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REVIEW

Stem Cell-Based Approaches to Improve Nerve Regeneration: Potential Implications for Reconstructive Transplantation?

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Abstract Reconstructive transplantation has become a viable option to restore form and function after devastating tissue loss. Functional recovery is a key determinant of overall success and critically depends on the quality and pace of nerve regeneration. Several molecular and cell-based therapies have been postulated and tested in pre-clinical animal models to enhance nerve regeneration. Schwann cells remain the mainstay of research focus providing neurotrophic support and signaling cues for regenerating axons. Alternative cell sources such as mesenchymal stem cells and adipose-derived stromal cells have also been tested in pre-clinical animal models and in clinical trials due to their relative ease of harvest, rapid expansion in vitro, minimal immunogenicity, and capacity to integrate and survive within host tissues, thereby overcoming many of the challenges faced by culturing of human Schwann cells and nerve allografting. Induced pluripotent stem cell-derived Schwann cells are of particular interest since they can provide abundant, patient-specific autologous Schwann cells. The majority of experimental evidence on cell-based therapies, however, has been generated using stem cell-seeded nerve guides that were developed to enhance nerve regeneration across "gaps" in neural repair. Although primary end-to-end repair is the preferred method of neurorrhaphy in reconstructive transplantation, mechanistic studies elucidating the principles of cell-based therapies from nerve guidance conduits will form the foundation of further research employing stem cells in end-to-end repair of donor and recipient nerves. This review presents key components of nerve regeneration in reconstructive transplantation and highlights the pre-clinical studies that utilize stem cells to enhance nerve regeneration.

Keywords Reconstructive transplantation · Vascularized composite allotransplantation · Nerve regeneration · Functional recovery · Stem cells · Schwann cells

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Introduction

Recent advances in microsurgical techniques, basic and translational research, and immunosuppressive protocols have enabled wider clinical applicability of reconstructive transplantation or as more recently referred to vascularized composite allotransplantation (VCA). As such, over 100 hand/forearm and face transplants have been performed worldwide with highly encouraging functional, immunological, and esthetic results over the past decade (Petruzzo and Dubernard 2011; Sarhane et al. 2012). However, the unique requirement for nerve regeneration over long distances to regain full motor and sensory function of such transplants still significantly hampers expansion of the

indications for VCA to arm or lower extremity transplantation, and therefore, its full utilization as a reconstructive modality for devastating limb loss. Stem cell-based therapies have been studied extensively in vitro, in autologous nerve reconstruction, and in peripheral nerve regeneration; while the application of stem cell-based therapies to VCA remains speculative at present; they might have significant potential to enhance the pace and degree of nerve regeneration after VCA, providing new hope to overcome such hurdles of functional recovery after transplantation. In this article, we discuss basic mechanisms of nerve regeneration as they relate to VCA and review current available stem cell-based approaches to improve nerve regeneration and assess their applicability to reconstructive transplantation.

Mechanisms of Nerve Regeneration and Functional Recovery after VCA

Prior to the first successful hand transplantation in 1998, restoration of normal function of musculature and nerves was considered unlikely (Tobin et al. 2009). However, this has not proven to be the case in the clinical experience with hand or face transplantation over the last decade, with rapid restoration of motor and sensory feedback consistently reported (Petruzzo et al. 2010; Shanmugarajah et al. 2012). Yet, several challenges remain to be addressed before this innovative reconstructive modality can realize its full potential and gain widespread clinical applicability. Among these is the improvement of long-term functional outcomes especially for above-elbow or full-arm transplants and lower extremity transplants, which necessitates the establishment of novel clinical strategies to enhance nerve regeneration. However, mechanisms of nerve regeneration and functional recovery in VCA have not been studied extensively; therefore, much of our understanding must be gleaned from research in peripheral nerve injury and nerve allografting. In this section, we will focus on the mechanisms of peripheral motor nerve regeneration, which may be translated to functional recovery after VCA.

After injury to peripheral motor nerves, Wallerian degeneration occurs distal to the site of injury (Geuna et al. 2009). Initially, Schwann cells (SCs) and macrophages remove degenerating segments of the distal axon and myelin debris (Bigbee et al. 1987; Bunge 1994; Fu and Gordon 1997; Stoll and Jander 1999), and subsequently support the regenerating axons via release of cytokines and neurotrophic factors that stimulate axonal growth and guide axonal regeneration (Brushart 1988; Lundborg et al. 1986, 1994; Mackinnon et al. 1986; Madduri and Gander 2010) (Fig. 1). However, axonal regeneration and SC support are interdependent, as the injured axon also releases mitogenic cytokines that induce SCs to change from a myelinating phenotype to a proliferative phenotype (Heumann 1987; Funakoshi et al. 1993; Mews and Meyer 1993; Rogister et al. 1993; Thoenen et al. 1988) and cause SCs to form columns that serve as pathways for regenerating axons, known as bands of Büngner (Bhatheja and Field 2006; Ide 1996; Webber and Zochodne 2010) (Fig. 2). Axonal pruning occurs proximal to the site of injury, with each injured axon eventually sprouting multiple growth cones, with several daughter axon sprouts per parent axon (Glaus et al. 2011; Mackinnon et al. 1991; Toft et al. 1988). Each of these daughter axons seeks to reconnect with the neuromuscular junction, and if they fail to do so in a timely fashion, they undergo pruning. However, regeneration progresses relatively slowly, at approximately 1–2 mm per day (Sunderland 1990). Therefore, for upper extremity repairs, time to re-innervation of target structures may take several months or even years, which may leave SCs without axonal contact for an extended period of time resulting in progressive loss of their ability to assist in nerve regeneration and ultimately resulting in poor functional recovery (Dedkov et al. 2002).

In VCA, host axonal regeneration is dependent on intact endoneurial architecture of the donor nerve contained within the allograft together with donor SCs (Glaus et al. 2011). Donor SCs support the regenerating axon, as outlined above, but are also the most immunogenic component of the nerve (Mackinnon et al. 1982; Lassner et al. 1989; Gulati and Cole 1990; Yu et al. 1990; Trumble and Shon 2000). In nerve allografts, host SCs flank the proximal and distal ends of the allograft, essentially containing donor SCs in between. In this setting, subclinical episodes of acute rejection eventually deplete these donor SCs, which galvanizes host SCs to migrate from both the proximal and distal host nerve stumps into the allograft to replace the donor cells (Fornaro et al. 2001; Fukaya et al. 2003; Hayashi et al. 2007; Tseng et al. 2003; Whitlock et al. 2010) (Fig. 2). Notably, studies have shown that a greater number of host SCs migrate into the allograft from the distal end (Fukaya et al. 2003). This environment is significantly different in VCA, as there is no distal source of host SCs, and all points of potential re-innervation distal to the site of injury are comprised of donor tissue (Glaus et al. 2011) (Fig. 3). Furthermore, in VCA, the skin and muscle components are more immunogenic than SCs, which necessitates a more aggressive immunosuppressive regimen (Lee et al. 1991). Therefore, the episodes of subclinical rejection that serve as an impetus for host SC migration into the allograft are likely mitigated in VCA and this repopulation may fail to occur sufficiently, although the exact mechanisms of rejection in VCA are not yet fully delineated (Sarhane et al. 2014c). However, in the event of a clinically relevant acute rejection, the donor SCs residing within the allograft may be rejected, which could

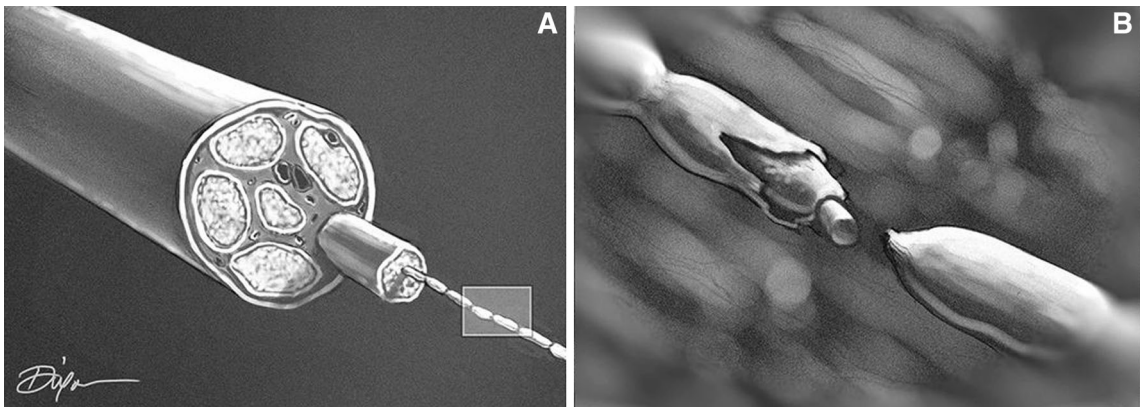

Fig. 1 **a** Cross-sectional architecture of a nerve demonstrating nerve fascicles and neurite outgrowth. **b** Higher magnification of the *gray inset* from **a**, showing axonal growth and regeneration after nerve transection from the proximal stump

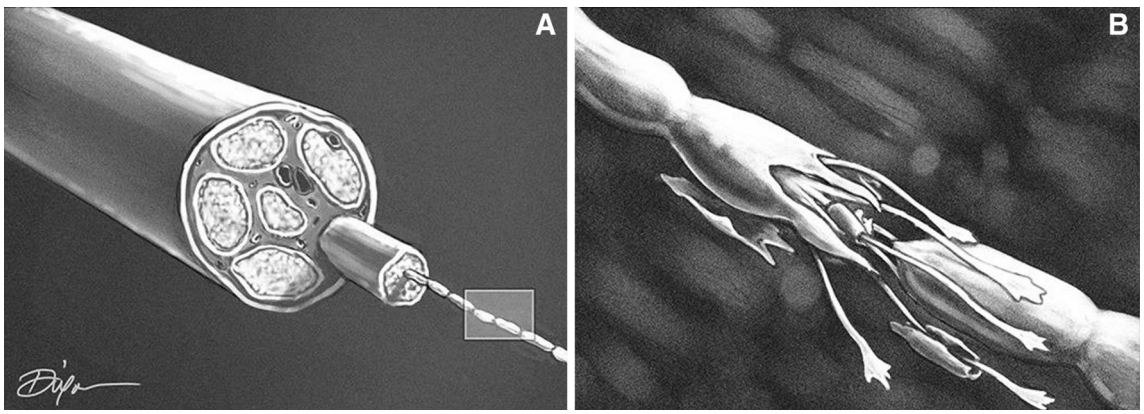

Fig. 2 **a** Cross-sectional architecture of a nerve demonstrating nerve fascicles and neurite outgrowth. **b** Higher magnification of the *gray inset* from **a**, showing Schwann cell migration from the proximal stump and the formation of the bands of Büngner, which support axonal growth

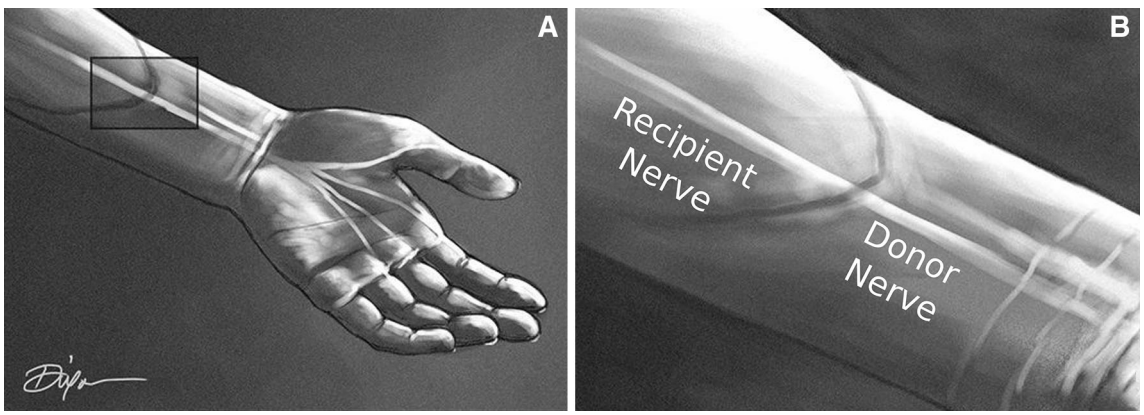

Fig. 3 **a** Hand transplantation illustrating the attachment of a donor hand to the recipient's upper extremity. All tissues distal to the site of attachment are of donor origin, which is distinctly different than conventional peripheral nerve repair. **b** Higher magnification of the gray inset from **a**, showing the attachment of the proximal recipient nerve to the distal donor nerve

potentially cause a devastating nerve conduction block as all axonal support would be lost (Glaus et al. 2011). Therefore, it is imperative that the entire length of the graft becomes populated with host SCs and novel strategies be developed to enhance nerve regeneration in VCA by targeting SC migration.

Schwann Cells as a Key Cellular Element in Nerve Regeneration

Despite significant advances in microsurgical techniques that led to considerable improvements in neural repairs, functional recovery has failed to reach pre-injury status, both in peripheral nerve injury and in VCA. These suboptimal outcomes result from intrinsic and extrinsic nerve factors, some of which are potentially modifiable, e.g., the rate of nerve regeneration. A considerable amount of research has aimed at addressing these various factors by developing strategies to manipulate SCs and promote their role in neurotrophic and axonal support.

The role of SCs in Wallerian degeneration, remyelination, and support of axonal growth are best assessed in experimental models in which these cells were either decreased in number or made non-functional. Such experiments demonstrated that diminution of SCs resulted in nerve growth arrest and poor functional outcomes, underscoring that SCs are an integral component of the regenerative process (Gordon et al. 2009).

SCs in peripheral nerve trunks exist in two forms: myelin-forming and non-myelin-forming cells, both of which arise from a common pool of immature SCs that are derived from the neural crest via intermediate cells called SC precursors. After peripheral nerve injury, SCs become activated, assume a dedifferentiated phenotype, and stimulate axonal growth by two inter-related mechanisms: (1) establishing a supportive growth matrix, and (2) secreting neurotrophic support molecules (Mirsky and Jessen 1996).

Functionalization of Grafted Schwann Cells for Nerve Regeneration

Efficient regeneration is a time-sensitive matter, especially when large distances must be regenerated, as is typically the case in both traumatic peripheral nerve injury and VCA (Gordon 2009). One reason is that while denervated SCs at first provide a trophic cue to attract regenerating axons, this expression of neurotrophic factors eventually subsides (Höke et al. 2002). Perhaps even more important for allotransplantation is the observation that the regenerative potential of motor neurons is reduced after chronic axotomy, i.e., lack of target muscle to innervate (Furey et al. 2007). Furthermore, it has long been known that the event when axons are to cross the lesion site is a major hurdle, as they spend considerable time sampling the pathways at the surgical interface (Cajal 1928; Gordon 2009; Sarhane et al. 2014b).

A potential approach to circumventing these detrimental effects is through supplementation of growth factors that support the regeneration process. It has been shown that supplementation with a combination of glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor can improve regeneration of motor axons following 2 months of chronic axotomy. Indeed, GDNF supplementation to the chronically axotomized group resulted in a comparable number of retrograde-labeled motoneurons as compared to the group receiving immediate repair (Boyd and Gordon 2003).

To achieve a prolonged supplementation with bioactive neurotrophic factors, transgenic functionalization of engrafted cells has gained recent interest. A recent study by Shakhbazau et al. (2012) demonstrated that the trophic support from SCs functionalized to overexpress nerve growth factor (NGF) through lentiviral transduction significantly enhanced the early events of regeneration across a 5-mm rat sciatic nerve gap in a silicon tube. At 2 weeks following surgery, animals receiving NGF-transduced SCs had significantly improved profiles of axon extension through the length of the tube when compared to animals receiving green fluorescent protein-transduced SCs. Furthermore, the engrafted NGF-expressing SCs provided an enhanced concentration of NGF in the segment distal to the site of injury (Shakhbazau et al. 2012).

Similarly, Deng et al. (2013) recently demonstrated that a continuous growth-promoting pathway can be constructed in the adult spinal cord subsequent to spinal cord injury by grafting lentiviral infected SCs that overexpress GDNF within the site of the lesion. The authors report that this pathway leads to anatomical regeneration of damaged propriospinal axons from their transected ends to caudal targets of innervation, and leads to the formation of new synapses and myelin thereafter. Moreover, groups treated with the experimental protocol recovered partial electrophysiological and behavioral activity. These results represent proof of principle that specially engineered SCs may promote axonal regeneration, remyelination, and synaptic formation (Deng et al. 2013).

However, due to patient-safety concerns related to immunogenicity and tumor formation, the application of lentiviral vectors should be avoided in non-terminal conditions. The use of plasmid-transfected SCs overexpressing ciliary neurotrophic factor has been reported to improve the regeneration of optic nerves through poly (lactide-co-glycolide) conduits (Fang et al. 2010). Conventional plasmid transfection may, however, not provide the desired duration of transgene expression for efficient regeneration of larger nerve defects, as is the case in VCA. Within a nerve guide, new approaches of plasmid DNA transfection from porous hydrogel fillers could be employed to maintain a prolonged transgenic expression of neurotrophic support (Lei et al. 2010a, b). Transfection from nanoparticles embedded within hyaluronic acid hydrogels can be

accomplished for at least 6 weeks following subcutaneous implantation in mice (Tokatlian et al. 2014). However, this approach will not be able to functionalize cells where hydrogels are not implanted. To accomplish this, prolonged episomal maintenance of plasmids has been demonstrated using scaffold/matrix-attached regions (S/MARs) incorporated in the plasmid backbone. A passive episomal maintenance of plasmids containing S/MAR can be achieved for at least 6 months in vivo, as determined through its transgene expression in the livers of mice after hydrodynamic administration. Such long maintenance required the synergistic action of S/MAR with the liver-specific human alpha1-antitrypsin (AAT) promoter in the context of this study, as the transgene expression from plasmids lacking the combination of S/MAR and AAT promoter could not be maintained past 2 weeks (Argyros et al. 2008). Such a technique may have significant clinical implication for VCA, and is currently being investigated in pre-clinical models of reconstructive transplantation.

The Fate of Implanted Schwann Cells

Once implanted, cultured SCs can maintain self-survival (Fansa et al. 1999; Levi and Bunge 1994), secrete neurotrophic factors (Tuszynski et al. 1998), support the neuronal cytoarchitecture (Li and Raisman 1997), and effectively myelinate regenerating axons. The effect of cultured host SCs on axonal regeneration in peripheral nerve allografts was studied by Ogden et al. (2000) in a rodent model; SCs were shown to remain viable after injection, and facilitated axonal regeneration without causing SC-derived tumors or iatrogenic nerve injury. Other studies have demonstrated that exogenous SCs have the ability to migrate, re-myelinate, and promote clinical recovery in experimental models of auto-immune demyelination (Zujovic et al. 2012).

Although the aforementioned studies have demonstrated the safety and efficacy of ex vivo cultured primary SCs after implantation, further in vivo studies evaluating the survival, migration, and myelination potential of induced SCs from various stem cell sources are still needed to assess their safety, efficacy, and clinical translation. Indeed, clinical translation of cell-based therapy for peripheral nerve repair is still in its infancy. A clinical trial at Stanford University investigated the use of scaffold tubes filled with longitudinal collagen fibers as guides for axonal growth (Sabelman et al. 1995). These tubes were seeded by autologous cultured SCs to replace nerve autografts, and aimed at repairing short and long gaps. However, results were only partially reported, and clinical outcomes have not yet been published (Rodrigues et al. 2012). Forthcoming data from clinical trials such as this are eagerly anticipated and will likely direct the clinical application of such cell-based therapies in VCA.

The fate of implanted SCs is also modulated by the milieu of neurotropic factors. The identification of growth factors and signaling cues expressed by SCs significantly contributed to the development of novel cell-based treatment strategies as previously discussed. When SCs are cultured in vitro, various factors can be used to expand this cell population (Levi et al. 1995; Morrissey et al. 1995), and these SCs can subsequently be implanted into brain (Hermanns et al. 1997; Neuberger et al. 1992), spinal cord (Li and Raisman 1997; Tuszynski et al. 1998), muscle (Fansa et al. 1999), xenografts (Levi and Bunge 1994; Levi et al. 1994), acellular grafts (Gulati et al. 1995), and synthetic or extracted neural conduits (Brown et al. 1996; Dumont et al. 1996; Levi et al. 1997).

Pharmacologic modulation of SC biology to enhance nerve growth has also been evaluated utilizing various modalities including vitamins (Chabas et al. 2008), ligands targeting GABAergic, glutamatergic, or cholinergic systems (Magnaghi et al. 2009), or recombinant key basal lamina molecules (Lee et al. 2007b), all of which have shown encouraging results.

Nerve Guidance Conduits Supplemented with Autologous Schwann Cells

Cellular supplementation of synthetic or de-cellularized grafts with SCs is necessary to obtain a good regenerative outcome in large nerve defects. Without support from engrafted SCs within the scaffold, the host SCs are required to proliferate and migrate into the guide. Recent evidence suggests that in large defects, this proliferative pressure on host SCs leads to the development of senescence in these host cells (Saheb-Al-Zamani et al. 2013). This likely contributes to the difficulties encountered in achieving robust regeneration with increasing defect size.

Autologous primary SCs would be the most desirable cell type to employ for supporting peripheral nerve regeneration, as they would not require immunosuppression. In small animal models, for example, Berrocal et al. (2013) showed that adding SCs to an absorbable collagen-based guidance channel significantly enhanced the gap distance that can be repaired after peripheral nerve injury with critically long segmental defects (13 mm). In large animal models, Hess et al. (2007) grafted autologous SCs into a cold-preserved allograft to support the regeneration of a 6-cm ulnar nerve gap in macaques over a six-month recovery period. When autologous SCs were supplemented into the guide, an increased diameter and vascularization of the regenerated nerve were observed, attesting to the benefit of SC engraftment. Histological evaluation of the nerve

distal to the graft also demonstrated more robust axon regeneration when SCs were employed (Hess et al. 2007). Moreover, an ongoing phase I clinical trial evaluating the use of autologous SCs isolated from the sural nerve to support regeneration of subacute spinal cord injuries has demonstrated promising early results (Levi 2013).

Other biomaterial-based strategies have relied upon the use of specially designed scaffolds, e.g., collagen–chitosan nerve scaffolds with longitudinally oriented micro-channels, which recapitulate the dimensions of the basal lamina micro-channels in native peripheral nerves (Hu et al. 2009). The incorporation of supportive cells into these structures has closely replicated the permissive environment of native peripheral nerves and has resulted in improved axonal growth and functional recovery in a 15-mm-long sciatic nerve defect in rats (Zhang et al. 2013).

These studies demonstrate great promise for the clinical application of primary autologous SCs, when suitable donor tissue is available. However, these examples have relied on the isolation of SCs from large nerve segments. While SCs can be isolated from smaller nerve biopsies, their purification and expansion are difficult and time-consuming. This is the main obstacle precluding the widespread clinical applicability of autologous primary SCs. Therefore, an emphasis has been placed on cellular reprogramming and transdifferentiation techniques in an effort to accelerate the time required to generate sufficient quantities of highly functional SC-like cells that can be derived from easily accessible autologous tissue.

Genetic engineering of SCs has also been utilized to induce them to up-regulate specific cell adhesion molecules to improve their regenerative capacity. Lavdas et al. (2006) investigated the effects of genetically modified SCs that overexpress cell adhesion molecules, e.g., neural cell adhesion molecules, and their role in nervous system repair (Papastefanaki et al. 2007). The authors suggest that such adhesion molecules promote transplanted SC migration, enhance their interaction with the host environment, and therefore facilitate a more effective functional integration. Additionally, cell adhesion molecules promote axonal growth and remyelination, and effectively increase the rate of re-innervation (Siu 2010; Zhang et al. 2008).

Although achieving robust regeneration with increasing defect size has been a major challenge for nerve regeneration in peripheral nerve injury and VCA, the use of SCs to repair large nerve defects has been relatively successful. Hood et al. (2009) investigated the neuroregenerative effects of SCs in a sciatic nerve gap model in rodents using an axonal guidance channel seeded with autologous SCs. They reported increased axonal regeneration and myelination distal to the site of injury; however, this approach may be limited by substantial cell loss, especially if a natural extracellular environment favoring proliferation and survival is not recapitulated (Ansselin et al. 1997; Hood et al. 2009; Koshimune et al. 2003; Zhang et al. 2002). Thus, the combination of transplanted SCs with special axonal scaffolds designed to provide a favorable environment for proliferation would be a very attractive option, such as the conduits filled with a SCs-seeded hydrogel described above. Indeed, this strategy has demonstrated improved functional outcomes (Evans et al. 2002; Pfister et al. 2007; Udina et al. 2004), and continues to be explored to facilitate accelerated nerve regeneration in VCA.

Although successful, such strategies are technically complicated, costly, and may be limited by the high number of cells required for each intervention, which carries the risk of potential injury to the donor nerve, donor-site morbidity, and fibroblast contamination of cultures (Niapour et al. 2010). Therefore, alternative sources of cells have been sought.

Stem Cell-Based Approaches to Enhance Nerve Regeneration

Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) represent a fibroblast-like subset of stromal stem cells that can be isolated from various adult tissues of mesenchymal origin, umbilical cord blood, and Wharton's jelly. They are considered multipotent precursor cells that are capable of differentiating into various types of mesenchymal tissue cells. Bone marrow stromal cells (BMSCs) can differentiate in vitro into primarily mesodermal lineages including osteocytes and osteoblasts, chondrocytes, myocytes, and adipocytes as well under special culturing conditions have been successfully stimulated towards SCs differentiation and used to support nerve regeneration in vitro and in vivo (Ladak et al. 2011). However, a minor population distinguished by being negative for CD44, CD45, MHC class I, MHC class II and c-kit seems to display greater multi-lineage differentiation potential (Serakinci et al. 2014). In general, MSCs can be characterized by three criteria proposed by Dominici et al. (2006) (1) specific cell surface antigen expression (CD29, CD44, CD71, CD90, CD105 and CD106) or absence (CD45, CD34, CD14, CD11b, CD19, CD80, CD86 and HLA class II); (2) adherence to plastic; and (3) multilineage differentiation potential (toward the adipogenic, chondrogeneic, and osteogenic lineages as outlined above. These stem cells can be induced to differentiate into SC-like cells by using platelet-derived growth factor, basic fibroblast growth factor, and glial growth factor-2 (Keilhoff and Fansa 2011). Studies have demonstrated that more than 50 % of cells differentiated with this protocol (Dezawa

et al. 2001) typically exhibit SC-like phenotypes and, more importantly, that they successfully support nerve regeneration (Caddick et al. 2006; Keilhoff et al. 2006a, b; Lin et al. 2008). Specifically, differentiated BMSCs exert a significant neurotrophic effect via secretion of factors that support neuronal survival and growth affecting both outgrowing fibers and nerve cell bodies in a dorsal root ganglion neuronal functional assay (Caddick et al. 2006; Mahay et al. 2008). Furthermore, the microenvironment of a regenerating peripheral nerve, particularly the bands of Büngner, promote both differentiated and undifferentiated BMSCs to assume a SC-like phenotype, thereby supporting nerve regeneration and improving functional outcomes (Cuevas et al. 2004). Notably, the microenvironment of a transplanted composite tissue allograft is similar, since locally secreted factors and cell–cell interactions within the regenerating axons of the graft could assist in programming the implanted MSCs towards SC differentiation, thereby inducing a reciprocally beneficial effect. The mechanisms of MSC-induced nerve regeneration, thus, include in vivo transdifferentiation into neural phenotypes as well as paracrine effects on SCs via released cytokines and growth factors.

Recently, MSCs, apart from their capacity for multilineage differentiation and neuroprotection, have also been identified to have various immunomodulatory and immunosuppressive properties to inhibit the activation and proliferation of immune cells. Ample evidence exists demonstrating such immunomodulatory capabilities of every class of MSCs (Yoo et al. 2009). MSCs have a broad range of target immune effector cells and are able to inhibit key functions of the innate and adaptive immune response as well as during inflammatory conditions. Numerous in vitro studies have demonstrated that MSCs can alter differentiation, maturation and cytokine secretion profiles of dendritic cells, B cells, natural killer cells, as well as T cells, and that they are capable to suppress alloreactive T cell responses in mixed lymphocyte reactions (Tse et al. 2003; Wolbank et al. 2007), while reducing inflammation in vivo (Hong et al. 2010). Studies have also shown that MSCs stimulate the production of antigen specific Tregs and anti-inflammatory cytokines, and inhibit the production of pro-inflammatory cytokines (Gonzalez-Rey et al. 2010). Transplantation of allogeneic MSCs have also controlled graft-versus-host disease (GvHD) in murine models (Yanez et al. 2006), successfully treated GvHD in seven out of nine patients (Fang et al. 2007a, b), and led to resolution of refractory red cell aplasia in patients after major ABO-incompatible HSC transplantation (Fang et al. 2009). In total, there have been more than 290 clinical trials involving infusion or transplantation of MSCs registered at clinicaltrials.gov, the largest part of which investigate the immunomodulatory properties of MSCs in pathologies such as lupus erythematosus, rheumatoid arthritis, ulcerative colitis, HSC transplantation, diabetes, acute renal failure, hepatic failure, and myocardial infarction (Dorronsoro et al. 2013). The mechanism responsible for these improved outcomes is likely due to a shift from a pro-inflammatory to anti-inflammatory cytokine milieu (Lin et al. 2012). Therefore, the immunosuppressive properties of MSCs together with their lack of expression of MHC II potentially allows for their use in allogeneic transplantation without the need for immunosuppression (Gonzalez-Rey et al. 2009, 2010). MSCs are, thus, considered to be immunoprivileged by their low immunophenotype and it has been shown that autologous and allogeneic MSCs have comparable immunosuppressive capacity.

Whether these immunomodulatory properties are a by-product of soluble factors or a result of direct cell–cell contact remains to be fully elucidated. Puissant et al. (2005) suggest that soluble factors, such as indoleamine 2, 3 dioxygenase (DelaRosa et al. 2009), prostaglandin E2 (Cui et al. 2007), and leukemia inhibitory factor (Najar et al. 2010), act to mitigate an active T cell response. Several of the aforementioned studies have shown that inhibition of each of these soluble factors has nullified the immunosuppressive effects of MSCs, thereby supporting the notion that soluble factors play an important role in modulating the immune response. On the other hand, the role of cell–cell contact is less clearly defined. Some studies have suggested that MSCs can exert an immunosuppressive effect without cell–cell contact, whereas others have demonstrated that such contact is necessary to achieve this beneficial effect (Cui et al. 2007; Puissant et al. 2005; Wolbank et al. 2007). It is likely that the immunomodulatory effects of MSCs are due to a combined paracrine and direct cellular effect, which is mediated both by cytokine secretion and regulation of peripheral blood mononuclear cells (Aggarwal and Pittenger 2005; Rasmusson et al. 2005; Wang et al. 2009).

Although BMSCs have shown considerable promise in small and large animal models, the invasive nature of BMSC harvest has prompted research in alternative sources of MSCs (Chen et al. 2007; Dezawa et al. 2001; Tohill et al. 2004; Wakao et al. 2010).

Adipose-Derived Stem Cells

Adipose tissue has a potent, readily available source of stem cells, termed adipose-derived stem cells or adipose-derived stromal cells (ASCs). ASCs are very similar to BMSCs in function and phenotype, as both classes of MSCs lack expression of HLA-DR (MHC II), which renders these cells significantly less immunogenic than other cell types (Gronthos et al. 2001; Hong et al. 2010; Strem et al. 2005). Similarly, both ASCs and BMSCs have the

potential for multi-lineage differentiation, as in vitro experiments have verified their capacity for adipogenic, chondrogeneic, and osteogenic differentiation (Gimble et al. 2007; Planat-Benard et al. 2004; Safford et al. 2002; Winter et al. 2003; Zuk et al. 2002). However, ASCs are a more attractive choice for augmentation of nerve and tissue regeneration, since larger quantities can be harvested through minimally invasive techniques (Hong et al. 2010).

The relevance of ASCs in tissue engineering may be better appreciated when one considers the stem cell yield of adipose tissue from a single liposuction procedure, which may produce liters of fat that is typically discarded. A single milliliter of this fat is enough to produce 250,000 ASCs in a single passage, one billion cells by passage three or four, with an additional 64-fold expansion in less than a month (McIntosh et al. 2006; Mitchell et al. 2006; Ra et al. 2011). Therefore, by utilizing all of the fat from a standard liposuction procedure, one can generate trillions of stem cells with minimal culture time. Furthermore, the quality of ASCs is not affected by long-term culture, unlike other classes of MSCs, which have been shown to undergo senescence (Di Summa et al. 2010; Marchesi et al. 2007; Nishiura et al. 2004; Walsh et al. 2009; Wang et al. 2012), compromised differentiation potential, and diminished proliferative capacity when exposed to these conditions (Bonab et al. 2006; Jung et al. 2012; Wislet-Gendebien et al. 2003). Thus, ASCs have superior accessibility, genetic stability, and proliferative capacity, which provide them with a significant advantage over other types of stem cells.

Notably, the neuroregenerative potential of ASCs has been demonstrated in a variety of in vitro and in vivo models. Kingham et al. (2007) showed that ASCs promote neurite outgrowth in vitro and Erba et al. (2010) demonstrated that undifferentiated ASCs seeded into fibrin conduits led to enhanced nerve regeneration distances. In a canine model of spinal cord injury, allogeneic ASCs injected at the site of injury resulted in significantly improved hind limb function and nerve conduction (Ryu et al. 2009). Furthermore, allogeneic ASCs seeded into bioscaffolds accelerated spinal fusion in a rat model of lumbar compression fracture (Lopez et al. 2009). A comparison of BMSCs and ASCs seeded into fibrin nerve conduits in a rat sciatic nerve model showed that both cell types significantly increased the distance of axonal regeneration and that BMSCs and ASCs were equivalent in their regenerative potential (Di Summa et al. 2010). Thus, both classes of MSCs are poised to make a significant impact on nerve regeneration and functional outcomes in VCA.

Neural Crest Stem Cells

Recent research has focused on the induction of human neural crest stem cells (NCSCs) from various human pluripotent stem cell lines (Lee et al. 2007a, 2010) for use in peripheral nerve regeneration and VCA. The neural crest is a well-described transient, multi-potent, migratory cell population unique to vertebrates that can give rise to diverse cell lineages (Le Douarin 1982). Several protocols for differentiating human embryonic stem cell-derived NCSCs into SCs have been explored and shown promise in the treatment of traumatic injuries of the peripheral nervous system. Liu et al. (2012) found that the combination of several growth factors in an optimized medium on a two-dimensional (2-D) substrate promoted efficient SC differentiation. Morphologically, most of the NCSCs were changed from a monolayer of polygonal shaped cells to a bipolar, spindle-like shape 3 weeks post-differentiation. Immunocytochemical analysis showed that approximately 78 and 85 % of the differentiated cells were positive for glial fibrillary acidic protein (GFAP) and S100β, respectively, after 6 weeks of differentiation, and 90 % of these differentiated cells were positive for p75 and Sox9 (Liu et al. 2012). Notably, these cells also showed myelination capability in neuron co-culture.

Another differentiation approach, using electrospun fibers of different diameters and alignments, was investigated by Ren et al. (2013). Human embryonic stem cell-derived NCSCs were directed towards the SCs lineage using a combination of an optimized differentiation medium with an electrospun nanofiber scaffold that was previously shown to enhance the maturation of de-differentiated SCs (Chew et al. 2008). The aim of using such a scaffold was to recapitulate an extracellular environment favorable for regeneration. This method of differentiation (using fiber matrices) yielded about 85 % $GFAP^+$ cells after 4 weeks of differentiation in culture. Although these differentiated SCs were not yet mature enough to express promyelinating markers, such results provided proof of concept that fibrous topography, as a contact guidance cue to stimulate the morphology of the differentiating NCSCs, can successfully mediate stem cell differentiation signals (Ren et al. 2013).

Induced Pluripotent Stem Cells

Recent advances in induced pluripotent stem (iPS) cell research and technology have enabled the generation of patient-specific cell lines that may be utilized as a therapeutic modality in various disorders (Dimos et al. 2008; Ebert et al. 2009; Lee et al. 2009; Park et al. 2008). In a series of experiments, Liu et al. (2012) demonstrated that neural crest cells can be derived from iPS cells in a similar manner as from human embryonic stem cells (hESC) lines, and these can subsequently give rise to many cell types of the neural crest lineage, including functional SCs that are able to myelinate rat dorsal root ganglion neurons. In clinical

VCA, recipient-specific iPS cells can potentially be obtained from a patient's skin fibroblasts or peripheral blood cells prior to transplantation (Takahashi et al. 2007), differentiated into functional SCs, and then transplanted simultaneously with the graft to enhance nerve regeneration. Furthermore, these cells have the potential to secrete NGFs and myelinate regenerating axons, thereby additionally supporting neuroregeneration. Another potential clinical application of iPS cells in reconstructive transplantation is in drug screening assays of various immunomodulatory protocols to evaluate their responsiveness before administration to patients. Immunosuppression minimization strategies could, thus, be coupled with iPS cell-derived SCs to enhance the neuroregenerative effect of these protocols. Successful generation of these patient-specific iPS cell-derived SCs, thus, provide an exciting new avenue to aid in developing novel therapies for human nerve regeneration in both VCA and peripheral nerve injury.

Nerve Guidance Conduits Seeded with Stem Cells

Substantial experimental evidence in stem cell-based augmentation of nerve regeneration comes from nerve guides developed to bridge gaps during nerve repair. Although primary repair is the preferred method of neurorrhaphy in VCA, the data from gap models can form the basis of further research utilizing stem cell sources in direct nerve repair. Furthermore, the development of nerve guidance conduits has attracted considerable research efforts, attempting to develop good alternatives for nerve autografts, and thus alleviate the issues related to sacrifice of donor tissue with limited availability. It has been repeatedly demonstrated for various types of conduits that supplementation with stem cells is a potent way to functionalize these conduits, rendering them with improved regeneration potential (Di Summa et al. 2010; Marchesi et al. 2007; Nishiura et al. 2004; Walsh et al. 2009; Wang et al. 2012). These studies, hence, provide valuable information about performance and benefit from the various cell sources.

Notably, topographical and trophic support, as well as biomolecular presentation from the scaffolds, creates the niche in which stem cells act, thereby imparting a significant influence on their phenotype and function (Chew et al. 2008; Fu et al. 2010; Huebsch et al. 2010). While tissue-derived conduits do not offer as well defined structure as synthetic conduits, they often contain biological cues and ligands for cell attachment and tissue growth. To investigate sources of autologous grafting material other than nervous tissue, Nishiura et al. (2004) compared freeze-thawed muscle grafts to tendon autografts in rats, both with and without seeding of primary rat SCs. While performances between tendon- and muscle-derived conduits were comparable, both displayed markedly enhanced regeneration upon pre-seeding with SCs. Moreover, resident SCs from both proximal and distal ends of the 10-mm sciatic nerve gaps more rapidly populated the cell-seeded conduits. Already at 7 days post-injury, endogenous SCs fully populated both types of cell-seeded conduits, as opposed to a required period of 14 days for conduits without cell-seeding (Nishiura et al. 2004). SCs derived from ASCs and BMSCs in a fibrin hydrogel conduit have been compared to primary rat SCs in an analogous injury model. While the longest axonal regeneration after 2 weeks was found for primary SCs, the stem cell-derived SCs improved upon the results of acellular fibrinogen conduits (Di Summa et al. 2010).

Collagen is another commonly employed degradable biomaterial with good cell compatibility. Marchesi et al. (2007) compared hollow tubular conduits with porous walls based on either collagen type I or poly-L-lactide-trimethylene carbonate (PLA-TMC) seeded with skin-derived stem cells in a 16-mm rat sciatic nerve gap model. Most of the cells employed in this study were nestin-positive, and negative for hematopoietic markers, endothelial markers, and the SC marker p75NGFR prior to transplantation. The supplementation of cells improved the regeneration for both types of conduits, as determined by a sciatic function index and compound muscle action potential (CMAP) of the gastrocnemius muscle at 90 days following injury. CMAP was not detectable in conduits seeded with vehicle alone, highlighting the impact of cell supplementation. The collagen conduits outperformed that of the PLA-TMC, displaying the most robust myelination. However, it was not the seeded cells that directly contributed to the myelination, as they were only rarely found positive for the SC marker S100β. Another possible mechanism is that of trophic support, but the assays employed could not find significant differences in the expression of neurotrophin 4/5 or brain-derived neurotrophic factor. The particular mechanism of enhanced regeneration, thus, remains unknown (Marchesi et al. 2007). It cannot, however, be ruled out that other means of trophic support contributed to the observed effect. Between the scaffold materials employed, collagen type I benefits from the presence of robust integrin binding motifs (Jokinen et al. 2004) which could improve cellular infiltration. Furthermore, differences in scaffold topography were not investigated. As demonstrated by Chew et al. (2008), aligned micro- to nano-scale topographies can greatly affect the phenotype of SCs. In their study, micron-sized diameter of aligned poly-ε-caprolactone (PCL) promoted the promyelinating phenotype, as evidenced by upregulation of myelin-associated glycoprotein, and downregulation of neurotrophic factors. Notably, randomly oriented fibers did not display this effect on the cells (Chew et al. 2008). The study, thus, demonstrates the potency of microtopographical cues on the gene expression profiles of cells.

Recently Matsuse et al. (2010) provided promising results from umbilical cord-derived MSCs when grafted into a Matrigel-filled conduit bridging an 8-mm sciatic nerve gap. The cells were able to promote regeneration of axons to the same extent as primary human SCs at 3 weeks post-injury. Engrafted cells actively myelinated host axons, and co-localization of engrafted cells with myelin-associated glycoprotein expression was comparable with the primary human SCs, 16.6 and 18.7 %, respectively (Matsuse et al. 2010). It would have been interesting to see how this would compare to primary rat SCs. While the use of primary human SCs avoids concerns related to species mismatch when comparing the cells, the human SCs were derived from fetal tissue, thus prior to the onset of myelination. It is entirely possible that this reduces the myelination functionality of the engrafted primary human SCs compared to adult cells.

The results from cell therapies are likely impacted by the immunocompatibility of the transplanted cells, which is of particular interest in the field of VCA where donor SCs are likely to interact with host axons. Guenard et al. (1992) compared the performance of syngeneic primary SCs in inbred Fisher 344 rats to that of heterologous primary SCs in outbred CD rats, using hollow acrylonitrile vinylchloride copolymer conduits. Their study indicated that an immune response hampered the regeneration in the outbred rats using the heterologous SCs, as compared to the performance of syngeneic cells employed in inbred animals (Guenard et al. 1992).

Phenotype Stability of Stem Cell-Derived Cells

While SCs-like cells have been derived from many different sources, little is known about their phenotypic stability and the impact thereof on regenerative outcome. Dedifferentiation of the stem cell-derived SCs can hamper their long-term support in the regenerated nerve, and in a worst-case scenario lead to tumor formation, as has occurred in human clinical trials employing neural stem cells (Amariglio et al. 2009). Bone marrow stromal cells represent an accessible autologous source of precursor cells that can undergo in vitro expansion and differentiation into functional SCs, and several groups have shown the possibility of in vitro derivation of SC-like cells from BMSCs (Hou et al. 2006; Keilhoff et al. 2006a; Shimizu et al. 2007; Zhao et al. 2005). Previously, the fate of these cells seemed to be dependent on a permanent contact with their induction medium, as withdrawal of this medium resulted in dedifferentiation into myofibroblast phenotype (Zurita et al. 2008). Recently, however, Shea et al. (2010) were able to overcome this necessity by co-culturing the BMSC-derived SCs-like cells with dorsal root ganglion (DRG) neurons, achieving fate commitment in the rat bone marrow-derived SCs-like cells. The authors tested the hypothesis that the juxtacrine signaling provided from axons during SCs development would improve the maturation and fate commitment of bone marrow-derived SCs as well. Indeed, co-culture with embryonic rat DRG neurons was capable of producing SCs-like cells that maintained the fate commitment even after withdrawal of inducing factors (Shea et al. 2010). While this may not be necessary for SCs-like cells derived using all protocols, it stresses the importance of confirming phenotypic stability of the derived cells. Ao et al. (2011) seeded these cells into a chitosan conduit filled with Matrigel, and tested the efficacy of this tissue-engineered composite in bridging a 12-mm gap in a rodent sciatic nerves transection model. Functional and histological assessment indicated axonal regrowth and remyelination in the bridged nerves, providing the basis to pursue BMSC as an autologous source of SCs for transplantation therapy in larger animal species (Ao et al. 2011). It remains to be seen how these findings translate to human cells, and if the juxtacrine signals can be provided by accessible nerve cell sources such as iPS cell-derived neurons.

Concerns with Cell-Based Approaches to Nerve Regeneration

The summation of the aforementioned studies provides an important framework for future trials utilizing cell-based approaches to induce nerve regeneration in VCA. It is worth noting, however, that there are certain limitations to the translation of hESC-derived therapies. These include governmental and ethical constraints, as well as the cost of materials (differentiation media, trained staff, facilities costs, etc.). Furthermore, there are regulatory concerns over the safety of undifferentiated cells that can form teratomas, migrate or differentiate unpredictably in a diseased environment, and the lack of imaging technologies to follow transplanted cells (Csete 2010).

To date, there is limited clinical data on the safety of hESC-derived therapies, with no long-term safety records. The first cell therapy using ESC-derived cells was initiated by Geron to treat severe thoracic spinal cord injuries using ESC-derived oligodendrocyte progenitor cells. The results from this phase I safety testing were recently reported by Asteria Biotherapeutics who took over the study (Asteria Biotherapeutics 2010). The patients received the cell transplant at 7–14 days post-injury, followed by a two-month period of immunosuppression. In the five treated patients, there were no serious adverse events associated with the treatment. Importantly, there was no evidence of expansive tumors or cysts as determined by magnetic

resonance imaging, and there were no detectable immune responses to the grafted cells over the one-year period, but some grade 1–3 adverse events were reported (Lebkowski 2014). The trial was, thus, successful in demonstrating the short-term safety in a small cohort, alas phenotypic stability and long-term safety requires further clinical investigation. Additional phase I clinical trials using hESC-derived cells are currently being conducted for cardiac progenitors in heart failure (Menasché 2013), and retinal pigment epithelial cells (Bainbridge and Dhillon 2011; Phizer 2012; Schwartz 2011; Song 2012).

Induced pluripotent stem cells have emerged as the premiere cell source in international stem cell biology, owing to their pluripotent therapeutic potential with limited ethical and political constraints. Thus, iPS cells hold great potential for providing a source of patient-specific SCs from simple somatic cells (Csete 2010).

Moreover, metrics to accurately elucidate the clinical efficacy of cell-based therapies in inducing nerve regeneration are currently lacking; therefore, discovery of biomarkers for nerve regeneration is also critical (Sarhane et al. 2014a). Such biomarkers can be used to devise and guide appropriate therapies (Sarhane 2012) and can be utilized to objectively monitor the neuroregenerative effects of the various cell or non cell-based neuroregenerative strategies.

Nevertheless, the evidence presented herein suggests an optimistic future for stem cell-based approaches to nerve regeneration. The development of patient-specific autologous SCs and mobilization and migration of host SCs will play a key role in this regard to promote optimal functional recovery following VCA.

Conclusion

Reconstructive transplantation is a viable treatment option for hundreds of thousands of patients living with debilitating limb injury or facial disfigurement. However, functional recovery is a critical determinant of the overall success of such transplants. Stem cell-based therapy has proven in both in vitro and in vivo experiments to positively modulate SCs and enhance the pace of peripheral nerve regeneration. Greater understanding of their role and potential application in reconstructive transplantation will emerge from exploring specific molecular mechanisms underlying axonal growth in transplant surgery, the role of axonal transport in regeneration, and the molecular and cellular changes that impede regeneration over long distances. Deciphering these mechanisms may enable the clinical application of targeted stem cell-based nerve therapy with improved functional outcomes, thereby broadening the scope of VCA to arm and lower limb transplantation in the near future.

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