Protein O-GlcNAcylation: A novel regulator of cardiomyocyte stress response

J.C. Chatham, Division of Molecular and Cellular Pathology, Department of Pathology, University of Alabama at Birmingham, 1670 University Boulevard, Birmingham, AL 35294-0019, USA.

The hexosamine biosynthesis pathway (HBP) is a nutrient-sensing pathway that integrates glucose, amino acid, fatty acid and high energy phosphate metabolism. The end product of the HBP, UDP-N-acetylglucosamine is not only the building block for the synthesis of N-linked and O-linked glycans, but is also the essential sugar donor for O-GlcNAc transferase (OGT). OGT is an atypical glycosyltransferase, which catalyzes the attachment of a single β-N-acetyglucosamine moiety via an O-linkage to Ser/Thr residues of nuclear and cytosolic proteins (O-GlcNAc). The post-translational modification of proteins by O-GlcNAc has emerged as a key regulator of a wide range of biological processes critical for normal cell function including signal transduction, proteasome activity, apoptosis, nuclear transport, translation and transcription. In the heart sustained increases in O-GlcNAc levels have been implicated as a pathogenic contributor to glucose toxicity associated with diabetes and diabetic complications (McLarty, Marsh & Chatham, 2013). However, active synthesis of O-GlcNAc is essential for cell viability and in the heart acute activation of O-GlcNAc levels, either by increasing O-GlcNAc synthesis or inhibiting its degradation affords remarkable protection against ischemia/reperfusion (I/R) injury (Chatham & Marchase, 2010; Darley-Usmar *et al.* 2012). Of particular interest, increasing O-GlcNAc levels at the time of reperfusion, significantly improves functional recovery and attenuates tissues injury in an O-GlcNAc dependent manner. In a rat model of hemorrhagic shock, activation of O-GlcNAc levels during resuscitation, improved cardiac function, decreased tissue injury and attenuated inflammatory responses (Chatham & Marchase, 2010; Darley-Usmar *et al.* 2012). At the cellular level, in isolated cardiomyocytes, over-expression of OGT protected against hypoxia/reoxygenation, oxidative stress and inflammatory stimuli; conversely, decreasing OGT levels reduced tolerance to these stimuli. The specific mechanisms underlying O-GlcNAc mediated cardioprotection remain to be determined; however studies point to decreased calcium overload and attenuation of mitochondrial dysfunction as contributing factors (Chatham & Marchase, 2010; Darley-Usmar *et al.* 2012).

Diabetic cardiomyocytes from type 2 db/db mice have increased O-GlcNAc levels and this was associated with impaired hypertrophic and autophagic signaling. Inhibition of the HBP normalized the response of db/db cardiomyocytes to hypertrophic and autophagic stimuli; moreover, increasing O-GlcNAc levels in normal cardiomyocytes mimicked the response of diabetic cardiomyocytes to the same stimuli (McLarty *et al.* 2013). These data suggest that elevated O-GlcNAc levels could be a contributing factor to the adverse cardiac remodeling and increased progression to heart failure associated with diabetes. An increase in cytosolic calcium plays a key role in activating pathological hypertrophic signaling, and earlier studies have shown that this can be inhibited by hyperglycemia. We have recently demonstrated that in cardiomyocytes the ER/SR Ca^{2+} sensing protein Stromal Interacting Molecule 1 (STIM1) an O-GlcNAc target and that increased O-GlcNAc levels attenuates STIM1 function and blunts Ca^{2+} entry. O-GlcNAcylation of STIM1 provides a novel intersection between metabolic and Ca^{2+} signaling pathways.

Thus, alterations in O-GlcNAc turnover are clearly associated with mediating a number of different cardiomyocyte stress responses and these exciting findings indicate a complex role of O-GlcNAc in the normal regulation of the cardiovascular system.

Chatham JC, Marchase RB. (2010) *Biochimica et Biophysica Acta*, **1800:** 57-66.
Darley-Usmar VM, Ball LE, Chatham JC. (2012) *Journal of Molecular and Cellular Cardiology*, **52:** 538-549.
McLarty JL, Marsh SA, Chatham JC. (2013) *Life Sciences*, **92:** 621-7.

Supported by Grants: HL101192 and HL-110366 from the National Institutes of Health.