SCALABLE IPSC-BASED PLATFORM TO PRODUCE TISSUE-SPECIFIC EXTRACELLULAR VESICLES

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Key Words: Extracellular Vesicles; Hydrogels; Mesenchymal Stem Cells; Induced Pluripotent Stem Cells; Scale Up

Extracellular vesicles (EVs) contain a heterogeneous cargo of proteins, nucleic acids, and metabolites derived from their cells of origin. Mesenchymal stem cells (MSCs) naturally produce therapeutically relevant EVs that have potential to treat many diseases such as graft versus host disease, rheumatoid arthritis, and Crohn's disease. However, primary MSCs vary extensively between different tissues and donors, have limited replicative potential, and are typically grown in 2D monolayers. Collecting sufficient EVs for a therapeutic treatment is therefore resource-, cost-, and labor-intensive. MSCs differentiated from induced pluripotent stem cells (iPSCs) can provide a reproducible non-invasive source of MSCs that avoids obstacles due to donor-to-donor variability and scarcity of human tissue. This study aims to develop a scalable platform to produce EVs from tissue-specific cell types, using iPSC-derived MSCs as a proof of concept. We are optimizing EV production by adapting MSCs into a pseudo-suspension culture using GelMA-Cad hydrogel microspheres. GelMA-Cad is a gelatin with N-cadherin attached to it to support cell growth by mimic cell adhesion to the extracellular matrix. We have shown that GelMA-Cad supports cell growth in both 2D and 3D culture. By seeding MSCs into hydrogel microspheres, adherent cells can be grown in a pseudo-suspension culture allowing for increased cell density and EV production per volume of culture. Consistently sized microspheres are formed using a custom microfluidic device to support efficient cell growth and EV production. MSC growth and EV production has been confirmed in GelMA-Cad layers, and EV yield and particles size was compared to traditional 2D adherent cultures. Here, we found that MSCs seeded in GelMA-Cad produced a similar number of small EVs but produced a greater number of large EVs than MSCs grown in a 2D adherent culture. A key objective of this study is to determine if the production of EVs from MSCs embedded in GelMA-Cad leads to higher volumetric productivity and greater reproducibility than adherent cultures. Future work will expand this platform to other iPSC-derived cell types beyond MSCs.