AGGREGATION KINETICS OF HUMAN MESENCHYMAL STEM CELLS UNDER WAVE MOTION

Teng Ma,Department of Chemical and Biomedical Engineering, Florida State University
teng@eng.fsu.edu
Ang-Chen Tsai, Department of Chemical and Biomedical Engineering, Florida State University
Yijun Liu, Department of Chemical and Biomedical Engineering, Florida State University
Ravindran Chella, Department of Chemical and Biomedical Engineering, Florida State University

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Human mesenchymal stem cells (hMSCs) are a primary candidate in cell therapy and regenerative medicine to treat a wide range of diseases in clinical trials. Recent studies showed that hMSC have innate ability to self-assemble into three-dimensional (3D) aggregates that enhances their therapeutic functions with augmented multi-lineage differentiation potential, migration ability, secretion of anti-inflammatory and angiogenic factors, and resistance to ischemic conditions post-transplantation. To date, many laboratory methods have been developed for hMSC aggregation, including hanging drops, centrifugation with microfabricated surface, cell suspension on a low attachment surface, thermal lifting, and microfluidic technologies. However, these methods have limited scalability and/or poor control in aggregate size, and cannot meet the required production in clinical trials.

The objective of current study is to investigate the conditions for the scalable production of hMSC aggregates in non-adherent plates under wave motion. The repeated back and forth wave motion induced by rocking provides mixing of bulk medium under low shear stress that facilitates cell-cell collisions and subsequent aggregation. Our results showed that aggregate size can be controlled by adjusting the combination of rocking angle (3˚, 6˚, and 9˚) and rocking speed (10, 15, and 20 rpm). To quantify the impact of fluid shear stress on aggregation kinetics, simulation of shear stress distribution by COMSOL Multiphysics® showed a time-dependent oscillatory function under different rocking condition. In addition, an inverse correlation between aggregate size and maximum shear stress was observed and that both can be regressed by a two-variable linear regression of rocking angle and rocking speed. In the regression, the coefficient of rocking angle is much higher than that of rocking speed, revealing that rocking angle has a more significant effect than rocking speed on both aggregate size and shear stress. In addition to fluid shear stress, the effects of cell binding molecules, the frequency of cell-cell collision, and the extension of cultivation time on aggregate size distribution were also investigated. Analysis of the therapeutic functional supported that hMSCs derived from engineered aggregates in the wave motion system have enhanced their therapeutic properties compared to those from monolayer culture.