A Role for ASCs in the Treatment of Type 1 Diabetes

Review of “Human adipose derived stromal/stem cells (hASCs) protect against STZ-induced hyperglycemia; analysis of hASC-derived paracrine effectors” from Stem Cells by Stuart P. Atkinson.

Stem cell-based therapies under investigation as a strategy for the treatment of Type 1 diabetes mellitus (T1DM) include the differentiation of cells towards engineered β cells [1] and the use of mesenchymal stem cells (MSCs) in the prevention or reversal of autoimmune and chemical-induced diabetes [2]. In diabetic non-obese diabetic (NOD) mice, adipose-derived MSCs (ASCs) have been shown to decrease hyperglycemia and insulitis through attenuation of the Th1 immune response and expansion of T regulatory lymphocytes [3]. Up till now, such a response has not been described for human ASCs. Now, in a study in Stem Cells, Carmella Evans-Molina from Indiana University School of Medicine, Indianapolis, USA, have studied a role for hASC-derived factors in a mouse model of streptozotocin (STZ)-induced hyperglycemia [4].

![Diagram](https://via.placeholder.com/150)

Initial work studied the effects of hASC injection 10 days after STZ-induced diabetes in NOD-SCID mice as outlined in the adjoining figure. hASC administration improved glucose tolerance and increased serum insulin levels after glucose injection up to day 25, in comparison to STZ/vehicle treated mice. hASC treatment also mediated a significant preservation of insulin staining and β cell...
mass, boosted β cell number, and also induced β cell proliferation, while hASC-conditioned medium (hASC-CM) was also able to support mouse islet survival after dissociation in vitro. Assessment of hASC-CM composition found high expression of various human growth factors (IL-6, IL-8, IL-12, eotaxin, IP10, MCP-1, VEGF, and TIMP-1) in the supernatant following the co-culture of hASCs with islet cells, while IP10, eotaxin, VEGF, and TIMP-1 became increased with time during islet co-culture, suggesting the presence of paracrine cross-talk between islets and hASCs. TIMP-1, previously described as being able to protect against cytokine and STZ-induced β cell death [5, 6], was one of the most enriched factors in co-culture experiments using mouse and human islet cells, and the authors found that TIMP-1 was induced by pro-inflammatory factors which are commonly associated with T1DM. Addition of TNF-α, IFN-γ, and IL-1β significantly increased TIMP-1 secretion from hASCs, and also led to increased insulin secretion from islets co-cultured with hASCs, while blocking TIMP-1 with a specific antibody reduced its protective effect. Finally, whilst TIMP1 expression was undetectable without hASC injection in STZ-treated NOD-SCID, the group found that the systemic injection of hASCs increased TIMP-1 expression to around 20ng/ml.
ASCs isolated from the stromal vascular fraction of fat have advantages over other mesenchymal stem cell sources; they are easy to isolate and expand and aid in the repair of damaged tissues [7], including islet graft survival and revascularization [8]. Through assessment of hASCs potential role in protecting against STZ-induced hyperglycemia and loss of β cell mass, the authors have uncovered a novel role for the matrix metalloproteinase inhibitor TIMP-1 in promoting β cell survival.

Independent of MMP activity, TIMP-1 can promote growth and inhibit apoptosis through various pathways, including P13K and PKA [9] and, furthermore, TIMP-1 is able to provide β cell-specific pro-survival effects [5, 6, 10]. Whilst we require the further delineation of the mechanisms by which TIMP-1 mediates its effects, these findings may soon have direct relevance for T1DM therapeutics.

References
