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INVITED REVIEW

The role of exosomes in peripheral nerve regeneration

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Abstract

Peripheral nerve injuries remain problematic to treat, with poor functional recovery commonly observed. Injuries resulting in a nerve gap create specific difficulties for axonal regeneration. Approaches to address these difficulties include autologous nerve grafts (which are currently the gold standard treatment) and synthetic conduits, with the latter option being able to be impregnated with Schwann cells or stem cells which provide an appropriate micro-environment for neuronal regeneration to occur. Transplanting stem cells, however, infers additional risk of malignant transformation as well as manufacturing difficulties and ethical concerns, and the use of autologous nerve grafts and Schwann cells requires the sacrifice of a functioning nerve. A new approach utilizing exosomes, secreted extracellular vesicles, could avoid these complications. In this review, we summarize the current literature on exosomes, and suggest how they could help to improve axonal regeneration following peripheral nerve injury.

***Key Words:** axonal regeneration; exosome; extracellular vesicle; microRNA; microvesicle; nerve gap; neurite outgrowth; peripheral nerve injury; Schwann cell; stem cell*

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Introduction

Peripheral nerve injuries have a profound effect on both individual patients and society as a whole, with the majority of those affected of working age (Asplund et al., 2009). Despite advances in care (Khuong and Midha, 2013), patients are still often left with a significant functional disability (Terenghi et al., 2011).

Nerve injuries were first classified by Sir Herbert Seddon (Seddon, 1942) according to the extent of anatomical disruption to the nerve. The least severe injuries include neurapraxia, when there is a transient conduction block (*e.g.*, in compression injuries or blunt trauma) with no loss of nerve continuity. Axonotmesis involves axon injury without significant connective tissue damage and results in some distal degeneration that usually recovers, albeit over weeks to months. The most severe type of injury is neurotmesis, or complete nerve transection which allows only a limited functional recovery. With the speed of axon regeneration occurring at a rate of approximately 1 mm/day (Seddon et al., 1943), more proximal nerve injuries have an increased likelihood of prolonged end-organ denervation and irreversible atrophy. Furthermore, injuries involving a loss of nerve tissue confer additional problems to the already limited regeneration. Regenerating axons need to traverse the gap and connect with the distal segment. A prolonged denervation of the distal segment limits the possibility for functional recovery. Autologous nerve grafting remains the gold standard for treating nerve gap injuries but various studies over the years have focussed on developing ways to assist regeneration without the need to sacrifice a healthy functioning nerve (di Summa et al., 2011; Daly et al., 2012). Synthetic conduits of varying materials, structures, and contents have been shown to be beneficial (Nectow et al., 2012; Reid et al., 2013), and impregnation with both Schwann cells and stem cells, which release various growth factors and cytokines (their secretome), have further provided good results (di Summa et al., 2011; Ren et al., 2012; Kingham et al., 2014).

Recently, another area of cell research has heralded an improvement in nerve regeneration, with Schwann cell-derived exosomes having shown the ability to enhance neurite outgrowth (Lopez-Verrilli et al., 2013). Exosomes are nanovesicles secreted by most cell types (Lai and Breakefield, 2012; Khalyfa and Gozal, 2014), and they are a newly identified form of intercellular interaction (Kowal et al., 2014). This review summarizes the current research in the field of exosomes and the future implications that exosomes could have for treating peripheral nerve injuries.

Exosomes

Exosomes are a subclass of extracellular vesicles (EVs) which have been identified in a multitude of body fluids (Witwer et al., 2013; Khalyfa and Gozal, 2014). They are formed by the fusion of multi-vesicular bodies (MVBs) within the cell cytoplasm to the plasma membrane, releasing the vesicles now known as exosomes into the extracellular milieu (**Figure 1**). Exosomes are the smallest identified

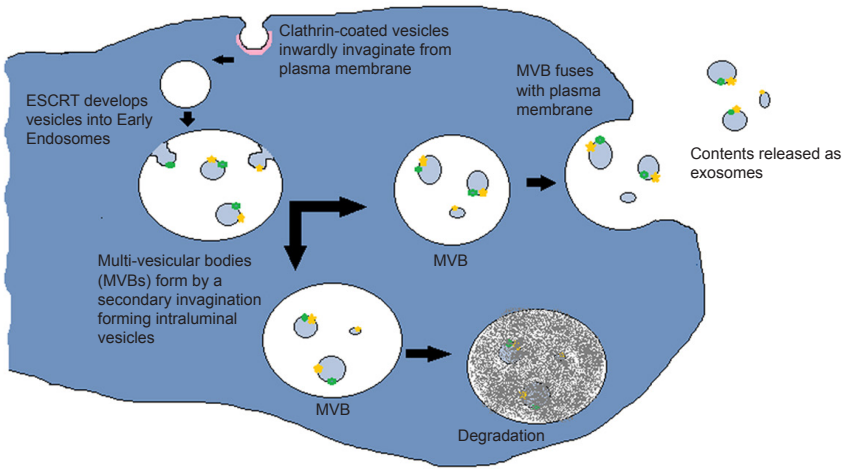

Figure 1 The pathway to exosome biogenesis (adapted from Raposo and Stoorvogel, 2013).
Exosomes originate from multi-vesicular bodies (MVBs). The MVBs can either fuse with the lysosome for degradation or with the plasma membrane, thereby releasing exosomes into the extracellular space where they mediate cell-to-cell communication.

EVs with documented size ranging 10–100 nm (Baglio et al., 2012; Lai and Breakefield, 2012; Katsuda et al., 2013; Kalani et al., 2014). In contrast, microvesicles are larger and derived from the cell plasma membrane rather than the MVBs in the cytoplasm (Raposo and Stoorvogel, 2013). Both types of vesicles are released by cells into the extracellular space, but due to their similarities they are, as yet, impossible to definitively physically separate (Witwer et al., 2013; Kowal et al., 2014).

Originally considered as waste eliminators for cells, more recently exosomes have been shown to mediate intercellular communication (Hagiwara et al., 2014; Khalyfa and Gozal, 2014). Implicated in the transfer of pathogens (Lee et al., 2012; Kalani et al., 2014), as well as having a role in tumour aggression (Chistiakov and Chekhonin, 2014), it was the discovery of genetic material in exosomes (Valadi et al., 2007) that solidified their position as a vital area for current research. Exosomes have been shown to transfer messenger RNA (mRNA) and microRNA (miRNA) from a parent cell to a distant recipient cell. This represents a new method of horizontal gene transfer by affecting protein production and function at a distant site (Lee et al., 2012; Yu et al., 2014).

The therapeutic possibilities of exosomes are seemingly boundless (Katsuda et al., 2013; Sun et al., 2013; Kalani et al., 2014) and include RNA interference (RNAi) therapy (Alvarez-Erviti et al., 2011; Hagiwara et al., 2014), drug delivery systems (Sun et al., 2013), and as biomarkers of disease (Skog et al., 2008; Alvarez et al., 2012; Khalyfa and Gozal, 2014). RNAi involves target-specific gene silencing, usually performed by either small interfering RNAs (siRNAs) or miRNAs binding to mRNAs resulting in post-transcriptional gene silencing (Hagiwara et al., 2014; Kalani et al., 2014). The discovery that these small RNA types are present in exosomes has enabled their specific delivery to target organs, and overcomes the problem with immunogenicity associated with other delivery strategies. The study by Alvarez-Erviti et al. (2011) was the first to show altered protein production and mRNA expression in a target organ as a consequence of delivery of artificially loaded siRNA in exosomes. The fact that exosomes are immunologically inert is also key to their role as drug delivery vectors (Sun et al., 2013). Additionally, their size means they are able to cross the blood-brain barrier and travel trans-dermally (Sun et al., 2013), with the phospholipid bilayer protecting the exosomal contents from degradation. The selective nature of recipient cell uptake of exosomes, which minimises systemic side effects, adds to their appeal.

For a biomarker to be clinically useful it needs to be accurate, specific, sensitive, reproducible, readily accessible and aid clinicians in decision making (Khalyfa and Gozal, 2014). Circulating miRNAs fulfil these criteria (Duttagupta et al., 2011), and EVs, along with their miRNAs, are also now of interest in this field. EV composition and cargo are both dependent on the type and status of the parent cell. Analysis of EVs in healthy and diseased states has been used to identify cardiovascular, metabolic and renal disease (Gyorgy et al., 2011; Hu et al., 2012; Khalyfa and Gozal, 2014). EVs also show promise for tumor diagnosis and monitoring with the detection of tumour-derived EVs in the bloodstream of sufferers showing unique markers and transported miRNAs (Skog et al., 2008; Gyorgy et al., 2011; Chistiakov and Chekhonin, 2014).

In addition to their role as simple carriers of cargo, exosomes derived from mesenchymal stem cells (MSCs) have been shown to induce biological effects on target tissues. Initial studies identified the homing of MSCs to injured tissues in order to repair and regenerate (Baglio et al., 2012; Katsuda et al., 2013; Yu et al., 2014). Since then it has been confirmed that the beneficial effects of MSCs are mediated by their EVs (Lai et al., 2010; EL Andaloussi et al., 2013; Tomasoni et al., 2013). This paracrine effect is due to exosomes released by MSCs promoting angiogenesis (Lopatina et al., 2014) and reducing inflammation (Villarroya-Beltri et al., 2014) by the transfer of genetic material and growth factor proteins. These discoveries have placed exosomes as alternatives for cell-free therapy for a multitude of diseases, including kidney, cardiac and brain injuries (Katsuda et al., 2013). The utilisation of exosomes, rather than their stem cell of origin, could avoid the concerns associated with transplanting cells such as malignant transformation and difficulties in cell manufacturing (Baglio et al., 2012; EL Andaloussi et al., 2013; Lamichhane et al., 2014).

Schwann Cells and Exosomes

Cortical neurons (Faure et al., 2006), microglia (Potolicchio et al., 2005), oligodendrocytes (Kramer-Albers et al., 2007) and astrocytes (Fruhbeis et al., 2012) in the central nervous system (CNS), as well as Schwann cells in the peripheral nervous system (PNS) (Lopez-Verrilli and Court, 2012) have been shown to release exosomes. Thus exosomes have been suggested to play a significant role in neurodevelopment, neurodegeneration and neuroprotection (Lai and Breakefield, 2012; Kalani et al., 2014). Most studies have focussed on exosomes in the CNS (Xin et al., 2012; Pegtel et al., 2014; Pusic et al., 2014); however the discoveries in the PNS are equally exciting.

Peripheral nerve injury initiates a chain of molecular and cellular reactions, named Wallerian degeneration, and critical to these are the peripheral glia (the Schwann cells) which dedifferentiate into a non-myelinating cell type (Monje et al., 2010), and proliferate to clear the endoneurial myelin and axonal debris that impedes axonal re-growth (Rotshenker, 2011). Schwann cells activate non-resident macrophages to the site of injury to complete the myelin phagocytosis and also release cytokines and secrete neurotrophic factors that guide the resultant regeneration (Rotshenker, 2011; Bosse, 2012). Schwann cell exosomes have been shown to be internalized by peripheral nerve axons and can enhance neurite outgrowth *in vitro* (Lopez-Verrilli et al., 2013). These effects are specific to exosomes derived from Schwann cells since fibroblast exosomes had no effect in the *in vitro* studies. The study also confirmed potency in an *in vivo* crush injury model. Daily injections of exosomes into the distal segment resulted in a two-fold increase in axon growth (Lopez-Verrilli et al., 2013). The functionality of the regeneration was confirmed by a positive response to the pinch test at longer distances from the site of injury for the exosome group.

These findings signify the special nature of the relationship between Schwann cells and axons, and provide an interesting base to further explore the specific composition and potential genetic cargo that make the exosomes so valuable to regenerating axons.

Exosome Cargo and Nerve Regeneration

Schwann cell exosomes, and their genetic cargo, likely represent a vital component in the process of Wallerian degeneration and nerve regeneration. Exosomes modulate cell phenotype through the transport of mRNAs, miRNAs and protein-based transcription factors in a variety of organs (Lee et al., 2012), and their presence following injury could instigate the switch of a Schwann cell phenotype from mature to non-myelinating through the transfer of miRNA (Adilakshmi et al., 2012). It has also been shown that Schwann cells themselves are able to transfer genetic material to the axon (Court et al., 2008, 2011; Sotelo et al., 2013) and are likely involved in governing axonal regeneration at a local level, separate to the neuronal cell body. In 2008, Court et al. (2008) identified the transfer of polyribosomes from Schwann cells to desomatised axons in mice by tagging the Schwann cell ribosomes with enhanced green fluorescent protein, and showed that this process was upregulated in injured neurons. The fluorescently tagged ribosomes persisted in regenerating neurons for up to 8 weeks following injury suggesting their role in local protein synthesis (Court et al., 2011). It has also been shown that this transfer process passes newly-synthesised RNA to axons, likely via the nodes of Ranvier and Schmidt-Lanterman incisures, and is dependent on functioning F-actin and myosin-Va (Sotelo et al., 2013).

MicroRNAs are short (~22 nt), non-coding RNAs that impact on protein expression at a post-transcription level by binding with corresponding sections of the 3′UTR segments of mRNA resulting in either a blockage of translation, or mRNA degradation. It has been estimated that 60% of mammalian genes are regulated by miRNAs in this way (Friedman et al., 2009). Analysis of Schwann cell miRNA expression following axonal injury suggests that there is an important local genetic component to the regenerative process (Viader et al., 2011; Yu et al., 2011; Chang et al., 2013). Proliferation and myelination of Schwann cells during both development and following injury have been shown to be mediated by miRNAs (He et al., 2012; Svaren, 2014). The discovery of an abundance of miRNAs in the axon or nerve terminal versus the cell body supports their direct transfer from Schwann cells (Natera-Naranjo et al., 2010). These miRNAs affect the expression of genes encoding for receptors, transcription and translation factors, and proteins involved in cytoskeletal organisation and vesicle transport (Natera-Naranjo et al., 2010), and they have the potential to coordinate axonal growth (Kaplan et al., 2013). Furthermore, studies into specific miRNA (for example, miR-222 (Zhou et al., 2012), miR-133b (Xin et al., 2012), miR-17-92 cluster (Zhang et al., 2013)) have shown that their overexpression can enhance neurite outgrowth. Previously miRNAs were thought to be shuttled from the neuron cell nucleus (Kosik, 2006) to the axon but with the more recent discovery of exosomal miRNA transfer between cells (Valadi et al., 2007), this newer option cannot be ignored.

In addition to the genetic component of an exosome's cargo, there are also numerous proteins, key in both exosome biogenesis as well as cell-type specific actions (Choi et al., 2014). Those found in most cell exosomes, including glial cells, are membrane and cytoskeletal proteins, such as actin and β-tubulin (Kramer-Albers et al., 2007; Fruhbeis et al., 2012) which would be required for axonal growth. The presence of cytoplasmic, nuclear and enzyme proteins, such as heat shock protein 70 (Lopez-Verrilli and Court, 2012), indicates a role in metabolic support and protection of neurons by the glia (Potolicchio et al., 2005; Fruhbeis et al., 2013). More specific to the nervous system, galectin-3, up-regulated by Schwann cells following injury and associated with myelin phagocytosis (Rotshenker, 2011; Bosse, 2012), has been identified in EVs (Choi et al., 2014). Myelin proteins such as myelin-associated glycoprotein (MAG) and proteolipid protein (PLP) have also been isolated from oligodendrocyte exosomes (Kramer-Albers et al., 2007). Proteins from neuronal exosomes have also been investigated. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor subunits are transferred

between neurons via exosomes and this contributes to local plasticity (Lee et al., 2012). Altogether this evidence infers a strong potential role for exosomal RNAs and proteins in regeneration and remodelling of the nervous system.

The Future

This is a promising time for novel therapies targeting peripheral nerve injuries. The aforementioned studies illustrate just some of the many areas which are currently being researched, which could hopefully result in significant improvements for patients. Current Schwann cell-based approaches to nerve repair are not ideal since there is the inherent need to sacrifice a functioning nerve in order to culture the cells. The use of patient-specific Schwann cell exosomes could be used as an adjunct for autologous nerve grafting to enhance regeneration but, in the case of simple repairs, does not overcome the obstacle of needing to sacrifice a healthy nerve to obtain the exosomes. Mesenchymal stem cells have already been shown to mimic Schwann cell activity (Pan and Cai, 2012), and in the case of adipose-derived stem cells are easily accessible and have proven efficacy in improving neurite outgrowth (Kingham et al., 2007). Stem cell transplantation using nerve conduits has shown beneficial effects in various animal models of nerve gap injuries (Hundepool et al., 2014). Recent evidence from our laboratory has shown that exosomes from differentiated adipose-derived stem cells can enhance axonal regeneration *in vitro* (unpublished results), like their Schwann cell counterparts, and provides an exciting prospect for the future treatment of nerve injuries. Stem cell derived exosome supplementation of nerve conduits or by injection into the nerve stumps could be an alternative to the use of living cells (overcoming many of the regulatory hurdles associated with cell therapy) and would make the need for a nerve harvest redundant.

Conclusion

The field of exosomes is advancing at a fast pace, with significant potential for future clinical applications in many areas. The role of exosomes in peripheral nerve regeneration is only just being elucidated, but the first studies suggest that exosome transfer from Schwann cells to axons has beneficial effects on the injured nerves. Further characterisation of their genetic cargo, the mechanisms of exosome transfer and axonal uptake, as well as how stem cells can replicate this are important steps required to advance our knowledge in the field and to aid the translation of exosomes into clinical use.

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Conflicts of interest: *None declared.*

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