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Can VEGF-B Be Used to Treat Neurodegenerative Diseases?

Xuri Li, Anil Kumar, Chunsik Lee, Zhongshu Tang,
Yang Li, Pachiappan Arjunan, Xu Hou and Fan Zhang
National Eye Institute, National Institutes of Health, Rockville, Maryland
United States of America

1. Introduction

Studies on vascular endothelial growth factor B (VEGF-B) during the past decade or so have shown that VEGF-B appears to be a mysterious molecule with obscure, if not controversial, functions. When VEGF-B was initially discovered (Grimmond et al., 1996; Olofsson et al., 1996a), it was naturally believed to be an angiogenic factor, due to its high sequence homology and similar receptor binding pattern to VEGF, the prototypic angiogenic molecule. Much of our research effort was focused on this speculated angiogenic activity of VEGF-B for a long time. However, studies into this aspect, most of the time, turned out to be disappointing because of the negative findings. Unlike VEGF-A, VEGF-B did not seem to play a significant role in inducing blood vessel growth or vascular permeability, etc (Li et al., 2009). In addition, VEGF-B deficiency in mice did not seem to matter greatly, since VEGF-B-null mice appeared largely healthy (Aase et al., 2001; Bellomo et al., 2000; Louzier et al., 2003; Reichelt et al., 2003), in contrast to the early embryonic lethality of VEGF-A null mice (Carmeliet et al., 1996; Ferrara et al., 1996). Based on the negative findings, we had once suspected that VEGF-B might be a redundant molecule. In recent years, VEGF-B has been shown to be a potent neuroprotective factor and an apoptosis inhibitor (Li et al., 2009; Li et al., 2008b; Poesen et al., 2008; Sun et al., 2004; Sun et al., 2006), opening up a new research avenue in VEGF-B biology.

Thus far, there are five members within the VEGF family, VEGF-A, VEGF-B, PlGF, VEGF-C and VEGF-D (Li and Eriksson, 2001; Lohela et al., 2009). As a prototypic angiogenic factor, VEGF-A has a potent and "universal" angiogenic effect under most physiological and pathological conditions (Carmeliet & Jain, 2000; Ferrara & Kerbel, 2005; Folkman, 2007). The placenta growth factor (PlGF) is required for pathological angiogenesis (Luttun et al., 2002). However, when PlGF-1 is produced in the same population of cells with VEGF-A, it can also act as a natural antagonist of VEGF-A (Cao, 2009; Eriksson et al., 2002). VEGF-C and VEGF-D are important players in lymphangiogenesis (Alitalo et al., 2005; Lohela et al., 2009). Remarkably, the biological function of VEGF-B has remained less studied. VEGF-B displays a high degree of sequence homology to VEGF-A and PlGF, and also binds to the tyrosine kinase VEGF receptor-1 (VEGFR-1) and neuropilin-1 (NP-1), like VEGF-A and PlGF (Olofsson et al., 1998; Olofsson et al., 1996a). VEGF-B is abundantly expressed in most tissues and organs (Aase et al., 1999; Li et al., 2001; Olofsson et al., 1996a). However, VEGF-B under most conditions appeared to be "redundant" or "inert" with no obvious function. The

in vivo role of VEGF-B therefore remained enigmatic for a long time. In this review, we summarize the recent advances on VEGF-B biology, with a particular interest in its neuroprotective/survival effect on neuronal and vascular cells (Claesson-Welsh, 2008; Karpanen et al., 2008; Lahteenvuo et al., 2009; Li et al., 2008a; Li et al., 2008b; Poesen et al., 2008; Zhang et al., 2009), and further discuss the therapeutic potential of VEGF-B in treating different types of neurodegenerative diseases.

2. VEGF-B is a neuronal protective factor

VEGF-B is highly expressed in different types of neural tissues, such as the brain (Li et al., 2001; Sun et al., 2004), retina (Li et al., 2008b), spinal cord (Poesen et al., 2008), etc.

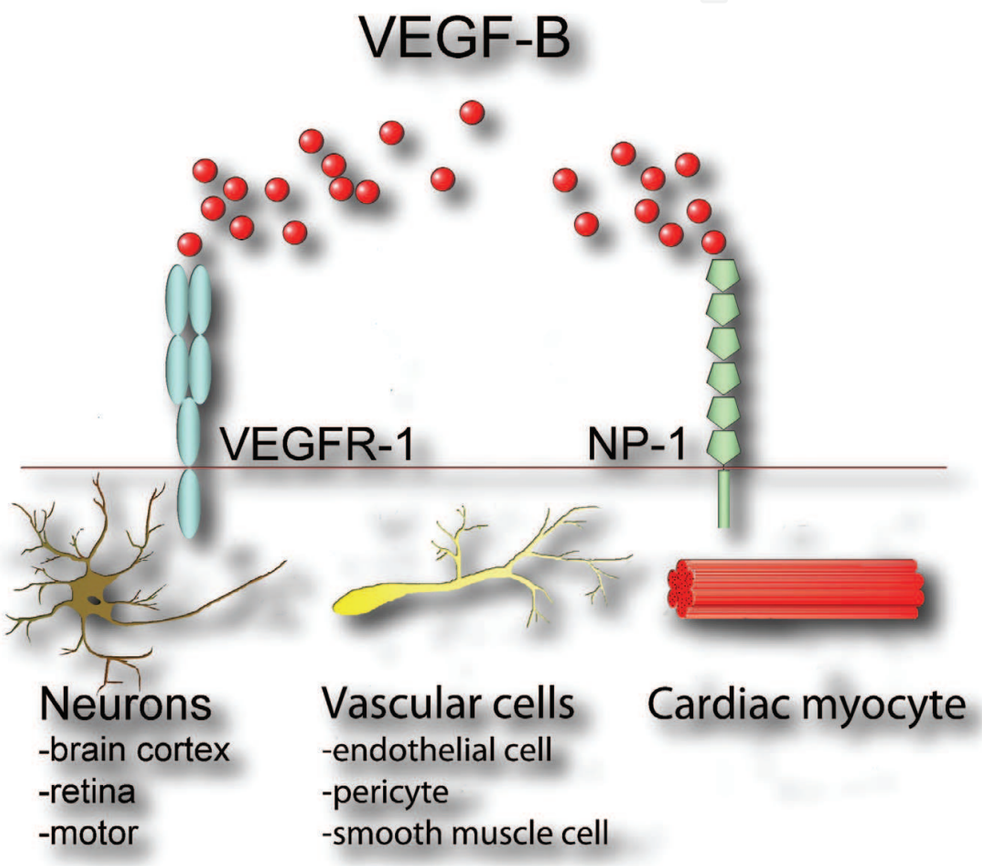

Fig. 1. Pleiotropic protective/survival effect of VEGF-B on multiple cell types. Both *in vitro* data derived from cultured neurons and *in vivo* work using different types of animal models have shown that VEGF-B is a critical protective/survival factor for different types of neurons, including cortical, retinal, and spinal cord motor neurons. In addition, VEGF-B is also a potent protective/survival factor for different types of vascular cells, including vascular endothelial cells, smooth muscle cells and pericytes. Moreover, VEGF-B has also been reported to be a protective factor for cardiac myocytes

We and others have shown that VEGF-B is a potent protective/survival factor for different types of neurons, including brain cortical neurons (Li et al., 2008b; Sun et al., 2004), retinal

neurons (Li et al., 2008b), and motor neurons in the spinal cord (Poesen et al., 2008). *In vitro,* VEGF-B protein treatment dose-dependently increased the survival of cultured primary brain cortex neurons (Li et al., 2008b; Sun et al., 2004). *In vivo,* VEGF-B treatment inhibited apoptosis of brain cortical neurons and reduced stroke volume in a middle cerebral artery ligation-induced brain stroke model (Li et al., 2008b). In the retina, we have shown that VEGF-B treatment protected different types of retinal neurons from apoptosis under different pathological conditions. In an optic nerve crush injury model, VEGF-B treatment increased the survival of retinal ganglion cells. In a NMDA-induced retinal neuron apoptosis model, VEGF-B treatment protected retinal neurons in the ganglion cell layer, inner nuclear layer, and outer nuclear layer (Li et al., 2008b). Moreover, Poesen, K *et al* recently showed that VEGF-B treatment protected cultured primary motor neurons from apoptosis (Poesen et al., 2008). Indeed, the neuroprotective effect of VEGF-B was further confirmed using mice in which VEGF-B was genetically deleted. VEGF-B deficiency led to more severe strokes in an experimental stroke model, and exacerbated retinal ganglion cell death in an optic nerve crush injury model (Li et al., 2008b). Moreover, VEGF-B deficient mice developed a more severe form of motor neuron degeneration when intercrossed with the mutant SOD1 mice, whereas VEGF-B intracerebroventricular injection prolonged the survival of mutant SOD1 rats (Poesen et al., 2008). Taken together, both *in vitro* data derived from cultured neurons and *in vivo* work obtained using different animal models showed that VEGF-B is a critical survival factor for different types of neurons (Fig. 1).

3. VEGF-B is a vascular survival factor

VEGF-B and its receptors are expressed by different types of vascular cells (Aase et al., 1999; Li et al., 2008a; Zhang et al., 2009). We recently found that VEGF-B is a potent survival factor for multiple types of vascular cells, including vascular endothelial cells (EC), pericytes (PC), and smooth muscle cells (SMC) (Li et al., 2009; Zhang et al., 2009). *In vitro,* in both cultured primary vascular cells and established vascular cell lines, VEGF-B treatment increased the survival of not only ECs, but also that of PCs and SMCs (Zhang et al., 2009). In contrast, VEGF-B inhibition by shRNA treatment led to apoptosis in the ECs and PCs. Moreover, increased apoptosis was found in VEGF-B deficient ECs and SMCs isolated from VEGF-B null mice, when the cells were cultured in serum-free medium or under H_2O_2-induced oxidative stress (Zhang et al., 2009). *In vivo*, VEGF-B deficiency led to poorer blood vessel survival in the cornea after withdrawal of the implanted growth factors, fewer surviving hyaloid vessels in postnatal mouse eyes, and greater oxygen-induced retinal blood vessel degeneration in neonatal mice (Zhang et al., 2009). Thus, both gain- and loss-of-function analyses showed that VEGF-B is required for the survival of multiple types of vascular cells, especially, under pathological conditions (Fig. 1).

4. VEGF-B promotes energy metabolism

The human brain weighs only about 2% of the total body weight. However, it consumes about 20% of the total energy produced in the body, demonstrating the importance of energy metabolism to the neural systems. Indeed, numerous reports have shown that energy deficit is involved in various neurodegenerative disorders, such as Alzheimer's disease (AD) (Beal, 2007), Huntington's Disease (HD) (Browne and Beal, 2004), Parkinson's disease (PD) (Elstner et al., 2011) and Amyotrophic lateral sclerosis (ALS) (D'Alessandro et

al., 2011). In addition, dysregulation of lipid pathways has been implicated in AD (Di Paolo and Kim, 2011). These findings thus warrant investigating and developing therapeutic reagents that can regulate neuronal bioenergetic pathways. Recently, VEGF-B has been shown to be involved in energy metabolism, where it facilitates fatty acid uptake from circulation and transfer to metabolically active tissues (Hagberg et al., 2010). We have also seen that VEGF-B upregulated the expression of a number of key enzymes that are involved in lipid and glucose metabolism in cultured cells (our own unpublished data). Based on the above findings, VEGF-B might be an important molecule that could be used to regulate neuronal bioenergetic pathways. Further studies are needed to verify this.

5. VEGF-B does not induce blood vessel permeability

It is known that all the other VEGF family members, VEGF-A (Dvorak et al., 1995), PlGF (Carmeliet et al., 2001), VEGF-C (Joukov et al., 1997), VEGF-D (Rissanen et al., 2003) and VEGF-E (Ogawa et al., 1998), induce blood vessel permeability. However, numerous studies using different models and approaches, such as VEGF-B deficient and transgenic mice, recombinant protein or gene transfer, have shown that VEGF-B does not affect blood vessel permeability (Aase et al., 2001; Mould et al., 2005; Reichelt et al., 2003) (Fig. 2). Intradermal injection of VEGF-A_{165}, VEGF-A_{121}, and VEGF-C in mice ears increased vascular permeability, while VEGF-B administration had no such effect (Brkovic & Sirois, 2007). VEGF-B_{167} recombinant protein injection into mouse brain or eye did not induce blood vessel permeability (Li et al., 2008b). In preserved lung grafts, VEGF-A and VEGF-C, but not VEGF-B mediate increased vascular permeability (Abraham et al., 2002). Indeed, when overexpressed in the lung by adenoviral gene transfer, VEGF-B had no effect on blood vessel permeability (Louzier et al., 2003). Adenoviruses expressing VEGF-A and VEGF-D delivered into rabbit hind limb skeletal muscles induced vascular permeability, while adenovirus encoding VEGF-B did not affect blood vessel permeability when administered into skeletal muscles (Rissanen et al., 2003). Thus, data derived from different model systems showed that VEGF-B is the only member of the VEGF family that does not have a significant role in inducing blood vessel permeability

6. Minimum side effect of VEGF-B and its negligible role in angiogenesis

Due to its high sequence homology and similar receptor binding patterns to VEGF-A (Li and Eriksson, 2001; Nash et al., 2006), VEGF-B was initially believed to be an angiogenic factor. However, studies along this line using VEGF-B deficient and transgenic mice and gene transfer approaches have, most of the time, led to negative findings (Fig. 2).

VEGF-A or VEGF-C deficiency caused embryonic lethality in mice (Carmeliet et al., 1996; Ferrara et al., 1996; Karkkainen et al., 2004). VEGF-B deficient mice, however, are largely healthy with normal physiological angiogenesis (Aase et al., 2001; Bellomo et al., 2000; Louzier et al., 2003; Reichelt et al., 2003). PlGF deficient mice display impaired pathological angiogenesis (Carmeliet et al., 2001; Luttun et al., 2002). VEGF-B deficiency, however, does not affect pathological angiogenesis in most organs studied, such as the wounded skin, hypoxic lung, ischemic retina and limb (Li et al., 2008a). Even though one study reported a role of VEGF-B in pathological (inflammatory) angiogenesis using arthritis models (Mould et al., 2003), we did not observe such an effect in our study (unpublished observation). In contrast to VEGF-A and PlGF, VEGF-B is not required for neovessel formation in

proliferative retinopathy (Reichelt et al., 2003) or blood vessel remodeling in pulmonary hypertension (Louzier et al., 2003).

Transgenic expression of all the other VEGF family members, such as VEGF-A (Detmar et al., 1998; Larcher et al., 1998; Xia et al., 2003), PlGF (Odorisio et al., 2002), VEGF-C (Jeltsch et al., 1997), VEGF-D (Karkkainen et al., 2009) or VEGF-E (Kiba et al., 2003) induced either angiogenesis or lymphangiogenesis. VEGF-B is the only member of the VEGF family, transgenic overexpression of which in different organs did not induce angiogenesis or lymphangiogenesis (Karpanen et al., 2008; Mould et al., 2005). VEGF-B overexpression in cardiac myocytes under the alpha-myosin heavy chain promoter did not induce angiogenesis in the heart (Karpanen et al., 2008). Instead, blood vessel density was decreased in the hearts overexpressing VEGF-B (Karpanen et al., 2008). In addition, VEGF-B

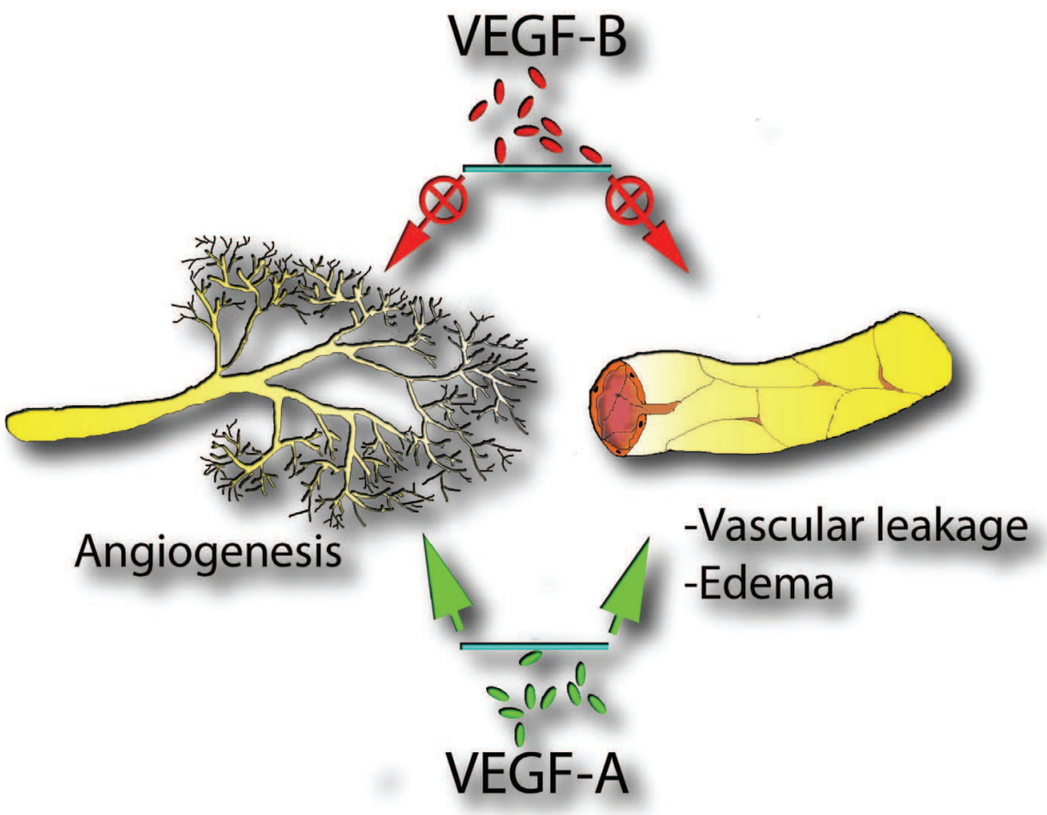

Fig. 2. VEGF-B does not induce blood vessel permeability and is minimally angiogenic. Adenoviral gene transfer of the other VEGF family members, such as VEGF-A, VEGF-C and VEGF-D, into rabbit hindlimb skeletal muscles induced strong angiogenesis, vascular permeability, or lymphangiogenesis (Rissanen et al., 2003). VEGF-B adenoviral gene transfer, however, did not induce angiogenesis or lymphangiogenesis in the same model system (Rissanen et al., 2003). Similarly, adenoviral gene transfer of VEGF-A and VEGF-D to rabbit carotid arteries induced robust adventitial angiogenesis, whereas VEGF-B adenoviral gene transfer failed to do so (Bhardwaj et al., 2003, 2005). Another study also showed that VEGF-B_{167} gene delivery to the mouse skin or ischemic limb did not induce blood vessel growth (Li et al., 2008a)

transgenic expression in endothelial cells under Tie2 promoter did not induce angiogenesis in different types of organs (liver, heart, kidney, etc) (Mould et al., 2005), and VEGF-B transgenic expression in the skin under keratin-14 promoter only marginal potentiated angiogenesis (Karpanen et al., 2008).

Studies using VEGF-B protein treatment also showed a minimum side effect of VEGF-B and a negligible role in angiogenesis. VEGF-B_{167} recombinant protein injection into adult mouse eyes at a dose effective for retinal neuron survival did not induce ocular angiogenesis (Li et al., 2008b). Poesen, K., *et al* has also shown that intracerebroventricular injection of the VEGF-B_{186} recombinant protein did not cause any blood vessel growth or blood-brain barrier leakage (Poesen et al., 2008).

VEGF-B is most abundantly expressed in the heart (Li et al., 2001; Olofsson et al., 1996a). Using a cardiac ischemia model, we found that VEGF-B has a restricted role in the revascularization of ischemic myocardium (Claesson-Welsh, 2008; Li et al., 2008a). Indeed, this observation was also reported by another study demonstrating that in pigs and rabbits, VEGF-B_{186} gene transfer induced myocardium-specific angiogenesis and arteriogenesis (Lahteenvuo et al., 2009). Thus, ours and others' work have shown that in most organs, VEGF-B is dispensable for blood vessel growth in development, normal physiology, and many pathological conditions but with a selective angiogenic activity in the ischemic heart. Taken together, compared with the other VEGF family members, VEGF-B appears to have a unique safety profile that is highly desirable as a potential therapeutic reagent to treat human diseases.

7. Therapeutic potential of VEGF-B in treating neurodegenerative diseases

Currently, for most neurodegenerative diseases, there are no effective treatments. Although novel remedies such as gene or cell therapies are being explored intensively, few have proved to be clinically beneficial. Neurodegenerative diseases often involve complex multi-etiological aspects. Neuronal apoptosis is a central characteristic of neurodegenerative diseases. In addition, blood vessel degeneration in the relevant neural system is often seen in many of the neurodegenerative disorders. Therefore, therapeutic reagents targeting one pathway only will most likely not be sufficient to cure the disease. Reagents that can improve multiple pathological aspects are more desirable. Based on our recent findings that VEGF-B is a potent protective/survival factor for both the neuronal and vascular systems, which are two critical components in most neurodegenerative disorders, we hypothesize that VEGF-B may have therapeutic implications in treating various types of neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) stroke, retinitis pigmentosa (RP), glaucoma, diabetic retinopathy (DR) and atrophic age-related macular degeneration (AMD). Below, we discuss the therapeutic potential of VEGF-B in relation to these pathologies.

7.1 Alzheimer's Disease

Alzheimer's Disease (AD) is a major contributor to dementia in the elderly, and affects about 2% of the population in developed countries. The total number of AD patients is estimated to increase significantly in the near future due to the growing aging population (Mattson, 2004). In AD patients, plaques containing the beta-amyloid protein deposit extracellularly,

and neurofibrillary tangles of hyperphosphorylated tau protein accumulate intracellularly in the brain, leading to the degeneration of synapses and neurons, and eventually the loss of memory and cognitive ability (Mattson, 2004). Both genetic and environmental factors contribute to the development of AD. Several drugs are currently available for AD treatment, such as tacrine, donepezil, rivastigmine tartrate and galantamine hydrobromide. These drugs can sometimes relieve the symptoms of early stage AD patients. However, they cannot stop or reverse the progression of the illness, and the effects of these drugs are often inconsistent and diminished over time. Therefore, more effective treatments are still needed. Many new reagents have been tested in preclinical or clinical studies, such as intravenous immunoglobulin (Relkin et al., 2008), γ-secretase inhibitors (Siemers et al., 2006; Wilcock et al., 2008), blockers of the receptor for advanced glycation end product (Chen et al., 2007), Dimebon (Doody et al., 2008), etc. However, their therapeutic efficacies are yet to be proven. It is noteworthy that in recent years, AD has been considered more as a vascular, rather than a neural disease based on clinical imaging, epidemiological, pharmacotherapy and histopathological evidence (Chow et al., 2007; de la Torre, 2002; de la Torre, 2004; Kalaria and Hedera, 1995). Indeed, vascular degeneration has been observed in different experimental Alzheimer's disease models (Girouard and Iadecola, 2006; Wu et al., 2005),(Hsu et al., 2007). In addition, it has been known that the functional relationships among neuronal, glial, and vascular cells within the so-called neurovascular unit is compromised in Alzheimer's disease (Salmina, 2009). Thus, mounting evidence indicates that vascular abnormalities, such as capillary degeneration, are important factors that can initiate Alzheimer's disease. Due to the potent survival effect of VEGF-B on both neuronal and vascular cells, VEGF-B may have a therapeutic potential in the prevention and treatment of Alzheimer's disease. Further studies are needed to verify this.

7.2 Parkinson's Disease

Parkinson's Disease (PD) is the second most prevalent neurodegenerative disease following AD. PD is characterized by the age-related progressive loss of dopaminergic neurotransmission in the basal ganglia (Nutt and Wooten, 2005). The etiology of PD is complicated and involves multiple factors and mechanisms. PD patients suffer from severe motor symptoms, including uncontrollable resting tremor, bradykinesia, rigidity and postural imbalance. Current treatment for PD can only attenuate the symptoms. There is no effective drug that can stop the neuronal death in PD patients. Levodopa, in combination with a peripheral dopa decarboxylase inhibitor, is the most effective therapy thus far (Lees et al., 2009). However, levodopa motor and nonmotor complications are challenging issues to overcome clinically (Jankovic, 2005). Dopamine agonists and monoamine oxidase-B inhibitors can reduce the symptoms either as a monotherapy or in combination with levodopa (Jankovic, 2006). However, even though the symptoms may be controlled after the administration of these drugs, at least following the initial treatment, the death of the dopaminergic neurons persists and the disease continues to progress.

Neuroprotection is at the forefront of PD research, and many neuroprotective reagents have been investigated (Bonuccelli and Del Dotto, 2006; Djaldetti and Melamed, 2002). The glial cell derived neurotrophic factor (GDNF) has been shown to enhance the survival of midbrain dopaminergic neurons *in vitro* and rescued degenerating neurons *in vivo* (Love et al., 2005). However, a multicenter clinical trial showed no clinical benefit (Lang et al., 2006), and GDNF antibody development was observed in some PD patients (Sherer et al., 2006).

Indeed, in a rat α-synuclein PD model, overexpression of GDNF failed to exert effective neuroprotection (Decressac et al., 2011). The vascular endothelial growth factor–A (VEGF-A) has been shown to induce neuroprotection in a PD model of the 6-hydroxydopamine (6-OHDA) lesioned rats (Yasuhara et al., 2004). However unwarranted side effect of VEGF-A proved to be detrimental to the brain, since VEGF-A also induced edema and undesired angiogenesis in the brain (Yasuhara et al., 2005). In addition, it has also been reported that VEGF-A induces astrogliosis, microgliosis and disrupts the blood-brain barrier (Rite et al., 2007). Thus, new and better neuroprotective reagents are still needed.

Apart from neuronal death, normal contact between nigral neurons and capillaries is often impaired in the brains of PD patients. Capillary basement membrane thickening and collagen accumulation are often seen in PD patients, suggesting that capillary dysfunction may play an important role in PD development (Farkas et al., 2000; Faucheux et al., 1999). Indeed, it is believed that markers of cerebrovascular disease may predict the development of different types of dementia, including PD (Staekenborg et al., 2009). Recent work has shown that VEGF-B expression was upregulated by neurodegenerative challenges in the midbrain, and exogenous application of VEGF-B has a neuroprotective effect in a culture model of PD (Falk et al., 2009). In another study, VEGF-B_{186} was used to test its neuroprotective effect in a PD model since it is more diffusable and hardly binds to extracellular matrix than VEGF-B_{167} (Olofsson et al., 1996b; Poesen et al., 2008). In this study, a single dose of VEGF-B_{186} (3μg/rat) rescued dopaminergic neurons from death in the caudal sub region of substantia nigra in rats (Falk et al., 2011). Thus, as a potent neuronal and vascular protective factor, VEGF-B may have therapeutic implications in PD treatment. Future investigations are needed to investigate into this.

7.3 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a devastating adult-onset neurodegenerative disorder characterized by progressive loss of motoneurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord, leading to muscular paralysis and eventually death (Wijesekera and Leigh, 2009). The pathogenesis of familial ALS is unclear. Sporadic ALS is believed to be related to superoxide dismutase (SOD) 1 mutation in about 20-30% of the patients (Yamamoto et al., 2008). Although many drug candidates have been tested, such as antioxidants, neurotrophic factors, anti-apoptotic, anti-inflammatory and anti-aggregation reagents, the only drug currently available for ALS patients is Riluzole, a glutamate antagonist (Traynor et al., 2006; Yamamoto et al., 2008). Recently, it is believed that vascular defect may be a critical contributor to the pathogenesis of ALS. In the amyotrophic lateral sclerosis-linked SOD1 mutant mice, vascular endothelial damage accumulates before motor neuron degeneration and plays a central role in ALS initiation (Segura et al., 2009). The therapeutic promise of VEGF-B in ALS treatment has been shown by Poesen et al. VEGF-B_{186} protected cultured primary motor neurons against degeneration (Poesen et al., 2008). *In vivo*, VEGF-B treatment protected motor neurons from degeneration in several experimental ALS models (Poesen et al., 2008). In the future, it will be exciting to see whether this effect of VEGF-B holds true in ALS patients.

7.4 Stroke

Ischemic stroke due to sudden loss of blood supply in the brain is a leading cause of morbidity and mortality in the United States. Currently, there is no satisfying therapy for

stroke patients despite extensive effort on identifying better interventions. Since early 1990s, neuroprotection as a potential therapeutic strategy for stroke treatment has received much attention (Ginsberg, 2008). During the past decade or so, about 160 clinical trials on neuroprotection for ischemic stroke treatment have been conducted (Ginsberg, 2008). However, no effective neuroprotective drug has been identified. The potential therapeutic value of VEGF-B for stroke treatment has been supported by several studies. It has been shown that VEGF-B is a potent survival factor for cortical neurons. VEGF-B deficiency in mouse increased stroke volume by about 40% in an experimental stroke model, and led to more severe neurologic impairment (Sun et al., 2004). Indeed, VEGF-B protein treatment protected cultured cerebral cortical neurons from hypoxic injury, demonstrating a direct survival effect of VEGF-B on neurons (Sun et al., 2004). Furthermore, intraventricular administration of VEGF-B decreased stroke volume (Li et al., 2008b) and restored neurogenesis to normal level in VEGF-B deficient mice (Sun et al., 2006). Mechanistically, we have shown that VEGF-B exerts its neuronal survival effect by inhibiting the expression of many proapoptotic BH3-only protein genes (Li et al., 2008b). In summary, both *in vitro* and *in vivo* data from several groups have suggested a therapeutic potential of VEGF-B in stroke treatment and warrant further studies to investigate into this.

7.5 Huntington's Disease

Huntington's Disease (HD) is a hereditary autosomal dominant neurodegenerative disorder characterized by the selective degeneration of striatal projection neurons that are responsible for choreic movements, resulting in progressive movement disorder, cognitive decline and psychiatric disturbances. Over the course of HD, the mutated huntingtin protein leads to intracellular dysfunctions and neuronal death in the striatum, selected layers of the cerebral cortex, as well as other brain regions (Gil and Rego, 2008). Currently, no effective therapy exists for HD. Pharmacological treatment may ameliorate hyperkinesis and psychiatric symptoms, but neuropsychological deficits and dementia remain untreatable. The apoptotic cascade is believed to be a possible cause of neurodegeneration in HD (Pattison et al., 2006). The therapeutic potential of some neuroprotective reagents in HD treatment, such as GDNF, coenzyme Q10, minocycline and unsaturated fatty acids, has been investigated (Alberch et al., 2002; Bonelli and Hofmann, 2007). Since VEGF-B is a potent apoptosis inhibitor (Li et al., 2008b), it will be interesting to test whether VEGF-B could slow down, if not stop, neuronal degeneration in HD.

7.6 Retinal degenerative diseases

Retinal degenerative diseases are a group of disorders involving degeneration of the retina. Progressive loss of retinal neurons is a common characteristic of such disorders and the major reason for vision impair or loss. Further, blood vessel deterioration is often seen in many of the retinal degenerative diseases. Unfortunately, thus far, there is no efficacious treatment for most of the retinal degenerative diseases.

7.6.1 Retinitis pigmentosa (RP)

Retinitis pigmentosa (RP) is a heterogeneous retinal dystrophy characterized by the progressive loss of photoreceptors and subsequent degeneration of retinal pigmented epithelial (RPE) cells (Hartong et al., 2006). RP is the leading cause of blindness in inherited

retinal degeneration-associated diseases world-wide. The first symptom of RP is often night blindness, followed by the gradual loss of peripheral visual field, and ultimately blindness. Apart from the photoreceptor dystrophy, retinal arterioles are attenuated in RP, leading to poor oxygenation of rods and cones and increased apoptosis in the neural retina. It is known that about 45 genes/loci are involved in this pathology. Due to the large number of genes and mutations implicated, correcting the defective genes/mutations represents an overwhelming challenge. The current available therapies are vitamin supplement and sunlight protection, which can only slow down the degenerative process (Hamel, 2006). There is no treatment that can stop the progress of the disease or restore vision in RP patients. Since VEGF-B can protect both neuronal and vascular cells from apoptosis, VEGF-B administration may preserve both the photoreceptors and blood vessels in RP. Future studies are needed to verify this.

7.6.2 Glaucoma

Glaucoma is the most prevalent form of adult optic neuropathies affecting approximately 2% of the population over the age of 40 (Levin, 2005; Marcic et al., 2003). Glaucoma is characterized by the increased apoptosis of retinal ganglion cells, loss of optic nerve fibers, and, if uncontrolled, impair or loss of vision (Weinreb, 2005). Apoptosis of retinal ganglion cells is believed to be an early event in glaucoma (Cheung et al., 2008). The number of glaucoma patients is significantly increasing because of the growing ageing population and other factors (Morley and Murdoch, 2006). Currently, there is no general treatment effective for all glaucoma patients. Recent years have seen increasing evidence showing that glaucoma is, to a large extent, a neurodegenerative disease similar to other neurodegenerative disorders in the central nervous system, such as Alzheimer's disease (Cheung et al., 2008). Traditionally, lowering the intraocular pressure (IOP) has been a major therapeutic goal in glaucoma treatment. However, such therapeutic approaches have not been effective in preventing many patients from progressive vision loss. Thus, the fact that retinal ganglion cells (RGC) continue to die in some glaucoma patients with normal or even lower IOP has changed the research focus to neuroprotection for glaucoma treatment in recent years. Therefore, neuroprotective reagents used to treat other neurodegenerative diseases have been under considerable investigation for glaucoma treatment, and neuroprotection in glaucoma treatment has gained more and more attention. However, the number of effective neuroprotective reagents is limited. We have recently revealed that VEGF-B is expressed in normal retinal ganglion cells (Li et al., 2008b). Importantly, the expression of VEGF-B is up-regulated after optic nerve crush injury in the retina (Li et al., 2008b), suggesting a role of VEGF-B in retinal ganglion cell function. Indeed, VEGF-B inhibits the expression of many apoptotic genes in the retina and protected retinal ganglion cells from axotomy-induced apoptosis (Li et al., 2008b). These data have provided evidence that VEGF-B may be a promising drug candidate for glaucoma treatment as a neuroprotective factor. Further studies are warranted to investigate this.

7.6.3 Diabetic retinopathy

Diabetic retinopathy (DR) is a common complication of diabetes. About 50-75% of diabetic patients develop DR. In the United States, DR is the leading cause of legal blindness in the 20 to 74 year-old population (Imai et al., 2009). Conventionally, DR is believed mainly to be

a microvascular disease. However, it is now considered to be also a neurodegenerative disease involving functional and structural defects of different types of neurons in the retina (Imai et al., 2009). Indeed, neuronal apoptosis has been found to be an early event in a rat model of diabetes (Barber et al., 1998). Four months after the onset of diabetes, there were only about 50% of total neurons left in the retinae of the rats (Barber et al., 1998), and the number of retinal ganglion cells (RGC) and the thickness of the inner retina layer were significantly reduced (Barber et al., 1998). In diabetic patients, increased apoptosis was also observed in the retina (Imai et al., 2009). Moreover, significant nerve fibre loss in the superior segment of the retina was observed in type 1 diabetic patients, suggesting RGC loss (Kern and Barber, 2008; Lopes de Faria et al., 2002). In addition, thinning of the inner retinal layer was observed in early stage of type 1 diabetic patients (van Dijk et al., 2009). It is reported that the mitochondria- and caspase-dependent cell-death pathways are involved in the neuronal degeneration in diabetic retinopathy (Oshitari et al., 2008). The potential role of VEGF-B in diabetic retinopathy has not been investigated thus far. However, given that VEGF-B is a potent apoptosis inhibitor and has a strong protective effect on both retinal ganglion cells and different types of vascular cells, it is reasonable to speculate that VEGF-B could be used to rescue the chronic retinal degeneration in DR. However, further investigation and research into this aspect are still needed.

7.6.4 Atrophic AMD

Age-related macular degeneration (AMD) is the most common cause of blindness in developed countries. Atrophic (dry) AMD is a late-onset, multifactorial, slowly progressing retinal neurodegenerative disease caused by the degeneration of retinal pigment epithelium (RPE) that lies beneath the photoreceptor cells in the retina. Although RPE is a central element in the pathogenesis of age-related macular degeneration, RPE dysfunction results in the secondary death of macular rods and cones due to abnormal metabolic support from the RPE, eventually leading to irreversible vision loss (de Jong, 2006). Drusen formation, oxidative stress, accumulation of lipofuscin, local inflammation and reactive gliosis are believed to be involved in the pathogenesis of atrophic AMD (Petrukhin, 2007). Currently, there is no effective treatment for atrophic AMD. There are reports showing that antioxidants supplement can provide protection against age-related macular degeneration. A high dietary intake of beta carotene, vitamin C, vitamin E, and zinc may reduce the risk of AMD in elderly people substantially (Johnson, 2009; van Leeuwen et al., 2005). Compared with the other types of retinal degenerative diseases, neuroprotection as a potential therapeutic strategy has been less studied in atrophic AMD. Our recent findings showed that VEGF-B is a potent apoptosis inhibitor. Moreover, the anti-apoptotic property of VEGF-B is likely a general effect on many different types of cells, including RPE cells (Li et al., 2009; Li et al., 2008b; Zhang et al., 2009). VEGF-B therefore might potentially be used to enhance RPE survival for AMD treatment.

8. Conclusion

In summary, despite the complex etiology of different types of neurodegenerative diseases, one common characteristic of them is the apoptotic neuronal death. In addition, degeneration of the blood vessels is often seen in many of the neurodegenerative diseases. Thus, combination therapy acting on both aspects is highly desirable. We and others have

recently shown that VEGF-B appears to be a multi-functional molecule with a potent protective/survival effect on both the neuronal and vascular systems. Importantly, the protective/survival effect of VEGF-B is accompanied by a unique and rare safety profile, since VEGF-B under most conditions appears to be inert, but acts only when there is a pathological challenge. Thus, VEGF-B may have important therapeutic values in treating different types of neurodegenerative diseases by preserving both the endangered neurons and blood vessels, and, possibly, other cell types as well.

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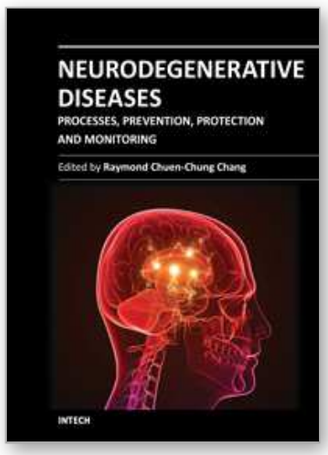

Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring

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Neurodegenerative Diseases - Processes, Prevention, Protection and Monitoring focuses on biological mechanisms, prevention, neuroprotection and even monitoring of disease progression. This book emphasizes the general biological processes of neurodegeneration in different neurodegenerative diseases. Although the primary etiology for different neurodegenerative diseases is different, there is a high level of similarity in the disease processes. The first three sections introduce how toxic proteins, intracellular calcium and oxidative stress affect different biological signaling pathways or molecular machineries to inform neurons to undergo degeneration. A section discusses how neighboring glial cells modulate or promote neurodegeneration. In the next section an evaluation is given of how hormonal and metabolic control modulate disease progression, which is followed by a section exploring some preventive methods using natural products and new pharmacological targets. We also explore how medical devices facilitate patient monitoring. This book is suitable for different readers: college students can use it as a textbook; researchers in academic institutions and pharmaceutical companies can take it as updated research information; health care professionals can take it as a reference book, even patients' families, relatives and friends can take it as a good basis to understand neurodegenerative diseases.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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