
Deciphering Proneurotrophin Actions

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Abstract

Like most growth factors, neurotrophins are initially synthesized as precursors that are cleaved to release C-terminal mature forms. The well-characterized mature neurotrophins bind to Trk receptors to initiate survival and differentiative responses. More recently, the precursor forms or proneurotrophins have been found to act as distinct ligands by binding to an unrelated receptor complex consisting of the p75 neurotrophin receptor (p75) and sortilin to initiate cell death. Induction of proNGF and p75 has been observed in preclinical injury models and in pathological states in the central nervous system, and strategies that block the proNGF/p75 interaction are effective in limiting neuronal apoptosis. In contrast, the mechanisms that regulate expression of other proneurotrophins, including proBDNF and proNT-3, are less well understood. Here, recent findings on the biological actions, regulation of expression, and pathophysiological effects of proneurotrophins will be reviewed.

Keywords

ProNGF • ProBDNF • ProNT3 • p75NTR • Synaptic plasticity • Neurodegeneration • Long term depression • Long term potentiation • Sortilin • Cell death • Apoptosis

Neurotrophins are a family of proteins, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT-3), and neurotrophin 4 (NT-4/5). They exhibit well-characterized activities to promote neuronal survival and differentiation, to modulate synaptic plasticity and to play important roles in both the developing and adult nervous system (Chao 2003). While only four

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neurotrophin genes are found in mammals, they are sufficient to modulate a diverse repertoire of functions in the peripheral and central nervous systems and in non-neuronal organs. Indeed, several conceptual advances have been made during the last decade that reveal how this might be accomplished. Here we will focus on proneurotrophins as unique ligands that complement and oppose the actions of mature neurotrophins. Given the breadth of this rapidly moving field, it is difficult to acknowledge all contributions, and oversights are unintended. Related areas including mechanisms of p75 activation and signaling, mature neurotrophin actions, and functions of sortilin family members are reviewed in other chapters of this publication.

Like most growth factors, neurotrophins are initially synthesized as precursors or proneurotrophins consisting of a N-terminal prodomain and a C-terminal mature domain. Following translation, proneurotrophins form noncovalent dimers via interactions of the mature domain which forms a cysteine knot-like structure (Bradshaw et al. 1993). Dimeric proneurotrophins can be cleaved by intracellular proteases, including furin and proconvertase, in the Golgi or in secretory vesicles to generate mature neurotrophins, which are dimers consisting of the mature domains (Seidah et al. 1996). Mature neurotrophins selectively bind to members of the family of Trk receptor tyrosine kinases, as well as to 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 the differentiative and synaptic activities of mature neurotrophins. Mature neurotrophins also bind to the p75 receptor, although the biological outcomes depend upon whether p75 is expressed independently or as a receptor complex with Trk receptors. When p75 is co-expressed with TrkA, mature NGF binds to the complex with higher affinity than is observed when TrkA is expressed in the absence of p75 (Hempstead et al. 1991). Although these results have been interpreted as evidence that p75 can bind and then pass mature NGF to TrkA to facilitate binding (Barker 2007), other studies suggested that p75 was exerting an allosteric action on TrkA and that binding of mature NGF to p75 was not required for this effect (Esposito et al. 2001). Application of mature neurotrophins to p75 expressing cells has also been found to induce apoptosis, and genetic deletion of p75 in mice results in impaired sympathetic neuron or retinal ganglion cell death (Bamji et al. 1998; Frade and Barde 1999). However, high concentrations of mature neurotrophins were required to initiate cell death by p75 in vitro (Casaccia-Bonnel et al. 1996; Yoon et al. 1998; Kenchappa et al. 2006), suggesting that an alternate form of neurotrophins might selectively activate p75 at more physiologic concentrations. Indeed, the precursor form of NGF, proNGF, can be released intact from cells and has been found to selectively activate p75 to induce apoptosis at subnanomolar concentrations (Lee et al. 2001). This finding suggests that the precursor is a distinct, biologically active ligand and that mature and proNGF can induce opposing actions. Subsequent studies have further defined the receptor complex to which proNGF binds: proNGF interacts with high affinity to complex consisting of p75 and the type I transmembrane protein sortilin, wherein the NGF mature domain binds to p75, and the prodomain

binds to sortilin (Nykjaer et al. 2004). Sortilin specifically recognizes the prodomains of the three proneurotrophins (proNGF, proBDNF, and proNT-3) and forms a co-receptor complex with p75^{NTR} to convey proneurotrophin-induced apoptotic signaling at subnanomolar ligand concentrations (Nykjaer et al. 2004; Teng et al. 2005; Jansen et al. 2007; Willnow et al. 2008; Yano et al. 2009). Thus, the specificity of neurotrophin action is regulated by the form of ligand that is released from cells (proneurotrophin or mature), as well as by the interaction with distinct receptor complexes, with proneurotrophins preferentially activating p75 and sortilin, whereas mature neurotrophins activate Trk receptors.

More recent studies have determined that proNGF can also interact with another sortilin family member, SorCS2, when it is co-expressed with p75 (Deinhardt 2011; Siao 2012). SorCS2 is a transmembrane protein that is closely related to sortilin and is highly expressed in the developing and adult nervous system (Willnow et al. 2008). Like sortilin, SorCS2 interacts with the prodomain of proNGF.

1 Actions in ProNGF in Development

The ability of proNGF to induce apoptosis during development has been studied using several strategies. Although it would be tempting to generate a gene-targeted mouse that lacks the prodomain of NGF as a means to discriminate proNGF from mature NGF function, this is not an effective strategy as the prodomains of neurotrophins are required for efficient protein folding and intracellular trafficking (Suter et al. 1991; Chen et al. 2005). Also, the results obtained upon deletion of p75 must be interpreted carefully, as p75 interacts with all forms of neurotrophins, and with multiple co-receptors including TrkA, TrkB, and TrkC to modulate mature neurotrophin responsiveness, and with the Nogo receptor, Lingo-1 and ephrin A, to regulate axonal guidance (Schecterson and Bothwell 2008). Thus, genetic deletion of p75 can yield multiple and complex phenotypes based on potential interactions with other receptor components and thus attributing a specific phenotype to proNGF requires careful analysis of the expression patterns of other ligands and co-receptors.

However, utilization of neurons from *p75*-deficient mice has been a valuable tool to assess proNGF actions, as this imparts a proNGF-resistant phenotype in vitro (Lee et al. 2001). Mice deficient in *sortilin* have also been generated and characterized regarding proNGF-induced apoptosis during development (Jansen et al. 2007). Prior studies have documented impaired apoptosis of developing retinal ganglion cells in E15.5 embryos that were deficient in *p75* or *ngf* (48 % or 56 % reduction, respectively) (Frade and Barde 1998, 1999). Similarly, embryos deficient in *sortilin* exhibit reduced retinal ganglion cell death (63 % reduction) (Jansen et al. 2007). The immunodetection of proNGF but not mature NGF at this developmental window, together with the protection of these neurons in *sortilin*-deficient and *p75*-deficient mice, suggests that elimination of post-mitotic retinal ganglion cells is mediated by proNGF in late development. Surprisingly, neonatal mice deficient in *sortilin* exhibit no reduction in the numbers of sympathetic

ganglion neurons (Jansen et al. 2007), suggesting that other co-receptors may regulate sympathetic neuron elimination in vivo. An additional challenge in attributing the phenotypes of *sortilin*-deficient mice to proNGF activities is that sortilin binds to numerous other ligands, including proBDNF, proNT-3, TGF- β family members, and apolipoprotein B (Strong et al. 2012; Kjolby et al. 2010; Kwon and Christian 2011); thus, documenting expression of proNGF and p75 is required to confirm that the effects of *sortilin* deficiency reflect the specific actions of proNGF.

2 ProNGF in Aging

ProNGF levels are very low in the central and peripheral nervous systems of uninjured young adult rodents (Harrington et al. 2004; Jansen et al. 2007). However, several studies indicate that proNGF levels are upregulated in adults of advanced age. For example, proNGF levels are elevated in the peripheral nerves of 60-week-old mice, and this expression correlates with age-dependent death of sympathetic neurons (Jansen et al. 2007). A more extensive analysis of ligand and receptor levels in aged or young adult rats documented increased levels of proNGF and p75 and decreased levels of mature NGF and phosphoTrkA in the prefrontal cortex and hippocampus of aged rats, as compared to younger adults (Terry et al. 2011; Allard et al. 2012). Although these effects correlated with impaired performance in spatial learning and recognition memory, a causal role was not investigated. New studies using transgenic overexpression of proNGF suggests it induces memory deficits (Tiveron et al. 2013). A systematic and quantitative analysis of proNGF levels in postmortem human brains from aged but cognitively normal individuals has not been performed. However, a report in aged rodents suggests that proNGF is an apoptotic ligand in basal forebrain cholinergic neurons (Al-Shawi et al. 2008). Indeed, proNGF levels have been found to be elevated in Alzheimer's disease patients (Fahnestock et al. 2001; Pedraza et al. 2005) and in animal models of Alzheimer's disease (3xTg-AD mice; Perez et al. 2011). Future studies will be required to determine whether impairment of the interaction of proNGF with sortilin may prevent age-associated neuronal loss, as has been proposed for proNGF:p75 antagonists (Massa et al. 2006). However, a transgenic line approach has been used to selectively deplete mature NGF, but not proNGF (line AD-11) (Capsoni et al. 2010). This strategy results in an imbalance, with impaired TrkA signaling, but sustained proNGF:p75 signaling. These studies have suggested that imbalance of the proNGF:mature NGF ratio in the CNS can trigger cholinergic neuron loss similar to that observed in Alzheimer's disease (Capsoni et al. 2010). Consistent with this hypothesis, the activation of p75 by proNGF was observed to suppress survival signaling by TrkA, specifically by impairing PTEN induction that blunts PI3-kinase-Akt activation (Song et al. 2010). Collectively, these studies suggest that selectively shifting the balance between pro-apoptotic and pro-survival pathways, triggered by proNGF or mature NGF, respectively, one can potentially prevent neuronal loss.

3 ProNGF Actions Following Injury

Because apoptosis was the first identified action of proNGF in vitro, many studies have examined the roles of proNGF following acute injury in the peripheral and central nervous systems. Following spinal cord injury in rodents, proNGF and p75 expression are induced within a few days and maintained for at least 1 week; in a related model of corticospinal neuron axotomy, p75, sortilin and proNGF are all coordinately up regulated, and overexpression is maintained for 2 weeks (Brunello et al. 1990; Beattie et al. 2002; Harrington et al. 2004; Arnett et al. 2007; Jansen et al. 2007). To examine a causative role for proNGF in promoting neuronal apoptosis following corticospinal axotomy, two approaches have been used. First, genetic deletion of *p75* or *sortilin*, or haploinsufficiency of *ngf*, rescues most of the death of corticospinal neurons after axotomy (Harrington et al. 2004; Jansen et al. 2007). In addition, infusion of function-blocking antibodies specific for the prodomain of proNGF markedly reduces apoptosis, strongly suggesting that proNGF is an inducible, proapoptotic cytokine (Harrington et al. 2004). More recently, administration of a ProNGF/p75 antagonist has been shown to promote functional recovery following spinal cord injury (Tep et al. 2013).

ProNGF has also demonstrated pro-apoptotic actions in cultured spinal motor neurons that express p75 and sortilin (Domeniconi et al. 2007). Using peroxynitrite as an oxidant and to generate of free radicals, reactive astrocytes were found to upregulate proNGF production, suggesting that proNGF may be a potential therapeutic target for the treatment of motor neuron disease. Astrocytes are also a significant source of the proNGF that is induced following seizures in rodents (Volosin et al. 2008). In a pilocarpine model of seizure induction, proNGF and proBDNF are upregulated by astrocytes, but not by microglia. Following seizures, infusion of function-blocking antibodies specific for the prodomain of NGF impairs hippocampal neuron apoptosis in vivo, suggesting that proNGF is the relevant ligand that mediates the apoptotic effects (Volosin et al. 2008).

Increased proNGF expression has been observed in spongiform encephalomyelopathy (Stoica et al. 2008) and Parkinson's disease models (Wang et al. 2008); however, a mechanistic role for proNGF in these slow onset neurodegenerative diseases has not been demonstrated. However, recent studies have examined a potential role for progranulin, as progranulin loss of function has been associated with frontotemporal lobar degeneration (FTLD), and modulates sortilin function (Hu et al. 2010). Although the precise mechanisms by which progranulin deficiency contributes to neuronal dysfunction in aging, the enhanced expression of proNGF in aging rodent animal models (Terry 2011) raises the possibility that proNGF might compete with the binding of progranulin to sortilin to augment the progression or onset of cognitive degeneration in a p75^{NTR}-independent mechanism. This potential action, however, will require experimental validation.

Studies of models of retinal injury 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 elevation 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). More recent studies have examined a

potential role for proNGF in promoting retinal neurodegeneration in the retina of diabetic rodents (Al-Gayyar et al. 2013). In the peripheral nervous system, injured sciatic neurons express proNGF and this may result in the loss of p75-expressing neurons following transection (Arnett et al. 2007). Collectively, these diverse models of injury or aging suggest that proNGF may be a pathophysiologically relevant proapoptotic ligand.

3.1 ProNGF Actions in Non-neuronal Organ Systems

As NGF is normally synthesized by many organs to promote innervation during development, misregulation of NGF expression, or impaired conversion of proNGF to mature NGF in disease could contribute to pathology. Several recent reports have established that proNGF is misregulated in breast cancer, following myocardial infarction, and in psoriasis. In human breast cancer specimens, proNGF is upregulated and appears to mediate cell invasion, an effect requiring TrkA and sortilin, rather than p75 (Demont et al. 2012). These studies suggest that NGF and TrkA may be relevant preclinical targets for further examination (Hondermarck 2012). ProNGF and p75 have also been studied in dermatologic diseases, including psoriasis where a failure to induce apoptosis of transit amplifying cells in the dermis, in a p75-dependent manner, may contribute to this disease (Truzzi et al. 2011). Although initial studies focused on proNGF as the relevant p75 ligand, due to its expression in keratinocytes, additional p75 ligands such as BDNF may contribute. Lastly, prior studies have documented induction of the *ngf* gene by cardiac myocytes following ischemic injury using rodent models of myocardial infarction (Hiltunen et al. 2001; Meloni et al. 2010). More recently, the *ngf* isoform that is induced has been shown to be proNGF, which is upregulated by cardiac myocytes following ischemia reperfusion injury in rodents and in humans following fatal myocardial infarction. Coordinate upregulation of p75 and SorCS2 is observed by the pericytes and smooth muscle cells in cardiac vessels in the ischemic zone. Furthermore, deletion of *p75* limits the infarct size, suggesting that proNGF represents a new target to limit microvascular dysfunction (Siao et al. 2012). Additional studies will be required to determine whether proNGF plays a role in the vasculature of other organ systems.

4 Acute Proneurotrophin Actions on Neuronal Morphology

Recent studies have examined relatively acute, non-apoptotic functions for proNGF and proBDNF. These studies build upon older reports that document that p75 interacts with RhoA (Yamashita et al. 1999) and fascin (Shonukan et al. 2003), signaling intermediates that are coupled to cytoskeletal reorganization. Two seminal studies have also indicated that p75 regulates neuronal morphology: (a) loss of p75 in gene-targeted mice leads to enhanced dendritic arborization (Zagrebelsky et al. 2005) and (b) p75 activation by BDNF leads to axonal pruning (Singh et al. 2008). However, these studies did not directly compare the effects

proneurotrophins vs. mature neurotrophins in eliciting morphological actions. In more recent experiments using live imaging of neuronal growth cones, proNGF was found to induce rapid growth cone collapse in neurons expressing p75 and the sortilin family member, SorCS2 (Deinhardt et al. 2011). These effects were dependent upon two coordinated signaling pathways. First proNGF induced a dissociation of the Trio GEF from the p75/SorCS2 receptor complex, which resulted in local Rac inactivation. This was coupled with PKC activation and fascin phosphorylation, leading to a reduction in actin bundling and neurite retraction.

ProBDNF has also been demonstrated to exert rapid morphological effects on neurons, specifically at the neuromuscular junction, where proBDNF secreted from myocytes induces retraction of motor neuron axons, as well as synaptic depression (Yang et al. 2009a; Je et al. 2012). A similar effect of recombinant proBDNF has been observed using dorsal root ganglion neurons, where proBDNF led to acute neurite collapse in a Rho A-dependent fashion (Sun et al. 2012). This retraction requires expression of p75. Lastly, using cultured retinal ganglion cells, Marler and colleagues have provided evidence that proBDNF is secreted from these cells and acts locally to enable repellant axon guidance in a p75-ephrin A-dependent fashion (Marler et al. 2010). Further studies will be required to identify whether proBDNF interactions with p75 can be mediated by a range of co-receptors, including sortilin family members and/or ephrins, in a cell type-specific manner.

5 ProBDNF Effects on Synaptic Plasticity

The effects of mature BDNF on hippocampal structure and synaptic plasticity are well described (Korte et al. 1998; Keng et al. 1997; Lu et al. 2008, and recently reviewed by Park and Poo 2013); however, the effects of proBDNF are less clear. Several studies suggest that endogenous proBDNF can be released from neurons. One study has used hippocampal neurons from a knock-in mouse expressing HA-epitope-tagged BDNF (Yang et al. 2009b) to quantitatively detect secreted proBDNF and mature BDNF using antibodies to the HA-tag, rather than relying on antibodies that recognize either proBDNF or mature BDNF. With this approach, both proBDNF and mature BDNF were secreted following depolarization. In contrast, mature BDNF was the predominant secreted form secreted from hippocampal neurons cultured with astrocytes and the GABA_A receptor antagonist bicuculline (Matsumoto et al. 2008). However, using electrical stimulation of cultured hippocampal neurons, proBDNF was the predominant form secreted after low-frequency stimulation (LFS; used to induce LTD), whereas mature BDNF was released following high frequency stimulation (HFS; used to induce LTP; Nagappan et al. 2009). It is well established that tPA is secreted following depolarization (Lochner et al. 2006, 2008) and thus proBDNF may be locally converted to mature BDNF by the coordinated release of proBDNF and tPA from axons.

The actions of proBDNF have been best described using recombinant proBDNF protein. Treatment of cultured neurons with recombinant proBDNF promotes

neuronal death and process retraction, mediated by p75^{NTR} (Teng et al. 2005; Sun et al. 2012). Recombinant proBDNF also influences synaptic plasticity in area CA1 of the hippocampus; following perfusion of slices with cleavage-resistant proBDNF, LTD was significantly enhanced, an effect that requires expression of p75 (Woo et al. 2005). In contrast, mature BDNF is required for the maintenance of LTP induced by stimuli that simulates theta rhythm (TBS) (Korte et al. 1998; Chen et al. 2010; Keng et al. 1997; and recently reviewed, Park and Poo 2013). Together, these results suggest that proBDNF and mature BDNF have opposing effects in vivo, with proBDNF supporting LTD and mature BDNF important to LTP. The effects of exogenous proBDNF have been extended to other classes of neurons, as proBDNF negatively regulates neuromuscular synaptic activity via p75^{NTR} (Yang et al. 2009a; Je et al. 2012).

One aspect of proBDNF and mature BDNF action in the hippocampus that is unresolved is the relative levels of the two isoforms that are expressed during postnatal development and in adulthood. In one study, hippocampal proBDNF expression was found to be highest in the second postnatal week, when axonal projections are being established and synapses are forming, as quantitated using a tagged *bdnf* allele to measure proBDNF and mature BDNF levels (Yang et al. 2009b). In the adult mouse, however, mature BDNF was found to be the predominant form (Yang et al. 2009b). Other studies suggest that mature BDNF is the predominant isoform from postnatal day 4 until 12 weeks of age (Rauskolb et al. 2010). However, the levels of p75^{NTR} are highest in early postnatal life and diminish in adulthood (Yang et al. 2009b). Thus the effects of endogenous proBDNF may be most prominent in early postnatal development and further studies to document the levels of endogenous proBDNF and its effects in vivo are warranted.

6 ProBDNF in Disease States

ProNGF has been most intensively studied regarding its expression in disease states in humans and in preclinical rodent models, as noted above. However, several studies have documented elevated levels of proBDNF in postmortem brain sections from subjects with cognitive impairment from HIV neurotoxicity (Bachis et al. 2012). The levels of proBDNF and mature BDNF have also been studied in a small number of postmortem sections from subjects with autism or unaffected controls. In the fusiform gyrus, increased levels of proBDNF and decreased levels of mature BDNF were observed in subjects with autism, suggesting local defects in proteolytic processing (Garcia et al. 2012). These results contrast with those obtained using brain tissue from Alzheimer's disease patients, where reduction in both proBDNF and mature BDNF was observed, as compared to control (Peng et al. 2005). Further studies with larger sample sizes, as well as in vivo models that identify actions of endogenous proBDNF will be helpful in clarifying the potential roles of this isoform in disease.

7 Other Proneurotrophins: ProNT-3 and ProNT-4

The majority of studies to date have focused on the biological actions of proNGF and proBDNF. However, the NT-3 and NT-4 mature products are derived from precursor proteins, raising the possibility that proNT-3 and proNT-4 may exhibit biological actions distinct from their mature neurotrophin counterparts. ProNT-3 has been biochemically generated, and it mediates apoptotic actions on SCG neurons, utilizing p75 and sortilin as co-receptors (Yano et al. 2009). In addition, proNT-3 has been detected in the developing inner ear, and sortilin and p75 receptors are also present on spiral ganglion neurons. Although no changes in spiral ganglion numbers have been detected in *sortilin* null mice during development, proNT-3 may play a role following barotrauma injury (Tauris et al. 2011). Currently, there are no reports as to whether proNT-4 exhibits pro-apoptotic activity or other biological actions. However, its prodomain is substantially smaller than those of the other three proneurotrophins and the NT-4 prodomain does not bind sortilin (Chen et al. 2005); suggesting that NT-4 might exist strictly as a TrkB ligand.

8 Regulation of Conversion of Proneurotrophins to Mature Neurotrophins

In adult tissues, mature NGF and mature BDNF are the predominant isoforms, present at very low, subnanomolar levels (Shetty et al. 2003; Rauskolb et al. 2010). Thus, it is not clear how proNGF, secreted in injury response states, escapes the mechanisms that normally ensure efficient intracellular conversion to mature NGF. In neuroendocrine cells and hippocampal neurons, proNGF is cleaved efficiently by furin and the mature domain is trafficked to secretory vesicles in the constitutive pathway, whereas the prodomain remains in the cell body and sorted to lysosomes for degradation (Mowla et al. 1999). Indeed, secretion of a soluble proNGF prodomain has been difficult to detect, although Dicou and colleagues have observed peptides of the prodomain in inflammatory states (Dicou 2008). These studies suggest that there is efficient conversion of proNGF to mature NGF in uninjured organs, and constitutive secretion of mature NGF is the norm. However, the intracellular chaperones that traffic proNGF to the trans-Golgi network where furin cleavage occurs have not been 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, direct experimental evidence to support this is currently lacking. ProBDNF has been demonstrated to bind to sortilin to direct intracellular trafficking of to regulated secretory vesicles (Chen et al. 2005), where proBDNF can be cleaved by proconvertase (Seidah et al. 1996). However, sortilin can also traffic proBDNF and other cargo, including sphingomyelinase, to the lysosome (Evans et al. 2011; Ni and Morales 2006), and it is not clear how these targeting decisions are regulated. Other chaperones including carboxypeptidase E bind to the mature domain of BDNF, but not mature NGF (Lou et al. 2005). Therefore, many questions still remain regarding the intracellular

proteins that regulate proNGF intracellular trafficking, and release, as well as the mechanisms that regulate the efficiency of proBDNF cleavage within secretory vesicles. Recent reports, however, have documented that the prodomain of BDNF is detectable in vivo (Dieni et al. 2012; Anastasia et al. 2013).

9 Extracellular Cleavage of Proneurotrophins

Recombinant proNGF and proBDNF are susceptible to cleavage by numerous proteases, including plasmin, tryptase, and specific matrix metalloproteinases (MMPs) (Lee et al. 2001; Bruno and Cuello 2006; Althaus and Kloppner 2006; Spinnler et al. 2011). Nonetheless, intact proNGF is detectable for several days to weeks following central nervous system injury, with little evidence of conversion to mature NGF in these vivo settings (Beattie et al. 2002; Harrington et al. 2004; Jansen et al. 2007). These observations suggest that proteolysis of extracellular proNGF is impaired following in vivo injury and may result from the coordinate induction of inhibitors of MMPs and plasmin, such as tissue inhibitors of metalloproteinase (TIMPs), neuroserpin, and alpha-2 macroglobulin. This is in agreement with prior studies documenting that these proteins are induced in neurodegenerative diseases such as Parkinson's and Huntington's diseases and following neuronal excitotoxicity (Bruno and Cuello 2006; Dzwonek et al. 2004; Jaworski et al. 1999; Lorenzi et al. 2003). Indeed, recent studies using a seizure model of CNS injury demonstrates that MMP-7 is downregulated, whereas its inhibitor, TIMP-1, is induced, leading to stabilization of proNGF. Furthermore, exogenous delivery of MMP-7 following seizures enhances proNGF cleavage and reduced neuronal apoptosis (Le and Friedman 2012), suggesting that the efficiency of proNGF to NGF conversion can be experimentally manipulated to provide neuroprotection.

10 Molecular Strategies to Alter ProNGF Effects

Given the induction in proNGF and p75 in numerous pathophysiologically relevant preclinical models that result in cellular apoptosis or acute morphological remodeling, there has been broad interest in targeting proNGF/p75 signaling. The low levels of p75 and proNGF in the uninjured central nervous system and induction of both ligand and receptor within several hours to days of acute injury suggest that there is a window of opportunity for administration of agents to block the induction of ligand or receptors or their interaction. By 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). These molecules are now being tested in rodent models of spinal cord injury (Tep et al. 2013). Additional modeling approaches to impair proNGF/p75/sortilin interactions may provide additional reagents to block proNGF actions. The crystallographic structure of p75 with

mature NGF, p75 with proNGF, and the structure of sortilin are all available (He and Garcia 2004; Quistgaard et al. 2009; Feng et al. 2010). Although the structure of the proNGF/p75/sortilin complex has remained elusive, its eventual solution may provide information for the development of antagonists in the future.

Lastly, the activation of intracellular or extracellular proteases to specifically cleave proneurotrophins to mature neurotrophins is another attractive target. To this end, a more detailed understanding of the regulation of intracellular trafficking of proNGF in injured cells, and mechanisms that permit inefficient intracellular cleavage are 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, and strategies to locally manipulate the proteolytic landscape following acute injury are being studied (Le and Friedman 2012). A quantitative assessment of locally produced proteases and their specific inhibitors in the injured central nervous system will provide specific candidate molecules to promote proneurotrophin to mature neurotrophin conversion.

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