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Review

O-GlcNAc cycling: Emerging roles in development and epigenetics

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ABSTRACT

The nutrient-sensing hexosamine signaling pathway modulates the levels of O-linked N-acetylglucosamine (O-GlcNAc) on key targets impacting cellular signaling, protein turnover and gene expression. O-GlcNAc cycling may be deregulated in neurodegenerative disease, cancer, and diabetes. Studies in model organisms demonstrate that the O-GlcNAc transferase (OGT/Sxc) is essential for Polycomb group (PcG) repression of the homeotic genes, clusters of genes responsible for the adult body plan. Surprisingly, from flies to man, the *O-GlcNAcase* (*OGA*, *MGEA5*) gene is embedded within the NK cluster, the most evolutionarily ancient of three homeobox gene clusters regulated by PcG repression. PcG repression also plays a key role in maintaining stem cell identity, recruiting the DNA methyltransferase machinery for imprinting, and in X-chromosome inactivation. Intriguingly, the *Ogt* gene resides near the Xist locus in vertebrates and is subject to regulation by PcG-dependent X-inactivation. OGT is also an enzymatic component of the human dosage compensation complex. These 'evo-devo' relationships linking O-GlcNAc cycling to higher order chromatin structure provide insights into how nutrient availability may influence the epigenetic regulation of gene expression. O-GlcNAc cycling at promoters and PcG repression represent concrete mechanisms by which nutritional information may be transmitted across generations in the intra-uterine environment. Thus, the nutrient-sensing hexosamine signaling pathway may be a key contributor to the metabolic deregulation resulting from prenatal exposure to famine, or the 'vicious cycle' observed in children of mothers with type-2 diabetes and metabolic disease.

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1. Introduction

The cycling of O-GlcNAc at serine and threonine residues is a nutrient-responsive, post-translational modification (PTM) that impacts target protein activity. The diverse set of proteins (over 600) that are regulated by this PTM are found both in the nucleus and cytoplasm and participate in many fundamental aspects of cellular homeostasis such as cell signaling, mRNA transcription, and protein stability [1,2]. It has been twenty years since O-GlcNAc was first localized to transcription factors and chromatin [3–5]. This discovery suggested the possibility for nutrient-responsive control of the transcriptional machinery through O-GlcNAc modification.

Since those initial observations, our understanding of the role of O-GlcNAc cycling has matured. The enzymes responsible for the addition and removal of this modification have been identified and cloned in several model systems [6–9]. Additionally, upstream modulators that control the level of the donor sugar, UDP-N-acetylglucosamine, are also known [10–13]. Finally, a variety of inhibitors and sensors of O-GlcNAc cycling have been developed [14–16]. Armed with these tools, a number of laboratories have identified O-GlcNAc cycling as a key regulator of nutrient sensing (reviewed in [2]). Additionally, dysregulation of this pathway has a profound impact on diseases of nutrient sensing, such as type II diabetes, and neurodegeneration [17].

In this review, we will focus on the evolution of nutrient responsive O-GlcNAc cycling, detail the impact of O-GlcNAc cycling in the embryonic development of several model systems, and discuss its role in epigenetic programming of developmental fate.

2. Hexosamine signaling—a nutrient-responsive pathway evolves

O-GlcNAc cycling at serine and threonine residues is maintained by the action of OGT and the OGA, enzymes that add and remove O-GlcNAc, respectively. UDP-N-acetylglucosamine (UDP-GlcNAc) is the donor sugar for the transferase reaction. This reaction is the terminal step of the hexosamine biosynthetic pathway.

The hexosamine biosynthetic pathway is acutely sensitive to nutrient flux. Approximately 2–5% of total glucose is shunted into this pathway to produce UDP-GlcNAc. The hexosamine biosynthetic pathway integrates the nutrient status of the cell by utilizing glucose, acetyl-CoA, glutamine, and UTP to produce UDP-GlcNAc (Fig. 1). Interestingly, glucosamine can rapidly increase the levels of UDP-GlcNAc by bypassing the rate-limiting enzyme in this pathway, glutamine:fructose-6-phosphate amidotransferase (GFAT) [10,11]. OGT transmits this nutrient information throughout the cell by glycosylating target proteins. While UDP-GlcNAc is used throughout the secretory pathway as a building block for the synthesis of N-linked and O-linked glycans, as well as the assembly of GPI-anchors, nuclear and cytosolic O-GlcNAc-modified proteins appear to be particularly sensitive to physiological flux of the UDP-GlcNAc pools.

2.1. Evolutionary conservation of the hexosamine signaling pathway

The analogy between phosphorylation and O-GlcNAc modification is often made as these two signaling pathways share many common features and targets. However, these two signaling pathways differ in one important respect; where there are hundreds of kinases and phosphatases, most organisms contain only one OGT and one OGA. The exception appears to be vascular plants and mosses, each containing two OGTs; *spindly* (*spy*) and *secret agent* (*sec*) (reviewed in [18]). In animals, a single OGT appears to be the rule with zebrafish being the only exception. Zebrafish has two *ogt* genes termed *ogta* and *ogtb*. These genes do not appear to be the result of the teleost specific gene duplication event as other teleost fish genomes contain only one *ogt* gene [19,20].

The genomic location of OGT encoding genes in some animals is also intriguing. In the fly, *Ogt*/*sxc* is present in a distinct

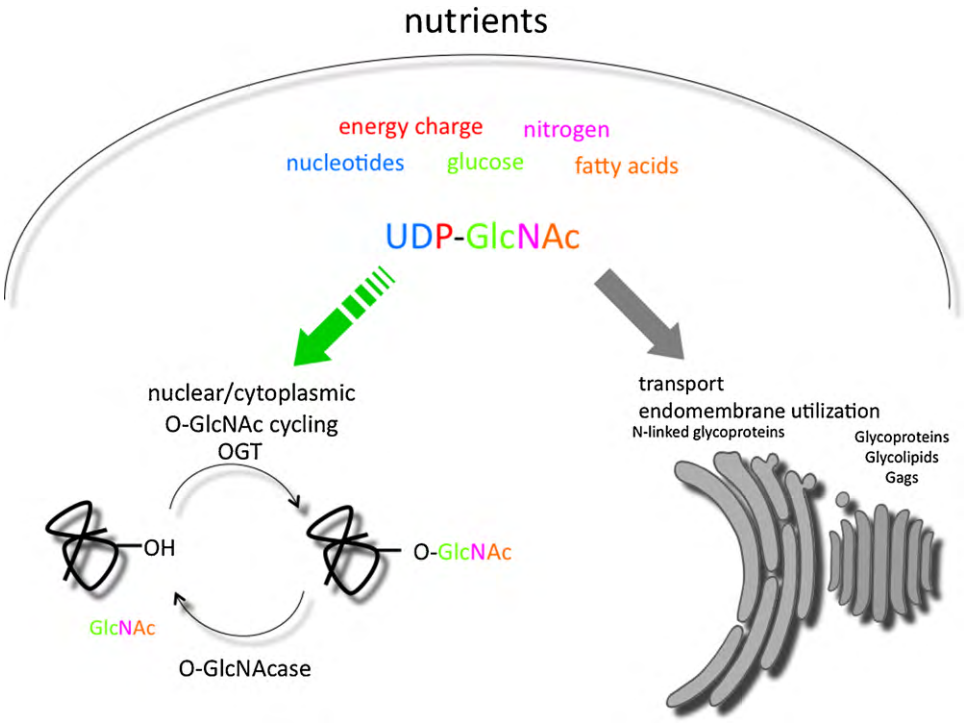

Fig. 1. The nutrient-responsive hexosamine pathway. The concentration of UDP-GlcNAc is responsive to levels of the indicated precursors and serves as a sensor of nutrient status. Pools of UDP-GlcNAc are utilized in the nuclear/cytoplasmic compartment by O-linked GlcNAc transferase (OGT) or transported into the endoplasmic reticulum and golgi (shown in gray) for utilization in N-linked and O-linked glycoprotein biosynthesis and in the formation of glycosaminoglycans (GAGS). O-GlcNAc cycling is maintained by OGT and the O-GlcNAcase and is acutely sensitive to physiological flux of UDP-GlcNAc (green arrow).