**P90RSK REGULATES CHIP UB LIGASE ACTIVITY VIA ERK5 AND PROMOTES CARDIAC DYSFUNCTION**

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Diabetes mellitus (DM) is an independent risk factor for both mortality and morbidity after myocardial infarction (MI). Previously, we have reported that activation of ERK5, an atypical mitogen activated protein kinase with transcriptional activity, inhibits apoptosis and left ventricular (LV) dysfunction in DM mice following MI (DM+MI). We reported that ICER levels were significantly increased in DM+MI mice, and this increase in ICER levels was blunted in transgenic mice expressing a cardiac-specific constitutively active form of MEK5, suggesting the cardio-protective action of ERK5 in DM+MI mice via downregulation of ICER levels and inhibition of apoptosis. In addition, we have shown the association of ERK5 with CHIP ubiquitin (Ub) ligase and subsequent up-regulation of CHIP ligase activity, which induces ICER ubiquitination and subsequent protein degradation. However, the regulatory mechanism governing ERK5/CHIP interaction is unknown. Recently, we have demonstrated a critical role for p90RSK activation in the reduction of CHIP Ub ligase activity and subsequent increase in the ICER protein levels. p90RSK activation promotes its association with ERK5 and phosphorylates it at S496. This phosphorylation appears to be a necessary and sufficient step in the ability of p90RSK to promote the dissociation of the ERK5-CHIP complex, which leads to reduced CHIP Ub ligase activity. The physiologic significance of p90RSK activation in DM+MI lies in its ability to decrease CHIP Ub ligase activity. Our data strongly suggest that the activation of p90RSK abrogates ERK5-mediated CHIP Ub ligase activation, and accelerates apoptosis and cardiac dysfunction in the DM+MI condition.