OUTLOOK

Cross-regulatory circuits linking inflammation, high-fat diet, and the circadian clock

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Mammalian physiology resonates with the daily changes in the external environment, allowing processes such as rest–activity cycles, metabolism, and body temperature to synchronize with daily changes in the surroundings. Studies have identified the molecular underpinnings of robust oscillations in gene expression occurring over the 24-h day, but how acute or chronic perturbations modulate gene expression rhythms, physiology, and behavior is still relatively unknown. In this issue of *Genes & Development*, Hong and colleagues (pp. 1367–1379) studied how acute and chronic inflammation interacts with the circadian clock. They found that NF-κB signaling can modify chromatin states and modulate expression of genes in the core clock network as well as circadian locomotor behavior. Interestingly, a high-fat diet (HFD) fed to mice also triggers this inflammation pathway, suggesting that cross-regulatory circuits link inflammation, HFD, and the circadian clock.

Mammals evolved under daily changes in the environment, such as light availability, food availability, and ambient temperature. These daily oscillations in environmental conditions resonate with the circadian timing system, which allows physiology to predict and adapt to daily cycles in the surroundings. The central pacemaker, located in the suprachiasmatic nuclei (SCNs) of the hypothalamus, is synchronized to the external light–dark cycles through photic cues from the retina and subsequently synchronizes peripheral clocks to establish phase coherence (Schibler et al. 2015). At the molecular level, there is a genetically encoded molecular clock that ticks in virtually every cell of the body. In a simplified model, this genetic circuit consists of an activator arm (BMAL1–CLOCK), which induces gene expression, and a repressor arm (PERIODs [PERs], CRYPTOCHROMEs [CRYs], and REV-ERBs), which down-regulates transcriptional activity of BMAL1–CLOCK and thereby represses gene expression (Schibler et al. 2015).

These rhythms are self-sustained but are also entrainable by external stimuli such as light, food, or body temperature rhythms. Such stimuli resynchronize the clock typically by an immediate early activation of *Period* gene transcription, which can occur through many different signaling pathways (Schibler et al. 2015). In this issue of *Genes & Development*, Hong et al. (2018) demonstrate that inflammation also plays a role in resynchronizing the circadian clock through the activation of the NF-κB pathway, highlighting exciting new links between the circadian clock, the immune system, and inflammation (Nobis et al. 2018). In particular, the investigators show that lipopolysaccharide (LPS)-induced NF-κB activation in the mouse liver regulates the expression of clock genes specifically involved in the repressive arm of the feedback loop. Specifically, activation of NF-κB modified chromatin states and altered DNA-binding activity of BMAL1–CLOCK at promoters of *Per*s, *Cry*s, which are components of the repressive arm. LPS treatment also activated *p65*, a subunit of NF-κB, to bind to promoters of repressive arm genes. Overall, p65 activation inhibited transcription of clock repressors, while clock activators remained unchanged.

An emerging view is that the expression of clock genes in the negative arm relies on not only binding of core clock transcription factors (BMAL1–CLOCK) to promoters but also other transcription factors that transduce systemic or environmental signals. Indeed, *Per1* and *Per2* gene expression continues to oscillate even in *Clock* or *Bmal1* knockout mice (Schibler et al. 2015). Hong et al. (2018) now show that activating the NF-κB pathway can inhibit gene expression of clock repressors. Additionally, this repressive arm (in particular *Per2*,

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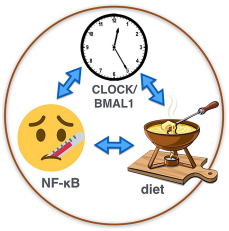

Figure 1. Cross-regulatory interactions linking inflammation, a HFD, and the circadian clock. The new study by Hong et al. (2018) found that acute or chronic activation of NF-κB signaling during infection-related or HFD-induced inflammation interferes with master transcriptional regulators (CLOCK/BMAL1) of the circadian clock.

Cry1, or *Cry2*) has been shown to directly interact with other transcription regulators (Kriebs et al. 2017). Thus, environmental and systemic signals cross-talk with the clock at both the level of transcription regulation and protein interactions.

Interestingly, activation of the NF-κB pathway is also linked to insulin resistance in mice fed with a high-fat diet (HFD). Hong et al. (2018) fed mice a HFD and observed an increase in p65 binding at core clock repressors but not activators, similar to the effect from LPS treatment. HFD has been shown previously to induce insulin resistance in part through activation of NF-κB (Cai et al. 2005). Hong et al. (2018) now show that this pathway links to altered rhythmic gene expression. These data suggest that cross-regulatory circuits link inflammation, a HFD, and the circadian timekeeping system (Fig. 1).

Indeed, a HFD and obesity have been shown to decrease the amplitude of circadian activity and rhythmic gene expression (Kohsaka et al. 2007). Reciprocally, such alterations of circadian rhythms were also observed during chronic inflammation (Guo et al. 2015). More broadly, other conditions that alter circadian rhythms, such as aging or sleep deprivation, are also associated with activation of the NF-κB pathway (Osorio et al. 2016), suggesting a general link between inflammation and disruption of circadian timekeeping.

This hypothesis is supported by other studies showing that, reciprocally, chronic disruption of circadian rhythms is associated with altered inflammatory response, obesity, insulin resistance, carcinogenesis, and aging. Moreover, most of these observations also hold true in humans (Wright et al. 2015; Kim et al. 2018), highlighting the relevance of this discovery to health and disease.

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