THREE-DIMENSIONAL ISLET-CELL STRUCTURES AS A NEW SOURCE FOR CELL-BASED DIABETES THERAPY

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Islet transplantation is an option for type I diabetes treatment, however, it is still limited by the scarcity of cadaveric donors. *In vitro* expansion of ß-cells is an attractive alternative to increase donor tissue. Recent studies suggest that these cells may be expanded through a process called epithelial-mesenchymal transition (EMT). The purpose of this study was to investigate whether ß-cell function agonists (growth factors, extracellular matrix elements) could regulate differentiation of islet-derived mesenchymal monolayers into insulin-producing cells during islet-cell cluster (ICC) formation. Fibroblast-like cell monolayers, derived from adult human islets, were induced to form ICCs and cultured for 4-6 days in differentiation medium +/- ß-cell agonists. Under control conditions, clusterization increased the cumulative glucose-induced peptide-C/insulin secretion ($p<0.01$). Immunohistochemistry and mRNA measurements demonstrated that islet-cell clusterization restored the epithelial beta cell phenotype. Subsequently, cultivation of ICCs with HGF/EGF, prolactin, FGF, retinoic acid, exendin-1/nicotinamide, activin-1, BMP and laminin had varying effects on the expression of transcription factors and pancreatic endocrine cell markers, when compared with control conditions. Intra-peritoneal implantation of control ICCs reverted glycemic levels of diabetic NUDE mice, when compared with untreated diabetic mice. Further *in vivo* experiments allow us to conclude that *ex-vivo* expansion of fibroblast-like cells and clusterization constitute an appropriate alternative tool for cell-based diabetes therapy. FAPESP, FINEP and CNPq.