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Growth factor signaling: Implications for Disease & Therapeutics

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Abstract

Cells possess complex growth factor networks that play vital roles in regulating fundamental life processes. Such protein factors exert their action by binding to cognate cell specific receptors resulting in regulation of cell division, differentiation, chemotaxis or apoptosis. Engagement of receptors by their respective ligands results in activation of sequential protein phosphorylation cascade, culminating downstream into activation of gene transcription. These factors are expressed ubiquitously under a variety of conditions by normal as well as transformed cells, thereby underpinning their function in autocrine and paracrine stimulation of cells under several physiological and pathological conditions. Despite major advances in our understanding of growth factors, their paradoxical roles in normal cellular homeostasis and pathologies underpin the need to examine their roles in disease and health. The goal of this special issue is to present emerging trends in the roles that growth factors play in inflammatory disease processes that include cardiovascular, cancer, stroke and neurodegenerative processes associated with aging, viral infection and substance abuse with the ultimate aim to pave the way for future therapeutic breakthroughs.

Keywords

Growth factors; Platelet-derived growth factor; HIV-associated cognitive disorders; Therapeutics; Cell signaling; Brain-derived neurotropic factor

Growth factor signaling in neurodegenerative diseases

In the central nervous system (CNS), neuronal homeostasis is a fine balance between neurotrophic versus neurotoxic factors. A common underlying feature of all neurodegenerative processes is that they elicit neuroinflammatory cascades. Specifically, the collective effects of dysregulated expression of neurotrophins/cytokines/chemokines, activated glia, a compromised blood–brain/spinal cord barrier, infiltrating leukocytes lead to a tissue environment that favors neuronal dysfunction/cell death with a concomitant inhibition of mechanisms regulating endogenous repair (Norenberg et al., 2004; Fleming et al., 2006; Popovich and Longbrake, 2008). Since mature CNS neurons are post-mitotic with a poor regenerative capacity, the destructive effects of disease coupled with neuroinflammation often renders affected individuals permanently disabled. Neuronal apoptosis is often observed as a consequence of neuronal dysfunction during

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neuroinflammation. It must be noted that the United States is facing an epidemic of dementias. Currently, there is not a single effective medicine that halts or even slows any neurodegenerative disease. Additionally, since neurodegenerative disorders manifest primarily in mid-to late-life, the incidence is expected to ascend as the population ages. If left unchecked 30 years from now, more than 12 million Americans will suffer from neurodegenerative diseases. Identification of neuroprotective agent(s) that play critical roles in promoting neurogenesis while also promoting survival of neurons (Pixley et al., 1998; Jin et al., 2002; Ohori et al., 2006) is thus of paramount importance. The search for therapeutic options that reduce neuronal injury requires a better understanding of the pathogenic mechanisms and the various steps involved in the pathogenic cascade.

Various factors such as brain-derived neurotrophic factor (BDNF), fibroblast growth factor (FGF), nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF) and platelet-derived growth factor (PDGF) have been implicated in the protection of neurons against neurotoxins (Alzheimer and Werner, 2002; Almeida et al., 2005; Deierborg et al., 2008; Colafrancesco and Villoslada, 2011). For example, in the context of HIV infection, factors such as FGF and BDNF, have been shown to protect neurons by down-modulating the expression of the coreceptor CXCR4, activating cell-survival signals, and inhibiting the internalization of HIV-1 coded proteins (Sanders et al., 2000; Bachis et al., 2003). Similarly, it has been shown that PDGF that is widely expressed in both embryonic and adult CNS exerts strong neurotrophic effects(Pietz et al., 1996). It is an essential factor that is involved in neuroprotection, promotes neuronal differentiation (Williams et al., 1997; Erlandsson et al., 2001), and modulates synaptic transmission (Valenzuela et al., 1997).

Growth Factor Mimetics & Antagonists as Therapeutics

While signaling via PDGF plays a critical role in neuronal survival (Peng et al., 2008b; Peng et al., 2008a; Peng et al., 2010; Peng et al., 2012), it is also becoming increasingly recognized that overactive PDGF signaling can promote tumorigenesis and other pathologies characterized by increased cellular proliferation. This brings up the issue of paradoxical roles exhibited by these factors. In recent years increasing evidence points to the fact that neurotropins (and chemokines) that are ubiquitous in nature can actually exhibit diverse and opposing functions depending on the physiological state of the cells. For example, fractalkine that function as an inflammatory mediator can also carry out a neuroprotective role (Tong et al., 2000; Eugenin et al., 2003), while also regulating neuronal survival through its anti-apoptotic effects (Meucci et al., 1998). Similarly, while there is reduced expression of the trophic factor – PDGF, in neurons in response to certain neurotoxins(Peng et al., 2008b; Peng et al., 2008a; Yao et al., 2009; Peng et al., 2010; Peng et al., 2012), the same factor is upregulated in endothelial cells and leukocytes following exposure to the same toxins (Yao et al., 2011a; Yao et al., 2011b). Based on the premise that paradoxical regulation by growth factors is more common occurrence, caution has to be exercised when developing cell-targeted therapeutics involving these mediators.

The current issue on “Growth factor signaling: Implications in Disease & Therapeutics” in *Journal of Neuroimmune Pharmacology* brings together a collection of contributions from leaders in the field on emerging trends in two relevant areas: a) Growth factor signaling in

the context of neurodegenerative disorders with emphasis on HIV associated neurocognitive disorders (HAND) and b) Targeting growth factor signaling for therapeutics. In all there are 9 review articles, including a perspective. Five of the invited reviews are on the roles of growth factors in the neurodegenerative disease processes specifically HAND. Another one is on the role VEGF in inflammatory diseases. Three others are based on latest trends in current therapeutic strategies aimed at either enhancing or dampening growth factor signaling depending on the disease state.

Currently over 40 million people live with HIV worldwide. In the US, the aging population represents one of the fastest growing groups with HIV. The Center for Disease Control (CDC) estimates that by the year 2015, half of all Americans living with HIV will be over the age of 50. While the advances in anti-retroviral therapy have transformed the conception of HIV/AIDS from a death sentence to a manageable chronic condition, as these individuals continue to enjoy increased longevity, paradoxically almost 25–30% of them will go on to develop HAND that affects adherence to treatment and increases morbidity. HAND comprises a range of symptomatology, including minor cognitive/motor disorder, asymptomatic neurocognitive impairment and in its severe form HIV-associated dementia. HAND impact daily functioning and quality of life of those afflicted, thereby necessitating development of adjunctive and combined therapies to prevent and perhaps reverse the neurologic deficits observed in these individuals.

An elegant review in this issue by Mocchetti *et al* emphasizes the need for such alternative therapies employing BDNF for HAND, that take into account multiple neurotoxic effects of HIV while also restoring the innate ability of the CNS to enhance neurogenesis, restore neuronal plasticity and survival (Mocchetti et al., 2013). Previous studies by these authors pointed to BDNF-mediated down-regulation of CXCR4 expression. Additionally, HIV gp120 mediated down-regulation of pro-BDNF processing in neurons reduces furin levels, which in turn, leads to alterations in balance of pro-versus anti-apoptotic neurotropins (Bachis et al., 2012). Along these lines, the review by Woodbury and Ikezu(Woodbury and Ikezu, 2013) describes the essential role of FGF2 in adult neurogenesis based on its expression and regulation of neural stem and progenitor cells in neuroanatomical niches such as the subventricular zone and the subgranular zone of the hippocampus. Similar to PDGF, overactivation of FGFR1 has also been shown to result in exacerbation of disease pathogenesis by eliciting inflammatory signaling via the surface glycoprotein CD200. This in turn, leads to increased microglial activation. This review highlights the key role of targeting FGF2/FGFR1 axis as a therapeutic intervention for CNS diseases (aging and HAND), with the goal of promoting neurogenesis, restoring synaptic plasticity and modulating neuron-glial interactions and inflammation. A comprehensive review by Fields *et.al* further corroborates the role of FGF1 and FGF2 in neuroprotection against toxicity mediated by HIV proteins in both cell culture and rodent models (Fields et al., 2014). These authors have elegantly discussed how aging and HIV interact to affect various neurotrophins via different mechanisms. Convergence of trophic factors and viral proteins thus modulates host response to neurodegenerative diseases, thereby underscoring neuro-regulatory processes as therapeutic targets. The review by Ramakrishnan *et al* describes the role of Hypoxia Inducible Factor (HIF) as a molecular oxygen sensing switch in inflammatory

conditions such as cardiovascular diseases, cancer, stroke and infection with the ultimate regulation of the downstream target gene – VEGF (Ramakrishnan et al., 2014). Another review by Suh *et. al.* on the paradoxical roles of progranulin (PGRN) in modulating antiviral immunity as well as neuronal dysfunction in the context of HIV infection further emphasizes the dual roles of neuronal growth factors (Suh et al., 2013). These authors propose CSF PGRN as a candidate surrogate marker of HAND. Similar to the neurotropins described above, review by Pozniak *et al* touches on the TNF-α signaling axis and NFkB translocation to function as either pro-survival or pro-apoptotic depending on their interactions (Pozniak et al., 2013). Downstream activation of EphB2 gene has been suggested as the missing link in the neuroprotective effects mediated by TNF-α. Targeting EphB2 could thus be envisioned as a critical therapeutic strategy for controlling neurodegeneration involving TNF-α. Review by Yao *et. al.* further corroborates the opposing roles of PDGF in the context of HAND – on one hand it has a neuroprotective role against HIV proteins gp120 and Tat while it can also function as a cerebrovascular permeant with deleterious effects on the blood-brain barrier resulting in neuroinflammation (Yao et al., 2013).

So how do we harness growth factor signaling for therapeutic advantage? An excellent perspective by Professor Carl-Henrik Heldin summarizes how dampening overactivated PDGF signaling by PDGF antagonists can have therapeutic benefits in the treatment of non-malignant diseases (Heldin, 2013). Since most fibrotic non-malignant diseases of the lung, heart, liver and kidney are driven by increased PDGF signaling among the many other growth factors and cytokines, it is suggested that development of multi-kinase inhibitors or adjunctive therapies with inhibitory antibodies or aptamers against several molecules could prove beneficial in the treatment of these diseases. Review by Funa and Sasahara also corroborates the role of PDGF in development and maintenance of dendritic spine morphology with a pivotal function in memory consolidation (Funa and Sasahara, 2013). Development of pharmacological inhibitors of PDGF receptor signaling in conjunction with iPS-based replacement therapies is well described. The review by Ramakrishnan *et al* highlight HIF as an important molecular regulator of key pathological processes, thus making it amenable to drug targeting for intervening signaling pathways involved in hypoxia and inflammation (Ramakrishnan et al., 2014). Conversely, pathological angiogenesis can also be inhibited by strategies aimed at neutralizing VEGF or by dampening its signaling cascade.

The review by Steiner and Nath delves deep into the challenges of delivery of peptidic neurotropin such as BDNF to the CNS based on its poor bioavailability, shorter half-life and low permeability through the blood-brain barrier (Steiner and Nath, 2014). Various strategies of BDNF delivery involving viral vectors, cell-based conduits, polymer encapsulation, peptide mimetics with improved pharmacokinetics and brain permeability, small molecule mimetics, and use of small molecule inducers that are FDA approved are elegantly discussed.

In summary neurodegenerative diseases, collectively, are the leading cause of disability in the elderly. The outstanding articles presented here will pave the way for future therapeutic breakthroughs by accommodating a paradigm shift involving neurotropin-based therapeutics. It is predicted that detailed understanding of the complex and converging

signaling pathways mediated by neurotropins in both normal homeostasis and tissue pathologies will accelerate over the coming years as scientific tools and insights gain momentum. In closing, we are delighted with the exceptional quality of the articles and thank each of the contributors for their stimulating submissions.

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