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Regulating ProNGF Action: Multiple targets for therapeutic intervention

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Abstract

Neurotrophins are initially synthesized as precursor forms, that are cleaved to release C-terminal mature forms that bind to Trk receptors to initiate survival and differentiative responses. Recent studies suggest that the precursor form of NGF (proNGF) acts as a distinct ligand by binding to a receptor complex of p75 and sortilin to initiate cell death. Induction of proNGF and p75 have been observed in multiple pathological states and injury models in the central nervous system, and blockade of proNGF/p75 interaction are efficacious in limiting neuronal apoptosis. Multiple strategies that may act to limit proNGF action are considered, as potential therapeutic targets for future development.

Neurotrophins consist of a family of proteins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3) and neurotrophin 4 (NT-4/5) with well-characterized differentiative, survival and synaptic activities in the developing and adult nervous system (Chao, 2003). Although neurotrophins are initially synthesized as precursor forms (proneurotrophins), cleavage by intracellular proteases, such are furin or proconvertases, generates carboxyl- terminal mature neurotrophins. Mature neurotrophins bind to Trk receptor tyrosine kinases and with the p75 neurotrophin receptor, a TNFR superfamily member (Huang and Reichardt, 2001; Dechant and Barde, 2002; Hempstead, 2002). The interaction of mature neurotrophins with Trk receptors initiates many of the differentiative and synaptic activities of mature neurotrophins. Neurotrophins and p75 have also been found to induce apoptosis, detected using genetic models in which mice lacking p75 exhibit impaired sympathetic neuron or retinal ganglion cell death (Bamji et al, 1998, Frade and Barde, 1999). However, cell death mediated by p75 in cultured cells required high concentrations of mature neurotrophins (Casaccia-Bonnefil et al, 1996; Yoon et al, 1998; Kenchappa et al, 2006), suggesting that another form of neurotrophins might selectively activate p75. Indeed, we have shown that the precursor form of NGF, or proNGF, can be released by cells and is a specific and selective ligand for p75 that initiates apoptosis (Lee et al, 2001). This unexpected finding suggests that the precursor form is a biologically active ligand, and that the mature and pro-forms of NGF may execute opposing actions. Subsequent studies demonstrate that proNGF preferentially interacts with high affinity to a heteromeric receptor complex of p75 and the type I transmemebrane protein sortilin, wherein p75 binds to the mature domain of NGF, and sortilin interacts with the prodomain (Nykjaer et al, 2004). Thus, the specificity of neurotrophin action is dictated both by the form of ligand that is released (pro or mature), and by the differential utilization of receptors, with proNGF preferentially binding to and activating p75 and sortilin, and mature NGF binding to TrkA.

ProNGF Effects in Development and Aging

The activity of proNGF in inducing apoptosis has been studied in development, and in aged animals. Although it would be attractive to evaluate a mouse model lacking the prodomain

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of NGF as a means to dissect proNGF and mature NGF actions, this has not been possible as neurotrophin prodomains subserve important functions in protein folding and intracellular trafficking (Suter et al, 1991; Chen et al 2005). In addition, p75 interacts with all forms of neurotrophins, and with multiple co-receptors including TrkA, TrkB and TrkC to modulate neurotrophin activities, and with the Nogo receptor, Lingo-1 and ephrin A to alter axonal guidance (Schecterson and Bothwell, 2008). *p75* deficient mice have been a valuable tool to assess proNGF actions as neuons cultured from these animals are resistant to proNGF action. However, genetic deletion of p75 is likely to impart multiple and complex phenotypes based on effects of p75 in regulating Trk activity and on axon guidance by coupling with other receptor components, and thus determining proNGF-specific phenotypes using p75 null animals is difficult. However, a *sortilin* deficient mouse has been generated and studied to evaluate proNGF-induced developmental apoptosis (Jansen et al, 2007). Consistent with the impaired apoptosis of developing retinal ganglion cells observed in E15.5 embryos deficient in p75 or NGF (48% or 56% reduction, respectively), embryos deficient in sortilin also exhibit reduced retinal ganglion cell death (63% reduction) (Frade and Barde, 1998, Frade and Barde, 1999, Jansen et al, 2007). This result, together with prominent immunoreactivity for proNGF, but not mature NGF in the developing retina, strongly suggests that developmental elimination of post mitotic retinal ganglion cells is mediated by proNGF.In contrast, no reduction in sympathetic ganglion neurons was observed in neonatal sortilin deficient animals, suggesting that other, sortilin-independent mechanisms regulate sympathetic neuron elimination in vivo.

In the uninjured central and peripheral nervous systems, proNGF levels are very low in young adult rodents (Harrington et al, 2004; Jansen et al 2007). However, proNGF levels are up regulated with advanced age. Specifically, proNGF levels are elevated in peripheral nerves of aged (60 week old) mice, where it mediates age-dependent sympathetic neuron death (Jansen et al, 2007). Although systematic and quantitative analysis of proNGF levels in postmortem human brains from aged but cognitively normal individuals is not available, elevated proNGF levels have been observed in patients with Alzheimer's disease (Fahnestock et al, 2001, Pedraza et al, 2005). Interestingly, proNGF extracted from these human brains can mediate apoptosis of cultured sympathetic neurons. Further studies, using animal models that develop Alzheimer's-like pathology, may be informative in identifying whether proNGF is mechanistically linked to disease progression.

ProNGF effects in models of neuronal injury

The effects of proNGF have been most extensively characterized in acute injury models in the peripheral and central nervous systems. In spinal cord injury, both proNGF and p75 expression are induced and maintained for at least one week; in a related model of corticospinal motor neuron axotomy, proNGF, p75 and sortilin are all coordinately up regulated for two weeks (Brunello et al, 1990; Beattie et al, 2002; Harrington et al, 2004; Jansen et al, 2007). In the corticospinal axotomy model, genetic deletion of *p75* or *sortilin*, or haploinsufficiency of *NGF*, largely rescues corticospinal neuron cell death. Importantly, infusion of function-blocking antibodies to the prodomain of proNGF also markedly reduce cell death, strongly suggesting that proNGF is an endogenous, inducible, proapoptotic cytokine.

ProNGF has also demonstrated pro-apoptotic actions in cultured spinal motor neurons, cells which express p75 and sortilin (Domeniconi et al, 2007). In this study, reactive astrocytes were observed to upregulate proNGF production in response to peroxynitrite, an oxidant and producer of free radicals. Although these in vitro results have not yet been extended to in vivo models, these studies provide a potential therapeutic target for the treatment of motor neuron disease. Astrocytes also appear to be a significant source of the elevated proNGF

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levels that occur following pilocarpine induced seizures (Volosin et al, 2008). In this model, both proNGF and proBDNF are up regulated by astrocytes, but not microglia. Infusion of function-blocking antibody specific for the prodomain of NGF, following seizure induction, impairs hippocampal neuron death in vivo, suggesting that proNGF is the relevant neurotrophin in mediating the apoptotic effects. Additional studies indicate that proNGF is an apoptotic ligand in basal forebrain cholinergic neurons is aged rodents (Al-Shawi et al, 2008). In addition, injured sciatic neurons express proNGF and this may result in the loss of p75-expressing neurons following transection (Arnett et al, 2007). Further studies in the retina suggest that proNGF is induced in microglia in a model of retinal dystrophy (Srinivasan et al, 2004), and that sortilin and p75 are induced in retinal ganglion cells following elevations in intraocular pressure, suggesting that proNGF may play a role in the retinal neuron death that occurs in this ischemic setting (Wei et al, 2007). Collectively, these diverse models of injury or aging suggest that proNGF may be a potent proapoptotic ligand. However, cell death in each of these models is self-limiting, suggesting that there are endogenous regulatory mechanisms to modulate the actions of proNGF. These potential mechanisms, and their relevance as future therapeutic targets, will be considered below.

Regulation of proNGF to mature NGF intracellular conversion

In both adult tissues, and in cultured cells, mature NGF is the predominant isoform, present at very low (nanogram/g) levels (Shetty et al, 2003). These observations pose the question of how proNGF, secreted in injury response states, escapes the mechanisms that normally ensure efficient intracellular conversion of proNGF to mature NGF. Mowla and colleagues have demonstrated that in heterologous neuroendocrine cells and hippocampal neurons, proNGF is cleaved efficiently by furin and the mature domain is trafficked to constitutive secretory vesicles, whereas the prodomain remains in the region of the cell body where it may be sorted to lysosomes for degradation (Mowla et al, 1999). Indeed, secretion of a soluble prodomain has been very difficult to detect by most investigators, although Dicou and colleagues have detected prodomain peptides in inflammatory states (Dicou, 2008). These studies suggest that in uninjured cells, efficient conversion of proNGF to mature NGF, and constitutive secretion of mature NGF is the norm. However, the intracellular chaperones that bind to proNGF, and traffic it to the trans-Golgi network where furin cleavage occurs have not been well characterized. One candidate is sortilin, a VpS10p protein that has been well characterized, as described above, as a cell surface co-receptor with p75 for proNGF. However, sortilin has a predominantly intracellular location (McCormick et al, 2008), and has a well characterized role in regulating the intracellular trafficking of proBDNF to regulated secretory vesicles, and other cargo, including sphingomyelinase, to the lysosome (Chen et al, 2005; Ni and Morales, 2006). Thus it is possible that sortilin may promote the trafficking and degradation of the cleaved prodomain to lysosomes, although formal experimental proof of this is lacking. Other chaperones known to bind to the mature domains of neurotrophins, such as carboxypeptidase E that binds to BDNF, do not effectively bind to mature NGF (Lou et al, 2005). Therefore, the intracellular mechanisms that regulate proNGF intracellular trafficking, promote intracellular proNGF to mature NGF conversion, and regulate proNGF release remain to be determined.

Impaired cleavage of secreted proNGF

In several injury models in the central nervous system, proNGF expression is detectable for several days to weeks following injury. Surprisingly, little conversion of proNGF to mature NGF is observed in these vivo settings (Beattie et al, 2002; Harrington et al, 2004; Jansen et al, 2007), despite the susceptibility of recombinant proNGF to multiple proteases, including select MMPs and plasmin (Lee et al, 2001; Bruno and Cuello, 2006; Althaus and Kloppner,

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2006). These observations suggest that proteolysis of extracellular proNGF is regulated following in vivo injury, and may involve the coordinate induction of known inhibitors of MMPs and plasmin. These include tissue inhibitors of metalloproteinase (TIMPs), neuroserpin and alpha -2 macroglobulin, proteins that are transcriptionally regulated and induced in neurodegenerative disease, and with neuronal excitotoxicity (Bruno and Cuello, 2006). Indeed, alterations in MMP and TIMP expression have been documented in Huntington and Parkinson's diseases (Dzwonek et al, 2004; Jaworski et al, 1999; Lorenzi et al, 2003). The detection of intact proNGF in the cerebral spinal fluid of rodents follow spinal injury suggests that inhibitors may also be present in significant amounts, a hypothesis which is awaiting formal evaluation.

Induction of p75

Expression of the p75 receptor has emerged as a key regulatory element in proNGF-induced cell death. In most adult tissues, p75 is expressed at low levels, in contrast to higher and more widespread distribution in development. (Yang et al, 2009; Roux and Barker, 2002). However, in pathologic states, including seizure, brain injury, ischemia, and excitotoxicity, p75 expression in induced, as noted above. The significant reduction of injury-induced apoptosis observed in *p75* deficient mice (Troy et al, 2002; Harrington et al, 2004) underscores the importance of p75 induction in determining cell loss following injury.

However, the molecular mechanisms that regulate p75 expression, both in development and in injury, remain largely unknown. The p75 promotor resembles a housekeeping gene, with high GC content, multiple Sp1 binding sites, but no TATA or CAAT elements (Sehgal et al 1988; Patil et al, 1990). A transgenic approach has been undertaken to evaluate *p75* transcriptional regulation (Huber and Chao, 1995, Carroll et al, 1995); in one study, mice harboring 4kb of 5' sequence of human p75 and the human p75 cDNA as a minigene exhibited expression by mesenchymal cells during development, mimicking endogenous expression (Huber and Chao, 1995). In addition, this p75 minigene was induced following sciatic nerve injury, although expression in uninjured peripheral neurons was lacking. In a second approach, analysis of a 8.4kb murine *p75* promotor, using a lacZ reporter, documented appropriate expression in peripheral neurons and the retina, but no induction in Schwann cells during Wallerian degeneration (Carroll et al, 1995). Collectively, these observations suggest that multiple promoter elements exist, and that injury-response elements that regulate neuronal, but not glial expression are encoded within the proximal 4kb of the promoter.

More recent studies have evaluated the role of hypo-osmolar stress in inducing p75, as brain edema is a common complication of seizures, and traumatic brain injury (Peterson and Bogemann, 2003: Ramos et al, 2007). In examination of 25kb upstream of rat *p75*, proximal SP1 elements were found to be critical for *p75* induction. Furthermore, p75 transcription appeared to be regulated by the enhanced expression of SP1, mediated by inhibition of SP1 degradation in hypo-osmolar states. High levels of expression of SP1 persist in neurons for at least 14 days following ischemic injury, providing a mechanism by which prolonged induction of p75 may occur. Interestingly, sortilin expression is unaffected by hypo-osmolarily, and indeed the elements that regulate transcription of sortilin are unknown.

Molecular strategies to attenuate proNGF action

As summarized above, studies by multiple laboratories provide mounting evidence that the induction of proNGF and p75 in several pathophysiologically relevant states may result in cellular apoptosis in a p75 and sortilin dependent manner. The low levels of p75 and proNGF in the uninjured central nervous system, and the observations that proNGF and p75 induction occurs over several hours to days, suggests that a window of opportunity exists

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during which administration of pharmacologic agents to block the induction of ligand and receptors, or their interaction, may attenuate neuronal apoptosis. One successful strategy has been through the identification of small molecular inhibitors that impair the interaction of p75 with its ligands. Through in silico modeling, small molecules have been identified that interact with a p75 structural domain important for mature NGF binding; in addition, these molecules block proNGF actions in cultured neurons (Massa et al, 2006). The development of these, as well as other molecules identified by screening or modeling approaches to impair proNGF/p75/sortilin interactions may provide useful reagents to block proNGF actions. Although the crystallographic structure of p75 with mature NGF is available, as well as the crystallographic structure of sortilin, the structure of the proNGF/p75/sortilin complex has remained elusive (He and Garcia, 2004; Quistgaard et al, 2009), but may provide information for the development of antagonists in the future.

Other pharmacological strategies may involve the development of drugs that block the induction of p75 or proNGF. As noted above, the key promoter elements of p75 that direct neuronal and injury-responsive expression remain to be described, and far less is known about *NGF* transcriptional regulation than related neurotrophins, such as *BDNF*. However, minocycline treatment of rodents with spinal cord injury has been shown to attenuate proNGF and p75 induction, suggesting this approach may be feasible, and could be optimized once the relevant promoter elements have been identified (Yune et al, 2007).

Lastly, the activation of intracellular or extracellular proteases to specifically cleave proNGF to mature NGF is another attractive target. To this end, a more detailed understanding of the mechanisms that regulate intracellular trafficking of proNGF in injured cells, and permit inefficient intracellular cleavage is needed. In addition, the stability of proNGF in the injured central nervous system suggests that specific protease inhibitors in the local inflammatory environment may prevent efficient extracellular cleavage of proNGF. Thus quantitative assessment of locally produced proteases and their specific inhibitors in the injured central nervous system may provide candidate molecules for manipulation, to promote proNGF to mature NGF conversion.

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