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COMMENT

Could the control of O-GlcNAcylation play a key role in cardiac remodeling?

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The O-linked β-N-acetylglucosamine (O-GlcNAc) modification of proteins affects a variety of cellular activities, including those important to the function of the heart and cardiovascular system [1]. O-GlcNAc modifications have also been closely associated with several diseases, including cancer, neurodegenerative disorders, and diabetes. O-GlcNAcylation is a dynamic posttranslational modification that, analogous to phosphorylation, involves the deposition and removal of O-GlcNAc from the hydroxyl groups of specific serine and threonine residues. The O-GlcNAc modification cycle is regulated by the concerted actions of O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) (Fig. 1).

Although intracellular glucose is primarily metabolized to pyruvate during glycolysis, from ~2 to 4% of free glucose enters the hexosamine biosynthetic pathway; this pathway ultimately produces the modified nucleotide UDP-GlcNAc, which is consumed as a sugar donor in multiple reactions, including O-GlcNAcylation [2]. O-GlcNAc levels have been observed to change in response to stimuli such as the cell cycle and stress [3], suggesting the functional significance of this modification. Specifically, O-GlcNAcylation presumably influences protein–protein interactions, as many O-GlcNAcylated proteins form multimeric complexes [4], and O-GlcNAc is also thought to regulate protein function in a manner similar to that of phosphate groups [5]. Interestingly, all O-GlcNAc-modified proteins are substrates of protein kinases, and proteins mediating phosphorylation sometimes compete with those mediating O-GlcNAcylation for the same or adjacent serine or threonine residues [5].

O-GlcNAc modification status has been shown to alter the functions of certain proteins involved in cellular stress responses [3]. In a recent issue of Hypertension Research, Yokoe et al. provided evidence showing the functional impact of protein O-GlcNAcylation on the stress response [6]. Specifically, the authors proposed a potential interaction between phosphorylation and O-GlcNAcylation in the context of hypoxic stress. This interaction is particularly interesting in light of evidence suggesting that the interplay between protein phosphorylation and O-GlcNAcylation may influence protein degradation kinetics [7].

Heart failure has been associated with an increased O-GlcNAcylation rate, compromising cardiac contractility during postmyocardial infarction and leading to heart failure, suggesting a possible role for O-GlcNAcylation in the development of chronic cardiac dysfunction [8]. The authors of this study had previously reported that augmented O-GlcNAcylation mitigated cardiac remodeling and dysfunction induced by 2 weeks of exposure to intermittent hypoxia [9]. In this prior report, the authors hypothesized that when O-GlcNAcylation augmentation continues longer than 2 weeks, cardiac dysfunction may be aggravated. To test this hypothesis, we investigated the effect of augmented O-GlcNAcylation on cardiac remodeling and function induced by 4 weeks of exposure to intermittent hypoxia. The authors of the previous study demonstrated that increased O-GlcNAcylation was critical for hypertrophy, fibrosis, and cardiac remodeling inhibition induced by short-term exposure to intermittent hypoxia [9]. This finding was in agreement with another previous report that showed that the hexosamine biosynthetic pathway and subsequent protein O-GlcNAcylation were activated in response to cellular stress or during the development of cardiac hypertrophy [10]. Moreover, these authors had previously shown that augmented O-GlcNAcylation attenuated cardiac remodeling

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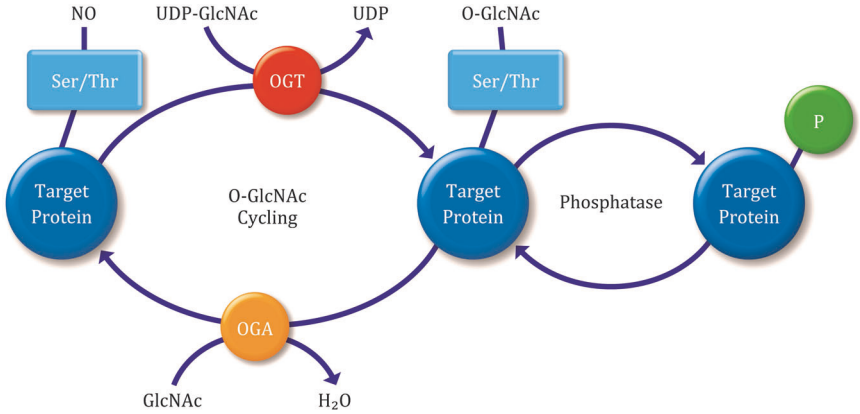

Fig. 1 O-GlcNAc is a dynamic posttranslational modification that, analogous to phosphorylation, cycles on and off the hydroxyl groups of specific serine and threonine residues. Cycling of O-GlcNAc is regulated by the concerted actions of O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA)

induced by 2 weeks of exposure to intermittent hypoxia. Notably, in the present study, augmented O-GlcNAcylation aggravated right ventricular remodeling induced by 4 weeks of exposure to intermittent hypoxia. The authors of the present study considered this apparent paradox and sought to determine the potential importance of the duration of exposure to intermittent hypoxia in the modulation of O-GlcNAcylation. Therefore, the authors of the present study discussed the opposite effects of augmented O-GlcNAcylation on phosphorylation in the 2-week vs. 4-week hypoxia groups and found partial modification of O-GlcNAcylation sites after 2 weeks of exposure to intermittent hypoxia, with some of the O-GlcNAcylation sites showing more O-GlcNAc deposition than others. Since the sites for phosphorylation are likely those where O-GlcNAc can readily interact with a protein, protein phosphorylation may tend to be decreased due to competition with O-GlcNAcylation machinery when exposed to intermittent hypoxia for less than 2 weeks.

Other researchers have proposed that energy depletion may drive differences in the time-dependent effects of hypoxia exposure. In the present study, the glycolytic rate remained high during the entire time that the proteins were exposed to intermittent hypoxia. In the short term, increased glycolysis may have offset increases in the pool of UDP-GlcNAc induced by stress-induced glucose uptake [3]. O-GlcNAcylation increased with cardiac pressure overload, and the increased rate of glycolysis may have led to a decrease in energy storage [11, 12].

This paper is the most interesting report describing the time dependence of a metabolic process that I have ever read. In addition to the experimental findings, the use of a mouse model of intermittent hypoxia is a key advance. For example, the mouse model may be useful for the evaluation of the cardiac pathophysiology associated with sleep apnea, which has been associated with ventricular dysfunction and heart failure due to the intermittent hypoxic ventilatory response. In sleep apnea, remodeling and dysfunction are curiously more pronounced in the right ventricle than in the left ventricle, and the use of animal models such as the model employed in this study may help scientists determine the reason for this imbalance.

Compliance with ethical standards

Conflict of interest ST has received honoraria from Otsuka Pharmaceutical, Daiichi Sankyo, AstraZeneca, Ono Pharmaceutical, Bayer, and Novartis. The other author reports no competing interests.

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