지역혁신 선도연구센터(RLRC)
4차년도 정기세미나

❍ **일정** : 2023년 09월 27일(수), 16:30~17:30

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❍ **주제** : IGFBP2 Medicates Human iPCS-Cardiomyocyte Proliferation in a Cellular Contact-Depedent Manner

❍ **Abstract** :

Inducing cardiomyocyte proliferation in situ is an attractive approach for achieving cardiac regeneration after myocardial injury. However, numerous inhibitory mechanisms are present in mature cardiomyocytes to silence the ability of pro-proliferative signals to expand cardiomyocytes. We hypothesized that cell-cell contact exerts a major suppressive effect on cardiomyocyte proliferation. This study aims to uncover the molecular mechanisms underlying cell contact-mediated inhibition of cardiomyocyte proliferation and leverage such mechanism to enable a sustained proliferation of cardiomyocytes despite the presence of cell-cell contact. Using human iPSC-derived cardiomyocytes (iPSC-CMs) as a model system we found that the proliferative capacity of iPSC-CMs is initially increased proportional to cell density up to the point when cells formed intercellular contacts. With a greater cell density increase, we found that cell-cell contact exerts a strong inhibitory effect on iPSC-CM proliferation. scRNAseq analysis and cellular phenotyping revealed that cell-cell contact is accompanied by adherens junction formation, enhanced sarcomere organization, and increased contractility. Disruption of adherens junction or sarcomere assembly via siRNA-mediated knockdown of N-cadherin or a-actinin, respectively, result in increased cell cycle activity of iPSC-CMs. Furthermore, disruption of cell-cell contact enhanced nuclear translocation of β-catenin and LEF/TCF transcriptional activity that contributed to iPSC-CM proliferation. Additional screening for secreted growth factor in conditioned media from sparsely-plated hiPSC-CMs revealed that IGFBP2 is sufficient to drive proliferation of iPSC-CMs in the presence of cell-cell contact in 3D constructs. The presence of cell-cell contact inhibits iPSC-CM proliferation via adheren junction formation, sarcomeric assembly, and decreased IGFBP2 secretion. Exogenous supplementation of IGFBP2 can overcome cell contact-mediated inhibition of hiPSC-CM proliferation and enhance 3D cardiac tissue generation for disease modeling, drug screening, and regenerative therapies.