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“Expansion and Directed Differentiation of Human Pluripotent Stem Cell in Scalable Stirred-suspension Bioreactors”

Stem cells with their ability for multilineage differentiation and their extensive proliferative capacity can serve as an inexhaustible source of cellular material for therapies. Realization of the therapeutic potential of stem cells will require the development of scalable bioprocesses for their expansion and directed commitment to specific cell types in clinically relevant quantities. For this purpose, we explored the use of stirred suspension bioreactors, which have a simple design and provide flexibility for the cultivation of cells as aggregates or on suitable surfaces. We have successfully propagated human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) on microcarriers in a stirred suspension bioreactor. The effects of agitation rate and hESC seeding density on the culture outcome were investigated and appropriate operating conditions were established. Analysis by quantitative RT-PCR, immunocytochemistry and flow cytometry showed that the hESCs cultured in the bioreactor retained the expression of pluripotency markers. Subsequent to their expansion, hESCs on microcarriers were directed towards the definitive endoderm (DE) and primitive gut tube cells, which are precursors of pancreatic cells. Differentiating hESCs transitioned through a mesendoderm state and the efficiency of hESC-to-DE conversion was higher in the bioreactor than in static cultures. Current efforts focus on extending the differentiation of hESC-derived cells towards a pancreatic islet cell fate. Parallel work on directing the differentiation of human pluripotent cells to cardiac progeny will also be discussed. Our findings support the use of bioreactors for the scalable production of hESCs, hiPSCs and their progeny for cell therapies.