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Searching for New Therapeutic Approaches for Heart Failure

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Abstract

Heart failure (HF) is a major health burden in worldwide. As the end point of numerous cardiovascular diseases, HF is the main cause of disability and death, and its five-year mortality is even higher than that of malignant tumor. The etiologies of heart failure are various, foremost among them is cardiac hypertrophy and myocardial ischemia. We have been committing to research the mechanisms of the development and progression of HF, and found some potential therapies to inhibit cardiac remodeling and improve heart failure.

Keywords: Myocardial hypertrophic preconditioning; Myocardial hypertrophy; Heart failure

Introduction

We have been working attentively on the basic researches of heart failure (HF), mainly focusing on HF induced by myocardial ischemia, pressure overload, emphasizing on the mechanism of heart failure as well as the novel therapies, and has accumulated abundant research experience and achievements. The group leader, Prof. Liao Yulin has published more than 100 research articles in authoritative international journals such as Circulation, Circulation Research, European Heart Journal, Cardiovascular Research. He is now a consulting editor for Am J Physiol Heart Circ Physiol.

Research Achievements

During the recent 15 years, our team has been devoting to find the molecular mechanisms and new therapeutical interventions for HF induced by myocardial hypertrophy and ischemia. We have proved that metalloproteinase inhibition [1], activation of adenosine α1 receptor [2], β-blocker inhibition [3], α-glucosidase inhibition [4], ablation of C/EBP homologous protein [5], inhibition of fractalkine by resveratrol [6], disruption of histamine H_2 receptor [7,8] that converge on different downstream pathways were beneficial for attenuating cardiac hypertrophy and/or myocardial ischemia, while adiponectin-deficient [9], activation of fractalkine [6,10], deficiency of type 1 cannabinoid receptors [11], activation of histamine H_2 receptor [7,8] and overexpression of ankyrin repeat domain 1 [12] exacerbated HF. We have demonstrated that the oxidative stress [4,13], apoptosis [8,10,12,14,15], autophagy [14-16], endoplasmic reticulum stress [5,13,17], fibrosis [8,18,19], and myocyte regeneration [20] play influential roles in the progress of cardiac remodeling.

Recent Focus: Hypertrophic Myocardial Preconditioning

It is well known that a similar level of pressure overload (e.g., hypertension) can cause different degrees of myocardial hypertrophy. Also the prevalence of myocardial hypertrophy is less than 50% in patients with essential hypertension, suggesting that factors which resist prohypertrophic stimulation exist in many patients. Experimental studies have demonstrated that some factors can prevent cardiac hypertrophy independent of an antihypertensive effect, but it remains unclear how to induce such antihypertrophic factors for therapeutic purposes. Based on the points mentioned here, we propose a new concept termed “myocardial hypertrophic preconditioning”. Our hypothesis is that short-term hypertrophic stimulation can render the heart resistant to subsequent hypertrophic stress and slow the progression to heart failure (Figure 1). Up to now, we have provided the first evidence that preconditioning by prohypertrophic factors increases the resistance of the heart to subsequent hypertrophic stress and delays progression from hypertrophy to heart failure, indicting the existence of hypertrophic preconditioning phenomenon. We further showed that upregulation of S100A8/A9 following the removal of transient hypertrophic stimulus contributes to the anti-hypertrophic and anti-heart failure effect of hypertrophic preconditioning, at least partly by suppressing the calcineurin/NFAT pathway (Figure 2) [18]. These findings implicate that induction of hypertrophic preconditioning has the potential to become a new approach to

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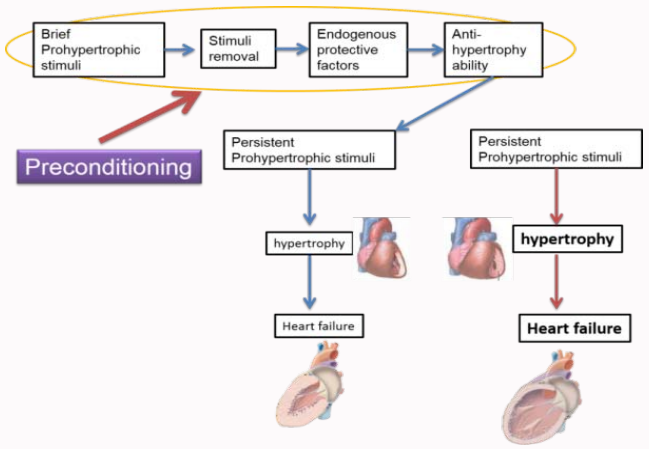

Figure 1: Withdraw of short term stimulation of prohypertrophic factor produces endogenous protective factors to render the heart resistant to subsequent hypertrophic stress.

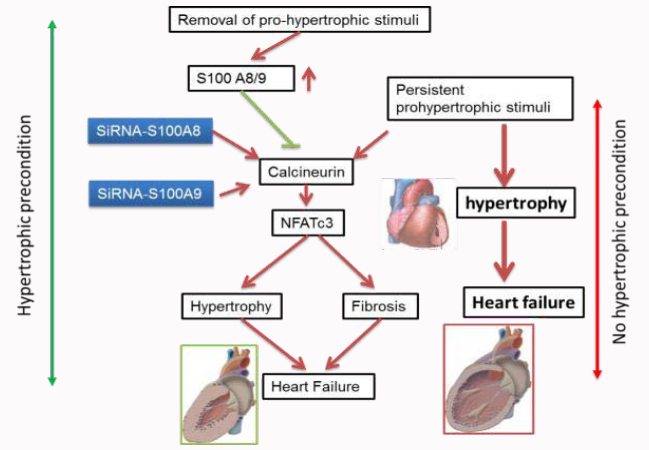

Figure 2: Withdraw of short term stimulation of prohypertrophic factor produces endogenous protective factors S100A8/A9 which render the heart resistant to subsequent hypertrophic stress by inhibiting calcineurin-NFAT signal pathway. →: promotion; ⊥: inhibition.

protect cardioprotection for patients with pressure overload. An editorial comment pointed out the findings in our study offer a new possibility of hypertrophic suppression through preconditioning [21]. Further studies are needed to find out whether the physiological stimuli such as physical exercise or pregnancy may also render the heart to subsequent persistent pathological hypertrophic stress and if so it would be interesting to explore the precise mechanisms for this phenomenon.

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