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Review Article

Interaction between stress responses and circadian metabolism in metabolic disease☆

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ABSTRACT

Circadian rhythms play crucial roles in orchestrating diverse physiological processes that are critical for health and disease. Dysregulated circadian rhythms are closely associated with various human metabolic diseases, including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease. Modern lifestyles are frequently associated with an irregular circadian rhythm, which poses a significant risk to public health. While the central clock has a set periodicity, circadian oscillators in peripheral organs, particularly in the liver, can be entrained by metabolic alterations or stress cues. At the molecular level, the signal transduction pathways that mediate stress responses interact with the key determinants of circadian oscillation to maintain metabolic homeostasis under physiological or pathological conditions. In the liver, a number of nuclear receptors or transcriptional regulators, which are regulated by metabolites, hormones, the circadian clock, or environmental stressors, serve as direct links between stress responses and circadian metabolism. In this review, we summarize recent advances in the understanding of the interactions between stress responses (endoplasmic reticulum stress response, oxidative stress response, and inflammatory responses) and circadian metabolism, and the role of these interactions in the development of metabolic diseases.

1. Introduction

The circadian rhythm is the biological process that orchestrates behavior and physiology in most living organisms over a 24 h period. In mammals, circadian oscillations are generated by a network of clock-controlled genes (CCGs) that form a transcriptional auto-regulatory feedback loop. Several inter-connected transcriptional and post-translational negative feedback loops play vital roles in generating and maintaining circadian rhythms. The core circadian transcription factors CLOCK and aryl hydrocarbon receptor nuclear translocator-like protein-1 (BMAL1) exist as a heterodimer and constitute the positive arm of the molecular clock. Genes that are directly regulated by the CLOCK/BMAL1 heterodimer are referred to as first-order CCGs.[1,2] The core clock regulators also drive circadian expression of many transcription factors, thus extending and enhancing their regulatory functions. Expression of the *Bmal1* gene is regulated by the nuclear receptor RORα/γ and PPARγ coactivator-1α (PGC-1α),[3] while the major negative regulator of *Bmal1* mRNA expression is REV-ERBα (also known as NR1D1).[4] Other circadian proteins, including period 1 (PER1), PER2, PER3, cryptochrome 1 (CRY1), and CRY2, which are targets of BMAL1, also play roles in the negative regulation of *Bmal1* expression.[4] The components of the core clock are also regulated by post-translational modifications, including phosphorylation, acetylation, deacetylation, and ubiquitination.[5]

The mammalian circadian clock orchestrates diverse physiological processes by synchronizing with the nervous system, cardiovascular system, immune response, and metabolic homeostasis. The master clock oscillators residing in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus orchestrate the cascade of events that control physiological rhythms and ensure temporal coordination of metabolism and behavior through the synchronization of peripheral oscillators.[6] The circadian oscillators in peripheral organs, such as the liver and kidney, respond differently to

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entraining signals and control specific physiological outputs, thus producing the coordinated response required to regulate cellular and physiological functions. In particular, circadian rhythm and liver metabolism are intrinsically linked in order to synchronize the storage and utilization of energy with the light-dark cycle.[7] The integration of circadian rhythm and hepatic energy metabolism is mediated through reciprocal crosstalk between these two regulatory networks.

Dysregulation of the circadian rhythm in humans is closely associated with the development of metabolic diseases, including non-alcoholic fatty liver disease (NAFLD), obesity, and type 2 diabetes (T2D). Previous work has demonstrated intimate and reciprocal interaction between the circadian clock system and fundamental metabolic pathways.[1,8,9] *Clock* gene mutations or BMAL1 deficiency impair lipid and glucose metabolism, evidenced by the development of hyperlipidemia, hepatic steatosis, and defective gluconeogenesis in CLOCK- or BMAL1-deficient animals.[10–13] A survey of nuclear receptor mRNA profiles in metabolic tissues suggested that approximately half of the known nuclear receptors and transcriptional regulators exhibit rhythmic expression.[14] Bioinformatic analysis of genome-wide and phase-specific DNA-binding by the core circadian transcriptional oscillators indicated that BMAL1-binding sites are associated with carbohydrate and lipid metabolism.[15] In the liver, nuclear receptors and other transcription factors can be induced by metabolites or hormones, and therefore, they may serve as direct links between metabolic pathways and the circadian control of gene expression. For example, the nuclear receptor peroxisome proliferator-activated receptor α (PPARα), which binds fatty acid ligands, serves as a sensor of nutrient and energy status to temporally entrain peripheral clocks. PPARα and BMAL1 reciprocally regulate each other to provide a feedback loop that integrates lipid metabolism and circadian oscillations.[16–18]

The clock-controlled nuclear receptors REV-ERBs are key regulators of circadian lipid biosynthesis in the liver, and their ablation causes hepatic steatosis through de-repression of lipogenesis.[19,20] PGC-1α also provides a link between the clock and energy metabolism, as PGC-1α expression varies rhythmically and is able to stimulate expression of *Bmal1* and nuclear receptors of the ROR family.[3] Recent studies have shown that the nuclear receptor small heterodimer partner (SHP) is also critical for the control of REV- and ROR-mediated neuronal PAS domain protein 2 (NPAS2) expression in NAFLD, and of the nuclear receptor FOXA1 expression in alcoholic fatty liver disease (AFLD).[21,22] Additionally, the clock component CRY1 functions as a circadian regulator of hepatic gluconeogenesis.[23] By interacting with the Gsα subunit of G proteins, CRY1 can temporally regulate glucagon signaling, thereby activating hepatic gluconeogenesis. Furthermore, recent evidence implicates distinct signaling pathways synchronized by the circadian clock in circadian metabolism at the translational or post-transcriptional level.[24,25] For example, the circadian clock synchronizes the rhythmic activation of the primary endoplasmic reticulum (ER) stress sensor IRE1α (inositol requiring enzyme 1).[24] Lack of a functional circadian clock disrupts the rhythmic activation of the IRE1α pathway, leading to impaired lipid metabolism through aberrant activation of the sterol-regulated SREBP transcription factors.

2. ER stress response and circadian metabolism

In mammalian cells, the ER is an essential organelle that is responsible for protein folding and assembly, synthesis of sterols and lipids, and calcium storage and homeostasis.[26–28] As a protein folding compartment, the ER plays a crucial role in cellular protein quality control by ensuring only correctly folded proteins are transported to their final destinations, and by assembling incorrectly folded proteins into native complexes and degrading them. When cellular or environmental stressors disrupt ER function, unfolded or misfolded proteins accumulate in the ER lumen, a condition referred to as ER stress. To deal with ER stress, cells activate a sophisticated and coordinated series of signal transduction pathways known as the unfolded protein response (UPR). The UPR is a survival response which modifies transcriptional and translational programs to restore ER homeostasis. The UPR pathways in mammals are primarily initiated by three major cell stress sensors: IRE1α, double-stranded RNA activated protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF6). Under ER stress conditions, PERK phosphorylates the serine51 residue on the alpha subunit of eIF2α, which attenuates the translation, thus reducing the workload of the ER. In addition, IRE1α, a bifunctional transmembrane protein, functions as a ribonuclease (RNase) to splice the mRNA encoding X-box binding protein (XBP1), leading to the transcriptional reprogramming of stressed cells. Also under ER stress, ATF6 translocates into the Golgi apparatus, where it is processed into its active form by the site-1 protease (S1P) and site-2 protease (S2P). Upon proteolytic activation, ATF6 travels to the nucleus, where it induces the expression of UPR target genes by binding to ER stress response elements (ERSEs) located within their promoter regions. It is important to note that the UPR pathway can also be triggered by inflammatory stimuli, chemical toxicity, infection by pathogens, and even by the differentiation of specialized cell types, such as the differentiation of B-lymphocytes into antibody-secreting plasmocytes.[29,30]

A number of enzymes involved in liver metabolism are located in the ER membranes. Lipid metabolism is associated with the physiological UPR, and circadian clock circuitry influences hepatic lipid metabolism and ER-localized enzymes. The UPR plays a key role in maintaining hepatic lipid homeostasis, and disruption of the UPR leads to hepatic steatosis and non-alcoholic steatohepatitis (NASH) under conditions of pathophysiological stress. Deletion or suppression of the UPR transducer IRE1α or ATF6 in mouse liver results in hepatic steatosis under acute ER stress or after consumption of a high fat diet.[31–34] Animals with a defect in the liver-enriched, ER-tethered stress sensor cAMP response element binding protein-hepatic specific (CREBH) develop severe NASH when fed an atherogenic high fat diet.[35–40] Additionally, deficiency of the ER stress-induced transcriptional activator XBP1 in the liver also leads to hepatic lipid accumulation.[41–43] Thus, a wealth of evidence indicates that UPR pathways are required to prevent hepatic lipid accumulation and the development of NAFLD under acute ER stress or chronic pathophysiological stress conditions.

ER stress and UPR signaling have significant impacts on circadian activity. A recent study has demonstrated that activation of the IRE1α-mediated UPR pathway exhibits circadian rhythmicity in mouse liver.[24] Disruption of the circadian clock perturbs the circadian rhythmicity of IRE1α-mediated UPR activation and provokes deregulation of ER-localized enzymes (Fig. 1). This disruption causes aberrant activation of sterol regulatory element-binding protein (SREBP) transcription factors and impaired hepatic lipid metabolism, which can potentially lead to the development of metabolic disorders.

Another example of an interaction between ER stress and circadian metabolism is the integrative role of the liver-enriched ER stress sensor CREBH in circadian regulation and hepatic energy metabolism (Fig. 1).[39,40] The proteolytic activation of CREBH protein, but not expression of *CrebH* mRNA, exhibits typical circadian rhythmicity in mouse liver. This process is controlled by the core clock oscillator BMAL1 and the AKT/glycogen synthase kinase 3β (GSK3β) signaling pathway.[40] Importantly, GSK3β-mediated phosphorylation of CREBH within its b-ZIP domain modulates the

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