Hepatology Snapshot:

The liver by day and by night

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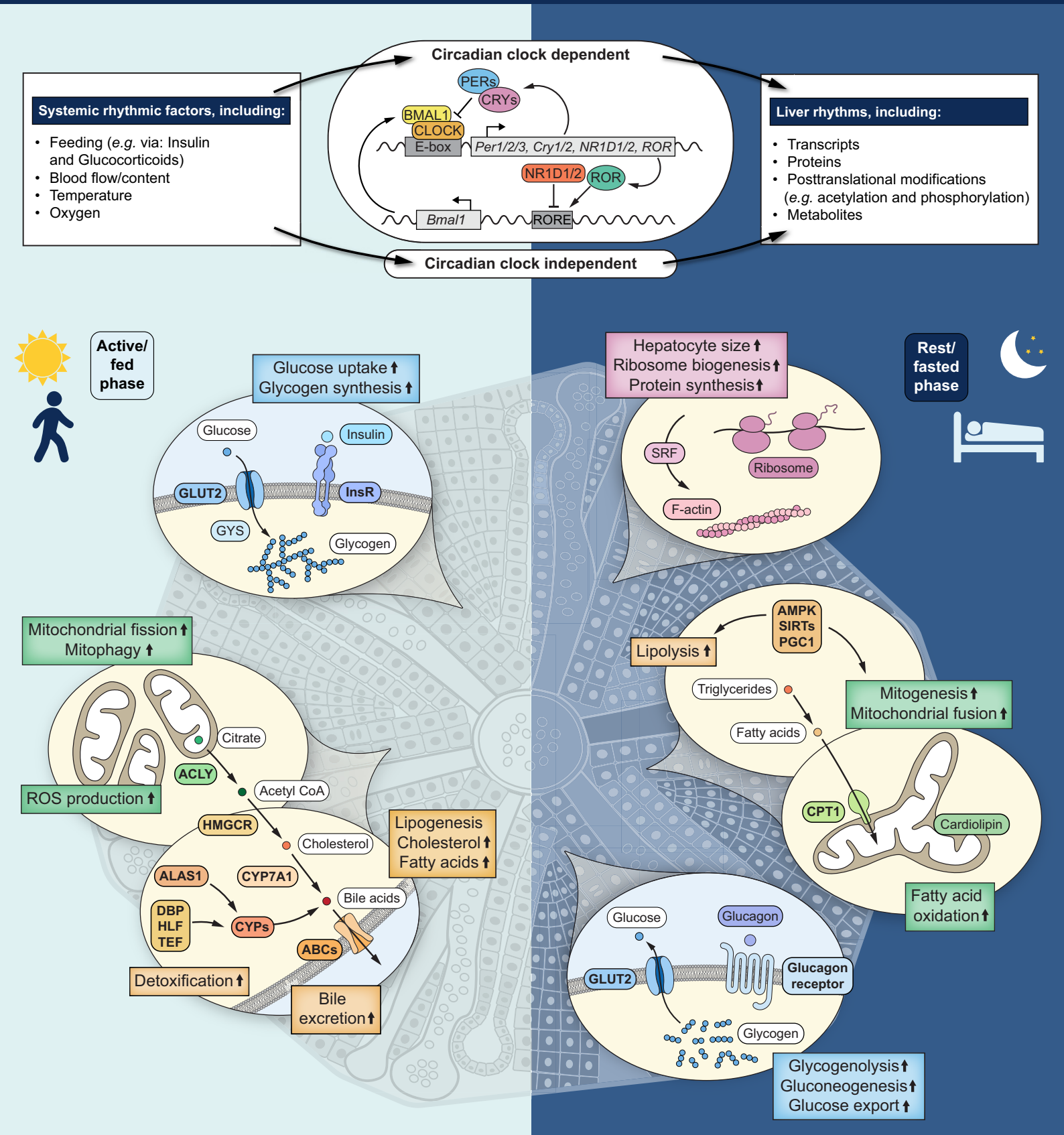

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Introduction

Circadian clocks oscillate over a period of ≈24 h in light-sensitive organisms and coordinate a wide variety of behavioral, physiological, and molecular functions with geophysical time. In mammals, clocks are present in virtually every cell of the body and function in a cell autonomous and self-sustained manner. The molecular clockwork relies on transcription-translation feedback loops, which generate self-sustained oscillations in the expression levels of the clock components (*e.g.* PERs, CRYs, CLOCK, BMAL1, NR1D1,2, RORs). These oscillations further control downstream processes through transcriptional and post-transcriptional regulation.[1]

The mammalian circadian system is hierarchical: a central clock in the suprachiasmatic nucleus of the brain synchronizes millions of clocks in peripheral tissues. The peripheral clocks are synchronized through a multitude of input mechanisms such as hormonal signals and temperature cycles. Of the peripheral organs, the liver circadian system is probably the most well characterized. Indeed, many of the liver's key functions exhibit rhythmicity. Roughly 15% of the hepatic transcriptome is circadian (*i.e.* exhibits rhythms of ≈24 h) along with rhythms in protein levels, post-translational modifications, and various metabolites.[2–4] Liver rhythmicity can be driven both by the liver clock and directly by rhythmic systemic signals. In addition, the clock itself is synchronized by various timing cues. These systemic cues include oscillations in body temperature, oxygen levels, and a myriad of signaling factors (hormones, metabolites) delivered via the blood stream.[5] In this Snapshot, we highlight key rhythmic processes and emphasize the main regulators and metabolites involved.

Glucose homeostasis

The liver is critical for maintaining glucose homeostasis. Both food intake and the glucose demand of different organs change throughout the day. Accordingly, the liver anticipates and counteracts these variations, in a clock-controlled manner. In the active phase (day for human, night for mouse), following mealtime, blood glucose rises, and the liver takes up glucose and stores it as glycogen. In the rest phase, due to fasting, the liver is required to address the changing energetic demand and therefore gluconeogenesis and glycogenolysis are elevated. Key rhythmic factors that play a role in these processes include: glucose transporter 2 (GLUT2), glycogen synthase (GYS), glycogen synthase kinase 3 (GSK3), and the insulin receptor (InsR).[6,7]

Lipids and mitochondrial dynamics

The overall organization and structure of mitochondria is rhythmic. Fusion is increased in the rest phase, while fission is increased in the active phase – coinciding with higher turnover (mitophagy) and the peak in reactive oxygen species (ROS) levels.

Moreover, the levels and activity of many mitochondria-related proteins are rhythmic, which eventually leads to rhythmic activity. For example, CPT1 rhythmicity gates fatty-acid oxidation mostly to the rest phase, while the production and export of Acetyl-CoA is more prominent in the active phase, facilitating lipogenesis. Among the key regulators of these rhythms are AMPK, SIRTs and PGC1, which are mostly activated in the rest phase to facilitate lipid catabolism and mitochondrial biogenesis, while inhibiting lipogenesis.[8]

In general, liver lipid metabolism exhibits robust circadian rhythmicity that is manifested in the transcript levels of relevant enzymes and the lipids themselves. Both phospholipids and triglycerides undergo daily changes, as do organelle-specific lipids and cholesterol synthesis.[8,9]

Detoxification and bile acid metabolism

A related and important process is that of bile production and secretion, which peak in the beginning of the active phase.[3] Detoxification processes peak around this time as well, due to multilevel regulation. CYP enzymes' expression is largely regulated by the PARbZip transcription factors (*Dbp*, *Tef*, *Hlf*), which are themselves highly rhythmic. In addition, ALAS1, which is required for CYP activity, displays daily rhythmicity. Last, the expression of many ABC transporters, responsible for the excretion of various compounds into the bile duct, is rhythmic as well, and mostly elevated during the rest-active transition.[10]

Hepatic size

The overall size of the liver, and specifically the size of hepatocytes, undergoes daily rhythmicity. The underlying mechanism involves rhythmic control of SRF over G-ACTIN and F-ACTIN accumulation alongside rhythmic ribosomal assembly and protein synthesis.[11,12]

Abbreviations

ABCs, ATP-Binding Cassette transporters; ACLY, ATP citrate lyase; ALAS1, 5'-Aminolevulinate Synthase 1; AMPK, 5' AMP-activated protein kinase; BMAL1, Brain and Muscle ARNT-like 1; CLOCK, Circadian Locomotor Output Cycles Kaput; CPT1, Carnitine Palmitoyl Transferase 1; CRYs, Cryptochromes; CYPs, Cytochrome P450 family; DBP, D-Box Binding PAR BZIP Transcription Factor; GLUT2, Glucose Transporter 2; GYS, Glycogen Synthase; HLF, Hepatic Leukemia Factor; HMGCR, HMG-CoA reductase; InsR, Insulin Receptor; NR1D1/2, Nuclear Receptor 1 D1/2; PERs, Periods; PGC1, Peroxisome proliferator-activated receptor gamma coactivator 1; ROR, Retinoic Acid Receptor-Related Orphan Receptor; RORE- ROR responsive element; ROS, Reactive Oxygen Species; SIRTs, Sirtuins; SRF, Serum Response Factor; TEF, Thyrotroph Embryonic Factor

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Conflict of interests

The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contribution

R.A, G.M., and G.A.: conceptualization, writing and figure design.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.01.011.

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