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Cardiac Hypertrophy in Diabetes; The Role of Factor Forkhead Box Class O-Regulation by O-GlcNAcylation

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Abstract : Cardiac hypertrophy arises in response to persistent increases in hemodynamic loads. In comparison, diabetic cardiomyopathy is defined by an abnormal myocardial changes without other cardiac-related risk factors. Pathological cardiac hypertrophy and myocardial remodeling are hallmarks of cardiovascular diseases and are risk factors for heart failure. The transcription factor forkhead box class O (FOXOs) can protect heart tissue by hostile oxidative stress and stimulating apoptosis and autophagy. FOXO proteins, as sensitive elements and mediators in response to environmental changes, have been revealed to prevent and inverse cardiac hypertrophy. FOXOs are inhibited by insulin and are critical mediators of insulin action. Insulin deficiency and uncontrolled diabetes lead to a catabolic state. FOXO1 acts downstream of the insulin-dependent pathways, which are dysregulated in diabetes. It regulates cardiomyocyte hypertrophy downstream of IGF1R/PI3K/Akt activation, which are critical regulators of cardiac hypertrophy. The complex network of signaling pathways comprising insulin/IGF-1 signaling, AMPK, JNK, and Sirtuins regulate the development of cardiovascular dysfunction by modulating the activity of FOXOs. Insulin receptors and IGF1R act via the PI3k/Akt and the MAPK/ERK pathways. Activation of Akt in response to insulin or IGF-1 induces phosphorylation of FOXOs. Increased protein synthesis induced by activation of the IGF-I/Akt/mTOR signaling pathway leads to hypertrophy. This pathway and the myostatin/Smad pathway are potent negative muscle development regulators. In cardiac muscle, insulin receptor substrates (IRS)-1 or IRS-2 activates the Akt signaling pathway and inactivate FOXO1. Under metabolic stress, p38 MAPK promotes degradation of IRS-1 and IRS-2 in cardiac myocytes and activates FOXO1, leading to cardiomyopathy. Sirt1 and FOXO1 interaction play an essential role in starvation-induced autophagy in cardiac metabolism. Inhibition of Angiotensin-II induced cardiomyocyte hypertrophy is associated with reduced FOXO1 acetylation and activation of Sirt1. The NF-κB, ERK, and FOXOs are de-acetylated by SIRT1. De-acetylation of FOXO1 induces the expression of genes involved in autophagy and stimulates autophagy flux. Therefore, under metabolic stress, FOXO1 can cause diabetic cardiomyopathy. The overexpression of FOXO1 leads to decreased cardiomyocyte size and suppresses cardiac hypertrophy through inhibition of the calcineurin–NFAT pathway. Diabetes mellitus is associated with elevation of O-GlcNAcylation. Some of its binding partners regulate the substrate selectivity of O-GlcNAc transferase (OGT). O-GlcNAcylation of essential contractile proteins may inhibit protein-protein interactions, reduce calcium sensitivity, and modulate contractile function. Uridine diphosphate (UDP)-GlcNAc is the obligatory substrate of OGT, which catalyzes a reversible post-translational protein modification. The increase of O-GlcNAcylation is accompanied by impaired cardiac hypertrophy in diabetic hearts. Inhibition of O-GlcNAcylation blocks activation of ERK1/2 and hypertrophic growth. O-GlcNAc modification on NFAT is required for its translocation from the cytosol to the nucleus, where NFAT stimulates the transcription of various hypertrophic genes. Inhibition of O-GlcNAcylation dampens NFAT-induced cardiac hypertrophic growth. Transcriptional activity of FOXO1 is enriched by improved O-GlcNAcylation upon high glucose stimulation or OGT overexpression. In diabetic conditions, the modification of FOXO1 by O-GlcNAc is promoted in cardiac troponin I and myosin light chain 2. Therefore targeting O-GlcNAcylation represents a potential therapeutic option to prevent hypertrophy in the diabetic heart.

Keywords : diabetes, cardiac hypertrophy, O-GlcNAcylation, FOXO1, Akt, PI3K, AMPK, insulin
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