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Minireview Series on the Thirtieth Anniversary of Research on *O*-GlcNAcylation of Nuclear and Cytoplasmic Proteins: Nutrient Regulation of Cellular Metabolism and Physiology by *O*-GlcNAcylation

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The dynamic cycling of *N*-acetylglucosamine (termed *O*-GlcNAcylation) on serine or threonine residues of nuclear or cytoplasmic proteins serves as a nutrient sensor, both independently and also via its interplay with other post-translational modifications, to regulate signaling, transcription, and cellular physiology. Emerging evidence suggests that dysregulation of this ubiquitous post-translational modification contributes to the etiology of some the most important human chronic diseases.

O-GlcNAcylation (first described in the *Journal of Biological Chemistry* about 30 years ago (1, 2)) is the cycling of a monosaccharide, β-*N*-acetylglucosamine, derived directly from glucose, that is attached to serine or threonine hydroxyl groups of most of a cell's nuclear and cytosolic proteins. *O*-GlcNAcylation is essential in mammals and plants and serves as a nutrient sensor to regulate signaling, transcription, and cytosolic functions in a manner that is similar to and often cross-talking with protein phosphorylation and other post-translational modifications. The extent of *O*-GlcNAcylation is directly tied to flux through glucose, amino acids, acetyl-CoA, and nucleotides, and the donor for *O*-GlcNAcylation, UDP-GlcNAc, is second only to ATP in abundance as a high-energy small molecule. *O*-GlcNAcylation not only regulates practically every cellular process in response to nutrients, but also is emerging as a major molecular player in the etiology of diseases of aging, such as diabetes, cancer, and Alzheimer disease (3, 4).

This thematic minireview series provides an overview of our current knowledge about the myriad roles of *O*-GlcNAcylation in cellular physiology. Janetzko and Walker (5) describe the state of our understanding of the *O*-GlcNAc transferase (OGT). OGT, which has thousands of specific substrates, is a multifunctional enzyme that not only is a unique glycosyltransferase, but also serves as a specific protease by a novel mechanism. Alonso, Schimpl, and van Aalten (6) describe the state of our knowledge concerning *O*-GlcNAcase (OGA), the enzyme that removes *O*-GlcNAc from polypeptides. OGA is a unique β-*N*-acetylglucosaminidase with two major domains, a catalytic domain and a GNC5-type histone acetyltransferase domain. Caspase-3 cleaves the enzyme in half upon apoptosis. Several laboratories have studied the OGA enzyme mechanism, produced highly specific and potent inhibitors, and determined the crystal structure of bacterial isoforms. Lewis and Hanover (7) highlight how *O*-GlcNAcylation serves as a direct link from nutrient metabolism to gene expression by regulating transcription. Recent work has shown that nutrient regulation of transcription by *O*-GlcNAcylation is fundamentally important to nearly all aspects of transcription. RNA polymerase II and virtually of its transcription factors are *O*-GlcNAcylated. Assembly of the preinitiation complex requires *O*-GlcNAc on the C-terminal domain of RNA polymerase II, and its removal is required for elongation. Histones are *O*-GlcNAcylated in response to nutrients and stress. *OGT* has been identified as a polycomb gene, which controls major developmental genes (*e.g. HOX* genes). *O*-GlcNAc has been shown to regulate key transcription factors in many ways, most famously as described for NFκB, p53, and many others. *O*-GlcNAcylation also cross-talks with other epigenetic modifications on histones and DNA. Marsh, Collins, and Chatham (8) critically analyze the important roles that *O*-GlcNAc cycling plays in the cardiovascular system. They discuss the many studies that illustrate the roles of *O*-GlcNAcylation both in cardioprotection and in mechanisms underlying diabetic cardiomyopathy. Ma and Vosseller (9) describe recent work showing that increased *O*-GlcNAcylation is a general feature of cancer and is linked to cancer etiology and phenotype. *O*-GlcNAc modifies nearly all oncogene proteins and tumor suppressor proteins, especially those in the nucleus. Depending upon the protein, *O*-GlcNAcylation regulates turnover, expression, or localization. The authors also discuss the potential application of drugs that alter *O*-GlcNAcylation for the treatment of cancer. Vaidyanathan and Wells (10) discuss the many roles that *O*-GlcNAcylation plays both in the etiology of diabetes and in molecular mechanisms underlying diabetic complications, often termed "glucose toxicity." Nutrient excess and hyperglycemia dramatically elevate *O*-GlcNAc in all tissues. Increased *O*-GlcNAcylation disrupts insulin signaling at many points, and the effects of elevated *O*-GlcNAcylation on signaling, mitochondrial functions, and transcription are emerging as a major underlying cause of glucose toxicity. Zhu, Shan, Yuzwa, and Vocadlo (11) discuss the emerging links between glucose hypometabolism in the brain and the concomitant reduction of *O*-GlcNAcylation of neuronal proteins to the progression of Alzheimer disease. *O*-GlcNAcylation is highly abundant in the brain, where it appears to serve many functions, one of which is the protection of brain proteins from hyperphosphorylation and protein aggregation.

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Thus, in the past 30 years, it has become apparent that not only is *O*-GlcNAcylation an abundant, ubiquitous, and dynamic post-translational modification, which serves as a nutrient sensor to regulate signaling, transcription, and cellular physiology, but it is also emerging that dysregulation of *O*-GlcNAc cycling appears to play a significant role in the major chronic diseases of aging. This thematic minireview series provides a succinct and cutting-edge summary by leading experts of the major findings in this rapidly emerging field of research.

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