Cell Metabolism
Resource

Circadian Clocks and Feeding Time Regulate the Oscillations and Levels of Hepatic Triglycerides

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SUMMARY

Circadian clocks play a major role in orchestrating daily physiology, and their disruption can evoke metabolic diseases such as fatty liver and obesity. To study the role of circadian clocks in lipid homeostasis, we performed an extensive lipidomic analysis of liver tissues from wild-type and clock-disrupted mice either fed ad libitum or night fed. To our surprise, a similar fraction of lipids (~17%) oscillated in both mouse strains, most notably triglycerides, but with completely different phases. Moreover, several master lipid regulators (e.g., PPARα) and enzymes involved in triglyceride metabolism retained their circadian expression in clock-disrupted mice. Nighttime restricted feeding shifted the phase of triglyceride accumulation and resulted in ~50% decrease in hepatic triglyceride levels in wild-type mice. Our findings suggest that circadian clocks and feeding time dictate the phase and levels of hepatic triglyceride accumulation; however, oscillations in triglycerides can persist in the absence of a functional clock.

INTRODUCTION

Circadian clocks play a principal role in coordinating our daily physiology and metabolism. Animal studies and epidemiological evidence suggest that disturbance of circadian rhythms through environmental and genetic effects can lead to metabolic diseases such as hyperlipidemia, fatty liver, and obesity (Asher and Schibler, 2011; Bass, 2012; Froy, 2010; Green et al., 2008). These observations highlight the central role of circadian regulation in lipid homeostasis. Dyslipidemia and obesity are associated with high morbidity and mortality rates, hence elucidating the mechanisms involved in temporal regulation of lipids is of great interest.

The mammalian circadian clock is comprised of a master pacemaker, located in the brain, that synchronizes subsidiary peripheral oscillators, present in virtually all cells of the body. The master clock is entrained by daily light/dark cycles, whereas feeding time appears to be the dominant timing cue (Zeitgeber) for peripheral clocks. Both the master and peripheral clocks tick in a self-sustained and cell-autonomous fashion. The currently held molecular model for the generation of circadian rhythms is based on interlocked negative transcription feedback loops that drive daily oscillations of core clock and clock-controlled genes (Brown et al., 2012; Dibner et al., 2010; Feng and Lazar, 2012). Briefly, BMAL1/CLOCK drives the expression of *Period* (i.e., *Per1*, *Per2*, and *Per3*) and *Cryptochrome* (i.e., *Cry1* and *Cry2*) genes. In turn, PER and CRY proteins accumulate and repress the transcription of their own genes. An additional essential feedback loop involves the orphan nuclear receptors of the REV-ERB and ROR families. BMAL1 activates *Rev-erb* transcription, which in turn suppresses *Bmal1* expression (Bugge et al., 2012; Cho et al., 2012; Preitner et al., 2002; Solt et al., 2012).

Extensive transcriptome profiling performed throughout the day in liver and additional peripheral organs has demonstrated the pervasive circadian control of physiology and metabolism (Akhtar et al., 2002; McCarthy et al., 2007; Panda et al., 2002; Storch et al., 2002; Vollmers et al., 2009). These studies have revealed that a substantial fraction (~10%) of all liver mRNAs are expressed in a rhythmic fashion; many of them play a role in metabolic processes, including cholesterol and lipid metabolism. Several enzymes participating in lipid biosynthesis and catabolism are expressed in a daily manner (e.g., cytochrome P450s, HMGCoA reductase, and lipin) (Panda et al., 2002). Additional studies have shown diurnal regulation of triglyceride and cholesterol levels in plasma (Hussain and Pan, 2009). Consequently, various genetic mouse models for disrupted clock exhibit impaired lipid metabolism. *Clock* mutant and *Bmal1* knockout mice develop hyperlipidemia and hepatic steatosis (Shimba et al., 2011; Turek et al., 2005). PER2-deficient mice display altered lipid metabolism (Grimaldi et al., 2010), and ablation of REV-ERBs can lead to hepatic steatosis (Bugge et al., 2012).

Hitherto, circadian research in mammals has largely been focused on dissecting transcription expression profiles of core clock and output genes including genes involved in metabolism and cellular homeostasis. Though these gene expression profiles have hinted that many metabolic pathways and their products are oscillating during the day, direct measurements of metabolites throughout the day are still in their infancy. Ueda and colleagues have quantified the spectra of hundreds of metabolites throughout the day, both in mouse and human plasma samples (Kasukawa et al., 2012; Minami et al., 2009). They successfully established a metabolite

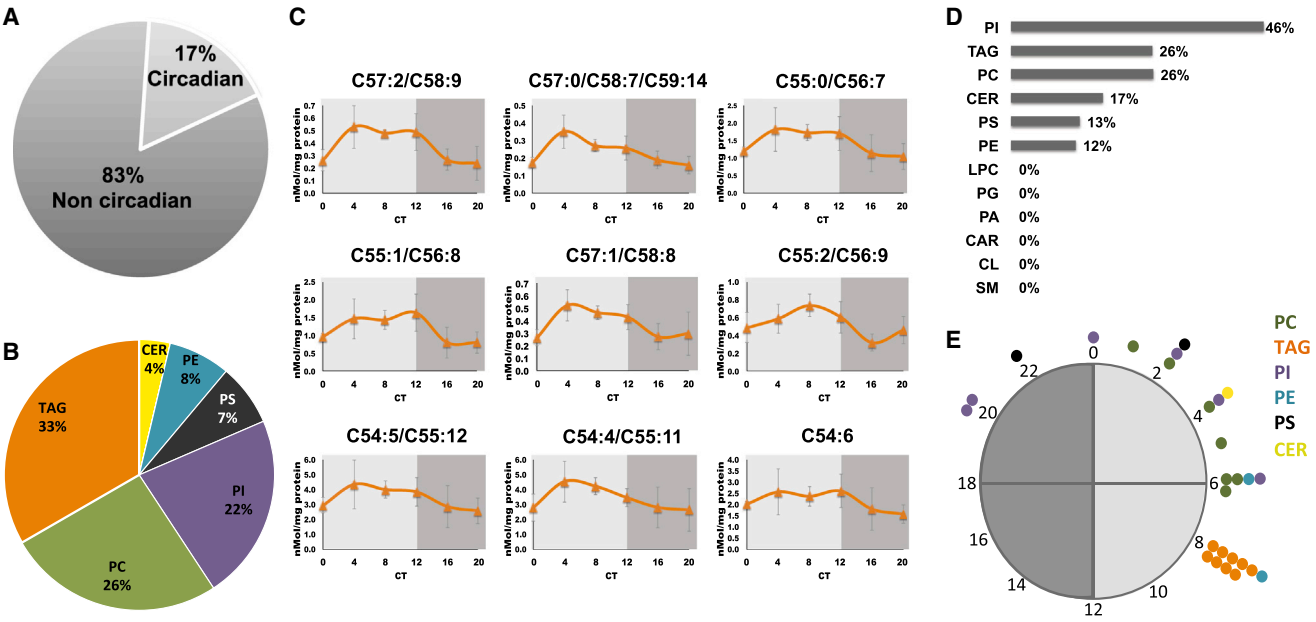

Figure 1. Analysis of Mouse Liver Lipidome

(A) The percentage of lipids found to exhibit a circadian pattern of accumulation in livers of WT mice based on JTK_CYCLE analysis (six time points, n = 4 for each, $p < 0.05$). Out of the 159 measured and identified, 27 lipids exhibited circadian pattern of accumulation.

(B) Oscillating lipids species distributed according to their types.

(C) Accumulation profiles of oscillating TAG presented as mean ± SD.

(D) The percentage of oscillating lipid species within each lipid type.

(E) Daytime distribution of peak phases of oscillating lipids. TAG in orange, PC in green, PI in purple, PS in black, PE in light blue, and CER in yellow. CT0 is when the light was routinely turned on, and CT12 is when the light was turned off in the animal facility. Dark gray represents the subjective night and light gray the subjective day. See also Figure S1.

timetable method to determine internal body time using these profiles. These studies have primarily focused on measuring internal body time by blood metabolomics and to a lesser extent aimed at identifying these metabolites, their metabolic pathways, and circadian clocks dependency. Recent studies performed with human (i.e., blood plasma and saliva) and mouse samples (i.e., liver) identified and measured the levels of about 300 named metabolites throughout the day (Dallmann et al., 2012; Eckel-Mahan et al., 2012). These analyses screened for a variety of primary metabolites (e.g., amino acids, carbohydrates, nucleotides, and lipids). Remarkably, a large fraction of oscillating metabolites identified by these recent reports were lipids.

In this study, we extensively examined the circadian changes in lipid abundance in mouse liver and dissected its clock/feeding dependency. To this aim, we performed a temporal and quantitative lipidomic analysis of livers from wild-type (WT) and clock-disrupted mice (i.e., *Per1/2* null mice) fed either ad libitum or exclusively during the night. We found that a similar fraction of lipids (~17%) oscillated in both mouse strains, most notably triglycerides (TAG), but with completely different phases. Moreover, several master lipid regulators and enzymes involved in TAG metabolism retained their circadian expression in clock-disrupted mice. Feeding time had a prominent effect on the phase and levels of hepatic TAG in both WT and *Per1/2* null mice. Remarkably, upon nighttime-restricted feeding, WT mice exhibited a sharp decrease (~50%) in hepatic TAG levels. Our findings suggest that circadian clocks and feeding time dictate the phase and levels of hepatic TAG accumulation; however, oscillations in TAG can persist in the absence of a functional clock.

RESULTS

Mouse Liver Lipidome

To obtain a temporal depiction of the circadian changes in lipid abundance in mouse liver, we performed a wide lipidomic analysis. WT mice were fed ad libitum and housed under a 12 hr light/dark regimen for several consecutive days. Throughout the last day of the experiment, animals were maintained in constant darkness and sacrificed every 4 hr. Livers were harvested, and lipids were identified and quantified by shotgun lipidomics (Han et al., 2012). Altogether 159 lipids were measured (see Table S1A available online). These include different triglycerides (TAG), phospholipids (i.e., phosphatidylinositol [PI], phosphatidylcholine [PC], lysophosphatidylcholine [LPC], phosphatidylethanolamine [PE], phosphatidylserine [PS], phosphatidic acid [PA], and phosphatidylglycerol [PG]), sphingolipids (i.e., ceramide [CER] and sphingomyelin [SM]), cardiolipin (CL), and acyl carnitine (CAR). A nonparametric algorithm, JTK_CYCLE (Hughes et al., 2010), was used to identify lipids that display circadian rhythmicity. Out of the 159 lipids, 27 (~17%) were identified as oscillating with p value <0.05 (Figures 1A and S1; Table S1B). Among the 27 oscillating lipids, the majority consisted of TAG species (~33%), (Figures 1B and 1C). When dissected

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