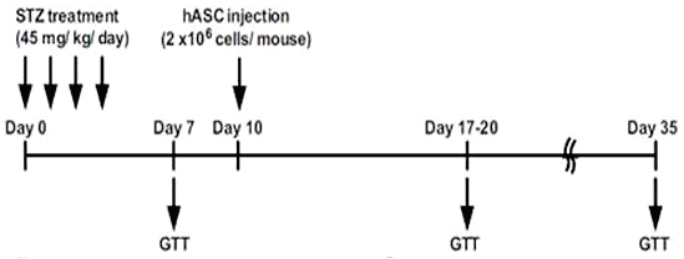
A Role for ASCs in the Treatment of Type 1 Diabetes

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].



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, ?8, ?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

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