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Commentary

Clocks and Cholesterol: Co-agonists in Cardiovascular Disease?

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Circadian (i.e. 24-hour) rhythms regulate much of our physiology, a regulation that is supported by rhythmicity in individual cells of the body. Maintenance of cellular rhythms as well as proper coordination of circadian clocks across different tissues is increasingly recognized to be important for metabolic health and in disease prevention (Roenneberg and Merrow, 2016). Long term follow up of rotating night shift workers strongly supports a link between circadian rhythm disturbance and coronary disease (Vetter et al., 2016). With a growing interest in what "zietgebers"—or time-givers—influence our internal 24-h clock, the study by Akashi et al. in this issue of *EBioMedicine* starts to address the question as to what extent the link between metabolism and circadian rhythmicity is bidirectional in the context of cardiovascular disease (Akashi et al., 2017-in this issue). Using a mouse model of human familial hypercholesterolemia, the authors reveal that ablation of the low density lipoprotein receptor (LDLR) itself induces circadian abnormalities that may further exacerbate the phenotype expected from loss of LDLR alone.

First addressed for its potential role in familial hypersholesterolemia almost 30 years ago (Francke et al., 1984), the LDLR is a cell surface-associated protein that binds to and uptakes a variety of cholesterol-containing molecules. Specifically, its interactions include those with apolipoprotein B100 and apolipoprotein E, both of which contribute to the phospholipid component of low density lipoprotein (LDL) or very low density lipoprotein (VLDL) cholesterol transport particles, respectively. Thus, the LDLR serves as a primary mechanism of cholesterol transport in vivo. Using an *Ldlr* knockout model ($Ldlr^{tm1Her}$) which has an elevated serum cholesterol (200–400 mg/dL under normal diet and >2000 mg/dL under high fat diet [HFD] feeding conditions), Akashi et al. reveal that severe hypercholesterolemia in *Ldlr* −/− mice, induces a significant increase in period length under "free-running" (24-h constant dark/DD) conditions compared to WT controls on HFD. Furthermore, *Ldlr* −/− mice fed a HFD show a bimodal activity pattern of activity in free running conditions.

To determine whether circadian disruption itself exacerbates the effects of the loss of LDLR at the level of hypercholesterolemia-induced arteriosclerosis, Akashi et al. crossed mice mutant for the circadian gene *Period2* ($mPer2^{Brdm1}$) (Zheng et al., 1999) with *Ldlr* −/− mice (*Ldlr* −/− *Per2* m/m). Using the double *Ldlr* −/− *Per2* m/m mice, the authors reveal that HFD produces an accelerated arteriosclerosis phenotype, with double knockout mice having larger aortic lesions slightly earlier under HFD compared to *Ldlr* −/− single mutants under entrained (LD) lighting conditions. Perhaps surprisingly, under free-running conditions elevation in plaque size compared to single *Ldlr* −/− knockout mice occurred somewhat later after the introduction to HFD in *Ldlr* −/− *Per2* m/m mice.

In spite of these interesting observations, some additional questions arise from the study. For example, consistent with previous reports, circadian phase and period length are influenced by diet (Kohsaka et al., 2007; Pendergast et al., 2013). However, here the HFD has the general effect in WT mice of shortening period length rather than lengthening it. Some differences between this study and others include the time of HFD feeding onset and the percent of kilocalories from fat, which could plausibly influence the effects of the severe hypercholesterolemia alone on period length. But perhaps additional factors such as micronutrient contribution could also contribute to this change in free-running period. Furthermore, additional studies using littermate controls for the *Ldlr* −/− *Per2* m/m model could be used to validate changes in HFD-induced aortic plaque size in single vs. double knockout models under entrained LD vs. free-running DD conditions, as well as the circadian behavior phenotype in entrained conditions. While the expected genetic variance between the WT and double knockout strain used in the study lies somewhere between 0.01 and 2%, this still corresponds to between 0.27 and 5.4 million base pairs of the mouse genome. As a growing number of intracellular factors with zeitgeber properties are identified, it is not impossible that even subtle effects of genetic background could contribute to the observed phenotypes.

In summary, the authors reveal a novel and interesting contribution of the LDLR to circadian behavior. Provocatively, these results suggest that the recently recognized contributions of the LDLR in the brain should be studied more directly at the level of signaling within the central pacemaker. Furthermore, *ApoE* −/− mice have recently been reported to also have altered circadian behavior (Zhou et al., 2016) and LDLR is the primary receptor for ApoE in the brain, where it plays a particularly important role in amyloid-beta clearance (Kim et al., 2009). It is interesting to speculate the extent to which the observed phenotype depends on LDLR interaction with ApoE vs. other functions of the LDLR. Interestingly, a HFD induces de novo oscillation of *Ldlr* expression in the liver, mostly likely a necessary adaptation to such nutrient insult (http://circadiomics.igb.uci.edu). With new studies revealing the importance of peripheral signals in regulating circadian behavior and clock function in the CNS (Chavan et al., 2016), the authors may have discovered a unique role for cholesterol in maintaining this important circadian crosstalk between tissues and thereby implicating LDLR as a protective mechanism for the clock under nutrient challenge conditions.

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Disclosures

The authors declare no conflict of interest.

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