Circadian clock genes: Their influence on liver metabolism, disease development and treatment (Review)

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Abstract. The present review comprehensively discusses the impact of circadian clock genes on hepatic metabolism, liver disease progression and therapeutic strategies. The circadian rhythm, as a fundamental regulatory system, governs metabolic, immune and endocrine processes through an integrated central-peripheral network. Disruption of this rhythm plays a pivotal role in the pathogenesis of various liver diseases, including non-alcoholic fatty liver disease, alcoholic liver disease, liver fibrosis and hepatocellular carcinoma. Key circadian regulators, including circadian locomotor output cycles kaput, brain and muscle ARNT-like protein 1, period circadian regulator 1/2 and cryptochrome 1/2 modulate critical pathways, including lipid and glucose metabolism, bile acid synthesis, inflammatory responses and cellular repair, thereby contributing to the progression of liver disease. Chronotherapeutic approaches, such as targeted pharmacological treatments, time-restricted feeding and light therapy, show promising clinical potential. However, further research is essential to clarify the underlying mechanisms and enable clinical application. By integrating foundational studies with clinical evidence, the present review provides a framework for chrono-precision medicine in hepatology, while identifying current challenges and proposing strategies to accelerate the development and clinical implementation of circadian rhythm-based therapies for liver disease.

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Abbreviation: ACC, acetyl CoA carboxylase; ACTA2, actin α2; α-SMA, α smooth muscle actin; α-KG, α-ketoglutarate; ALD, alcoholic liver disease; Bmal1, brain and muscle ARNT-like protein 1; CYP7A1, cholesterol 7α-hydroxylase; CCl_4, carbon tetrachloride; CHOP, C/EBP homologous protein; ChREBP, carbohydrate response element binding protein; COL1A1, collagen type I α1; Cry1/2, cryptochrome 1/2; DEN, diethylnitrosamine; FASN, fatty acid synthase; HCC, hepatocellular carcinoma; HFD, high-fat diet; HSC, hepatic stellate cell; IDH1, isocitrate dehydrogenase 1; LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease; LPS, lipopolysaccharide; NTCP, sodium taurocholate co-transporting polypeptide; Per1-3, period circadian regulator 1-3; PPARα/γ, peroxisome proliferator-activated receptor α/γ; Rev-erbα, reverse erythroblastosis virus α; SCN, suprachiasmatic nucleus; SHP, small heterodimer partner; SIRT2, sirtuin 2; SREBP-1c, sterol regulatory element binding protein-1c; TGF-β1, transforming growth factor-β1

Key words: circadian clock genes, circadian rhythm, liver disease, chronotherapy, phototherapy

Contents

1. Introduction

The circadian clock is a fundamental biological phenomenon observed across the natural world (1). As an endogenous regulatory system, it is present in nearly all organisms and has evolved to enable adaptation to time-dependent environmental changes (2,3). This system comprises a network of oscillators in which a central clock synchronizes multiple peripheral clocks in alignment with light and dietary cycles, thereby coordinating internal rhythms, regulating metabolism, and influencing the onset and progression of various diseases (4).

Epidemiological studies have demonstrated that individuals with circadian rhythm disruptions in the central master clock, such as those caused by shift work or jet lag, have an elevated risk of developing tumors, digestive disorders, neurological diseases, immune dysfunction, cardiovascular conditions and endocrine disorders (5-9). This suggests that disturbances of the master clock contribute to the development of diverse pathologies. Similarly, disruptions in the peripheral circadian clock have been associated with damaging gene mutations, inflammation and fibrosis in organs such as the heart, kidneys, lungs and pancreas (10-12). These findings highlight that both master and peripheral clock disruptions can drive disease. Importantly, the master and peripheral clocks interact to regulate physiological and pathological processes. Light signals are transmitted to the suprachiasmatic nucleus (SCN) via the hypothalamic tract, resetting the central clock, while the peripheral clock is synchronized with the master clock through neural and hormonal pathways (13-15). However, external environmental factors may disrupt this synchronization; for example, in nocturnal animals under food restriction, the peripheral clock is altered while the central clock remains unaffected (6,16).

Disruptions in the circadian clock of the liver contribute to the onset and progression of acute and chronic liver disorders, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), liver fibrosis (LF) and hepatocellular carcinoma (HCC) (17-20). Therapeutic approaches, such as pharmacological interventions, time-restricted feeding, chronotherapy, phototherapy and time-dependent pharmacology, have shown potential in the treatment of circadian rhythm-related disorders (21-24). The present review summarizes recent advances in the exploration of the mechanisms underlying the relationship between circadian rhythms, liver homeostasis and disease. It also discusses time-based treatment strategies with potential in the management of liver diseases.

2. Basic structure and function of the biological clock

Core molecular oscillation mechanism. The mammalian circadian clock operates on an ~24-h cycle, regulating various rhythmic behaviors such as sleep, feeding and hormone secretion. The SCN, located in the hypothalamus, serves as the central oscillator of the circadian system, coordinating peripheral clocks by modulating the nervous system, glucocorticoid signaling and feeding behavior (14). The circadian system is synchronized daily by external cues, including light and food. Light is the most critical factor, conveying information via the retina and the retinohypothalamic tract to the SCN (15). Peripheral circadian clocks are present in various tissues and organs, including the liver, kidneys, adipose tissue, pancreas and heart (25-28) (Fig. 1). The SCN maintains the synchronized oscillation of peripheral clocks through neuronal connections and rhythmic humoral factors. At the molecular level, several core proteins form basic feedback loops for the circadian clock. These include circadian locomotor output cycles kaput (Clock), period circadian regulator 1-3 (Per1-3), cryptochrome 1 and 2 (Cry1 and 2), brain and muscle ARNT-like protein 1 (Bmal1), retinoic acid receptor-related orphan receptor α (RORα) and nuclear receptor subfamily 1, group D member 1, also known as reverse erythroblastosis virus α (Rev-erbα) (29-34) (Table I).

The core feedback loop of the circadian clock begins with the heterodimerization of Bmal1 and Clock, which activates *Per* and *Cry* genes, along with other circadian regulators, by binding to E-box elements in their promoters (13,32,33). As Cry protein accumulates in the cytosol, it binds with Per protein to form a stable complex that re-enters the nucleus. This complex binds to the Bmal1-Clock dimer, inhibiting its transcriptional activity and reducing the synthesis of Per and Cry proteins. This negative feedback cycle generates the oscillatory expression of circadian clock molecules (13,14,34). A second stabilizing loop involves Bmal1 expression. The Bmal1-Clock dimer binds to E-box elements in the promoters of the *Rev-erbα* and *RORα* genes. The Rev-erbα and RORα proteins compete for the RRE site on the *Bmal1* promoter, with RORα activating *Bmal1* transcription and *Rev-erbα* inhibiting it (14) (Fig. 2).

Physiological function of the biological clock

Participating in metabolic balance. The biological clock regulates circadian rhythms as well as various physiological and metabolic processes within the body. Disruptions in core circadian clock genes can lead to metabolic disturbances, affecting the metabolism of sugars, lipids and bile acids (BAs) (Fig. 3) (35-37). For example, mice with liver-specific knockout (KO) of the *Bmal1* gene exhibit dysregulated expression of glucose-regulated genes, leading to hypoglycemia and increased glucose uptake following fasting (38). In addition, *Bmal1* KO mice exhibit elevated levels of circulating triglycerides (TGs) and free fatty acids (FFAs), along with increased hepatic fat accumulation (39). Furthermore, when these mice are fed a high-cholesterol diet, they exhibit excessive cholesterol accumulation in the liver compared with that in wild-type (WT) mice. This may occur due to the circadian dysregulation of genes involved in cholesterol metabolism, including 3-hydroxy-3-methylglutaryl-CoA reductase, low-density lipoprotein receptor and cytochrome P450 7A1 (*CYP7A1*), the gene encoding cholesterol 7α-hydroxylase (40). In addition, Clock regulates the circadian rhythm of hepatic glycogen synthesis by transcriptionally activating glycogen synthase 2 (41). In a diabetic mouse model, the overexpression of Cryl or Cry 2 protein interferes with cyclic adenosine monophosphate-mediated gluconeogenesis, which reduces fasting blood glucose levels in these mice (42). Furthermore, *Rev-erbα* KO mice exhibit abnormal BA metabolism and altered expression of CYP7A1. In mice, Rev-erbα regulates BA and CHOL biosynthesis by modulating the expression of sterol regulatory element binding protein-1c (SREBP-1c) and CYP7A1. The activity of Rev-erbα is regulated by the oxysterol-mediated activation of liver X receptor signaling (43). These findings highlight the critical role of clock genes and proteins in metabolic regulation. In addition, clock genes interact with other signaling pathways to maintain metabolic homeostasis, ensuring efficient energy utilization and the timely synthesis of essential biomolecules.

Regulating endocrine rhythm. The expression patterns of circadian clock genes not only govern the sleep-wake cycle but also play a pivotal role in the regulation of human metabolism,

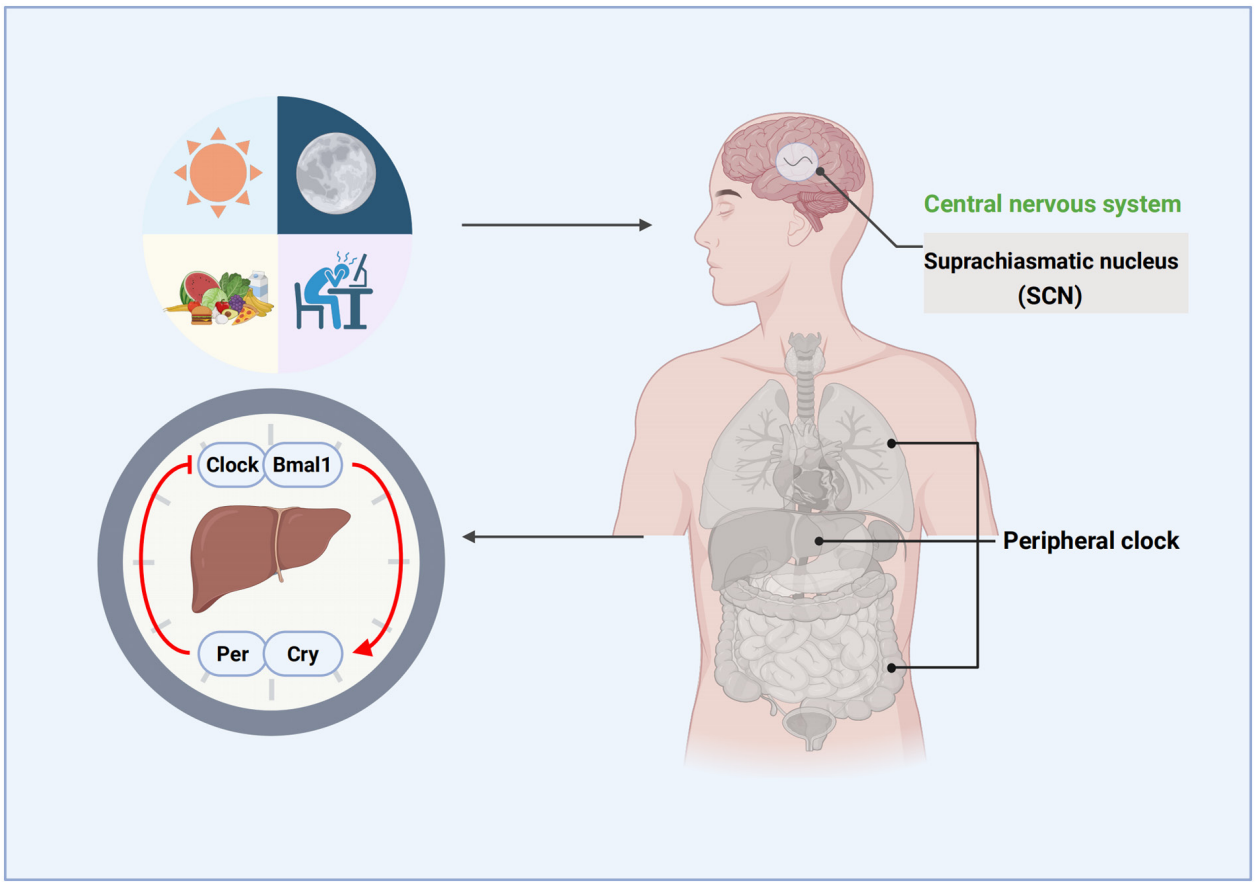

Figure 1. Regulation process of the central and peripheral biological clocks. The circadian system undergoes daily regulation by natural light, food intake and other external cues. Light serves as the principal zeitgeber, transmitting signals via the retina and retinohypothalamic tract to the suprachiasmatic nucleus, thereby resetting the central pacemaker. While the master clock resides within the hypothalamic center, peripheral oscillators exist in the liver, kidneys, adipose tissue, pancreas and heart, all synchronized by the master clock. Bmal1, brain and muscle ARNT-like protein 1; Clock, circadian locomotor output cycles kaput; Cry, cryptochrome; Per, period circadian regulator.

growth, development and emotional well-being. For example, melatonin secretion promotes sleep, modulates immune function and exerts antioxidant effects. It indirectly protects against oxidative stress by upregulating the expression of glutathione and antioxidant enzymes such as superoxide dismutase and catalase (44). Melatonin, which is secreted by the pineal gland and regulated by the hypothalamic SCN, follows a distinct circadian rhythm, peaking at night and decreasing during the day (45). In turn, melatonin provides feedback that influences the SCN, thereby modulating the oscillation of core clock genes (42).

Xiang *et al* (46) investigated the differential expression of core circadian clock genes, including *Clock*, *Bmal1*, *Per2*, as well as clock-controlled genes (CCGs) in MCF-10A human mammary epithelial cells and MCF-7 breast cancer cells, focusing on the regulatory role of melatonin. The study revealed that circadian gene oscillations are impaired in breast cancer cells, and melatonin partially restores rhythmicity by activating melatonin receptor 1, thereby inhibiting *RORα* transcriptional activity and leading to reduced *Bmal1* promoter activity (46).

The morning surge in cortisol not only facilitates wakefulness but also contributes to stress responses by enhancing alertness and the adaptive capacity of the body (47-49). Cortisol suppresses *Bmal1* gene transcription by promoting Cry expression, thereby regulating its own circadian peak (50). Glioblastoma cells can synchronize their biological clock with the host circadian rhythm in response to cortisol signaling via *Bmal1* and *Cry* genes, and the inhibition of cortisol signaling or Bmal1 function significantly suppresses tumor growth (50).

Quagliarini *et al* (51) explored how the glucocorticoid receptor (GR) regulates hepatic metabolism through circadian chromatin binding. The study identified synergistic interactions between the GR and core clock genes. Specifically, the GR cooperates with Clock and Bmal1 to co-regulate genes involved in carbohydrate, lipid and amino acid metabolism, including peroxisome proliferator-activated receptor γ (*PPARγ*), *CD36* and 4-aminobutyrate aminotransferase. In addition, GR directly influences core clock components: GR binding sites are present in the promoters or enhancers of all core clock genes, including *Per1*, *Per2* and *Rev-erbα*. The expression of Per1 and Per2 is induced by GR and Clock/Bmal1, with GR binding preceding the accumulation of Per1 and Per2. By contrast, GR suppresses *Rev-erbα* transcription, while Cry1 and Cry2 inhibit the GR-mediated activation of gluconeogenic genes, such as phosphoenolpyruvate carboxykinase 1 (*Pck1*), through direct interaction (51). These findings enhance our understanding of the roles of GR and circadian clock genes in hepatic metabolic regulation and offer new insights and strategies for the treatment of metabolic disorders.

Table I. Circadian clock proteins and their functions.

Circadian gene	Circadian function
Bmal1	bHLH-PAS domain-containing transcription factor; positive regulator
Clock	bHLH-PAS domain-containing transcription factor with histone acetyltransferase activity; co-activator of *Per-Cry* transcription; positive regulator
Cry1/2	Negative regulator/co-repressor of the Clock-Bmal1 complex
Per1/2	PAS-domain-containing protein; co-repressor of the Clock-Bmal1 complex; negative regulator
PGC-1α	Transcriptional coactivator
PPARg	Regulator of metabolism and adipocyte differentiation
Rev-erbα	Nuclear receptor; repressor of *Bmal1* transcription and regulator of clock-controlled genes; negative regulator
RORα	Activator of *Bmal1* transcription; regulator of clock-controlled genes

The information was obtained from the published literature (32-34). bHLH, basic helix-loop-helix; Bmal1, brain and muscle ARNT-like protein 1; Clock, circadian locomotor output cycles kaput; Cry1/2, cryptochrome 1/2; Per, period circadian regulator; PGC-1α, PPARγ coactivator 1α; PPARγ, peroxisome proliferator-activated receptor γ; Rev-erbα, reverse erythroblastosis virus α; RORα, RAR-related orphan receptor α.

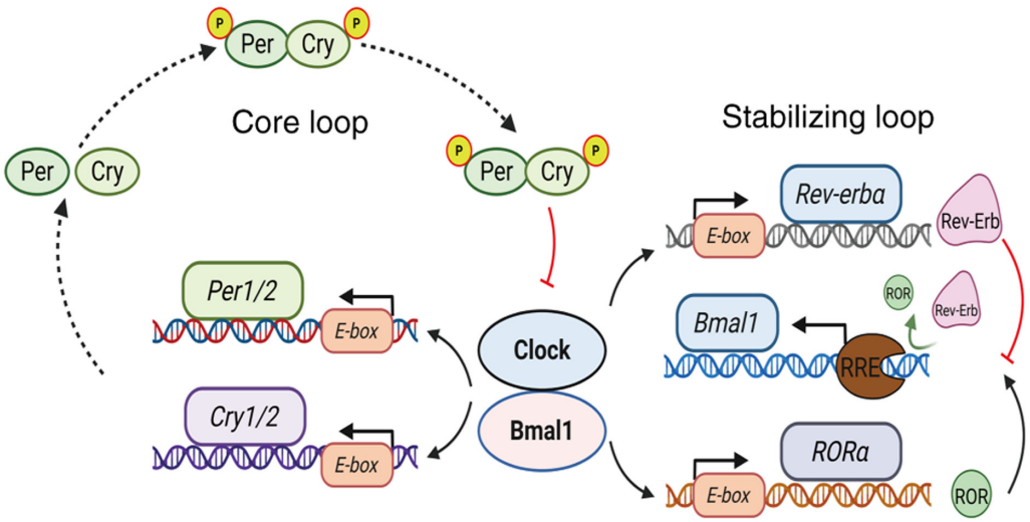

Figure 2. Schematic diagram of the liver circadian clock. The liver clock is composed of three parts: The input pathway, central oscillator and output pathway. The central oscillator comprises two regulatory loops: The core loop and the stabilizing loop. In the core loop, Bmal1 and Clock form heterodimers in the cytoplasm and translocate to the nucleus, where they bind to *E-box* sequences in the promoters of target genes *Per* and *Cry*, initiating their transcription. As Cry protein accumulates in the cytosol, it combines with Per protein to form a stable complex that re-enters the nucleus and binds to the Bmal1-Clock heterodimer, inhibiting its transcriptional activity and reducing Per and Cry protein synthesis. This cycle forms the oscillatory expression of circadian clock molecules. The stabilizing loop regulates Bmal1 expression. Bmal1-Clock dimers bind to *E-box* elements in the promoters of the nuclear receptor genes *Rev-erbα* and *RORα*, activating the transcription of *Rev-erbα* and *RORα*, which compete for the RRE site of the *Bmal1* promoter: RORα activates Bmal1 expression, while Rev-erbα inhibits it, thereby maintaining the stability of the circadian rhythm (32-34). Bmal1, brain and muscle ARNT-like protein 1; Clock, circadian locomotor output cycles kaput; Cry, cryptochrome; P, phosphor; Per, period circadian regulator; Rev-erbα, reverse erythroblastosis virus α; RORα, retinoic acid receptor-related orphan receptor α.

The secretion of growth hormone (GH) during deep sleep is essential for the growth and repair of bones, muscles and visceral organs (52,53). A study performed by Schoeller *et al* (54) demonstrated that male *Bmal1* KO mice exhibit feminized GH secretion patterns, characterized by increased pulse frequency, reduced regularity and shortened trough periods. In addition, liver-specific *Bmal1* KO mice display intermediate GH pulsatility patterns, lying between those of global *Bmal1* KO and WT mice, suggesting that *Bmal1* regulates GH secretion in tissues other than the liver. Notably, serum insulin-like growth factor-1 (IGF-1) levels are significantly lower in *Bmal1* KO mice compared with WT controls, while hepatic *IGF-1* mRNA levels are elevated, indicating disruption of the IGF-1/GH feedback loop. By contrast, liver-specific *Bmal1* KO mice show no significant difference in serum IGF-1 levels compared with WT controls, suggesting

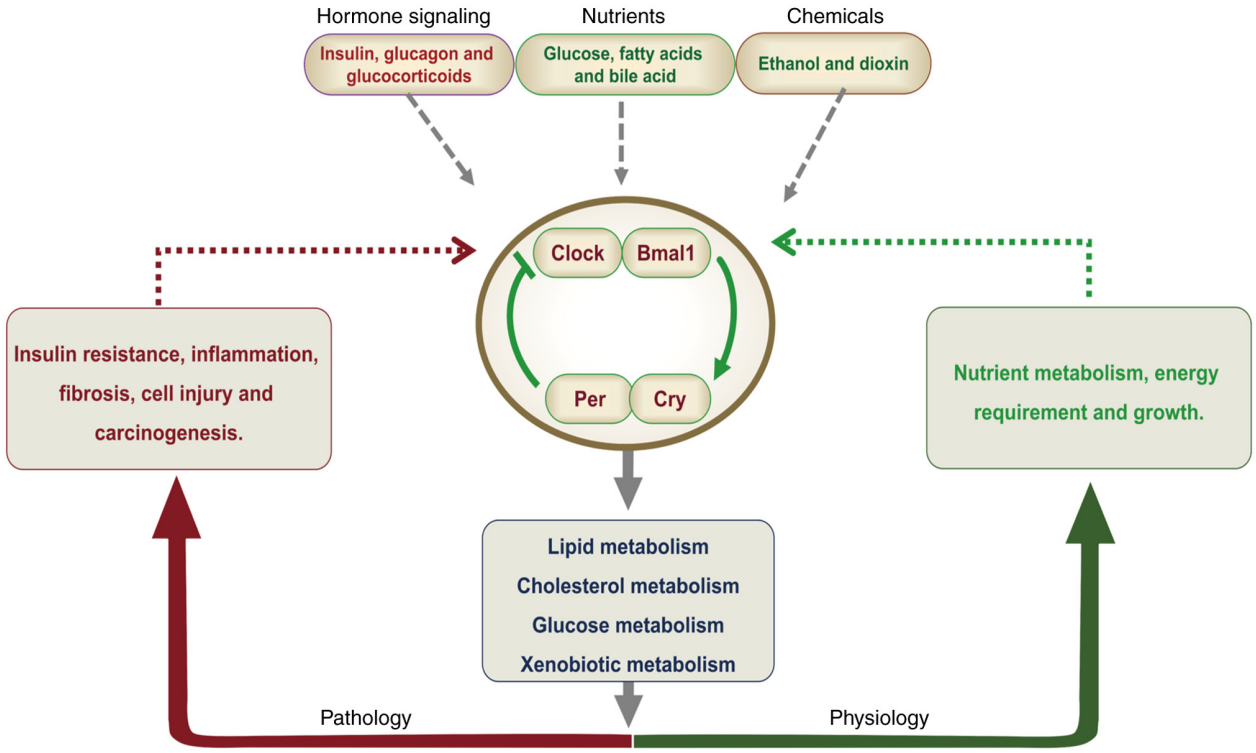

Figure 3. Physiology and potential disease associations of the liver circadian clock. The hepatic circadian clock can be disrupted or phase-shifted by various factors, including hormones, nutrients and environmental chemicals. These input signals reset or alter the molecular clock, impacting downstream outputs such as nutrient and xenobiotic metabolism, as well as the cell cycle. Impairment of the circadian clock may contribute to the development and progression of chronic liver disease. Bmal1, brain and muscle ARNT-like protein 1; Clock, circadian locomotor output cycles kaput; Cry, cryptochrome; Per, period circadian regulator.

the involvement of extrahepatic mechanisms in IGF-1 regulation (54). This research highlights the critical role of Bmal1 in the GH axis and hepatic metabolism, offering new insights into the interaction between the circadian clock and endocrine regulation.

The oscillatory secretion of sex hormones and thyroid hormones plays a vital role in the regulation of reproductive function and basal metabolic rate, thereby maintaining reproductive health and energy balance (55,56). Sex steroids such as estrogen and testosterone also exhibit circadian rhythmicity. By binding to their respective receptors, these hormones modulate the expression of core circadian clock genes, influencing overall circadian rhythms (15,57). Research has revealed sex-specific differences in the distribution and effects of estrogen and testosterone within the SCN. Estrogen primarily stabilizes the central circadian clock by modulating astrocytes in the SCN shell subregion, while testosterone influences the responsiveness of the clock to light signals by affecting neuronal activity in the SCN core (58,59).

Circadian rhythms often undergo significant changes with aging, and thyroid function is also subject to circadian regulation (60). The expression of core circadian regulators Bmal1 and Clock is downregulated in aging thyroid follicular epithelial cells, suggesting a decline in circadian regulatory capacity, contributing to age-related circadian disruptions (60). Furthermore, the downregulation of Bmal1 expression suppresses the expression of NF-κB inhibitor a, leading to persistent activation of the NF-κB signaling pathway. This chronic activation promotes thyroid cell senescence (60). These findings indicate that circadian rhythm disruption accelerates thyroid functional decline by inducing thyroid cell senescence, providing a theoretical framework for understanding thyroid aging and potential strategies to maintain thyroid function.

Regulating immunity and cell repair. Circadian clock genes regulate immune system functions through intricate molecular mechanisms (61). Liu *et al* (62) demonstrated that the administration of concanavalin A to mice at the start of the light phase leads to more severe liver injury and inflammation, evidenced by elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and increased necrotic areas, compared with those induced by administration at the beginning of the rest phase. This effect is mediated by rhythmic regulation of the Bmal1-jun B proto-oncogene (Junb) axis in macrophages. Specifically, Bmal1 protein directly binds to the *Junb* promoter, enhancing its transcription. Junb then activates the AKT/ERK signaling pathway, promoting the secretion of pro-inflammatory cytokines, including TNF-α and IL-6, in M1 macrophages (62). These findings deepen our understanding of how circadian regulation influences immune responses in liver diseases. In addition, Bmal1 modulates the transcriptional activity of nuclear factor erythroid 2-related factor 2 (*NRF2*) in macrophages by binding to E-box sequences within the *NRF2* gene promoter. This regulation influences antioxidant responses and IL-1β production (63). Bmal1 deficiency reduces NRF2 activity, leading to the accumulation of reactive oxygen species and excessive IL-1β secretion, thereby inducing a pro-inflammatory phenotype (63). These findings provide mechanistic insights into the circadian regulation of

immune responses in liver diseases and suggest that targeting the Bmal1-NRF2-IL-1β axis may offer therapeutic benefits in inflammatory conditions such as rheumatoid arthritis and sepsis.

Circadian clock genes play a critical role in cellular repair by ensuring that damaged cells are restored at optimal times to maintain homeostasis (64). Peng *et al* (64) demonstrated that Bmal1 collaborates with hypoxia-inducible factor-1α to bind the E'-box motif in the glucose-6-phosphate dehydrogenase X promoter, driving rhythmic transcriptional activity and pentose phosphate pathway (PPP) metabolic flux, which is essential for supplying the nucleotide precursors, such as ribose-5-phosphate, and NADPH required for DNA replication and repair. Chronodisruption, due to *Bmal1* KO or mistimed feeding, impairs PPP function, leading to nucleotide deficiency, oxidative stress and delayed hepatocyte S-phase progression. This compromises post-hepatectomy regeneration, exacerbates DNA damage-induced cellular senescence, and promotes inflammation through the stimulator of interferon genes pathway. These findings highlight how the circadian clock coordinates tissue regeneration through metabolic reprogramming, emphasizing the critical role of nucleotide availability in repair processes (64). They also provide new perspectives on circadian-immune interactions and suggest potential therapeutic targets for disorders associated with immune dysfunction and cellular damage.

Neurological and behavioral regulation. Circadian clock genes precisely regulate behavioral rhythms through a tripartite pathway involving molecular oscillatory networks, SCN-based synchronization mediated by cilia and glial cells, and coordination with peripheral organs (65). Genetic variations or aberrant expression of these genes are associated with neurobehavioral disorders, including sleep disorders, major depressive disorder and anxiety. For example, *Bmal1*-KO rhesus monkeys exhibit disrupted locomotor rhythms, fragmented sleep and psychiatric abnormalities (66). Mechanistically, SCN astrocytes rhythmically release γ-aminobutyric acid (GABA) to synchronize neuronal oscillations. Inhibition of GABA synthesis leads to circadian desynchronization, which has been suggested to increase the risk of Alzheimer's disease (67). These findings underscore the essential role of circadian clock genes in neural and behavioral regulation.

3. Disruption of circadian rhythm

The biological clock uses environmental signals to optimize energy use, enabling the body to adapt to cycles of rest and activity, as well as eating and fasting within the circadian rhythm (68,69). Factors such as sleep deprivation (70), sleep quality (71,72), exposure to nighttime light (73), shift work (74) and altered feeding patterns (75) can disrupt circadian timing. Such disruptions may impair metabolic homeostasis and contribute to the development of various diseases.

Shortened sleep duration leads to marked metabolic disturbances (70,76). In animal models, restricted sleep results in increased leptin secretion, heightened lipogenesis and elevated appetite, all of which contribute to obesity (77). A meta-analysis of 11 longitudinal studies confirmed that inadequate sleep increases the risk of becoming overweight or obese (78). Furthermore, sleep deprivation can interfere with the expression of core circadian clock genes, including *Per1* (77), contributing to sleep-wake cycle disorders by altering the rhythmicity of physiological processes such as body temperature and hormone secretion.

Sleep quality is influenced by multiple factors, including potential sleep disorders, eating times and environmental factors such as alcohol and caffeine consumption (79,80). In young, healthy adults without total sleep deprivation, interruptions in light or slow-wave sleep for three consecutive nights lead to reduced insulin sensitivity and impaired glucose tolerance (81).

The industrialization of society has led to a substantial increase in nighttime exposure to artificial light, which alters the circadian rhythm and disrupts the biological clock (82). Individuals engaged in night shift work are particularly vulnerable to the adverse effects of excessive nighttime light exposure (83). A meta-analysis of 13 studies revealed that such workers face a significantly higher risk of developing metabolic syndrome. Furthermore, a dose-response relationship between the duration of night shift work and the risk of metabolic syndrome was identified, further supporting the association between circadian disruption and metabolic disease (73).

Eating time has been identified as an independent time cue for the peripheral circadian oscillator (84). Shifts in eating patterns can lead to elevated plasma glucose and insulin levels, as well as reduced nighttime plasma peaks of melatonin and leptin, all of which are associated with the onset of metabolic syndrome (75,85). The interplay between eating time, peripheral circadian rhythms and hormonal fluctuations may represent a fundamental mechanism linking eating habits to metabolic diseases. Further human studies are necessary to determine the optimal timing of food intake and its association with circadian rhythms.

The regulatory mechanisms of the biological clock are both complex and precise, allowing it to respond to environmental cues and anticipate future changes. Disruption of this system impairs homeostasis, thereby increasing the risk of metabolic disorders.

4. Circadian clock genes and liver diseases

The liver plays a pivotal role in the maintenance of metabolic homeostasis, performing vital functions such as regulating blood glucose and ammonia levels, detoxifying drugs, synthesizing bile, and storing and transforming nutrients (86,87). Studies have demonstrated that cell-autonomous rhythm oscillators exist in peripheral organs, including the liver, where they exert significant effects on the metabolism of nutrients and exogenous substances. Furthermore, key genes involved in hepatic metabolic functions also exhibit circadian rhythms and reciprocally regulate the hepatic circadian clock system (17,88,89). Disruptions in the circadian clock of the liver can accelerate the progression of liver diseases, including NAFLD, ALD, LF and HCC (90-93) (Fig. 4 and Table II); conversely, these diseases can also impair circadian clock function.

NAFLD. The pathogenesis of NAFLD remains incompletely understood, and likely involves a multifactorial interplay of genetic and environmental factors (94). Given the role of

circadian rhythms in metabolic homeostasis, disruptions to these rhythms may contribute to the development of metabolic syndrome and NAFLD (95,96). For example, *Clock* mutant mice fed a high-fat diet (HFD) exhibit significantly higher hepatic TG levels than those observed in control mice. Similarly, *Bmal1* KO mice develop hepatic steatosis even when fed a standard chow diet (97), suggesting that circadian disruption is a key predisposing factor for liver pathology. In addition, a study of WT mice fed an HFD for 11 months identified upregulated expression levels of genes associated with gluconeogenesis, such as *Pck1*, and genes associated with lipid metabolism, such as pyruvate dehydrogenase kinase 4. The hepatic expression levels of the core clock genes *Bmal1*, *Per1-3*, *Cry1* and *Cry2* were also significantly elevated in these mice (98), indicating that chronic HFD intake disrupts metabolic rhythms by altering the expression of circadian genes, thereby exacerbating obesity and metabolic syndrome. The interaction between circadian clock genes and energy metabolism pathways, encompassing glucose and lipid metabolism as well as fluid-electrolyte balance, may underpin these disruptions.

A recent study found that *Bmal1* KO mice fed an HFD for 20 weeks exhibited significantly lower fasting blood glucose, insulin levels and homeostatic model assessment of insulin resistance values compared with those of HFD-fed WT controls. Additionally, glucose tolerance and insulin sensitivity were markedly improved in the KO mice. Liver weight and hepatic TG content in the KO group were reduced by ~50% compared with those in the controls, accompanied by significantly fewer lipid vacuoles and a reduction in lipid droplet deposition (99). Mechanistic analysis revealed that *Bmal1* deficiency mitigated HFD-induced obesity and NAFLD by suppressing the PPARγ-CD36 pathway, thereby reducing hepatic fatty acid uptake (99). This was the first study to implicate Bmal1 in the regulation of hepatic lipid uptake via the PPARγ-CD36 axis, suggesting a novel therapeutic target for NAFLD. However, it did not establish a direct regulatory relationship between PPARγ and Bmal1, highlighting that further experimental validation is necessary.

Saturated fatty acids can disrupt circadian rhythms (100). Palmitic acid, the most abundant circulating saturated fatty acid, has been shown to induce liver cell toxicity and inflammation. Using the PH5CH8 non-cancerous immortalized hepatocyte cell line and HepG2 liver cancer cells, Aggarwal *et al* (101) revealed that palmitic acid induces hepatocyte lipotoxicity and lipoinflammation by disrupting the Bmal1-sirtuin 2 (SIRT2) axis. Specifically, it suppresses the chromatin-binding capacity of Bmal1 and impairs its interaction with E-box elements in the *SIRT2* promoter, thereby downregulating SIRT2 transcription. The study also found that in the liver tissues of patients with NAFLD, Bmal1 expression levels positively correlate with SIRT2 levels, and Bmal1 nuclear localization is significantly decreased during cirrhosis (101). This study was the first to identify Bmal1 as a direct transcriptional regulator of SIRT2 and implicate palmitic acid-induced circadian disruption in hepatic inflammation. Activation of the Bmal1-NAD^+-SIRT2 axis is thus suggested to be a novel therapeutic strategy for NAFLD/nonalcoholic steatohepatitis (NASH), while SIRT2 and Bmal1 levels may serve as biomarkers for NAFLD progression. However, given the small sample size, with only 10 healthy controls and 15 NAFLD cases, further clinical validation is necessary before these findings can be translated into clinical practice.

PPARα is a target gene of the Clock/Bmal1 heterodimer and contributes to the upregulation of Bmal1 expression in peripheral tissues. In *PPARα* KO mouse models, *Bmal1* mRNA levels remain stable in most peripheral tissues but are significantly decreased in the liver compared with those in WT mice, indicating the critical role of PPARα in the circadian regulation of the liver (102). One study demonstrated that hepatic *PPARα* mRNA exhibits diurnal oscillations in WT mice, peaking during the light phase and declining in the dark phase (103), suggesting rhythmic regulation of PPARα expression. In addition, fatty acid synthase (*FASN*) and acetyl-CoA carboxylase (*ACC*) mRNA levels markedly increase during the dark (feeding) phase of WT mice, but not in *PPARα* KO mice, which instead exhibit persistently low expression levels (103). This finding underscores the role of PPARα as a regulator of the circadian rhythm of hepatic lipid metabolism genes. Following prolonged fasting, both systemic $PPAR\alpha^{-/-}$ and liver-specific $PPAR\alpha^{hep-/-}$ mice develop hepatic steatosis. After 6 months of chronic HFD intervention, *PPARα* KO mice exhibit exacerbated hepatic steatosis and steatohepatitis compared with WT controls. However, PPARα agonists prevent steatohepatitis and fibrosis and even ameliorate existing fibrosis in mice with steatohepatitis (103). These results highlight circadian-regulated PPARα as a critical factor in the pathogenesis of NAFLD.

Sleep deprivation can alter the circadian rhythm of GH and testosterone secretion; however, following liver transplantation, improvements in testosterone and GH levels, together with reduced sleep disturbances associated with NAFLD, suggest that the liver plays a pivotal role in the regulation of both endocrine and circadian rhythms (78,104). In humans, sleep-wake disorders disrupt the secretion of insulin, leptin and norepinephrine, while circadian rhythm disturbances caused by insufficient sleep increase insulin resistance (78,105).

Miyake *et al* (106) conducted a study of 2,429 participants, including 669 men and 1,760 women, without baseline NAFLD to explore the association between sleep duration and the onset of NAFLD. Sleep duration was self-reported and categorized as ≤4, 5-6 or 7-8 h, with a mean follow-up of 3.3 years. During the follow-up period, 296 new cases of NAFLD were observed, affecting 145 men and 151 women. Among men, a sleep duration of ≤6 h was significantly associated with a reduced risk of NAFLD [odds ratio (OR), 0.551; 95% CI, 0.365-0.832; P=0.005], and NAFLD incidence increased progressively with longer sleep (12.5% in the ≤4 h group vs. 27.4% in the 7-8 h group; P=0.02) (106). However, no significant association was observed between sleep duration and NAFLD incidence in women. The authors suggested that prolonged waking hours in men may increase basal energy expenditure, counteracting the negative metabolic effects of sleep deprivation (106). This longitudinal cohort study was the first to reveal sex-specific associations between sleep duration and the development of NAFLD. The findings indicate that short sleep duration may be a protective factor in men, suggesting that differentiated intervention strategies may be appropriate for this population. Another study, published the same year, explored the same topic in a study of 2,172 Japanese individuals, including

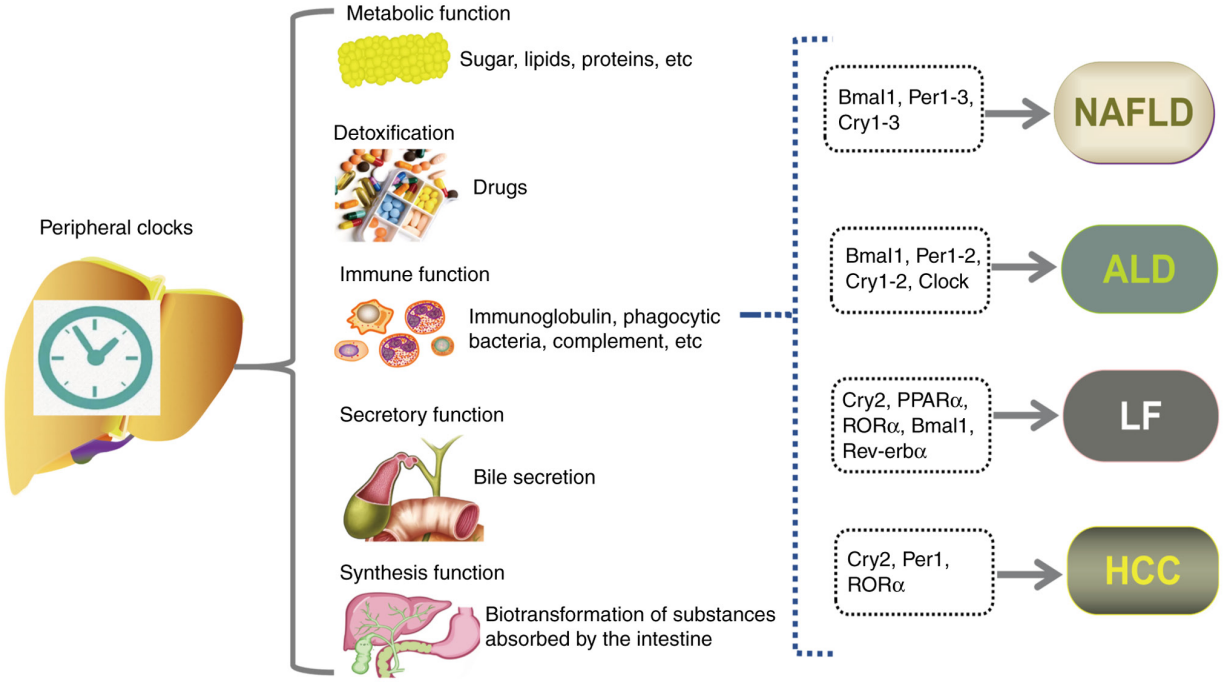

Figure 4. Impact of circadian clock disturbance on liver diseases. The liver performs multiple critical functions, including metabolism, detoxification, immune defense, secretion and synthesis. Disruption in the expression of circadian clock genes within the liver can impair its normal physiological functions, contributing to the pathogenesis of liver diseases, including NAFLD, ALD, LF and HCC. ALD, alcohol-related liver disease; Bmal1, brain and muscle ARNT-like protein 1; Clock, circadian locomotor output cycles kaput; Cry, cryptochrome; HCC, hepatocellular carcinoma; LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease; Per, period circadian regulator; PPAR, peroxisome proliferator-activated receptor; Rev-erbα, reverse erythroblastosis virus α; RORa, retinoic acid receptor-related orphan receptor α.

731 men and 1,441 women. The study reported an overall NAFLD prevalence of 29.6%, with rates of 38.0% in men and 25.3% in women (107). In men, NAFLD prevalence showed a non-significant decline with longer sleep duration, while in women, a U-shaped relationship was observed, with prevalence being highest in those having ≤6 or >8 h sleep and lowest in those having 6-7 h sleep. Women with ≤6 h of sleep had a significantly increased risk of NAFLD (age-adjusted OR, 1.44; 95% CI, 1.06-1.96), which is potentially attributable to a higher body fat percentage and unhealthy dietary habits such as skipping breakfast (107). These two studies emphasize sex-specific differences in sleep duration and NAFLD within the Japanese population. The divergent findings may reflect hormonal factors, body fat distribution or behavioral factors such as dietary patterns. However, these studies have some limitations, including a reliance on self-reported sleep duration without objective monitoring of sleep quality or sleep apnea, and a lack of adjustment for potential confounders such as psychological health or occupational stress. Despite these limitations, the evidence clearly implicates sleep deprivation in the development of NAFLD.

Shift work can disrupt circadian rhythms, lead to insufficient sleep and contribute to metabolic abnormalities. Balakrishnan *et al* (108) conducted a cross-sectional analysis of National Health and Nutrition Examination Survey (NHANES) data from 8,159 employed participants aged 20-79 years, to examine the potential link between shift work and NAFLD risk. The overall prevalence of NAFDL was 15.7%. Although a higher prevalence of NAFLD was observed among shift workers, multivariate analysis did not find a significant association between shift work and increased NAFLD risk. Despite shift work being associated with conditions such as obesity and diabetes, no significant relationship with NAFLD was observed in the study, possibly due to the limitations of its cross-sectional design, which cannot account for long-term exposure (108). Longitudinal studies are necessary to clarify the effects of shift work duration and sleep quality on NAFLD development.

ALD. Alcohol can directly influence the expression of peripheral clock genes (109,110). Huang *et al* (111) examined circadian clock gene expression in peripheral blood mononuclear cells (PBMCs) from 22 male alcohol-dependent (AD) patients and 12 healthy controls. The results revealed that the mRNA expression levels of *Clock1*, *Bmal1*, *Per1*, *Per2*, *Cry1* and *Cry2* in the PBMCs of patients with AD were significantly lower compared with those in the healthy controls. After 1 week of abstinence, gene expression showed a limited recovery, but remained significantly lower than that in the control group. This study was the first to demonstrate an association between chronic alcohol consumption and circadian gene dysregulation in humans, suggesting that alcohol may exacerbate addictive behaviors by interfering with circadian regulation. However, the small sample size, reliance on a single time-point measurement (9:00 am), and lack of assessment of circadian fluctuations limit the ability of the study to fully capture the dynamics of circadian gene expression. The underlying mechanisms require further investigation. In another study, Zhou *et al* (112) explored how chronic alcohol consumption disrupts hepatic circadian clock function and promotes alcohol-induced hepatic steatosis in mice. The results revealed that that short-term alcohol

Table II. Molecular mechanisms associated with circadian clock dysfunction and liver disease.

Disease	Mechanism	Impact	(Refs.)
NAFLD	Bmal1↓ → PPARγ↓ → CD36↓ → fatty acid intake↓; Bmal1↓ → SIRT2↓ → inflammation↑; PPARα↓ →Bmal1↓ → steatosis↑	Aggravation	(99,101,103)
ALD	Alcohol → NAD/NADH ratio↓ → Clock/Bmal1↓ → bile acid synthesis↓, inflammation↑; Clock mutation → serum LPS↑ → inflammation↑; SHP↓ → Rev-erbα↓ → CHOP↓ → inflammation↑; Bmal1↓ → AKT↓ → ChREBP↓ → lipogenesis, fatty acid oxidation↓	Aggravation	(112,114, 115,116)
LF	Per2↓ → CHOP↓ → TRAIL-R2↓ → HSC apoptosis↓; Per2↓ → CYP7A1, NTCP↓ → accumulation of bile acids↑; Per2↓ → α-SMA↑ → collagen deposition↑; Bmal1↓, Rev-erbα↓ → TGF-β/Smad↓ → Col1α, α-SMA↑ → HSC activation↑	Aggravation	(92,127, 128,130)
	Bmal1↑ → IDH1↑, α-KG↑, HK2↓, PKM2↓ → glycolysis↓ → HSC activation↓	Alleviation	(131)
HCC	Per1/2↓, Cry1/2↓, Rev-erbα↓ → c-Myc↑, c-Fos↑, FAH↓, Nr1h4↓ → inflammation and EMT↑	Aggravation	(142)

α-SMA, α-smooth muscle actin; α-KG, α-ketoglutarate; CHOP, C/EBP homologous protein; ChREBP, carbohydrate response element binding protein; ALD, alcoholic liver disease; Bmal1, brain and muscle ARNT-like protein 1; Clock, circadian locomotor output cycles kaput; Cry1/2, cryptochrome 1/2; CYP7A1, cholesterol 7α-hydroxylase; Col1α, collagen type I α; EMT, epithelial-mesenchymal transition; FAH, fumarylacetoacetate hydrolase; HCC, hepatocellular carcinoma; HK2, hexokinase 2; HSC, hepatic stellate cell; IDH1, isocitrate dehydrogenase 1; LF, liver fibrosis; NAFLD, non-alcoholic fatty liver disease; LPS, lipopolysaccharide; Nr1h4, nuclear receptor subfamily 1 group H member 4; NTCP, sodium taurocholate co-transporting polypeptide; Per1/2, period circadian regulator 1/2; PKM2, pyruvate kinase M2; PPAR, peroxisome proliferator-activated receptor; Rev-erbα, reverse erythroblastosis virus α; SHP, small heterodimer partner; SIRT2, sirtuin 2; TGF-β, transforming growth factor-β; TRAIL-R2, TNF-related apoptosis-inducing ligand-receptor 2; ↑, promote; ↓, inhibit.

feeding for 1 week did not significantly alter the expression of core clock genes, including *Per2*, *Per3* and neuronal PAS domain protein 2 (*Npas2*), or hepatic lipid accumulation. However, after long-term alcohol feeding for 4 weeks, Per2 and Per3 expression significantly increased, while Npas2 expression decreased. These changes were accompanied by hepatic steatosis and phase shifts in the circadian rhythms of lipid metabolism genes, including *Cyp7a1* and D-box binding PAR bZIP transcription factor (*Dbp*) (112). The mice with long-term alcohol feeding also exhibited elevated hepatic TG and CHOL levels, with TG rhythms phase-advanced by 5 h, a 12-h phase shift in BA synthesis, and a significant reduction in the NAD/NADH ratio, along with an inverted circadian rhythm. The authors proposed that chronic alcohol intake disrupts the NAD/NADH balance and impairs the DNA-binding activity of Clock/Bmal1, which disturbs circadian gene expression and alters lipid and BA synthesis pathways, thereby exacerbating alcohol-induced hepatic inflammation and injury (112). Although these findings underscore the critical role of the circadian clock in metabolic homeostasis, as the study was conducted in a mouse model, further clinical validation is necessary to establish the relevance of these findings in humans.

Alcohol directly disrupts the intestinal barrier and induces gut microbiota dysbiosis, creating a harmful 'gut-liver axis' cycle that accelerates the development of ALD (113). Therefore, targeting intestinal permeability may represent a novel therapeutic approach for ALD. Summa *et al* (114) demonstrated that *Clock*$^{\Delta 19/\Delta 19}$ mutant mice exhibited significantly increased colonic permeability, with further exacerbation of intestinal leakage following alcohol feeding. Mice subjected to weekly 12-h light cycle phase shifts showed increases in colonic permeability comparable to those observed in alcohol-fed mice. Alcohol-fed *Clock*$^{\Delta 19/\Delta 19}$ mutant mice also displayed significantly elevated serum lipopolysaccharide (LPS) levels and aggravated hepatic steatosis. Mechanistic investigations revealed that circadian disruption caused the translocation of occludin protein from the cell membrane to the cytoplasm, impairing intestinal barrier integrity and promoting endotoxin translocation. The resultant endotoxemia activated inflammatory responses, further aggravating alcoholic fatty liver and hepatocyte injury (114). These findings underscore the critical role of circadian rhythms in the maintenance of intestinal barrier function and metabolic health. Targeting the circadian clock or components regulating the intestinal barrier, such as occludin, may provide innovative therapeutic strategies for alcohol-related liver disease.

In a clinical study, Swanson *et al* (115) explored the impact of circadian disruption, such as night-work, on alcohol-induced increases in intestinal permeability and its potential association with ALD.The study enrolled 22 healthy adults, equally divided into day-shift (07:00-19:00) and night-shift (19:00-07:00) workers, each with at least 3 months of consistent work schedules. All participants underwent a 7-day alcohol intervention, involving the intake of 0.5 g/kg/day red wine, with 24-h circadian assessments conducted before and after the intervention. Following the intervention, night-shift workers exhibited significantly increased colonic and whole-gut permeability, as indicated by elevated 24-h urinary sucrose excretion, whereas day-shift workers showed no significant changes. In the

night-shift group, melatonin secretion rhythms were delayed by nearly 2 h and exhibited an inverse correlation with increased colonic permeability. This group also had higher baseline levels of the inflammatory markers LPS, LPS-binding protein and IL-6, which lost circadian rhythmicity following alcohol exposure. Alcohol also significantly altered the amplitude and phase of core clock genes, including *Clock*, *Bmal1* and *Per1*, in PBMCs; however, differences between the groups were more pronounced in central circadian markers than in peripheral gene expression (115). These findings provide the first clinical evidence that circadian misalignment in shift workers exacerbates alcohol-induced intestinal hyperpermeability, thereby increasing susceptibility to ALD. They also highlight the vital role of circadian rhythms in the maintenance of intestinal barrier integrity and metabolic health, and suggest that targeting the circadian clock or intestinal barrier components, such as occludin, may help to mitigate alcohol-related hepatotoxicity. However, this study is limited by a small sample size, reliance on indirect inferences from PBMCs rather than intestinal epithelial tissue, and the lack of circadian-targeted interventions, such as melatonin supplementation or light therapy. Therefore, further investigation is necessary to validate these observations.

Research has highlighted the critical roles of circadian clock genes *Rev-erbα* and *Bmal1* in the pathogenesis of ALD (116,117). Yang *et al* (116) demonstrated that the nuclear receptor small heterodimer partner (SHP) mitigates alcohol-induced hepatic steatosis by inhibiting the Rev-erbα-mediated transcriptional activation of C/EBP homologous protein (CHOP). In addition, dual deficiency of SHP and Rev-erbα was found to prevent the development of ethanol-induced fatty liver. The adenovirus-mediated knockdown of Rev-erbα in *SHP*$^{-/-}$ mice alleviated ethanol-induced hepatic steatosis, and reduced hepatic TG levels, serum ALT/AST levels and the expression of lipogenic genes, including *FASN* and *ACC2*. This establishes Rev-erbα as a key regulator in the pathogenesis of alcoholic fatty liver (116). This study was the first to provide evidence that SHP and Rev-erbα influence the development of alcoholic steatosis by modulating diurnal oscillations of CHOP, revealing novel chronotherapeutic targets for alcohol-related liver disease.

In study by Zhang *et al* (117), liver-specific *Bmal1* KO mice developed aggravated steatosis, hepatic injury and mitochondrial dysfunction following ethanol feeding. By contrast, Bmal1 overexpression significantly alleviated ethanol-induced hepatic lipid accumulation and injury. This protective effect primarily resulted from enhanced carbohydrate response element binding protein (ChREBP)-mediated *de novo* lipogenesis via AKT signaling activation, along with increased PPARα-dependent fatty acid β-oxidation (117). Observations in patients with ALD also revealed significantly reduced hepatic levels of Bmal1, AKT phosphorylation and ChREBP protein. Animal experiments further demonstrated that treatment with fenofibrate, a synthetic PPARα ligand, or the overexpression of AKT or ChREBP partially reversed the metabolic defects and liver injury in ethanol-fed mice with liver-specific *Bmal1* KO (117). These findings identify Bmal1 in hepatocytes as a critical protective factor against ALD, with the Bmal1-AKT-ChREBP axis representing a potential therapeutic target (117). However, the exact mechanism by which ethanol disrupts the Bmal1-Clock protein complex remains unclear, warranting further investigation.

LF. LF is a precursor to cirrhosis, and patients with cirrhosis often present with hepatic portal hypertension and disturbances in circadian rhythms, including delayed sleep cycles, altered melatonin and cortisol levels, and lethargy (118). However, the physiological mechanisms underlying these phenomena remain unclear. Montagnese *et al* (119) analyzed 87 patients with liver cirrhosis and found that 50-65% of them experienced difficulty falling asleep or woke up during the night, which was not directly associated with hepatic encephalopathy (HE). The patients also exhibited a delayed sleep phase syndrome (DSPS)-like pattern, characterized by staying up late and waking up late, with a delay of 2-3 h in the peak secretion of melatonin. Daytime melatonin levels were increased, nighttime clearance was delayed, and the urinary excretion of 6-sulfamoxy melatonin was reduced (120). Daytime sleepiness correlated significantly with HE severity and blood ammonia levels, with a negative predictive value of 92%. Abnormal SCN function in the patients led to delayed synchronization of melatonin and cortisol rhythms and a weakened response of melatonin to light exposure, suggesting SCN dysfunction (120,121). The authors proposed that reduced SCN photosensitivity involves disruption of the Clock/Bmal1 and Per/Cry protein feedback loops, causing delayed melatonin rhythms and a DSPS-like sleep phase. In addition, in a rat model of liver cirrhosis with portal shunt, delayed activity rhythms, decreased ammonia-induced deep sleep, and decreased liver SIRT1/PARP-1 activity were observed compared with those in controls (122-124). In the liver, an imbalance in SIRT1 and PARP-1 activities leads to the asynchronous expression of peripheral clock genes contributing to glucose and protein metabolism disorders (124). These findings indicate that both the peripheral and central circadian clocks were disrupted, affecting the liver and SCN, respectively. Notably, chronic light exposure accelerated liver tumor growth in cirrhotic mice, indicating a self-reinforcing cycle of circadian rhythm disruption and liver disease progression (125). Subjecting cirrhotic mice to chronic light exposure further accelerated liver tumor growth, suggesting that circadian rhythm disruption may exacerbate disease progression. These reports introduced a dual pathway model of 'central-peripheral circadian clock disconnection' and 'metabolism-neurotransmitter imbalance', supported by animal data revealing a downstream molecular cascade effect. However, further clinical translational research is required to validate these findings.

Studies using animal models have demonstrated disruptions in circadian clock gene regulation during LF (92,126). For example, in a carbon tetrachloride (CCl_4)-induced LF mouse model, a complete loss of rhythmicity in the *Cry2* gene was observed, along with significantly reduced daytime expression. In addition, Clock and Per1 expression exhibited an elevated mesor with reduced amplitude, Bmal1 and Per1 expression levels were markedly weakened in amplitude, and the peaks of Clock, Per1 and Cry1 expression were delayed. Per2 rhythmicity remained largely unaffected, suggesting a potential protective role against LF (126). Furthermore, the circadian oscillations of CCGs involved in hepatic metabolism, such as *PPARα* and cytochrome P450 oxidoreductase, were

abolished, with a marked reduction in expression levels. These findings imply that LF disrupts the transcriptional-translational feedback loop of Clock/Bmal1 and Per/Cry proteins (126). The loss of Cry2 rhythmicity may exacerbate lipid metabolic disorders via downstream targets such as PPARα. This study provided the first evidence that LF directly causes circadian clock dysregulation in peripheral tissues, particularly the liver, offering a molecular explanation for the circadian rhythm disturbances observed in patients with cirrhosis. However, as the data were validated only at the mRNA level, further studies examining protein expression are warranted (126).

In a separate study, Chen *et al* (92) demonstrated that in a CCl_4-induced LF model, *Per2* KO mice exhibited more severe collagen deposition and hepatic stellate cell (HSC) activation than WT mice. In addition, transfection of *Per2* cDNA into the HSC-T6 cell line significantly increased HSC apoptosis, accompanied by upregulation of the expression of TNF-related apoptosis-inducing ligand-receptor 2 (TRAIL-R2), also known as death receptor 5. Further analyses revealed that Per2 induces HSC apoptosis by upregulating CHOP transcription factors, thereby promoting TRAIL-R2 expression (92). This study was the first to demonstrate that Per2 protects the liver from chronic damage through a dual mechanism, involving the inhibition of HSC activation and promotion of apoptosis, highlighting Per2 and TRAIL-R2 pathways as potential anti-fibrotic targets.

In a bile duct ligation (BDL)-induced mouse model, *Per2* KO (*Per2*$^{-/-}$) mice exhibited more severe cholestatic liver injury than WT mice, including larger bile infarcts and increased hepatocyte necrosis (127). Serum and liver BA levels were significantly elevated, accompanied by loss of circadian rhythm in the expression of BA synthesis enzymes, such as CYP7A1, and transporter proteins, including sodium taurocholate co-transporting polypeptide (NTCP) and bile salt export pump. Furthermore, compared with WT mice, the *Per2*$^{-/-}$ mice exhibited aggravated LF, with increased collagen deposition, increased activation of HSCs as indicated by a-smooth muscle actin (α-SMA), and elevated mRNA levels of the pro-fibrotic factors transforming growth factor-β1 (TGF-β1), TNF-α and collagen type I α1 (Col1α1) in liver tissue (127). Mechanistically, Per2 deficiency disrupts the circadian rhythm of the rate-limiting BA synthesis enzyme CYP7A1, reducing its efficiency and decreasing the expression of the BA uptake transporter NTCP. This leads to hepatic BA accumulation, elevated serum BA levels, and exacerbated BA toxicity. In parallel, Per2 deficiency promotes excessive HSC activation, further driving collagen deposition and fibrosis (127). Similar findings were reported by Chen *et al* (128), confirming that Per2 plays a protective role in cholestatic liver injury by maintaining the circadian rhythm of BA metabolism and HSC function (92).

HSC activation plays a pivotal role in LF, with evidence suggesting that circadian clock genes directly regulate this process (92,128,129). Rev-erbα protein levels have been observed to be significantly elevated in both BDL- and CCl_4-induced LF models, as well as in human cirrhotic tissues, despite no significant changes in expression at the mRNA level, indicating post-translational regulation (130). Notably, TGF-β induction increases the cytoplasmic accumulation of Rev-erbα in HSCs, displaying a distribution pattern similar to that of myosin, while the synthetic Rev-erb ligand SR6452 reduces the cytoplasmic expression of Rev-erbα. They developed a Rev-erbα truncation mutant in which the N-terminus of the protein encompassing the DNA-binding domain (which encodes a nuclear localization signal) was deleted. Experiments using a *Rev-erbα* mutant demonstrated that cytoplasmic Rev-erbα enhances cellular contractility in NIH3T3 mouse fibroblasts and promotes fibrotic progression (130). Notably, SR6452 potentiated the ability of nuclear Rev-erbα to repress the transcription of its target gene plasminogen activator inhibitor-1, thereby reducing collagen deposition. Conversely, in the cytoplasm, SR6452 diminished Rev-erbα protein expression, thereby suppressing HSC activation and collagen accumulation (130). These findings highlight a dual role for Rev-erbα in HSCs, with both nuclear transcriptional repression and cytoplasmic pro-fibrotic activity, modulated by SR6452 (130). This study provided the first evidence that Rev-erbα regulates HSC phenotypic switching through differential nuclear-cytoplasmic distribution, positioning Rev-erbα ligands such as SR6452 as potential targeted therapies for LF and portal hypertension. A subsequent study revealed that Bmal1 expression was significantly downregulated and glycolytic activity increased in CCl_4-induced mouse LF models, and in primary HSCs and LX2 cells activated by TGF-β1 (131). The overexpression of Bmal1 inhibited the glycolysis, proliferation and phenotypic transformation of activated HSCs, including the downregulation of α-SMA and COL1α1 expression. The underlying molecular mechanism was shown to involve Bmal1-induced attenuation of HSC activation via the promotion of isocitrate dehydrogenase 1 (IDH1) expression and α-ketoglutarate (α-KG) generation, and the subsequent inhibition of key glycolytic enzymes, including hexokinase 2 and pyruvate kinase M2 (131). This study was the first to demonstrate that Bmal1 regulates HSC glycolysis via the IDH1/α-KG axis, and to propose a regulatory network linking the biological clock, metabolism and fibrosis. These findings suggest that Bmal1 or IDH1 agonists, such as α-KG supplementation, may be promising therapeutic strategies for LF, although further research is necessary to validate these findings.

In a recent study, Crouchet *et al* (20) found that in the livers of healthy mice, the circadian rhythm plays a time-gating role by regulating the expression of TGF-β target genes, including *Smad3*, *Smad7* and *TGF-βR1*, and inhibiting persistent pro-fibrotic signals. Analysis of a metabolic dysfunction-associated steatohepatitis mouse model revealed that circadian clock disorders, characterized by reduced expression of Rev-erbα, Per1, Per2 and Cry2, resulted in a loss of control over TGF-β signaling, thereby promoting HSC activation and collagen deposition. In addition, the treatment of primary human hepatocytes (PHHs) with FFAs disrupted the expression of circadian clock genes, such as *Bmal1* and *Rev-erbα*, and upregulated the expression of TGF-β target genes (20). Furthermore, reduced protein levels of Rev-erbα, Per1 and Per2 were observed in the livers of patients with cirrhosis, and these reductions were negatively correlated with the degree of fibrosis (20). These findings suggest that dysregulation of circadian clock genes directly contributes to sustained activation of the TGF-β signaling pathway and subsequent fibrosis. Subsequently, the roles of Bmal1 and Rev-erbα

were examined using *Bmal1* KO mice and hepatocyte-specific *Bmal1* KO (*Bmal1*$^{hep-/-}$) mice. In the livers of *Bmal1* KO mice, the rhythmic expression of TGF-β target genes was disrupted, confirming Bmal1 as a key regulator of TGF-β signaling (20). In *Bmal1*$^{hep-/-}$ mice, the circadian expression of TGF-β target genes was abolished, and Bmal1/Clock complex binding to the promoter regions of TGF-β target genes was significantly reduced. Rhythmic Bmal1/Clock binding to the promoter regions of TGF-β target genes, such as *Smad7* and *TGF-βR1*, was detected in the livers of healthy mice but not those of *Bmal1*$^{hep-/-}$ mice (20). Furthermore, in normal HSCs, Bmal1 and its downstream genes such as *Per1/2* and *Rev-erbα*, regulate the rhythmic expression of fibrosis-related genes. However, in a choline-deficient amino acid-defined high-fat diet (CDA-HFD) model of fibrosis in mice, the rhythmic expression of Bmal1 in HSCs was lost, pro-fibrotic genes, including actin a 2 (*ACTA2*) and *TGF-βR1*, were highly expressed and the expression of anti-fibrotic genes, including *Smad7* and matrix metalloproteinase 9, was decreased. Single-cell RNA sequencing confirmed that *Bmal1* KO disrupts the rhythmic dysregulation of fibrosis-related pathways, including the TGF-β and extracellular matrix pathways in HSCs (20). These findings indicate that reduced Bmal1 expression promotes HSC activation by modulating TGF-β signaling.

The KO of Rev-erbα from LX2 HSCs upregulates the expression of pro-fibrotic genes such as *ACTA2* and *Col1α1* (20), while the Rev-erbα agonist SR9009 reduces TGF-β-induced Smad2/3 phosphorylation and the expression of fibrosis marker proteins. Furthermore, in PHHs, SR9009 reverses FFA-induced lipid accumulation and the upregulation of TGF-β target genes (20). These findings suggest that Rev-erbα maintains liver homeostasis by rhythmically inhibiting TGF-β signaling, and its downregulation is a key driver of fibrosis progression. The pharmacological targeting of Rev-erbα using SR9009 induced a significant reduction in collagen deposition, hydroxyproline content and the expression of fibrosis-related genes *Col1α1* and *TGF-β1* in the CDA-HFD mouse model. SR9009 also decreased α-SMA expression and collagen deposition in human liver chimeric model mice, and significantly reduced the expression of fibrosis markers in hepatic spheroids from fibrotic patients (20). These results suggest that targeting *Rev-erbα* can restore circadian clock function, inhibit fibrosis, and provide a novel strategy for clinical anti-fibrotic therapy.

HCC. The circadian mechanism strictly regulates the cell cycle, cell proliferation, and the expression of tumor suppressor genes and oncogenes (132,133). The incidence of spontaneous tumors and radiation-induced HCC is significantly increased in *Per2*$^{-/-}$, *Bmal1*$^{\pm}$, *Cry1*$^{-/-}$ and *Cry2*$^{-/-}$ mice (134,135). Diethylnitrosamine (DEN) disrupts circadian rest-activity and body temperature rhythms (125,136,137), and reduces the oscillation amplitude of *Per1* in DEN-induced HCC mouse models (138). In such models, mice subjected to conditions simulating chronic jet lag develop more tumors compared with those under normal circadian conditions (125). DEN exposure upregulates the expression of core clock genes, including *Bmal1*, *Clock* and *Npas2*, while downregulating negative feedback genes, including *Per1-3* and *Cry1*, in mouse livers; melatonin treatment reverses these effects (136). *In vitro*, a combination of melatonin and SR9009 synergistically inhibits the proliferation of Hep3B HCC cells, while Bmal1 knockdown attenuates the pro-apoptotic and anti-proliferative effects of melatonin, indicating that Bmal1 is a key mediator of anticancer effects (136). These findings reveal a molecular mechanism by which melatonin suppresses HCC progression through circadian clock regulation. However, the study was limited to DEN-induced mouse HCC models and Hep3B cells, without validation in other models or clinical samples, and the downstream signaling pathways remain to be clarified.

Disrupted circadian rhythms are associated with hepatic metastasis (139). Huisman *et al* (139) compared the 24-h expression patterns of core clock genes in the hepatic and renal tissues of mice with C26 colorectal cancer liver metastases. In tumor tissues, the rhythmic expression of core clock genes *Bmal1*, *Rev-erbα* and *Per1/2*, and CCGs including *Dbp*, *Wee1* and *p21*, was abolished, indicating severe circadian dysfunction (139). In peritumoral hepatic tissues, the core clock genes exhibited phase advances relative to those in healthy controls, while renal tissues displayed phase delays, suggesting that tumor-derived signals disrupt clocks in distal organs (139). These findings highlight the phase interference caused by colorectal cancer liver metastases at the local and systemic levels, indicating that interactions occur between the tumor microenvironment and host rhythms. However, the molecular mechanisms mediating these shifts require further exploration.

NAFLD can progress to NASH, which is linked to LF, liver failure and HCC (140,141). Padilla *et al* (142) used humanized mouse models to investigate the mechanisms by which disrupted circadian rhythms contribute to NAFLD-associated HCC development. The study revealed that core clock genes exhibit robust circadian rhythmicity in healthy human and murine livers. However, during NAFLD and NASH progression, this rhythmic regulation diminishes, with dampened oscillation amplitudes and phase disturbances, and circadian gene rhythmicity is nearly abolished in HCC. These changes coincide with the upregulation of proto-oncogenes, including *c-Myc* and *c-Fos*, and the suppression of tumor suppressor genes, including fumarylacetoacetate hydrolase and nuclear receptor subfamily 1 group H member 4 (142). In addition, a chronic jet lag model in humanized mice accelerated the progression from NAFLD to NASH to HCC (142). Transcriptomic analysis showed that circadian disruption dysregulated thousands of genes, leading to impaired BA and fatty acid metabolism pathways, activation of NF-κB and TNF-α inflammatory signaling, suppression of oxidative phosphorylation, induction of epithelial-mesenchymal transition, and impaired DNA repair (142). These findings delineate how circadian dysregulation drives NAFLD-associated hepatocarcinogenesis by a metabolism-inflammation-cancer axis, emphasizing the importance of circadian homeostasis in HCC prevention. However, the molecular mechanisms require further investigation.

Human studies have established a strong association between disrupted circadian clock gene expression rhythms and the development and progression of HCC (93,143). A comparative analysis of 46 paired HCC and adjacent non-tumorous tissues found significantly reduced mRNA and protein expression levels of Per1, Per2, Per3, Cry2 and Timeless (TIM) in HCC tissues (93). This circadian gene

dysregulation was associated with the aberrant expression of cell cycle-related genes, suggesting uncontrolled tumor cell proliferation (93). However, the study was limited by its small sample size, incomplete coverage of core clock genes, and reliance on correlative observations that require further mechanistic validation. In another study, involving 337 patients with HCC undergoing transarterial chemoembolization, a significant association was observed between the rs2640908 *Per3* single-nucleotide polymorphism (SNP) and overall survival; this functional polymorphism correlated with reduced survival (143). A retrospective analysis using data from The Cancer Genome Atlas and International Cancer Genome Consortium demonstrated that high TIM expression or low Cry2, Per1 and RORα expression significantly predicted poor HCC prognosis (144). Furthermore, Cry2, Per1, and Rorα expression inversely correlated with B-cell and regulatory T-cell infiltration, while TIM showed a positive correlation, suggesting that these proteins contribute to the regulation of tumor immune evasion (144). This study highlights potential immune mechanisms that warrant experimental validation. Overall, human clinical data on circadian rhythms in HCC are limited, particularly regarding the practical efficacy of chronotherapy in HCC management. However, these findings support circadian clock genes as potential diagnostic biomarkers and therapeutic targets for HCC.

5. Treatment of liver diseases based on the biological clock

Drugs and active ingredients. A number of compounds have been shown to protect against liver diseases by modulating circadian clock pathways. For example, Melatonin treatment significantly ameliorates the dysregulation of hepatic clock gene oscillations induced by high-fat high-fructose diet and jet lag in mice, restoring the rhythmic expression of Bmal1 and Clock while partially correcting oscillations in the Nrf2-HO-1 pathway. This leads to reduced hepatic lipid accumulation, decreased serum AST/ALT levels, and improved expression of lipid metabolism-related genes (CPT-1, PPARα and SREBP-1c) (145). In the LX-2 human HSC line, melatonin suppressed the expression of fibrosis markers through the melatonin receptor 2-mediated upregulation of Bmal1 and antioxidant enzymes (146), suggesting a molecular pathway for the protective effects of melatonin against LF.

Ursolic acid (UA) has been shown to alleviate hepatic steatosis, fibrosis and insulin resistance in HFD-induced obese mice by regulating circadian gene expression (147,148). Treatment with UA reduced the expression of *Clock* and *Bmal1* in liver tissue, while increasing that of *Per1*, *Per2* and *Per3* compared with the respective levels in untreated HFD-fed mice. UA also promoted the expression of genes involved in lipid and BA metabolism, including nicotinamide phosphoribosyltransferase, forkhead box O3 and insulin-induced gene 1 (148).

A vitamin D-deficient diet has been shown to disrupt circadian synchronization in the liver, while quercetin supplementation alleviates this disorder. Specifically, a study revealed that Bmal1 expression was upregulated while Clock and Cry1 expression was downregulated in mice fed a vitamin D-deficient diet. However, following quercetin supplementation, Clock protein expression increased significantly, while *Bmal1* mRNA expression decreased (149).

Nobiletin, a polymethoxyflavone abundant in citrus fruits, enhances circadian rhythms and ameliorates diet-induced hepatic steatosis (150-152). In models of ALD, nobiletin activated AKT, increased the expression of ChREBP, ACC1 and FASN, and decreased SREBP-1 levels and ACC1 phosphorylation in a Bmal1-dependent manner, thereby alleviating liver injury (153).

Similarly, when the effects of sulforaphane were examined in HFD-fed mice with a disrupted circadian rhythm, significant enhancements in the abundance of beneficial gut flora, including *Lachnospiraceae*, *Lactobacillus* and *Alistipes* were observed. This was accompanied by a reduction in the expression of Rev-erbα, Per1 and Bmal1 proteins in the liver, and increased Clock expression in the hypothalamus (154).

Time-restricted feeding. Time-restricted feeding, which limits nutrient intake to a defined time window, significantly impacts biological, physiological, biochemical and behavioral processes. This regimen not only resets the liver clock but also dissociates it from the central circadian oscillator (16,155,156). In mice, restricted feeding prevented HFD-induced weight gain, hyperglycemia, hyperinsulinemia and insulin resistance. Long-term food restriction also reduced the expression of inflammatory cytokines in the liver, small intestine and white adipose tissue (156-158). By aligning the timing of nutrient intake with circadian timing, time-restricted feeding improves weight loss and metabolic homeostasis, supporting its integration with standard treatment strategies for liver diseases.

Phototherapy. Morning light therapy effectively advances circadian rhythms and sleep phases, with short blue-light pulses in the morning improving sleep integrity and quality. Intermittent light exposure appears to be more effective in altering circadian rhythms than continuous light (43). Therefore, phototherapy may offer potential benefits for liver diseases associated with circadian rhythm disruptions, although further studies are necessary to evaluate this.

Chronopharmacology. Temporal pharmacology highlights that numerous pharmacodynamic and pharmacokinetic parameters follow circadian rhythms, meaning that the efficacy and safety of drugs fluctuate with the time of administration. The circadian clock regulates every stage of hepatic drug metabolism, including absorption, distribution, transformation and elimination (159). During absorption, the liver takes up lipophilic drugs more rapidly in the morning than at night. In the distribution phase, the expression of several transporters, including organic cationic transporter 1 and organic anion transporting polypeptides 1 and 1A4, exhibits circadian variation. In metabolism, xenobiotic metabolism is divided into three phases, with the expression of relevant genes following a biological rhythm in the mouse liver (160). Furthermore, circadian-regulated transcription factors, including RORα/γ, DBP, hepatic leukemic factor and thyrotroph embryonic factor, control the expression of liver metabolic genes that encode enzymes involved in drug metabolism and elimination (159). Notably, the timing of administration is a crucial factor influencing drug efficacy. For example, circadian disruption induced by HFD feeding can be corrected with appropriately timed drug interventions (160). Due to strict timing requirements,

circadian-based drug administration is often impractical, reducing patient compliance. As a result, most drugs are not administered according to circadian rhythms. However, given accumulating evidence linking circadian rhythm disorders with metabolic diseases, the role of time-based therapy in disease prevention and treatment merits more attention.

6. Conclusions and future prospects

Circadian clock research remains a prominent frontier in the life sciences, highlighted by the 2017 Nobel Prize in Physiology or Medicine being awarded for the discovery of its molecular mechanisms. As a key peripheral clock, the liver clock plays a pivotal role in the regulation of energy balance and metabolic homeostasis, coordinating the daily rhythms of processes such as glucose and lipid metabolism. Disruptions in circadian clock genes have been observed in several chronic liver diseases, and circadian rhythm disorders promote the onset and progression of these conditions. For liver diseases associated with circadian disturbances, promising therapeutic approaches include natural drugs, time-restricted feeding, chronotherapy, phototherapy and the development of clock-targeting drugs.

Despite progress, research on the relationship between circadian rhythms and liver diseases remains limited. Mechanistic understanding is insufficient, with most studies relying on animal models, such as *Bmal1* KO mice, and lacking a comprehensive dissection of the spatiotemporal regulatory networks governing human circadian genes, including the Bmal1-PPARγ-CD36 axis. Critical molecular events, such as the nucleocytoplasmic shuttling of Rev-erbα, are largely described without dynamic single-cell tracking. Multi-organ interactions, particularly the cooperation between hepatic rhythms, gut microbiota and the central clock, remain underexplored. Methodological shortcomings also persist: Human studies such as the NHANES, predominantly use a cross-sectional design, which cannot establish causality, while animal models fail to replicate the long-term effects of human societal behaviors, such as shift work. Circadian monitoring technologies remain underdeveloped; static sampling methods, such as PBMC analysis, cannot capture dynamic oscillations of liver clock genes in real time. Clinical translation faces major barriers, as current interventions, including Rev-erbα targeting with SR9009 and time-restricted feeding. Time-restricted feeding has only been validated in small cohorts and lacks multi-center randomized controlled trial (RCT) evidence (21). In addition, inter-individual variations in circadian disruption have not been adequately addressed.

To address current limitations, several strategies are suggested. First, mechanistic investigations should be deepened: Single-cell sequencing technologies could be used to map circadian-specific regulatory networks within hepatocytes and HSCs. In addition, humanized mouse models could be established to simulate circadian disruption-related diseases in humans, with the synchronized acquisition of cross-organ parameters being achieved by the integration of functional magnetic resonance imaging for SCN neural activity, nanopore real-time sequencing for the 16S rRNA profiling of gut microbiota, and hepatic microdialysis for single-cell metabolic flux analysis. Second, methodological improvements are essential. Since cross-sectional studies, such as the NHANES, cannot establish causality, humanized mouse models mimicking human shift-work behaviors may be constructed. In addition, technological innovation could focus on the development of liver-specific biosensors paired with wearable devices for continuous circadian parameter monitoring. These wearables can be integrated with artificial intelligence predictive algorithms, such as long short-term memory time-series models, to generate personalized circadian profiles. Finally, clinical translation should be accelerated: Multi-center RCTs are needed to validate the efficacy of chronotherapeutic interventions, such as timed melatonin administration, in patients with cirrhosis. In addition, circadian gene variants, such as the *Per3* SNP rs2640908, along with broader expression signatures, should be developed as early diagnostic biomarkers for liver diseases.

To enhance clinical translation, circadian assessments may be incorporated into routine liver disease screening protocols, including genotyping for *Per3* variants alongside salivary melatonin rhythm profiling. Existing evidence should be integrated into liver disease management guidelines, advising patients with NAFLD to avoid nocturnal feeding and optimizing light-exposure schedules for shift workers. Long-term goals involve the development of small-molecule therapeutics targeting circadian proteins, such as the Rev-erbα agonist SR9009, and the refining of metabolic syndrome treatment regimens through combination with time-restricted feeding strategies. In conclusion, circadian research introduces a critical temporal dimension to hepatology, necessitating the integration of basic and clinical resources to overcome translational barriers and facilitate the transition from molecular mechanisms to precision medicine.

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Authors' contributions

JW was responsible for conceptualization, validation and writing the original draft of the manuscript. MC and SL revised and edited the manuscript. WP contributed to contributed to acquisition and analysis of data. JL and ZW ontributed to the conception and design, and critically revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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