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Gene and Cell Therapy for Peripheral Neuropathy

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1. Introduction

Peripheral neuropathy describes a range of degenerative processes that affect the peripheral nervous system and are largely untreatable. These neuropathies affect both sensory and motor fibers and include diabetic neuropathy, chemical neuropathy, post-herpetic neuralgia and peripheral nerve injury. Other causes of neuropathy include alcoholism, nutritional deficits, Guillian-Barre syndrome, AIDS related neuropathy and neuropathy caused by toxins such as heavy metals. Current treatments focus on pain management and on microsurgical intervention such as nerve grafting (Federici and Boulis 2009). Therapies that focus on promoting axon growth and regeneration subsequent to peripheral nerve degeneration or injury are suboptimal.

1.1 Peripheral nerve injury

Damage to peripheral nerves results in demyelination and axonal degeneration. Axonal degeneration can happen in several ways. Wallerian degeneration happens when the continuity of the nerve fibre is interrupted through traumatic, toxic, ischemic or metabolic events (Dubovy 2011). In neurodegenerative processes, there is progressive degeneration of the axons towards the cell body which remains intact over a longer period of time. This degenerative process is referred to as distal axonopathy or dying back axonal degeneration (Hoke 2006). Research on both super oxide dismutase 1 (SOD1) mice and on patients suffering from ALS have found degeneration of neuromuscular junctions prior to the loss of motor neurons. This indicated that ALS is considered to be a distal axonopathy (Fischer, Culver et al. 2004).

The peripheral nervous system has the ability to regenerate axons in response to an injury. Axonal stumps possess the ability to regenerate and grow in response to Schwann cells and their basal lamina (Fischer, Culver et al. 2004). Macrophages and Schwann cells phagocytose the myelin debris (Fansa and Keilhoff 2003) that results from the injury. Fibroblasts and Schwann cells provide a matrix for axonal regrowth. They secrete neurotrophic factors that support and enhance neuron survival (Ide 1996). In Wallerian degeneration Schwann cells carry out the first step in myelin sheath evacuation by myelin fragmentation. The degraded myelin is phagocytosed by macrophages for full myelin clearance (Stoll, Griffin et al. 1989). This is an important step prior to nerve regeneration. Schwann cells in the region of the damaged neurons secrete a number of growth factors such as glial-cell derived neurotrophic factor (GDNF), brain derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1) and nerve growth factor (NGF) (Funakoshi, Frisen et al. 1993).

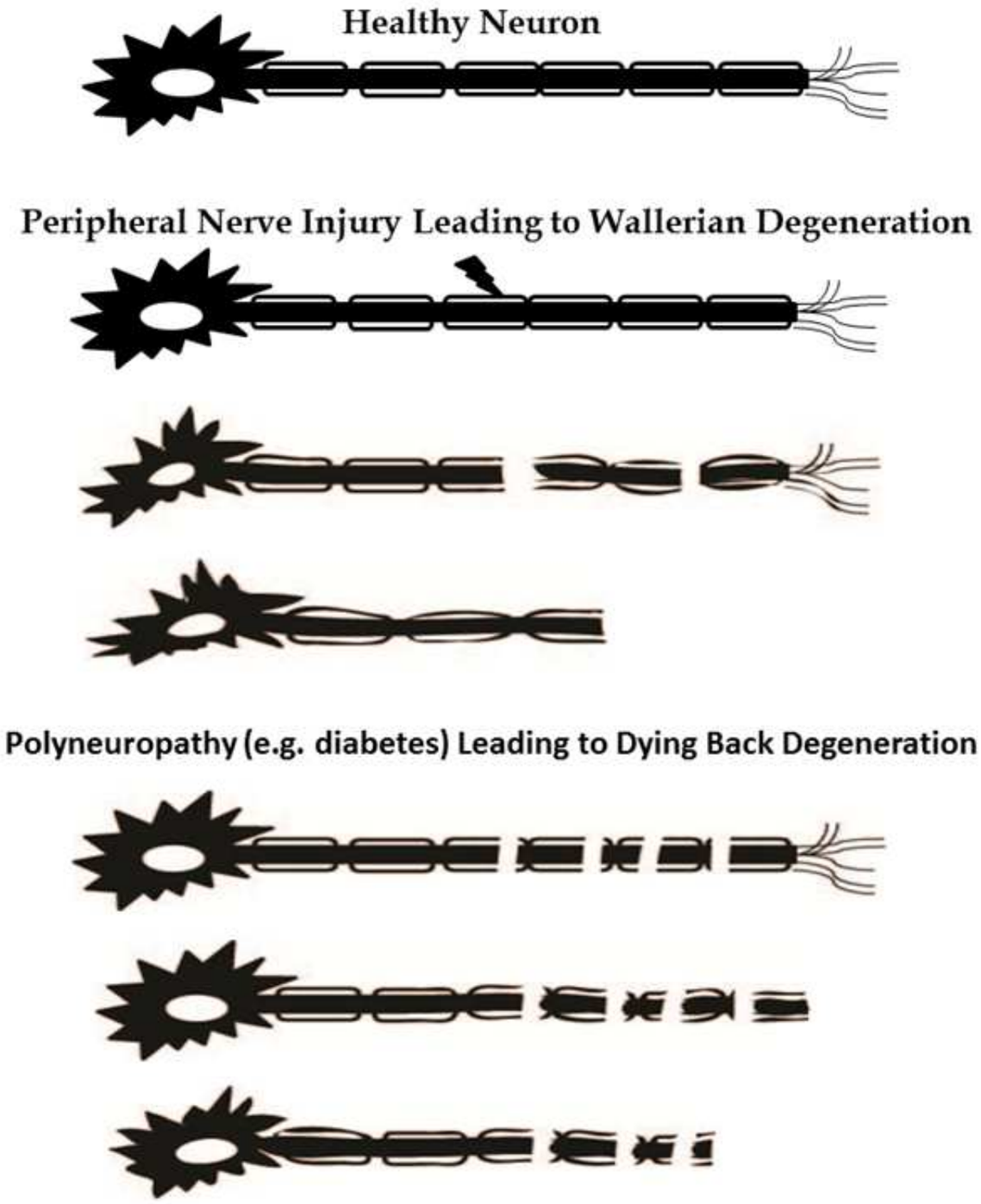

Fig. 1. Comparison of Wallerian and "Dying Back" degeneration in neurons.

Nerve regeneration starts at the node of Ranvier near the proximal stump. The basal lamina that remains post-injury, which surrounds the axon and the Schwann cells, acts as a conduit or tube for the regenerating axon. The damaged nerve stump distal to the injury supports regeneration by assisting regenerating sprouts to extend in the direction of the distal stump (Hoke 2006).
The next step in axonal regeneration occurs when the axons enter the distal stump. They have to grow over a long distance in an environment that is considerably different from the embryonic one originally encountered. The regenerating nerve also has to remyelinate. The last step to complete the regenerative process is for the axon to find and reinnervate their original targets be they muscle or sensory organs (Abrams and Widenfalk 2005).

1.1.1 Therapeutic targets

A damaged peripheral nerve can be divided into a number of parts. Each one needs to be considered individually as a therapeutic target (Figure 2).

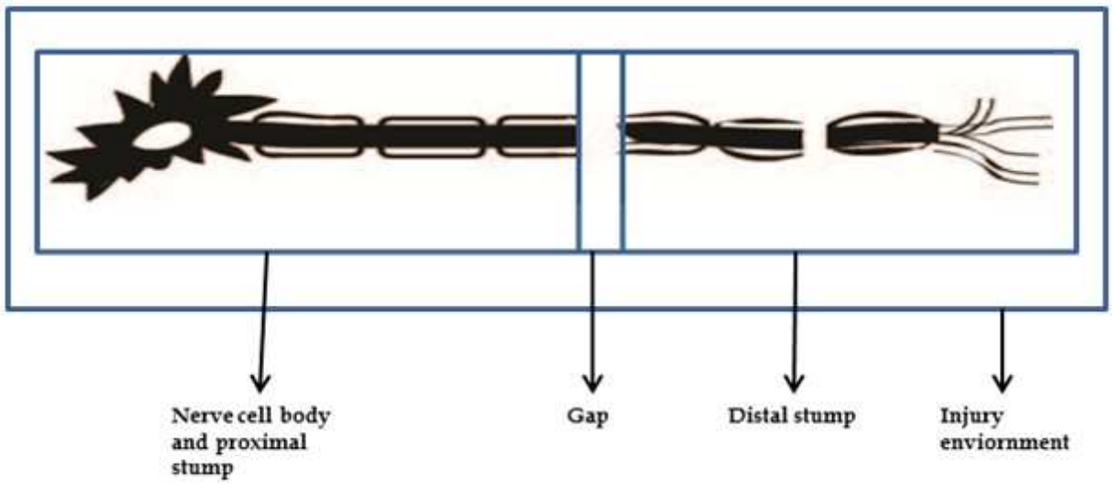

Fig. 2. Identification of the four different parts of a damaged neuron.

The first part is the nerve cell body and the proximal stump. The nerve cell body is necessary for providing the metabolic machinery to support axonal growth. Trauma and neurodegenerative processes affect the axon but can also damage the nerve cell body. Treatments that aim to protect nerve cell body health after injury have been aimed at neuroprotection and trying to minimise cell death. Neurotrophic factors mediate neuronal survival and factors such as nerve growth factor (NGF) (Levi-Montalich, 1987), glial derived neurotrophic factor (GDNF) (Lewis, Neff et al. 1993), IGF-1 (Henderson, Phillips et al. 1994) and vascular endothelial growth factor (VEGF) (Storkebaum, Lambrechts et al. 2004) have been employed for their neuroprotective effects. Other factors that are feasible in minimising nerve cell body death are anti-apoptotic factors. The X-linked inhibitor of apoptosis protein (XIAP) mediated protection of motor neurons as shown in *in vitro* models of ALS and in diabetic neuropathy (Garrity-Moses, Teng et al. 2004). Other anti-apoptotic factors such as Bcl-2 and Bcl-xL which prevent apoptosis both *in vitro* and *in vivo* (Yamashita, Mita et al. 2001; Matsuoka, Ishii et al. 2002; Yamashita, Mita et al. 2003; Garrity-Moses, Teng et al. 2005) are attractive for neuroprotection A problem associated with therapies that solely act on the proximal stump of a damaged nerve is the growth of axons

into this milieu without being able to leave it. Excessive neuronal growth can lead to neuromas which prevent reinnervation of the distal stump and cause pain.

The second part of the injured peripheral nerve that needs to be considered is the gap. The success of the axon regrowth depends on the severity of the injury, the distance that needs to be bridged and how soon any intervention occurs post-injury (Midha, Munro et al. 2005; Weber and Mackinnon 2005). Nerve grafts assist in directing nerve regrowth. Grafting along with gene therapy has been used to assist in this process. The principle was proven by adenoviral transduction of nerve grafts (Blits, Dijkhuizen et al. 1999). In this experiment, sections of peripheral intercostal nerves were transduced with adenovirus expressing LacZ as a reporter gene. These nerves were then grafted into transacted sciatic nerves, avulsed neutral root, hemi-sected spinal cord and intact brain. Expression of LacZ could still be detected up to 7 days post-implantation.

The third part of the injured nerve is the distal stump and the neuromuscular junction. The distal stump of the damaged nerve provides support for neuronal regrowth via the release of stimulatory factors. These factors assist generating nerve sprouts to extend towards the target tissue (Abrams and Widenfalk 2005). One therapeutic strategy is to silence the expression of genes that inhibit nerve regrowth. Silencing the expression of the components of the inhibitory signalling cascade, using siRNAs, such as p75NTR, NgR and RhoA was shown to promote neurite outgrowth in cultured DRGs (Ahmed, Dent et al. 2005). This is a viable strategy for peripheral nerve injury therapy (Abrams and Widenfalk 2005).

The fourth and final part of a damaged peripheral nerve is the environment in which it is situated. The environment surrounding a damaged peripheral nerve is a target for *ex vivo* gene therapy. Stem cells that have been genetically engineered to enhance neurotrophic factors are a therapeutic option for injured peripheral nerves that has received considerable attention (Tohill and Terenghi 2004). Periaxonal grafts of nerve stem cells that secrete GDNF have been found to assist in providing a supportive environment for nerve regeneration (Deshpande, Kim et al. 2006).

2. Gene and cell therapy

Gene and cell therapies have the potential to be effective in peripheral neuropathy treatment. A number of factors need to be taken into account to allow this to happen. The correct vector (viral or non-viral) or cell type has to be chosen for the neuropathy based on vector or cell tropism. The vector tropism will help determine the method of delivery of the vector. Delivery will either be directly into the site of injury or degeneration, or remote from the site of injury. In the case of remote delivery the choice of therapeutic will depend on its' ability to cross the blood nerve barrier, in the case of AAV-9, or its' ability to be moved via retrograde transport from, for example, an intramuscular injection to the site of nerve injury. The therapeutic gene delivered using a vector has to be selected for optimum effect and if cell therapy is used whether the cells are engineered to secrete a neurotrophic factor.

2.1 Gene therapy vectors

Gene therapy vectors can be divided into viral and non-viral vectors based on their origin. The intent is to deliver a therapeutic gene to the affected area and affect a positive outcome. A variety of different viruses can be converted to viral vectors with different affinities for the peripheral nervous system. For example, herpes vectors have a natural tropism for the

neurons of the Dorsal Root Ganglia (DRG) (Fink, Ramakrishnan et al. 1996). Similarly, a wide variety of methods exist for non-viral gene delivery. These can be engineered for enhanced gene delivery to the nerve.

2.1.1 Non-viral vectors

Non-viral vectors can include plasmid DNA containing the therapeutic gene of interest, cationic and polycationic polymers. The major advantage these have over viral vectors is their safety. The major disadvantage for gene transfer in the nervous system is they have a very low efficiency when compared to viral vectors (Costantini, Bakowska et al. 2000; Hsich, Sena-Esteves et al. 2002). The plasmid DNA vector can be delivered unmodified or with a targeting molecule attached to improve delivery. One such targeting molecule it the tet peptide developed by our research group (Liu, Teng et al. 2005). This peptide was identified based on its' homology to the tetanus toxin and it enhances neurotropism. This peptide was used by Park and colleagues to successfully target plasmid DNA the neural cells and DRG cells *in vitro (*Park, Lasiene *et al. 2007)* and *in vivo* via an injection into lateral ventricle of mice. The tet-1 complexed plasmid was found to target adult neural progenitor cells (NPCs) (Kwon, Lasiene et al. 2010).

2.1.2 Viral vectors

Viral vectors consist of viruses whose genome has been modified to carry the therapeutic gene. The genome is usually altered such that the vector is unable to replicate. In the peripheral nervous system there are a number of different viral vectors that have been used; Adenoviral vectors (Ad), Adeno associated vectors (AAV), Herpes simplex virus (HSV) type 1 and Lentiviral vectors.

2.1.2.1 Adenoviral vectors

Adenoviral vectors have been extensively used in gene therapy research. They have been shown to transduce post-mitotic dorsal root ganglions (DRGs), neurons (Glatzel, Flechsig et al. 2000) and Schwann cells (Shy, Tani et al. 1995; Dijkhuizen, Pasterkamp et al. 1998; Sorensen, Haase et al. 1998). They are non integrating vectors and therefore are limited to short-term expression which is a disadvantage. Ad vectors also have the drawback of eliciting an immune response which is an undesirable attribute in a therapeutic agent.

2.1.2.2 Adeno-associated vectors (AAV)

Adeno-associated vectors (AAV) are a very attractive vector for gene therapy. AAV vectors have long term and stable transgene expression and also efficiently transduce post-mitotic neurons. A disadvantage of AAV vectors is that there is a limit to the size of the transgene it can carry. This can make it unsuitable for larger transgenes. There are a number of AAV serotypes that have different tropisms for neural cells. AAV2 has been demonstrated to transduce DRGs, Schwann cells and fibroblasts (Fleming, Ginn et al. 2001). AAV9 has the ability to transduce a number of different neural cells types (Foust, Nurre et al. 2009). A study by our research group in mice showed that different AAV serotypes had different longitudinal spread within the spinal cord (Snyder, Gray et al. 2011) suggesting that similar differences in spread exist within the peripheral nervous system exist.

2.1.2.3 Herpes Simplex Virus (HSV) type 1

Herpes Simples Virus (HSV) type 1 is naturally neurotrophic. HSV-1 produces a lytic infection of skin cells and then migrates to the nerve processes. It is then transported in

retrograde fashion to the sensory cell body of DRGs (Pradat and Mallet 2003). The ability of HSV type 1 to transduce sensory neurons makes it an ideal choice for neuropathies affecting sensory neurons (Glorioso and Fink 2004). The main disadvantage of HSV type 1 vectors is the immune response elicited against the virus proteins and the cell toxicity of the virions (Pradat and Mallet 2003).

2.1.2.4 Lentiviral vectors

Lentiviral vectors are also naturally neurotrophic (Fleming, Ginn et al. 2001). They integrate into the host genome which makes the expression of the carried transgene both stable and long-term (Blits, Boer et al. 2002; Hu, Leaver et al. 2005). Lentiviral vectors have limited immunogenicity and can accommodate a larger transgene than AAV (Federici and Boulis 2009). The modification of the lentiviral coat, which is termed pseudotyping, to enhance its transduction ability has been extensively studied. Pseudotyping of lentivirus with the rabies-G glycoprotein exploits the natural uptake of the rabies virus by axon terminals at neuromuscular junctions. This has been used to improve motor neuron gene delivery (Mazarakis, Azzouz et al. 2001; Cronin, Zhang et al. 2005)

Vector	Advantages	Disadvantages
Adenoviral	Easily transduces post-mitotic cells	Short expression time Immunogenic
HSV type 1	Naturally neurotrophic Retrogradely transported	Naturally immunogenic
AAV	Integrates and gives prolonged expression. A number of different serotypes available	Small cloning capacity
Lentiviral	Stable, integrated expression Retrogradely transported Large cloning capacity	Integration mutagenesis

Table 1. Comparison of different viral vectors.

2.1.3 Transport of vectors

The ability of vectors to be transported in a retrograde manner into the nervous system makes them more amenable for gene therapy of peripheral neuropathies. It allows the therapy to be administered at a site distant from and less invasive for the targeted area. Although Ad and AAV vectors are not naturally neurotrophic, they both have the ability to be transported in a retrograde manner and infect both sensory and motor neurons. A number of research groups have shown Ad vectors to be transported in a retrograde manner after intramuscular and intraneural injections (Finiels, Ribotta et al. 1995; Ghadge, Roos et al. 1995; Boulis, Bhatia et al. 1999). It is also possible to modify these vectors to enhance their affinity for neurons and as a consequence increase the rate of retrograde transport. Inoculation with botulinum toxin was found to enhance Ad vector transport and increase expression of the transgene in motor neurons (Millecamps, Mallet et al. 2002).

Different AAV serotypes have been shown to be transported in a retrograde fashion following both intramuscular and intraneural delivery (Boulis, Noordmans et al. 2003; Kaspar, Llado et al. 2003; Kaspar, Vich et al. 2004). A number of research groups have been working on improving the affinity AAV vectors have for neural cells. One means of achieving this is to modify the protein coat of the vector to incorporate neurotrophic peptides to enhance its' therapeutic effect. Peptides that mimic the binding capacity of the tetanus toxin, the NMDA receptor and peptides that mimic the activity of dynein have been inserted into the protein coat of AAV2 vectors to improve their neurotropism (Xu, Ma et al. 2005; Federici, Liu et al. 2007).

HSV-1 is a viral vector that is naturally neurotrophic. Recombinant HSV-1 has demonstrated the ability to transduce both motor and sensory neurons after intramuscular and subcutaneous delivery (Yamamura, Kageyama et al. 2000; Glorioso and Fink 2004). However, HSV mediated gene expression is transient. The lack of durability in expression impedes the application of HSV mediated gene delivery to chronic and ongoing neuropathies.

There is extensive research to show that lentiviral vectors have the ability to be transported in a retrograde manner. In a similar manner to AAV, the lentiviral vector can be engineered to enhance its' effect. The rabies virus is transported axonally via a neuromuscular junction. A lentiviral vector that is pseudotyped with the rabies G protein will have increased axonal transport and will reach the spinal cord motor neurons (Cronin, Zhang et al. 2005). Transduction of motor neurons in the lumbar spinal cord by a rabies-G pseudotyped lentiviral vector has been shown after peripheral administration intramuscularly (Mazarakis, Azzouz et al. 2001). Our research group has published data demonstrating that a pseudotyped human immunodeficiency virus type 1 (HIV-1) based lentiviral vector was capable of transducing specific cells types and increasing retrograde axonal transport (Federici, Kutner et al. 2007).

2.2 Cell therapy

The use of cell therapy in peripheral neuropathy especially peripheral nerve injury has been the focus of research. The peripheral nervous system has the ability to regenerate axons and reinnervate end organs. However, this can be problematic in the case of chronic denervation of distal nerves.

2.2.1 Schwann cells (SC)

Schwann cells (SC) have been shown to support peripheral nerve repair. They achieve this by changing their phenotype from myleinating to growth supporting (Shy, Shi et al. 1996; Mirsky and Jessen 1999). If the Schwann cells themselves are denervated for a prolonged period of time their ability to support peripheral nerve regrowth is impaired and inhibited (de Medinaceli and Rawlings 1987; Fu and Gordon 1995). One therapeutic option is to supplement or replace the deprived Schwann cells with healthy ones from another nerve. Infusion of healthy Schwann cells has been able to support regeneration and remyleination of both the spinal cord (Takami, Oudega et al. 2002; Pearse, Pereira et al. 2004) and in peripheral nerves (Guenard, Kleitman et al. 1992). The limiting factor in this is the number of Schwann cells obtainable from this source. There is also the fact that obtaining the Schwann cells from nerve tissue itself causes damage.

2.2.2 Neural stem cells (NSCs)

Neural stem cells (NSCs) have the ability to differentiate into neurons, astrocytes and oligodendrocytes (Parker, Anderson et al. 2005). They can also be induced to differentiate into Schwann cells (Blakemore 2005). NSCs secrete the growth factors that help support nerve regeneration (Heath 2000). They can be sourced from either fetal, adult or a non-neuronal tissue source. Implantation of NSCs has been shown to promote axonal regeneration and to form Schwann cell like peripheral myelin sheaths (Blakemore 2005). Therefore NSCs transplanted into a peripheral nerve injury site can help overcome the issue of limited sources of healthy Schwann cells and they can also promote peripheral nerve regeneration. The fact that NSCs can be grown and amplified *in vitro* is an added advantage. NSCs have been used in sciatic nerve injury repair.

2.2.3 Mesenchymal stem cells (MSC)

Mesenchymal stem cells (MSC) are adult derived stem cells that have the ability to differentiate down three lineages; adipogenic, chondrogenic and osteogenic. There have been a number of studies that show MSCs possess immunomodulatory properties *in vitro* on cell populations of both passive and adaptive immunity(Uccelli, Moretta et al. 2006). A study in a mouse model of experimental autoimmune encephalomyelitis (EAE), which is a model for human multiple sclerosis (MS), injected MSCs on one side of the brain and induced peripheral T cell tolerance to myelin proteins. This reduced the migration of pathogenic T cells to the CNS. On the other side of the brain the MSCs were found to preserve axons and reduce myelination (Bai, Lennon et al. 2009; Constantin, Marconi et al. 2009). Injection of MSCs into the spinal cord of transgenic SOD1 (G93A) mice, a model for ALS, was found to improve motor neuron survival, prolong life and improve motor performance (Vercelli, Mereuta et al. 2008). There have been a number of studies looking at the therapeutic effect of MSCs in peripheral nerve injury models. In a rat model of sciatic nerve injury MSCs were injected into the lumber DRG. The MSCs were found to have an analgesic effect affecting the expression of neuropetides galanin and neuropeptide Y (NPY) (Coronel, Musolino et al. 2009). Treatment of damaged nerves directly with MSCs has also been demonstrated to be effective. In a rat model of facial nerve injury MSCs were applied to a transected facial nerve after anastomosis. Results showed that the MSC treated nerve did better in terms of axonal organisation and myelin thickness when compared to nerves that had only been sutured (Satar, Karahatay et al. 2009) In another study MSCs were injected subepineurally one week after sciatic nerve injury in rabbits. Nerves that were grafted with MSCs showed better functional recovery, and improved nerve regeneration (Duan, Cheng et al. 2011)

Cell Type	Source	Advantages
Schwann Cells	Nerve tissue	Autologous source
NSC	Fetal or adult	Neural in origin
MSC	Adult tissues (bone marrow, adipocytes)	Ability to differentiate into different lineages Home to injury site

Table 2. Comparison of different cell types.

3. Peripheral nerve disorders

3.1 Diabetic neuropathy

Diabetic neuropathy is a complication of both insulin-dependent and insulin-independent diabetes mellitus. There are a number of possible contributing factors to the development of diabetic neuropathy such as oxidative stress, non-enzymatic glycation of nerve endings and mitochondrial damage (Mata, Chattopadhyay et al. 2006). A lack of or a reduction in neurotrophic factor levels is also considered a possible factor. Research has demonstrated that supplementation of neurotrophic factors can help delay the progression of diabetic neuropathy and other polyneuropathies.

Both nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) have had therapeutic success in animal models of diabetic neuropathy. A HSV based vector expressing NGF was used to transduce dorsal root ganglion of diabetic mice. Results showed that it prevented loss of sensory nerve action potential (Goss, Goins et al. 2002). Subcutaneous delivery of VEGF in an HSV vector was transported in a retrograde manner to the DRGs and was found to preserve nerve fibres in diabetic mice (Chattopadhyay, Krisky et al. 2005). Placental growth factor (PlGF) is a member of the VEGF family. PlGF-2 has been found to display neurotrophic actions acting through neuropillin – 1 (NP-1) in DRGs *in vitro*. *In vivo*, PlGF-2 plasmid was injected with electroporation into the skeletal muscle of diabetic mice. Results showed a restoration of sensory deficits in these diabetic mice that was mediated via NP-1 (Murakami, Imada et al. 2011). Another study used a regulatable HSV vector to deliver erythropoietin (EPO) to diabetic mice. The HSV vector expression was controlled using the tet-on system which means EPO was expressed in response to presence of doxycycline (DOX). Mice were inoculated via their footpad and were administered DOX on a controlled basis. This regulated expression of EPO was found to be effective in protecting against the progression of neuropathy in these diabetic animals (Wu, Mata et al. 2011).

There is currently a clinical trial underway for diabetic neuropathy. VM202 which is human hepatocyte growth factor encoded in a plasmid. It is a Phase 1/2 open label trial examining safety and the effect of dose escalation with the gene therapy being administered via intramuscular injection into the calf muscle (www.clinicaltrials.gov , NCT01002235). A second phase 2 clinical trial is using zinc finger proteins in the treatment of diabetic neuropathy. Zinc finger proteins have the ability to increase expression of endogenous genes and can be designed to target specific genes (Davis and Stokoe 2010). In this trail the zinc finger protein is targeting VEGF and increasing its expression (www.clinicaltrials.gov, NCT01079325).

3.2 Peripheral nerve injury

A large number of the existing therapies for peripheral nerve diseases are concentrated on the proximal stump of the nerve (Federici and Boulis 2007). The ability of a number of viral vectors to be transported in a retrograde manner means they have been utilised to deliver neurotrophic factors (Romero, Rangappa et al. 2001; Natsume, Wolfe et al. 2003; Araki, Shiotani et al. 2006). In the case of peripheral nerve injury the site of the damaged nerve is first identified using current therapies. This has the advantage of exposing the damaged proximal stump of the nerve to allow the therapeutic vectors access. The viral vector can be engineered to enhance their uptake and retrograde transport. This can help improve their therapeutic effect and help prevent further nerve degeneration. Neuro-targeting peptides

can be incorporated into the viral coat and into plasmids to enhance vector uptake as previously outlined (Federici, Liu et al. 2005; Park, Lasiene et al. 2007; Kwon, Lasiene et al. 2010).

An adenoviral vector was used to deliver glial derived neurotrophic factor (GDNF) intramuscularly in a chronic constricted nerve injury rat model of peripheral nerve injury. The injury to the limb was found to increase mechanical and thermal hypersensitivity. GDNF/Akt signalling was lost, particularly, in the distal stump of the sciatic nerve. Ad-GDNF therapy was found to restore GDNF/Akt signalling and this was associated with improved myelination and behavioural outcomes (Shi, Liu et al. 2011). An Ad vector was also used to deliver bone morphogenetic protein 7 (BMP-7) in a rat model of sciatic injury. BMPs promote neuronal differentiation and have been implicated in the survival of peripheral nerves (Beck, Drahushuk et al. 2001; Guha, Gomes et al. 2004; Schluesener, Meyermann et al. 1995) and in this study Ad-BMP-7 improved hind-limb recovery and reduced macrophage activation, nerve demyelination and axonal degeneration (Tsai, Pan et al. 2010).

Stem cells can also be utilised in peripheral nerve injury repair. One group used neural stem cells that had been engineered to secrete glial cell-line derived neurotrophic factor (GDNF). These cells were administered to the sciatic nerve of rats that had previously received spinal cord embryonic stem cell-derived motor neuron transplantation (Deshpande, Kim et al. 2006). The increased level of expression of GDNF in the sciatic nerve attracted embryonic stem cell- derived axons. Theses axons reached the muscle and formed physiologically active neuromuscular junctions.

3.3 Neuropathic pain

Neuropathic pain is caused by either dysfunction of the CNS, PNS or a primary lesion. This can manifest itself as hypersensitivity to pain (hyperalgesia) or as a painful response to a stimulus that would not normally cause pain (allodynia). Currently opiates are the mainstay of treatment for the majority of chronic pain states (Beutler and Reinhardt 2009). Their use has generally improved outcome (Portenoy 1995; Levy 1996) but due to side-effects opiates have not been effective in a significant number of patients (Caraceni and Portenoy 1999; Weiss, Emanuel et al. 2001). The possibility of delivering a therapeutic gene to alleviate the symptoms of pain has been studied in a number of animal models of neuropathic pain as well as the possibility of also of modulating both the excitatory and inhibitory pathways of pain has also been examined in these disease models (Cope and Lariviere 2006).

As previously discussed the HSV-1 vector is naturally neurotrophic and it has been utilised extensively in sensory neuropathies. Administration of a HSV-1 vector expressing glutamic acid decarboxylase (GAD) subcutaneously has been found to alleviate pain in a model of spinal nerve ligation. Increased expression of GAD in the DRGs resulted in attenuation of the symptoms of mechanical allodynia and thermal hyperalgesia (Hao, Mata et al. 2003). GDNF expressed by either a HSV-1 or lentiviral vector has also been found to be effective in reversing pain manifestations in spinal nerve ligation pain model. The HSV-GDNF was delivered subcutaneously and the lentiviral-GDNF was delivered via intraspinal injections (Hao, Mata et al. 2003; Pezet, Krzyzanowska et al. 2006). Treatment with both vectors was found to significantly alleviate both thermal and mechanical hyperalgesia symptoms.

Another focus has been on the opiate system. HSV-1 vectors encoding human proenkephalin A, which is an opiate peptide precursor, has been found to have anti-hyperalgesia effects in mice models of hyperalgesia (Wilson, Yeomans et al. 1999; Yeomans, Jones et al. 2004).

A further possibility is to knockdown expression of gene involved in pain pathways. Lentiviral vectors have been used to deliver short hairpin RNAs to knockdown expression of a voltage-gated sodium channel (NaV1.8). This ion channel is thought to be involved in the pathogenesis of neuropathic pain in DRGs. Delivery of the lentivirus expressing the shRNA to primary DRGs was found to knockdown protein and messenger RNA (mRNA) levels and to also decrease the NaV1.8 mediated current densities (Mikami and Yang 2005). Another study used an AAV vector to deliver a shRNA to knockdown expression of GTP cyclohydrolase I (GCHI). Activation of expression of GTPI cyclohydrolase in DRGs has been shown to be significantly involved in development and longevity of pain symptoms. The shRNA was delivered to the sciatic nerve and expression of the transgene was detected in the DRGs. Knockdown of GTP1 cyclohydrolase resulted in a sharp decline in pain symptoms in the animal model and also showed reduced microglial activation in the dorsal horn which inferred a link between pain relief and reduced inflammation (Kim, Lee et al. 2009).

3.4 Motor neuron disease

Motor neuron diseases, which include amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), are progressive neurodegenerative diseases that result in progressive loss of both upper and lower motor neurons. Both diseases are invariably fatal and current therapies are merely palliative. The possibility of gene or cell therapy as a therapeutic option for motor neuron disease is being extensively researched.

Successful gene transfer has been achieved in motor neuron disease by both intramuscular (Kahn, Haase et al. 1996, Wang, Lu et al. 2002, Lesbordes, Cifuentes-Diaz et al. 2003) and intraneural delivery(Boulis, Noordmans et al. 2003; Boulis, Willmarth et al. 2003). *Ex vivo* gene therapy involving genetic modification of cells that are then transplanted into the injured region has also been investigated in relation to motor neuron disease. This has involved grafting cells that have to ability to secrete neurotrophic factors. An example of this involved the implantation of myoblasts that had been retrovirally transduced with GDNF. These cells were implanted into the hindlimb of SOD1 mouse model of ALS. GDNF gene delivery was found to prevent motor neuron loss and disease progression (Mohajeri, Figlewicz et al. 1999). There is a Phase 2 clinical trial for an ALS therapy currently taking place in which neural stem cells are being injected to the spinal cord of ALS patients (www.clinicaltrials.gov NCT01348451).

4. Conclusion

Peripheral neuropathies in the form of diabetic neuropathy, peripheral nerve injury and neuropathic pain are painful and debilitating conditions. Amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) are not peripheral neuropathies in the strictest sense but they are related as disorders of the cells that form the peripheral nerves. Current best clinical practise offers drug treatment for pain relief and nerve grafting for damaged nerves. These treatments have some success but room for improvement exists.

Gene and cell therapies have the potential to improve treatment outcomes in these peripheral neuropathies. Gene therapy vectors potential to transduce neurons and be transported in a retrograde manner has been exploited in animal models of these diseases and has shown beneficial effects. Efforts to improve tropism of vectors by pseudotyping and

by incorporating neurotrophic peptides into viral coats increase specificity of these vectors and reduce the problem of off-target effects. In a similar manner cell therapies can be used in these diseases. Cell therapies can be used in an unmodified state where they can effect change at the site of injury or can be engineered to secrete a specific factor that will support nerve regrowth and repair.

The movement of potential therapies into clinical trials is ongoing. In the meantime research continues to improve and refine understanding of peripheral neuropathies while working on therapy concepts to treat these conditions.

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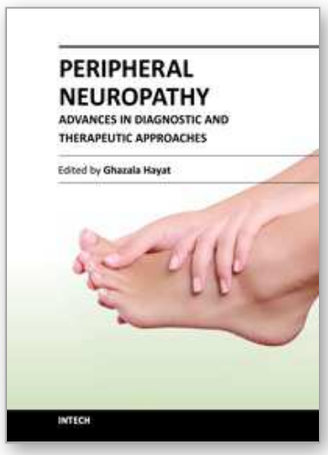

Peripheral Neuropathy - Advances in Diagnostic and Therapeutic Approaches

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Over the last two decades we have seen extensive progress within the practice of neurology. We have refined our understanding of the etiology and pathogenesis for both peripheral and central nervous system diseases, and developed new therapeutic approaches towards these diseases. Peripheral neuropathy is a common disorder seen by many specialists and can pose a diagnostic dilemma. Many etiologies, including drugs that are used to treat other diseases, can cause peripheral neuropathy. However, the most common cause is Diabetes Mellitus, a disease all physicians encounter. Disability due to peripheral neuropathy can be severe, as the patients suffer from symptoms daily. This book addresses the advances in the diagnosis and therapies of peripheral neuropathy over the last decade. The basics of different peripheral neuropathies is briefly discussed, however, the book focuses on topics that address new approaches to peripheral neuropathies.

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