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The Use of Adipose Derived Cells for Skin Nerve Regeneration – Short Review of Experimental Research

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Abstract

Burns and other severe skin injuries alter cutaneous perception of pain, temperature, and touch. During skin wound healing, peripheral nerve regeneration can occur from nerve endings of the wound bed, however, a functional recovery after an injury is often not sufficient due to scar formation or impaired wound healing.

Keywords Adipose-derived stem cells; Cell-based therapies; Skin wound healing; Stromal vascular fraction; Nerve regeneration; Innervation

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Burns and other severe skin injuries alter cutaneous perception of pain, temperature, and touch. During skin wound healing, peripheral nerve regeneration can occur from nerve endings of the wound bed, however, a functional recovery after an injury is often not sufficient due to scar formation or impaired wound healing.

Experimental studies have demonstrated that Schwann cells derived from nerves can enhance peripheral nerve regeneration [1-4]. Unfortunately, the clinical use of Schwann cells is problematic, as they have only limited *in vitro* expansion capacity. Therefore, alternatives are needed to promote nerve regeneration.

Recently, adult stromal vascular fraction (SVF) and adipose-derived stem cells (ASCs) emerged as promising cell sources for tissue-engineering and regenerative medicine applications due to their relative abundance and accessibility.

In this short review, we present possible applications of SVF and ASCs in the field of skin nerve regeneration as several reports have demonstrated that both SVF [5,6] and ASCs contribute to peripheral nerve regeneration [7,8].

The SVF is a heterogeneous population of various cell types including among many others adipose stromal and hematopoietic stem cells, progenitor cells, endothelial cells, lymphocytes, pericytes, as wells as monocytes and macrophages [9,10]. The culture of SVF cells on tissue culture plastic allows the expansion of a subset of adherent, multipotent stromal/stem cells. These cells are termed as adipose-derived stem cells (ASCs) and can be maintained in culture.

For nerve repair and regeneration, freshly isolated SVF or cultured ASCs are utilized. Mohammadi et al. demonstrated in implanted fibrin conduits containing SVF a rapid axon recovery, and an increased density and thickness of myelinated fibers [6]. Other strategies have demonstrated the effectiveness of ASCs seeded for instance in silicon conduits and applied *in vivo* to support functional nerve regeneration [11-14].

Further, another strategy is based on the differentiation of ASCs into Schwann-like cells before using them for nerve repair. Kingham et al. differentiated rat ASCs into Schwann-like cells employing several growth factors mimicking Schwann cell developmental stimuli such as FGF (fibroblast growth factor), PDGF (plateled-derived growth factor), and glial growth factor 2 [4]. Differentiated rat [4,15,16] and also human [17,18] Schwann-like cells expressed *in vitro* myelin proteins, glial markers, and induced neurite sprouting. Further, co-culturing of ASCs with Schwann cells resulted also in differentiation of ASCs into Schwann-like cells [19-21].

In vivo studies have revealed that ASCs-differentiated Schwann-like cells promoted nerve repair and regeneration when delivered in distinct scaffolds, such as fibrin and silicon [22-28]. Tomita et al. demonstrated improved cutaneous nerve regeneration in skin flaps after treatment with ASCs-differentiated Schwann-like cells [29]. Skin innervation was accelerated by pivotal neurotrophic factors and neurotransmitters such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) supporting regrowth of cutaneous axons from the wound bed.

However, there is still no clear evidence whether differentiated Schwann-like cells actively participate in the formation of new myelin sheets or if they only support already present "professional" Schwann cells by releasing various growth factors stimulating nerve regeneration.

To summarize, all aforementioned investigations using human freshly isolated SVF, cultured ASCs or ASCs-differentiated Schwann-like cells have been performed *in vitro* or in experimental *in vivo* studies, but no clinical translation was performed so far. However, further preclinical *in vivo* studies are needed to confirm the safety and effectiveness of human SVF or ASCs prior to their use in future clinical applications.

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