STEM CELLS ENGINEERED WITH LENTIVIRUS EXPRESSING HUMAN FIX FOR THE TREATMENT OF HEMOPHILIA B

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INTRODUCTION.

Hemophilia B is an X-linked inherited disease caused by a deficiency in factor IX, a key protein of the coagulation cascade [1]. Patients suffering from hemophilia B are unable to generate a clot following injury, and thus bleed excessively following trauma. Furthermore, severe hemophiliacs are at risk for spontaneous bleeding, which are life-threatening in the event of intracranial bleeds. Current treatment for hemophilia involves regular infusions of either plasma derived or recombinant FIX, at very high cost ($100,000 per patient/year). The aim of this study was to investigate an alternative treatment combining cellular and biomaterial therapy. Human mesenchymal stem cells (hMSC) have increasingly been investigated for cellular therapies due to their immunomodulatory properties and differentiation potential [2]. Enclosure of cells in alginate microcapsules offers immunoprotection to the cells and the added benefit of potential retrievability, enhancing the strategy's safety.

METHODOLOGY.

We have optimized biomaterials for the encapsulation for MSCs that can support high levels of FIX secretion by MSCs modified to secrete therapeutic end [3]. Umbilical cord blood (CB)-derived MSCs obtained from healthy human donors were transduced with a lentiviral plasmid and lentiviral particles expressing the human FIX gene. The total FIX protein expression was quantified by ELISA, and the FIX activity by aPTT, respectively.

RESULTS.

In vitro FIX expression levels from the lentivirally modified CB MSCs was very high, and exceeded 3μg/mL for 10^6 cells in a 24-hour period. Genetically engineered cells were able to differentiate into adipocytes, chondrocytes and osteoblasts. Encapsulated MSCs were injected into the intraperitoneal cavity of immune-deficient mice. Circulating levels of human FIX protein in selected treated mice were detected. Thus, lentiviral modification of human CB MSCs allows its differentiation and results in the expression of very high levels of FIX. MSCs encapsulated in alginate microcapsules and implanted in mice lead to the expression of therapeutic levels of FIX.

CONCLUSION.

The study demonstrates the potential of a safe cell-biomaterial therapy for the treatment of hemophilia B.

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