

Immunobiology Approach for Further Development of Precision Medicine in Heart Failure

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Heart failure is caused by a combination of genetic and non-genetic factors. A detailed understanding of how these factors contribute to cardiac phenotypes will lead to the development of precision medicine in heart failure. Genetic factors involved in cardiac dysfunction result in abnormal cardiac phenotypes such as dilated cardiomyopathy. Non-genetic factors such as pressure overload by hypertension or valvular disease induce transcriptional changes in cardiac cells. Therefore, comprehensive genetic analysis of patients with dilated cardiomyopathy and transcriptomic analysis of the heart from patients with heart failure may dissect the molecular pathology leading to precision medicine.

We have established a comprehensive genomic analysis pipeline to analyze mutations in all genes known to be causal for cardiomyopathy and found that titin (*TTN*) truncating mutations and lamin A/C (*LMNA*) mutations are major genomic factors for the development of dilated cardiomyopathy [1]. *TTN* truncating mutations are the most frequent cause of dilated cardiomyopathy and account for 15-25% of its cases [1,2]. The clinical phenotypes of *TTN* truncating mutations include low penetrance, relatively good prognosis, and a tendency for left ventricular reverse remodeling. In spite of the low penetrance of *TTN* truncating mutations, additional cardiac insults such as pregnancy, alcohol abuse, and chemotherapy might cause cardiac dysfunction [3-5]. Although cardiomyopathy patients with *TTN* truncating variants show severe left ventricular dysfunction at diagnosis, they tend to respond to appropriate medical therapy and their cardiac function improves drastically [1]. *LMNA* mutations are the second most frequent cause of dilated cardiomyopathy and account for 5-10% of its cases [1]. The clinical phenotypes of *LMNA* mutations include high penetrance, coexistence with a conduction system abnormality, poor prognosis, poor response to medical therapy, and frequent need for heart transplantation [1]. Due to the frequent coexistence of *LMNA* mutations with a conduction system abnormality, The European Society of Cardiology guidelines recommend the use of an implantable cardioverter defibrillator in patients with dilated cardiomyopathy and a confirmed disease-causing *LMNA* mutation in order to prevent sudden cardiac death [6].

We have also established a single-cardiomyocyte RNA-seq analysis pipeline to reveal the transcriptional signatures associated with cardiac phenotypes in mice and human [7]. Single-cardiomyocyte RNA-seq of heart failure model mice reconstructed a trajectory during cardiomyocyte remodeling and distinguished the molecular profiles of the adaptive and failing phenotypes during heart failure. Integrative analysis of single-cardiomyocyte morphology and transcriptome with the epigenome showed that mitochondrial gene expression was correlated with cellular hypertrophy and was linked with extracellular signal-regulated kinase 1/2 and nuclear respiratory factor 1/2 signaling transcriptional networks. Chronic pressure overload led to a bifurcation into adaptive and failing cardiomyocytes, and DNA damage-induced p53 signaling activation was necessary for the induction of failing cardiomyocytes, which were characteristic for repressed mitochondrial gene expression and morphological elongation.

Human single-cardiomyocyte analysis validated the conservation

of the pathogenic transcriptional signatures [7]. Cardiomyocytes from patients with heart failure had significant transcriptional heterogeneity and this heterogeneity could be explained by the expression of two gene modules, including DNA damage response genes and mitochondrial DNA genes. The expression levels of these two gene modules classified the pathogenesis of each patient and predicted their cardiac prognosis after medical and/or mechanical therapies. These findings elucidate the importance of the use of cardiomyocyte transcriptomes for assessing and predicting cardiac phenotypes.

Recently, the roles of macrophages in the heart have been elucidated. Tissue-resident macrophages were abundant in the mouse and human atrioventricular nodes and directly modulate the electrical properties of cardiomyocytes [8]. CCR2-negative resident macrophages have a potential to self-renew and limit adverse remodeling following myocardial infarction [9]. CCR2-positive recruited macrophages represent an inflammatory population and their abundance is associated with left ventricular remodeling and systolic function in patients with heart failure [10]. Further studies are needed to elucidate how the crosstalk between these cardiac macrophages and cardiomyocytes contributes to the pathogenesis of heart failure, leading to the further development of precision medicine in heart failure.

Conflict of Interest

The author declares no conflict of interest.

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