Endocrinology Committee of FOGSI
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Endocrinology & Biomedical Potential of Cord Blood Cells

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Introduction

In recent years, human umbilical cord blood (HUCB) has emerged as an attractive therapy for various kinds of diseases including different types of malignancies, metabolic, autoimmune and endocrinological disorders.

It is a kind of cell-based therapy. Although at present, the clinical application of HUCB is limited to the fields of haematology and oncology, a rising number of studies show scope and hope for further application in the treatment of non-hematopoietic and endocrinological diseases.

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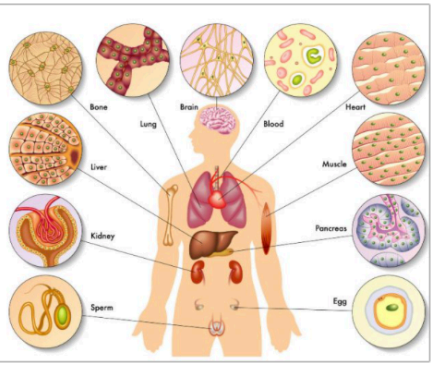
What Are Stem Cells?

Stem cells are undifferentiated cells with the capacity to both differentiate and multiply into the 200 cells types that form a human being.



Embryonic stem cell research will prolong life, improve life and give hope for life to millions of people.

(Jim Ramstad)

HUCB advantages (1)

- Simple collection procedure and hence does not need trained staff
- Large donor pool and hence available in abundance
- No donor attrition
- Easy accessibility
- HLA match not needed
- Low incidence of Graft versus Host reaction
- Easy to get same donor
- HLA match not needed
- No serious ethical dilemmas and hence minimal ethical concerns
- Valuable alternative to the use of other stem cell sources
- No risk to the donors in terms of pain or loss of tissue / organ
- Contains multiple types of stem cells that exhibit immune modulating potential and hold promise in remodelling of immune responses and thus one solution for many diseases.

HUCB disadvantages

- Available only at parturition and not repeatedly
- Unclear laws
- May not be of immediate use
- Uncertainty about future utilization
- Uncertainty about the storage conditions
- Cost involved over many years of storage

Type I Diabetes mellitus is a genetic – autoimmune- endocrinological -metabolic disorder.

Type 1 diabetes mellitus (T1DM) is a chronic auto immune disorder which leads to destruction and depletion of pancreatic islet β cells. Role of genetic susceptibility has been proved in this process. Several polymorphism genes play role in the risk of T1DM including those gene polymorphisms which lead to pancreatic β cell damage and

diabetes via environmental factors. Island cell auto antibodies (ICAs) are the first markers in the serum of patients with poly endocrine immunodeficiency and 85 percent of newly diagnosed diabetic patients are positive for ICAs .

So far, various drugs and immune regulators have been used to reduce the destruction of beta cell.

However, to date, no conventional intervention has successfully treated the disease (2).

Current approaches aiming to cure type 1diabetes (T1D) have made a negligible number of patients insulin-independent.

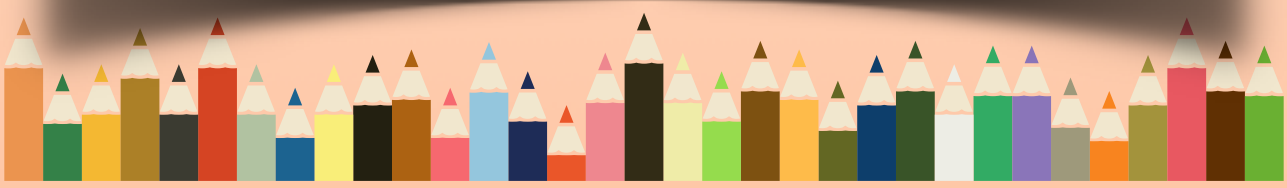
The optimal therapeutic method for T1DM should effectively

1. Control the autoimmunity
2. Restore immune homeostasis
3. Preserve residual β-cells
4. Reverse β-cell destruction, and
5. Protect the regenerated insulin-producing cells against re-attack of autoimmunity (2)..

Recently, reinfusion of autologous umbilical cord blood or immune cells from cord blood has been proposed as a novel therapy for T1DM.

HUCB derived MNC stem cells cure Type 1 DM

Generation of insulin-producing cells has been a major limitation for cellular replacement therapy in treatment of diabetes. HUCB stem cells have been successful in the treatment of type 1 diabetes. Some recent reports concerning pancreatic endocrine stem cells reported the potential for converting HUCB-derived stem cells into insulin-producing beta-cells. Differentiation of HUCB derived mononuclear cells to endocrine pancreatic lineage has been observed in some studies.



Thereby, Stem Cells (SCs) help to improve the treatment of T1DM. New hyperglycemic T1DM patients have been successfully reverted to normoglycemia with autologous hematopoietic SC transplantation

To understand the potential of HUCB derived MNCs in cell replacement therapy for diabetes, MNCs were isolated from 270 human umbilical cord blood samples. They were characterized by immunostaining and real time PCR and were studied for their ability to differentiate into insulin-producing cells. Freshly isolated MNCs as well as mesenchymal-like cells grown out by in vitro culture, expressed key pancreatic transcription factors: pdx1, ngn3, isl1, brn4 and pax6. However, after 32-fold expansion, MNCs show decreased abundance of pdx1 and ngn3, indicating that islet/pancreatic progenitors detected in freshly isolated MNCs die or are diluted during in vitro expansion. Therefore freshly isolated MNCs were transplanted in mice to check their ability to differentiate into insulin-producing cells. It was observed that, after 9 weeks of transplantation, about 25% grafts exhibited human insulin-producing cells. The number and abundance of pro- insulin transcript-containing cells also increased.

Further studies of this subset of pancreas-committed HUCB derived MNCs will provide us with an autologous source of “lineage-committed” progenitors for cell replacement therapy in diabetes.

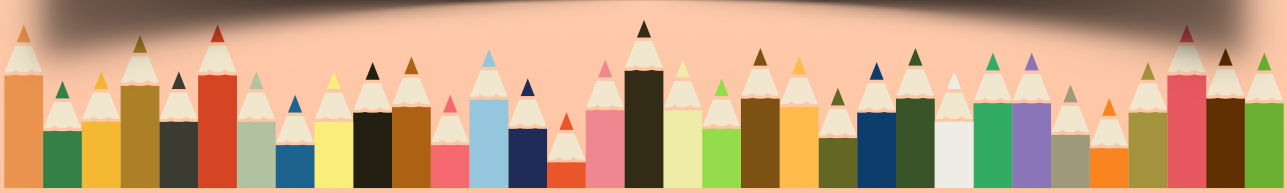
Patients with moderate type 1diabetes and some residual beta-cell function demonstrated improved fasting C-peptide levels (mean increase of 0.42 ng/mL at 12 weeks) and better 75 g oral glucose tolerance test results at 12 and 24 weeks after treatment. Those with severe type 1diabetes and no residual pancreatic islet beta – cell function also had improved fasting C-peptide levels at the end of 12 weeks.

Twelve weeks after treatment, the median daily dose of insulin was reduced by 38% in patients with moderate disease and some residual beta-cell function, and 25% in those with severe disease and no residual beta-cell function. The reduced daily insulin dose was maintained through 24 weeks in both sets of patients.

Additionally, HbA1c was reduced from 8.73% at baseline to 7.67% at 4 weeks after treatment (P=.036) and to 6.82% at 12 weeks after treatment (P=.019) in the moderate disease. Median HbA1c was reduced 1.68% in patients with severe disease. (4)

HUCB derived MNC stem cells not only cured Type 1 DM; they also improved metabolic control in type 1 diabetes.

According to a press release from Cord Blood America Inc, the stem cells have been used to re-instruct T cells so that the pancreas will begin producing insulin again, thereby reducing the amount of injected insulin needed. According to the press release, the treatment was successful in long-time diabetes patients believed to have no insulin-producing ability. (4)



MNCs reverse autoimmunity

Results from a phase 1 / phase 2, open-label clinical trial published in the January issue of BMC Medicine demonstrated that vivo cord blood stem cell treatment, reversed autoimmunity and promoted the regeneration of islet beta cells in patients with T1DM. This trial provides powerful evidence that exposing a patient's lymphocytes to cord blood stem cells can achieve the two essential outcomes required to cure T1DM: Reversal of autoimmunity and regeneration of islet beta cells. However, longer post-treatment observations with larger samples are needed.

Successful immune modulation by cord blood stem cell precursors and the resulting clinical improvement in patient status may have important implications for other autoimmune and inflammation-related diseases also.

Other Endocrine Disorders treatable by HUCB CELLS

Stem cell research can not only develop potential sources of cells for endocrine therapy, they can also be applied to endocrine diseases, including diabetes, infertility like poor ovarian reserve, and liver-associated metabolic disorders using isolated and defined stem cell precursors. (5)

Potential role of Human Cord Blood cells in Infertility

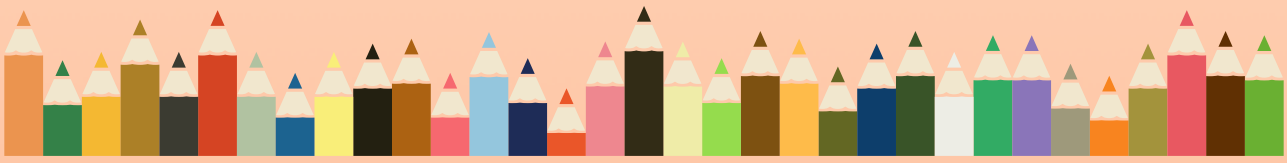
With the progress of regenerative medicine, mesenchymal stem cells (MSCs) from umbilical cord blood & stem cells have received attention as a way to restore ovarian function. Lot of research is underway in the potential use of MSC s in poor ovarian reserve & POF . MSC therapy secrete growth factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF) into culture medium , to reduce germ cell and stromal cell apoptosis, and to enhance folliculogenesis through improvements in the microenvironment. (6) MSCs could promote the recovery of ovarian function through inhibition of granulosa cell apoptosis and follicular atresia by upregulation of AMH (anti-Müllerian hormone) and FSH receptor expression in granulosa cells. Some studies have demonstrated detection of spermatogenesis in rats that were azoospermic and treated with MSCs. (7)

Calcitonin receptors and Bone resorption:

Cultured cord monocytes have role in parathyroid hormone production and are used in osteopenia. Calcitonin (CT) is a potent inhibitor of bone resorption and the presence of CT receptors was demonstrated on the new born cord monocytes.

Alliance of Mesenchymal stem Cells , Bone & Diabetes mellitus

Bone fragility has emerged as a new complication of Type 2 Diabetes (T2D). The pathophysiological link between bone fragility and diabetes is not completely understood. Several mechanisms may influence bone homeostasis by impairing the function of osteoblasts, osteoclasts, and osteocytes and/or changing the structural properties of the bone tissue. Notably, adipocytes and osteoblasts are derived from a common precursor, the mesenchymal stem cell (MSC), and the differentiation is modulated by several interacting pathways that may be disrupted in diabetes. Few studies have shown that mesenchymal stem cells from human amniotic fluid (huAFMSCs) and cord blood can differentiate into multiple lineages making them good



candidates for therapeutic purposes. The calcitonin receptor was seen to be expressed expressed in proliferating and osteo-differentiated huAFMSCs. Calcitonin triggered intracellular Ca(2+) and increases cAMP production. These data show that huAFMSCs represent a potential osteogenic model to study in-vitro cell responses to calcitonin (and other members of the calcitonin family). This leads the way to the opening of new lines of research as shown in these osteogenic model to study in-vitro cell responses to calcitonin . It hopes to add new insight both in cell therapies and in the pharmacological use of these molecules. (8)

To conclude

In stem cells Endocrinology, leading biologists discuss current research to modify stem cells, develop an endocrine-like cell, and use HUCB cells to treat autoimmune diseases, including endocrine-based autoimmune diseases. Topics of interest include a review of all stem cell subtypes and their characteristics, approaches to promoting endocrine development from stem cells, and evidence for endocrine cell function from stem cells.

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