, and hence of a link between neurotrophins and the actin cytoskeleton [4], is an important advance in our understanding of the molecular basis of the neurite-growth-promoting effects of NGF and other neurotrophins.

To understand the significance of this latest advance, it is necessary to consider the features and functions of the neurotrophin receptors. Two kinds of transmembrane glycoprotein are receptors for neurotrophins: members of the Trk family of receptor tyrosine kinases, which are receptors for different specific neurotrophins, and p75NTR, which is a common receptor for all neurotrophins [5]. Accordingly, the pattern of expression of these receptors in neurons differs: whereas each Trk receptor is restricted to a particular set of neurons, p75NTR is usually co-expressed with Trks in many different kinds of neurons and is additionally expressed by several other cell types.

Trik receptor tyrosine kinases undergo rapid transphosphorylation following ligand binding, leading to a cascade of protein phosphorylations in the cell. Expression studies in cell lines have shown that TrkA is a receptor for NGF, TrkB is a receptor for BDNF or NT-4, and TrkC is a receptor for NT-3. NT-3 can also bind and signal, albeit less efficiently, via TrkA and TrkB [5].

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sympathetic ganglia and cholinergic basal forebrain nuclei in vivo [9]. Neurotrophin receptor interacting factor (NRIF), a recently identified protein that interacts with the intracellular domain of p75NTR, appears to be involved in transducing the cell-death signal, because the reduced cell death observed in the developing retina of axo<sup><i>+</i></sup> mice is quantitatively indistinguishable from that seen in p75<sup>+/−</sup> and ngf<sup>−/−</sup> mice [10].

A recent study [4] has identified additional factors that interact with p75NTR; it has also shown that p75NTR may also enhance neurite outgrowth by the p75 receptor. In future work it will be important to ascertain the relative importance of p75NTR and Trk receptors.

Several earlier observations have also implicated p75NTR in neurite growth and cell migration, though they provided little indication of the underlying mechanism. For example, embryonic chicken dorsal root ganglion neurons cultured at the stage when their axons are starting to grow to their targets were found to have a more immature appearance, with shorter neurites, in medium containing antisense oligonucleotides that decrease p75NTR expression compared to a control [12]. This delay in neurite growth appears to depend on the production of BDNF by early dorsal root ganglion neurons, as antisense BDNF oligonucleotides have a similar effect to antisense p75NTR oligonucleotides [12]. The absence of sympathetic innervation of the pineal gland and a subset of sweat glands in p75<sup>−/−</sup> mice [13], despite no apparent loss of sympathetic neurons in these mice, suggests that p75NTR is required for some sympathetic axons to innervate their targets. The finding that Schwann cells, which express p75NTR but not TrkA, migrate more rapidly on cryostat sections of sciotic nerve when treated with NGF, and the observation that this effect of NGF is abolished by anti-p75NTR antibodies, suggest that NGF enhances the migration of these cells by binding to p75NTR [14].

Although the precise region of the p75NTR intracellular domain that interacts with RhoA has not yet been ascertained, there is a short sequence in the intracellular domain that is similar to mastoparan, a 14-residue peptide of wasp venom which is known to be capable of activating Rho [15]. Interestingly, a peptide identical to this sequence in the p75NTR intracellular domain enhances neurite growth in PC12 cells and sensory neurons cultured in the presence of sub-saturating concentrations of NGF, without having any effect on cell survival [16]. In addition to regulating neurite growth by modulating Rho activation, a recent study suggests that ligand binding to p75NTR may also enhance neurite outgrowth by the production of ceramide [17]. NGF was found to accelerate neurite formation and outgrowth from cultured hippocampal pyramidal neurons at a stage when they express p75NTR but not TrkA. NGF treatment stimulated the production of ceramide, and blocking ceramide production with the sphingomyelinase inhibitor scyphostatin inhibited the neuritogenic effects of NGF [17]. In addition to promoting or modulating neurite growth by binding to p75NTR, it is important to point out that neurotrophins also promote neurite growth by binding to Trk receptors and activating downstream signalling pathways [5].

The new study by Yamashita et al. [4] has brought to the forefront a new and exciting chapter in the biology of the p75 receptor. In future work it will be important to ascertain the relative importance of p75NTR and Trk receptors.
10. Wright EM, Vogel KS, Davies AM: Neurotrophic factors promote the maturation of developing sensory neurons before they become dependent on these factors for survival. Neuron 1992, 8:139-150.

References
12. Wright EM, Vogel KS, Davies AM: Neurotrophic factors promote the maturation of developing sensory neurons before they become dependent on these factors for survival. Neuron 1992, 8:139-150.

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