New ways of thinking about old things: the role of O-GlcNAc in cellular metabolism

Chad Slawson¹

Received: 14 May 2018 / Accepted: 22 May 2018 / Published online: 29 May 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Metabolism has always been important. However, metabolism is more than both the catabolic and anabolic functions that maintain nutrient levels and generate high-energy substrates for chemical reactions. Importantly, metabolites derived from metabolic processes are used to sense the environment and signal within the cells. Cellular metabolites are used as “nutrient” sensors allowing cells to rapidly respond to changes in the cellular environment, nutrient influx, or energy levels. Hence, most post-translational modifications derived from metabolites are nutrient sensors. Phosphorylation, acetylation, methylation, to name just a few types of post-translational modifications are used to modulate protein function to respond to the environment. Of singular interest in this special issue of the *Journal of Bioenergetics and Biomembranes* is how the O-GlcNAc post-translational modification responds to metabolic flux.

O-GlcNAc is the attachment of the single N-D-acetylglucosamine sugar to serine and threonine amino acids in nuclear, cytoplasmic, and mitochondrial proteins (Torres and Hart 1984). This ubiquitous modification is found in all higher eukaryotes, O-GlcNAc Transferase (OGT) and O-GlcNAcase (OGA) add and remove the modification respectively, and O-GlcNAcylation is essential for metazoan cell function (Hart et al. 2011). O-GlcNAc is especially sensitive to nutrient inputs since the concentration of the metabolic substrate for OGT, UDP-GlcNAc, is responsive to fluctuations in carbohydrate, amino acids, lipid, and nucleotide pools via the Hexosamine Biosynthetic Pathway (HBP) (Yki-Jarvinen et al. 1997). Hence, O-GlcNAc acts as a master nutrient sensor since UDP-GlcNAc concentrations are sensitive to multiple nutrient inputs. Changes in UDP-GlcNAc concentration alter OGT activity (Kreppel et al. 1997), while

prolonged increased or decreased O-GlcNAc levels leads to transcriptional alterations in OGT and OGA (Kazemi et al. 2010; Zhang et al. 2014). Thus, the cell maintains a homeostatic level of O-GlcNAcylation that is sensitive to nutrient flux. However, prolonged disruptions in O-GlcNAc homeostasis due to nutrient excess or metabolic stress contribute to disease pathogenesis.

The articles within this issue grapple with implications of O-GlcNAc nutrient sensing and disruptions in O-GlcNAc homeostasis in metabolic disease. The review by Hanover, Chen, and Bond brings to focus how O-GlcNAc is disrupted in cancer metabolism and provides a comprehensive overview of oncometabolism. Next, Vasconcelos Dos Santos *et al.* addresses the role of hyperglycemia and glucose flux through the HBP and how this flux alters O-GlcNAc in cancer progression. Bacigalupa, Bhadiadra, and Reginato explore key connections as to how O-GlcNAcylation can modulate glycolytic pathways during cancer progression. Trinca and Hagan then take a deep dive into the role of O-GlcNAc in cancers that affect women highlighting the current state of knowledge and what critical questions still need to be addressed to understand the contribution of altered O-GlcNAcylation in women’s cancers. Sharma, Saluja, and Banerjee investigate how O-GlcNAc contributes to self-renewal and how cancer cells can exploit O-GlcNAcylation to continue growing. Finally, Very *et al.* present an original work exploring the crosstalk between O-GlcNAcylation and another nutrient sensor, mTOR, and present data showing that aberrant O-GlcNAcylation in cancer cells alters mTOR signaling.

Next, the special issue transitions into immunometabolism with a review by Machacek, Slawson, and Fields exploring our current understanding of how O-GlcNAcylation contributes to the function of different immune cell populations while adding new perspectives about the unique metabolic demands of immune cells and the role of O-GlcNAc in regulating those demands. Drake *et al.* present an original work applying a novel stability assay to query the affect of O-GlcNAc on the stability of the Nod2 immune receptor. The special issue

✉ Chad Slawson
cslawson@kumc.edu

¹ Department of Biochemistry and Molecular Biology, University of Kansas Medical Center, Kansas City, KS, USA

closes with a comprehensive analysis by Lagerlöf of the role of O-GlcNAc in neurometabolism while critically analyzing the divergent publications in this subfield. Together, these articles demonstrate the breadth of roles O-GlcNAc plays in sensing nutrients and metabolic flux and demonstrate how disruptions in O-GlcNAc homeostasis contribute to metabolic disease.

References

- Hart GW, Slawson C, Ramirez-Correa G, Lagerlof O (2011) Cross talk between O-GlcNAcylation and phosphorylation: roles in signaling, transcription, and chronic disease. *Annu Rev Biochem* 80:825–858. <https://doi.org/10.1146/annurev-biochem-060608-102511>
- Kazemi Z, Chang H, Haserodt S, McKen C, Zachara NE (2010) O-linked beta-N-acetylglucosamine (O-GlcNAc) regulates stress-induced heat shock protein expression in a GSK-3beta-dependent manner. *J Biol Chem* 285:39096–39107. <https://doi.org/10.1074/jbc.M110.131102>
- Kreppel LK, Blomberg MA, Hart GW (1997) Dynamic glycosylation of nuclear and cytosolic proteins. Cloning and characterization of a unique O-GlcNAc transferase with multiple tetratricopeptide repeats. *J Biol Chem* 272:9308–9315
- Torres CR, Hart GW (1984) Topography and polypeptide distribution of terminal N-acetylglucosamine residues on the surfaces of intact lymphocytes. Evidence for O-linked GlcNAc. *J Biol Chem* 259:3308–3317
- Yki-Jarvinen H et al (1997) UDP-N-acetylglucosamine transferase and glutamine: fructose 6-phosphate amidotransferase activities in insulin-sensitive tissues. *Diabetologia* 40:76–81. <https://doi.org/10.1007/s001250050645>
- Zhang Z, Tan EP, VandenHull NJ, Peterson KR, Slawson C (2014) O-GlcNAcase expression is sensitive to changes in O-GlcNAc homeostasis. *Front Endocrinol (Lausanne)* 5:206. <https://doi.org/10.3389/fendo.2014.00206>