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Hypoxia suppresses myocardial survival through HIF-1α-IGFBP-3-dependent signaling and enhances cardiomyocyte autophagy and apoptotis via FoxO3a-induced BNIP3 expression.

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Abstract

In the present study, heart-derived H9c2 cells and neonatal rat ventricular myocytes (NRVMs) were incubated in normoxic (21% oxygen) or hypoxic (1% oxygen) conditions for up to 48 h. Results showed that hypoxia primarily highly increased HIF-1α, activated downstream genes as BNIP3 and IGFBP-3, and further triggered mitochondria-dependent apoptotic pathways. Moreover, IGF1R/PI3K/Akt signaling obviously attenuated by up-regulated expression of HIF-1α-dependent IGFBP-3 expression to enhance hypoxia-induced cell apoptosis. In addition, suppression of autophagy with 3-methyladenine (3MA) or siRNA of ATG5 or Beclin-1 significantly decreased the myocardial apoptosis under hypoxic conditions. The data also showed that the activation of autophagy during hypoxia was obviously induced by Forkhead box O3 (FoxO3a)-dependent BNIP3 expression. Importantly, knockdown of FoxO3a or BNIP3 significantly abrogated hypoxia-induced autophagy and mitochondria-dependent apoptosis effects. Taken together, our present results confirmed that autophagy is a pivotal regulator for hypoxia-induced cardiomyocyte apoptosis modulated by FoxO3a-dependent BNIP3 expression. Moreover, prolonged-hypoxia induced HIF-1α not only stimulated BNIP3 expression but also enhanced IGFBP-3 activation to inhibit IGF1R/PI3K/Akt survival pathway and mediate mitochondria-dependent cardiomyocyte apoptosis.