Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Biology

Nutrient regulation of gene expression by O-GlcNAcylation of chromatin

Stéphan Hardivillé and Gerald W Hart

O-GlcNAcylation is a dynamic post-translational modification that is responsive to nutrient availably via the hexosamine biosynthetic pathway and its endproduct UDP-GlcNAc. O-GlcNAcylation serves as a nutrient sensor to regulate the activities of many proteins involved in nearly all biological processes. Within the last decade, OGT, OGA and O-GlcNAcylation have been shown to be at the nexus of epigenetic marks controlling gene expression during embryonic development, cell differentiation, in the maintenance of epigenetic states and in the etiology of epigenetic related diseases. OGT O-GlcNAcylates histones and epigenetic writers/erasers, and regulates gene activation, as well as gene repression. Here, we highlight recent work documenting the important roles O-GlcNAcylation and its cycling enzymes play in the nutrient regulation of epigenetic partners controlling gene expression.

Address
Department of Biological Chemistry, Johns Hopkins University, School of Medicine, 725 N. Wolfe St., Baltimore, MD 21205-2185, USA

Corresponding authors: Hardivillé, Stéphan (shardiv1@jhmi.edu) and Hart, Gerald W (gwhart@jhmi.edu)

Current Opinion in Chemical Biology 2016, **33**:88–94

This review comes from a themed issue on **Chemical genetics and epigenetics**

Edited by **Danica G Fujimori** and **Stuart Conway**

http://dx.doi.org/10.1016/j.cbpa.2016.06.005

Introduction

Can what we eat change our genetics? Beside toxic compounds that have the ability to induce mutations, our eating habits do not change the nucleotide sequence of our genes. However, organisms with a predefined set of genes have to maintain proper homeostasis and adapt to their environment, especially to adapt to nutrient availability. Phenotype adaptation is a long-term adjustment to the environment and can be done by heritable encoded information on DNA without changes in the gene sequence [1]. This second layer of information is called epigenetics and includes DNA methylation, post-translational modifications (PTMs) of histones and chromatin remodeling. Epigenetics is also an important feature of embryogenesis and cell fate, controlling and defining transcriptional pattern crucial for cellular lineage.

The first evidence that link O-GlcNAcylation to chromatin and transcription was found in Drosophila [2]. O-GlcNAcylation is a versatile PTM controlled by two non-redundant enzymes: the O-GlcNAc transferase (OGT) transfers the GlcNAc moiety from UDP-GlcNAc to a serine or a threonine residue, while the O-GlcNAcase (OGA) removes the modification. UDP-GlcNAc is a main cellular nutrient sensor since its synthesis through the hexosamine biosynthetic pathway (HBP) depends on flux through every major metabolic pathway (graphical abstract). Since OGT's enzymatic activity and substrate specificity varies according UDP-GlcNAc concentration, variation in metabolism that feed the HBP have profound effects on protein O-GlcNAcylation [3]. Within the last decade, studies have defined O-GlcNAcylation as an epigenetic mark and linked its cycle to the regulation of chromatin modifications.

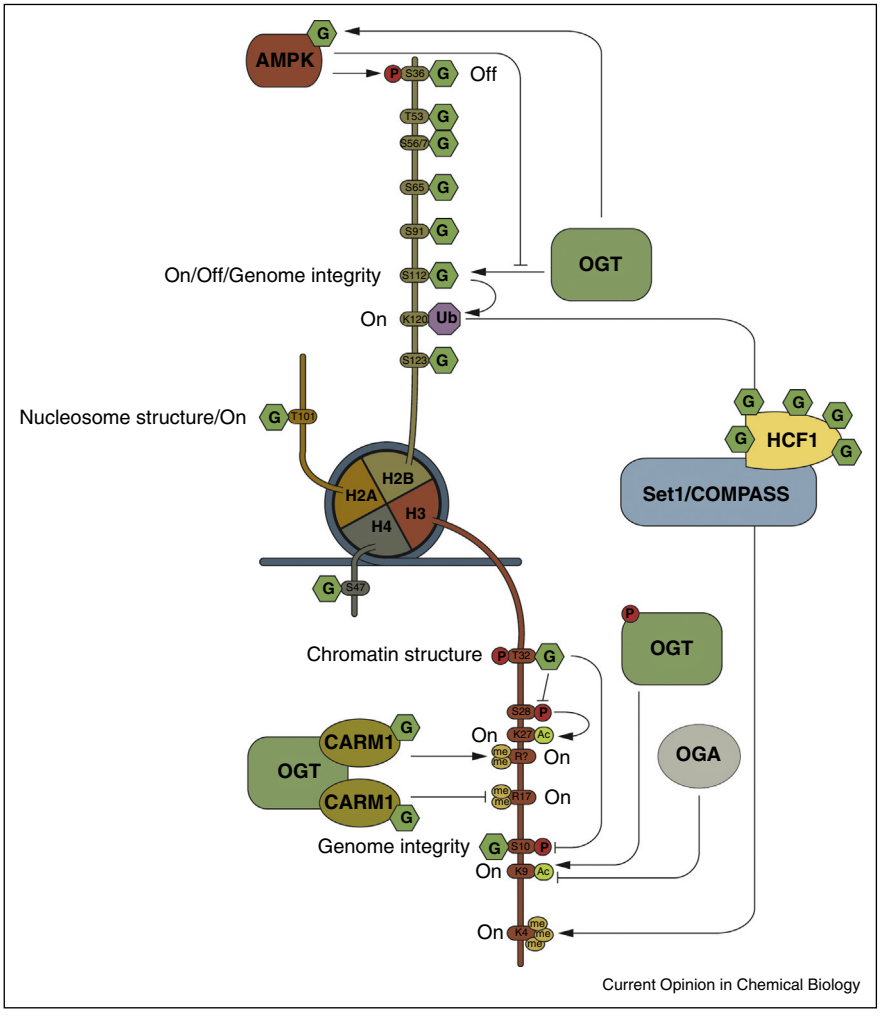
Multiple roles of histone O-GlcNAcylation

The histone code is written by molecular complexes that add or remove part of the code in response to various cellular stimuli or metabolism. Although a recent paper called into question histone O-GlcNAcylation [4], the presence of the sugar on each subunit of the nucleosome has been reported independently by many laboratories and some sites have been mapped (reviewed in [2]). Some of the site-specific functions have been documented (Figure 1).

The O-GlcNAc/phosphorylation interplay on histone H3 is essential for mitosis. Overexpression of OGT reduces phosphorylation of $H3^{S10}$ and leads to errors in chromosomal segregation, while OGA inhibition impairs G2-M transition [5,6]. The $H2B^{S112O\text{-}GlcNAc}$ mark is associated with DNA damage response and genomic stability [7]. O-GlcNAcylation at $H2B^{S112}$ is increased at DNA double strand breaks. Down-regulation of OGT or $H2B^{S112A}$ mutant over-expression impairs homologous repair (HR) and non-homologous end joining. Since $H2B^{S112O\text{-}GlcNAc}$ stimulates $H2BK^{120}$ ubiquitination that activates the ring finger protein 20 [8], OGT and O-GlcNAcylation could be key initiators for the recruitment of the HR complex in response to DNA damage.

Histone O-GlcNAcylation is linked to gene transcription. The sugar at T101 of H2A destabilized H2A/H2B dimmers in the nucleosome, promoting an open chromatin

Figure 1



Nucleosome O-GlcNAcylation. The O-GlcNAcylation (G) of the histone core is extensive and interplays with other PTMs, such as phosphorylation (P), methylation (me), acetylation (Ac), or ubiquitination (Ub). All four subunits of the nucleosome are modified by the sugar, and site specific O-GlcNAcylation is involved in gene transcription activation (on) or repression (off), chromatin structure or genomic stability.

state [9•]. This suggests that O-GlcNAcylation at $H2A^{T101}$ would lower the barrier for RNA polymerase passage and hence increase transcription. H2B O-GlcNAcylation at S112 has been reported to have multiple roles. In HepG2 cells, activated AMPK phosphorylates OGT, which lowers $H2B^{S112}$ O-GlcNAcylation and inhibits expression of genes regulated by $H2B^{S112O\text{-}GlcNAc}$ [10]. In HeLa cells, $H2B^{S112}$ O-GlcNAcylation co-localizes with $H2B^{K120Ub}$ mark. The $H2B^{K120Ub}$ mark acts as a platform for the SET1/COMPASS complex that stimulates $H3^{K4}$ trimethylation and gene transcription. Conversely, H2B O-GlcNAcylation is a stable chromatin landmark during adipocyte differentiation [11••]. Ronningen *et al.* identified long $H2B^{S112O\text{-}GlcNAc}$ enriched domains, called GADs, ranging from 60 kb to about 10Mb. At the early stage of adipogenesis, lamin-associated domains rearrange following GADs pattern, releasing the repression of genes mainly related to metabolic processes, but repressing genes within GADs [11••], suggesting a repressive role for $H2B^{S112O\text{-}GlcNAc}$ in cell fate.

While yeast apparently lack O-GlcNAcylation and O-GlcNAcylation enzymes, it was recently reported that O-Man glycosylation of nuclear and cytoplasmic proteins mirror mammals O-GlcNAcylation [12••]. A peptide covering the K123 of yH2B (ubiquitination of $yH2B^{K123}$ is homologue of the mammalian $H2B^{K120Ub}$) is O-Man glycosylated. Considering that glucose metabolism increases both mammalian $H2B^{K120ub}$ and yeast $H2B^{K123Ub}$ [13,14], O-Man glycosylation of yH2B could mimic the molecular mechanism of $H2B^{K120}$ ubiquitination mediated by $H2B^{S112O\text{-}GlcNAc}$ observed in mammals.