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Review

X marks the spot: Does it matter that *O*-GlcNAc Transferase is an X-linked gene?

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ABSTRACT

O-GlcNAcylation has emerged as a critical post-translational modification important for a wide array of cellular processes. This modification has been identified on a large pool of intracellular proteins that have wide-ranging roles, including transcriptional regulation, cell cycle progression, and signaling, among others. Interestingly, in mammals the single gene encoding *O*-GlcNAc Transferase (OGT) is located on the X-chromosome near the *Xist* locus suggesting that tight dosage regulation is necessary for normal development. Herein, we highlight the importance of *OGT* dosage and consider how its genomic location can contribute to a gender-specific increased risk for a number of diseases.

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Contents

1. *O*-GlcNAcylation: OGT as a nutrient sensor

O-GlcNAc cycling links sugar metabolism to post-translational modifications (PTM) that cause changes in protein functions [1]. Two complementary enzymes regulate this modification: *O*-GlcNAc Transferase (OGT), which adds *O*-GlcNAc onto serine and threonine residues of proteins, and *O*-GlcNAcase (OGA), which removes *O*-GlcNAc (Fig. 1). Thus, *O*-GlcNAcylation is a dynamic process, contrary to classical static *N*- and *O*-glycosylation [2,3]. Importantly, *O*-GlcNAcylation is directly modulated by extracellular glucose concentration. Indeed, 2–3% of glucose entering the cell is shuttled through the hexosamine biosynthetic pathway (HBP) whose ultimate product, UDP-GlcNAc, is the substrate of OGT [4]. In addition, because UDP-GlcNAc formation also requires contribution from other metabolic pathways, including those that generate nucleotides, amino acids and fatty acids, *O*-GlcNAcylation is poised to act as a nutrient sensor, regulating proteins involved in major signaling pathways in response to glucose variations [5] (Fig. 1).

Because this glycosylation is added to serine and/or threonine residues on nuclear, cytosolic and mitochondrial proteins, competition exists between *O*-GlcNAcylation and phosphorylation for the same or adjacent sites [6]. Unlike phosphorylation, which is managed by over 1000 kinases and 150 phosphatases [7,8], only two enzymes regulate *O*-GlcNAcylation. Consequently, in response to glucose flux, *O*-GlcNAcylation likely relays a more general signal to the proteome than phosphorylation, which targets particular proteins with specific kinases. Therefore, the interplay between protein *O*-GlcNAcylation and phosphorylation allows the cell to

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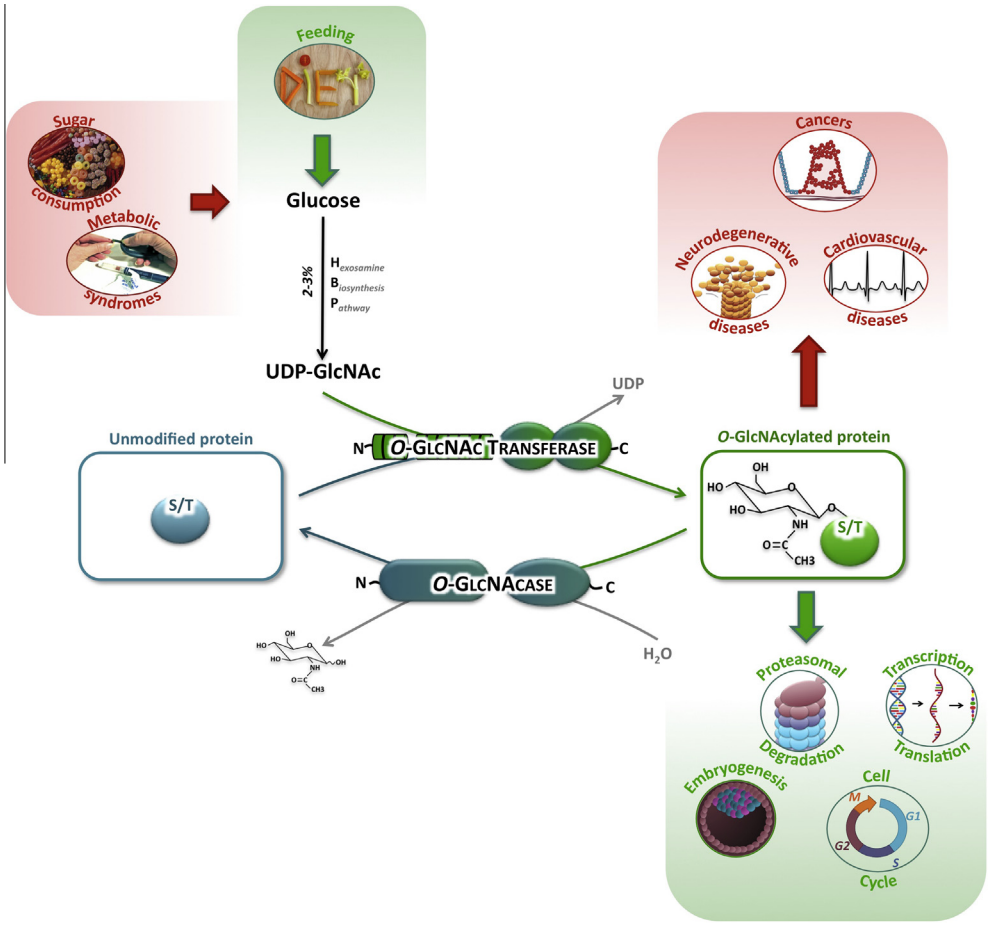

Fig. 1. *O*-GlcNAc cycling: a link between glucose input and physiological/pathological processes. Glucose input is processed partly (2–3%) by the hexosamine biosynthetic pathway, to provide UDP-GlcNAc. This nucleotide sugar is used by *O*-GlcNAc Transferase (OGT) to add a single N-acetylglucosamine onto serine and threonine residues. *O*-GlcNAcase (OGA) removes this modification, yielding a dynamic process. *O*-GlcNAcylated proteins are numerous and varied and impact physiological processes like proteasomal degradation, transcription, translation, cell cycle progression and embryogenesis (outlined in green). Increasing extracellular glucose concentration directly impacts intracellular *O*-GlcNAcylation and may trigger or worsen pathologies such as cancers, cardiovascular and neurodegenerative diseases (outlined in red).

interpret environmental cues and coordinate the appropriate cellular response.

Identified *O*-GlcNAcylated proteins (~4000) have a wide array of functions, from structural proteins to transcription factors to OGT and OGA themselves [9–11]. Hence, the consequences of *O*-GlcNAcylation are likely broad, ranging from conformational changes and altered partner interactions, to changes in protein half-life, sub-cellular localization or activity. By modification of a large number of proteins, *O*-GlcNAcylation is able to alter transcription, translation or proteasomal degradation, each of which are known to regulate complex processes such as the cell signaling and embryonic development [12]. Importantly, aberrant *O*-GlcNAcylation is involved in pathologies including neurodegeneration, cardiovascular disease, type II diabetes and cancer development [13–16]. In these cases, deregulation of nutrition could impact protein modification and exacerbate disease development [17,18] (Fig. 1).

Overall, *O*-GlcNAcylation is a good candidate linking environmental factors, like nutrition, to signaling pathway regulation or deregulation. Modifying intracellular OGT levels impacts *O*-GlcNAc cycling in cells [19]. Accordingly, it is imperative to understand the mechanisms underlying normal OGT regulation in order to gain insights into the consequences of *O*-GlcNAc deregulation. Due to its location on the X-chromosome the gene encoding OGT is subject to complex mechanisms of dosage compensation in females [20], implicating that tight control of OGT dosage is necessary for normal health.

2. Mammalian sex-chromosome dosage compensation

In mammals, sex is determined by the presence of a Y chromosome. Whereas females have two X chromosomes, males have an X and Y chromosome. Thus, Dosage compensation mechanisms are necessary in order to balance transcription from the X-chromosome between males and females. This process for dosage compensation in mammals is called X-inactivation, and is defined by silencing of one of the two X-chromosomes in females [21]. X-chromosome inactivation occurs during early embryogenesis, however, this process occurs differently for extraembryonic *vs* embryonic tissues. In the trophectoderm, which gives rise to extraembryonic tissues, the paternally inherited X-chromosome (Xp) is silenced (imprinted X-inactivation, iXCI) [22]. Within the inner cell mass (ICM), from which the embryo is derived, cells undergo random X-inactivation (rXCI), where about half the cells silence the Xp and the other half silence the maternally-inherited X-chromosome (Xm) [23].

The X-inactivation process is divided into three steps: (1) counting and selection of inactive X (Xi)/active X (Xa) chromosome(s); (2) inactivation, including coating of the Xi by *XIST* RNA and transcriptional repressors; and (3) maintenance of Xi status through long-term modifications of DNA and histones (Fig. 2). The initiation of X-inactivation is achieved by the counting of X-chromosome(s) present in the cell. Only one X has to be active and, as a consequence, each extra X-chromosome is subjected to X-inactivation [24,25]. During this step, the cell also selects the