Modeling of an Oxygenation-Aided 3D Culture for Functional Beta-Cell Expansion

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Abstract

Introduction

Diabetes has become a growing medical problem worldwide. The disease affects millions of people and its prevalence is increasing by 2-5% per year. The number of patients with diabetes is predicted to rise to 552 million people by the year 2030. Diabetes is related to the inability to regulate blood glucose levels because of problems with the secretion of glucose-responsive insulin. A promising method for the control of diabetes is the replacement of pancreatic beta-cell mass. Unfortunately, there is a shortage of the donor tissue that is needed to replace beta-cell mass. A potential source of the tissue needed for beta-cell mass replacement is the production of clinical relevant beta-cells in vitro. However, currently there is no efficient way of producing beta-cells in vitro. The proliferation rate of beta-cells is very slow, and elevating the proliferation rate can result in loss of proper cell function. As a matter of fact, normoxic or hyperoxic conditions are required to increase beta-cell viability. Furthermore, beta-cells consume large amounts of oxygen during insulin secretion. We observed that beta-cells benefit from being cultured in a 3D environment. However, a lack of oxygen supply inside a three-dimensional (3D) scaffold causes beta-cell death. The goal of this work is to evaluate the utility of an oxygenation-aided 3D beta-cell culture system for producing biologically functional beta-cells by using a mathematical modeling approach.

Use of COMSOL Multiphysics®

In this study, we established a mathematical model to calculate the oxygen-release capacity of an oxygenator that is made of hydrogen peroxide (H_2O_2) encapsulated in polydimethlysiloxane (PDMS). We then developed a simulation model to estimate the spatiotemporal changes in oxygen concentrations inside an oxygenator embedded beta-cell-collagen scaffold culture using COMSOL Multiphysics® software. Furthermore, the software was used to model cell culture experiments designed to provide the cells with sufficient oxygen, which would prevent hypoxic conditions deep inside a 3D scaffold.

Results

We fabricated an oxygen-releasing biomaterial made of H_2O_2 encapsulated in PDMS. We determined the net oxygen release from the biomaterial in a PBS buffer solution after completely removing all the air from the testing tube and the solution. Our experiments demonstrate that oxygen is gradually released from the oxygenator for at least two weeks. Using the diffusion features in COMSOL we were able to estimate the distribution of oxygen in a culture system. Increasing the availability of oxygen by using the oxygenator can enhance proper beta-cell function. Because of this the oxygenator-cell culture system was modeled for optimization of islet beta-cell production using COMSOL Chemical Reaction Engineering Module for simulations.

Conclusion

The mathematical model developed herein is employed to design an optimized 3D culture system for functional beta-cell expansion. The model also helps in designing the oxygenator to demonstrate the utility of oxygenation-aided 3D cell culture system for producing various therapeutically relevant cells.