World Academy of Science, Engineering and Technology
International Journal of Nutrition and Food Engineering
Vol:17, No:04, 2023

# Identification of Nutrient Sensitive Signaling Pathways via Analysis of O-GlcNAcylation

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**Abstract :** The majority of glucose metabolism proceeds through glycolytic pathways such as glycolysis or pentose phosphate pathway, however, about 5% is shunted through the hexosamine biosynthetic pathway, producing uridine diphosphate N-acetyl glucosamine (UDP-GlcNAc). This precursor can then be incorporated into complex oligosaccharides decorating the cell surface or remain as an intracellular post-translational-modification (PTM) of serine/threonine residues (O-GlcNAcylation, OGN), which has been identified on over 4,000 cytosolic or nuclear proteins. Intracellular OGN has major implications on cellularprocesses, typically by modulating protein localization, protein-protein interactions, protein degradation, and gene expression. Additionally, OGN is known to have an extensive cross-talk with phosphorylation, be in a competitive or cooperative manner. Unlike other PTMs there are only two cycling enzymes that are capable of adding or removing the GlcNAc moiety, O-linked N-aceytl glucosamine Transferase (OGT) and O-linked N-acetyl glucoamidase (OGA), respectively. The activity of OGT has been shown to be sensitive to cellular UDP-GlcNAc levels, even changing substrate affinity. Owing to this and that the concentration of UDP-GlcNAc is related to the metabolisms of glucose, amino acid, fatty acid, and nucleotides, O-GlcNAc is often referred to as a nutrient sensing rheostat. Indeed OGN is known to regulate several signaling pathways as a result of nutrient levels, such as insulin signaling. Dysregulation of OGN is associated with several disease states such as cancer, diabetes, and neurodegeneration. Improvements in glycomics over the past 10-15 years has significantly increased the OGT substrate pool, suggesting O-GlcNAc's involvement in a wide variety of signaling pathways. However, O-GlcNAc's role at the receptor level has only been identified in a case-by-case basis of known pathways. Examining the OGN of the plasma membrane (PM) may better focus our understanding of O-GlcNAc-effected signaling pathways. In this current study, PM fractions were isolated from several cell types via ultracentrifugation, followed by purification and MS/MS analysis in several cell lines. This process was repeated with or without OGT/OGA inhibitors or with increased/decreased glucose levels in media to ascertain the importance of OGN. Various pathways are followed up on in more detailed studies employing methods to localize OGN at the PM specifically.

**Keywords :** GlcNAc, nutrient sensitive, post-translational-modification, receptor
**Conference Title :** ICNSPMRM 2023 : International Conference on Nutritional Sciences, Physiology, Metabolism and Regulatory Mechanisms
**Conference Location :** New York, United States
**Conference Dates :** April 24-25, 2023