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Perturbation of the circadian clock and pathogenesis of NAFLD

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Abstract

All living organisms including humans, experience changes in the light exposure generated by the Earth's rotation. In anticipation of this unavoidable geo-physical variability, and to generate an appropriate biochemical response, species of many phyla, including mammals have evolved a nearly 24-hour endogenous timing device known as the circadian clock (CC), which is self-sustained, cell autonomous and is present in every cell type. At the heart of the 'clock' functioning resides the CC-oscillator, an elegantly designed transcriptional-translational feedback system. Notably, the core components of the CC-oscillator not only drive daily rhythmicity of their own synthesis, but also generate circadian phase-specific variability in the expression levels of thousands of target genes through transcriptional, post-transcriptional and post-translational mechanisms. Thereby, this 'clock'-system provides proper chronological coordination in the functioning of cells, tissues and organs. The CC governs many physiologically critical functions. Among these functions, the key role of the CC in maintaining metabolic homeostasis deserves special emphasis. Indeed, the several features of the modern lifestyle (e.g. travel-induced jet lag, rotating shift work, energy-dense food) which, force disruption of circadian rhythms have recently emerged as a major driver to global health problems like obesity, cardiovascular disease and metabolic liver disease such as non-alcoholic fatty liver disease (NAFLD). Here we review, the CC-dependent pathways in different tissues which play critical roles in mediating several critical metabolic functions under physiological conditions and discuss their impact for the development of metabolic disease with a focus on the liver.

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Author contributions

AM designed the concept, focus areas and overall structure of the manuscript. MD prepared the figures. TFB conceptualized the section on the liver disease and therapeutic implications. AM, MD and TFB discussed, wrote and edited the different versions of the manuscript.

Declaration of competing interest

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1 Introduction

Diurnal alteration between the light (day) and the darkness (night) is unavoidable, and to adopt to this environmental variable in a manner which best suits to physiology, circadian rhythms have evolved over billions of years, and are displayed by nearly all living organisms. This clear separation between light-dark periods induces active- and rest-phases in various phyla including mammals. The circadian clock (CC) an endogenous 'time-keeper' is the key link between these environmental variable factors and organismal physiology, as it sets an adaptive rhythm for physiological mechanisms, as it allows them to be anticipated [1–6]. The idea of CC regulating critical functions was noted as early as the 18th century regarding the diurnal movement of plant leaves. In 1959, Franz Hallberg coined the term 'circadian rhythm' (latin origin: about a day) to acknowledge the periodicity of these biological rhythms. Subsequently, landmark investigations conducted in Drosophila provided the first evidence of genes controlling the circadian rhythm [7]. Since then, numerous studies have established plethora of molecular mechanisms which generate and maintain these ~24 h rhythms. The importance of investigations on the CC was exemplified by the award of the Nobel Prize in Medicine and Physiology (2017) to professors Jeffrey C. Hall, Michael Rosbash and Michael Young. The CC-rhythms have allowed mammals to anticipate changes in the external environment (e.g. day-night), and to respond by adjusting cellular CC-machinery driven numerous physiological functions, e.g. metabolism and endocrine functions [1–6]. Accordingly, recent molecular- and genetic-studies have demonstrated that, in mammals, the expression of numerous genes in different organs display circadian rhythmicity, thus enabling control of both anabolism and catabolism. As an example, food absorption, processing, assimilation and oxidative burning of nutrients all display through circadian variations, thus enabling their temporal adjustment with food availability and bio-energetic need of the organism [1–6]. Under physiological conditions these 'metabolic rhythms' are generated and maintained by the dynamic interactions between the CC and timing cues e.g. light and food (eating time and its quality). Importantly, in our modern industrialized world, various human behaviors and activities such as shift work, jet lag, energy-dense fatty foods and sleep deprivation often interfere with these rhythms and disrupt CC-functioning. Unsurprisingly then that disruption of CC functioning has recently emerged as a major contributor to different metabolic diseases, as well as carcinogenesis [1–5,8–16]. Therefore, detailed comprehension of the mechanistic basis of the CC-control on gene expression is critical to develop novel therapeutics for metabolic disorders whose therapeutic efficacy may be administration time-of-day dependent.

In this review, we lay emphasis on how the CC regulates metabolism in different peripheral organs to maintain metabolic homeostasis and provide overview of how the disruption of these CC-regulated processes could lead to the development of NAFLD. Furthermore, we also briefly discuss the potential of chronopharmacology in therapeutics.

2 Mammalian circadian clock: anatomic and molecular organization

Well-known light receptors (rods and cones) converts the energy of the light signal to electrical impulses and relays them to the brain by utilizing retinal ganglion cells (RGC).

It has been demonstrated that the melanopsin (photopigment) expressing RGCs directly relay the photic signal to a group of neurons in the anterior hypothalamus known as the suprachiasmatic nucleus (SCN;8–9), which by anatomical design acts as the 'central/master' CC. The SCN-CC in turn, by utilizing barely understood humoral and neuronal mechanisms transmits the 'time information' (a. k. a; 'Zeitgeber'; ZT) to other peripheral organs (synchronization of peripheral CCs; 1–6,8–9).

The molecular architecture of the CC-functioning has been discovered over the 30 years [1–6,17]. Remarkably, the SCN-CC and PCCs are constituted by identical molecular components which regulate themselves using a similar transcriptional-translational feedback loops (TTFL). At the core of the molecular CC functioning (in mammals) resides the heterodimer of transcription factors BMAL1 and CLOCK, which acts as the trans-activator of genes containing *E*-box DNA binding sequences (DBS). BMAL1/CLOCK-drives the transcription of the *Period* (PER1/2) and the *Cryptochrome* (CRY1/2) genes, whose protein products heterodimerise to inhibit the transcriptional functions of the BMAL1/CLOCK-complex [1–6], thereby leading to the reduction in their own expression, thus constituting the so-called first loop of the CC-oscillator (Fig. 1). During the early rest phase, high transcriptional activity of BMAL1/CLOCK drives the accumulation of its products CRY1/2 and PER1/2 (in late rest phase) which subsequently dimerise and inhibit BMAL1/CLOCK-activity during the active phase [17]. In the 'second' loop of the oscillator, BMAL1/CLOCK- activates the transcription of the nuclear receptors (NR) *Rev-Erbα* and *Rev-Erbβ* [18] during the rest phase [1–5]. Molecularly, REV-ERBs act as transcriptional repressors by binding to the ROR-response elements (RORE) present in numerous target genes including themselves. Importantly, REV-ERBs by repressing the transcription of *Bmall* and *Clock* genes reduce their own expression, thus closing this second loop. Importantly, during the active phase another set of NRs RORα/γ are recruited to these same RORE-DBSs to activate the expression of *Bmal1* and *Clock* genes [1–5]. This phase-specific recruitment and accumulation of RORα/γ (activators) and REV-ERBα/β (repressors) induces rhythmicity in *Bmal1* and *Clock* expression, thus generating a variability in not only CC-oscillator functions but also in the transcription of numerous RORE-DBS containing target genes which are transcribed exclusively during the active phase (Fig. 1; [1–5]). Moreover, REV-ERBs repress and RORα/γ induce the E4BP4 repressor, which in turn represses the transcription of D-box DBS-containing CC-controlled genes (CCGs) in active phase. While the BMAL1/CLOCK-induced DBP transactivates these D-box CCGs strictly during the rest phase (Fig. 1). Moreover, post-translational modifications of CC-components as well as epigenetic modifications-induced by the recruitment of CC-components on their respective DBSs also generates further regulation of the CC-functioning. Altogether, by utilizing several sophisticated molecular mechanisms the CC-oscillator drives a time of the day-dependent gene expression program, which lies at the heart of producing distinct critical biochemical outputs in different organs (Fig. 2). Importantly, this CC-governed temporal coordination in gene-expression between organs is the major driver of metabolic homeostasis.

3 Cross talk between clock and feeding cycles

Feeding cycles are one of the most prominent *zeitgeber* for peripheral tissues [4,5,19,20], and investigations have uncovered the existence of multi-layered cross-talk between metabolism and the CC, and the number of ways through which metabolism and CC influence each other are rapidly increasing [1–5]. Not only the CC exerts a remarkable control of metabolism, but also the information about metabolic state is transmitted back to the CC, thus creating a crosstalk between metabolic and circadian cycles. In this regard, the 'clock' receives information (e.g. changes in feeding time or composition) from a range of metabolic sensors which can modify PCCs rhythms. Specifically, the importance of feeding time on the hepatic-CC was demonstrated in *Cry1/2* mutant mice, in which an imposed night-time only feeding largely restored the circadian gene expression pattern [21]. Changing the feeding time from the active phase to the rest phase in mice is known to shift peripheral CCs by nearly 12 h [19,20]. At the molecular level, this change is orchestrated by metabolic alterations which induce the activity of well-known transcription factors PPARα and CREB [22]. One highly relevant physiological setting of CC-metabolism crosstalk is exemplified by BMAL1/CLOCK-dependent expression of the nicotinamide phosphoribosyl transferase (*Nampt*) gene, which is the rate-limiting enzyme in NAD^+ synthesis [23,24]. 'Clock'-gated NAMPT transcription generates a rhythmicity in NAD^+ synthesis which in turn dictates the biochemical activities of NAD^+ -dependent proteins, e.g. the SIRT1 deacetylase and the PARP-1. Remarkably, SIRT1-activity is known to determine: (i) the functioning of BMAL1/CLOCK-complex and, (ii) the 'half-life' of PER2 protein, which in unison maintain CC-oscillator functioning [1–3]. In accordance, genetic ablation of *Sirt1* or its pharmacological inhibition is known to desynchronize circadian rhythmicity. Another highly relevant feedback regulation exists between the CC and heme biosynthesis and activity has also been uncovered [25,26]. Altogether, extensive investigations have unraveled multifaceted CC-metabolism crosstalk as a tuning fork for the CC-oscillator functioning, which has systemic repercussions as: (i) a change in the feeding time in mice to the "rest" phase leads to features resembling metabolic syndrome [27] and, (ii) high-fat diet (HFD)-induced reprogramming of the hepatic CC-functioning in mice can be largely prevented by restricting the food access to the circadian active phase [28,29].

4 Pathophysiology of the non-alcoholic fatty liver disease (NAFLD)

Over the last decades, lifestyle modifications have shifted the health care priorities worldwide from infectious to metabolic diseases [30–34]. In the context of liver disease, availability of vaccines and antiviral therapies have started to reduce the disease burden caused by hepatotropic viruses such as chronic hepatitis B and C and their complications [35–39]. In contrast, the prevalence of metabolic liver disease such as non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) have increased dramatically. Indeed, with an estimated worldwide prevalence of ~25%, NAFLD has emerged as the most common chronic liver disease [30–34]. This increase in global prevalence of NAFLD is closely associated with the world-wide epidemic in the incidence of other metabolic disorders e.g. type 2 diabetes and obesity. Importantly, 20–25% of fatty liver patients progress to develop NASH, which is a major aetiology of liver transplantation required by cirrhotic and hepatocellular carcinoma (HCC) patients [30,31,40]. "Fatty liver"

is a complex spectrum of disease and considering the current knowledge of the pathology and the understanding of patient heterogeneity, the scientific community has recently [34] suggested metabolic (dysfunction) associated fatty liver disease (MAFLD) to be more appropriate. NAFLD generally initiates with the accumulation of excessive triglyceride (TG) in hepatocytes, a largely benign state commonly referred as simple steatosis [30–33]. Importantly, persistent fatty liver drives simple steatosis to steatohepatitis (NASH), which is characterized by simultaneous presence of both inflammation and hepatocytic damage (a.k.a ballooning). Furthermore, NASH proceeds to fibrosis, which can eventually progress to cirrhosis and hepatocellular carcinoma (HCC) [30–33,40]. Like metabolic syndrome, development of NAFLD is highly complex and has been extensively reviewed elsewhere [30–34,40–43]. Despite large research and development efforts, there are no approved drugs specifically targeting metabolic liver disease and compounds in late stage of development are frequently characterized by limited efficacy [30,32,33].

The pathogenesis of “fatty liver” was initially postulated in 1998 [44] to be “a tale of two hits”-first involving excessive hepatic triglyceride (TG) accumulation which was followed by secondary insults such as oxidative stress. However, recent investigations in chronic metabolic diseases have now clearly established that pathogenesis of NAFLD is a complex multi-step metabolic disorder [30–34,40–43]. Several studies have indeed uncovered crucial roles for deregulations in the functioning of pancreas, intestine, adipose tissue and immune system in NAFLD development ([30–33,40–43]; Fig. 3). Physiologically, mammalian bioenergetics is maintained by intricate intra- and inter-organ communications and deregulations of which lie at the core of metabolic disease, including NAFLD. At the basic level NAFLD arises due to the inability of the hepatocytes to effectively metabolize carbohydrates and free fatty acids (FFA). Mechanistically, NAFLD is a consequence of an imbalance between adipocytic FFA supply, hepatic de novo lipogenesis and FFA utilization through mitochondrial β-oxidation and production of ketone bodies, and finally disposal through secretion of TGs in very low-density lipoprotein (VLDL) particles [1,30–33]. Fat accumulation in the liver can be traced to either an increased incidence of de novo lipogenesis or overwhelming of the capacity to oxidize FFA. Additionally, mitochondrial dysfunction could impair fatty acid β-oxidation and cause lipid accumulation, which usually precedes NAFLD [45–47]. Furthermore, excessive TG is transported out of the hepatocytes by binding to liver-produced VLDL and, with impaired β-oxidation or TG transport, the capacity of the liver to clear accumulated TG is compromised, which further contributes to the development of NAFLD [30,31,45]. As discussed above, the complexities of NAFLD pathogenesis and its progression to steatohepatitis are barely understood with both genetic and environmental factors playing crucial roles. Importantly, due to the overwhelming role of the CC in maintaining metabolic homeostasis (Fig. 2), it can be postulated that disruption in the CC-functioning can drive NAFLD [1–3,15]. In the subsequent chapters we describe some of these functions to further illustrate the link between CC and NAFLD.

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5 Peripheral circadian clocks: regulation of metabolism and impact on pathogenesis of NAFLD

5.1 Liver

Unarguably, the liver plays a central role in governing whole-body physiology (Fig. 2). Considering its preeminent role in metabolism several genomic studies have utilized time-course in mouse models to uncover circadian cistrome [48–51], transcriptome [52,53], proteome [54–56], and lipidome [57,58]. Analyses of circadian gene expression have revealed two broad time-periods of transcription in liver, which correspond to the periodic transition between alternating active and rest phases [1–4]. These two 'peaks' reflect the highly differential physiological requirements, such as in energy demand or detoxification activity, as per their necessity during the periods of activity or rest [1–5]. Analyses of CC-components and epigenetic factors binding [48–51] uncovered that these two circadian phase-specific distinct mRNA pools are generated due to the intrinsic rhythmicity of the CC-oscillator. Furthermore, CC is also known to post-transcriptionally control cellular processes like DNA repair, ribosome biogenesis, autophagy, ER-stress [54–56].

Mammalian gluconeogenesis is principally controlled by the liver. Indeed, along with several other organs (brain, pancreas, muscle), the liver-CC largely contributes to maintain homeostatic blood glucose levels [59]. In a critical genetic study it was demonstrated that *Bmal1* ablation in the liver reduces expression of the glucose transporter (*Glut2*), which lead to a decreased post-feeding glucose uptake in mutant mice, thus revealing a role for the liver-CC-oscillator in glucose metabolism [60]. Remarkably, the liver-CC also regulates glucose metabolism post-hepatocytic entry at multiple levels, by controlling expression of glucokinase (*Gck*; regulator of glycogen synthesis) [1–5]. By controlling either the expression or the activity of several gluconeogenic transcription factors e.g. *Klf10* [61], *Hnf4α* [18,62], *CREB* [63], *Pgc1α* [64], the liver-CC thoroughly controls glucose metabolism.

Along with its influence on carbohydrate metabolism, several genetic studies have established that liver CC as a predominant regulator of lipid metabolism [65–67]. These investigations have established plasma levels of FFA, TG and cholesterol display diurnal variations, and are altered upon mutations of CC-genes. To illustrate, liver-restricted mutation of *Rev-Erbα/β* profoundly increased plasma levels of FFA, TG and cholesterol [67]. Mechanistically, the hepatic-CC regulates either the expression or the activity of enzymes that are critically involved in regulating multiple critical steps of lipid metabolism. As an example, TG synthesis in liver is a multistep process and requires the activity of several enzymes (*Gpat2*, *Agpat1/2*, *Lipin1/2* and *Dgat2*) expression of which are CC-controlled [56], thereby leading to a prominent crest and trough of hepatic TG levels (in mice) during the rest and active phases, respectively [56]. Furthermore, REV-ERBα by regulating the transcription of *Insig2* controls the activity of SREBP1c (master regulator of lipogenesis; [68]). Additionally, the hepatic CC-oscillator also participates in: (i) fatty acid synthesis by controlling the expression of *Elovl3*, *Elovl6*, *Fas* etc. [1–3,6], (ii) regulating β-oxidation and ketone-body production [69,70] and, (iii) determining the expression of key lipid-responsive NRs LXRs, PPAR α and δ [1–3,18]. Recent studies have established

BA-signaling as a major regulator of TG, cholesterol and glucose homeostasis [71,72]. BA synthesis is controlled by a transcriptional feed-back loop consisting of the NRs FXR and SHP and intestinal hormone FGF15 (FGF19 in humans; [71–72]). Importantly, CC-regulates the expressions of both FXR and SHP [18,62] as well as FGF15 secretion [73], thereby controlling the diurnal expression of cholesterol 7α-hydroxylase (*Cyp7a1*), the rate-limiting enzyme in BA synthesis. Additionally, both REV-ERBα and DBP (CC-output regulator) are known to control *Cyp7a1* transcription [74,75]. Furthermore, in mice an essential molecular feedback exists between SHP and the neuronal PAS domain protein 2 (NPAS2; *Clock* gene paralog) which not only contributes towards their own circadian rhythmicity but also enables to maintain hepatic lipid, BA and lipoprotein metabolism [76]. Taken together, these mechanisms combine to generate circadian rhythmicity in BA levels which is also observed in humans [77]. To further illustrate the intimate connection between the lipid-and BA-metabolism and CC-functioning, it has been noted that atorvastatin (routinely to treat hyperlipidemia) administration in mice alters the expression of not only *Cyp7a1* but also of key CC-components e.g. *Bmal1* and *Npas2* [78]. The liver CC is also well known to regulate several cellular processes e.g. autophagy, ER stress and oxidative stress [79–83], all of which have been implicated in pathogenesis of NAFLD and has been extensively described elsewhere [30,31].

5.2 Pancreas

The pancreas is well known to play a critical role in maintaining glucose homeostasis through production of hormones insulin and glucagon (Fig. 2). Pancreatic function is controlled by both the central SCN-clock as well as Pancreatic CC-oscillator and aligns biochemical activities in pancreatic islets as per the metabolic demands [2,3,84,85]. The ‘clock’ is known to regulate both the exocrine [84] and endocrine [86] functions of the pancreas. The presence of an autonomous circadian pancreatic clock has been demonstrated not only in rodents [85–87], but also in human islets and dispersed human islet cells [87]. The pancreatic clock is synchronized to the light-dark cycle via signals derived from the SCN-clock that include autonomic neuronal system, melatonin and glucocorticoids [88]. The pancreatic CC-oscillator in β cells drives highly rhythmic oscillation of insulin secretion which is strictly aligned with the expression of genes encoding insulin secretion and signaling [85]. Mechanistically, pancreatic CC-components helped in the spatiotemporal recruitment of key transcription factor PDX1 to specific enhancers to regulate transcription of insulin and other genes of insulin signaling pathway [85]. Importantly, β-cell-specific mutation of either *Bmal1* or *Clock* leads to wide-spread changes in the transcriptome, and specifically reduces genes encoding cell cycle, synaptic assembly and secretion of insulin, thereby leading to diabetes in mutant mice [86]. Notably, non-alcoholic fatty pancreas disease (NAFPD) a recently described dysmetabolic phenotype (akin to NAFLD), has been shown to perturb the expression of several CC-components in murine pancreas which correlates with pancreatic inflammation and fibrosis development [89]. As insulin-resistance often accompanies NAFLD [30], deregulation of the pancreatic-CC-controlled insulin signaling could play a critical role in the predisposing to fatty liver development (Fig. 3).

5.3 Intestine and microbiota

Several critical aspects of the intestinal physiology e.g. motility, intestinal permeability, hormone secretion, nutrient absorption, cell proliferation and interactions with microbiota are CC-controlled and have been thoroughly reviewed [90–92]. However, in recent years the relationship between intestine and resident microbiota has gained spotlight as a major regulator of metabolic health and disease including, NAFLD [93–96]. Indeed, obesity has been shown to not only alter the composition of gut microbiota (dysbiosis) composition but also perturbs their nature of interactions with the host (intestinal epithelial cells; IEC), both of which have been suggested as an etiological agent in the pathogenesis of metabolic diseases, including NAFLD [93–96]. One of the proposed mechanisms through which dysbiosis could induce NAFLD is by augmenting lipopolysaccharide (LPS) production and delivery to the liver via the portal circulation, a consequence of increased intestinal permeability [97,98]. This abnormal presence of microbiota-associated LPS in liver perturbs lipid metabolism by affecting the generation of short-chain fatty acids and altering the BA pool composition which may influence intestinal and hepatic FXR activity, thus affecting both glucose and lipid homeostasis [97].

The ‘clock’ and the microbiota intersect at many levels. Most notably, the IEC CC has been demonstrated to regulate the circadian expression of microbial pattern recognition receptors (e.g. TLRs, NOD2) which creates a ‘temporal window’ for the microbiota-signals to regulate gene expression in IEC to maintain homeostasis [99]. Importantly, absence of this IEC CC-microbiota crosstalk leads to metabolic disorders [99]. Interestingly, it was also demonstrated that the gut microbiota undergoes circadian oscillations in composition and function [100,101]. These microbiota oscillations were found to be controlled by the timing of food intake and the diet composition. Furthermore, it was also demonstrated that the gut microbiota undergoes circadian oscillations in biogeographical localization and metabolome patterns which in turn determine the diurnal exposure of the intestinal epithelium to different bacterial species and their metabolites [102,103]. Importantly, this circadian variations in microbial behavior in turn regulates the transcriptome and metabolome of both gut and distant tissues e.g. liver [102,103]. Most importantly, dysbiosis-induced by ‘clock’ perturbations (either through genetic ablation of CC-components or jet lag) lead to and development of metabolic pathologies [93,94,103].

5.4 Immune system

The immune system is heavily influenced by time-of-day cues, both under steady-state conditions and in response to inflammatory challenges. Indeed, diurnal host responses to endotoxins were noted more than 6 decades back [104]. Importantly, several inflammatory diseases e;g. myocardial infarction, rheumatoid arthritis and asthma are known exhibit pronounced circadian rhythmicity in their pathology [105–108]. Recently, molecular evidence has started emerging to reveal that numerous aspects of immune functions including lymphocyte trafficking, host-pathogen interactions, cytokine secretion and activation of innate and adaptive immunity are thoroughly controlled by the CC [107–110]. Taken together, investigations have established the CC operates to as a gating mechanism to control the magnitude of immune response in a diurnal fashion and has been described [107–110]. The role of the deregulated immune system and fatty liver disease have been

extensively reviewed [41–43]. Here we briefly discuss the immune components which are known to be controlled by CC under physiological conditions [107–110].

Like every other aspect of the metabolic syndrome, pathogenesis of `fatty liver` is strongly linked with inflammation, and both innate and adaptive branches of immunity have been implicated in this process [31,32,41–43]. However, the innate immune system has received more attention. Although in initial studies focused on Kupffer cells, more recent investigations have revealed that several specialized immune cells (resident and infiltrating) participate in hepatosteatosis [42]. Kupffer cells are activated by a variety of stimuli including FFA, peroxidized lipids, microbiota-derived LPS and ROS [43]. Importantly, both FFA and LPS drive Kupffer cell stimulation through TLR2 and TLR4, which leads to perpetual activation of inflammatory signaling pathways like ASK-1, JNK, IL-6 etc. thereby enabling sustained induction of NF-κB and STATs, thus augmenting cytokine production (TNF-α, IL-1β etc.). In murine models, reducing the number of Kupffer cells through clodronate administration considerably ameliorates NASH pathology [111]. In addition, the inflammasome which can both sense and be activated by danger-associated molecular patterns (DAMPs) such as FFA and pathogen-associated molecular patterns (PAMPs) e.g. LPS, has recently emerged as a critical molecular link between metabolic stress and fatty liver development [31]. In animal models of NAFLD, triggering inflammasome activity enhances the expression of the pro-inflammatory cytokines IL-1β and IL-18 which subsequently through caspase-1 promote cell death in liver [111]. Recent studies have also shed light on the role of the IL17-secreting Th17 cells in metabolic diseases including NAFLD [112]. It has been observed that the obesity-induced dysbiosis elevates IL-17 production [113,114] and, in the setting of NAFLD, this cytokine drives neutrophil and monocyte infiltration in the liver, thereby potentiating hepatic insulin resistance and steatosis progression [115]. Consistently, abrogation of IL17-induced signaling activity in a diet-induced murine model of NASH reduces steatosis [116]. Taken together, these studies indicate how possibly deregulated CC-functioning in immune cells could predispose towards fatty liver development.

6 Circadian clock-related therapeutic interventions

In the past few years, many studies have investigated the effects of the timing of drug treatment on the circadian appearance or exacerbation on of disease symptoms, leading to the development of a concept known as chronomedicine [117–119]. Chronomedicine is described as the approach employed to maximize the efficacy and minimize the side effects when drugs are administered in accordance with the CC as ‘timing’ of drug-administration is of crucial but still a less-appreciated factor in drug efficacy considerations [117–119]. This is not surprising considering that to a large extent CC control over pharmacology arises from its ability to thoroughly regulate almost all steps of xenobiotic detoxification in the liver, including absorption, biotransformation and elimination [[118],120–122]. Thereby, CC-controls pharmacological parameters such as pharmacokinetics and pharmacodynamics [118,119]. Remarkably, 56 of the top 100 best-selling drugs in the USA are known to target the product of a circadian gene [122]. Until now, this approach of chronomedicine has been evaluated for several diseases, such as hypertension [123,124] and cancers [125,126]. The most important example is that of the circadian hormone melatonin that has been

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used in combination with cancer therapy to minimize toxicity or enhance chemotherapeutic viability in clinical and laboratory settings [126]. To further illustrate, influenza vaccine when administered in the morning produces higher titers of antibodies than when given in the evening [127].

Pharmacological therapies are not yet available for NASH [30–34], although several compounds are in preclinical and clinical development, including obeticholic acid (INT-747; [128]) which activates FXR and, elafibranor (currently in phase 3 trial; [129]) which activates NRs PPAR-α/β. Notably, physiological targets of potential NASH-modulating compounds [30–32], e.g. resveratrol (SIRT1-agonist) and inhibitors of acetyl-CoA carboxylase1 (ACC1) are also CC-regulated [1–4], thereby further strengthening the CC-connection to the development of novel therapeutics. Considering, the role of the CC in regulating the expression and activities of FXR, PPARs, SIRT1 and ACC chronopharmacology could very well dictate the efficacy of these approaches. Circadian "misalignment" between central and peripheral CCs has been found to be a core feature of almost every dietary or environmental model of metabolic disease including NAFLD. For therapeutic treatment of metabolic diseases like NAFLD a strategy could be to give to patients more scheduled eating habits, the so-called chrononutrition. In this regard, time-restricted feeding (TRF), a behavioral approach where feeding is solely restricted to the circadian active phase not only prevents circadian misalignment but also has been shown to correct several metabolic pathologies in animal models [130–132]. TRF is distinct from intermittent fasting and when applied to humans, the amount of calory ingested is not relevant [130–132]. Importantly, several small-scale human TRF investigations have indicated its usefulness in improving outcomes in patients with metabolic syndromes [133–135], however, the usefulness of TRF on NAFLD endpoints are yet to be ascertained.

7 Conclusion

As the prevalence and economic burden of the metabolic syndrome and NAFLD/NASH/MAFLD continues to rise worldwide, the knowledge about the mechanisms contributing to the development of this disease has been progressively increasing over the last two decades. Circadian misalignment has been associated with increased incidence of metabolic and cardiovascular disorders in various human studies [136–142]. These discoveries have led to the recognition of CC rhythms as an essential piece of the complex puzzle that depicts our physiologic homeostasis. The understanding of the multi-faceted role of the 'clock' in the pathogenesis of fatty liver (Fig. 3), is not only crucial to advance scientific knowledge, but also to improve public health by identifying new therapeutic targets and life-style modifications. Disruption of the CC has been shown to play an important role in the increasing incidence of metabolic homoeostasis with a key contribution to the metabolic syndrome and NAFLD. Hence, it is necessary to investigate in detail the CC-controlled pathways and elucidate how they are linked with the development of fatty liver disease (Fig. 3).

Expanding our knowledge about the genetic and environmental risk factors making individuals more susceptible to metabolic dysfunction combined with the discovery of new therapeutic approaches to restore the perturbed circadian machinery will ultimately

contribute to improve the outcome of this rapidly growing pandemic of metabolic liver disease.

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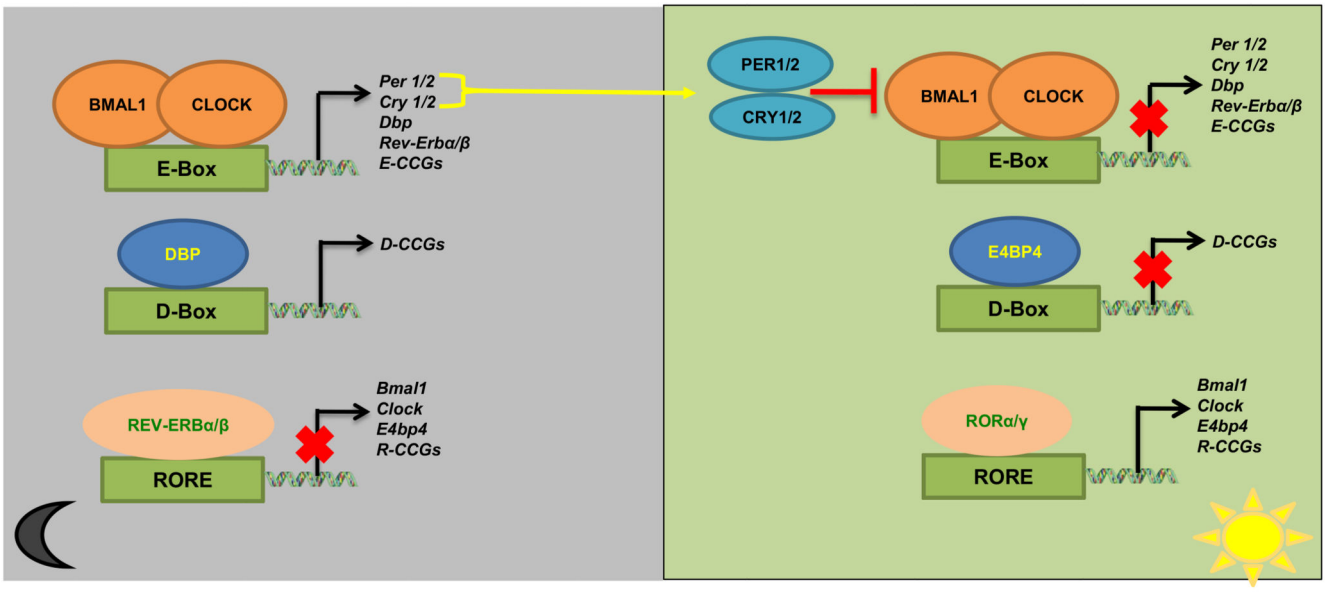

Fig. 1.

Model of the molecular 'clock': The BMAL1/CLOCK-heterodimer binds to the E-Box DBS present in the promoter-enhancer elements of numerous CCGs, including their inhibitors Periods (Per1/2) and Cryptochromes (Cry1/2) and increases their expression during the rest phase. Subsequently, PERs and CRYs proteins dimerize to inhibit (in the active phase) the transcriptional activity of BMAL1/CLOCK. Additionally, BMAL1/CLOCK-dependent expression of Rev-Erbα/β, leads to the trans-repression of several RORE-DBS-containing CCGs including, Bmal1,Clock and E4BP4 during the rest phase. A reduction in REV-ERBs levels (during active phase) permit the RORα/γ-dependent RORE-mediated activation of CCGs including Bmal1 and Clock, which enables the turning of the circadian clock. DBP expression during the rest phase leads to the expression of D-Box DBS containing CCGs, which are transcriptionally repressed by E4BP4 during the active phase. CCGs-Clock Controlled Genes, DBP-D-Box binding protein, E4BP4-E4 promoter binding protein 4, E-CCGs: E-Box DBS-containing CCGs, R-CCGs: RORE-containing CCGs, D-CCGs: D-Box-containing CCGs. See text for details.

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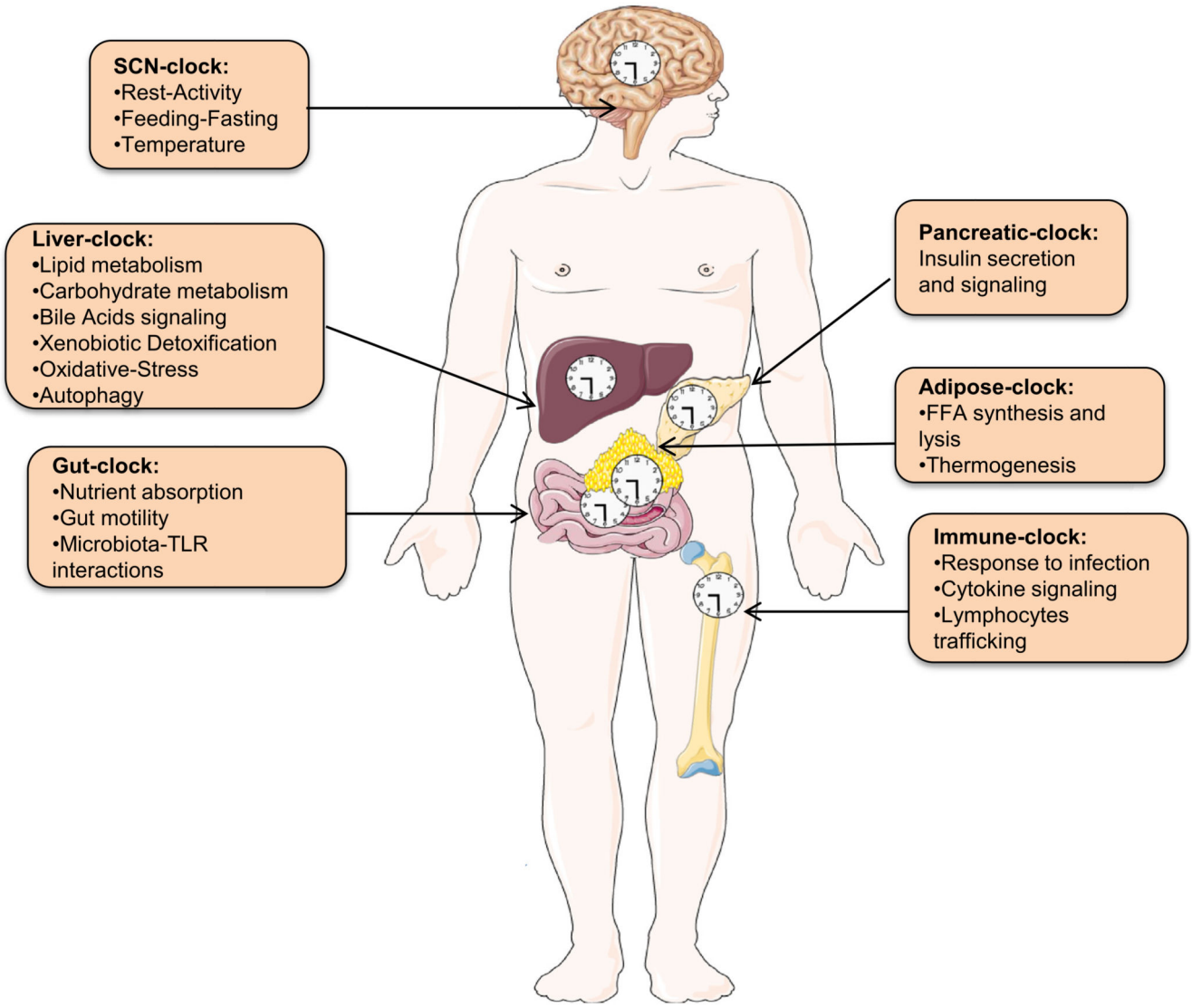

Fig. 2.

Coordinated regulation of metabolic physiology by central and peripheral clocks: The light-entrained central SCN-clock not only governs rest-activity and feeding-fasting cycle but also synchronizes peripheral tissue clocks. Indicated in the boxes are some of the major peripheral clocks and the critical physiological functions they perform. Importantly, deregulations in the functioning of peripheral clock-regulated pathways are often encountered in NAFLD. SCN-Supra Chiasmatic Nucleus. See text for details.

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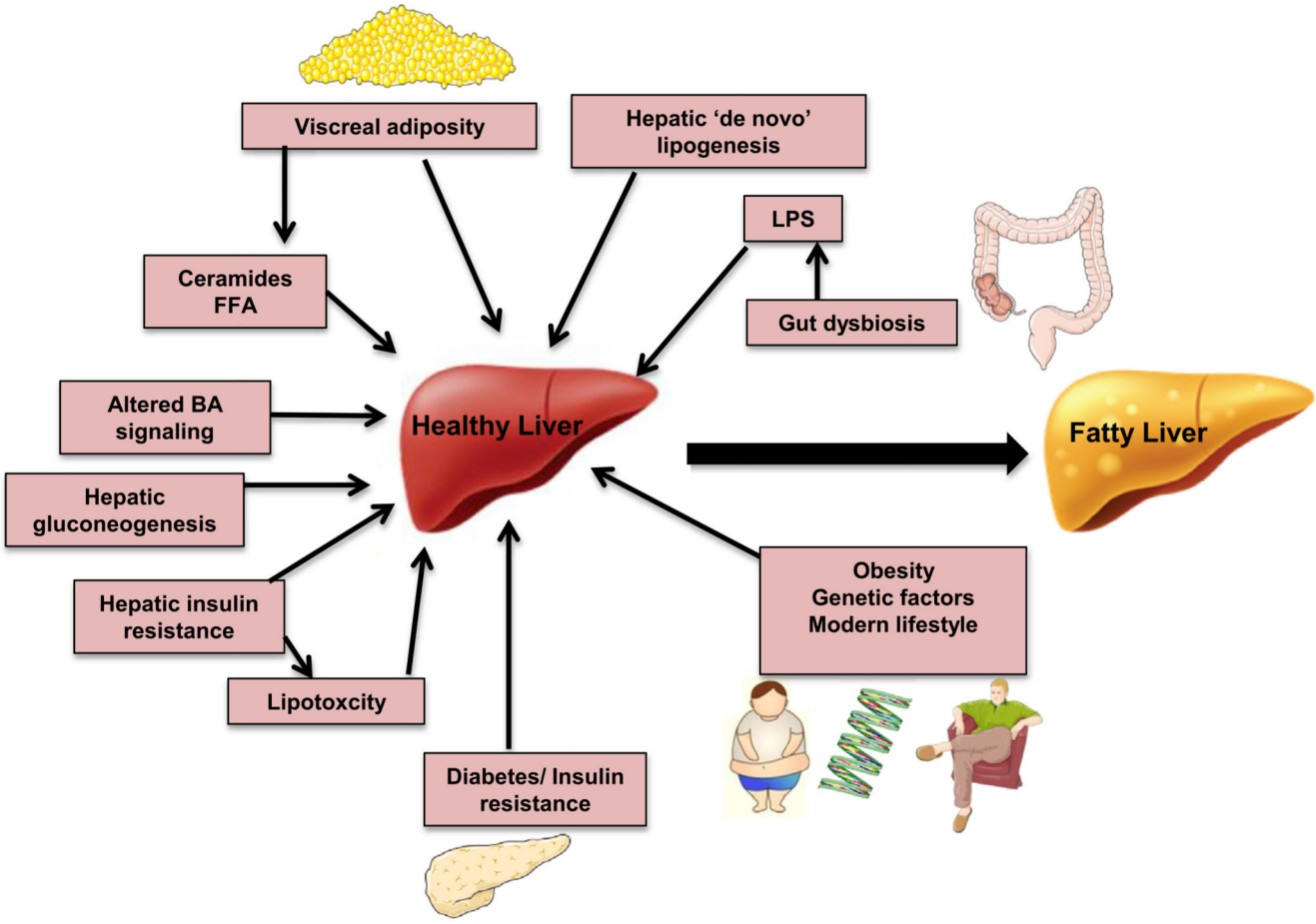

Fig. 3.

Model of NAFLD pathogenesis: The scheme depicts an overview of how alterations in the circadian clock-controlled functions/pathways and processes in different peripheral tissues may predispose to NAFLD pathogenesis and contribute to therapeutic intervention. See text for details.