Editorial

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Cell–cell crosstalk in the heart

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Cardiovascular disease remains the top threat to human health. As the prevalence and mortality of cardiovascular diseases have been persistently increasing in China, the cardiovascular disease becomes the leading cause of death, accounting for nearly half of all deaths in China [1]. In order to improve the situation, many basic cardiovascular studies have been conducted and have obtained great achievement, which is fundamental to the future advance in clinical practice [2]. In the current issue, several excellent cardiovascular scientists summarize the advance of basic cardiovascular research from different perspectives, from particular critical molecules to cellular function and animal models, as well as the advanced technology. These reviews collaboratively bring us an overall vision of the frontiers and trends of cardiovascular research. Although focused on distinct areas, most of these reviews highlight the mechanism involving the interaction between different cells. The cell–cell crosstalk plays a fundamental role in the physiological and pathological progress in the heart and thus has received more and more attention from researchers. Recently much progress has been achieved in this area, which brings us a new view on the importance of cell–cell crosstalk in the heart.

How many cell types in hearts

Cardiomyocytes are the major cells that make up the myocardial tissue and they contribute to cardiac contraction to pump blood throughout the body. The injury or abnormality of cardiomyocytes is fundamental to the pathogenesis of many cardiac diseases, such as cell loss in myocardial infarction and hypertrophy during heart failure. Cardiac fibroblasts are the main interstitial cells that maintain the homeostasis of the extracellular matrix, while their dysregulation leads to excessive deposition of collagen and the resultant cardiac fibrosis, another type of pathologic remodeling in heart failure. Besides these two widely recognized cell types, the cells of coronary arteries, such as endothelial cells, are also investigated in the heart, especially for atherosclerosis and angiogenesis. Moreover, some other cells are especially investigated under specific pathologic conditions. For example, when considering cardiac inflammation, the infiltration of immune cells including macrophages and neutrophils has become a key indicator of the severity of inflammation. In addition to the recruitment from circulating immune cells, a tissue-resident population of macrophages has been shown to exist in the heart and may contribute to tissue repair [3].

Increasing cell types are investigated in cardiac research, one of them is the stem cell. Although the existence of adult cardiac stem cells is controversial, there are still other stem cells or progenitor cells in the heart. Gong et al. review the current advances in cardiac resident stem cells or progenitor cells and discuss their function during cardiac repairment [4]. Cardiac stem/progenitor cells are traditionally considered to be from the perivascular circulating system, but they are recently shown also located in the heart as resident cells, such as endothelial progenitor cells, smooth muscle progenitor cells, adipose-derived stem cells, pericytes, mesenchymal stem cells, and cardiosphere-derived cells. However, our understanding of the nature and specific functions of these cells remains limited.

Most of the basic cardiac research is based on the assumption that the cells within each cell type are homogeneous, or only investigates the subpopulation according to the expression of a single marker gene. The heterogeneity in the cells is often omitted.

The single-cell RNA-seq brings us a powerful tool to clarify the cell diversity in the heart. For example, less than 20% of fibroblast-enriched genes overlapped between different organs as revealed by single-cell RNA-seq analysis; and even within the same organ, the fibroblasts are heterogeneous with different lineage contributions in the heart [5]. The cell diversity in adult human hearts has been determined with single-cell RNA-seq and single-nucleus RNA-seq (the latter is for large cardiomyocytes), which highlights the heterogeneity of cardiomyocytes, pericytes, and fibroblasts in human hearts [6]. The multiple cell types

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and their heterogeneity indicate the complexity of the organ, and the interaction between cardiac cells may be more important than expected.

The crosstalk mechanism between cells

The intercellular crosstalk has been longly investigated in the heart, including indirect paracrine of cytokine and direct contact with adjacent cells or extracellular matrix. The cytokines are critical in the regulation of the heart; and the heart itself has been considered as a secretory organ to secret multiple cytokines, known as cardiokines [7]. With regard to the direct contact, cadherins, and connexins intercellular communication and mechanosensors such as integrins sense the signals from the change in the extracellular matrix. A vicious circle can be formed between cardiac fibroblasts and the extracellular matrix during cardiac fibrosis, as fibroblasts produce collagen resulting in increased stiffness of the extracellular matrix, which in return promote the transdifferentiation of fibroblasts [8].

Besides these classical interaction mechanisms, some new approaches of crosstalk have been investigated recently including exosomes and membrane nanotubes. Exosomes are small membrane vesicles that carry various cargos including proteins and non-coding RNAs. They can be released by various cells and enabled the long-distance delivery of signaling molecules. Wang et al. summarized the interaction between adipocytes and cardiomyocytes and highlighted the role of exosomes in the crosstalk [9]. They suggest adipocytes can release either cytoprotective exosomes or cytotoxic exosomes, which are transported to cardiomyocytes to induce protective or detrimental effects, respectively. Membrane nanotubes, also named tunneling nanotubes, are a recently recognized long and thin cellular structure that directly connected cells over a long distance; the structure allows for the transfer of various cargos between cells including calcium ion, lipid droplet, mitochondria, and inflammasomes [10]. The membrane nanotubes are investigated in many cells, including cardiomyocytes and cardiac fibroblasts, with cellular experiments, but the research on the *in vivo* function of membrane nanotubes is rather limited. Nevertheless, a recent study observed in mouse retina a nanotube-like structure connecting different pericytes, which plays a critical role in regulating neurovascular coupling [11]. As to the heart, although immunofluorescence suggests the existence of the structure in heart sections, the exact functions of membrane nanotubes in heart tissue remain to be elucidated.

Exosomes and membrane nanotubes enable the long-distance indirect and direct cell–cell crosstalk. Exosomes can mediate the intercellular interaction across organs and tissues; membrane nanotubes may help to form a direct connection network in the tissue. These new mechanisms broaden our understanding of the cell–cell crosstalk and can be a new focus for cardiac research.

Which cell is responsible under pathologic conditions

The multiple cell types with heterogeneity form the complex cell populations in the heart, while the intercellular crosstalk concordances these cells to perform the normal cardiac function. Whereas, when dysregulated, the crosstalk also aggravates the pathologic progression of cardiac diseases. During sympathetic stress, the inflammasome is activated in cardiomyocytes causing activation and release of interleukin-18, which initiate cardiac inflammation involving the crosstalk among cardiomyocytes, fibroblasts, and macrophages [12]. Interestingly, although myocardial ischemia/reperfusion also caused cardiac inflammation via inflammasome intercellular crosstalk, the inflammasome is activated in fibroblasts but not cardiomyocytes [13]. Thus, different cells may be responsible under different pathologic conditions, even though the results and mechanisms are similar.

Sympatho-adrenergic system plays a central role in cardiac regulation and overactivation of the system is a key pathologic condition to promote heart failure. The adrenergic signaling in heart failure is traditionally investigated in cardiomyocytes. Dr. Du comprehensively summarizes the recent research on sympatho-adrenergic system in heart failure [14]. One of the major recent advances for heart failure research is the role of β-adrenergic signaling in immune cells and fibroblasts in addition to cardiomyocytes. The signaling in these cells promotes cardiac inflammation and heart failure via cell–cell crosstalk. Therefore, even for the intensively investigated cardiac conditions, the possible involvement of new cell types and intercellular crosstalk remains to be further investigated.

Gene editing nucleases are used to produce genetically modified experimental animals and conditional knockout or overexpression of targeted genes in these animals has been widely used to evaluate their role in specific tissues or cells. Besides the usage in basic research, gene editing nuclease-based therapy is developed and is promising to treat many human diseases [15]. Considering the complex cell populations and cell–cell crosstalk in the heart, the

targeted cell needs to be carefully selected when testing the therapy for cardiac diseases. Collectively, Current studies have demonstrated the critical role of cell–cell crosstalk in the heart, but more work remains to be fulfilled to fully clarify its role and the underlying mechanism.

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