Comment

Nuclear Factor-κB to the Rescue of Cytokine-induced Neuronal Survival

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During the development of the vertebrate nervous system, a balance is maintained between the formation of neurons and their synapses and neuronal death and synaptic remodeling. Neurotrophic cytokines are known to promote the survival of certain classes of neurons during development. The signaling pathways activated by these cytokines, however, have not been defined. In this issue, Middleton et al. (2000) provides evidence that neurotrophic cytokines activate the transcription factor nuclear factor kappa B (NFκB), which is crucial for the survival of cytokine dependent neurons.

In many populations of developing neurons, more than half of the neurons generated die by apoptosis. This is believed to ensure that the correct number and type of neurons innervate target cells. The survival or death decision of neurons appears not to be predetermined, but is instead the consequence of the integration of multiple intracellular signaling pathways activated by external stimuli. Such external stimuli include neurotrophic factors, which are present in limiting quantities. Neurons that obtain an adequate supply of the required neurotrophic factor survive, whereas neurons that are unsuccessful in the competition die.

Neurotrophic cytokines are a family of neurotrophic factors that play an important role in regulating neuronal survival in the developing nervous system. Middleton et al. (2000) describes new results showing that neurotrophic cytokines (including ciliary neurotrophic factor [CNTF]; leukemia inhibitory factor [LIF]; cardiotrophin-1 [CT-1]; and interleukin-6 [IL-6]) activate NFκB and that this pathway is essential for the survival of developing sensory neurons. When the authors introduce a NFκB repressor (super-repressor IκB) into embryonic sensory neurons or culture cells lacking the NFκB subunit p65, the neurons show impaired survival response to cytokines. Moreover, Middleton et al. (2000) finds that p65 null mutant mice display an increased apoptosis of cytokine-dependent neurons during development in vivo. They therefore conclude that NFκB plays a key role in meditating the survival response of developing sensory neurons to cytokines.

NFκB

NFκB is activated by numerous, diverse signals through a few common intracellular mediators. When cytokines bind to their receptors, the receptor associates with TNF receptor-associated factors (TRAF) 2 or 6, which in turn activates the NFκB-inducing kinase (NIK) via activation of the TAT-associated kinase-1 (TAK1). NIK phosphorylates and activates IκB kinase (IKK) which phosphorylates the inhibitory NFκB binding protein IκB, leading to its degradation and the release and translocation of NFκB to the nucleus (Ninomiya-Tsuji et al., 1999, and references therein; Fig. 1). TRAF6 also mediates NFκB activation following the binding of NGF to the p75 neurotrophin receptor (Khursigara et al., 1999; Fig. 1).

NFκB is activated in vivo in a number of different animal model systems as well as human neurodegenerative diseases. Whether the elevated NFκB activity contributes to cell survival or cell death has been a controversial issue. Whereas some studies report that elevated activity of NFκB in cerebral ischemia, oxidative stress, and excitotoxicity promote cell death of central neurons (Post et al., 1998; Schneider et al., 1999), other findings suggest it is protective against oxidative stress (Lezoualc'h et al., 1998; Yu et al., 1999) and exposure to b-amyloid (Barger et al., 1995; Kaltschmidt et al., 1999). In contrast to the conflicting results obtained in studies of pathological conditions affecting adult neurons, results on the role of NFκB in the developing nervous system are more consistent. NFκB activity protects sympathetic neurons against oxidative cell death (Lezoualc'h et al., 1998) and sensory and sympathetic neurons against trophic factor deprivation (Maggirwar et al., 1998; Hamanoue et al., 1999; Middleton et al., 2000).

Neurotrophic Factors and Receptor Signaling

In addition to neurotrophic cytokines, the neurotrophic factors of the neurotrophin family are essential for the survival of many kinds of neurons during development and the intracellular signaling pathways mediating their effect are beginning to be understood. The neurotrophin family members, including NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT3), and neurotrophin-4 (NT4), mediate their effects through the trk tyrosine kinase receptors which activate Ras/MAPK, PI3K/Akt, and PLCγ signaling pathways (Barbacid, 1995).

An important substrate for the survival effects of the neurotrophin receptors is PI3K, which activates the serine-threonine kinase Akt. Akt has been shown to be necessary and sufficient for neurotrophin-mediated neuronal survival of sympathetic neurons (Crowder and Freeman, 1998; Vaillant et al., 1999). Activated Akt prevents apoptosis by inactivating the intracellular apoptosis-promoting protein Bad (Datta et al., 1997), by inhibiting mitochon-

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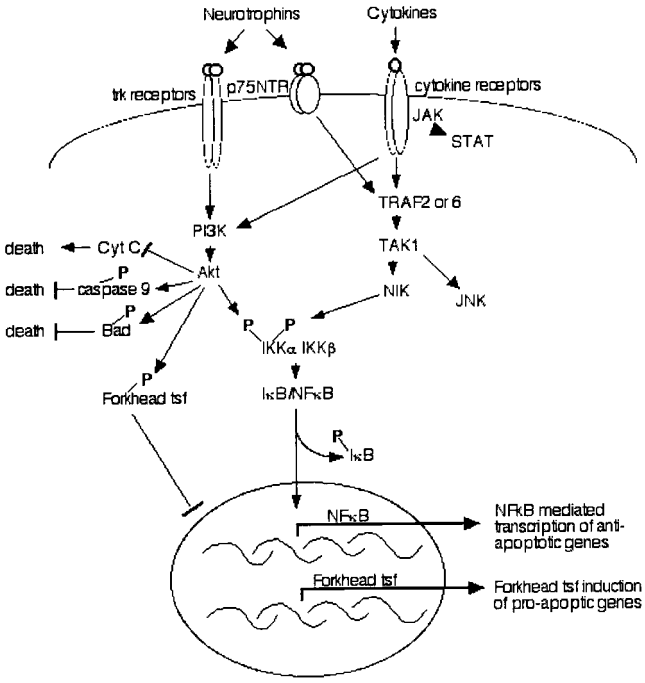

Figure 1. Convergence between cytokine and neurotrophin survival signaling pathways. Neurotrophins bind to their corresponding trk tyrosine kinase receptors leading to the activation of PI3K and Akt. Akt then (a) prevents mitochondrial cytochrome C release; (b) inhibits caspase-9; (c) inactivates bad; (d) phosphorylates forkhead transcription factors thus preventing transcriptional activation of cell death–promoting genes; (e) activates IKKα leading to phosphorylation of IκB, release and nuclear translocation of NFκB, and transcriptional activation of anti-apoptotic genes. Cytokine receptors (a) activate NIK via TAK1 association with TRAF2 or 6 leading to activation of IKKα; (b) activate PI3K and Akt resulting in the activation of IKKα. PI3K and NIK phosphorylate IKKα at distinct sites and data suggest that phosphorylation of both is required for activation of IKKα in some cells. Cytokine receptors can also activate the JAK/STAT and jun-NH_2–terminal kinase (JNK) pathways. p75NTR activates NFκB by interacting with TRAF6.

drial cytochrome C release, which is required for activation of the intracellular suicidal program, and by phosphorylating and inactivating caspase-9 (Crowder and Freeman, 1998; Ashcroft et al., 1999; Vaillant et al., 1999). In addition, Akt also prevents apoptosis by phosphorylation and inactivation of a forkhead transcription factor (Brunet et al., 1999).

Convergence in Neuronal Survival/Death Pathways by Cytokines and Neurotrophins

Recent results provide a direct link from cytokine receptors to the PI3K/Akt pathway and from Akt to NFκB activity via IKKα-IKKβ activation, IκB degradation, and subsequent NFκB nuclear translocation (Chen et al., 1999; Kane et al., 1999; Ozes et al., 1999; Romashkova and Makarov, 1999). This raises the question whether neurotrophins and cytokines accomplish their survival promoting effects largely through the same intracellular signaling pathways (Fig. 1). NFκB has been shown to participate in NGF-elicited, p75 neurotrophin receptor-mediated neuronal survival, but its relative contribution is not as important as it is in mediating the survival response of developing sensory neurons to cytokines (Maggirwar et al., 1998; Hamanoue et al., 1999). Furthermore, in contrast to NGF, other members of the neurotrophin family, including BDNF and NT3, do not activate NFκB (Middleton et al., 2000).

How is specificity generated? An essential intracellular mechanism for regulating speed and specificity of signal transduction is the restriction of the subcellular localization of signaling components. This is achieved through anchor proteins bound to specific subcellular structures (proteins or lipids) and scaffold proteins which assemble various signaling components. Recently, two scaffold proteins which could provide a platform for the assembly of NFκB signaling components were reported (Scheidereit, 1998). Such higher order control of signaling and interactions between signaling pathways highlights the importance of functional studies on real primary cells, tissues and animals.

The possible participation of the PI3K/Akt pathway in survival signaling by neurotrophic cytokines has yet to be directly examined. Recent results on Akt signaling confirms the importance of context since it can act in different ways in different cell types and following activation by different ligands. For example, Akt is necessary for tumor necrosis factor-mediated NFκB activation in epithelial but not in fibroblast cells (Ozes et al., 1999; Romashkova and Makarov, 1999). Furthermore, whereas both BDNF and platelet-derived growth factor (PDGF) leads to phosphorylation of Akt, NFκB is activated only after PDGF treatment (Middleton et al., 2000; Romashkova and Makarov, 1999).

In light of the new results implying an important role for cytokine-induced NFκB activation in survival/death signaling during development of the peripheral nervous system, the next issues to be addressed will almost certainly be whether Akt participates in neuronal survival by cytokines, and whether cytokine activation of NFκB involves NIK and/or Akt. A bigger challenge, however, will be to determine when and how cytokine and neurotrophin signaling pathways converge and their consequences for physiological as well as disease processes in the nervous system.

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