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Review

Use of engineered Schwann cells in peripheral neuropathy: Hopes and hazards

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ABSTRACT

Many diseases of the peripheral nervous system affect the function of Schwann cells. Recent developments in stem cell technology offer the opportunity to engineer stem cell derived glial cell populations that reveal essential phenotypic characteristics of Schwann cells including growth support and myelination of peripheral axons. Potential applications of these cells include its use as platform for human cell-based disease models as well as potential source for cell transplantation strategies. In this review we provide an update on the latest developments in engineering Schwann cells as diagnostic tools or for cell replacement therapies in peripheral neuropathic conditions.

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Contents

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1. Schwann cells as essential component of peripheral nerve fibers

Schwann cells, the glial cells of the peripheral nervous system (PNS), originate from the neural crest and represent the most abundant cell type in the PNS. They are subdivided into myelinating Schwann cells, non-myelinating Schwann cells, satellite cells and perisynaptic Schwann cells (Armati and Mathey, 2014). The most obvious function of Schwann cells is the establishment of compact myelin around large diameter axons, which is essential for fast saltatory nerve conduction. In contrast to the CNS in which most axons are myelinated, many fibers in the PNS are surrounded by Schwann cell cytoplasm, which do not from myelin. These include small diameter axons organized as Remak bundles, terminal branches of motor neurons (perisynaptic Schwann cells) and sympathetic nerve fibers (Griffin and Thompson, 2008). Independent of the myelin formation, Schwann cells are also crucial for maintaining the integrity of axons. Under normal conditions axonal maintenance is secured by bidirectional signaling of axons and engulfing Schwann cells. Loss of signaling molecules on Schwann cells or on the axons may result in axonal loss. In addition, Schwann cells provide trophic support to axons via expression of neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF). These growth factors are essential to promote axonal outgrowth and prevent neurons from initiating programmed cell death (Fu and Gordon, 1997; Sherman and Brophy, 2005; Sulaiman and Gordon, 2000). Other axonoprotective molecules that are secreted by Schwann cells include neuropoietic cytokines such as IL-1 and CNTF and hormones such as erythropoietin (Campana and Myers, 2001; Campana, 2007; Keswani et al., 2004).

Because of their fundamental role in maintaining the integrity of peripheral nerve fibers, it is not surprising that malfunction of Schwann cells plays a pivotal role in the pathogenesis of traumatic nerve injury and also in many hereditary, metabolic and inflammatory neuropathic conditions. As a consequence, there are increasing attempts to implement novel treatment strategies to prevent damage and to restore the function of Schwann cells.

Recent innovations in stem cell technology now provide an opportunity to differentiate various types of embryonic or adult stem cell populations to cell lineages that may adopt a Schwann cell phenotype (reviewed by Ma et al., 2015) (Fig. 1). These cells could be used either for novel cell-based therapies that include transplantation paradigms or as screening tool to develop novel drugs to target dysfunctional Schwann cells in specific neuropathic conditions.

1.1. *Embryonic stem cells*

Basically, cells with a Schwann cell phenotype can be generated from a variety of different stem cell populations. Mouse embryonic stem cells (mESC) may represent a valuable source as in vitro disease models, and their differentiation into neural crest cells (Kawaguchi et al., 2010; Rathjen et al., 2002) and lineages with Schwann cell characteristics can be achieved by cell culture methods that include neuregulin containing Schwann cell medium (Roth et al., 2007; Roth et al., 2008).

Human embryonic stem cells (hESC), derived from human blastocysts are pluripotent, immortal cells that can be differentiated into neural crest cells as well. Earlier studies have demonstrated that those cells can be further propagated into neuronal cell lineages of the PNS (Brokhman et al., 2008; Lee et al., 2007; Pomp et al., 2005). By use of culture methods that include use of glial growth factors such as ciliary neurotrophic factor (CNTF) or neuregulin 1β these cells can be further differentiated to cells that express Schwann cell markers such as GFAP (Lee et al., 2007), S100β (Lee et al., 2007) or, less specific, P75NTR (Jiang et al., 2009; Pomp et al.,

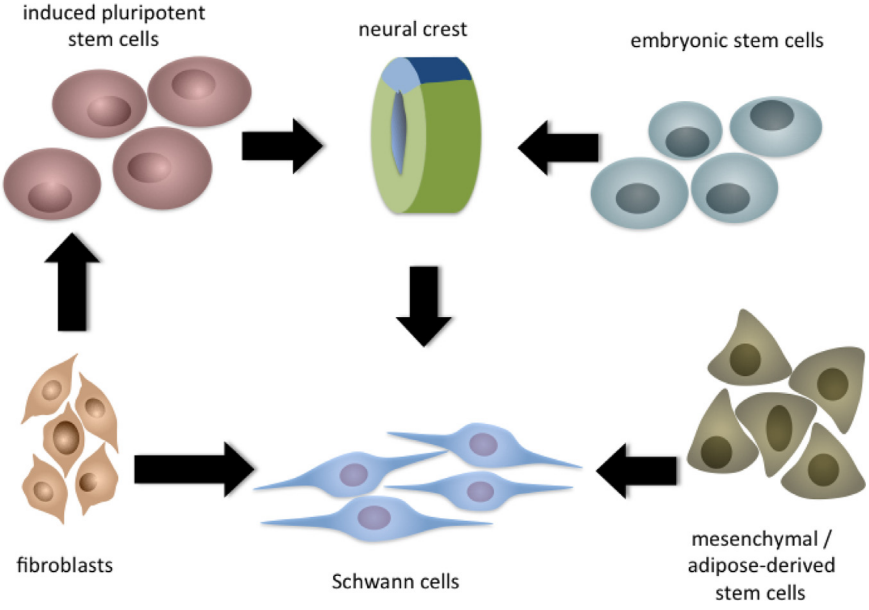

Fig. 1 – : Differentiation of Schwann cells by use of different stem cell populations.