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Telomerase-immortalized human mesenchymal stem cells (hMSCTERT) can be directed towards an endocrine differentiation pathway with insulin production

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Introduction:

Adult stem cells are investigated as alternative source for beta-cell replacement therapy. So far, no consistent differentiation capacity for insulin producing cells has been shown in human bone marrow-derived mesenchymal stem cells (hMSC). Here we investigated the ability of hMSC-TERT cell line to differentiate into insulin-producing cells under regulation of hNgn3 and hPdx-1.

Materials & Methods:

hMSC-Tert endocrine progenitor potential was analysed. Subsequently, stably overexpressing hNgn3 and/or hPDX-1 cell lines were generated (hMSC-TN, hMSC-TP and hMSC-TN/P). Islet gene regulation and protein synthesis were analysed by RT-PCR, Western Blotting, reporter gene assays and immunocytochemistry. Insulin content and secretion were evaluated by ELISA.

Results:

hMSC-Tert expressed progenitor cell markers, nestin and c-met and displayed pancreatic endocrine gene expression under specific culture conditions. Generated cell lines highly overexpressed the ectopic genes along with regulation of multiple islet genes, including insulin. In hMSC-Tert, Ngn3 induced expression of endogenous Pdx-1. hMSC-TP revealed direct activation of insulin gene. Coexpression of Ngn3 and Pdx-1 did not show synergistic effect on insulin expression efficiency. Insulin was expressed, produced and stored under regulation of hNgn3 and/or Pdx-1. However, no glucose dependent insulin secretion was observed in these cells.

Conclusions:

In a human system of MSCs: introduction of key endocrine transcription factors is able to induce differentiation towards insulin-producing phenotypes; hNgn3 is able to trigger pancreatic endocrine differentiation cascade, lying upstream of Pdx-1; higher endocrine maturation must be achieved, in order to obtain functional hMSC that are suitable to the cell-based therapy of type1 diabetes.