Regulation and clinical significance of O-GlcNAc transferase in cancer

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ABSTRACT

O-GlcNAc Transferase (OGT) resides in both cytosolic and nuclear compartments and catalyzes O-GlcNAcylation of myriad proteins. Numerous excellent reviews concerning roles of OGT in organismal and cellular physiology have exist, and aberrant OGT and protein O-GlcNAcylation have been implicated in progression and metastasis of different cancer types. Thus, understanding the regulation mechanisms of OGT and O-GlcNAcylation in tumor cells and their difference compared to non-tumor cells may elucidate new mechanisms related to tumor generation and development, could provide a new marker to diagnosis and prognosis in patients with cancer and indicate a new target to cancer chemotherapy. While it has become evident that OGT plays critical roles in cancers, it remains unclear how they are deregulated. This review provides an overview of our current knowledge about the known/potential regulation of OGT, and also discusses the inhibition of OGT as a potential novel therapeutic target for cancer treatment.

INTRODUCTION

O-GlcNAcylation is the covalent connection of O-GlcNAc sugars to serine or threonine residues of nuclear and cytoplasmic proteins in metazoans [1–5]. Like phosphorylation, O-GlcNAcylation is an inducible, reversible, and dynamic posttranslational modification. To date, more than 4,000 O-GlcNAcylated proteins have been detected [6] and these proteins have been involved in nearly every aspect of the cellular physiology [7], including gene expression [8–11], metabolism [12–16], cellular stress responses [17, 18], signal transduction [19, 20], and proteostasis [21–24] in response to nutrient availability [7, 25]. Given the myriad functions concerned with O-GlcNAcylation, it is exceedingly reasonable that this posttranslational modification plays a fundamental role in the etiology of tumors [6, 14, 26–28]. Indeed, O-GlcNAcylation is deregulated in many cancer types, including breast [29, 30], pancreatic [31], prostate [32, 33], colorectal [34, 35], lung [34], liver [36], gastric [37, 38], laryngeal [39], bladder [40], endometrial [41], esophageal squamous cell carcinoma [42], and nonsolid cancers such as chronic lymphocytic leukemia [43], and contributes to cancer cell metabolic reprogramming, cell proliferation, survival, angiogenesis, invasion, metastasis and cancer cell epigenetics [14, 44].

Unlike phosphorylation, which is orchestrated by hundreds of phosphatases and kinases, O-GlcNAc cycling is regulated by a unique pair of highly conserved enzymes that add and hydrolyze O-GlcNAc moieties from target proteins. OGT catalyzes the transferal of O-GlcNAc moieties from the donor substrate UDP-GlcNAc to proteins and OGA removes the sugar [45]. Thus it can be seen that both OGT and OGA are essential to biological processes in which O-GlcNAc participates and alteration of either of them plays a decisive role in O-GlcNAc-induced carcinogenesis. Actually, deregulation of OGT appears to be an important cause of tumorigenesis and tumor aggravation, as levels of OGT are positively correlated with O-GlcNAcylation in all cancers examined except for live cancer [29, 31, 32, 34–38, 42, 43, 46–48]. Understanding how OGT is regulated will be helpful in
claritying the whole process that OGT and subsequent O-GlcNAcylation are involved in cancers. This review highlights findings on OGT regulation, focusing on the regulation of OGT expression, degradation, enzyme activity, substrate selectivity and cellular localization.

**FUNCTIONAL ROLE OF OGT AND O-GLCNACYLATION**

Many OGT targets implicated in diversified cellular processes have already been explored and to date, many excellent reviews on O-GlcNAc functions have been published [7, 49–56]. Thus, in this review, the main functions of OGT and O-GlcNAcylation are summarized briefly as follows:

**Regulation of transcription**

More than 25% of O-GlcNAcylated proteins are involved in transcriptional regulation [52]. This modification can affect the functions of transcription factors by several means, including protein-protein interaction (e.g., NF-κB, STAT5a, CREB, YY1, PGC-1α, etc.), protein stability (e.g., p53, ER-α, ER-β, etc.), nucleo-cytoplasmic translocation (e.g., NeuroD1, CRTC2, NFATc1, Elf-1, etc.), transcriptional activity transactivation (e.g., c-Myc, FoxO1, etc.), DNA binding activity (e.g., Pdx-1, C/EBPβ, etc.) and expression (e.g., MafA, Id2, USF, etc.) [49, 52].

**Regulation of epigenetic programmes**

Histones are modified by O-GlcNAc and histone O-GlcNAcylation regulates mitosis, chromatin dynamics and gene expression [28]. Moreover, diverse proteins which are related to the regulation of histone modification and DNA methylation such as HCF-1, EZH2 and TET are regulated by OGT [28, 57–59]. HCF-1 can interact with several kinds of histone modifying enzymes such as histone methyltransferases MLL5, demethylase LSD1, HATs and HDACs, and recruit these enzymes to chromatin [28]. Recently, OGT is found to promote proteolytic maturation of HCF-1, thus OGT can mediate these histone modifications indirectly via HCF-1 [60, 61]. EZH2 is a histone methyltransferase which can catalyze the formation of H3K27me3 by transferring methyl groups to the K27 residue of histone H3 [62]. OGT interacts with EZH2, glycosylates it at Ser75 and improves its protein stability [62]. TET proteins catalyze the hydroxylation of 5-methylcytosine (5 mC) to 5-hydroxymethylcytosine (5 hmC) and further to 5-formylcytosine (5 fC) and 5-carboxylcytosine (5caC) [63]. TET1, TET2 and TET3 are all O-GlcNAcylated by OGT and OGT promotes the cytoplasmic relocation of exogenous TET3, the protein stability of TET1 [64]. In turn, TET2 and TET3 recruit OGT to the chromatin and facilitate O-GlcNAcylation of histone H2B [65, 66].

**Regulation of cell signalling**

O-GlcNAc modification plays a fundamental role in regulating nutrient- and stress-induced signal transduction [67]. The crosstalk between O-GlcNAcylation and O-phosphorylation of proteins controls insulin signalling. Upon insulin stimulation, PIP3 targets AKT and PDK1 to the cell membrane, where AKT is phosphorylated and activated by PDK1. Interestingly, insulin stimulation also causes PIP3 to drive the localization of OGT from the nucleus to the plasma membrane, thus OGT is tyrosine phosphorylated by insulin receptor (IR), leading to increase OGT activity [68]. Multiple downstream targets of this signaling pathway including IR-β, IRS-1 and AKT, are O-GlcNAcylated and inhibited by activated OGT, resulting in an attenuation of insulin signal transduction [19, 69–71].

**Response to stress**

Global O-GlcNAc levels are induced by diverse forms of cellular stress; for instance, thermal stress [72]. Knockout of OGT gene using the Cre/loxP system or knockdown of OGT by RNAi reduces cell's tolerance to stress [72]. These findings suggest that O-GlcNAcylation protects cells against stress. O-GlcNAc mediates stress tolerance by different mechanisms, including inhibiting protein degradation or protein deposition [73, 74], inducing the expression of Hsp70 and Hsp40 [72], promoting interactions of Hsp70 with O-GlcNAcylated proteins during stress [23] and reducing capacitive calcium entry [56].

**Regulation of cell cycle**

Ogt deletion in mouse embryonic fibroblasts increases levels of p27, a cyclin-dependent kinase inhibitor, blocks cell division and causes cell death [75]. In Hela cells, altered O-GlcNAc level caused by overexpression of OGT or O-GlcNAcase prolongs M phase, disrupts mitotic phosphorylation and alters the expression of cyclins A and B in the Late M Phase [76]. Raising levels of O-GlcNAc by PUGNAc delays G2/M progression; conversely, lowering O-GlcNAc level by DON (a glutamine fructose-6-amidotransferase inhibitor) promotes the course of cell cycle [76]. Together, these data indicate that O-GlcNAc plays a critical role in cell cycle progression and cell division.

**Regulation of O-GlcNAc signalling**

As a nutrient/stress sensor, O-GlcNAc signaling can response to various endogenous and exogenous cues transiently, thus its dynamic process must be controlled tightly and temporally. According to various reports, increased O-GlcNAc levels increase OGT expression and decrease OGA expression, suggesting that a feedback loop...
exists to maintain O-GlcNAc homeostasis [77–79]. It can thus be inferred that modulation of gene expression of OGT and OGA is likely to be one mode of moderation for the O-GlcNAc cycling. However, fluctuations in cellular O-GlcNAc levels often occur in minutes, which are faster than gene expression regulation [19, 80, 81]. For example, stimulating Jurkat T cells with T-cell receptor (TCR) for 5–10 min, the O-GlcNAc level of the transcription factor NFATC1 increases~14-fold; similarly, O-GlcNAc-modified NFATc1 levels are risen evidently after 5–10 min in BJAB cells and primary human T lymphocytes which are stimulated by IgM and TCR respectively [80]. Thus, the factors affecting activities of OGT and OGA such as their posttranslational modifications may be the primary regulators of O-GlcNAc signalling under transient response.

FUNCTIONAL SIGNIFICANCE OF OGT AND O-GLCNACYLATION IN NORMAL BIOLOGY

OGT is found in all metazoans [82]. Ogt-1 is the Caenorhabditis elegans homolog of OGT, and is important for worms’ embryogenesis at high temperatures [83]. However, under normal physiological conditions, Ogt-1 is not essential for development and morphogenesis of Caenorhabditis elegans [84]. It doesn’t mean that OGT is not important in the course of Caenorhabditis elegans’ life, because OGT-1 modulates their metabolism and longevity [84–86]. Knockout of ogt-1 in Caenorhabditis elegans suppresses dauer formation and lipid stores [84], elevates trehalose levels and glycogen stores [84], and reduces median adult lifespan [85, 86]. OGT-1 removal also appears to promote autophagosome maturation in a nutrient-dependent manner [87] and deregulate UV-stress- and immune-responsive genes [85, 88].

Super sex combs (sxc) is the Drosophila homolog of OGT, and is necessary for larval development during embryogenesis because sxc mutation in larvae results in posterior displacement of most segments, and no sxc− homozygotes can survive beyond the completion of embryogenesis [89]. Maternally rescued sxc− Drosophila which will deplete the maternally supplied sxc several cell divisions later, can grow from the embryonic stage to the pupal stage [89–91], although can not enter the mature period (adults) [89, 92]. These results indicate that, in Drosophila, OGT is not essential in dividing cells [82].

Different from what we find in Caenorhabditis elegans and Drosophila, OGT is indispensable for cellular viability in mammalian systems and complete knockout of OGT results in embryonic lethality due to incomplete embryogenesis [75, 93]. Conditional knockout of mouse Ogt gene using the Cre/loxP system in thymocytes significantly inhibits the production of mature T cells and induces apoptosis [75]. Fibroblasts derived from floxed Ogt embryos and transected with the Cre recombinase to block Ogt expression, exhibit no alteration in protein synthesis and degradation, but grow old rapidly and die after 12 days [75]. Neuron-specific knockout of Ogt in mice reduces their size, deprives their locomotor activity, increases the level of total tau and hyperphosphorylated tau, and causes death within 10 days of birth [75]. Only 12% of the cardiomyocyte-specific OGT knockout (cmOGT KO) mice survive to weaning age and only 5% of male mice survive to adult [94]. Freshly weaned cmOGT KO male mice are observably smaller, undergo fibrotic, dilated cardiomyopathy [94].

ALTERED LEVELS OF OGT AND O-GLCNACYLATION IN CANCERS AND THEIR INVOLVEMENT IN MALIGNANT TRANSFORMATION AND CANCER PROGRESSION

The contribution function of alterations in O-GlcNAc signaling in the onset, progression and metastasis of cancer has been heavily reported recently [27, 45, 54] (Table 1). Elevated O-GlcNAcylation and OGT levels are existed in breast cancer cell lines and patient tissues [29, 30, 95, 96], and induce tumorigenesis and metastasis via FoxM1 and E-cadherin respectively [29, 30]. O-GlcNAcylation, OGT and hexosamine biosynthetic pathway (HBP, a branch of glucose metabolism, controls the level of intracellular UDP-GlcNAc) related proteins are all up-regulated in prostate cancer tissues [33, 97], and the hyper-O-GlcNAcylation causes invasion through inhibiting the formation of the E-cadherin/catenin complex and inducing the expression of MMP-2 and MMP-9 [32, 33]; in addition, targeting OGT reduces angiogenic potential and VEGF expression via FoxM1 in prostate cancer [32], and increased O-GlcNAc level associates with the poor prognosis of prostate cancer patients [98]. OGT and O-GlcNAcylation elevations are examined in lung and colon cancer tissues and cell lines, and contribute to the etiology and progression of cancer [34, 35]. Tumor reoccurrence in patients undergoing liver transplantation results in rising O-GlcNAc levels and reducing OGA expression in the cancerous region, but has no significant correlation for OGT levels [36]. Moreover, the migrating and invasive capability of HepG2 is heightened by elevated O-GlcNAcylation, because this modification decreases E-cadherin expression and increases MMP-1, MMP-2 and MMP-3 expression [36]. OGT mRNA level and protein O-GlcNAc modification are progressively increased during the carcinogenesis of gastric cancer, and patients with hyper-O-GlcNAcylation have poor prognosis [37, 38, 99]. Reduction of O-GlcNAcylation by OGT siRNA inhibits and increment of this modification by OGA inhibitors enhances cell proliferation and tumor growth of gastric cancer through regulating the activation of ERK signaling pathway and the expression of CDK-2 and cyclin D1 [37]. OGT silencing also induces apoptosis of gastric cancer by inducing the expression of PUMA and cleaved caspase-3.
Upregulation of O-GlcNAcylation by Thiamet-G, an OGA specific inhibitor, enhances invasion of gastric cancer cells in vitro partially via PI3K/AKT signaling pathway [99]. Increased HBP flux, elevated OGT level and reduced OGA level lead to hyper-O-GlcNAcylation in human pancreatic ductal adenocarcinoma [31]. Downregulation of O-GlcNAcylation via OGT knockdown suppresses cell proliferation in vitro and tumor growth in vivo, and induces apoptosis through decreasing transcriptional activity of NF-kB [31]. The levels of O-GlcNAc, OGT and OGA are all up-regulated in laryngeal cancer tissues, and they boost tumor enlargement and lymph node metastasis, indicating that hyper-O-GlcNAcylation acts as a poor prognostic marker [39]. The mRNA expression of OGT in bladder cancer patients is higher that that in healthy persons, and the OGT level is positively related to degree of histological differentiation (grade II and III > grade I) [40]. Moreover, hyper-O-GlcNAcylation may trigger invasion of bladder cancers because the amount of OGT expressed in invasive or advanced cancers is larger than that expressed in early cancers [40]. Similar phenomena is identified in endometrial cancer, that the expression of OGT and OGA is visibly higher in tumors of grade II and III than in grade I, and they contribute to myometrial invasion [41]. Compared to the normal tissues, OGT and O-GlcNAc activation are higher in esophageal squamous cell carcinoma samples [42]. Although OGT expression isn’t discovered clear correlation with tumor size, the clinical stage and metastatic lymph nodes, O-GlcNAcylation level is higher in esophageal squamous cell carcinoma tissues with lymph node metastasis [42]. Changes in O-GlcNAc, OGT and OGA in anaplastic thyroid cancer have not been described, however several research groups have found that increased O-GlcNAcylation is closely related to the development of this cancer [101–103]; Krzeslak et al. showed that up-regulation of O-GlcNAc level by PUGNAc or OGA siRNA increased cell proliferation of anaplastic thyroid cancer via the stimulation of IGF-1/AKT1/GSK3β/cyclin D1 pathway partially [101]; Cheng and colleagues determined that O-GlcNAcylation enhanced not only cell proliferation but also colony formation ability, migration and invasion of anaplastic thyroid cancer cells in vitro [102], and Zhang et al. observed that elevated O-GlcNAcylation acquired by OGA inhibition or OGT overexpression induced the invasion of anaplastic thyroid cancer cells rather than cell proliferation partially by PI3K/AKT signaling [103]. Increased O-GlcNAcylation, OGT and UDP-GlcNAc levels are also detected in lymphocytes of chronic lymphocytic leukemia patients [43]; unlike what we have obtained in above-mentioned tumor types, higher O-GlcNAc levels in chronic lymphocytic leukemia patients depress CD38 expression, prolong lymphocyte doubling times and indicate a relatively good prognosis [43]. Distinguishingly, O-GlcNAcylation is decreased in ovarian tumors compared with normal tissue [104]; however, O-GlcNAcylation augments the migration and invasion of SKOV3 and 59M

| cancer type | OGT/ O-GlcNAc expression | targeted pathways | targeted proteins |
|-------------|--------------------------|-------------------|-------------------|
| Breast [29, 30, 95, 96] | ↑/↑ | tumorigenesis↑, metastasis↑ | FoxM1↑, E-cadherin↓ |
| Prostate [32, 33, 97, 98] | ↑/↑ | invasion↑, angiogenesis↑ | E-cadherin/catenin complex↓, MMP-2↑, MMP-9↑, FoxM1↑ |
| Lung [34] | ↑/↑ | progression↑, invasiveness↑ | unknown |
| Colon [34, 35] | ↑/↑ | progression↑, invasiveness↑ | unknown |
| Liver [36] | -/+ | metastasis↑, invasion↑ | E-cadherin↓, MMP-1↑, MMP-2↑, MMP-3↑ |
| Gastric [37, 38, 99, 100] | ↑/↑ | cell viability↑, apoptosis↓, invasion↑ | CDK-2↑, cyclin D1↑, pERK1/2↑, PUMA↓, caspase-3↓, pAKT↑ |
| Pancreatic [31] | ↑/↑ | cell proliferation↑, apoptosis↓ | NF-kB↑ |
| Laryngeal [39] | ↑/↑ | Tumor growth↑, metastasis↑ | unknown |
| Bladder [40] | ↑/↑ | invasion↑ | unknown |
| Endometrial [41] | ↑/↑ | invasion↑ | unknown |
| Esophageal [42] | ↑/↑ | metastasis↑ | unknown |
| Anaplastic thyroid [101–103] | unknown | cell viability↑, invasion↑ | pAKT↑ |
| CLL [43] | ↑/↑ | aggression↓ | pAKT↓, TNF-α↓, pJNK↓ |
| Ovarian [48, 104, 105] | ↓/↓ | migration↑, invasion↑ | RhoA↑, E-cadherin↓ |

pERK1/2, phosphorylated ERK1/2; pAKT, phosphorylated AKT; CLL, chronic lymphocytic leukemia; pJNK, c-Jun N-terminal kinase; -, no change; ↑, upregulated; ↓, downregulated.
ovarian cancer cells via the RhoA/ROCK/MLC signaling pathway [105] or E-cadherin [48].

REGULATION OF OGT EXPRESSION AND PROTEIN STABILITY IN NORMAL CELLS

Transcription

In colon macrophages, the transcription factor Nrf2 binds to the OGT promoter region and increases gene transcription [106]. Elevated OGT protein mediates the up-regulation of STAT3 O-GlcNAcylation at Thr717 and this modification leads to decreased STAT3 phosphorylation, which is accompanied by exacerbated colonic inflammation and inflammation-driven tumorigenesis [106]. Interestingly, Cullin-3 can depress Nrf2-induced OGT expression via Nrf2 degradation, inhibit STAT3 O-GlcNAcylation, promote STAT3 phosphorylation correspondingly and then protect against intestinal inflammation [106].

Post-transcription

Several miRNAs have been validated to interact with 3′-UTRs of OGT mRNAs and lead to the suppression of OGT expression [107, 108]. MiR-423-5p can induce apoptosis of cardiomyocytes through binding to OGT mRNA and decreasing OGT protein level [107]. MiR-15b has also been described as negative regulator of OGT [108]; Liu et al. documented that miR-15b can target OGT and inhibit O-GlcNAcylation of NF-κB, resulting in differentiation suppression of Th17 cells both in vivo and in vitro [108].

Protein stability

OGT is observed to interact with the tetratricopeptide repeat binding site of Hsp90 in endothelial cells and inhibition of Hsp90 destabilizes OGT and enhances its degradation by the proteasome [109]; however, the precise mechanism underlying Hsp90-induced OGT protein stability remains unclear. Hypoxia or hypoxia-mimetic agents can reduce OGT protein levels rather than its gene expression to induce endothelial inflammatory response [110]; hypoxia stimulates generation of ROS/RNS which heightens 26S proteasome activity [110]; activated 26S proteasome works in coordination with E3 ubiquitin ligase β-TrCP1 to achieve proteasomal degradation of OGT [110].

Unknown mechanisms

In human aortic smooth muscle cells, high glucose increases OGT expression, however Cr+ significantly inhibits glucose-induced OGT expression and exhibits antioxidant and antiproliferative effects [111].

REGULATION OF OGT EXPRESSION AND PROTEIN STABILITY IN CANCER

Transcription

The elevation of OGT mRNA levels in non-small cell lung cancer and prostate cancer cells is partly due to the hyper-activated MAPK/ERK signaling [112]. Over-expression of constitutively activated MEK1DD induces OGT transcription via transcription factor Elk-1, while suppression of MAPK/ERK signaling by a MEK inhibitor U0126 greatly reduces OGT mRNA level [112]. Moreover, elevated O-GlcNAcylation rescues the inhibitory effect of ERK inactivation on cell proliferation and clone-forming ability of H1299 cells [112]. In 293T cells, E2F1 transcription factor can directly bind to the OGT promoter and repress endogenous OGT protein level and RB1 is required for E2F1-mediated suppression. [113]. It is reported that glucose deprivation increases protein O-GlcNAcylation through up-regulation of OGT in cancerous cells [78, 79, 114]; Cheung et al. discovered that, in Neuro-2a neuroblastoma cells, the increase of OGT mRNA and protein expression induced by glucose deprivation was due to the activation of AMPK [77]; however, Taylor et al. found that, in contrast to HepG2 cells cultured under normal condition, glucose-treated HepG2 cells expressed increased OGT through decreasing hexosamine flux rather than activating AMPK pathway [78, 79].

Protein stability

OGT protein can be degraded by the ubiquitin-proteasome pathway and the autophagy pathway [60, 109, 110, 115]. As mentioned earlier, beyond its well-known role as the O-GlcNAc transferase, OGT also can hydrolyze HCF-1 to achieve the maturation of HCF-1 [60, 61]. HCF-1, in turn, stabilizes OGT against proteasomal degradation in several kinds of tumor cells [60] (Figure 1A). Nearly one half of the total nuclear OGT forms stable complexes with HCF-1 in Hela cells [60]. And a positive correlation exists between HCF-1 and OGT protein levels; a decrease in HCF-1 leads to a decrease in OGT, correspondingly, an increase in HCF-1 causes an increase in OGT [60]. The change in OGT levels caused by HCF-1 is not at the level of mRNA or promoter but at the protein level [60]. The above results suggest that HCF-1 inhibits protein degradation of OGT. Deubiquitinating enzyme BAP1 is mutated in diverse malignant tumors [116]. Strikingly, Bap1 deletion can decrease the levels of OGT and HCF-1, suggesting that BAP1 is propitious to stabilize these epigenetic regulators [116]. Studies show that BAP1 not only stabilizes HCF-1 by preventing HCF-1 proteasomal degradation, but also deubiquitinates and stabilizes OGT. Together, BAP1, HCF-1 and OGT can
form a ternary complex to preserve normal hematopoiesis by recruiting additional histone-modifying enzymes to regulate gene expression [116]. PI3K/AKT/mTOR pathway stimulates the expression of OGT and the level of global O-GlcNAcylaition in breast and live cancer cells [115, 117]. This pathway increases the expression of the oncogenic transcription factor c-Myc which induces the transcription of Hsp90 in breast cancer [117]; Hsp90 interacts with OGT and inhibits its proteasomal degradation, which is consistent with previous findings in endothelial cells [117] (Figure 1B). In addition to by the proteasome pathway, PI3K/AKT/mTOR pathway also can promote OGT degradation by the autophagy pathway, although the underlying mechanism is not fully clear [115, 117]. The histone demethylase LSD2 can perform as an E3 ubiquitin ligase to promote proteasome-dependent degradation of OGT [118] (Figure 1C). Overexpression of LSD2 increases the ubiquitination of OGT in 293T and H1299 cells [118]. Reduction of LSD2 by shRNA promotes colony-forming ability of 293T and H1299 cells via OGT inhibition, and up-regulation of OGT rescues LSD2-inhibited cell growth [118].

Unknown mechanisms

As described above, a variety of stimuli can induce OGT and O-GlcNAc levels by unknown molecular mechanisms [55, 72]. Insulin can stimulate the expression of OGT [119] [120] and enhances cytosolic staining of OGT [119] in H-411E and HepG2 hepatoma cells. In addition, rapidly elevated global O-GlcNAcylation displays a feedback inhibition of OGT levels in several types of cancer cells [18, 76, 82, 121]; pharmacologic inhibition of OGT leads to OGT protein levels either remain constant [122] or increase slightly [123]; correspondingly, pharmacologic inhibition of OGA results in a decrease of OGT at protein levels rather than at mRNA level in HeLa cervical carcinoma, SH-SY5Y neuroblastoma, and K562 leukemia cells [121]. Information on how the global O-GlcNAcylation regulates OGT is limited, appearing to regulate OGT’s protein stability.

REGULATION OF OGT GLYCOSYLTTRANSFERASE FUNCTIONS IN NORMAL CELLS

UDP-GlcNAc

UDP-GlcNAc is an end product of HBP and acts as the donor substrate of OGT. Its levels are responsive to flux through metabolic pathways of glucose, nucleotide, fatty acid and amino acid [124–126]. UDP-GlcNAc concentration dominates the affinity of OGT for peptides [2, 127, 128]; in vitro studies show that, aiming at different protein substrates of OGT, UDP-GlcNAc displays different values of Km; for example, the Km values of UDP-GlcNAc for Nup62 and CaMKIV are about 1 μM and 25 μM respectively [129, 130]. This phenomenon may be explained at least partly by the contact mode exhibited in the crystal structures between UDP-GlcNAc and protein substrates. Structural analyses show that UDP-GlcNAc and protein substrate bind to OGT in an ordered sequential manner, and UDP-GlcNAc combines with OGT firstly then the target protein binds to the amino acids surrounding the UDP-binding cleft subsequently [126]. Thus, UDP-GlcNAc which has binded to OGT preferentially may alter the three-dimensional structure of OGT which affects the subsequent binding of protein substrates.

AMPK

Pharmacological and genetic inactivation of AMPK in endothelial cells or knock out of AMPK in mice increases 26S proteasome activity [131]. Conversely, activation of AMPK effectively suppresses 26S proteasomes [131]. The inhibition of 26S proteasome caused by AMPK activation is realized through increasing the interaction between 26S proteasome and OGT which can O-GlcNAcylate 26S proteasome and suppress its assembly and activity [131]. In general, these data show that AMPK regulates OGT by some ill-defined mechanism and further blocks the proteasome [131]. As reported, compared with undifferentiated myoblastic cells, differentiated myotubes display a significant increase OGT localized in cytoplasmic [132]. However, activated AMPK can directly phosphorylate OGT at Thr444 [132, 133] and OGT Thr444 phosphorylation increases its nuclear localization [132].

Insulin

Insulin triggers the tyrosine phosphorylation of OGT in T3-L1 adipocytes, probably through stimulating the interaction of OGT with PDK1 [69], and results in the increase of catalytic activity and nucleo-cytoplasmic translocation of OGT [68]. In addition, insulin treatment of 3T3-L1 adipocytes also stimulates self-GlcNAcylation of OGT and this modification may also contribute to the activity of OGT [68].

Salts

OGT activity and its affinity for UDP-GlcNAc can be restrained by several salts [134–136]. The inhibitory effects of NaCl, KCl, and NaH2PO4 have been determined and IC50 values of them are 45, 50, and 4 mM individually [134, 135]. Another study extends this observation by revealing that NaVO4 is more potent in inhibiting OGT activity (IC50 of 55 μM in brain cytosol and 150μM in nucleosol) [136].
REGULATION OF OGT GLYCOSYLTRANSFERASE FUNCTIONS IN CANCER

UDP-GlcNAc

Oxidative phosphorylation replaced by aerobic glycolysis (the Warburg effect) is one of the critical features in cancer [137]. The product of aerobic glycolysis, acetyl-CoA, is required to biosynthesize UDP-GlcNAc. Thus, this especial metabolic model of cancer causes an increase in flux through the HBP [45, 138]. As mentioned above, besides glucose flux, amino acid flux, especially glutamine can remarkably affect the concentration of intracellular UDP-GlcNAc levels. Interestingly, cancer cells have a clear preference for glutamine and glutamine consumption in cancer cells is much higher than that in normal cells [139], thereby letting glutamine be the other major metabolic material into the HBP. Actually, elevated HBP flux and HBP related enzymes have been confirmed to contribute to hyper-O-GlcNAcylation in human tumors, suggesting that an increase in UDP-GlcNAc level might an incentive to the hyper-O-GlcNAcylation in cancer cells [31, 33, 97].

Protein interactions

OGT associates with multiple protein partners and the interactions influence OGT’s substrate selectivity, chromatin association, cellular localization and glycosyltransferase activity (Table 2). It has well-documented that OGT’s substrate selectivity is altered by associations with the mitochondrial trafficking protein Trak1, the transcriptional co-repressor mSin3A, the transcriptional coactivator PGC-1α, the subunit of myosin phosphatase MYPT1, the arginine methyltransferase CARM1 and the kinases p38MAPK and AMPK. Trak1 (previously known as OIP106) interacts with the tetratricopeptide repeats (TPRs) of OGT [140, 141]. Meanwhile, Trak1 has been verified to localize to nucleus and co-localize with RNA polymerase II in Hela cells [140, 141]. These results suggest that Trak1 may recruit OGT to the promoter of different genes for O-GlcNAcylation of RNA polymerase II and transcription factors [140, 141]. A specific interaction between the OGT (TPR 1–6) region and the mSin3A PAH4 domain (amino acids 888–967) is ascertained in HepG2 cells [142, 143]. MSin3A also can draw OGT to chromatin to depress the activity of RNA polymerase II and transcription factors by O-GlcNAc modification, which plays a synergistic role with histone deacetylation to silence gene expression [142, 143]. Under hyperglycemic conditions, the interaction between PGC-1α and OGT boosts the O-GlcNAc modification of the transcription factor FoxO1 [144, 145]. MYPT1 and CARM1 both interact with OGT and a mutual regulation is existed between them; OGT can O-GlcNAcylate MYPT1 and CARM1 and moderates their activity, MYPT1 and CARM1 in turn affect OGT substrate specificity in vitro [146]. And besides, MYPT1 knockdown by siRNA results in changes in O-GlcNAcylation of partial proteins in Neuro-2a neuroblastoma cells, indicating that MYPT1 decides OGT substrate specificity in vivo [146]. OGT interacts directly with p38MAPK using its C terminus; although p38MAPK don’t phosphorylate OGT, it can target OGT to specific targets, including neurofilament H under the condition of glucose starvation in Neuro-2a neuroblastoma cells [77]. As we know, AMPK phosphorylates OGT at Thr444 and increases its nuclear localization in non-tumor tissues (myotubes) [132]. Similarly, AMPK also phosphorylates OGT at Thr444 in 293T and HepG2 cells [132, 133]. Differently, phosphorylation of OGT at Thr444 triggered by AMPK in tumor cells alters the substrate selectivity of OGT [132] and reduces its affinity for chromatin, thereby suppressing O-GlcNAcylation of histone H2B and downstream gene expression [133]. The chromatin localization of OGT is regulated not only by AMPK, but also TETs and OGA. TETs associate with OGT at transcription starting sites and facilitate OGT localization on chromatin [65, 147–150]. TET2 directly interacts with OGT in vivo, despite their specific interactions doesn’t alter the enzymatic activity of TET2, they are propitious to OGT-dependent histone O-GlcNAcylation [147–149]. TET3 is reported to interact with OGT via its H domain and stabilizes the protein levels of OGT, the stabilization of OGT protein enhances its recruitment to chromatin [65, 148–150]. OGA and OGT can associate strongly through specific domains and this OGA-OGT complex locates to repressed promoters [151]. LXR, PIP3 and Aurora B regulate OGT activity through affecting its cellular localization. The interaction of LXR and OGT increases the nuclear location of OGT and that LXRs deficiency strikingly reduces nuclear O-GlcNAc signaling [152]. After induction with insulin, PIP3 interact with the phosphoinositide-interaction domain of OGT (PPO) and facilitates the nuclear-cytoplasmic transport of OGT, then OGT catalyses dynamic O-GlcNAcylation of insulin signaling related proteins at the plasma membrane [19, 120]. Extensive research data show that dynamic O-GlcNAc cycling controls cellular growth [75, 76, 153–155]. Interestingly, in mammalian cells OGT localizes to the mitotic spindle at M phase and during cytokinesis OGT relocates to the midbody [76]. Further studies in Hela cells show that during cytokinesis, OGT forms a transient complex with PP1, OGA, and Aurora B at the midbody [156]. The activity of Aurora B, which is an essential regulator of mitotic progression, determines correct cellular localization of this quaternary complex because Aurora B repression blocks localization of the complex to the midbody [156]. The quaternary complex can regulate...
both the O-GlcNAcylation and phosphorylation state of midbody substrates vimentin at M phase [156]. Finally, URI, OGT and PP1γ can form a heterotrimeric complex [157]. Glucose deprivation induces the phosphorylation of URI at Ser-371 and the release of PP1γ from the complex and then promotes URI-mediated OGT inhibition, resulting in a decrease of c-Myc-dependent survival [157]. These results show that OGT associates with and is regulated in different ways by distinct groups of binding partners in response to distinct signals, which may provide reasons why no conservel sequence motifs involved in the peptide substrate binding is founds in OGT protein.

### Post-translational modification

OGT is modified by phosphorylation [2, 68, 81, 158, 159], O-GlcNAcylation [2, 68, 158, 160–162], S-nitrosylation [158, 163] and ubiquitination [60] (Table 3). All these posttranslational modifications have been proposed to regulate OGT, although the functional sites of these modifications have not been elucidated clearly. Active Ca²⁺/CaMKIV can phosphorylate OGT and then elevate its activity in NG-108–15 cells [81]. Activated AMPK can directly phosphorylate OGT at Thr444 [132, 133] and OGT Thr444 phosphorylation does not alter the enzymatic activity of OGT, but promotes its dissociation from chromatin and alters its substrate selectivity in 293T, HepG2 and HeLa cells [132, 133] (mentioned in “Protein interactions” sections). OGT is found to be phosphorylated on Ser3 or Ser4 (data could not distinguish between these potential sites) by GSK3β and the phosphorylation enhances OGT activity [159]. Interestingly, Mass Spectrometer analysis also reveals that both Ser3 and Ser4 of OGT can be O-GlcNAc modified. Hence, phosphorylation by GSK3β and O-GlcNAcylation must compete with and regulate each other at this N-terminal site of OGT [159]. Seo et al. identified that Ser389 is the major O-GlcNAc modification site of OGT, this O-GlcNAc modification doesn’t alter the enzyme activity and protein-protein interaction but regulates the nuclear localization of OGT through exposure of hidden NLS of OGT and its association with Importin α5 and β [164]. In resting cells, OGT is S-nitrosylated, however the innate immune response induced by LPS can trigger its denitrosylation and heighten its catalytic activity [163]. As mentioned above, HCF-1 can stabilize OGT and this process is achieved through inhibiting the ubiquitination of OGT which leads to its proteasomal degradation [60].

Besides the moderators mentioned above, stress stimulation also affects the activity of OGT. Thermal stress increases the activity of OGT remarkably by currently unknown mechanisms [72] and facilitates OGT to translocate from cytoplasm to the nucleus [18].

### THERAPEUTIC EFFECTS OF OGT MODULATION

Exploring credible biomarkers for diagnosis, prognosis, and confirmation of recurrence is a critical aspect of treating human cancer. In fact,
Table 3: Regulation of OGT glycosyltransferase functions by post-translational modification in cancer

| Post-translational modifications | Sites | Regulator | Functions |
|----------------------------------|-------|-----------|-----------|
| **Phosphorylation**              |       |           |           |
| unknown                          |       | Ca²⁺/CaMKIV | activates OGT activity [81] |
| S3/S4                            |       | GSK3β     | enhances OGT activity [159] |
| T444                             |       | AMPK      | promotes OGT’s dissociation from chromatin and alters its substrate selectivity [132, 133] |
| **O-GlcNAcylation**              | S3 & S4 | OGT      | competes with phosphorylation by GSK3β and regulates each other [159] |
| S389                             |       | OGT      | regulates the nuclear localization of OGT [164] |
| **S-nitrosylation**              | unknown | NO       | decreases catalytic activity of OGT in resting cells [163] |
| **Ubiquitination**               | unknown | Ubiquitin ligase E3 | leads to OGT’s proteasomal degradation [60] |

NO, nitric oxide.

Figure 1: Regulation of OGT stability in cancer OGT catalyzes site-specific proteolysis of HCF-1, and HCF-1, in turn, stabilizes OGT against proteasomal degradation. BAP1 promotes the interaction between HCF-1 and OGT (A) Hsp90 associates with OGT and inhibits its proteasomal degradation, and this process is enhanced by the PI3K/mTOR/Myc pathway (B) LSD2 not only is a well-known histone H3K4me1/me2 demethylase but also can promote ubiquitylation and degradation of OGT as an E3 ubiquitin ligase (C).
hyper-O-GlcNAcylation has been detected in many different types of cancer and contributes to the formation and progression of tumors. As the unique O-GlcNAc transferase, OGT is elevated together with O-GlcNAcylation in almost all cancers examined. An inhibition of OGT results in a corresponding downregulation of tumor cell survival rate, division and invasion [31]. Thus, discovering the specific inhibitor of OGT will be conducive to further comprehensive elucidation of the biological function of O-GlcNAcylation and may obtain a potential therapeutic agent against cancer.

In fact, in the last 15 years, researchers have discovered and designed several categories of OGT inhibitors (Table 4). The first category means the donor substrate and product analogues. UDP, as a product of O-GlcNAcylation processes, can inhibit OGT in vitro with an IC$_{50}$ of 1.8 μM [165, 166]. Unfortunately, it is inapposite for cell biology researches because it is unable to cross cellular membranes and is a substrate for extensive other enzymes. Then C-UDP, a UDP mimic, is discovered and reported to perturb O-GlcNAc in vitro (IC$_{50}$ = 9 μM) [165]. Moreover, two UDP-GlcNAc analogues UDP-S-GlcNAc (IC$_{50}$ = 93 μM) and UDP-C-GlcNAc (IC$_{50}$ = 41 μM) are demonstrated to inhibit OGT activity [165]. However, the three compounds are also not cell-penetrant. Substrate analogue Ac$_{5}$-SS-GlcNAc (IC$_{50}$ = 5 μM) is cell-permeable and has been used in a number of studies [31, 120, 123, 167], but the main pitfall of it is that it depresses the intracellular deposits of UDP–GlcNAc by impeding the HBP [122]. The uracil analogue alloxan (IC$_{50}$ = 18 μM) was the first OGT inhibitor reported and is cell-permeable [168–171]. Sadly, alloxan has potential off-target effects and general cellular toxicity [172]. Finally, a N-acetylglactosamine (GalNAc) mimic, BADGP, is shown to target OGT usually but suppresses the flux of the HBP [173, 174]. The second category is high-throughput screening-derived inhibitors, such as ST045849 (IC$_{50}$ = 53 μM) [175], BZX (IC$_{50}$ = 10 μM) [175] and OSMI-1 (IC$_{50}$ = 2.7 μM) [122]. ST045849 (also named compound 4) is used to prove the function of O-GlcNAcylation in pancreatic β-cell development [176], insulin production [176], gluconeogenesis [177], embryonic stem cell self-renewal [177], and protein stability [178]. BZX (also named compound 5) has been used to test if O-GlcNAcylation induces growth and invasion in breast cancer cells [29] and if the stability of the oncogene c-Myc is controled by O-GlcNAcylating in human prostate cell lines [97]. OSMI-1 decreases global O-GlcNAc levels in various mammalian cell lines [122] and has recently been used to discuss the effects of O-GlcNAc in the reproduction of Herpes Simplex Virus [179]. Unfortunately, these compounds also have potential toxic and off-target effects. Bisubstrate inhibitors, including goblin 1 (IC$_{50}$ = 18 μM) and goblin 2, are the third categories [180]. They are designed by replacing the GlcNAc moiety of UDP-GlcNAc with an acceptor peptide, aiming to achieve selective inhibition. The major current limitation with this class of compounds is the lack of cell permeability. Based on the above analysis, future work requires optimizing the current tools or creating novel molecules to gain a cell-permeable, specific OGT inhibitor which is appropriate for laboratory experiments and even clinical cancer therapy.

| Categories                        | Compound            | IC$_{50}$ | Advantages and limitations                  |
|-----------------------------------|---------------------|-----------|---------------------------------------------|
| Substrate and product analogues   | C-UDP$^b$ [165]     | 9 μM      | lack of cell permeability                   |
|                                   | UDP-S-GlcNAc$^c$ [165] | 93 μM    | lack of cell permeability                   |
|                                   | UDP-C-GlcNAc [165]  | 41 μM    | lack of cell permeability                   |
|                                   | Ac$_{5}$-SS-GlcNAc$^c$ [31, 120, 123, 167] | 5 μM | cell-permeable, but reduces intracellular pool of UDP–GlcNAc |
| HTS-derived inhibitors            | Alloxan$^d$ [168–172] | 18 μM | cell-permeable, but has potential off-target effects and general cellular toxicity |
|                                   | BADGP [173, 174]    | unknown  | reducing intracellular pool of UDP–GlcNAc  |
|                                   | ST045849 [175–178]  | 53 μM    | having potential toxic and off-target effects |
| Bisubstrate inhibitors            | BZX [29, 97, 175]   | 10 μM    |                                             |
|                                   | OSMI-1 [122, 179]   | 2.7 μM   |                                             |
|                                   | goblin 1 [180]      | 18 μM    | lack of cell permeability                   |
|                                   | goblin 2 [180]      | unknown  |                                             |

$^a$high-throughput screening-derived inhibitors; $^b$ UDP analogue; $^c$ UDP-GlcNAc analogues; $^d$ Uracil analogue; $^e$ GalNAc analogue.
CONCLUSIONS

In the last 30 years, extremely large number of publications have elaborated the significance of O-GlcNAc in manifold cellular functions and diseases. Deregulation of O-GlcNAcylation is an event detected in a variety of cancer types and this aberrant O-GlcNAcylation is conducive to tumorigenesis, cell proliferation, invasion and metastasis, and resists to therapy. Considering the modification’s involvement in cancer, OGT has become attractive candidates for pharmacological targeting. However, the research on the regulatory mechanism of OGT is still in the early stage. In this review, we summarize the regulation of OGT expression and glycosyltransferase functions in cancer (Figure 2). OGT can be regulated by multiple ways to increase cell growth and survival, including OGT expression, degradation, localization and posttranslational modification. Interestingly, a large proportion of the moderators of OGT are also the downstream targets of OGT, such as Trak1 [140, 141], mSin3A [142, 143], PGC-1α [144, 145], HCF-1 [60, 61], TET/3 [65, 147–150], c-Myc [181], MYPT1 [146], CARM1 [146], 26S proteasome [131], OGT [132] and GSK3β [129]. This endows it with the ability to regulate cellular physiology in a feedback loop. The existing research results show that the regulation of OGT is extremely complicated and OGT operates as a central hub for controlling multiple important physiological processes such as metabolism and cell cycle progression.

Abbreviations

O-GlcNAc, O-linked β-D-N-acetylglucosamine; OGT, O-GlcNAc transferase; UDP-GlcNAc, Uridine 5'-diphosphate N-acetylglucosamine; OGA, O-GlcNAcase; ER-α/β, Estrogen Receptorα/β; NeuroD1, neurogenic differentiation 1; CRTC2, transducer of regulated cyclic adenosine monophosphate response element-binding protein; NFATc1, nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1; Elf-1, E74-like factor 1; Pdx-1, pancreatic and duodenal homeobox 1; C/E/BPβ, CCAAT enhancer-binding protein; MafA, m-Maf musculoaponeurotic fibrosarcoma oncogene homolog A; Id2, inhibitor of differentiation 2; HCF-1, Host Cell Factor 1; EZH2, enhancer of zeste homolog 2; TET, ten-eleven translocation enzymes; MLL5, Mixed lineage leukemia 5; HATs, histone acetyltransferases; HDACs, histone deacetylases; FoxM1, forkhead box M1; MMP-1/-2/-3/-9, matrix metalloproteinase-1/-2/-3/-9; VEGF, vascular endothelial growth factor; CDK-2, cyclin dependent kinase 2; PUMA, BCL2 binding component 3; RhoA, ras homolog family member A; ROCK, Rho-associated protein kinase; MLC, myosin light chain; PDK1, 3-phosphoinositide-dependent kinase 1; IRS-1, insulin receptor substrate 1; Cre, Cyclization Recombination Enzyme; MEK1DD: an activated mutant of MEK1, with serine to aspartic acid substitutions at residues Ser218 and Ser222; Elk-1, ETS domain-containing protein; RB1, Retinoblastoma-associated protein 1; Nrf2, NF-E2 related factor 2; AMPK, AMP-activated protein kinase; miRNA, microRNA; Hsp90, heat shock protein 90; ROS/RNS, reactive oxygen or nitrogen species; β-TrCP1, β-transducin repeat-containing protein 1; LPS, lipopolysaccharide; 1B; Nup62, Nuclear pore glycoprotein p62; CaMKIV, calcium/calmodulin-dependent protein kinase IV; Trak1, trafficking kinesin protein 1; LPS, lipopolysaccharide; PGC-1α, Peroxisome proliferator-activated receptor gamma coactivator 1-alpha; FoxO1, Forkhead box protein O1; MYPT1, myosin phosphatase target subunit 1; CARM1, coactivator associated arginine methyltransferase 1; LXR, Liver X receptor; PIP3, Phosphatidylinositol 3,4,5-triphosphate; URI, prefoldin like chaperone; PPIγ, protein phosphatase 1 catalytic subunit gamma; NLS, Nuclear localization sequence; Importin α5, Importin subunit alpha-5; BADGP, benzyl-N-acetyl-α-D-galactosaminide (GalNAcα-O-benzyl); ST045849, 3-(2-adamantanylethyl)-2-[(4-chlorophenyl)azamethylene]-4-oxo-1, 3-thiazaperyd roine-6-carboxylic acid; BZX, 4-methoxyphenyl 6-acetyl-2-oxo-2H-carboxylate.
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