STEM CELLS TRANSLATIONAL MEDICINE®

PREVIEWS

Previews highlight research articles published in the current issue of STEM CELLS TRANSLATIONAL MEDICINE, putting the results in context for readers.

Stuart P. Atkinson

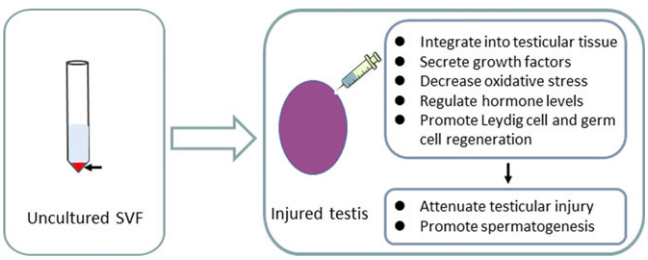
Centro de Investigación Príncipe Felipe, Valencia, Spain. E-mail: satkinson@cipf.es

The enzymatic or mechanical processing of human adipose tissue harvested by liposuction generates a heterogeneous cell population known as the stromal vascular fraction (SVF). This clinically relevant mixture of cells comprises a high proportion of adipose-derived mesenchymal stem cells (ASCs), as well as adipocytes, pericytes, endothelial cells, smooth muscle cells, and various leukocytes [1]. While ASCs can be easily isolated from the SVF, expanded in vitro, and then used in treatment strategies for a range of disease and disorders, the application of "fresh" uncultured SVF cells can also attenuate injury and improve the function of various tissues and organs. Importantly, this approach avoids culture-related risks regarding contamination or the possible introduction of xenogenic products [2] and studies have highlighted the therapeutic equivalence of ASCs and uncultured SVF cells in the treatment of disorders such as renal ischemia–reperfusion injury [3] and penile dysfunction [4]. Of additional interest, the generation of SVF cells and subsequent reapplication to the same patient can take place in a single surgical intervention, therefore making autologous uncultured SVF cells a safe and efficient alternative to ASCs or other culture-expanded mesenchymal stem cells (MSCs) in a therapeutic context. In our first Featured Article this month from *Stem Cells Translational Medicine*, Zhou et al. report that autologous uncultured SVF cells can also protect the testes from ischemia–reperfusion injury and promote spermatogenesis in a rat testicular torsion-detorsion model [5]. In a Related Article from *Stem Cells*, Bowles et al. establish that immunomodulation as a consequence of SVF cell treatment improves clinical scoring, behavior, motor function, and histopathologic analyses in a murine model of late-stage multiple sclerosis [6].

The excessive level of glucose circulating in the blood plasma of diabetic patients induces oxidative stress and the generation of reactive oxygen species and can cause systematic disruption of physiological functions and the onset of comorbidities such as chronic kidney disease, foot ulcers, eye damage, and chronic wound healing. Autologous MSC therapy represents an efficient and patient-specific means to resolve many diabetes-related complications, with, for example, MSCs previously demonstrated to enhance epidermal cell growth and angiogenesis, dampen inflammation, and promote wound closure to improve diabetic wound healing [7]. However, metabolic syndromes such as diabetes or obesity can also negatively affect MSCs themselves, triggering elevated levels of apoptosis, reduced migrational potential [8, 9], and the onset of other functional deficits that prompt an overall decrease in therapeutic activity post-transplantation. In an autologous setting, pretreatment of MSCs derived from metabolic syndrome patients with specific stimuli can promote the recovery of lost function and enhance therapeutic potential. Meanwhile, pretreatment of healthy donor MSCs with cytoprotective agents can guard against cell death and loss of function following transplantation into a metabolic syndrome patient. In our second Featured Article this month from *Stem Cells Translational Medicine*, Ariyanti et al. demonstrate how pretreatment with the small molecule drug salidroside can reverse the functional deficits observed in MSCs cultured under hyperglycemic conditions and promote MSC-mediated wound closure and re-epithelialization in a murine model of diabetes [10]. In a Related Article from *Stem Cells*, Serena et al. report that obesity and diabetes prompt an increase in the expression of inflammatory markers in human (h)ASCs leading to a reduction in their in vitro immunosuppressive capabilities when compared with cells derived from lean control donors [11].

FEATURED ARTICLES

Stromal Vascular Fraction Protects from Testicular Injury and Infertility



Stem cell therapy represents a potentially valuable treatment option for testicular torsion, a condition in which the spermatic cord that delivers blood to the testicles rotates and becomes twisted. Even given immediate surgical intervention to return blood flow (testicular

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distortion) and prevent further testicular injury [12], the associated ischemia–reperfusion injury involved can trigger a significant loss of spermatogenesis that requires additional treatment modalities [13]. Now, researchers led by Ruipeng Jia (Nanjing Medical University, Jiangsu, PR China) have assessed the potential of autologous uncultured SVF cells to improve recovery in a rat testicular torsion-detorsion model. Reporting in a recent *Stem Cells Translational Medicine* article [5], Zhou et al. established that a single local injection of SVF cells protected the testes from severe testicular injury and promoted spermatogenesis. Following injection, SVF cells integrated into the interstitial region, seminiferous tubules, and vascular wall of the injured rat testes where they then enhanced the secretion of various growth factors (including basic fibroblast growth factor and stem cell factor), restored sexual hormone homeostasis, decreased oxidative stress, and promoted Leydig cell and germ cell regeneration. These new findings underline the feasibility of autologous uncultured SVF therapy for the treatment of testicular ischemia–reperfusion injury and the prevention of infertility, and therefore provide support for further clinical trials. The authors now hope to move forward by studying both the long-term effects of SVF cell treatment as well as SVF cell fate in their rat model.

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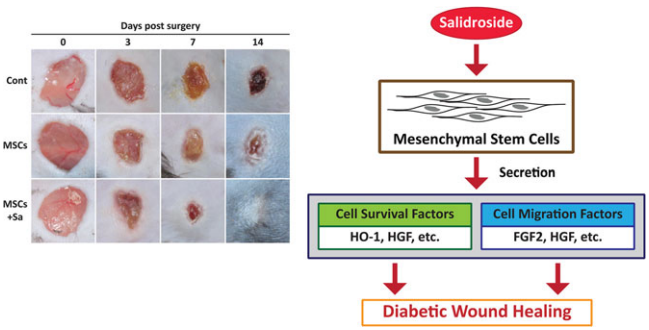
Small Molecule Pretreatment Boosts Mesenchymal Stem Cell-Mediated Diabetic Wound Healing



Inadequate levels of survival and low migrational potential after transplantation have limited the application of MSCs as a means to promote wound healing in diabetic patients and prevent the risk of amputation linked to progression to chronic wound healing [14]. Researchers led by Vivi Kasim and Shourong Wu (Chongqing University, PR China) knew from their previous studies that the small molecule salidroside possessed cytoprotective effects and boosted paracrine function of skeletal muscle cells in diabetic mice [15, 16] and so sought to test the impact of salidroside on MSCs. In their new *Stem Cells Translational Medicine* article [10], Ariyanti et al. discovered that pretreatment of MSCs with salidroside reduced levels of intracellular reactive oxygen species, inhibited apoptosis, and increased migratory potential. Furthermore, salidroside boosted the expression and secretion of crucial factors normally inhibited under hyperglycemic conditions, including heme oxygenase-1 (HO-1), fibroblast growth factor 2 (FGF2), and hepatocyte growth factor (HGF). Excitingly, the salidroside-mediated improvements to survival and migration potential of MSCs cultured in vitro under hyperglycemia conditions translated to increased levels of wound closure and re-epithelialization following the transplantation of salidroside pretreated MSC into full-thickness skin wounds in a murine model of diabetes. Overall, the authors believe that salidroside pretreatment of MSCs represents an effective means to improve diabetic wound healing and reduce the risk of limb amputation.

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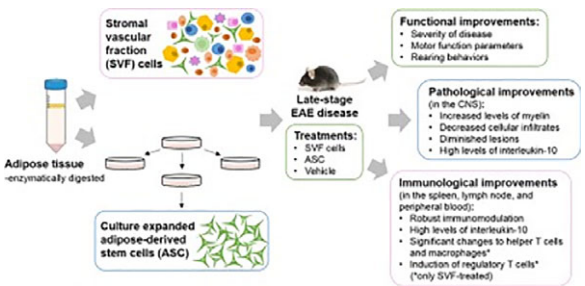
Related Articles

Stromal Vascular Fraction: An Effective Treatment Option for Late-Stage Multiple Sclerosis?



The common neurodegenerative disease multiple sclerosis involves an autoimmune response in the central nervous system that results in inflammation and demyelination leading to symptoms including tremors, fatigue, and the progressive loss of motor function [17]. Recently, researchers from the laboratory of Bruce A. Bunnell (Tulane University School of Medicine, New Orleans, Louisiana, USA) assessed the therapeutic potential of both SVF cell and ASC treatment in an experimental autoimmune encephalomyelitis murine model of human multiple sclerosis at a late-stage time point after the onset of neuropathology [6]. Encouragingly, Bowles et al. observed significant improvements in clinical scoring, behavior, motor function, and histopathologic analyses following intraperitoneal injection of SVF cells or ASCs at 20 days post-induction of disease. Treatment with SVF cells and ASCs prompted the modulation of inflammatory mediators in central nervous system tissues, a marked increase in myelin levels, and a decrease in cell infiltrates; however, SVF cells offered the greatest amelioration of disease through greater anti-inflammatory activity, thanks to the higher expression of the anti-inflammatory cytokine interleukin-10 and the added induction of regulatory T cells in the lymph nodes. These findings suggest that SVF cells represent the optimal therapeutic modality by preferentially altering peripheral immune cells resulting in improvements within the central nervous

system. Overall, the results from this *Stem Cells* study provide the first support for the therapeutic application of SVF cells in human multiple sclerosis patients.

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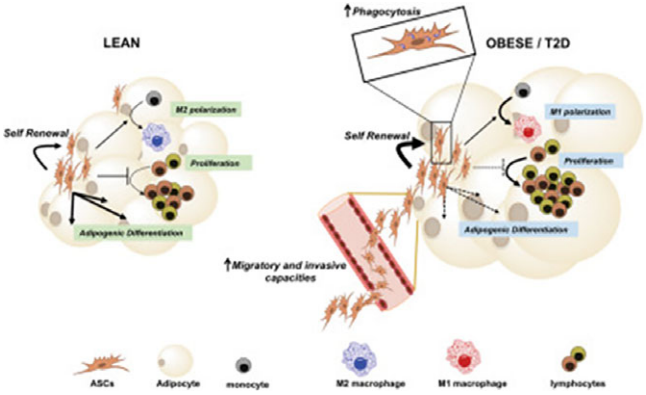
Obesity and Diabetes Impact the Immunomodulatory Capabilities of Human Adipose-Derived Mesenchymal Stem Cells



Microenvironmental alterations associated with metabolic disorders such as diabetes and obesity have the potential to negatively impact patient-derived hASCs and reduce their therapeutic capacity [18]. To explore this possibility, researchers led by Sonia Fernández-Veledo and Joan Vendrell (University Hospital of Tarragona Joan XXIII, Tarragona, Spain) compared hASCs derived from adipose tissue of obese or diabetic donors with those derived from age-matched lean donors. In this recent *Stem Cells* article [11], Serena et al. demonstrated that hASCs from obese and especially diabetic donors displayed increases in the expression and secretion of inflammatory markers, activation of the NLRP3 inflammasome, and improved migration, invasion, and phagocytosis when compared with lean hASCs. However, hASCs from obese and diabetic donors also exhibited diminished immunosuppressive function, leading to increased lymphocyte proliferation, reduced polarization of macrophages to the pro-regenerative/anti-inflammatory M2 phenotype, and decreased transforming growth factor beta 1 (TGFβ1) secretion. Encouragingly, treatment with an interleukin-1 receptor antagonist alongside TGFβ1 reversed the impairments observed in hASCs from obese and diabetic donors; therefore, the authors suggest this potent combination as a promising approach to boost hASC-based therapies in metabolic disorder patients. Overall, the authors posit that the hostile, inflammatory environment associated with metabolic disorders negatively influences the functionality of patient-derived stem cells, although their findings also highlight a possible approach to mitigate any negative impact and improve therapeutic outcomes.

DOI: 10.1002/stem.2429

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