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Pharmacological Inhibition of RUNX1 Suppresses Cardiac Cathepsin Expression and Preserves Cardiac Function Following Myocardial Infarction in Rats

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***Abstract*—Cardiac cell death following myocardial infarction (MI) leads to irreversible loss of myocardium which in turn leads to adverse structural and functional changes of the heart, referred to as cardiac remodelling. Progression of adverse remodelling causes heart failure which is linked to increased deaths or hospitalizations. Runt-related transcription factor-1 (RUNX1) is a member of the core-binding factor family of transcription factors which regulate gene expression. Recent evidence showed that RUNX1 expression is increased following MI and negatively correlates with cardiac function. Dr He's previous study performed with a cardiomyocyte-specific Runx1-deficient mouse revealed that reducing RUNX1 function preserves myocardial contractility and prevents adverse cardiac remodeling. Cathepsin is a family of lysosomal proteases and is involved in multiple cell death pathways. Our recent study showed that inhibition of RUNX1 reduced infarct size after acute MI, paralleled with repressed cardiac cathepsin levels. The present work sought to investigate whether the inhibition of RUNX1 preserves cardiac function post-MI. MI was surgically induced by performing coronary artery ligation and echocardiography was used to assess cardiac function. Here, we report that cardiac systolic function, as indicated by fractional shortening, decreased in control rats. In contrast, rats treated with RUNX1 inhibitor Ro5-3335 demonstrated a markedly preserved fractional shortening that was 128% of the control animal at 1-week post-MI (39.1±1.4% versus 30.6±2.9%; P<0.05). This beneficial effect is in line with our previous work and might be due to repressed cathepsin expression as revealed by our recent proteomic study. Taken together, our data demonstrate that pharmacological inhibition of RUNX1 not only reduces infarct size but also preserves cardiac function following MI, thereby suggesting the translational potential of RUNX1 as a new therapeutic target for cardiac protection against MI.**

Keywords—RUNX1, cathepsin, myocardial infarction, cell death, cardiac function