Cross-communication between fibroblasts and cardiomyocytes

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The myocardium is composed of various cell types including cardiomyocytes, fibroblasts, endothelial cells, and leukocytes. Although cardiomyocytes count for up to 85% of a heart's volume, the actual cell number of cardiomyocytes account for just 30–40% of all cardiac cells. Non-cardiomyocytes constitute 60–70% of a cardiac cell and approximately 90% of these non-cardiomyocytes represent fibroblasts (1,2). Previously, the function and viability of cardiomyocytes have been treated as a primary research interest area, while fibrosis was considered as a secondary effect from the changes in cardiomyocytes. However, recent studies have suggested an influence of fibroblasts over cardiomyocytes (3,4).

To this effect, as noted by Dr. Franco, our group showed evidence of how fibroblasts affect cardiomyocytes' function (2). Our group reported that fibroblasts express miR-146a and secrete it through the extracellular vesicle (EV)-mediated mechanism. The EVs secreted from fibroblasts are taken up into cardiomyocytes, and miR-146a, the content of the EVs, suppresses small ubiquitin-like modifier 1 (SUMO1) expression, consequently reducing sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) activities in cardiomyocytes. Various studies have suggested that SUMOylation plays a crucial role in cardiac physiology and pathology. The genetic animal models manipulated SUMOylation machinery have shown the significance of SUMOylation in cardiac development and function (5,6).

Our group has specifically found that SUMO1 positively regulates SERCA2a activity and SUMO1 gene-transfer restores cardiac dysfunction in the setting of heart failure (HF) (7-9). Despite the critical role of SUMO1 in HF, the regulatory mechanisms underlying SUMO1 expression were not understood. Notably, our recent study is the first one to report a specific mechanism that regulates SUMO1 expression through intercellular communication.

Intriguingly, our group found that the SUMO1 expression in cardiomyocytes is regulated by miR-146a secreted from fibroblasts in the setting of HF, which raises a question why fibroblasts secrete miR-146a to harm cardiomyocytes in HF. In order to investigate this question, our group needs to study how fibroblasts interact with cardiomyocytes, specifically by analyzing the contents of the EVs from fibroblast during HF along with its implications. If the implications hint toward cell death or cardiomyocytes' dysfunction, the potential therapeutic approach will be consisted of a strategy that hijacks the fibroblast-derived EVs. Unfortunately, such a technique to sort EVs into its origin is not currently available. Our group expects to understand the cross-communication between fibroblasts and cardiomyocytes as technology progresses in the near future.

Our group is also extending the study to determine the role of miR-146a in fibroblasts. Since this role has yet to be fully defined, we currently strive to investigate targets of miR-146a in fibroblasts and therefore elucidate target-associated signaling pathways. This will be particularly interesting to show the multiplicity of an identical microRNA function in different cardiac cell types. The evolution on the disease is complex in all its stages and the consequent impacts in patients go beyond a single gene or a single cell. Manipulations within a single microRNA may stimulate various cellular responses across all cell types. The integrated knowledge gathered in a variety of cell types allows for a more targeted simulation in patients. In this

context, our group believes that this study on miR-146a's role in fibroblasts may add to clinical insight.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Zhou P, Pu WT. Recounting Cardiac Cellular Composition. Circ Res 2016;118:368-70.
2. Oh JG, Watanabe S, Lee A, et al. miR-146a Suppresses SUMO1 Expression and Induces Cardiac Dysfunction in Maladaptive Hypertrophy. Circ Res 2018;123:673-85.
3. Jeong D, Lee MA, Li Y, et al. Matricellular Protein CCN5 Reverses Established Cardiac Fibrosis. J Am Coll Cardiol 2016;67:1556-68.
4. van Spreeuwel ACC, Bax NAM, van Nierop BJ, et al. Mimicking Cardiac Fibrosis in a Dish: Fibroblast Density Rather than Collagen Density Weakens Cardiomyocyte Function. J Cardiovasc Transl Res 2017;10:116-27.
5. Lee A, Oh JG, Gorski PA, et al. Post-translational Modifications in Heart Failure: Small Changes, Big Impact. Heart Lung Circ 2016;25:319-24.
6. Kim EY, Zhang Y, Ye B, et al. Involvement of activated SUMO-2 conjugation in cardiomyopathy. Biochim Biophys Acta 2015;1852:1388-99.
7. Kho C, Lee A, Jeong D, et al. SUMO1-dependent modulation of SERCA2a in heart failure. Nature 2011;477:601-5.
8. Tilemann L, Lee A, Ishikawa K, et al. SUMO-1 gene transfer improves cardiac function in a large-animal model of heart failure. Sci Transl Med 2013;5:211ra159.
9. Kho C, Lee A, Jeong D, et al. Small-molecule activation of SERCA2a SUMOylation for the treatment of heart failure. Nat Commun 2015;6:7229.