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REVIEW

Stromal vascular fraction: A regenerative reality? Part 2: Mechanisms of regenerative action

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Summary Adipose tissue is a rich source of cells with emerging promise for tissue engineering and regenerative medicine. The stromal vascular fraction (SVF), in particular, is an eclectic composite of cells with progenitor activity that includes preadipocytes, mesenchymal stem cells, pericytes, endothelial cells, and macrophages. SVF has enormous potential for therapeutic application and is being investigated for multiple clinical indications including lipotransfer, diabetes-related complications, nerve regeneration, burn wounds and numerous others. In Part 2 of our review, we explore the basic science behind the regenerative success of the SVF and discuss significant mechanisms that are at play. The existing literature suggests that angiogenesis, immunomodulation, differentiation, and extracellular matrix secretion are the main avenues through which regeneration and healing is achieved by the stromal vascular fraction.

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Introduction

The concept of adipose tissue as a reservoir of regenerative cells has gained widespread interest after adipose derived stem cells (ADSCs), a form of mesenchymal stem cells (MSCs), were characterized by Zuk et al. in 2001.[1] ADSCs, which are easily extracted from adipose tissue, have been intensely studied due their multipotent differentiation capacity, surface markers and adherence to plastic.[2] A recent shift of focus has directed the attention from the study of ADSCs to that of a heterogeneous mixture of cells from which they are derived, the stromal vascular fraction (SVF).[2,3]

Despite the burgeoning research on these two populations of cells, few studies compare the therapeutic effects of ADSCs with SVF cells. In those that do, SVF treatment provided similar therapeutic effects to ADSC treatment, as seen in osteochondral defects and myocardial infarction therapies.[4,5] In experimental autoimmune encephalitis studies, SVF demonstrated similar neuroprotective effects and greater immunomodulatory properties than ADSCs.[6] These studies indicate that SVF treatment is not only comparable, but in some cases better than ADSC treatment.

The growing research on SVF has been validated by its use in several therapeutic models, including radiation therapy, retinopathy and nerve regeneration.[7–9] When applied to such models, SVF demonstrates angiogenic, immunomodulatory, differentiation, and extracellular production qualities that are important in regeneration and repair.

The regenerative capacity of SVF is likely derived from the heterogeneity of its constituents that provide numerous mechanisms for regeneration to occur. SVF is a source of progenitors and stem cells, which have the potential to differentiate along different lineages. Numerous studies have previously demonstrated the ability of cells found in the SVF,[1,10,11] including M2 macrophages,[12] to differentiate into osteogenic, adipogenic, chondrogenic cell types.

One of the most abundant cell types is the preadipocyte, the precursor to the mature adipocyte. Recent evidence suggest that this cell, also described as a supra-adventitial adipose stromal cell or dedifferentiated adipose cell, shares many of the same phenotypic markers and characteristics of MSCs, implicating its involvement in regeneration.[13,14] SVF also contains endothelial progenitor cells (EPCs), which have the capacity to induce angiogenesis through the release of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1).[15] The macrophages and monocytes found in SVF have been shown to mediate the immune response through the expression of various cytokines,[16] and some exhibit plastic adherence and the ability for multilineage differentiation seen in ADSCs.[12] These macrophages are modulated by T regulatory cells, which can have immunosuppressive properties.[17] Additionally, pericytes found in adipose-derived SVF have been demonstrated to regenerate muscle tissue when injected into damaged mouse muscle,[18] and stromal cells can secrete extracellular matrix components that may improve the general capacity for cellular adhesion, migration, cell–matrix interaction and regeneration.[19,20]

The aim of this review is to present and discuss the cellular and molecular mechanisms behind the regenerative properties observed with stromal vascular fraction. We have included an overview of the surface markers important to SVF cellular interaction, as well as sections addressing the regenerative mechanisms and theories surrounding the tissue survival sequence following SVF implantation.

Cell surface markers (Table 1)

Cell surface molecules, including the clusters of differentiation (CD), are crucial for cell–cell and cell–environment interactions, but are also used to define this mixed population. Despite position papers from the International Federation for Adipose Therapeutics and Science (IFATS) and the International Society of Cellular Therapy (ISCT), there is little consensus with regards to CD characterization of the cells that comprise the SVF. We have identified the markers that are most commonly cited in recent literature specifically related to the regenerative component of uncultured human SVF cells (Table 1).