【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy Ⅱ)

Title of Project : Novel glycolytic signalosomes and energy metabolism in insulin-resistant heart diseases

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Research Area : Medicine, dentistry, and pharmacy
Keyword : Molecular cardiology

【Purpose and Background of the Research】

Heart failure (HF) is a terminal stage of various heart diseases. The prevalence rate of HF is rising with increases in the aging population. Despite advances in therapy for HF, mortality due to HF is still high.

Alteration of cardiac energy homeostasis is a consistent feature of HF. In HF, insulin resistance develops in the myocardium, which induces impaired energy metabolism, mitochondrial dysfunction, elevated oxidative stress, and subsequent cell death. HF therefore could be pathologically realized as 'insulin-resistant heart disease'. So far, we have found that p53, SCO2 (synthesis of cytochrome oxidase 2), and TIGAR (TP53-induced glycolysis and apoptosis regulator) regulate energy metabolism in the heart, and that ARIA (apoptosis regulator through modulating IAP expression) and MURC (muscle-restricted coiled-coil protein) are potentially involved in insulin signaling and regulate cell death in cardiac myocytes through glycolytic signalosomes. However, roles of p53, SCO2, TIGAR, ARIA, and MURC in insulin-resistant heart disease are unknown. Therefore, analysis of their roles in insulin-resistant heart disease will be important to understand HF and may contribute to the development of novel therapeutic strategies against HF. Accordingly, the following specific aims are proposed:

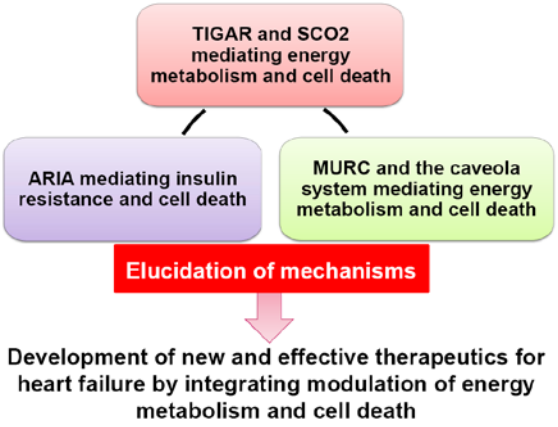
1). To elucidate mechanisms regulating energy metabolism and cell death mediated by TIGAR and SCO2.
2). To elucidate mechanisms regulating energy metabolism and cell death mediated by MURC and the caveola system.
3). To elucidate mechanisms regulating insulin resistance and cell death mediated by ARIA.
4). To develop new and effective therapeutics for HF by integrating modulation of energy metabolism and cell death

【Research Methods】

We will use molecular- and cell biological, histological, biochemical, and physiological methods in cultured cardiac myocytes and mouse models.

【Expected Research Achievements and Scientific Significance】

We expect that our study will provide new insights into mechanisms of insulin-resistance, energy metabolism, and cell death in the heart. Our study would also lead to the invention of new therapeutics to effectively treat in refractory HF.



【Publications Relevant to the Project】

1. Ikeda K, Matsubara H et al. Identification of ARIA regulating endothelial apoptosis and angiogenesis by modulating proteasomal degradation of cIAP-1 and cIAP-2. **Proc Natl Acad Sci USA** 106: 8227-8232, 2009
2. Ogata T, Matsubara H et al. MURC, a muscle-restricted coiled-coil protein that modulates the Rho/ROCK pathway, induces cardiac dysfunction and conduction disturbance. **Mol Cell Biol** 28: 3424-3436, 2008
3. Matoba S et al. p53 regulates mitochondrial respiration. **Science** 312: 1650-1653, 2006

【Term of Project】 FY2011-2015

【Budget Allocation】 165,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.kpu-m.ac.jp/k/med2/index.html