Biochimica et Biophysica Acta 1800 (2010) 67–79

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Dysregulation of the nutrient/stress sensor *O*-GlcNAcylation is involved in the etiology of cardiovascular disorders, type-2 diabetes and Alzheimer's disease

Tony Lefebvre [a,*], Vanessa Dehennaut [b], Céline Guinez [a], Stéphanie Olivier [a], Ludivine Drougat [a], Anne-Marie Mir [a], Marlène Mortuaire [a], Anne-Sophie Vercoutter-Edouart [a], Jean-Claude Michalski [a]

[a] *CNRS-UMR 8576, Unit of Structural and Functional Glycobiology, IFR 147, University of Lille 1, Villeneuve d'Ascq, France*
[b] *CNRS-UMR 8161, Institute of Biology of Lille, Pasteur Institute of Lille, Lille, France*

ARTICLE INFO

Article history:
Received 25 March 2009
Received in revised form 17 August 2009
Accepted 24 August 2009
Available online 2 September 2009

Keywords:
O-GlcNAcylation
Cardiovascular disorders
Type-2 diabetes
Type-3 diabetes
Alzheimer's disease
Stress
OGT
OGA
Hsp70
HGBA
Hsp70–GlcNAc binding activity

ABSTRACT

O-GlcNAcylation is widespread within the cytosolic and nuclear compartments of cells. This post-translational modification is likely an indicator of good health since its intracellular level correlates with the availability of extracellular glucose. Apart from its status as a nutrient sensor, *O*-GlcNAcylation may also act as a stress sensor since it exerts its fundamental effects in response to stress. Several studies report that the cell quickly responds to an insult by elevating *O*-GlcNAcylation levels and by unmasking a newly described Hsp70–GlcNAc binding property. From a more practical point of view, it has been shown that *O*-GlcNAcylation impairments contribute to the etiology of cardiovascular diseases, type-2 diabetes and Alzheimer's disease (AD), three illnesses common in occidental societies. Many studies have demonstrated that *O*-GlcNAcylation operates as a powerful cardioprotector and that by raising *O*-GlcNAcylation levels, the organism more successfully resists trauma–hemorrhage and ischemia/reperfusion injury. Recent data have also shown that insulin resistance and, more broadly, type-2 diabetes can be controlled by *O*-GlcNAcylation of the insulin pathway and *O*-GlcNAcylation of the gluconeogenesis transcription factors FoxO1 and CRCT2. Lastly, the finding that AD may correspond to a type-3 diabetes offers new perspectives into the knowledge of the neuropathology and into the search for new therapeutic avenues.

1. Characteristics of *O*-GlcNAcylation

1.1. O-GlcNAcylation differs from other types of glycosylation

Glycosylation refers to a group of post-translational modifications (PTMs) that alter more than 50% of human proteins. The finding that 2%–4% of the genome encodes proteins involved in glycosylation processes underlines the fundamental role of these modifications. Among the types of glycosylation described so far, *O*-GlcNAcylation occurs on nucleocytoplasmic [1] and mitochondrial [2] proteins and consists of the addition of a single residue of *N*-acetylglucosamine to the hydroxyl group of serine and threonine. This *N*-acetylglucosaminyl moiety is neither epimerized nor elongated. Hundreds of proteins have been described so far as being *O*-GlcNAcylated, including cell signaling proteins such as the insulin receptor and its receptor substrates [3], the MAP kinase erk2 [4] and prohibitin [5], cell cycle regulators such as Myc [6] and beta-catenin [7], and several structural proteins such as vimentin [8] and actin [4]. *O*-GlcNAcylation was first demonstrated 25 years ago [9] and has been the subject of intensive investigation ever since. The discovery of *O*-GlcNAc groups constituted a major breakthrough in the field of glycobiology, in that it challenged two dogmas of our understanding of glycosylation: for the first time, a kind of glycosylation was found to occur at high levels in the cytosolic and nuclear compartments of eukaryotes, whereas glycosylation had until then been considered to be confined to the lumen of the endoplasmic *reticulum* and Golgi apparatus, to membranous proteins and to the secretory pathway; secondly, the versatility of *O*-GlcNAcylation demonstrated that glycosylation was not always static (as for *N*-glycans or the classic *O*-glycans). The discovery of *O*-GlcNAcylation led a new era in the world of PTM since it was then accepted that nucleocytoplasmic proteins possessed their own glycosylation.

1.2. O-GlcNAcylation is versatile, polyvalent and its level depends upon glucose availability

As mentioned above, one of the main features of *O*-GlcNAcylation is its versatility, and for this reason it is often compared to phosphorylation [10]. However, unlike phosphorylation–dephosphorylation processes, which are regulated by a set of perhaps a thousand kinases (the kinome) and fewer than two hundred phosphatases, the *O*-GlcNAcylation/de-*O*-GlcNAcylation process is only controlled by a few forms of two cytosolic and nuclear enzymes

* Corresponding author. Tel.: +33 3 33 20 43 47 58; fax: +33 3 33 20 43 65 55.
E-mail address: tony.lefebvre@univ-lille1.fr (T. Lefebvre).

0304-4165/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbagen.2009.08.008

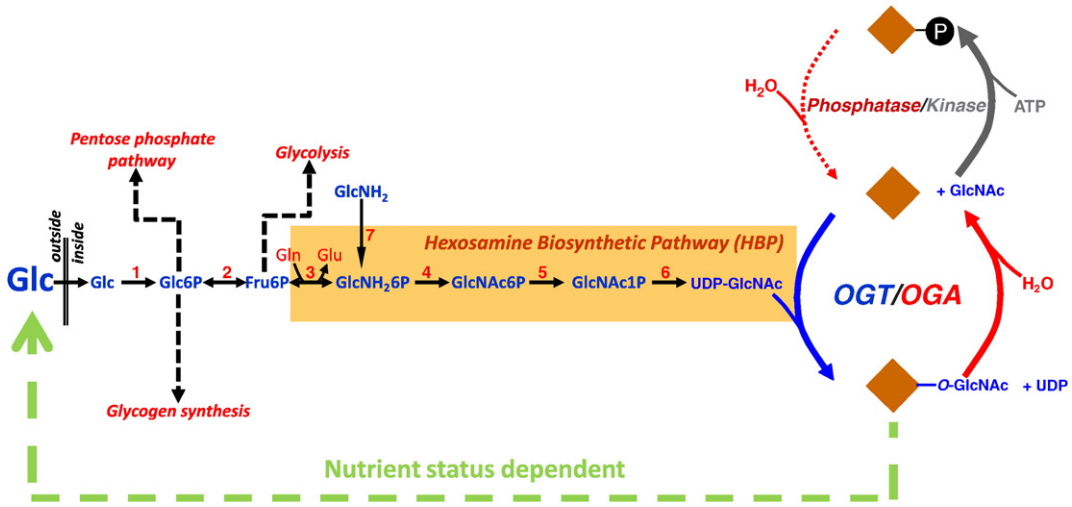

Fig. 1. The *O*-GlcNAcylation processes are dependent upon the nutrient status of the cell and are controlled by two enzymes: OGT and OGA. *O*-GlcNAcylation dynamics is managed by the unique glycosyltransferase OGT that transfers the GlcNAc moiety from UDP-GlcNAc to target proteins, and by the glycosidase OGA that hydrolyses the glycosidic bond. *O*-GlcNAcylation can compete with phosphorylation either at the same site or at an adjacent one. UDP-GlcNAc is the end-product of the hexosamine biosynthetic pathway, which flux is controlled by GFAT. The level of UDP-GlcNAc, and consequently of *O*-GlcNAcylation, is tightly dependent upon the nutrient status of the cell (green dashed arrow). **1**, hexokinase; **2**, phosphoglucose isomerase; **3**, glutamine:fructose-6-phosphate amido transferase (GFAT); **4**, glucosamine-6-phosphate acetyl transferase; **5**, phospho-*N*-acetylglucosamine mutase; **6**, uridine di-phospho-*N*-acetylglucosamine pyrophosphorylase; **7**, glucosamine kinase; **Fru6P**, fructose-6-phosphate; **Glc**, glucose; **Glc6P**, glucose-6-phosphate; **GlcNAc**, *N*-acetylglucosamine; **$GlcNH_26P$**, glucosamine-6-phosphate; GlcNAc6P, *N*-acetylglucosamine-6-phosphate; **GlcNAc1P**, *N*-acetylglucosamine-1-phosphate; **Gln**, glutamine; **Glu**, glutamate; **OGA**, *O*-GlcNAcase (*O*-linked *N*-acetylglucosaminidase); **OGT**, *O*-GlcNAc transferase (*O*-linked *N*-acetylglucosaminyl transferase); **UDP**, uridine di-phosphate; **UDP-GlcNAc**, uridine di-phospho-*N*-acetylglucosamine.

[11]: OGT or *O*-linked *N*-acetylglucosamine transferase (E.C. 2.4.1.94), which transfers the monosaccharide from UDP-GlcNAc to the protein, and OGA or *O*-linked-*N*-acetylglucosaminidase or *O*-GlcNAcase (E.C. 3.2.1.52), which removes the GlcNAc moiety (Fig. 1). Three forms have been described for the former: the 110 kDa ncOGT (nucleocytoplasmic OGT), the 78 kDa sOGT (short OGT) and the 103 kDa mOGT (mitochondrial OGT) [12]. Two forms have been described for OGA [13]: a 130 kDa long form with two distinct activities, an N-terminal *O*-GlcNAcase activity and a C-terminal putative histone acetyl transferase activity, and a 75 kDa short form which lacks the second activity. In addition to being highly dynamic, *O*-GlcNAcylation displays the unique characteristic of competing with phosphorylation at the same site or in its vicinity, leading to mutual exclusion [14,15]. Consequently, owing to the physical differences created by the two types of PTM, this reciprocal relationship may result in behavioral differences in the modified protein: the neutrality of the GlcNAc moiety is in striking contrast to that of phosphate acidity, with the first remaining uncharged regardless of pH, whereas the second is negatively charged at physiological pH (conformational differences in the protein breed an assembly with distinct partners and then the activity is modified). Beyond the competition between *O*-GlcNAc and phosphate, the role played by *O*-GlcNAcylation is still unclear, in spite of abundant investigation. Nevertheless, it appears that *O*-GlcNAcylation plays a pivotal role in many fundamental cellular processes such as transcription [16], translation [17], cell signaling [18], cell trafficking [19,20], cell cycle control [8,21–23] and development

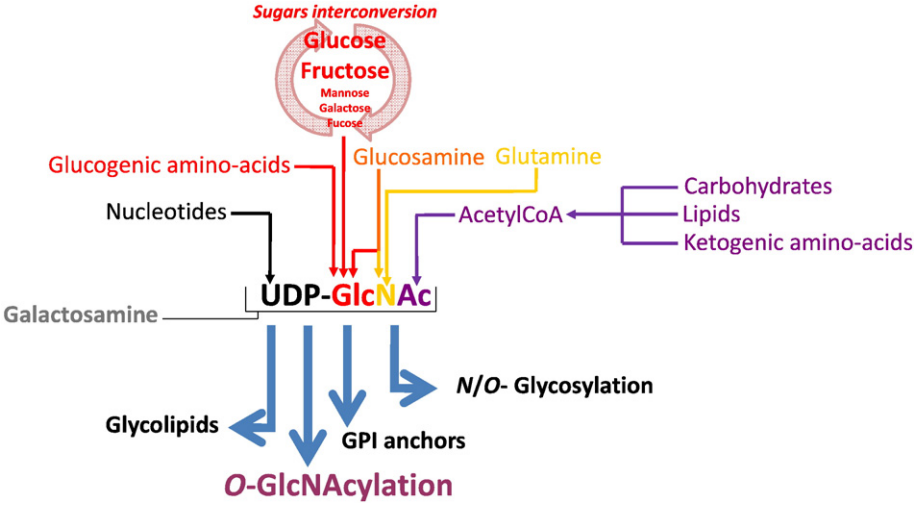

Fig. 2. UDP-GlcNAc is at the crossroad of many metabolisms. The level of UDP-GlcNAc is tightly correlated to the nutrient status of the cell, since many catabolic pathways converge on the nucleotide-sugar: nucleotides supply the UDP part of the molecule; the glucogenic amino acids and many carbohydrates, through interconversion reactions, contribute the carbohydrate backbone of UDP-GlcNAc; glucosamine directly participates in the elaboration of the glucosaminyl moiety (bypassing GFAT-mediated control); the amino group is donated by glutamine through the activity of GFAT; acetyl-coenzyme A (AcetylCoA) is provided by the beta-oxidation of fatty acids, by glycolysis and by metabolism of the ketogenic amino acids. Galactosamine can also quickly provide UDP-GlcNAc (interconversion of UDP-GalNAc and UDP-GlcNAc by 4-epimerase). UDP-GlcNAc is the donor of the GlcNAc group for many glycosylation processes.