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Angiogenic Effect of Amniotic Mesenchymal Stem Cell Spheroid-Derived Secretome as a Cell-Free Therapy in Cardiac Repair

Ida Derish, McGill University

A myocardial infarction (MI) occurs when one of the coronary arteries of the heart is obstructed and induces necrosis and maladaptive cardiac remodeling. The native cardiomyocytes and cardiac vascular cells are unable to efficiently proliferate and repair the heart tissue after MI. Inevitably, patients suffering from MI develop heart failure, one of the leading causes of death worldwide with no curative therapies available. Many studies have investigated the use of stem cells for cardiac tissue regeneration, but dozens of clinical trials yielded low engraftment of injected cells and unreliable cardiomyocyte differentiation. More recently, the stem cell secretome has been shown to have regenerative properties. The secretome contains soluble factors such as proteins, microRNA, long-noncoding RNA involved in cell proliferation, angiogenesis and anti-apoptosis, while reducing tumorigenicity. Some of these factors are considered components in paracrine communication-mediated tissue regeneration.

In this study, we examined a novel cell-free strategy utilizing amniotic stromal mesenchymal stem cell (ASMC) secretome, which mitigates the limitations of stem cell therapy while improving cardiac function. We hypothesized that the secretions derived from 3-dimensional (3D) spheroid ASMC cultures will increase the metabolic activity within human cardiac microvascular endothelial cell (HCEC) cultures as well as blood vessel formation, which is crucial to proper cardiac functioning.

Expression of prominent cardiac markers connexin 43 (CXN43), sarcoendoplasmic reticulum Ca2+ ATPase (SERCA2), GATA4 and Troponin T was first confirmed in the spheroid ASMC cultures with immunocytochemistry. We found a significant increase of metabolic activity in HCECs treated with 3D cell culture-derived secretome, compared to untreated HCEC controls ($P < 0.0001$), while no significant difference was detected between controls and HCECs treated with 2D cell culture-derived secretome. We also found significantly elevated protein expression of cardiac markers CXN43, SERCA2 and Troponin T ($P < 0.05$) in 3D ASMC cultures compared to 2D cultures. We finally examined the mRNA expression of cardiac progenitor cell marker ISL1, which was significantly elevated in ASMC spheroids ($P < 0.01$), suggesting their higher cardiogenic potential.

This data suggests that the ASMC spheroids are an advantageous source of secretome with angiogenic properties, which can increase metabolic activity in HCECs to a higher degree than the 2D ASMC culture-derived secretome. We provide the groundwork for the use of this novel and readily harvestable therapeutic agent for cardiovascular repair to improve patient outcomes and recuperate healthy heart function. Future studies will investigate the effects of the spheroid-derived secretome on tube formation and cardiac function in an animal MI model.