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Review

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Nutrient-sensitive protein O-GlcNAcylation shapes daily biological rhythms

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O-linked-*N*-acetylglucosaminylation (O-GlcNAcylation) is a nutrient-sensitive protein modification that alters the structure and function of a wide range of proteins involved in diverse cellular processes. Similar to phosphorylation, another protein modification that targets serine and threonine residues, O-GlcNAcylation occupancy on cellular proteins exhibits daily rhythmicity and has been shown to play critical roles in regulating daily rhythms in biology by modifying circadian clock proteins and downstream effectors. We recently reported that daily rhythm in global O-GlcNAcylation observed in *Drosophila* tissues is regulated via the integration of circadian and metabolic signals. Significantly, mistimed feeding, which disrupts coordination of these signals, is sufficient to dampen daily O-GlcNAcylation rhythm and is predicted to negatively impact animal biological rhythms and health span. In this review, we provide an overview of published and potential mechanisms by which metabolic and circadian signals regulate hexosamine biosynthetic pathway metabolites and enzymes, as well as O-GlcNAc processing enzymes to shape daily O-GlcNAcylation rhythms. We also discuss the significance of functional interactions between O-GlcNAcylation and other post-translational modifications in regulating biological rhythms. Finally, we highlight organ/tissue-specific cellular processes and molecular pathways that could be modulated by rhythmic O-GlcNAcylation to regulate time-of-day-specific biology.

1. Introduction

Organisms from all domains of life exhibit daily biological rhythms to adapt to changes in their environment over the 24 h day–night cycle. In animals, daily rhythms of physiology, metabolism and behaviour are strongly regulated by the circadian clock, an endogenous biological timer that enables animals to anticipate predictable changes in biotic and abiotic factors [1,2]. The circadian clock is a molecular oscillator that relies on transcriptional–translational feedback mechanisms operated by key clock transcription factors to generate daily oscillations in gene expression. In coordination with processes that are regulated by post-transcriptional mechanisms, clock-regulated rhythmic gene expression programs that are often tissue- and cell-specific produce daily rhythms in clock outputs. The outputs of animal circadian clocks are all-encompassing and include rhythmic processes such as sleep–wake cycles, feeding–fasting cycles, metabolism, hormone production and secretion, immune response, neuronal excitability and even permeability of the blood–brain barrier [3–10]. There is growing evidence that some clock outputs are themselves zeitgebers (i.e. time-givers) and can feedback to the molecular oscillator to reinforce and/or modulate daily biological rhythms. The feeding–fasting cycle is one such clock output and studies have shown that key clock transcription factors that form the core of the molecular oscillator can be regulated by metabolites or nutrient-sensitive hormones, such as heme, NAD/NADH (nicotinamide adenine dinucleotide/reduced form of nicotinamide adenine dinucleotide), AMP/ATP (adenosine monophosphate/

adenosine triphosphate), acetyl coenzyme A, glucocorticoids and glucagon (reviewed in [11]).

Besides impacting daily biological rhythms by modulating the activities of key clock transcription factors, metabolic feedback from feeding–fasting cycles can also regulate daily rhythms through other mechanisms beyond the circadian clock. For example, feeding–fasting cycles can drive rhythmic production of NAD^+, which serves as coenzyme for histone deacetylases class III, also known as sirtuins, to regulate daily rhythmicity in epigenomic landscape and global gene expression [12,13]. Feeding activity also contributes to daily oscillation of protein translation [14]. This was shown to be mediated by the nutrient-sensitive mTOR pathway, amino acid sensing pathways and metabolic modification of mRNA.

We recently established that integration of circadian signals and rhythmic metabolic input can regulate daily cellular physiology through rhythmic protein O-linked-*N*-acetylglucosaminylation (O-GlcNAcylation) [15]. O-GlcNAcylation has the potential to modify the function of thousands of proteins [16–19], and has been shown to play a critical role in maintaining animal circadian rhythms [20–23]. Furthermore, since both O-GlcNAcylation and phosphorylation modify serine and threonine residues [16,17,24], rhythmic O-GlcNAcylation may contribute to robust oscillation of the 24 h phosphoproteome and regulate its time-of-day specific function [25–28]. These post-translational mechanisms could bypass regulation at the transcriptional level to directly modulate protein function in a time-specific and nutrient-sensitive manner. Interestingly, our studies showed that the amplitude of daily protein O-GlcNAcylation rhythm is severely dampened if animals are fed at an unnatural time window (i.e. time of day at which they are normally fasting [15]). This suggests that rhythmic functions of cellular proteins could be impaired by mistimed meals, a common occurrence in modern society. Our findings point to the likelihood that the beneficial effects of time-restricted feeding [29–35], a practice that limits food consumption to 8–12 h during an individual's natural active period and has been shown to maintain robust circadian rhythms, enhance health span and alleviate metabolic diseases, may be partially mediated via daily O-GlcNAcylation rhythm.

In the remainder of the review, we will summarize the regulation of daily rhythmicity in O-GlcNAcylation by metabolic and circadian signals, outline interactions between O-GlcNAcylation and other post-translational modifications (PTMs), and highlight cellular processes that are potentially regulated by rhythmic O-GlcNAcylation.

2. Regulation of O-GlcNAcylation in the context of daily biological rhythm

Protein O-GlcNAcylation is nutrient-sensitive and is tightly linked to cellular metabolic status. For this reason, the regulation and function of O-GlcNAcylation have been extensively studied in the context of metabolic diseases, specifically diabetes and cancers [17,36]. On the contrary, although metabolism and energy status are highly rhythmic over the day–night cycle, the number of studies on rhythmic O-GlcNAcylation and the consequences of its disruption dwarfs in comparison. The cycling of O-GlcNAc groups on proteins is regulated by the level of UDP-GlcNAc (the substrate) and the activities of two O-GlcNAc processing enzymes, O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA) (figure 1). UDP-GlcNAc is produced from the hexosamine biosynthetic pathway (HBP), which integrates metabolites from glucose metabolism (glucose), amino acid metabolism (glutamine), lipid metabolism (acetyl-CoA) and nucleotide metabolism. In this section, we discuss current findings on the regulation of O-GlcNAcylation under the framework of rhythmic biology over a 24 h day–night cycle.

2.1. Regulation of HBP pathway by daily rhythm of nutrient availability

Nutrient availability directly determines the level of building blocks for producing UDP-GlcNAc. Given that there is strong support from metabolomics studies showing that nutrient input correlates with feeding activity [15,94–96], metabolic influx into the HBP is expected to be highly rhythmic over the day–night cycle and probably contributes to daily rhythmicity in O-GlcNAcylation. In studies conducted using cultured cells or tissues, elevated production of UDP-GlcNAc has been shown to correlate with higher nutrient concentration in cell media, including glucose, glutamine, glucosamine (GlcN), acetylglucosamine (GlcNAc), free fatty acids and uridine [37,50,97–105]. However, some glucose starvation studies showed contradictory results; glucose starvation was observed to result in elevation of O-GlcNAcylation level [38,50,51]. These conflicting observations could be explained by divergent properties of cell lines or tissue types. For example, Pham *et al.* [106] showed that O-GlcNAcylation levels in different subtypes of diffuse large B-cell lymphoma cell lines respond differently to glucose deprivation. Additionally, increased O-GlcNAcylation upon glucose starvation could be due to altered levels of OGT, OGA or glutamine:fructose-6-phosphate amidotransferase (GFAT) [38,50,51].

Although cell culture and *ex vivo* studies have firmly established the importance of nutritional regulation of HBP and O-GlcNAcylation, *in vivo* studies especially ones that take into account daily rhythmic biology and feeding–fasting cycles are still limited. In the 1990 s, Hawkins *et al.* [107] showed that continuously infusing lipid emulsion, uridine or GlcN for 7 h increases UDP-GlcNAc levels in rat skeletal muscles. To establish the relationship between feeding activity and levels of HBP metabolites including UDP-GlcNAc, we recently monitored feeding rhythm and HBP metabolites in *Drosophila* flies over a 24 h day–night cycle [15]. We observed strong correlation between fly feeding rhythm and daily rhythms in HBP metabolites in fly body tissues. Significantly, we found that shifting the time of food consumption significantly altered the peak time of HBP metabolite rhythm. In summary, we conclude that HBP metabolites and UDP-GlcNAc level are strongly regulated by clock-controlled feeding–fasting cycle and metabolic input. Whether this phenomenon is consistent in other animals, including nocturnal animals, will need to be explored in future studies.

2.2. Daily regulation of HBP enzymes

Besides rhythmic metabolic input into the HBP facilitated by clock-controlled feeding–fasting cycles, rhythmic expression and activity of HBP enzymes could also contribute to daily rhythms in protein O-GlcNAcylation. Searching through CirGRDB, a mammalian circadian transcriptomic database

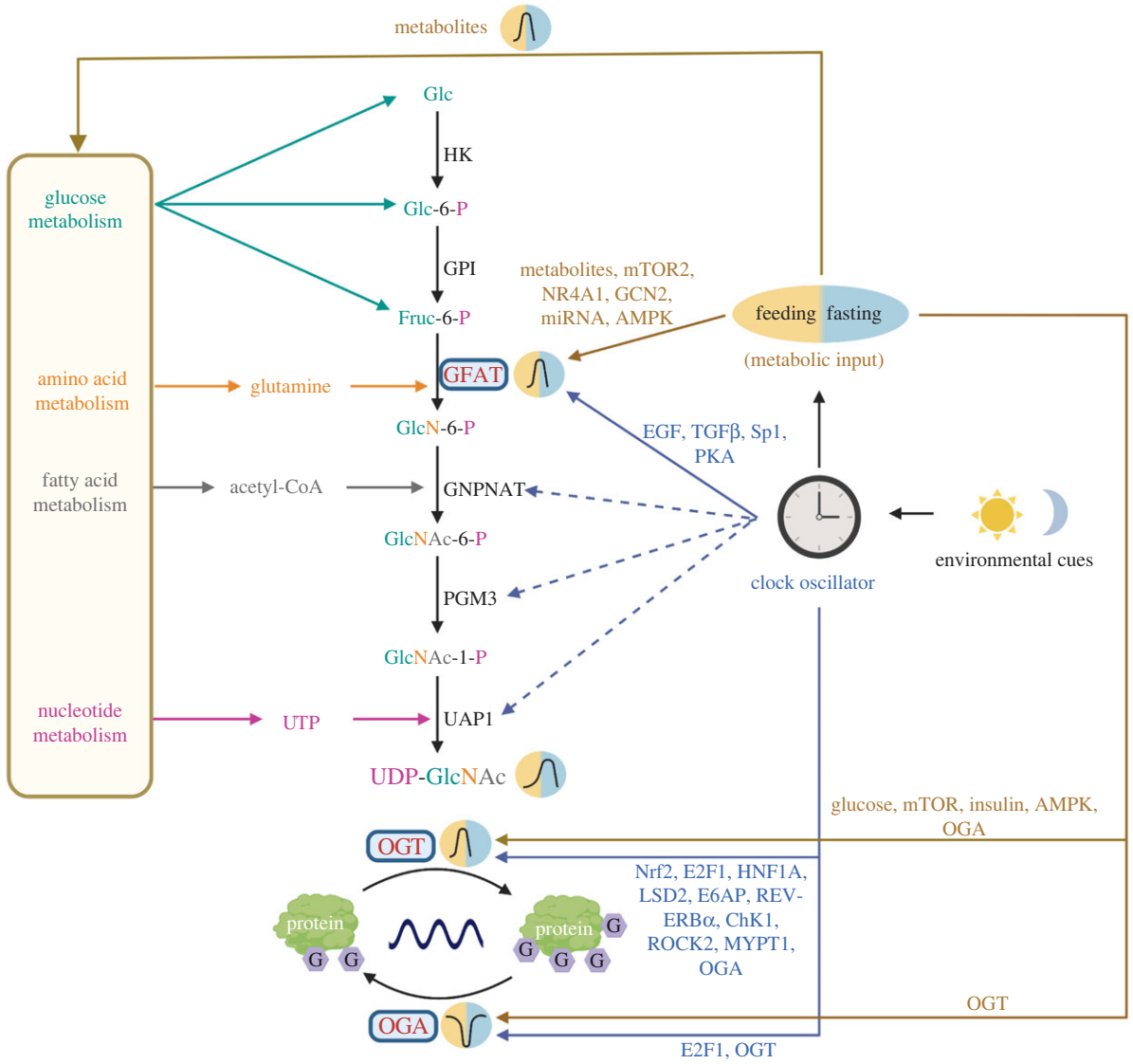

Figure 1. Schematic illustrating metabolic and circadian regulation of rhythmic protein O-linked-*N*-acetylglucosaminylation (O-GlcNAcylation). The circadian clock oscillator receives environmental signals and regulates daily feeding–fasting cycles. Feeding–fasting cycles rhythmically provide input to hexosamine biosynthetic pathway (HBP), which contributes to rhythmic production of UDP-GlcNAc [15]. O-GlcNAc transferase (OGT) takes UDP-GlcNAc as a substrate and transfers GlcNAc onto serine and threonine residues of proteins. This process is recognized as O-GlcNAcylation (O-GlcNAc is depicted as G on protein molecules). Metabolic input can also regulate the O-GlcNAcylation rhythm through modifying the activities of glutamine:fructose-6-phosphate amidotransferase (GFAT) [37–49], OGT [21,50–63] and O-GlcNAcase (OGA) [64]. Additionally, the clock oscillator not only regulates feeding–fasting cycles, but also regulates the expression or enzymatic activities of all the HBP enzymes [39,47,65–76] and O-GlcNAc processing enzymes [62,63,71,72,77–93]. The potential mediating factors of metabolic and circadian inputs are illustrated in the schematic diagram; metabolic inputs are depicted in brown and circadian inputs are depicted in blue. The dashed arrows indicate potential regulation without known mechanisms. HK, Hexokinase; GPI, phosphoglucose isomerase; GFAT, glutamine–fructose-6-phosphate aminotransferase; GNPNAT, glucosamine-phosphate *N*-acetyltransferase; PGM3, phosphoacetylglucosamine mutase; UAP1, UDP-*N*-acetyl glucosamine pyrophosphorylase 1; OGT, O-GlcNAc transferase; OGA, O-GlcNAcase; Glc, glucose; Glc-6-P, glucose-6-phosphate; Fruc-6-P, fructose-6-phosphate; GlcN-6-P, glucosamine-6-phosphate; GlcNAc-6-P, *N*-acetylglucosamine-6-phosphate; GlcNAc-1-P, *N*-acetylglucosamine-1-phosphate; UTP , uridine triphosphate; UDP-GlcNAc, uridine diphosphate *N*-acetylglucosamine; mTOR, mammalian target of rapamycin; NR4A1, nuclear subfamily 4 group A member 1; GCN2, general control nonderepressible2; miRNA, microRNA; AMPK, AMP-activated protein kinase; EGF, epidermal growth factor; TGFβ, transforming growth factorβ; Sp1, specificity protein 1; PKA, protein kinase A; Nrf2, nuclear factor E2-related factor-2; E2F1, transcription factor E2F1; HNF1A, hepatocyte nuclear factor 1 homologue A; LSD2, lysine-specific histone demethylase 1B; E6AP, ubiquitin ligase E6AP; ChK1, checkpoint kinase 1; ROCK2, Rho-associated coiled-coil forming protein kinase 2; MYPT1, myosin phosphatase target subunit 1.

[108] and published *Drosophila* transcriptomic datasets [27,109], we found that transcripts encoding all HBP enzymes oscillate in at least one study. Additionally, data mining in circadian proteomic and phosphoproteomic datasets [25,27,110] revealed that the majority of the HBP enzymes have oscillating protein levels and/or phosphorylation. Our recent study reported that GFAT enzyme activity oscillates over a 24 h cycle in flies and rhythmic GFAT activity is regulated by the integration of metabolic and circadian signals [15]. In this section, we will elaborate on our findings and discuss potential mechanisms mediating daily regulation of HBP enzymes. In particular, we will focus on the regulation of GFAT, the rate-limiting enzyme of HBP and the most well studied of all HBP enzymes (figure 1).

The expression of *gfat* mRNA is highly regulated by nutrient availability and nutrient-sensing pathways. *gfat* has two isoforms in animals, *gfat1* and *gfat2*. Both isoforms encode GFAT enzymes that perform the same catalytic function but

have distinct tissue-specific distribution (reviewed in [111]). We showed that the expression of *gfat*2 mRNA in fly body tissues is strongly induced by food consumption in *Drosophila* [15], although we did not explore the mechanisms that mediate the observed induction. In tissue culture, expression of *gfat* mRNA has been shown to be stimulated by various nutrients [37,39–42] and mediated by multiple molecular pathways, including mammalian target of rapamycin2 (mTOR2) [41,43], nuclear subfamily 4 group A member 1 (NR4A1) [40], microRNA (miR)-27b-3p [42] and general control nonderepressible2-activating transcription factor 4 pathway [38]. Expression of *gfat* mRNA can potentially be regulated by clock-controlled factors/processes in addition to feeding–fasting cycles and rhythmic metabolic input. These include angiotensin II [112–114], epidermal growth factor (EGF) [39,65,66], transforming growth factorβ (TGFβ) [67–69] and Specificity protein 1 [70–72], all of which are known to influence *gfat* expression.

Beyond transcriptional regulation, GFAT enzyme activity is known to be influenced by PTMs and feedback regulation from HBP metabolites. We reported that the circadian clock strongly regulates daily GFAT activity through unknown post-transcriptional and/or post-translational mechanism(s) [15]. Interestingly, the kinases that have previously been identified to regulate GFAT activities are also known effectors of circadian signals or clock-controlled metabolic signals. These include AMP-activated protein kinase (AMPK) [44,45], mTOR2 [46] and protein kinase A (PKA) [47,73–76]. In particular, PKA-directed phosphorylate site at GFAT1 S235 [74] is shown to oscillate over a circadian cycle in mouse liver [25]. However, the function of GFAT1 pS235 is currently unclear. Finally, glucosamine-6-phosphate (GlcN-6-P) and UDP-GlcNAc, the direct product from the GFAT-catalysed reaction and end product of the HBP respectively, can feedback to inhibit GFAT activity [47–49]. As our study found that GlcN-6-P and UDP-GlcNAc levels oscillate over the day–night cycle with peak time corresponding to feeding period [15], HBP metabolites likely represent important signals to shape daily GFAT activity.

In summary, as we concluded in our studies in *Drosophila* [15], the HBP enzyme GFAT represents an important integration hub of circadian and metabolic signals to regulate the production of UDP-GlcNAc and cellular protein O-GlcNAcylation.

2.3. Daily regulation of O-GlcNAc processing enzymes

There is strong evidence showing that OGT and OGA, the two O-GlcNAc processing enzymes that drive the cycling of GlcNAc group on and off proteins, are subjected to control by the circadian clock, but data on direct measurements of OGT and OGA enzyme activities over a daily cycle are still lacking to the best of our knowledge. Circadian transcriptomic and proteomic analyses showed that the *oga* mRNA and OGA protein oscillate in mouse livers and fly heads [27,71,115–119], while *ogt* mRNA but not OGT protein was observed to oscillate in mouse livers and fly heads [20,21,27,71,109,110,120–122]. We showed that in *Drosophila* fly bodies, the transcripts and encoded proteins of the two O-GlcNAc processing enzymes are modulated by both circadian and metabolic input [15]. This section is devoted to review potential molecular mechanisms that mediate metabolic and circadian regulation of OGT and OGA.

ogt mRNA and its encoded protein OGT are regulated by nutrient levels and nutrient-sensing pathways that are expected to be highly rhythmic over the day–night cycle. There are two nutrient-sensing pathways that are known to regulate OGT protein level, mTOR [52–54] and insulin signalling [55], and glucose itself [50,51,56] has also been shown to modulate *ogt* mRNA expression. Currently, it is unclear how expression of *ogt* mRNA and their encoded proteins are regulated by the circadian clock. The clock can potentially orchestrate rhythmic *ogt* mRNA expression by targeting rhythmically active transcription factors. Candidates include nuclear factor E2-related factor-2 (Nrf2) [77–80], E2F1 transcription factor [81,82] and hepatocyte nuclear factor 1 homologue A (HNF1A) [72,83,84], which are known to regulate *ogt* expression. With regard to OGT protein cycling, lysine-specific histone demethylase 1B (KDM1B or LSD2) and ubiquitin ligase E6AP have been shown to facilitate OGT ubiquitylation and degradation through their ubiquitin ligase activity [85,86]. Interestingly, *LSD2* and *E6AP* transcripts are both observed to oscillate in circadian transcriptome studies [71,72,82]. Finally, the clock protein REV-ERBα directly interacts with OGT and stabilizes OGT in different cellular compartments, as the cellular localization of REV-ERBα oscillates [87]. Whether and how these mechanisms contribute to circadian regulation of OGT levels will need to be explored in future studies. When compared with the regulation of *ogt* expression, much less is known about pathways that modulate *oga* expression. Given that E2F1 regulates *oga* expression in addition to *ogt* expression [81], it represents a transcription factor candidate [82] that can drive rhythmic *oga* expression.

At the post-transcriptional level, OGT enzymatic activity is regulated by multiple PTMs, which have been shown to respond to metabolic or circadian signals. Metabolic input has been shown to regulate OGT phosphorylation and thereby enzymatic activity through insulin signalling [21,57,58], as well as AMPK [59] and CAMKII [60,61] phosphorylation. Glycogen synthase kinase 3β (GSK3β), which happens to be an insulin signalling effector and a clock kinase, is shown to phosphorylate OGT at S3 or S4 to increase its enzymatic activity [21]. GSK3β-dependent phosphorylation of OGT can also change substrate selectivity [58]. Moreover, the circadian clock has been shown to rhythmically regulate the kinases and phosphatases that modify OGT, such as Checkpoint kinase 1 (ChK1) [88,89], Rho-associated coiled-coil forming protein kinase 2 (ROCK2) [71,72,90], myosin phosphatase target subunit 1 (MYPT1) [71,72,91,92]. Finally, O-GlcNAcylation of OGT S389 is shown to increase OGT nuclear localization [62]. As O-GlcNAcylation can integrate both metabolic and circadian signals [15], it will be interesting to explore whether OGT exhibits daily oscillation of subcellular localization. OGA can also be modified by phosphorylation and O-GlcNAcylation [123]. However, the functional role of these PTMs on OGA is less defined. Whether the phosphorylation and O-GlcNAcylation status of OGT and OGA is rhythmically regulated over a 24 h day–night cycle and how that modulates their activities needs future investigation.

To conclude the discussion on daily regulation of O-GlcNAc processing enzymes, it is important to point out that OGT and OGA impose reciprocal regulation against one another to maintain O-GlcNAc homeostasis. For example, as OGT protein level decreases, OGT forms a repressor complex

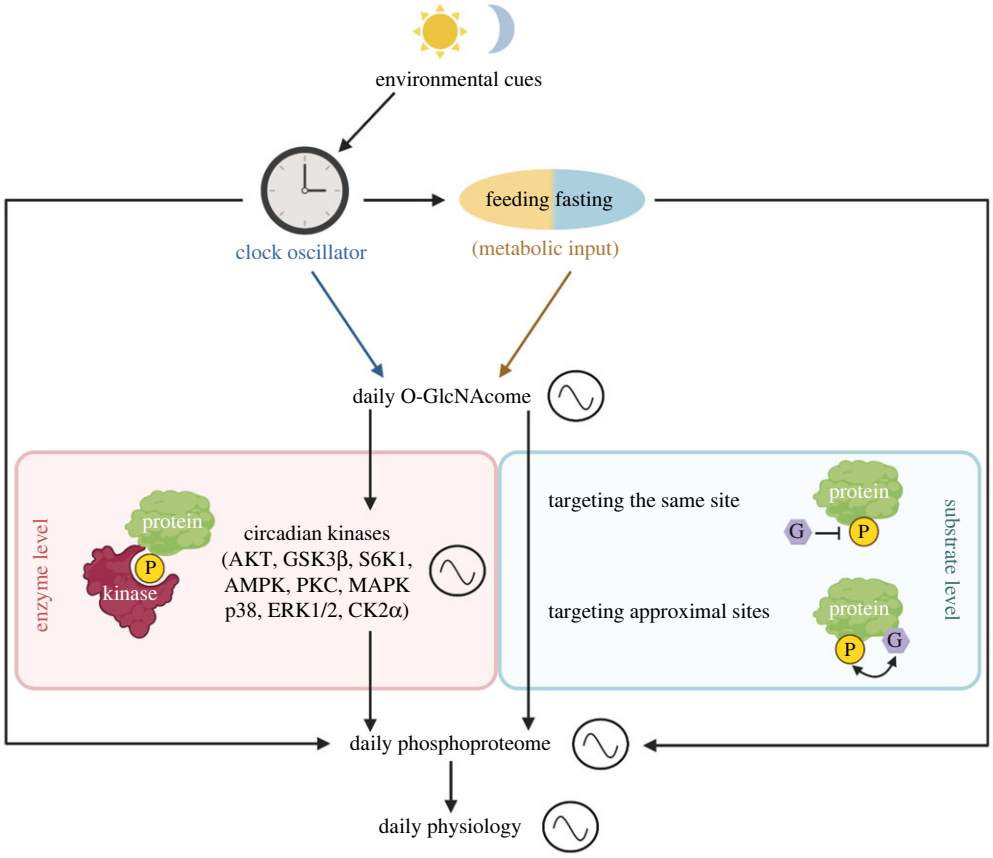

Figure 2. Daily rhythmicity of the O-GlcNAcome can integrate metabolic and circadian signals to modulate rhythmicity of the phosphoproteome. O-GlcNAcylation can modulate rhythmic activities of 'circadian kinases', which have been previously identified by analysing circadian/daily phosphoproteomic datasets [25,27]. We define this as enzyme level regulation. For substrate level regulation, O-GlcNAcylation can directly compete with phosphorylation by targeting the same residue on substrate proteins and/or modulate the protein conformation to promote or inhibit phosphorylation by targeting an approximal site [129–133]. Independently, phosphorylation is also sensitive to environmental and metabolic signals. In sum, interplay between daily phosphorylation and O-GlcNAcylation regulates time-of-day functions of cellular proteins and daily physiological rhythms. GSK3β, Glycogen synthase kinase3β; S6K1, ribosomal protein S6 kinase 1; AMPK, AMP-activated protein kinase; PKC, protein kinase C; MAPK p38, mitogen-activated protein kinase p38, ERK1/2, extracellular signal-regulated kinase1/2; CK2α casein kinase2α.

with mSin3A and histone deacetylase1 (HDAC1) at the promoter of *oga* to inhibit its expression [64]. OGA can promote *ogt* expression by reducing O-GlcNAcylation of CCAAT/enhancer-binding proteinβ (C/EBPβ) recruited to the promoter of *ogt* [63]. Notably, increasing O-GlcNAcylation level using an OGA inhibitor has been observed to elevate OGA protein while decreasing OGT protein level [93]. The reciprocal regulation of the two O-GlcNAc processing enzymes is expected to contribute to shaping daily rhythmicity of O-GlcNAcylation.

3. Crosstalk between O-GlcNAcylation and other post-translational modifications to regulate daily cellular physiology

Different types of PTMs co-occur on proteins to regulate their functions in response to diverse physiological and environmental signals. O-GlcNAc modifications have been shown to exhibit crosstalk with other PTMs, such as phosphorylation (reviewed in [24]), acetylation [124–126] and ubiquitination [127,128]. The crosstalk between O-GlcNAcylation and phosphorylation has attracted the most attention, as both PTMs target serine and threonine residues. Given that circadian proteomics studies in recent years demonstrated that phospho-occupancy in many cellular proteins exhibit daily rhythmicity to regulate time-of-day protein functions [25–28], it is intriguing to explore how O-GlcNAcylation and phosphorylation (and possibly other PTMs) could work in conjunction to regulate daily rhythmicity in protein functions. Crosstalk between O-GlcNAcylation and other PTMs can present itself in two manners: (i) modify the function of writers and erasers (enzyme level), or (ii) modify the same sites or nearby sites on protein substrates to modulate the level of other PTMs (substrate level) (figure 2). With an emphasis on phosphorylation, we next review the mechanisms by which O-GlcNAcylation could shape daily rhythmicity in phosphoproteome to regulate biological rhythms.

3.1. Daily O-GlcNAcylation-phosphorylation crosstalk (O-P crosstalk) at the enzyme level

Since global O-GlcNAcylation level oscillates over a 24 h cycle [15] and O-GlcNAcylation has been shown to regulate the function of a myriad of kinases and phosphatases [24,134,135], time-of-day specific O-GlcNAcylation of kinases and phosphatases could represent an important mechanism to remodel daily rhythmicity in the phosphoproteome. In 2012, Dias *et al.* [136] systematically analysed O-GlcNAcylation of kinases using an *in vitro* OGT assay. They screened through 152 full-length human kinases and identified 42 O-GlcNAcylated kinases. More recently, Schwein & Woo

Table 1. O-GlcNAcylation of kinases known to regulate circadian rhythm. GSK3β, glycogen synthase kinase3β; S6K1, ribosomal protein S6 kinase 1; AMPK, AMP-activated protein kinase; PKC, protein kinase C; MAPK p38, mitogen-activated protein kinase p38; ERK1/2, extracellular signal-regulated kinase1/2, CK2α casein kinase2α.

kinases	O-GlcNAc sites	function of O-GlcNAcylation	references
AKT	T308, S473 (characterized by mutagenesis)	inhibit AKT phosphorylation at T308 and S473, and inhibit AKT activity	[137,138]
GSK3β	n.a.	promote GSK3β phosphorylation at S9, and inhibit GSK3 activity	[137,139,140]
S6K1	S489 (characterized by mutagenesis)	inhibit S6K1 phosphorylation at S418 and T229, and inhibit S6K1 activity	[141]
AMPK	n.a.	inhibit AMPKα phosphorylation at T174, and inhibit AMPK activity	[59,142]
PKCζ	T408, T410 (characterized by mutagenesis)	inhibit PKCζ phosphorylation at T410, and inhibit PKCζ activity	[143]
MAPK p38	n.a.	promote p38 phosphorylation, and activate p38 activity	[144]
ERK1/2	n.a.	promote ERK1/2 phosphorylation, and activate ERK1/2 activity	[144]
CK2α	S347 (validated by Edman sequencing)	inhibit CK2α phosphorylation at T344, reduce the interaction between CK2α and PIN1, promote CK2α degradation, and alter substrate selectivity	[145]

[135] reviewed the O-GlcNAcomic datasets, and found more than 100 O-GlcNAcylated kinases, which covers all six major kinase families (AGC, CMGC, CAMK, STE, CK1 and TK/TKL) and some atypical protein kinases. Not surprisingly, a number of phosphatases are also found to be O-GlcNAcylated, including MYPT1, PPFIA2–4, PPP6R2, PTPN6, PTPN7, PTPRC, TNS2 and SIRPA [135].

Much progress has been made in characterizing the function of O-GlcNAcylation on many kinases. In table 1, we highlight the O-GlcNAcylated 'circadian kinases', which we identified by analysing the circadian phosphoproteome [25,27]. Nevertheless, proteomic studies on how O-GlcNAc sites of certain kinases could modulate the phosphoproteome are still rather limited. Schwein *et al*. [146] recently used nanobody-OGT and nanobody-split OGA to specifically modify O-GlcNAc S347 on CK2α and analysed the phosphoproteome in HEK293 cells. They observed that increased CK2α O-GlcNAcylation promotes the phosphorylation of 39 proteins, enriched for chromatin modification, metabolism and ribosome, while decreasing the phosphorylation of 12 proteins. In conclusion, O-GlcNAcylation could regulate cellular physiology through modifying the kinome and thereby the phosphoproteome (figure 2). Future investigation is warranted to reveal the O-GlcNAcylation-kinome crosstalk under the framework of the 24 h day–night cycle.

3.2. Daily O-P crosstalk at the substrate level

Since the discovery that O-GlcNAcylation and phosphorylation can modify the same amino acid residue on the same protein [147], crosstalk between O-GlcNAcylation and phosphorylation on substrates is recognized as an important mechanism for regulating protein function. Early study investigating O-P crosstalk used OGA inhibitors to elevate the global O-GlcNAcylation level and assayed the phosphoproteome in cell culture [129]. Out of the 711 phosphopeptides detected, 148 phosphopeptides increased and 280 decreased upon OGA inhibition. The phosphoproteins identified by Wang *et al*. [129] were enriched for cytoskeleton, cytoskeleton binding and RNA/DNA binding proteins. In addition to using inhibitors to globally alter protein O-GlcNAcylation status, other approaches have also been used to characterize physiologically relevant O-P crosstalks. Trinidad *et al*. [130] studied O-P crosstalks at murine synapses, as both OGT and OGA are enriched at synapses [148,149]. They sequentially enriched for O-GlcNAc and phosphopeptides and successfully detected O-GlcNAcylation and phosphorylation on the same peptides [130]. Among the 1750 O-GlcNAc sites and 16 500 phosphosites detected, 135 sites can be modified by both O-GlcNAcylation and phosphorylation. More recently, Fan *et al*. [131] developed a HILIC enrichment method to simultaneously enrich for O-GlcNAc and phosphopeptides. They assayed O-P crosstalk on 1115 RNA binding proteins (RBPs) and found that 213 RBPs (25%) can be both O-GlcNAcylated and phosphorylated. Taken together, direct competition between O-GlcNAcylation and phosphorylation may not be the dominant mechanism for O-P crosstalk, and O-GlcNAcylation and phosphorylation are more likely to regulate each other through modifying approximal sites (figure 2).

To elucidate the mechanisms for O-P crosstalk, researchers have started to analyse potential consensus sequence of O-P crosstalk. Although sites modified by both O-GlcNAcylation and phosphorylation occur at a relatively low frequency, Yao *et al*. [132] extracted three motifs (Pxx[S], Txxx[S] and [T]xxxxxxxxP) that are overrepresented in S/T exhibiting O-P crosstalk at the same residue. For O-P crosstalk at approximal sites, Leney *et al*. [133] performed a systematic analysis using a MS-based *in vitro* kinetic assay and identified a motif with four amino acids: N-[S/T]P(V/A/T)[S/T]-C. Phosphorylation occurs at the N terminal S/T and O-GlcNAcylation modifies the C terminal S/T, and the two PTMs tend to reciprocally inhibit one other [133]. Data mining in PhosphoSite Plus showed that 1048 proteins could be regulated by this potential mechanism, and previous studies support that O-P crosstalk on proteins such as eukaryotic initiation factor 4 (eIF4) and Sin3A could be mediated by this motif [133,150,151]. Kinase prediction shows that extracellular signal-regulated kinase1 (ERK1), ERK2, CK1 and GSK3β are likely to modify the motifs mentioned above

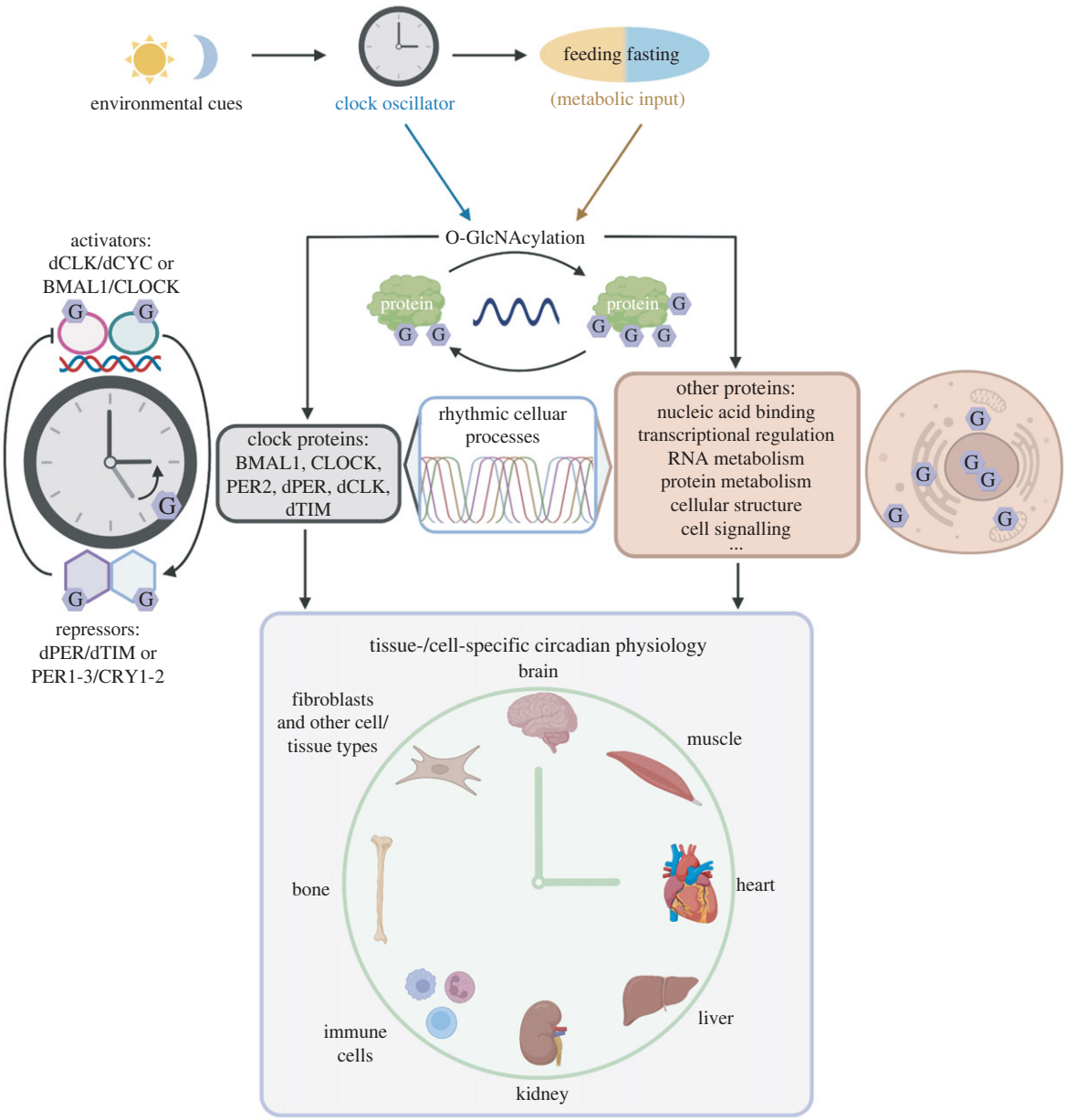

Figure 3. O-GlcNAcylation regulates daily biological rhythms from cellular to organismal level. O-GlcNAcylation rhythmically modifies circadian clock proteins, key components of the molecular oscillator [21–23]. Global increase in cellular O-GlcNAcylation slows down the pace of circadian clocks, which in turn alters timing of rhythmic cellular processes [20–22]. In addition to clock proteins, thousands of other cellular proteins are also O-GlcNAcylated. O-GlcNAcylation is directly involved in regulating basic cellular functions, such as transcriptional regulation, RNA metabolism, translation, protein metabolism [16–19]. Furthermore, O-GlcNAcylation can also modify activities of organ-, tissue- or cell-specific processes [153–173]. In summary, rhythmic O-GlcNAcylation ranging from subcellular to organ levels manifest into robust daily biological rhythms at the organismal level. dCLK, *Drosophila* CLOCK; dCYC *Drosophila* CYCLE; BMAL1, brain and muscle Arnt-like protein-1; CLOCK, circadian locomotor output cycles kaput; dPER, *Drosophila* PERIOD; dTIM, *Drosophila* TIMELESS; PER1-3, PERIOD1-3; CRY1-2, CRYPTOCHROME1-2.

[132,133]. Interestingly, these kinases overlap with 'circadian kinases' that can rhythmically phosphorylate proteins over a 24 h cycle [25,27], suggesting that daily cycling of O-GlcNAcylation could potentially regulate daily rhythmicity in the phosphoproteome at the substrate level (figure 2). Nevertheless, this hypothesis needs to be tested with the advances of O-P peptide enrichment methods and MS proteomics.

4. O-GlcNAcylation is an important mechanism that regulates daily cellular physiology

A large body of work contributed to our understanding of diverse mechanisms by which metabolic input interacts with the endogenous circadian clock to regulate daily biological rhythms (reviewed in [11,13,152]). Our recent study highlights protein O-GlcNAcylation as a key post-translational mechanism that integrates metabolic and circadian signals to regulate rhythmic physiology [15]. At the molecular level, there are two ways O-GlcNAcylation can regulate daily rhythms of cellular physiology: (i) O-GlcNAcylation can modulate core clock proteins and the pace of the molecular clock, which in turn alters rhythmicity of diverse cellular processes; (ii) O-GlcNAcylation can rhythmically modify cellular proteins outside of the molecular oscillator to regulate their time-of-day specific functions (figure 3). In this section, we review the impact of O-GlcNAcylation on clock protein functions and outline other rhythmic cellular

processes that can be modified by O-GlcNAcylation beyond the core clock.

4.1. Regulation of clock proteins within the core molecular oscillator by O-GlcNAcylation

The molecular oscillator of the animal circadian timing system relies on transcription-translation feedback mechanisms to maintain approximately 24 h biological rhythms (reviewed in [1,2]) (figure 3). Brain and muscle Arnt-like protein-1 (BMAL1) and circadian locomotor output cycles kaput (CLOCK) are the key transcriptional activators of the mammalian clock (*Drosophila* homologues are dCYCLE and dCLOCK (dCLK)), and as heterodimers, they drive the expression of thousands of clock-controlled genes including genes that encode their own transcriptional repressors, PERIOD1-3 (PER1-3) and CRYPTOCHROME1-2 (CRY1-2) (dPER and dTIMELESS (dTIM) in *Drosophila*) (figure 3). The molecular oscillator is critical for generating daily rhythmicity of gene expression that manifest into a range of rhythmic biological processes (reviewed in [1–10]).

PTMs, especially phosphorylation, have been established as essential mechanisms for maintaining the pace of the molecular oscillator [174–176]. Phosphorylation of the clock protein dPER was first characterized by Edery *et al.* [177] and subsequent studies continue to highlight diverse properties of clock proteins that are regulated by phosphorylation (reviewed in [178,179]). O-GlcNAcylation was first introduced as a mechanism to regulate the molecular clock and circadian rhythms by Kim *et al.* [20], Kaasik *et al.* [21] and Li *et al.* [22]. These pioneering studies showed that in both fly and mammalian models, increasing global O-GlcNAcylation slows down the pace of the clock and results in period lengthening of behavioural rhythms, while reducing O-GlcNAcylation has the opposite effect. Furthermore, these studies and subsequent studies [23,180] showed that many clock proteins, including dCLK, dPER, dTIM, BMAL1, CLOCK, are O-GlcNAcylated and period-altering effects are mediated by disrupting clock protein O-GlcNAcylation.

Interestingly but perhaps not surprisingly, some clock proteins even display daily rhythms of O-GlcNAcylation that are sensitive to feeding and nutrient input [21–23]. In *Drosophila*, O-GlcNAcylation of dPER promotes its stability and inhibits nuclear entry [20]. Transcriptional reporter assays in *Drosophila* S2 tissue culture showed that manipulating O-GlcNAcylation levels by overexpressing OGT or OGA also changes dPER and dCLK transcriptional activities [21]. To begin to dissect site-specific O-GlcNAc regulation, our group mapped dPER and dTIM O-GlcNAc sites in fly heads using MS proteomics [23,180]. We found that O-GlcNAcylation of dPER S942 inhibits the interaction of dPER and dCLK and reduces dPER repressor activity [23]. The function of O-GlcNAcylation on dTIM however remains to be determined. In mammalian clock, O-GlcNAcylation is shown to stabilize BMAL1 and CLOCK by inhibiting their ubiquitination [22]. In HEK293 cells, O-GlcNAcylation and phosphorylation compete at PER2 S662, and O-GlcNAcylation of S662 increases PER2 repressor activity [21]. In summary, O-GlcNAcylation is highly involved in the regulation of molecular oscillators (figure 3). Future site-specific characterization of clock proteins is needed to further understand the mechanisms by which metabolic input regulates molecular oscillators and biological rhythms through O-GlcNAcylation.

4.2. Regulation of rhythmic cellular processes beyond the molecular oscillator by O-GlcNAcylation

O-GlcNAcylation not only occurs on clock proteins, but also regulates the function of a large part of the proteome (figure 3). By cataloging results from over 1700 articles, O-GlcNAcome Database listed 7789 human O-GlcNAc proteins and 3503 mouse O-GlcNAc proteins [18]. Meta analysis on the human O-GlcNAcylated proteins from Wulff-Fuentes *et al.* [18] and combing through published O-GlcNAcomic papers [153–173] suggest that O-GlcNAc proteins are heavily involved in nucleic acid binding/transcriptional regulation/RNA metabolism, metabolism of proteins, cellular structure and cell signalling (figure 3). Many elegant reviews have summarized published functional investigations of O-GlcNAcylation on cellular proteins (e.g. [16,17,19,181,182]). To date, although circadian/daily rhythm of the O-GlcNAcome has yet to be conducted, our study showing robust daily rhythmicity in global protein O-GlcNAcylation in *Drosophila* tissues suggests that diverse cellular processes and molecular pathways could potentially be rhythmically regulated by daily cycling O-GlcNAcylation that is sensitive to metabolic input [15].

In table 2, we summarize published efforts to identify O-GlcNAcylated proteins in different cell types or tissues, which could provide insights into tissue- or cell-specific daily O-GlcNAc regulation on biological rhythms. In particular, we highlight pathways with O-GlcNAcylated factors that are critical for performing tissue- or cell-specific functions. We excluded O-GlcNAcomic studies conducted using cancer cell lines, as cellular O-GlcNAc status is known to be altered in cancer cells compared to cells under physiological conditions [183–185]. Finally, we also excluded studies conducted using whole organisms, such as *D. melanogaster* and *Caenorhabditis elegans* [186–188], since our focus in table 2 is on tissue-specific characterization.

In addition to tissue- or cell-specific studies, there are other in depth O-GlcNAcomic studies at the organelle level, such as mitochondria from rat heart [189,190] and rat liver [191], cardiac myofilament from rat [192], synapses from mouse brain [130,193,194], ribosome from rat liver [195] and nuclei from mouse embryonic stem cells [196]. Additionally, comparative O-GlcNAcomic studies have been carried out in cell culture systems to investigate the role of O-GlcNAcylation under different conditions [197–199] or during the progression of cell cycles [200,201]. However, comparative O-GlcNAcomic studies over different time points of a 24 h day and in different organs/tissues *in vivo* are warranted to reveal the role of O-GlcNAcylation in regulating daily rhythmicity in organ- and tissue-specific physiology and potential differential regulation by metabolic and circadian signals.

5. Conclusion

Significant progress has been made to elucidate the regulation of metabolic signals on daily rhythms in physiology and behaviour. Metabolic input regulates gene expression at specific times of day through nutrient-sensing pathways influenced by feeding–fasting cycles. This is accomplished through functional modification of core clock proteins and/or epigenetic regulation of the genomic landscape. Our recent study showed that O-GlcNAcylation is also an

Table 2. O-GlcNAcomic studies in animal tissues and cell lines.

tissue or cell type	organism	number of O-GlcNAc proteins	number of O-GlcNAc sites	tissue- or cell-specific function of O-GlcNAcylation	references
nervous system					
forebrain	rat	25	n.a.	cellular communication/signal transduction; intracellular transport	[153,154]
hippocampus	mouse	14	n.a.	neuronal structure; glucose metabolism	[155]
cerebral cortical tissue	mouse	274	n.a.	neurogenesis; synaptic transmission; learning and memory; cytoskeleton	[156]
cortex	mouse	278	n.a.	synaptic trafficking; notch/Wnt signalling; circadian clock proteins	[157]
brain	rat	30	n.a.	signal transduction; cytoskeleton and vesicle trafficking	[158]
brain	human	530	1094	receptor signalling; substrate-adhesion dependent cell spreading; cell projection assembly	[159]
muscular system					
gastrocnemius muscle	rat	14	n.a.	glycolytic pathway and energetic metabolism; contractile protein	[160]
C2C12 myotubes	mouse	342	n.a.	cytoskeleton and chaperones; transporter and binding proteins; cell adhesion molecules	[161]
right ventricle	rat	500	n.a.	oxidation–reduction process; intracellular transport; metabolism; cellular respiration and energy	[162]
excretory system					
embryonic kidney cells (HEK293)	human	1500	180	cell death; molecular transport; cellular assembly and organization; cell cycle, growth and proliferation; cell morphology; PTM	[163]
embryonic kidney cells (HEK293)	human	75	n.a.	cell-cell adhesion; cell cycle; molecular transport; Purine ribonucleoside monophosphate biosynthetic process; cellular response to heat; viral process	[164]
embryonic kidney cells (HEK293)	human	215	n.a.	Metabolism; Signal transduction; Translation; Transport	[165]
urine	human	457	n.a.	organelle organization; cell cycle; cellular localization; heterocycle metabolic processes; DNA repair; cellular response to stress; developmental processes; transport	[166]
immune system					
T cell	mouse	116	n.a.	metabolic process; cellular component organization/ biogenesis; DNA packing	[167]
T cell	human	133	n.a.	nucleotide, nucleic acid transport	[168]
T cell	human	1045	n.a.	viral process; cell-cell adhesion; cell cycle; cellular transport; protein sumoylation	[169]
embryonic macrophage-like cells (S2 cells)	fruit fly	51	n.a.	metabolism; stress response; cell cycle	[170]
other tissues or cell types					
liver	rat	68	n.a.	metabolism; transport; signal transduction	[165]

(*Continued*.)

Table 2. (*Continued.*)

tissue or cell type	organism	number of O-GlcNAc proteins	number of O-GlcNAc sites	tissue- or cell-specific function of O-GlcNAcylation	references
osteoblasts (MC3T3E1)	mouse	20	n.a.	post-translational regulation; systemic nutrient homeostasis	[171]
placental trophoblasts (BeWo)	human	829	n.a.	translational initiation; viral transcription; SRP-dependent co-translational protein targeting to membrane	[172]
fibroblasts (NIH3T3)	mouse	374	n.a.	metabolism; intracellular transport	[173]

important mechanism that integrates metabolic and circadian signals to regulate the daily biological rhythms [15]. In this review, we summarize published and potential mechanisms by which metabolic and circadian signals can shape daily O-GlcNAc oscillation, discuss crosstalk between O-GlcNAcylation and the phosphoproteome to regulate rhythmic protein functions, and highlight cellular pathways that may be regulated by oscillating O-GlcNAcylation in different tissues or cell types. As time-restricted feeding/eating is emerging as a non-invasive therapeutic strategy to alleviate metabolic syndromes [30,35,202,203], our review provides mechanistic insight into the significance of properly aligning our eating time with biological rhythm. Since we showed in *Drosophila* that food consumption at unnatural feeding time of the day–night cycle can dampen the oscillation of protein O-GlcNAcylation [15], it is likely that rhythmic functions of O-GlcNAc proteins/pathways would be disrupted with mistimed eating. This may contribute to deleterious effects of mistimed eating and high-fat diet, which has been shown to impair feeding–fasting rhythms and rhythmic metabolic input [204,205].

It is important to note that different organs or tissues are likely differentially regulated by metabolic input versus circadian input. For example, despite that the blood–brain barrier is expected to render brain tissues less sensitive to daily oscillation of metabolites, O-GlcNAcylation has been detected in brain tissues and shown to oscillate on clock proteins in fly heads [20,21,23]. Our understanding of the similarities and divergence among O-GlcNAcomes in multiple organs or tissues and how organisms coordinate organ/tissue-specific O-GlcNAcomic rhythms to properly maintain time-of-day physiology at the organismal level will improve with continued development of comparative O-GlcNAcomic methods [198,201].

In this review, we largely focused on O-GlcNAcylation as an intracellular mechanism that underlies metabolic regulation of daily biological rhythms. We briefly mentioned a few intercellular signals, such as insulin, EGF, TGFβ, which could contribute to regulation of protein O-GlcNAcylation. However, there are many other intercellular signals, including neuronal signals, hormones (melatonin, adrenal cortex hormones, thyroid hormones etc.) and gut microbiota, which can relay time-of-day specific metabolic signals to influence cellular protein functions. How O-GlcNAcylation responds to these intercellular signals is unknown and beyond the scope of this review.

Finally, it is important to note that O-GlcNAcylation is only one of many nutrient-sensitive PTMs. Feeding–fasting cycles likely regulate daily cellular physiology through other metabolite-driven PTMs. Figlia *et al.* [206] reviewed over 20 different types of PTM using metabolites, such as lipids, amino acids, Coenzyme-A, acetate, malonate and lactate. Future studies are warranted to determine whether these nutrient-sensitive PTMs are also involved in regulation of daily biological rhythms. Recently, Bludau *et al.* [207] developed an exciting tool to predict protein structure with PTMs. In combination with site-specific information of these metabolite-driven PTMs, the metabolic regulation of protein functions could be computationally predicted, which could provide a more comprehensive view on the metabolic effect on daily biological rhythms.

Data accessibility. This article has no additional data.

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All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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