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Review

Untamed aspects of OGT and O-GlcNAc functionality: Hyperthermal sensing and NO regulation

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ABSTRACT

Protein O-GlcNAcylation is a unique glycosylation process in nucleocytoplasm compared to typical glycosylation machinery in ER and Golgi. This is a Ser/Thr-linked O-glycosylation process which is formed with GlcNAc addition through β-O-linkage to serine and threonine residues. Either modification or elongation of O-GlcNAc with other sugars is not further continued in natural states. Thus, O-GlcNAc structure is conserved in high eukaryotes but not established in bacteria and yeast during evolution. Enzymatic catalysis of protein O-GlcNAcylation is exerted by OGT. OGT is known to be essential for cell viability and a single gene encoding OGT produces multiple OGT isoforms in mammalian system. Molecular basis of human OGT has been resolved by crystal structure analyses. During the last two decades, numerous proteins (500 - up to 1000) have been found to contain O-GlcNAc by which they are functioning in various biological processes. Popular aspect of protein O-GlcNAcylation suggests that it can interplay and cross-talk with protein phosphorylation. This concept of protein O-GlcNAcylation comprises of a wide range of cellular events, including signaling cascades, protein interactions, regulation of protein activity, and epigenetic controls. However, it is difficult to clearly define the physiological roles of OGT and O-GlcNAc *in vivo* primarily because a single enzyme OGT deals with considerable amount of different target proteins and also, within cells, there are combinatorial protein pools of O-GlcNAcylation, frequently together with other post-translational modifications. Here, challenging the multifaceted O-GlcNAc functionality, I present untamed aspects of OGT and O-GlcNAc highlighting hyperthermal sensing and NO regulation.

KEYWORDS: OGT, O-GlcNAc, hyperthermia, O-GlcNAcylation, NO, S-nitrosylation, denitrosylation

INTRODUCTION

In eukaryotic systems, since O-GlcNAc structure was initially described over 25 years ago [1], growing number of protein O-GlcNAcylation has been accumulated in various biological processes [2-4], including nuclear pore complexes [5, 6], RNA Pol II CTD [7], signaling kinases [8-10], transcription factors [11], proteosomes [12, 13], immune regulations [14, 15], and epigenetic controls [16]. In addition to normal states, emerging evidences imply that protein O-GlcNAcylation is involved in stress states of hyperthermia [17], and various chemicals including heating [18] as well as in disease states including diabetes, Alzheimer's disease, and cancers [19-21].

Protein O-GlcNAcylation is exclusively exerted in nucleocytoplasm unlike the typical N- and O-linked glycosylation in ER and Golgi and also, O-GlcNAcylation is recognized as analogous process like protein phosphorylation. Increasing evidences support the cross-talk and competitive

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interplay of O-GlcNAc with phosphorylation [22-24]. Homeostasis of O-GlcNAc structure is primarily maintained by catalytic balance of O-linked β-N-acetylglucosaminyltransferase (OGT) activity [25, 26] and cytosolic O-linked β-N-acetylglucosaminidase (OGA) activity [27]. Here, OGA will not be focused since it is well reviewed elsewhere [28, 29]. Formulation of O-GlcNAc structure is influenced by enzymatic activity of OGT, structural conformation of target proteins, and in situ level of UDP-GlcNAc which is generated via glucose flux into hexosamine biosynthetic pathway (HBP) [30]. It is becoming clear that protein O-GlcNAcylation and magnitude of O-GlcNAc content are affected by nutrient uptake in cells, such as high glucose and glucosamine.

Hence, controlling the OGT activity together with selectivity of target proteins is crucial for protein O-GlcNAcylation. Current knowledge about cellular regulation of OGT activity and target recognition is not sufficiently understood and the underlying mechanism has yet to be defined in detail. Still, there are many ambiguities to be addressed in the process of O-GlcNAcylation. What is the exact role of O-GlcNAc in cell physiology? How is OGT activity controlled? How are target proteins selected by OGT inside cells? Is there any mechanism to enhance or suppress OGT activity? Can target recognition of OGT be modulated by other factors?

Functionality of OGT and O-GlcNAc

1. A unique glycoconjugate by the specialized glycosyltransferase

Biosynthesis of O-linked β-N-acetylglucosamine (O-GlcNAc) structure on target proteins is constructed by O-GlcNAc transferase (OGT) [25, 26, 31]. For this post-translational modification (PTM) of protein O-GlcNAcylation, target proteins are initially recognized by tetratricopeptide repeat (TPR) domain of OGT and then, GlcNAc is linked through β-O-linkage to Ser/Thr residues from UDP-GlcNAc by catalytic (CAT) domain of OGT [32, 33]. Molecular basis of OGT action through TPR and CAT domain is resolved by 3-D structural analyses [34]. O-GlcNAc itself is a terminal structure which is not further processed in natural states, such as modification and elongation with other sugars.

OGT is a specialized glycosyltransferase acting in somewhat distinct way during evolution since it is catalyzing O-GlcNAcylation in nucleocytoplasm whereas almost other glycosyltransferases involved in protein N-/O-linked glycosylation or lipid-linked glycosylation play in ER and Golgi [35]. Hence, it is becoming evident that OGT and O-GlcNAc can be influenced by environmental changes in the nucleocytoplasm, including metabolic flux of glucose utilization via hexosamine biosynthetic pathway (HBP) [30, 36] affecting UDP-GlcNAc synthesis and ATP energy balance, oxidative stress and hypoxia [37], hyperthermia [17], nitric oxide (NO) induction [15], and other metabolite fluxes.

Since OGT gene was initially cloned in human and rat [25, 26], mammalian OGT homologs have been cloned in various species including mouse and *C. elegans* [25], *Arabidopsis* [38], *D. melanogaster* [39], and zebrafish [40], demonstrating that these OGT genes of metazoan are highly conserved and produce multiple OGT isoforms of splicing variants. In mammals, a single copy of OGT gene is located in X chromosome and OGT catalytic action is indispensable at a single cell level [41]. Mammalian OGT largely consists of TPR and CAT domain structures and in human, single OGT gene produces three isoforms, such as ncOGT (nucleocytoplasmic isoform, 1036 amino acid residues, 110 kDa), mOGT (mitochondrial isoform, 869 amino acid residues, 103 kDa), and sOGT (short isoform, 664 amino acid residues 74.5 kDa) depending on the number of TPR [42].

ncOGT has been known to be post-translationally modified with O-GlcNAc and tyrosine phosphorylation [43]. Recently, it has been found that ncOGT is modified with Cys-nitrosylation [15], demonstrating that Cys-nitrosylation can regulate OGT activity via SNO- and deNO-mechanism. sOGT was initially identified to be self-O-GlcNAcylated in *E. coli* system [44] and this was further confirmed in animal cell system [45]. Interestingly, mOGT is destined to mitochondria by a mitochondrial targeting signal in N-terminus whereas ncOGT and sOGT are present in nucleocytoplasm [46]. Particularly,

zebrafish (*Danio rerio*) OGT produces six different isoforms which are differentially regulated during embryogenesis [40] and these isoforms are critically involved in early embryo development [47]. OGT-catalyzed protein O-GlcNAcylation is known to be absent in bacteria and budding yeast, indicating no existence of OGT gene or if any OGT sequence, no functional OGT activity in these species.

2. Hyperthermal sensing: Proposed mechanism of OGT as a catalytic chaperone

a) In mammalian cells

Hyperthermal stress elicits deleterious effects globally in cell physiology and abnormality of protein folding is one of the central issues during hyperthermia [48, 49]. Functionality of O-GlcNAc and OGT in hyperthermia has been initially investigated in animal cell system (CHO and Hep3B cells) [17], demonstrating that hyperthermal stress triggers protein hyper-O-GlcNAcylation at early stage of less than 15 min. Notably, this early induced-hyper-O-GlcNAcylation was maximized until 60 min of thermal stress, during which heat shock proteins (Hsps) were not newly synthesized. In fact, OGT activity and its protein level were maintained to be constant.

Triggering cellular hyper-O-GlcNAcylation at early stage of thermal stress indicates that OGT can respond rapidly against hyperthermia without newly synthesized Hsps. Acute thermal response of OGT may be endowed by unfolding states of target proteins, in which potential sites for O-GlcNAc addition can be exposed and sensed by OGT with increased accessibility. Suppression of hyperthermia-induced hyper-O-GlcNAcylation by 6-diazo-5-oxo-norleucine (DON) treatment evoked more cell death than controls, suggesting that protein hyper-O-GlcNAcylation can function as a defense mechanism against thermal stress. Indeed, our data strongly supported this notion, showing that cells pre-expressing high level of O-GlcNAc represented less protein aggregation intracellularly and sustained to be more viable than native cells under hyperthermal stress [17].

The proposed mechanism of OGT as a catalytic chaperone in hyperthermia is illustrated in Figure 1. The concept of OGT catalytic chaperone is distinct from conventional chaperone function of Hsps in the context of followings; (i) acute sensing the exposed O-GlcNAc sites in unfolded or loosely folded target polypeptides by OGT, (ii) transferring the O-GlcNAc, and (iii) stabilizing unfolded polypeptide to avoid hydrophobic aggregation through O-GlcNAc's hydrophilic nature. In the context of acute hyperthermal sensing of OGT, it is possible to consider whether OGT plays the chaperone function by itself or by some co-work with Hsps. Currently, this is not known although it is likely that increased O-GlcNAc during thermal stress might have temporal effects on Hsp induction during the recovery stage at normal temperature [18].

b) In bacterial cells

Mammalian OGT (ncOGT, mOGT, and sOGT) was expressed in *E. coli*, showing that bacterial protein O-GlcNAcylation was not able to be detected whereas co-expression of OGT with p62 resulted in O-GlcNAcylation of p62 [44]. These intriguing observations suggest that bacterial cytosoilc environment is sufficient to proceed OGT reaction for p62 target protein, however, not significantly for endogenous bacterial proteins. Mammalian OGT seems to be a stranger toward bacterial proteins in terms of target recognition. Our continued works showed that co-expression of OGT with Sp1 gave rise to significant O-GlcNAcylation of bacterial proteins as well as Sp1 O-GlcNAcylation, implying that target recognition of OGT may be modulated by Sp1 [44]. Moreover, this Sp1-mediated endogenous O-GlcNAcylation in *E. coli* induced thermotolerance like in mammalian cell system although the identity of O-GlcNAcylated bacterial proteins is not known.

3. NO regulation: Control of OGT activity via S-nitrosylation and denitrosylation

Regulation of OGT activity can be conducted at transcriptional, translational level, and by PTMs of OGT itself. As an emerging PTM, protein S-nitrosylation is propagating in a wide range of cellular proteins [50]. Protein S-nitrosylation is primarily processed by nitric oxide synthase (eNOS, nNOS, and iNOS) within cells and S-nitrosoprotein (SNO-protein) and denitrosoprotein (deNO-protein) can be formed with NO addition and removal at Cys thiols [51, 52].

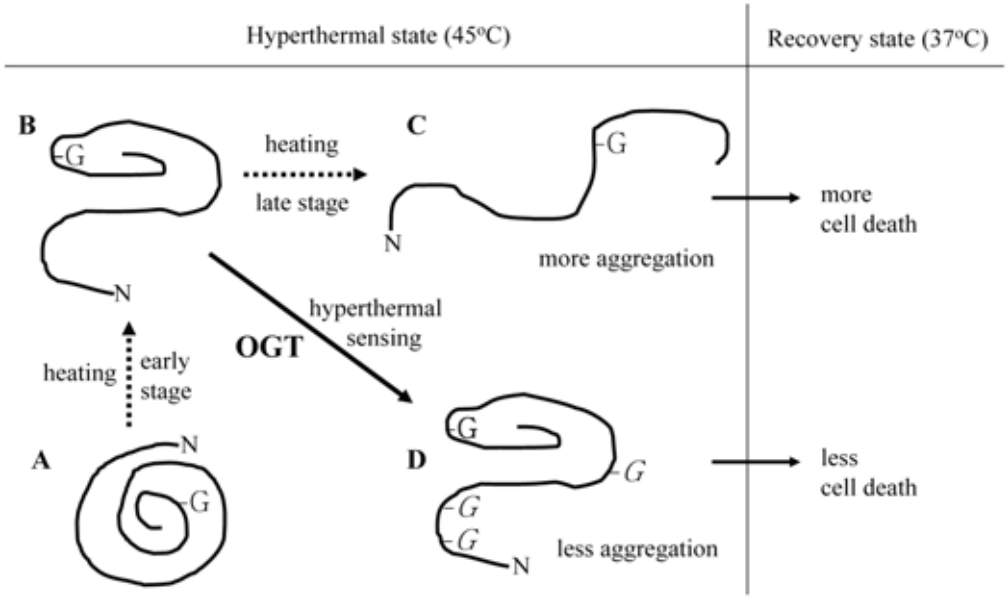

Figure 1. Diagram of OGT function as a catalytic chaperone: Pre-occupied with O-GlcNAc (**G**) on target protein (*N*-terminus indicated) is depicted in a native state (**A**). At early stage of thermal stress, OGT senses O-GlcNAc sites in unfolded target polypeptide (**B**) and transfers GlcNAc residues (***G***). Presence of new O-GlcNAc (***G***) stabilizes target polypeptide to be less aggregated at late stage of thermal stress and leads to more cell viability during recovery state (**D**). Absence of O-GlcNAc in unfolded polypeptide leads to more aggregation at late stage of thermal stress and less cell survival during recovery state (**C**).

S-nitrosylation of OGT was recently found in macrophage cells [15] and this is the first case of SNO-glycosyltransferase. Notably, OGT was present as SNO-form in resting state and triggering the denitrosylation of SNO-OGT occurred to generate deNO-OGT upon LPS stimulation both *in vitro* and *in vivo* system. OGT activity was strongly inhibited in SNO-form and vice versa. As shown in Figure 2, in LPS-stimulated macrophage cells, cellular state of hyper-O-GlcNAc is globally induced via conversion of SNO-OGT to deNO-OGT. Subsequently, hyper-O-GlcNAc state leads NFkB to be strongly O-GlcNAcylated and facilitates nuclear translocation of NFkB [14, 53]. These data provide good evidence that OGT activity is directly regulated via S-nitrosylation and denitrosylation. Currently, Cys residues of SNO-OGT are under site mapping.

Based on our observations, it is evident that "S-nitrosylation regulates O-GlcNAcylation" since the interconversion between SNO-OGT and deNO-OGT can globally regulate cellular state of O-GlcNAcylation, resulting in either hypo- or hyper-O-GlcNAc [15]. Moreover, it seems to be certain that "O-GlcNAcylation regulates S-nitrosylation". In the literature, the endothelial NO synthase (eNOS) has been known to be O-GlcNAcylated which causes reduced eNOS activity [54, 55]. Also, it has been shown that activation of HBP under high glucose treatment impairs arteriolar dilation due to increased O-GlcNAc modification of eNOS and subsequently, low level of NO synthesized [56]. These data imply that O-GlcNAcylation regulates eNOS activity by which both NO production and protein S-nitrosylation can be globally influenced. Furthermore, as shown in Figure 3B, we investigated cellular patterns of reciprocal relationship between O-GlcNAc and SNO-protein using RL2 immunoblotting and biotin switch assay [57, 58]. Our experimental data provide the first evidence that the more O-GlcNAcylation (hyper-O-GlcNAc state) makes the less S-nitrosylation (hypo-SNO state) within cells, and the more S-nitrosylation (hyper-SNO state) makes the less O-GlcNAcylation (hypo-O-GlcNAc state) in cultured cell systems (Figure 3B). Taken together, as schematically illustrated in Figure 3A,

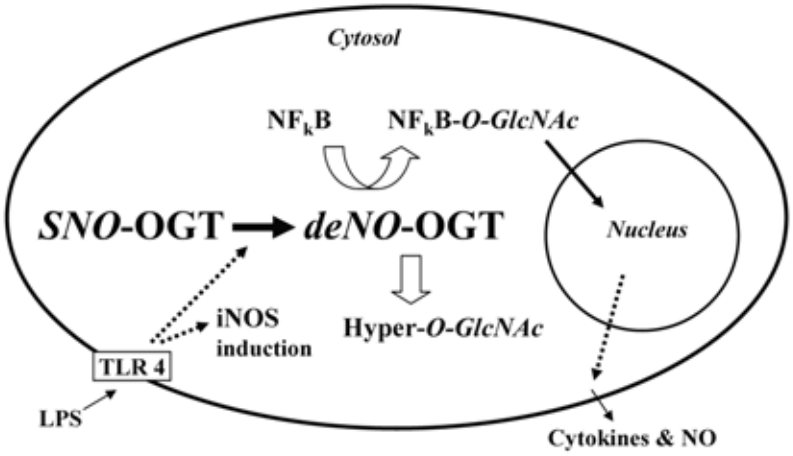

Figure 2. LPS-triggered denitrosylation of SNO-OGT: OGT exists as SNO-form in resting state of macrophage cells. LPS stimuli through toll like receptor (TLR4) induce iNOS expression and initiate to trigger denitrosylation of SNO-OGT to be deNO-OGT, resulting in hyper-O-GlcNAc at the global level within cells. DeNO-OGT leads NFkB to be O-GlcNAcylated which facilitates nuclear translocation of NFkB.

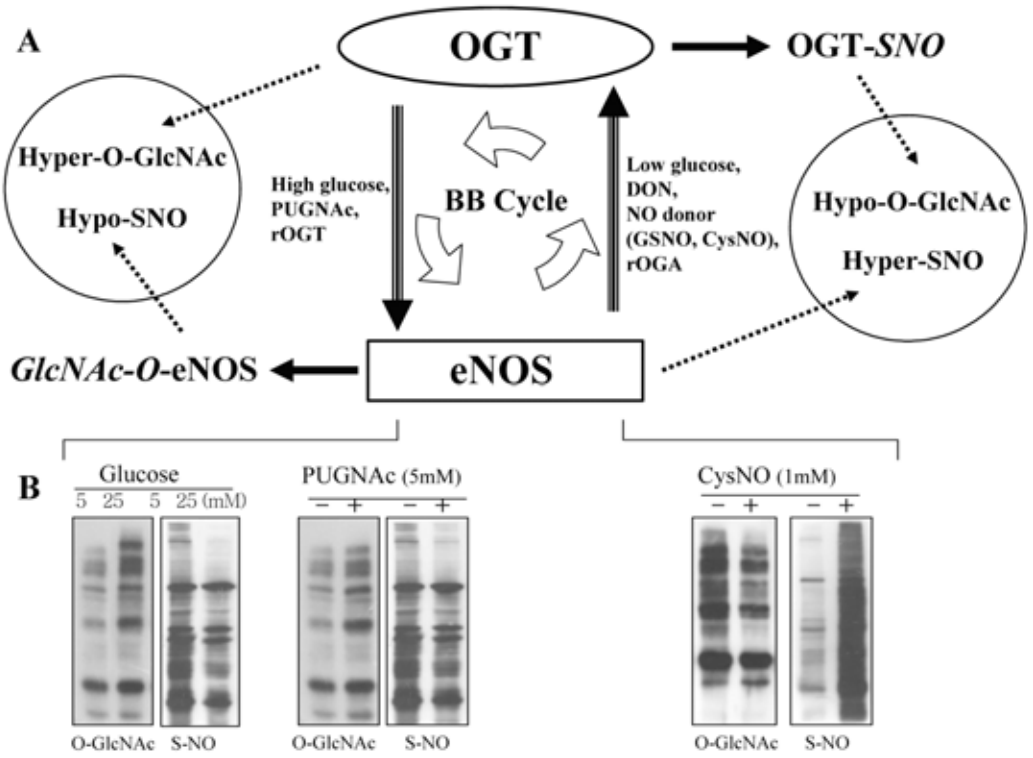

Figure 3. BB cycle between OGT and eNOS: (**A**) The BB cycle comprises the reciprocal PTMs of O-GlcNAc and S-NO between OGT and eNOS. PTMs between OGT and eNOS impairs enzyme activity reciprocally. Conditional factors affecting the BB cycle are listed and resultant cellular states of O-GlcNAcylation and S-nitrosylation are depicted in circle. rOGT and rOGA indicate over-expression of recombinant OGT and OGA, respectively. (**B**) Cell lysates of CHO-K1 cultured in the presence of normal (5 mM) and high glucose (25 mM), PUGNAc (OGA inhibitor, 5 μM), and CysNO (NO-donor, 1 mM) were subjected to SDS-PAGE and cellular patterns of O-GlcNAcylation (O-GlcNAc) and S-nitrosylation (S-NO) were analyzed by RL2 immunoblotting and biotin switch assay, respectively.

I originally propose the “Bite and Bitten cycle” (BB cycle) between OGT and eNOS. This cycle is responsible for generation of cellular state of inverse relationship between O-GlcNAcylation and S-nitrosylation through the reciprocal PTM-based impairing of OGT and eNOS activity. The BB cycle can be a general mechanistic principle for controlling O-GlcNAcylation and S-nitrosylaton not only in eNOS-related endothelial system but also in non-endothelial system.

In our works, denitrosylation of SNO-OGT under LPS stimuli seems to be unusual since LPS stimulation elicits NO production by iNOS induction and consequently, enhances SNO-protein formation [15]. This finding indicates that formation of SNO-OGT appears to be not facilitated by iNOS. It is very likely that S-nitrosylation of OGT is exerted by constitutive NOS activity, including eNOS, nNOS, or both. So far, how denitrosylation of SNO-OGT is triggered has yet to be determined although various denitrosylation mechanisms are described [53]. As a similar example, denitrosylation of SNO-CD40 has been reported in LPS-treated innate immune system and DeNO-CD40 can up-regulate its signaling capability although denitrosylation mechanism remains to be elucidated [59]. Probably, there might be some specific but unidentified mechanism for denitrosylating process under the special condition of iNOS induction in innate immune systems.

CONCLUDING REMARKS

In the present review, OGT and O-GlcNAc functionality is mainly summarized and discussed in terms of hyperthermal sensing and NO regulation. Coordination of OGT activity and O-GlcNAc structure is crucial for executing a variety of cellular functions via protein O-GlcNAcylation in the cytosol and nucleus. Homeostatic balance of O-GlcNAc level is pivotal for cell survival under normal, stress, and disease condition. Hence, a certain level of O-GlcNAc must be preserved at steady state but also, case by case, be changed to make an optimized balance of O-GlcNAc level inside cells. In hyperthermia and innate immune response, hyper-O-GlcNAc state is beneficial for cellular defense, but in case of hyperglycemia and cancer, hypo-O-GlcNAc state may be beneficial within cells.

Beyond the interplay and crosstalk of O-GlcNAcylation with phosphorylation, it is important to recognize that O-GlcNAcylation and S-nitrosylation can be inter-regulated through the BB cycle of reciprocal PTMs between OGT and eNOS. It is remarkable that NO regulates OGT, and O-GlcNAc regulates eNOS in cultured cells (Fig. 3B). In this context, S-nitrosylation of OGT gives an insight into novel understanding of inter-communication between O-GlcNAcylation and S-nitrosylation [15].

Conclusively, OGT itself together with O-GlcNAc on target polypeptides has to be continuously explored to provide full understanding about the OGT functionality including PTMs, target protein recognition, splicing system, epigenetic controls, and particularly, cellular defense controls in stress condition as well as disease states of diabetes, cancers and Alzheimer’s.

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