Angiotensin II increased IGF-IIR expression resulting in cardiomyocyte apoptosis via JNK activation impairing SIRT1- deacetylation of HSF1

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Abstract

Cardiac hypertrophy and apoptosis are the major characteristic at early stage of heart failure. Previous studies have indicated the hypertension-induced cardiac hypertrophy and apoptosis resulted in heart failure. Our previous studies found that the insulin-like growth factor receptor II (IGR-IIR) was critical in angiotensin II-induced cardiomyocyte apoptosis. However, the detailed mechanism of IGF2R in heart failure remains elusive. In this study, we found that ANG II activated its downstream kinases JNK to increase IGF-IIR expression via its receptor, AT_1R. By IGF-IIR promoter luciferase assay, we identified that ANG II-mediated IGF-IIR gene expression was determined at IGF-IIR promoter region (nt -748~ -585), containing a heat shock binding element (HSE). Our results showed that heat shock transcription factor 1 (HSF1) bound to IGF-IIR promoter under normal condition, while HSF1 loss its ability to bind IGF-IIR promoter after ANG II treatment. Moreover, we found the HSF1 acetylation was increased and SIRT1, the HSF1 deacetylase, was degraded after ANG II challenge and JNK activation, suggesting that JNK activation resulted in SIRT1 degradation to enhance HSF1 acetylation, which loses its DNA binding affinity at IGF-IIR promoter. Taken together, these results suggested that HSF1 repressed IGF-IIR gene expression under normal condition, whereas ANG II activated JNK to degrade SIRT1, followed with HSF1 acetylation, induced IGF-IIR expression, and eventually resulted in cardiac hypertrophy and apoptosis.