ANG II promotes IGF-IIR expression and cardiomyocyte apoptosis by inhibiting HSF1 via JNK activation and SIRT1 degradation

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Abstract

Hypertension-induced cardiac hypertrophy and apoptosis are major characteristics of early-stage heart failure. Our previous studies found that the activation of insulin-like growth factor receptor II (IGF-IIR) signaling was critical for hypertensive angiotensin II-induced cardiomyocyte apoptosis. However, the detailed mechanism by which angiotensin II (ANG II) regulates IGF-IIR in heart cells remains elusive. In this study, we found that ANG II activated its downstream kinase JNK to increase IGF-IIR expression through the ANG II receptor AT_1R. JNK activation subsequently led to SIRT1 degradation via the proteasome, thus preventing SIRT1 from deacetylating heat shock transcription factor 1 (HSF1). The resulting increase in the acetylation of HSF1 impaired its ability to bind to the IGF-IIR promoter region (nt -748 to -585). HSF1 protected cardiomyocytes by acting as a repressor of IGF-IIR gene expression, and ANG II diminished this HSF1-mediated repression through enhanced acetylation, thus activating the IGF-IIR apoptosis pathway. Taken together, these results suggest that HSF1 represses IGF-IIR gene expression to protect cardiomyocytes. ANG II activates JNK to degrade SIRT1, resulting in HSF1 acetylation, which induces IGF-IIR expression and eventually results in cardiac hypertrophy and apoptosis. HSF1 could be a valuable target for developing treatments for cardiac diseases in hypertensive patients.