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Editorial

# Mesenchymal Stem Cells at the Interface between Regenerative Medicine and Reconstructive Plastic Surgery

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Mesenchymal stem cells (MSCs) have been identified as ideal source for regenerative purposes. Over the past decade their potential to migrate, proliferate, differentiate and modulate has shown significant promise. MSCs were first described as non-hematopoietic pluripotent cell population in the bone-marrow adhering to plastic surfaces in culture. MSCs do neither express hematopoietic lineage markers like CD34 and CD45, nor adhesion markers like CD31 or CD56. But Stro-1, CD29, CD73, CD90, CD105 serve well for their characterization. These cells can be isolated and expanded *in vitro* for differentiation along multiple mesenchymal lineages such as osteocytes, chondrocytes, myocytes, adipocytes, and Schwann cells (SC). Thereby they are emerging as a promising tool for tissue engineering and cell based therapy. The cellular effects of MSCs are mostly based on paracrine secretion of cytokines and growth factors [1]. Current evidence points to a wide range of proliferative and modulatory functions and interaction with various cell types.

Plastic surgery is dealing with the reconstruction of body function with regards to form and function. MSCs have been applied successfully not only in the field of aesthetic regenerative medicine, where autologous fat grafting and stem cell enriched fat grafts are widely used to improve wrinkles and the skin texture, but also in scaffold base reconstruction of bone and nerve, soft tissue reconstruction in breast surgery, and vascular regeneration to promote wound healing. Liposuction allows for harvesting large quantities of adipose derived MSCs with minimal side effects in an expeditious approach. Fat is thus gaining increasing attraction braking ground for the implementation of cell-based strategies. Deploring the potential of MSCs in adults and finding adipose tissue as additional rich source of MSCs popularized the research interface between regenerative medicine and reconstructive surgery. With regards to translational science the impact of MSCs on vascular and nerve regeneration cannot be overestimated. Although these promotional aspects are tempting the immunomodulatory component should not be underestimated. Especially for regenerative support in the cancer and post-cancer scenario these functions should be carefully monitored.

## MSCs in Vascular Regeneration

Stem cells have been associated with the *de novo* formation of blood vessels (vasculogenesis) during ontogenic development and growth of the vasculature. There is now growing evidence that also in adult organisms, stem cells of various origins are released into the circulation, differentiate or trans-differentiate in order to contribute to the regeneration of various tissues, including the vasculature, where sophisticated signaling is required to orchestrate the process of mobilization, circulation, homing and differentiation of the stem cells. MSCs promote neo-vascularization, but do not necessarily differentiate into mature endothelial cells [2]. Several growth factors, cytokines and chemokines are involved, such as SDF-1, VEGF, Ang, interleukins and ephrins and G-CSF. The stimulation of vascular regeneration by therapeutic means in order to improve the outcome after vascular occlusive events has gained increasing scientific interest. MSCs have been demonstrated to improve vascularity in critical ischemia and wound healing by means of augmenting angiogenesis on the capillary level and arteriogenesis on the arteriolar vascular level [3].

## MSCs in Nerve Regeneration

For nerve reconstruction scaffold and conduit based techniques have been popularized taking advantage of cellular adherence to the material. Recently paracrine secretion of neurotropic factors enabled for systemic cell therapy to promote nerve regeneration. Based on *in vitro* data MSCs support nerve cell viability and neurite outgrowth. MSCs differentiate to Schwann cells under special culture conditions including additives of platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGF), and glial growth factor-2 (GGF-2). In animal models of peripheral nerve injury improved outcomes were demonstrated after MSCs treatment [4]. Augmented recovery has also been shown for systemic treatment [5]. In comparison to the bone marrow source adipose derived MSCs have superior viability and genetic stability, but show similar efficacy in terms of regenerative potential after axonal damage [6].

## Soft Tissue Regeneration and Reconstruction

Restoration of healthy body contour and function is a major aim after trauma or tumor surgery. Currently reconstructive plastic surgery offers specialized surgical techniques utilizing tissue transfer and artificial materials (e.g. silicone implants) to achieve this goal. Although the surgery is safe and the results are satisfying, multiple co-morbidities like obesity and diabetes impair the success rate. Additionally the perioperative risk is increased and enormous care costs are produced for the sequelae of these pathological conditions. Consequently the quest for appropriate and safe adjuncts or alternatives to the present surgical options is of utmost socioeconomic interest. During the last decade the regenerative potential of MSCs - especially from adipose tissue sources - has been identified for promotion of tissue regeneration and soft tissue reconstruction.

Tremendous efforts have been made to utilize stem cells for tissue engineering purposes. Several strategies have been developed: Scaffold guided and injectible systems containing stem cells, growthfactors or both were showing promising results. However few of these techniques have made their way to the clinical daily practice yet for cellular soft tissue reconstruction. Autologous fat grafting from lipoaspirates is thought to be a hopeful strategy and straight-forward application in this scenario. Although not purified, cultured or differentiated into any specific cell line, lipoaspirates and its stromal cell fraction show potential to create viable natural tissue also after severe tissue damage. MSCs in the stromal cell fraction are well characterized, but little is known on how the transplanted or differentiated cell will behave on a long term or in cell-cell interaction with highly reproductive tissue or residual tumor cells. MSCs have shown immunosuppressive and immunomodulatory function, that bear potential for cell-based therapies in allotransplantation aiming at the reduction or replacement of classic immunosuppression [7]. However these functions point out the necessity for more preclinical evidence before broad clinical application in soft tissue regeneration.

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