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O-GlcNAc Signaling in Cancer Metabolism and Epigenetics

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Abstract

The covalent attachment of β -D-N-acetylglucosamine monosaccharides (O-GlcNAc) to serine/threonine residues of nuclear and cytoplasmic proteins is a major regulatory mechanism in cell physiology. Aberrant O-GlcNAc modification of signaling proteins, metabolic enzymes, and transcriptional and epigenetic regulators has been implicated in cancer. Relentless growth of cancer cells requires metabolic reprogramming that is intertwined with changes in the epigenetic landscape. This review highlights the emerging role of protein O-GlcNAcylation at the interface of cancer metabolism and epigenetics.

1. Introduction

In the United States, it has been estimated that half of all men and one third of all women will suffer from cancer during their lifetime. The transition of normal cells to cancer cells is marked by a series of genetic and epigenetic changes associated with chromosomal instability, oncogene activation, tumor suppressor functions, gene silencing, and DNA repair deficiency. Epigenetic reprogramming, including alterations in DNA methylation and histone modifications, drive tumorigenesis by altering chromosomal structure and gene expression [11, 31, 39, 52]. Epigenetic DNA modifications such as global hypomethylation and tumor suppressor specific hypermethylation in CpG rich regions have been observed in multiple types of cancer cells [98]. Gene specific alterations in histone modifications, loss of histone H4 acetylation and trimethylation has frequently been observed in cancer cells [9, 11, 31].

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Among the most distinguished hallmarks of cancer, metabolic rewiring is characterized by increased glucose uptake and aerobic glycolysis to facilitate rapid cell growth and proliferation [116, 117]. Metabolic rewiring is closely associated with epigenetic reprogramming, which can be influenced by environmental factors, such as diet [65] and genetic defects in metabolic enzymes [2, 7, 24, 29, 57, 58, 89, 111]. Mounting evidence has shown that epigenetics can contribute to reprogramming of cancer metabolism by modulating gene expression [20, 56, 120, 123].

O-GlcNAcylation is a posttranslational covalent modification by O-linkage of a β -N-acetylglucosamine (O-GlcNAc) moiety at serine or threonine residues of proteins [40, 41, 110]. Similar to other posttranslational modifications such as phosphorylation and acetylation, O-GlcNAc can modify a wide spectrum of intracellular proteins, including signaling proteins, transcription factors, metabolic enzymes, and histones, through which it regulates crucial cellular processes, such as signal transduction, transcription, translation, and protein degradation [34, 40, 41, 122-125, 128]. Cellular O-GlcNAc levels are linked to both physiological and disease conditions. A growing body of evidence reveals its relevance to diabetes, cancer, neurodegenerative disease, and cardiovascular disease [22, 26, 30, 94, 126]. As reviewed elegantly elsewhere [32], aberrant O-GlcNAcylation has been observed in a wide range of cancer types, and a regulatory role of O-GlcNAcylation in cancer has begun to be uncovered (Table 1).

Yet unlike the cycling of phosphorylation, which involves 428 serine/threonine kinase and ~40 phosphatases [4, 76], the cycling of O-GlcNAcylation depends merely on two opposing enzymes: O-linked β -N-acetylglucosamine transferase (OGT) catalyzes the addition of the sugar moiety to the protein and O-GlcNAcase (OGA, NCOAT, or MGEA5) catalyzes the sugar removal. O-GlcNAc modification dynamically responds to environmental and physiological cues, among which nutrient availability is vital. Cellular O-GlcNAcylation levels can fluctuate in response to the availability of nutrients such as glucose, free fatty acid, uridine, and glutamine, endowing this modification with the unique property as a nutrient sensor [13, 32, 40, 67, 118, 127]. The addition of the O-GlcNAc moiety requires the high-energy molecule UDP-GlcNAc, as the donor substrate. UDP-GlcNAc is a major end product of hexosamine biosynthesis pathway (HBP), which is fed by nutrient flux into the cell. In this regard, the cellular O-GlcNAcylation level is believed to reflect on systemic metabolic status (Figure 1).

The role of O-GlcNAc modification in epigenetics has emerged as a topic of interest. OGT and OGA can target histones and enzymes involved in epigenetic modifications, which could potentially influence gene expression. O-GlcNAc can serve as the link between nutrient availability and epigenetics, as epigenetic modifications also require nutrient derived metabolites as substrates. In this review, we summarize the current understanding of the role of O-GlcNAc at the interface of cancer metabolism and epigenetics.

2. Protein O-GlcNAcylation in cancer metabolism

2.1 O-GlcNAcylation of signaling proteins

In analogy to phosphorylation, O-GlcNAcylation is a regulatory mechanism that modifies cellular proteins at serine and threonine residues in response to stress, hormones and nutrients. Crosstalk between O-GlcNAcylation and phosphorylation has been implicated in regulation of signal transduction in cancer [44, 107]. Direct O-GlcNAcylation of kinases and phosphatases may contribute to cancer phenotypes. Akt Ser 473 undergoes both phosphorylation and O-GlcNAcylation in murine pancreatic cells, and the balance between O-GlcNAcylation and phosphorylation determines cell survival or apoptosis [54]. In thyroid anaplastic cancer cells, down-regulation of OGA activity increases cell proliferation partially depending on the IGF-1-Akt1-GSK3 -cyclin D1 pathway [62]. OGT targets several mitotic kinases and inhibits cyclin-dependent kinase 1 (CDK1) activity by increasing phosphorylation, suggesting a vital role for OGT in cell division [115]. Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) plays an important role in various cancers, such as prostate cancer, liver cancer and neuroblastomas [72, 73, 91]. This kinase has been implicated as a link between metabolic state and apoptosis [82]. Moreover, acute hyperglycaemia triggers O-GlcNAcylation and autonomous activation of CaMKII in cardiomyocytes, pointing to the role of CaMKII O-GlcNAcylation as a metabolic sensor [30]. Further studies are expected to provide direct evidence that O-GlcNAcylation of kinases and/or phosphatases regulates cancer metabolism.

2.2 O-GlcNAcylation of metabolic enzymes

Cancer cells exhibit increased HBP flux and O-GlcNAcylation of multiple metabolic enzymes [18, 70]. The O-GlcNAc moiety has been detected on a majority of glycolytic enzymes. phosphofructokinase-1 (PFK1) catalyzes the first committed step unique to the glycolytic pathway. O-GlcNAcylation at Ser 529 inhibits PFK1 activity, thereby rerouting glucose flux through the pentose phosphate pathway (PPP) to increase biosynthetic precursors for cell growth. The mechanism of inhibition by O-GlcNAc is possibly due to shielding the substrate-binding site and dampening oligomerization of PFK1 [125]. Pyruvate kinase catalyzes the last committed step in glycolysis. O-GlcNAcylated pyruvate kinase muscle isozyme 2 (PKM2) is present in breast cancer but not the normal tissues; however, whether O-GlcNAcylation of PKM2 plays a regulatory role remains unknown [18]. Additionally, proteomic analysis reveals the presence of O-GlcNAc moieties on many enzymes involved in amino acid and nucleotide metabolism, such as, phosphoglycerate dehydrogenase (PHGDH), argininosuccinate synthetase (ASS), and thymidylate synthase (TYMS) [80]. Therefore, it is very likely that O-GlcNAcylation is involved in reprogramming the entire metabolic network in cancer cells.

2.3 O-GlcNAcylation of transcription factors

A growing number of transcription factors involved in cancer have been shown to harbor O-GlcNAc. This modification regulates transcription factors through multiple mechanisms, including protein-protein interaction, protein stability, transcriptional activity, DNA-binding activity, nucleo-cytoplasmic shuttling, and transcription factor expression [85]. The oncoprotein c-Myc is regulated by reciprocal glycosylation and phosphorylation at Thr 58

[20, 21, 53]. OGT increases the stability of c-Myc proteins and, on the other hand, c-Myc can drive global O-GlcNAc modification and act as a potential upstream regulator of OGT target genes [47] [77]. Consistently, the expression of c-Myc and OGT is tightly correlated in human prostate cancer samples [47]. NF- κ B is O-GlcNAcylated at Thr 322 and Thr 352, and Thr 352 O-GlcNAcylation is especially critical for releasing NF- κ B from I B inhibition and allowing nuclear translocation [121]. In pancreatic cancer cells, hyper-O-GlcNAcylation of NF- κ B promotes activating phosphorylation at Ser 536, nuclear translocation, and transcriptional activity [69]. Furthermore, the activation of the IKK-NF- κ B pathway by loss of tumor suppressor p53 increases aerobic glycolysis [55]. In MCF7 cells, serum-stimulated cell cycle entry is associated with progressive OGT binding and O-GlcNAcylation of β -catenin [83]. The expression of β -catenin in colon cancer cells is also correlated with HBP flux and O-GlcNAcylation [84]. Hence, O-GlcNAcylation of transcription factors may be an important layer of regulation of cancer cell growth, proliferation, and metabolism.

3. Protein O-GlcNAcylation in epigenetics

3.1 The epigenetic code

Genetic and epigenetic regulation is essential for life. Cancer arises from a combination of changes to the genome and the epigenome [10]. An epigenome is defined as the complete set of DNA methylation and posttranslational modifications of histone proteins [5, 12]. These covalent modifications alter chromatin structure and regulate gene expression [9, 59]. Histones can be posttranslationally modified by phosphorylation, acetylation, succinylation, malonylation, methylation, and ubiquitination [5, 59, 90, 119, 130]. Lysine acetylation of histones by histone acetyltransferases (HATs) generally correlates with increased transcriptional activity, whereas deacetylation by histone deacetylases (HDACs) is frequently involved in gene silencing in many human cancer types [92]. Histone lysine methylation is implicated in a wide range of processes such as tissue-specific gene expression, maintenance of genome stability, stem cell self-renewal and lineage commitment. Molecular consequences of histone lysine methylation at different sites vary widely. For example, H3K4 methylation is a signature for transcriptionally active genes, whereas H3K9 methylation is generally associated with repressed genes [105]. H3K27 trimethylation is typical of silent chromatin, but also present at the promoters of poised developmental genes in stem cells. Depending on the context and degree, H3K36 methylation regulates different molecular events such as transcriptional activation, suppression of aberrant transcription during transcriptional elongation, and alternative splicing [114]. Globally, H3K79 methylation is associated with actively transcribing genes, and is implicated in transcriptional regulation, DNA damage response, and cell cycle control [81]. Additionally, H2B monoubiquitination facilitates H3K4 and H3K79 methylation [104]. Monoubiquitination of histone proteins, primarily H2A and H2B, is linked to gene silencing and activation. These histone modifications are essential for fundamental biological processes and disease conditions, such as cancer [10, 51].

Recent studies reveal that histones also bear O-GlcNAcylation. Intriguingly, OGA is a bifunctional enzyme harboring O-GlcNAc cleavage activity as well as HAT activity, implying an intrinsic relationship between histone O-GlcNAcylation and acetylation. OGA

HAT activity has been implicated in orexin neurogenesis [43]. However, we are just beginning to understand the function of histone O-GlcNAcylation as part of the epigenetic code.

3.2 O-GlcNAcylation of histones

Recent reports indicate a regulatory role for histone O-GlcNAcylation in mitosis, chromatin dynamics and gene expression [33, 96, 97]. Analysis of histone proteins in HeLa cells has shown that histones H2A, H2B, and H4 are dynamically O-GlcNAcylated, which depends on the phase of cell cycle and cellular stress conditions [97]. Sakabe *et al.* reported that both OGT catalytic activity and O-GlcNAc levels on histones (particularly H3) are reduced during early mitosis and are gradually increased during late mitosis to G1 phase [96]. Zhang *et al.* described that histone O-GlcNAcylation is reduced in S phase and that H3 O-GlcNAcylation persists through late G2 and mitosis [130]. Forced expression of OGT alters a variety of histone modifications, such as H3K9 acetylation, S10 phosphorylation, and R17 and K27 methylation, indicating that O-GlcNAc signaling might regulate chromatin dynamics by affecting other histone marks [96, 97]. It was also reported that H2B O-GlcNAcylation at S112 is sensitive to glucose and facilitates adjacent K120-monoubiquitination that is associated with transcriptionally active loci [34]. Crosstalk between histone O-GlcNAcylation and phosphorylation may be important for epigenetic regulation. O-GlcNAcylation of histone H3 at T32 is inversely correlated with phosphorylation at S10, S28, and S32 during cell cycle progression, further indicating a role for histone O-GlcNAcylation in cell cycle regulation [33, 130]. Aurora B kinase and protein phosphatase 1 (PP1) mutually regulate H3 phosphorylation at S10, S28 and S32 [23, 36, 78]. Also, It is known that aurora B and PP1 are in a transient complex with OGT and OGA during mitosis [107, 108]. Therefore, it is possible that aurora B, PP1, OGT and OGA cooperatively regulate chromatin dynamics, gene expression and cell division by controlling histone phosphorylation and O-GlcNAcylation [19, 107].

3.3 O-GlcNAcylation of chromatin regulators

Oncogenic transformation frequently involves global DNA hypomethylation, gene promoter hypermethylation and aberrant histone posttranslational modifications. Evidence is emerging that OGT can affect local and global chromatin states by interacting with various enzymes responsible for DNA methylation and histone modifications [131].

The Polycomb group (PcG) proteins regulate patterning of body segments by silencing Hox genes during *Drosophila* development [86]. Among the earliest evidence that OGT is involved in epigenetic regulation, two groups reported that *Drosophila* OGT is encoded by a PcG gene known as super sex combs (*sxc*) [35, 106]. *Sxc/Ogt* glycosylates another member of PcG proteins, Polyhomeotic, to facilitate its binding to target sites [35, 106]. In *Drosophila* and mammals, PcG proteins assemble into two Polycomb repressive complexes (PRC1 and PRC2), which play critical roles in stem cell fate determination, embryonic development, and cancer [3, 100]. PRC1 mediates H2A monoubiquitylation that interferes with transcriptional elongation, whereas PRC2 is responsible for H3K27 di- and tri-methylation, known as repressive epigenetic marks. PRC2 integrity is essential for OGT protein stability and cellular O-GlcNAc distribution in mouse embryonic stem cells,

suggesting a link between O-GlcNAcylation and Polycomb repression in mammals [79]. Human homologues of *Drosophila* additional sex combs, ASXL1 and ASXL2, are frequently mutated in myeloid malignancies [1].

Genome-wide mapping reveals that histone methylation reliably discriminates the genes that are expressed, poised for expression, or stably repressed [75]. Mixed lineage leukemia 5 (MLL5) is a SET domain-containing methyltransferase that mediates H3K4 methylation amenable to transcriptional activation [132]. Host cell factor C1 (HCF-1) is a regulator of cell cycle that is subject to the proteolytic maturation catalyzed by OGT [15, 66]. HCF-1 can recruit MLL5 to E2F1-responsive promoters to induce H3K4 trimethylation, transcriptional activation, and cell cycle progression [132].

In addition to H3K4 methyltransferases, HCF-1 interacts with a variety of histone-modifying enzymes, such as the H3K9 demethylase LSD1, histone acetyltransferase, and mSin3/histone deacetylase (HDAC) complexes [60]. Strikingly, approximately 50% of nuclear OGT proteins are associated with HCF-1, suggesting a functional link between O-GlcNAcylation and distinct histone modifications through this abundant nuclear complex [15, 25]. Recently, we observed that the OGT/HCF-1 complex recruits the ubiquitin carboxyl-terminal hydrolase BAP1 (BRCA associated protein 1) to deubiquitinate and stabilize PGC1 α , a key metabolic regulator [95]. BAP1 is also a component of the Polycomb repressive deubiquitinase complex to deubiquitinate histone H2A [99]. BAP1 acts as a tumor suppressor and mutations in BAP1 have been observed in multiple cancer types such as melanoma, leukemia, lung, ovarian, breast and renal cancer [16, 113]. Therefore, O-GlcNAcylation may play a major role in epigenetic regulation by co-opting histone phosphorylation, methylation, acetylation and ubiquitination.

3.4 OGT and DNA methylation

DNA methylation at the 5-carbon position of cytosine (5mC) is an epigenetic mechanism that is important for embryo development, stem cell differentiation, tissue-specific gene expression, X-chromosome inactivation and oncogenic transformation [46]. This biochemical reaction is catalyzed by DNA methyltransferases (DMNTs) [17, 46]. Conversely, active DNA demethylation is initiated by a group of Fe(II)/2-oxoglutarate-dependent dioxygenases known as ten-eleven translocation (TET) proteins. TET proteins hydrolyze 5mC to produce 5hmC (5-hydroxymethyl cytosine) [37, 109]. Furthermore, TET proteins can convert 5mC to 5-formylcytosine (5fC) and 5-carboxylcytosine (5-CaC) in mouse embryonic stem cells and mouse organs [48]. Several recent studies elegantly illustrate physical and functional interactions between TET proteins and OGT [19, 71, 102, 112, 129]. One study reported that TET2 and TET3 bind to OGT, in which OGT does not seem to affect the function of TET proteins, but TET proteins facilitate the association of OGT with chromatin and O-GlcNAcylation of histone H2B at S112 [19]. Notably, S112 O-GlcNAcylation promotes K120 monoubiquitination of H2B and transcriptional activation [34]. Therefore, it can be speculated that TET2 facilitates gene transcription through DNA demethylation and OGT recruitment at transcriptionally active promoters. In embryonic stem cells, OGT preferentially associates with TET1 across the genome in close proximity of CpG-rich transcriptional start sites [112]. In 293T cells, TET2/3 and OGT co-localize at

active promoters and promote the binding of H3K4 methyltransferase SET1/COMPASS complex to chromatin [28]. These studies suggest that OGT and TET proteins act in concert to regulate transcription.

Conclusions

Posttranslational modifications are a major toolbox in cell physiology. Availability of metabolites, such as UDP-GlcNAc, acetyl-CoA and ATP, is essential for O-GlcNAcylation, acetylation and phosphorylation, respectively. Combinatorial changes in different posttranslational modifications, referred to as the “PTM code”, dictate protein activity and ultimately influence metabolic homeostasis (Figure 2). Cancer cells appear to alter HBP flux and O-GlcNAcylation to reprogram metabolism in favor of rapid growth. An exciting new area is to understand how O-GlcNAc orchestrates metabolic pathways for biosynthesis by interplaying with other posttranslational modifications on a wide variety of signaling proteins and metabolic enzymes.

O-GlcNAcylation is a recently identified addition to the epigenetic code. OGT can O-GlcNAcylate histones H2A, H2B, and H4 at specific residues; however, the molecular determinants of site specificity and the functional consequences of histone O-GlcNAcylation are largely unknown (Figure 3). OGT interacts with an assortment of protein complexes involved in phosphorylation, ubiquitination, methylation, and acetylation of histone proteins, but the functional link between these modifications remains to be determined (Figure 3). Another enzyme essential for O-GlcNAc cycling is OGA, which harbors HAT and O-GlcNAcase activities. Whether both activities are involved in gene regulation and how they cooperate warrant careful investigation. Association with both DNA methylation and histone modifications suggests a role for OGT in integrating transcriptional and epigenetic regulation. Further studies are required to decipher overall biological information encoded therein. This might provide an epigenetic explanation for the impact of aberrant O-GlcNAcylation on tumorigenesis. The epigenome is susceptible to metabolic disturbance such as diet, which is well known to affect cancer [40, 49]. Therefore, O-GlcNAc signaling may play a central role in integrating metabolic and epigenetic reprogramming in cancer. A better understanding of O-GlcNAc signaling in cancer initiation, progression and metastasis would help to identify new targets that can be used for diagnosis, prevention, and treatment of human cancer.

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Figure 1. Hexosamine biosynthetic pathway targets protein O-GlcNAc modification

Glucose (Glc) uptaken by cells is mainly used in glycogen synthesis and glycolysis pathways. 2~5% of glucose fluxes into hexosamine pathway through the conversion of fructose-6-phosphate (Fru-6P) to glucosamine-6-phosphate (GlcN-6P) by a rate-limiting enzyme glutamine:fructose-6-phosphate amidotransferase (GFAT). Subsequent acetylation and uridylation of GlcN-6P produce UDP-GlcNAc as a substrate for protein glycosylation. O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) catalyze the addition and removal of O-GlcNAc on proteins, respectively.

Figure 2. Nutritional and hormonal regulation of metabolism through the “PTM code”
 External hormonal and nutritional cues modulate intracellular fluctuation of ATP/AMP, UDP-GlcNAc, Acetyl-CoA and NAD⁺ levels. These metabolites influence phosphorylation, O-GlcNAcylation, and acetylation of a wide variety of intracellular proteins such as signaling proteins, metabolic enzymes, transcriptional factors/cofactors and histones. Combinatorial changes in these posttranslational modifications may constitute the “PTM code” that integrates environmental cues to regulate metabolic homeostasis. Alteration of the “PTM code” by carcinogens may be central to metabolic and epigenetic reprogramming in cancer.

Figure 3. OGT is associated with multiple epigenetic modifications

OGT interacts with the HCF-1/TET complex that mediates DNA demethylation, the HCF-1/BAP1 complex that mediates histone deubiquitination, the HCF-1/HNMT complex that mediates histone methylation, and the Sin3A/HDAC complex that mediates histone deacetylation. OGT directly modifies histones through unknown adaptor proteins.

Table 1

Studies related to O-GlcNAc modification in cancer

Cancer type	Remarks	Ref.
Colorectal	Aberrant O-GlcNAcylation	[88]
Pancreatic	Excessive O-GlcNAcylation is anti-apoptotic	[69]
Ovarian	O-GlcNAcylation, cell migration and changes in E-Catherin level are correlated	[50]
Prostate	OGT regulates stability of c-Myc	[47]
Breast	O-GlcNAcylation of cofilin promotes cell invasion	[45]
Breast	Proteomics of O-GlcNAcylation	[18]
Pancreatic	Triptolide induces cell death via O-GlcNAcylation of transcription factor Sp1	[8]
Hepatocellular	O-GlcNAcylation is linked with tumor recurrence	[133]
Bladder	Urinary content of OGT/OGA mRNAs helps predicting bladder cancer	[93]
Cholangiocarcinoma	OGT Overexpression and aggressiveness are correlated	[87]
Prostate	Role of OGT in invasion, angiogenesis, and metastasis	[68]
Endometrial	Clinicpathologic conditions are correlated with OGT and OGA mRNA expression	[64]
Breast	Gene expression of O-GlcNAc cycling enzymes	[61]
Liver	Crosstalk between HSP27 O-GlcNAcylation and phosphorylation	[38]
Lung and colon	O-GlcNAcylation regulates malignancy	[74]
Chronic Lymphocytic leukemia	Chronic lymphocytic leukemia is characterized by aberrant O-GlcNAcylation	[103]
Thyroid	OGA enzyme activity is increased in thyroid cancer	[63]
Breast	OGT regulates oncogenesis through FoxM1	[14]
Erwing sarcoma	O-GlcNAc regulates transcriptional activity of transcription factor FLI1	[6]
Uterus	O-GlcNAc containing epitope H expressed in smooth muscle cell tumors	[101]
Breast	O-GlcNAc-containing epitope H are localized in the nucleus of epithelial cells	[42]
Lymphoma	Role of O-GlcNAc modification and subcellular distribution of transcription factor Sp1	[27]
Lymphoma	c-Myc is O-GlcNAcylation at Thr 83, a mutational hot spot in lymphoma	[21]