Enzymatic and non-enzymatic post-translational modifications linking diabetes and heart disease

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COMMENTARY

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Diabetes-related morbidity and mortality is evident in the increased prevalence of cardiovascular diseases and the high-risk of heart failure. Diabetic cardiomyopathy is a well-known complication of diabetes, and is defined as a ventricular dysfunction independent of coronary heart diseases and hypertension. The Framingham study firmly established an epidemiological link between diabetes and heart failure[1]. Diabetes causes metabolic disturbances, cardiac fibrosis, endothelial and vascular smooth muscle cell dysfunctions, altered contractile performance, and arrhythmia. The underlying mechanisms of the adverse effects of diabetes on the heart remain poorly understood. However, it is certain that diabetic heart disease is a consequence of multiple factors including uncontrolled hyperglycemia, insulin resistance and dyslipidemia. Chronic hyperglycemia causes glucose toxicity, which mediates the detrimental effects of diabetes through the activation of a number of pathways, such as the polyol pathway, oxidative stress, mitochondrial dysfunction, activation of protein kinases, hexosamine biosynthesis pathway and non-enzymatic glycation reaction. The hexosamine biosynthesis pathway generates uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), which is an activated precursor for both *N*-linked and *O*-linked glycosylation of proteins, and the substrate for β-*O*-linked GlcNAc (*O*-GlcNAc) modification of proteins (Figure 1). Recently, *O*-GlcNAc covalent modification of cardiac proteins has received considerable attention as a key factor in diabetic cardiac pathology[2,3]. In contrast to non-enzymatic glycation reactions, *O*-GlcNAc glycosylation is a reversible and labile post-translational modification.

After entering a cell, glucose is phosphorylated to glucose-6-phosphate (Figure 1). It is further metabolized during glycolysis to fructose-6-phosphate, which leads to accessory pathways of glucose metabolism; one such pathway is the hexosamine biosynthesis pathway. Under normal physiological conditions, approximately 5% of intracellular glucose enters the hexosamine biosynthesis pathway; however, its flux is upregulated in diabetic cardiomyocytes[4]. The rate-limiting enzyme glutamine, fructose-6-phosphate aminotransferase (GFAT), converts fructose-6-phosphate to glucosamine-6-phosphate, which is then converted into UDP-GlcNAc and transferred onto target proteins by *O*-GlcNAc transferase (OGT). The enzyme, *O*-GlcNAcase, catalyzes the removal of the *O*-GlcNAc adduct from *O*-GlcNAcylated proteins (Figure 1)[2]. *O*-GlcNAcylation is reported to be involved in a number of cellular processes including signal transduction, protein–protein interactions, translation, protein degradation and gene expression

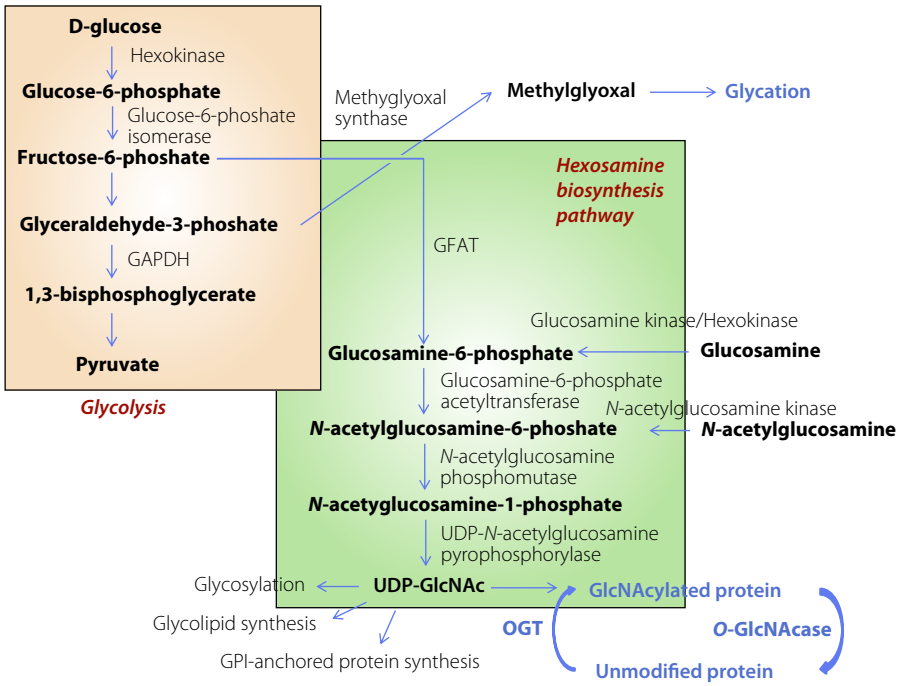

Figure 1 | Hexosamine biosynthesis pathway. GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GFAT, glutamine:fructose-6-phosphate amidotransferase; OGT, *O*-linked N-acetylglucosamine (GlcNAc) transferase; *O*-GlcNAcase, *O*-GlcNAc-selective beta-*N*-acetylglucosaminidase; UDP-GlcNAc, uridine diphosphate-*N*-acetylglucosamine.

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alteration[4]. Recently, *O*-GlcNAcylation has been shown in the regulation of cardiomyocyte excitation-contraction coupling by influencing intracellular Ca^{2+} homeostasis[5]. The multifunctional Ca^{2+} and calmodulin-dependent protein kinase II (CaMKII) is a serine-threonine kinase that is activated by an increase in cellular Ca^{2+}. The disruption of normal intracellular Ca^{2+} homeostasis is the event mainly responsible for initiating and perpetuating myocardial dysfunction, electrical instability, and arrhythmia. The CaMKII regulates Ca^{2+} homeostasis proteins in the myocardium. Recently, it has been reported that *O*-GlcNAc modification of CaMKII leads to cardiac arrhythmias associated with diabetes, which are linked to heart failure and sudden cardiac death[2]. CaMKII fusion with *O*-GlcNAc leads to chronic overactivation of CaMKII, triggering arrhythmias, and inhibition of *O*-GlcNAcylation of CaMKII prevented the occurrence of arrhythmias[2]. In addition to direct *O*-GlcNAc modification of proteins involved in excitation-contraction coupling, nuclear *O*-GlcNAcylation of transcription factors, histones and ribonucleic acid (RNA) polymerase II has been known to alter gene transcription, resulting in cardiac deterioration in patients with diabetes[3].

Compared with the dynamic and enzymatic regulation of *O*-GlcNAcylation, non-enzymatic glycation-modification is generally irreversible and obstructive. Both extracellular and intracellular formation of advanced glycation end-products (AGE) occurs in proteins such as collagen and other matrix components, and in cardiomyocyte intracellular proteins. The involvement of AGE-modification in excitation-contraction coupling has been described in type 1 diabetic rat myocardium, including the sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (ATPase; SERCA2) and ryanodine receptor 2 (RYR2), a Ca^{2+} release channel[6]. Remodeling and degradation of the extracellular matrix is also affected in diabetes as a result of reduced expression of matrix metalloproteinases and consequent lower collagen turnover[7]. Binding of AGE to the receptor for AGE (RAGE) on fibroblasts stimulates collagen production, further compromising ventricular compliance[8]. We also reported that AGE and RAGE impaired Ca^{2+} homeostasis in diabetic mouse myocytes; thus, accounting for the abnormal contractile and relaxation functions[9].

Diabetic cardiomyopathy involves various complex functional and structural abnormalities. Recent findings highlight the dynamic *O*-GlcNAcylation and irreversible glycation of fundamental cardiomyocyte proteins in the context of diabetes. This can potentially be used to study enzymatic and non-enzymatic post-translational modifications associated with glucose metabolism for diabetic cardiomyopathy interventions.

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