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Schwann cells as a therapeutic target for peripheral neuropathies

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Abstract

Schwann cells, the myelin forming cells in the peripheral nervous system, play a key role in the pathology of various inflammatory, metabolic and hereditary polyneuropathies. Advances in identifying growth factors and signaling molecules that are expressed by Schwann cells have paved the way to development of new treatment strategies that are aimed to improve the protective and regenerative properties of Schwann cells in peripheral nerve disorders. These include the exogenous application of growth factors and neurohormones, which have been advanced into clinical trials in humans and transplantation paradigms that have been moved into late stage preclinical models. In this review we will discuss the latest developments in these therapeutic approaches with special regard to peripheral nerve disorders, in which the progress in basic research have already been translated into clinical trials including HIV-associated distal sensory polyneuropathy and diabetic neuropathy.

Keywords

Schwann cells; myelination; regeneration; nerve injury; peripheral nerve

Schwann cells as therapeutic targets for polyneuropathies

Schwann cells, the myelin forming cells in the peripheral nervous system are crucial for the proper function and maintenance of peripheral nerves. They provide trophic support to axons via expression of various growth factors and hormones, especially after nerve injury [1, 2]. These include the neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF). The secretion of growth factors is necessary to promote axon growth and prevent neurons from initiating programmed cell death [3-5]. Apart from growth factors, Schwann cells express axon growth promoting surface cell adhesion molecules and assemble the basal lamina as a prerequisite for formation of myelin [6, 7]. The ability of Schwann cells to form myelin is essential for the saltatory conduction that allows the rapid conductivity of action potentials along neurons.

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Based on our understanding of the interactions between axons and Schwann cells, it is evident that Schwann cells play a key role in the pathologenesis of various inflammatory, metabolic and hereditary polyneuropathies. Over the last two decades, fundamental progress has been made in elucidating the molecular basis of Schwann cell biology. These advances have lead to the development of new treatment strategies that are aimed to improve the protective and regenerative properties of Schwann cells in peripheral nerve disorders. These include application of growth factors and neurohormones, which have been advanced to clinical trials in humans with mixed success, and Schwann cell transplantation paradigms, which have mostly been evaluated in preclinical models of traumatic nerve injury. Among the large spectrum of peripheral nerve disorders, there are three in which the progress in basic research paved the way for a particularly prompt translation into clinical trials. These include the HIV-associated distal sensory polyneuropathy (HIV-SN), the diabetic neuropathy and Charcot-Marie-Tooth disease type 1A. In the following review we will provide a brief overview of the role of Schwann cells in the pathogenesis of these three neuropathic conditions. In the second part, we summarize the most recent therapeutic approaches for these neuropathies and discuss future treatment strategies.

1.1 HIV-associated distal sensory polyneuropathy (HIV-SN)

The most frequent form of polyneuropathy in HIV infected individuals is HIV-associated distal sensory polyneuropathy (HIV-SN) [8-11]. HIV-SN can be further distinguished based on its pathogenesis in a subtype associated with HIV infection per se (distal symmetric polyneuropathy – DSP) and an antiretroviral toxic neuropathy (ATN) associated with the use of antiretroviral agents. The prevalence of the HIV infection associated sensory neuropathy varies between 10-35% in HIV infected individuals [9, 11]. Older studies indicated that risk factors for the development of HIV-SN are typically those that can be attributed to the advanced disease course including low CD4 cell counts and increased HIV virus load [12, 13]. However, this concept has been questioned from the results of more recent trials indicating that HIV-SN can be seen in earlier stages of the disease [14, 15]. Since the introduction of highly active antiretroviral therapy (HAART), the frequency of HIV-SN subtypes clearly shifted to the ATN, which is caused by the neurotoxicity of specific nucleoside reverse transcriptase inhibitors (NRTIs). The two forms are clinically undistinguishable and present with symptoms of distal symmetric pain such as hyperalgesia and allodynia, accompanied by mild to severe sensory deficits, which may progress over time and ascend to upper limbs [8, 9].

Pathological studies of HIV-SN have reported a distal degeneration of small myelinated and unmyelinated nerve fibers [8, 16]. This distal small sensory fiber loss is accompanied by proximal recruitment of HIV infected macrophages within the dorsal roots and dorsal root ganglia [17, 18]. Activated macrophages are known to exert pathologic effects to neurons and Schwann cells by release of proinflammatory cytokines and toxic mediators such as nitric oxide (NO) [19]. It remains controversial if HIV can mediate direct toxicity to neurons and/or Schwann cells. Transgenic mice that express the entire HIV genome in neurons under the transcriptional control of a neurofilament promoter, develop axonal degeneration in the absence of inflammatory infiltrates [20]. However, several studies have failed to provide evidence for a general infection of Schwann cells and/or neurons with HIV, arguing against

a direct toxic effect of HIV to those cells [8, 21, 22]. Thus, it has been hypothesized that soluble, neurotoxic mediators released by HIV-infected macrophages cause the sensory axonopathy in DSP subtype of HIV-SN. This concept is supported by studies demonstrating that the HIV-1 envelope glycoprotein gp120 can promote neurotoxicity [23-27]. The important role of activated Schwann cells in the pathogenesis of HIV-SN has been emphasized by *in vitro* studies showing that binding of gp120 to perineuronal Schwann cells can result in the release of inflammatory chemokines and tumor necrosis factor - alpha, which subsequently mediates neurotoxicity [23]. Apart from those pathways, which require perineuronal Schwann cells, gp120 can also mediate direct toxicity to sensory axons by activation of mitochondrial caspase pathways [24]. In contrast to the perineuronal Schwann cells that help mediate gp120 neurotoxicity, the periaxonal Schwann cells have a neuroprotective role that is likely mediated by erythropoietin. This erythropoietin-mediated neuroprotection is dependent on activation of hypoxia ischemic factor (HIF) in periaxonal Schwann cells via NO released from injured axons [25, 28]. Future studies can potentially exploit these differences between perineuronal and periaxonal Schwann cells for development of effective therapies that prevent distal axonal degeneration.

ATN is a frequent complication of NRTIs, especially didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) [8]. In contrast to pure HIV-SN, ATN predominantly targets the sensory axons without activation of Schwann cells. In vitro studies suggest that the toxic effect of NRTI is based on mitochondrial dysfunction, which subsequently leads to energy deprivation, and eventually results in necrotic cell death. ATN represents the dose-limiting toxicity of the above-mentioned drugs and the risk for developing ATN correlates with time and dose of drug exposure. Of note, a concomitant infection with HIV seems to be a prerequisite for the development of ATN, since high doses of any of these drugs alone fail to replicate ATN in rabbits and rodents and primates [8, 29, 30].

A strategy to overcome this obstacle is the use of transgenic mice, which express gp120 under the control of glial fibrillary acidic protein (GFAP) promoter. This strategy allows one to expose only the unmyelinated sensory axons to gp120, as the non-myelinating Schwann cells are the only Schwann cells that express GFAP. These mice normally develop a mild sensory neuropathy affecting unmyelinated axons but this occurs at around 12-15 months of age. However, when these mice are exposed to didanosine at age of 2 months for 4 weeks, they develop a distal axonal degeneration of small, unmyelinated fibers, similar to the pathologic changes in patients with HIV-SN [31]. This is useful model to study interactions between gp120 and didanosine in mediating neurotoxicity and perhaps more importantly it can serve as a tool to validate potential drug candidates for HIV-SN.

1.2. Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease encompasses a heterogeneous spectrum of hereditary neuropathies, which can be classified based on clinical, electrophysiological and genetic criteria [32, 33]. The most common form is CMT1A, which is caused by an intrachromosomal duplication for the gene that encodes the peripheral myelin protein 22 (PMP22) [32, 34]. Patients with CMT1A have three copies of the Pmp22 gene and pathologic overexpression of Pmp22 in Schwann cells is thought to be the primary

mechanism of abnormal myelin formation and subsequent axonal loss. Several rodent models of CMT1A have been generated, which have proven to be valuable tools to study the underlying pathogenic mechanisms and possible therapeutic interventions [33].

In contrast to CMT1A, where there is a duplication of the Pmp22 gene, in an allelic disorder, HNPP (hereditary neuropathy with liability to pressure palsies), there is a deletion of one of the Pmp22 alleles. The clinical phenotype of HNPP is distinct from that of CMT1A and this dose dependency of clinical phenotypes in CMT1A and HNPP suggests that a disequilibrium of the correct amount of Pmp22 in peripheral myelin results in abnormal myelination [34, 35]. Other mechanisms that have been proposed include a relative incapability of Schwann cells to degrade the increased levels of intracellular Pmp22 in CMT1A, which then forms intracellular protein aggregates [34, 36, 37]. Although CMT1A is caused by a mutation of a gene which is necessary for the proper function of Schwann cells during myelination, the degeneration of axons are a predominant feature of the clinical phenotype and accounts for the disability in advanced disease state. Schwann cell graft experiments in which human Schwann cells with PMP22 mutation transplanted to hosts with normal axons demonstrated a failure of axonal regeneration through the nerve graft with mutant Schwann cells. This observation provides further support that in addition to myelination defects, Schwann cells with Pmp22 duplication are unable to provide the trophic support, required for maintenance of axons [38, 39].

1.3. Diabetic Neuropathy

Diabetic neuropathy represent a group of neuropathies which can be classified according to the distribution of deficits and the predominant involvement of motor, sensory and autonomic nerve fibers [40-42]. The most frequent form, the diabetic polyneuropathy, is clinically characterized by paresthesia and pain, which are accompanied by modest to severe sensory deficits. Symptoms are distributed symmetrically in a length dependent stocking and glove fashion [42]. Diabetic polyneuropathy is the most frequent complication of diabetes and occurs in 13% to 40% of all diabetic individuals. Several excellent reviews dealing with pathogenesis of diabetic neuropathy have been published in the recent years [42-45], we will just briefly review the role of Schwann cells below.

Pathologically, diabetic polyneuropathy is characterized by multifocal axon loss, which includes large and small diameter fibers [46-49]. Apart from axonal degeneration, demyelination and remyelination are common pathological features that can be found in sural nerve biopsies [48, 49]. These morphological changes go along with an endoneurial microangiopathy, consisting of microthrombosis, perivascular basement membrane thickening and degeneration of pericytes. Current concepts assume that the pathogenesis of diabetic polyneuropathy is multifactorial and involve microvascular injury as well as metabolic causes. Microangiopathy is considered to lead to ischemic damage to neurons and Schwann cells, at least in part, by increased oxidative stress. Increased levels of intracellular glucose cause accumulation of alternate metabolism products, which modify function and structure of cell proteins by forming advanced glycated end products (AGE’s), which in turn can damage Schwann cells and neurons [50, 51]. Of similar importance is metabolism of glucose via the sorbitol/aldose reductase pathway (so called Polyol Pathway), which can

lead to cell damage by accumulation of polyols. Aldose reductase is the rate-limiting enzyme in the polyol pathway, and is mainly localized in Schwann cells. In vitro studies have shown that the activation of the polyol pathway in Schwann cells results in decreased production of NGF [52]. Furthermore, the increased levels of sorbitol lead to accumulation of sorbitol and reactive oxygen species, which further alter the function of protein kinases and Na+/K+ ATPases. Another component of the pathogenesis of diabetic polyneuropathy is mitochondrial dysfunction [53, 54]. High glucose in neurons leads to oxidative stress and mitochondrial dysfunction through proteins involved in mitochondrial fission.

2. Treatment strategies

2.1. Neurotrophins

Clinical application of neurotrophins represents the most advanced “causal” therapeutic approach in polyneuropathies discussed here. NGF has been tested in phase II/III trials for diabetic neuropathy [55, 56] and in a phase II study in HIV-SN [57]. The therapeutic utility of neurotrophin-3 has been evaluated in a small study for CMT1A [38]. In all these conditions, a relative reduced expression of neurotrophins either by Schwann cells in the pathway or the target tissues are thought to contribute to the pathogenesis; thus exogenous applications of those growth factors may enhance axon growth and neuronal survival.

In diabetic neuropathies this concept is supported by observations that NGF production of Schwann cells decreases after exposure to high glucose levels [58, 59]. Other studies reported that NGF treatment can reverse pathologic nerve fiber morphology and can enhance regeneration of injured nerve fibers in experimental diabetes [60, 61]. In 1998 the results from a phase II trial of rhNGF in patients with diabetic polyneuropathy were published [55]. In this randomized, double blind controlled study, 250 patients with symptomatic diabetic polyneuropathy were randomized to receive 0.1 μg/kg rhNGF, 0.3 μg/kg rhNGF or placebo subcutaneously three times a weekly for six months. Several endpoints were evaluated in this study including neurological status, quantitative measures of sensory function and symptom questionnaires. These multiple endpoints were stratified in three categories (group one with “objective” measures, group two with “objective” and more subjective criteria, i.e. symptom assessment, group three with small fiber sensory function parameters). Both doses of rhNGF lead to a significant improvement after six months in all three categories of measures, however “unblinding” due to injection site pain was a big problem in this study [55]. Nevertheless, these encouraging results lead to the initiation of a phase III trial for rhNGF in diabetic polyneuropathy. In this randomized double blind controlled trial, 1019 patients with diabetic polyneuropathy were enrolled to receive either placebo or rhNGF 0.1 μg/kg subcutaneously 3 times per week for 48 weeks [56]. Primary endpoint was defined as change in the Neuropathy Impairment Score for the Lower Limbs after 48 weeks. However, neither the primary end point nor secondary end points demonstrated a significant benefit of rhNGF. Thus this trial failed to confirm the promising result from the previous study, which has been attributed to the design of the primary endpoints (no adequate small fiber assessment in the phase III trial) and changes in drug formulation and manufacturing process [56].

First randomized double blind controlled study of rhNGF in HIV–SN was started in 1996 [57]. In this trial, 270 patients with confirmed HIV-SN were randomized to receive subcutaneously either 0.1 μg/kg rhNGF, 0.3 μg/kg rhNGF or placebo twice weekly for 18 weeks. Changes in pain intensity on a standardized pain scale (Gracely Pain Scale) served as primary outcome measure. The epidermal nerve fiber densities were evaluated in a subset of 60 patients. The two doses of rhNGF lead to a moderate, but statistically significant reduction of pain in comparison to placebo, whereas other secondary outcome parameter (neuropathy observer assessment and quantitative sensory testing [QST]) remained unchanged. No changes in the epidermal nerve fiber density were observed within the trial timeline of 18 weeks. A limitation of the study was the frequent occurrence of side effects on the injection site (temporal hyperalgesia), which were generally well tolerated but resulted in an incomplete blinding of a significant proportion of patients. The same group reported also similar long-time effects of rhNGF on pain in an extended open-label study with 200 patients [62].

The utility of exogenous application of neurotrophins has also been tested in a small trial in CMT1A [38]. Rationale for the use of neurotrophins in CMT1A is provided by observations that human Schwann cells with PMP22 mutation are unable to promote axonal regeneration, probably due to a lack of trophic support [38, 39]. Eight CMT1A patients were enrolled in a double-blind, randomized, trial to receive either placebo or 150 μg/kg NT-3 three times weekly for 24 weeks. Outcome measures included sural nerve biopsies, clinical assessment (Neuropathy Impairment Score), and electrophysiological measurements [38]. Patients treated with NT-3 showed an increased density of myelinated fibers in the sural nerve biopsy. These findings went along with improvement in the NIS score and in sensory but not in motor functions.

2.2 Schwann cells as therapeutic targets for hormones and vitamins

2.2.1 Eyrthropoetin—Erythropoietin (EPO) is a glycoprotein identified initially as a key regulator of development of erythrocytes. However, it has pleiotrophic effects outside the hematopoietic system and has been shown to prevent apoptosis in neurons in a variety of different experimental paradigms of CNS and PNS injury [63-66]. In the PNS, EPO and its receptor (EPOR) are expressed in axons and Schwann cells [28, 67]. Nerve injury leads to an increase of EPO mRNA levels in Schwann cells and EPOR mRNA in lumbar DRG [28, 67, 68]. In animal models of spinal crush injury and chronic sciatic nerve constriction injury, application of exogenous recombinant human EPO (rhEPO) has been shown to prevent apoptosis of DRG neurons and axonal degeneration and attenuate neuropathic pain [63, 69]. Based on previous observations that EPO can protect axons from degeneration in models of HIV-SN [25, 28] the Neurologic AIDS Research Consortium (NARC) initiated a randomized, controlled pilot study to evaluate the efficacy and safety of rhEPO in HIV-SN. Unfortunately the trial had to be suspended, because the strict inclusion-exclusion criteria in regard to hemoglobin levels resulted in low recruitment numbers.

In addition to injury models stated above, exogenous rhEPO has been shown to be neuroprotective in models of paclitaxel-induced neuropathy [70] and diabetic polyneuropathy [71]. These observations, however, have not resulted in clinical trials of

rhEPO, partly because of side effect concerns. A major drawback for the long-term use of rhEPO is its effect on the hematopoesis, which can result in potentially harmful increase in hemoglobin levels and lead to thromboembolic events. Furthermore, EPOR is expressed by blood vessel endothelial cells and chronic stimulation by rhEPO can lead to endothelial dysfunction contributing to thromboembolic events. A strategy to circumvent this obstacle is development of EPO-like derivatives, which retain the neuroprotective properties of EPO but do not bear the hematological side effects. One such example is carbamylated EPO (CEPO), which has been shown to prevent behavioral, electrophysiological and pathological changes of diabetic neuropathy in animal models [72, 73].

2.2.2. Progesterone—Progesterone is a neurosteroid, known to affect myelination of Schwann cells. It acts as a regulator of myelin gene expression and the application of progesterone to Schwann cells influences the Pmp22 expression [32]. The treatment with progesterone antagonist has been shown to reduce the overexpression of Pmp22 and to improve the phenotype in Pmp22 transgenic rats [74]. However, because of toxicity concerns (liver toxicity), progesterone antagonists are currently not suitable for the use for patients with CMT1A [75].

2.2.3. Ascorbic acid—Ascorbic Acid (Vitamin C) is an anti-oxidant, which is required for Schwann cell differentiation, assembly of basal lamina and formation of myelin [76, 77]. Schwann cell - neuron cell co-cultures fail to myelinate in the absence of ascorbic acid [7, 76-79]. In a proof-of-concept study, Passage and colleagues demonstrated a beneficial effect of ascorbic acid in an animal model of CMT1A [80]. Ascorbic acid treated mice that overexpress PMP22 showed reduced pathology in sciatic nerves, improved behavioral measures and in increased life span as compared to untreated mice [80]. Based on these encouraging findings, clinical trials for the use of ascorbic acid in CMT1A have been initiated [81] and are ongoing (NCT00271635, www.clinicaltrials.org).

2.3. Schwann cell transplantation as future direction

Studies that evaluated the utility of Schwann cell transplantation over the last years mainly focused on paradigms of spinal cord injury [82-85] and, to lesser extent, traumatic injury of optic nerves [86, 87] or peripheral nerves [88-91]. In the PNS, transplantation of Schwann cells into bioengineered conduits has been shown to improve regeneration by bridging nerve grafts. The regenerative capacity of these nerve grafts can be further improved by use of genetically modified Schwann cells that express high amounts of growth factors [92, 93]. However, Schwann cell transplantation as treatment strategy for polyneuropathies has not been systematically pursued over the years. Part of the reason that limits a bench-to-bedside application is that the function of Schwann cells has been mostly studied in rodent *in vivo* and *in vitro* models, which make it difficult to extrapolate those results into the human system. On the other hand, Schwann cells obtained from human donors are difficult to maintain in cell culture. This is due to the usually low yield of Schwann cells and a poor proliferation rate which facilitate the overgrowing with human fibroblasts [78, 94-96]. As a consequence, only intricate, time consuming purification and expansion procedures allow establishing primary human Schwann cell cultures in low numbers to study their functional characteristics and therapeutic potentials [94, 95, 97].

Furthermore, polyneuropathies are multifocal diseases, in which practical issues of cell transplantation such as timing and application route are poorly defined. These include volume and number of cells that can be transplanted. Other obstacles refer to general concerns of cell grafts, which include the possibility of infectious contamination, potential host immune responses and genetic instability, which may result in cell de-differentation and tumor growth. A recent report about development of brain tumor in an ataxia telangectasia patient receiving neural stem cells [98] underscores the importance of careful evaluation of these risks in preclinical studies.

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