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EXPANSION OF PANCREATIC PROGENITORS DERIVED FROM HUMAN PLURIPOTENT STEM CELLS UNDER GMP-COMPLIANT CONDITIONS

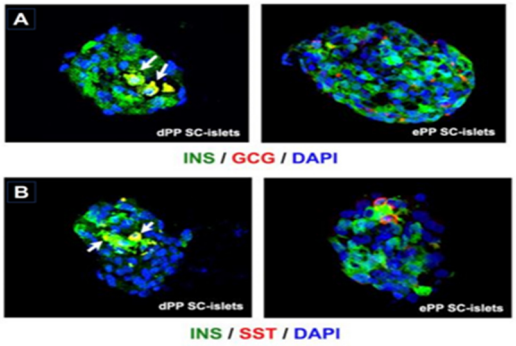
Keywords: hPS cells, pancreas progenitors, PDX1⁺/SOX9⁺/NKX6.1⁺ cells, GMP-compliant process, unlimited expansion, cryopreservation

INVENTION NOVELTY

While differentiation of human pluripotent stem (hPS) cells into pancreatic islets could provide an unlimited source of β-cells for transplantation and personalized medicine, numerous obstacles remain. These include incomplete conversion of hPS cells into endocrine cells, limited maturation of the resulting β-cells, and the requirement of large numbers of cells for a single transplantation. Elucidation of the mechanisms that maintain the self-renewal of pure pancreatic progenitors (PP) while inhibiting their differentiation would allow the establishment of expandable populations of pancreatic progenitors. The inventors found that the combined stimulation of specific mitogenic pathways, suppression, and inhibition of specific signaling pathways enabled a tremendous expansion of PP cells over many passages and under GMP-compliant conditions.

VALUE PROPOSITION

The unlimited expansion of PP cells is applicable to different hPS cell lines and presents several advantages. It reduces the number of differentiation procedures, thus eliminating a source of variability. It even allows the selection of the most optimally differentiated PP cell population for subsequent expansion and storage. The novel findings will enable the establishment of large banks of PP cells derived under GMP conditions from diverse hPS cell lines. This will also streamline the generation of homogeneous islet-like clusters (SC-islets) for further development of diabetes research, personalized medicine, and cell therapies.



IF analysis of SC-islets derived from p0 PP cells (dPP) or after 10 passages expansion (ePP) for insulin (INS), glucagon (GCG) and somatostatin (SST) expression (Source: A. Gavalas, Helmholtz Munich/TUD).

TECHNOLOGY DESCRIPTION

A hypothesis-driven iterative process has been used to define conditions that allow robust, unlimited expansion of hPS cell-derived PP cells. Expansion relies on a combination of specific mitogenic signals, suppression of retinoic acid signaling and selective inhibition of the TGFβ and Wnt signaling pathways. The chemically defined expansion conditions are GMP-compliant and enable the robust, reproducible and almost unlimited expansion, as well as cryopreservation, of PP cells derived from diverse hPS cell lines with very similar growth kinetics. These conditions significantly enrich the numbers of PDX1⁺/SOX9⁺/NKX6.1⁺ PP cells up to 90%, suggesting that they will be advantageous for hPS cell lines that may differentiate less efficiently into PP cells. Expanded PP cells differentiated with similar efficiency to non-expanded cells into SC-islet clusters that contain functional β-cells.

COMMERCIAL OPPORTUNITY

The technology is available for co-development as well as for licensing.

DEVELOPMENT STATUS

The method has been advanced to limit the appearance of alternative gut fate. Expanded PP cells are used to generate clusters SC-islets to be included in macroencapsulation devices as well as for the generation of vascularized SC-islets.

PATENT SITUATION

A European patent application has been filed in June 2023.

FURTHER READING

Jarc et al. (2023), eLife (reviewed preprint)

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