Receptor-interacting protein 140 overexpression impairs cardiac mitochondrial function and accelerates the transition to heart failure in chronically infarcted rats

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Heart failure (HF) is associated with myocardial energy metabolic abnormality. Receptor-interacting protein 140 (RIP140) is an important transcriptional cofactor for maintaining energy balance in high–oxygen consumption tissues. However, the role of RIP140 in the pathologic processes of HF remains to be elucidated. In this study, we investigated the role of RIP140 in mitochondrial and cardiac functions in rodent hearts under myocardial infarction (MI) stress. MI was created by a permanent ligation of left anterior descending coronary artery and exogenous expression of RIP140 by adenovirus (Ad) vector delivery. Four weeks after MI or Ad-RIP140 treatment, cardiac function was assessed by echocardiographic and hemodynamics analyses, and the mitochondrial function was determined by mitochondrial genes expression, biogenesis, and respiration rates. In Ad-RIP140 or MI group, a subset of metabolic genes changed, accompanied with slight reductions in mitochondrial biogenesis and respiration rates but no change in adenosine triphosphate (ATP) content. Cardiac malfunction was compensated. However, under MI stress, rats overexpressing RIP140 exhibited greater repressions in mitochondrial genes, state 3 respiration rates, respiration control ratio, and ATP content and had further deteriorated cardiac malfunction. In conclusion, RIP140 overexpression leads to comparable cardiac function as resulted from MI, but RIP140 aggravates metabolic repression, mitochondrial malfunction, and further accelerates the transition to HF in response to MI stress. (Translational Research 2017;180:91–102)

Abbreviations: Ad = adenovirus; ADP = adenosine diphosphate; ATP = adenosine triphosphate; ATP-5β = ATP synthase 5β; BNP = brain natriuretic peptide; β-MHC = β-myosin heavy chain; CPT = carnitine palmitoyltransferase; Cyt b = cytochrome b; ERR = estrogen-related receptor; FAO = fatty acid oxidation; FAs = fatty acids; GFP = green fluorescent protein; GLUT = glucose transporter; HF = heart failure; HIF-1α = hypoxia-inducible factor-1α; LAD = left anterior descending coronary artery; LCAD = long acyl-coenzyme A dehydrogenase; MCAD = medium acyl-coenzyme

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A dehydrogenase; MI = myocardial infarction; mRNA = messenger RNA; mtDNA = mitochondrial DNA; ND1 = NADH dehydrogenase subunit 1; NRFs = nuclear respiration factors; OXPHOS = oxidative phosphorylation; PCr = phosphocreatine; PDK4 = pyruvate dehydrogenase kinase-isoform 4; PPAR = peroxisome proliferate-activated receptor; PGC-1 = peroxisome proliferate-activated receptor γ coactivator-1; RIP140 = receptor-interacting protein 140; TEM = transmission electron microscopy; UCP = uncoupling protein

INTRODUCTION

AT A GLANCE COMMENTARY

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Background

Receptor-interacting protein 140 (RIP140) is an important transcriptional cofactor to maintain energy balance in heart. Mitochondrial energy metabolic derangements are associated with the development and progression of heart failure (HF), following pressure or volume overload, or regional myocardial infarction. The role of RIP140-mediated metabolic repression on HF is still unknown.

Translational Significance

In this study, we used the rat model of HF subjected to myocardial infarction to determine the metabolic regulation of RIP140 on the development of HF. Cardiac energy metabolic balance regulation strategy may be of therapeutic benefit in preventing the progress of human HF.

The high-workload heart requires a tight coupling of adenosine triphosphate (ATP) production and cardiac contraction to sustain proper cardiac function. Cardiac energetics are profoundly disturbed in experimental and clinical failing hearts, following pressure or volume overload, or regional myocardial infarction (MI).[1] It was hypothesized that the impaired substrate metabolism contributed to contractile dysfunction and to the progression of HF state. Impaired cardiac metabolism is characterized with downregulation in fatty acid oxidation, increased glycolysis and glucose oxidation, and reduced respiratory chain activity.[2] Moreover, the ratio of high-energy phosphate compound phosphocreatine to ATP is regarded as a superior predictor of cardiovascular mortality as compared with ejection fraction (EF).[3] Targeting myocardial mitochondrial metabolism would be a potential therapy strategy to improve cardiac function and slow down or prevent HF progression.[4-6]

Nuclear receptors and transcriptional factors superfamily, such as peroxisome proliferator–activated receptors (PPARs), estrogen-related receptors (ERRs), and nuclear respiratory factors, are transcriptional regulators important in maintaining energy balance in metabolism-sensitive tissues and cells. They regulate the metabolic gene networks involved in the oxidation of fatty acids (FAs) and glucose, and in oxidative phosphorylation program, as well as in mitochondrial biogenesis.[7,8] To some extent, the activation or repression of metabolic genes depends on the recruitment of coactivator or corepressor. Peroxisome proliferate–activated receptor γ coactivator-1 (PGC-1) is a well-studied transcriptional coactivator and identified as a central regulator in cardiac energetics and function.[9] Conversely, receptor-interacting protein 140 (RIP140) is a corepressor reported to suppress metabolic suppressor in white adipose tissue[10] and skeletal muscle[11] via RIP140/ERRs and RIP140/PPARs signaling pathways. Recently, it is of interest to investigate the role of RIP140 in heart. In nonstressed hearts from RIP140 transgenic mice, impaired mitochondrial activity and FAs metabolic genes, as well as defects in cardiac function, were observed.[12] Overexpression of RIP140 could antagonize the role of PGC-1α in the regulation of metabolic gene expressions and mitochondrial function in cultured primary neonatal cardiomyocytes.[13] However, the influence of RIP140 on mitochondrial metabolic regulation and cardiac function under a pathologic state, such as ischemia, hypoxia, or increased workload, remained unknown. Here, we sought to dissect the role of RIP140 by adenovirus (Ad) gene delivery in a rat MI model created by permanent ligation of the left anterior descending coronary artery (LAD).

METHODS

Recombinant Ad construction. Adenovirus encoding RIP140 (Ad-RIP140) was constructed with AdEasy transfer vectors as previously described.[13] In brief, the full length of RIP140 gene was cloned into pAdTrack-CMV shuttle vector, and then recombined with the virus backbone pAdEasy-1 vector in BJ5183 bacteria. Null control virus (Ad-Null) was made by the recombination between the pAdTrack-CMV and pAdEasy-1 vectors. Both Ad-RIP140 and Ad-Null