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NF-κB-mediated miR-30b regulation in cardiomyocytes cell death by targeting Bcl-2

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Abstract Angiotensin II(Ang II)-stimulated cardiomyocytes hypertrophy and apoptosis are associated with nuclear factor-κB (NF-κB) activation. NF-κB, a redox-sensitive transcription factor, contributes a critical role in cell death, but, Ang II-stimulated NF-κB-mediated cardiomyocytes apoptosis remains less understood. Recently, microRNAs (miRNAs) have been shown to be critical regulators in various cardiac remodeling processes; however, NF-κB-mediated miRNA's role in cardiomyocytes apoptosis remains undetermined. The miR-30b has been implicated in diverse cardiac remodeling; but, NF-κB-mediated miR-30b modulation in Ang II-induced cardiomyocytes death is currently unknown. In the present study, neonatal cardiomyocytes were pretreated with SN50, a selective cell permeable peptide inhibitor of NF-κB, or transfected with miR-30b mimetic and inhibitors separately, and then challenged with Ang II. The target gene, Bcl-2, and NF-κB transcriptional activity were analyzed. Our results demonstrated that NF-κB positively regulated miR-30b expression in Ang II-induced cardiomyocytes apoptosis, and Bcl-2 was a direct target for miR-30b. NF-κB further regulated the expression of Bcl-2 in the above setting. Furthermore, Ang II-induced cardiomyocytes apoptosis rescued by inhibiting either NF-κB or miR-30b provided an important role in cardiomyocytes cell death. We evaluated a critical role of NF-κB-mediated miR-30b modulation in Ang II-stimulated cardiomyocytes targeting Bcl-2. Our data may provide a new insight of miR-30b's role in myocardial infarction or ischemia.

Keywords miR-30b · NF-κB · Cardiac apoptosis · Bcl-2

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Introduction

Cardiomyocytes apoptosis elicits a major role in diverse cardiac pathological remodeling that includes cardiac hypertrophy, myocardial infarction, etc., both in humans and experimentally induced heart failure rodent models [1–4]. Earlier studies established that angiotensin II (Ang II), an important neurohormonal factor causes cardiomyocytes apoptosis in adult and neonatal cardiomyocytes, is associated with the development of cardiac dysfunction [5, 6]. Parallel to this, Ang II is shown to activate NF-κB in cardiac hypertrophy and apoptosis [7–9]. NF-κB is a pleiotropic transcription factor that, in addition to playing fundamental roles in immunity, also regulates the expression of genes controlling various cardiac diseases like myocardial infarction, ischemia reperfusion injury, left ventricular hypertrophy, and congestive heart failure [10–13]. Previously, we have shown that NF-κB activation was required in cardiac hypertrophy [14–16]; and inhibition of NF-κB-attenuated cardiac hypertrophy [15, 16]. However, Ang II-stimulated NF-κB-mediated cardiomyocytes apoptosis remains less understood.

MicroRNAs (miRNAs) are a class of short RNA molecules, on average 22 nucleotides long, encoded within the genome and derived from endogenous small hairpin

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