The paradoxical world of protein O-GlcNAcylation: a novel effector of cardiovascular (dys)function

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This editorial refers to ‘O-GlcNAcylation contributes to the vascular effects of ET-1 via activation of the RhoA/Rho-kinase pathway’ by V.V. Lima et al., pp. 614–622, this issue.

Post-translational modification of proteins is a common mechanism for the modulation of protein function, location, and turnover, and protein phosphorylation is probably the most widely studied form of post-translational modification. However, there is an increasing interest in modification of serine/threonine residues by the O-linked attachment of the monosaccharide β-N-acetyl-glucosamine (O-GlcNAc); this is referred to as protein O-GlcNAcylation, to contrast it with traditional N- and O-glycosylation within the secretory pathways. Similar to phosphorylation, O-GlcNAc modification of proteins alters their function, activity, subcellular localization, and stability. Furthermore, since the same residues can be targets for both phosphorylation and O-GlcNAcylation, there is a clear potential for direct interactions between them (Figure 1A).1

The study by Lima et al.2 focuses on the intersection of endothelin (ET-1) signalling and regulation of protein O-GlcNAc and their effects on vascular reactivity. They showed that both ET-1 treatment and augmentation of O-GlcNAc levels increased vascular reactivity to phenylephrine, and both of these effects could be blocked by inhibition of the RhoA/Rho-kinase pathway. Of particular interest, ET-1 itself increased the levels of O-GlcNAc on vascular proteins, and this was blocked by pharmacological inhibition or knockdown of O-GlcNAc transferase (OGT), which catalyses O-GlcNAc synthesis. The inhibition of the ET-1-induced increase in O-GlcNAc also attenuated the activation of RhoA/Rho-kinase, which raises the intriguing possibility that O-GlcNAcylated vascular proteins contribute to the regulation of ET-1 action. This study complements the previous work by the same authors in which they demonstrated that ET-1 augments O-GlcNAc in a time-dependent manner and that DOCA-salt rats have higher levels of O-GlcNAc protein in the vasculature.3,4

Together, these findings suggest that increased O-GlcNAc levels in the vasculature are a contributing factor to hypertension and that this could be mediated via activation of the RhoA/Rho-kinase pathway. These novel observations have potentially profound implications for our understanding of the regulation of vascular function in both normal and pathophysiological conditions; however, they also leave a number of key questions unanswered. Cellular O-GlcNAc levels increase in response to numerous stress stimuli,5 which raises the question as to whether vascular dysfunction is a stressor that induces O-GlcNAcylation and contributes to further dysfunction via modulation of other signalling pathways. Or, as suggested by Lima et al.,6 perhaps O-GlcNAc plays a direct role in mediating vascular dysfunction in response to activation by agonists such as ET-1. Although it is clear that the activation of O-GlcNAc levels has effects on vascular function that are similar to those of ET-1 and that blocking the increase in O-GlcNAc attenuates ET-1 activation of the RhoA/Rho-kinase pathway, the mechanism(s) by which ET-1 increases O-GlcNAc levels remain(s) to be determined. Since inhibition or knockdown of OGT inhibits the effects of ET-1, this would suggest that ET-1 acts by increasing O-GlcNAc synthesis; however, it is currently not known whether the activation of the ET-1 receptor leads to increased OGT activity or increased flux through the hexosamine biosynthesis pathway, leading to an increase in the levels of UDP-GlcNAc, the precursor for O-GlcNAc synthesis. Insulin stimulates the formation of an OGT–insulin receptor complex, resulting in phosphorylation, O-GlcNAcylation, and increased activity of OGT;6,7 therefore, there is precedence for receptor-mediated activation of OGT.

Our knowledge of the role(s) of O-GlcNAc on the regulation of the cardiovascular system is in its infancy, and although there has been a relatively rapid growth in reports of O-GlcNAc in cardiomyocytes over the past few years,7–9 O-GlcNAcylation of vasculature proteins has been much less well studied. Early work showed that O-GlcNAc and OGT proteins were increased in vascular smooth cells with hyperglycaemia,10 and subsequent studies demonstrated that diabetes and hyperglycaemia both result in lower endothelial eNOS protein but with an increase in inactivated and O-GlcNAcylated eNOS.11,12 In contrast to these earlier studies, more recent reports have demonstrated that acute increases in O-GlcNAc improved the inflammatory responses in balloon-injured rat carotid arteries and attenuated neointimal formation.13 Similarly, early studies in cardiomyocytes linked increased O-GlcNAc levels seen in diabetes with impaired contractile...
RhoA/Rho-kinase pathway as a downstream mediator of O-GlcNAc signalling in vascular smooth muscle is a novel and important finding. However, since more than 600 O-GlcNAc-modified proteins have been identified, ranging from transcription factors to cytoskeletal and contractile proteins, it is unlikely to be the only O-GlcNAc-mediated regulatory factor in vascular function. At this time, the move to more translational studies is limited by our marked lack of understanding of the basic mechanisms regulating O-GlcNAc synthesis and degradation combined with the fact that only two enzymes control O-GlcNAc turnover and these are ubiquitously expressed in all cells and tissues. Thus, future investigations into protein O-GlcNAcylation and cardiovascular signalling should focus on the characterization of specific O-GlcNAcylated proteins, including the identification of specific modification sites, as well as identify those factors involved in regulating OGT and OGA activity. Such studies will provide a greater understanding as to how O-GlcNAc exerts both positive and negative effects and potentially provide an avenue for targeted interventions and therapies.

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References