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3D Heterogeneous Islet Organoid Generation from Human Embryonic Stem Cells using a Novel Engineered Hydrogel Platform

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Abstract

Organoids, which exhibit spontaneous organ specific organization, function, and multi-cellular complexity, are in essence the *in vitro* reproduction of specific *in vivo* organ systems. Recent work has demonstrated human pluripotent stem cells (hPSCs) as a viable regenerative cell source for tissue-specific organoid engineering. This is especially relevant for engineering islet organoids, due to the recent advances in generating functional beta-like cells from human pluripotent stem cells. In this study, we report specific engineering of regenerative islet organoids of precise size and cellular heterogeneity, using a novel hydrogel system, Amikagel. Amikagel facilitated controlled and spontaneous aggregation of human embryonic stem cell derived pancreatic progenitor cells (hESC-PP) into robust homogeneous spheroids. This platform further allowed fine control over the integration of multiple cell populations to produce heterogeneous spheroids, which is a necessity for complex organoid engineering. Amikagel induced hESC-PP spheroid formation enhanced pancreatic islet-specific Pdx-1 and NKX6.1 gene and protein expression, while also increasing the percentage of committed population. hESC-PP spheroids were further induced towards mature beta-like cells which demonstrated increased Beta-cell specific INS1 gene and C-peptide protein expression along with functional insulin production in response to *in vitro* glucose challenge. Further integration of hESC-PP with biologically relevant supporting endothelial cells resulted in multicellular organoids which demonstrated spontaneous maturation towards islet-specific INS1 gene and C-peptide protein expression along with a significantly developed extracellular matrix support system. These findings establish Amikagel – facilitated platform ideal for islet organoid engineering.

Keyword: islet; human embryonic stem cells; organoid; hydrogel; aggregation; three dimensional

1. Introduction

Degenerative diseases and end-stage organ failure can be effectively treated by transplantation of donor organs. However, a critical shortage of donor tissue has ignited the search for alternate organ and tissue sources including from human pluripotent stem cell (hPSC) derived tissues. A synergistic goal is to develop model organs from hPSCs for drug screening and toxicity testing. A critical challenge to both these goals is to determine robust means of replicating the organ function, multicellular complexity, and three dimensional (3D) cellular organization in an *in-vitro* setting, which is the goal of current research on organoid generation[1]. An initial success in organoid engineering can be considered to be embryoid bodies derived from murine and human embryonic stem cells (ESC) that demonstrate both germ layer commitment and spatial patterning reminiscent of developing embryos [1]. More recently, organ-specific organoids, have been derived from both mouse and human pluripotent stem cells (PSC) [2-5]. hPSCs