【Grant-in-Aid for Scientific Research (S)】

Broad Section I

Title of Project : DNA damage and senescence in cardiomyocytes for the development of heart failure

KOMURO Issei
(The University of Tokyo, The University of Tokyo Hospital, Professor)

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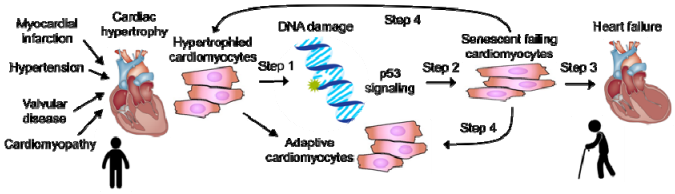
Keyword : Heart failure, DNA damage, Senescence

【Purpose and Background of the Research】

Heart failure is a leading cause of death worldwide. The main causes of heart failure are myocardial infarction, hypertension, valvular disease, and cardiomyopathy, all of which induce cardiac hypertrophy before the development of heart failure. Cardiac hypertrophy is an adaptive mechanism which reduces wall stress and maintains pump function, but if this mechanism collapses, cardiac function declines, leading to the induction of heart failure.

We developed a method to analyze gene expression of cardiomyocytes isolated from the heart at the single-cell level (single-cell RNA-seq) for the first time in the world. By applying this technology to heart failure model mice and human patients with heart failure, we revealed that DNA damage and subsequent p53 signaling activation disrupt the cardiomyocyte function, cause cardiomyocyte senescence, and induce heart failure. We further found that the degree of DNA damage in cardiomyocytes defines the cardiac reversibility in patients with heart failure.

Here, this study aims to uncover (1) the mechanisms of DNA damage accumulation in cardiomyocytes, (2) the mechanisms of how DNA damage and p53 signaling activation induce senescence, (3) the mechanisms of how senescent cardiomyocytes induce heart failure, (4) the pathological significance of senescent failing cardiomyocytes in patients with heart failure.



【Research Methods】

(1) Uncovering the mechanisms of DNA damage accumulation in cardiomyocytes
By integrating genome editing technology with single-cell RNA-seq analysis, we comprehensively analyze the functions of multiple genes and uncover the mechanisms of DNA damage accumulation in cardiomyocytes.
(2) Understanding the mechanisms of how DNA damage and p53 signaling activation induce senescence
We use a senescence induction system that regulates p53 function in vivo to understand the mechanisms of how DNA damage and p53 signaling disrupt the cardiomyocyte function and cause senescence.
(3) Revealing the mechanisms of how senescent cardiomyocytes induce heart failure
We leverage spatial gene expression analysis to dissect the effects of senescent cardiomyocytes on the surrounding cells and cardiac remodeling. We also develop a method to functionally reprogram senescent failing cardiomyocytes.
(4) Establishing the pathological significance of senescent failing cardiomyocytes in patients with heart failure
By integrating single-cell analysis of the heart and blood, we analyze the pathological significance of senescent failing cardiomyocytes, identify novel biomarkers, and develop new therapeutic options for heart failure.

【Expected Research Achievements and Scientific Significance】

We identified DNA damage as a cause of heart failure. Based on this concept, the present study aims to uncover the mechanisms of DNA damage accumulation, senescence induction, and heart failure, and to establish the pathological significance of cardiomyocyte senescence. By expanding the concept of cellular senescence, we will advocate a novel concept that DNA damage and senescence disrupt the homeostasis in non-proliferative cells, and develop novel therapeutics for heart failure.

By advancing our technology, we perform comprehensive functional analysis of multiple genes, spatial single-cell analysis, tissue single-cell analysis at the organism level to reveal the molecular pathogenesis of heart failure. This study is renewing the methodology of single-cell research at the temporal, spatial, and functional resolutions.

【Publications Relevant to the Project】

- Nomura S, Satoh M, Aburatani H, Komuro I et al. Cardiomyocyte gene programs encoding morphological and functional signatures in cardiac hypertrophy and failure. ***Nat Commun.*** 2018;9(1):4435.
- Yamaguchi T, Sumida TS, Nomura S, Naito AT, Komuro I et al. Cardiac dopamine D1 receptor triggers ventricular arrhythmia in chronic heart failure. ***Nat Commun.*** 2020;11(1):4364.
- Ko T, Fujita K, Nomura S, Aburatani H, Komuro I et al. Quantification of DNA Damage in Heart Tissue as a Novel Prediction Tool for Therapeutic Prognosis of Patients With Dilated Cardiomyopathy. ***JACC Basic Transl Sci.*** 2019;4(6):670-680.

【Homepage Address and Other Contact Information】

https://cardiovasc.m.u-tokyo.ac.jp/