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Post-translational Modifications of Proteins in Metabolic Syndrome

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Metabolic syndrome is accompanied by central obesity, dyslipidemia, compromised fasting glucose, and hypertension [1]. Unfortunately, all of these factors contribute to damage the endothelium that in turn, will conclude in the development of multiple complications observed in the metabolic syndrome. Endothelial dysfunction is mainly caused by a decrease in nitric oxide (NO) availability due to reduced NO production and/or increase in oxygen-derived free radicals (ROS) that can react with NO and inactivate the active molecule [2]. NO production in endothelial cells is mainly mediated by the endothelial isoform of NO synthase (eNOS), therefore, studies that investigate regulatory mechanisms of this enzyme are essential. Currently, the influence of metabolic syndrome on eNOS regulation is incompletely investigated. Recently, Guterbaum et al. [3] published a paper in this journal that describes the effects of H_2O_2 on phosphorylation of the eNOS of endothelial cells pretreated with supra-physiologic glucose concentrations. Their findings demonstrated that H_2O_2, with the concomitant increase ROS production, resulted in an increase in Thr495 phosphorylation while phosphorylation of Ser1177 was reduced. Furthermore, these authors demonstrated that combination of high glucose concentration with H_2O_2 induces phosphorylation of Thr495 through the PKC pathway. These phosphorylation sites confere fine regulation of eNOS activity [4] and the findings by Guterbaum et al. provide bases to understand more the complexity of pathophysiologic mechanisms that characterize the metabolic syndrome.

Post-translational regulation of eNOS, including phosphorylation, is a growing field that increased the complexity of endothelial function and the maladaptive effects resulting from the metabolic syndrome. Furthermore, integrating other post-translational modifications of proteins can complicate the picture even more. O-GlcNAcylation of serine or threonine residues of nuclear, cytoplasmic and mitochondrial proteins is a dynamic and ubiquitous protein modification. Protein O-GlcNAcylation is emerging as a key regulator of critical biological processes including nuclear transport, translation and transcription, signal transduction, cytoskeletal reorganization, proteasomal degradation, and apoptosis [5-9]. There is a complex interplay between phosphorylation and O-GlcNAcylation [10-13]. Increased levels of O-GlcNAcylation are a pathogenic contributor to glucose toxicity and insulin resistance. O-GlcNAcylation contributes to the adverse effects of diabetes on cardiovascular function as well as mediating the response to ischemic injury. Consequently, it is not surprising that O-GlcNAcylation can impaire the activity o eNOS [14,15]. Further work is needed to understand these complicated pathways and to identify therapeutic approaches to treat the metabolic syndrome.

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