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INVITED REVIEW

Adipose derived stem cells and nerve regeneration

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Abstract

Injuries to peripheral nerves are common and cause life-changing problems for patients alongside high social and health care costs for society. Current clinical treatment of peripheral nerve injuries predominantly relies on sacrificing a section of nerve from elsewhere in the body to provide a graft at the injury site. Much work has been done to develop a bioengineered nerve graft, precluding sacrifice of a functional nerve. Stem cells are prime candidates as accelerators of regeneration in these nerve grafts. This review examines the potential of adipose-derived stem cells to improve nerve repair assisted by bioengineered nerve grafts.

Key Words: *peripheral nerve injury; adipose derived stem cells; nerve guidance tubes; bioengineered nerve graft; axonal regeneration; Schwann cell; cell therapy; nerve repair*

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Introduction

Injuries to peripheral nerves are common presentations of trauma resulting in life-changing problems for patients alongside high social and health care costs for society (Noble et al., 1998; Zochodne, 2012). Peripheral nerves possess an intrinsic regenerative capability predominantly due to the plasticity of Schwann cells, the myelinating glia of the peripheral nervous system (PNS) (Chen et al., 2007). Nonetheless, functional recovery following nerve injury is often poor and alternatives to the current clinical treatments are being sought. In particular, in the repair of a nerve gap conventional treatment would sacrifice a length of nerve from elsewhere in the body to be used as a graft in the repair of a more functionally crucial defect. This has led to much work on developing a bioengineered nerve graft.

The development of bioengineered nerve grafts

Bioengineered nerve grafts consist of natural or synthetic nerve guidance tubes, and a multitude of experimental adjuncts have been considered including extracellular matrix molecules, growth factors, pharmaceutical adjuvants and transplanted cells in order to guide the regeneration of axons across nerve gaps (Bell and Haycock, 2012; Faroni et al., 2013a). Commercially available nerve conduits include polyglicolic acid (PGA, Neurotube®) (Weber et al., 2000; Shin et al., 2009), poly-lactic acid (PLA) (Evans et al., 1999; Evans et al., 2000), poly(L-lactide-co-glycolide) (PLGA) (Hadlock et al., 1998; Bini et al., 2004), as well as poly-ε-caprolactone (PCL, Neurolac®) (Bertleff et al., 2005; Sun et al., 2010a, 2010b) and poly-3-hydroxybutyrate (PHB) (Aberg et al., 2009). The clinical results of these nerve conduits has failed to match the results of nerve grafting, perhaps due to the fact that they do not attempt to address the biology of the Schwann cell. Schwann cells are a crucial component of peripheral nerve regeneration, releasing growth factors and assisting in re-myelination (Jessen and Mirsky, 2008). Conduits acting as a cellular scaffold will be all the more effective if transplanted cells, such as Schwann cells or similar alternatives, are translated into clinical practice.

Adipose-derived stem cells (ASCs) as an alternative to Schwann cells

The clinical translation of cell therapy in nerve injury has many issues to address before its clinical relevance can be assessed. The difficulties in the harvest and expansion of Schwann cells together with the morbidity of the donor nerve strongly limit their use towards nerve bioengineering (Tohill and Terenghi, 2004; Kingham et al., 2007). In the search of the ideal alternative to Schwann cells for peripheral nerve regeneration, many alternatives have been evaluated, especially in the field of stem cell research (Terenghi et al., 2009). Embryonic stem cells (ESC) (Cui et al., 2008; Ziegler et al., 2011), induced pluripotent stem cells (iPSC) (Lee et al., 2010; Kreitzer et al., 2013; Ikeda et al., 2014), and also mesenchymal adult stem cells (MSC) from various niches (that is bone marrow, fat, umbilical cord, dental pulp, skin) (McKenzie et al., 2006; Matsuse et al., 2010; Wakao et al., 2010; di Summa et al., 2011; Martens et al., 2014) have all been shown to be potential candidates as transplantable differentiated Schwann cell-like cells in nerve guidance tubes

for nerve regeneration. In particular adipose tissue, deriving from the embryonic mesenchyme, can be easily harvested and digested in order to obtain a stromal vascular fraction (SVF), containing a population of ASCs, which have shown multipotential capability (Zuk et al., 2002).

Indeed, ASCs can be differentiated *in vitro* towards adipogenic, osteogenic, chondrogenic, myogenic, and neurogenic lineages (Zuk et al., 2002; Gimble and Guilak, 2003). The expression profile of cell-surface markers of ASCs showed high similarities with bone marrow derived MSC (BM-MSC) (Gronthos et al., 2001; Zuk et al., 2001, 2002). For instance, ASCs are positive for CD9, CD29, CD44, CD71, CD73, CD90 and CD105, but negative for CD11b, CD14, CD18, CD31, CD45 and CD56 (Gronthos et al., 2001; Zuk et al., 2001, 2002; Gimble and Guilak, 2003). One of the advantages of using ASCs and other stem cells for allogeneic transplantation is the low immunological profile defined by the low expression of HLA-DR class II histocompatibility antigens, and high expression of HDLA-ABC class I histocompatibility proteins (Aust et al., 2004). Furthermore, the number of fibroblast-like and alkaline-phosphatase-positive colony-forming units (CFU-F) is reported to be 600-fold higher in ASCs compared to BM-MSCs (Fraser et al., 2006), and they can be expanded faster and for longer periods (Kern et al., 2006; Locke et al., 2009).

ASCs and peripheral nerve regeneration

All these favourable properties have made ASCs a promising candidate for the engineering of several tissues, including injured peripheral nerves. In this context, both undifferentiated ASCs and differentiated Schwann cell-like ASCs (dASCs) have been assessed in *in vitro* and *in vivo* models of peripheral nerve regeneration. The results of various *in vivo* nerve regeneration studies investigating the regenerative potential of ASCs are summarised in **Table 1**. Nerve regeneration was hindered in vein conduits filled with lipoaspirates (Papalia et al., 2013), but cultured or uncultured ASCs isolated from the SVF, and seeded in PCL or silicon conduits, have been shown to promote nerve regeneration and to survive up to 12 weeks *in vivo* (Santiago et al., 2009; Suganuma et al., 2013). In particular ASCs facilitated the regeneration of a functional nerve and reduced muscular atrophy, but they did not directly differentiate into Schwann cells *in vivo*; furthermore there was evidence of undesired differentiation towards adipocytes, which may be detrimental for nerve regeneration (Santiago et al., 2009). ASCs have also been successfully used for re-populating de-cellularised nerve grafts used to repair rat nerve gap models (Liu et al., 2011; Luo et al., 2012). Moreover, transplanted ASCs have been shown to rescue the neuropathic phenotype of laminin-deficient mice, by facilitating sorting of axons and myelination (Carlson et al., 2011). Following systemic injection of ASCs, a few cells have been shown to migrate to the nerve injury site contributing to reduced inflammation and improved nerve regeneration (Marconi et al., 2012). The anatomical site of harvest (Kaewkhaw et al., 2011; Engels et al., 2013), the depth of the fat layer (Kalbermatten et al., 2011; Tremp et al., 2013), and the age of the donor (Mantovani et al., 2012; Sowa et al., 2012) are known to affect the neurotrophic potential of ASCs. Rather than a commitment to a Schwann cell phenotype, the positive effects of ASCs on neuronal protection and nerve regeneration *in vivo* and *in vitro* has been hypothesised to be associated with the release of growth factors, in particular nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and brain derived neurotrophic factor (BDNF) (Zhao et al., 2009; Luo et al., 2012; Sowa et al., 2012). This may be important for endogenous Schwann cell recruitment; even when a considerable number of cells are lost a few weeks following transplantation (Erba et al., 2010).

Schwann cell-like ASCs further improve nerve regeneration

A different strategy for the use of ASCs in nerve repair consists in the differentiation *in vitro* into a Schwann cell phenotype before transplantation. This could prevent the risk of teratomas and *in vivo* differentiation towards undesired phenotype, and could potentially generate committed Schwann cell-like cells able to actively participate in the regeneration and re-myelination of the injured nerves. Kingham et al. showed first that rat ASCs could be differentiated into Schwann cell-like cells by exposure for two weeks to a cocktail of growth factors including fibroblast growth factor (FGF), plateled-derived growth factor (PDGF) and glial growth factor (Kingham et al., 2007). This differentiation mechanism, previously applied to bone marrow-derived MSC (Dezawa et al., 2001), mimic the environmental cues of Schwann cell development and it has been shown to be independent from notch signalling (Kingham et al., 2009). Schwann cell-like ASCs obtained by this means express glial markers, produce myelin proteins and release growth factors that are able to induce neurite sprouting *in vitro* (Kingham et al., 2007; Xu et al., 2008; Mantovani et al., 2010; de Luca et al., 2013). More recently, human Schwann cell-like ASCs have been shown to possess comparable molecular and functional properties (Tomita et al., 2013; Kingham et al., 2014). Schwann cell differentiation through the co-culture with primary Schwann cells or by the induction of neurosphere formation has also been successfully undertaken (Radtke et al., 2009; Wei et al., 2010; Razavi et al., 2012, 2013; Hsueh et al., 2014).

The potential of Schwann cell-like ASCs for nerve repair has been also demonstrated by several *in vivo* studies. These cells seeded in fibrin or silicon conduits have been shown to promote nerve regeneration and the functional outcome of nerve repair in 2 weeks (di Summa et al., 2010), 16 weeks (di Summa et al., 2011) and 6 months-long studies (Orbay et al., 2011). Nevertheless, they failed to enhance short-term nerve regeneration when seeded in commercially available collagen-based (Neuragen®) conduits (di Summa et al., 2014), unless dispersed in fibrin hydrogels (Carriel et al., 2013). Interestingly, magnetic resonance imaging (MRI) was proven effective to monitor the efficacy of Schwann cell-like ASCs to improve nerve growth, by monitoring the regenerating axon front over time (Tremp et al., 2013). Schwann cell-like ASCs have been successfully used to re-populate decellularised nerve allografts (Wang et al., 2012) or allogeneic artery

Table 1 Regenerative potential of adipose-derived stem cells (ASCs) *in vivo*

Study	Species	Injury type	Repair type	Duration	Outcome
Carlson et al. (2011)	Mouse	Laminin knockout	Sciatic nerve treated with ASCs	3 weeks	ASCs cause endogenous Schwann cells to differentiate and myelinate.
Carriel et al. (2013)	Rat	Sciatic nerve gap (10 mm)	Collagen conduit	12 weeks	ASCs in fibrin-agarose hydrogel improve remyelination and ECM organization.
di Summa et al. (2010, 2011)	Rat	Sciatic nerve gap (10 mm)	Fibrin conduit	2, 16 weeks	ASCs improve regenerative distance (2 wk), improve fiber diameter and reduce muscle atrophy (16 wk).
di Summa et al. (2014)	Rat	Sciatic nerve gap (10 mm)	Collagen conduit	2 weeks	ASCs show no short-term benefits.
Erba et al. (2010)	Rat	Sciatic nerve gap (10 mm)	PHB conduit	2 weeks	ASCs increase Schwann cell proliferation, increase regeneration distance.
Kingham et al. (2014)	Rat	Sciatic nerve gap (10 mm)	Fibrin conduit	2 weeks	ASCs improve regeneration distance.
Liu et al. (2011)	Rat	Sciatic nerve gap (15 mm)	Acellular nerve allograft	12 weeks	ASCs improve motor function recovery, reduce muscle atrophy, improve nerve conduction velocity, and increase myelination.
Luo et al. (2012)	Dog	Sciatic nerve gap (50 mm)	Acellular nerve allograft	6 months	ASCs in combination with TGFβ1 improve myelination, reduce muscle atrophy.
Marconi et al. (2012)	Mouse	Sciatic nerve crush	1 wk post-crush intravenous injection of ASCs	5 weeks	ASCs reduce inflammation, improve motor function recovery, improve number of regenerating fibers.
Orbay et al. (2011)	Rat	Sciatic nerve gap (10 mm)	Silicon conduit	6 months	ASCs improve long-term recovery of nerve conduction and myelination.
Reid et al. (2011)	Rat	Sciatic nerve gap (10 mm)	PCL conduit	2 weeks	ASCs decrease apoptotic gene expression in dorsal root ganglia neurons.
Santiago et al. (2009)	Rat	Sciatic nerve gap (6 mm)	PCL conduit	12 weeks	ASCs improve nerve thickness, reduce muscle atrophy.
Suganuma et al. (2013)	Rat	Sciatic nerve gap (10 mm)	Silicon conduit	2 weeks	ASCs cause faster regeneration.
Tomita et al. (2013)	Rat	Tibial nerve crush	Tibial nerve treated with ASCs	8 weeks	Human ASCs improve myelin formation.

Compilation of *in vivo* studies of nerve regeneration using ASCs in conjunction with injury treatments. ECM: Extracellular matrix; TGFβ1: transforming growth factor β1; PCL: polycaprolactone; PHB: poly-3-hydroxybutyrate.

conduits (Sun et al., 2011) used for nerve repair. Another reported effect of the transplantation of Schwann cell-like ASCs for nerve repair is the reduction of neuronal loss at the level of the dorsal root ganglia (DRG) neurons, probably due to the delivery of growth factors that prevent the activation of caspase-3, which leads to cell death (Reid et al., 2011).

At the Blond McIndoe Laboratories we have focused recently on the investigation of novel pharmacological targets to improve the survival and neurotrophic potential of Schwann cell-like ASCs. In particular, we have shown that Schwann cell-like ASCs express several neurotransmitters receptors (that is γ-amino butyric acid GABA type-A and -B receptors, as well as the ionotropic P2X receptors for adenosine triphosphate, ATP), which can be stimulated in order to modulate cell death and survival, proliferation and expression or release of neurotrophic factors (NGF and BDNF) (Faroni et al., 2011, 2012, 2013b, c). In particular, stimulation with GABA-A agonists increases cell growth (Faroni et al., 2012), whereas GABA-B stimulation reduces dASC proliferation (Faroni et al., 2011) and induces increased expression of BDNF and NGF, suggesting improved differentiation (Faroni et al., 2013b). Similar effects have been previously reported in primary Schwann cells (Magnaghi et al., 2004), which are known to express GABA-B receptors that are also involved in differentiation and myelination (Magnaghi et al., 2008; Faroni et al., 2014b). Interestingly, we showed that specific inhibitors to $P2X_7$ receptors are able to rescue the ATP-evoked cell death, which may be partially responsible for the low survival rate of transplanted ASC at the site of nerve injury (Faroni et al., 2013c). This was also confirmed by Luo et al. (2013) in primary Schwann cells, and we have recently shown that $P2X_7$ receptors in Schwann cells control peripheral myelination (Faroni et al., 2014a). We believe that this evidence may point towards the development of novel approaches for nerve repair combining a cell-based therapy and pharmacological intervention.

Remaining clinical problems

Although ASCs have proved to be a promising tool for nerve repair, many questions remain before clinical translation could be considered. Firstly, it is still not clear if culturing and expanding the cells *in vitro* is beneficial for transplantation strategies, or if a more immediate approach, using SVF obtained and transplanted on the day of nerve repair, would be a better option. Secondly, although differentiation of ASCs has proven to be an effective means to improve their neuro-

trophic potential, there is still little evidence that Schwann cell-like ASCs actively participate in the regeneration process by forming new myelin sheets. It seems, if anything, that their main role is to support endogenous Schwann cells by producing growth factors. In this scenario, it is worth considering what the benefits are of delaying nerve repair to obtain a sufficient number of transplantable Schwann cell-like ASCs (meaning a reduced risk of undesired differentiation), or if it is feasible to develop protocols for direct trans-differentiation *in vivo*. Another aspect that should be considered when working with ASCs is the high heterogeneity of this particular stem cell population. It is known that the adherent cells obtained from the SVF contain different cell subpopulations differentially expressing several surface markers. From a clinical point of view, it would be of interest to identify the specific subpopulation leading to the best outcome for nerve repair or generating better performing Schwann cell-like ASCs. Another area that could benefit from further investigation is to improve the interaction of ASCs with the different biomaterials that are currently used to generate nerve guides, by means of functionalization of the coating with biologically active substrates (Madduri et al., 2010). Finally, pharmacological intervention on ASCs has proven effective to improve survival and growth factor expression, thus further study on the identification of novel pharmacological targets on ASCs is worth further investigation.

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