A Bittersweet Modification

O-GlcNAc and Cardiac Dysfunction

Steven P. Jones

Data from the Framingham Study indicate that cardiac dysfunction in diabetic patients may occur without documented cardiovascular disease.1 Given the profound metabolic disturbance underlying diabetes, such dysfunction may not be surprising. Although it would be tempting to ascribe such dysfunction to simple energetic disturbances, a study in the current issue of Circulation Research2 suggests a specific and rather unusual suspect in cardiac biology.

The inability to handle glucose properly is a hallmark of diabetes. Of course, during any dialogue of glucose handling, discussion often focus on glycolysis or glycogen storage. Although up to 99% of intracellular glucose is destined for such fates, a small fraction (1% to 5%) of intracellular glucose is diverted to the hexosamine biosynthetic pathway which culminates in the formation of low millimolar levels of cytoplasmic uridine diphospho-N-acetylglucosamine (UDP-GlcNAc). Cells use cytoplasmic stores of UDP-GlcNAc for a variety of cell processes, but the present discussion focuses on one particular function: beta O-linkage of GlcNAc (O-GlcNAc) to intracellular proteins.

Unlike Golgi-mediated cotranslational modifications associated with the serial N-linkage of sugars, the O-linkage of GlcNAc occurs posttranslationally and is highly dynamic.3 There are 2 known enzymes regulating the presence of O-GlcNAc on proteins. Using UDP-GlcNAc as the monosaccharide donor, O-GlcNAc transferase (OGT) adds GlcNAc to proteins at serine or threonine residues whereas O-GlcNAcase removes the sugar moiety. Alterations in intracellular glucose flux can directionally change levels of the O-GlcNAc modification. Thus, a modified monosaccharide originating from glucose can function analogously to phosphorylation (O-phosphate linkage to proteins), the stereotypic posttranslational modification. Interestingly, O-GlcNAc modification and phosphorylation have been found to compete with one another for specific amino acid binding sites, further supporting the dynamic biological significance of O-GlcNAc modification.4

Like phosphorylation, the O-GlcNAc modification imparts functional changes in target proteins and can affect transcription, translation, and signaling.3,5 O-GlcNAc may modulate a veritable panoply of cellular events including: proteasome function,6 insulin resistance,7 cell cycle control,8 neutrophil function,9 and possibly Alzheimer’s disease.10 O-GlcNAc can occur at multiple serine or threonine sites on an ever-increasing catalog of proteins. Unlike the seemingly endless cavalcade of kinases and phosphatases associated with phosphorylation, only 2 enzymes regulate the existence of O-GlcNAc modifications on proteins. Such strict control of a seemingly ubiquitous process may reflect the role of O-GlcNAc as a metabolic, or nutrient, signal.11

Most germane to the current study is the origin of the sugar core of the O-GlcNAc modification: glucose. During diabetes, glucose concentrations can become significantly elevated. Such elevations increase flux through the hexosamine biosynthetic pathway, thereby augmenting cytosolic UDP-GlcNAc levels. In such conditions, a net increase occurs in the abundance of O-GlcNAc modifications. To counteract this change and potentially incriminate excessive O-GlcNAc modifications in the pathophysiology of cardiac dysfunction during diabetes, Dillmann’s group2 used adenoviral gene transfer of O-GlcNAcase (ie, the enzyme that removes O-GlcNAc modification). The authors found that adenoviral transfer of O-GlcNAcase reversed the excessive O-GlcNAc modifications associated with diabetes, blunted the contractile abnormalities, and improved intracellular calcium handling in the diabetic myocardium.

To address the molecular mechanism, the authors found SERCA and p-PLB (phosphorylated PLB) levels were augmented by adenoviral-mediated overexpression of O-GlcNAcase.2 Thus, not only might calcium handling be normalized by restoration of SERCA expression but enhanced p-PLB levels may imply alleviation of tonic inhibition of SERCA activity by PLB in the diabetic heart. Do such findings reflect a change in the O-GlcNAc modification level of an upstream kinase or phosphatase and consequent alteration in activity? Future studies are needed to answer such questions and identify other potential protein targets involved in this process. Although detailed mechanistic paradigms remain to be elucidated, the superimposition of O-GlcNAc modifications on our relatively young understanding of phosphorylation events in cardiac physiology creates a dizzying matrix of molecular possibilities. Nevertheless, the exciting investigation by Hu et al2 provides a seminal conceptual framework for further pursuit of the role of O-GlcNAc in the heart (Figure 1).

In the broader scope of cardiac physiology, we remain ignorant of the role of O-GlcNAc in cardiomyocyte function, especially considering that the discovery of O-GlcNAc occurred more than 2 decades ago.12 Because the present study provides stimulating insights regarding calcium handling proteins and O-GlcNAc, one might extrapolate the present experimental questions to interrogate potential direct modification of ion channels, accessory subunits, contractile proteins, respiratory complexes, and other likely conspirators in disease. In an even more global sense, could alterations in...
O-GlcNAc modifications play a role in heart failure? Considering its inextricable link to metabolism, it is likely that many functions in the heart will be affected by O-GlcNAc. In several cell lines, Zachara et al found O-GlcNAc to represent an intrinsic cellular response to acute stressors. Such findings may have important implications for heart failure, ischemia-reperfusion injury, stunning, and potentially any cardiac or vascular disease. What is even more interesting, the findings of Zachara and coworkers also imply that the role of O-GlcNAc may not be a simple case of good versus bad. Indeed, the role of O-GlcNAc may vary with disease, tissue, organelle, and protein.

The current study lays clear inroads into the emerging implications of O-GlcNAc in the heart. This study may be emblematic of a potential departure from an essentially monolithic understanding of post-translational modifications and embrace a more contemporary understanding of cellular and ultimately cardiac function. As our understanding of O-GlcNAc matures, we will cultivate a more thorough understanding of what appears to be the aurally repulsive cousin of phosphorylation, O-GlcNAc.

Acknowledgments

Dr. Jones is supported by an Intramural Research Incentive Grant from the Office of the Senior Vice President for Research.

References


KEY WORDS: glycosylation ■ post-translational modification ■ glucose
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Circ Res. 2005;96:925-926
doi: 10.1161/01.RES.0000168039.61228.67
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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