GLUCAGON LIKE PEPTIDE-1 PROMOTES DIFFERENTIATION OF INSULIN-PRODUCING CELLS FROM MOUSE EMBRYONIC STEM CELLS

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Embryonic stem (ES) cells have the ability to proliferate while remaining in an undifferentiated state, thus providing a potentially unlimited source of cells for medical/scientific purposes. ES cells are pluripotent, developing into all cell lineages, ecto-, meso- and endoderm. Endodermal cells represent a source of pancreatic stem cells that can develop into insulin-producing cells. Glucagon-like peptide-1 (GLP-1), a gut hormone, has been demonstrated to induce the differentiation of β cells from ductal progenitor cells in both adult and fetal pancreas. The aim of this study was to convert mouse ES cells into insulin-producing cells and improve the efficiency of such conversion by adding GLP-1. Mouse ES cells were cultured in 5 stages by a modification of a method previously described (*Science 2001; 292: 1389-94*) - stage 1: expansion of undifferentiated mES cells with leukemia inhibitory factor; stage 2: generation of embryoid bodies; stage 3: selection of progenitor cells in a defined medium supplemented with ITSFn (insulin, transferrin, selenium and fibronectin); stage 4: expansion of progenitor cells by addition of basic fibroblast growth factor (bFGF); stage 5 differentiation into insulin-producing cells by removing bFGF and adding nicotinamide or nicotimide plus GLP-1. Cell development was characterized at each stage by gene expression. Oct-4, a marker of undifferentiated ES cells, was downregulated at the late stages of development and was absent at stage 5. Insulin and glucokinase, markers of ß cells, were present at stage 5. Glucose transporter 2 (GLUT2) was present from stage 3; levels were enhanced in stage 5, especially in the presence of GLP-1 100 nM. Addition of GLP-1 in addition to nicotinamide 10 mM at stage 5 resulted in a 50% increase in insulin content compared with nicotinamide alone. Insulin secretion was enhanced 6-fold when exposed to 20 mM glucose. We conclude that it is possible to convert mouse ES cells into glucose-responsive insulin producing cells by varying the culture conditions. GLP-1 enhances the differentiation.

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