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REVIEW

Circadian Clocks and Inflammation: Reciprocal Regulation and Shared Mediators

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Abstract The immune system is deeply interconnected with the endogenous 24-h oscillators of the circadian system. Indeed, the connection between these two physiological systems occurs at multiple levels and in both directions. On one hand, various aspects of the immune system show daily rhythms, which appear to be essential for healthy immune maintenance and proper immune response. On the other hand, immune responses cause changes in circadian rhythms, disrupting their delicate balance and manifesting in disease. Indeed, immune challenges cause various time-, gene-, and tissue-specific effects on circadian-regulated factors. This article reviews the possible mediators of the cross talk between the circadian clock and the immune system, in particular the inflammatory pathways. The rhythmic expression of cytokines and their receptors, as well as other rhythmically regulated humoral factors such as glucocorticoids, melatonin, leptin, or prostaglandins, could gate the effects of the immune response on the circadian system. In addition, systemic cues such as body temperature and neuronal connections between the brain and peripheral tissues may underlie the immune–circadian communication.

Keywords Circadian rhythm · Clock gene · Cytokine · Fever · Innate immunity · Inflammation

Abbreviations

AA-NAT	Arylalkylamine-*N*-acetyltransferase
BMAL1	Brain and muscle ARNT-like protein 1
CLOCK	Circadian locomotor output cycles kaput
CRY	Cryptochrome
DBP	D-box binding protein
GC	Glucocorticoid
HPA	Hypothalamic–pituitary–adrenal
HSP	Heat-shock proteins
HSF	Heat-shock factor
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
NFκB	Nuclear factor of kappa light polypeptide gene enhancer in B cells
NK cell	Natural killer cell
PER	Period
PGE_2	Prostaglandin E_2
PNS	Parasympathetic nervous system
RA	Rheumatoid arthritis
ROR	Retinoic acid receptor-related orphan receptor
SCN	Suprachiasmatic nucleus
SNS	Sympathetic nervous system
TNF-α	Tumor necrosis factor α

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Circadian Clocks

Circadian rhythms organize physiological systems in time and align them to the 24-h environmental cycles (an explanation of chronobiology-related terms can be found in Table 1). Environmental cues including the light–dark, feeding, and temperature cycles adjust the timing of these endogenous rhythms. The circadian system confers adaptability and predictability in biology, ultimately maintaining homeostasis in health and well-being (Hastings et al. 2007; Nakagawa and Okumura 2010).

Table 1 Definition of chronobiology concepts used in the text

Term	Definition	Example
Circadian rhythm	Rhythm with a period of about 24 h, which persist in the absence of external timing cues. To observe circadian rhythms, one must use experimental conditions without time cues. If an experiment is done under conditions that provide timing cues (e.g., a light/dark cycle), one cannot distinguish between the effects of the external/environmental timing signal or the endogenous circadian system, and hence, one should talk of a daily rhythm rather than an internal circadian rhythm	Melatonin secretion and core body temperature both present circadian rhythms in animals, as these rhythms persist in constant conditions, with a period close to 24 h
Entrainment	Alignment of an endogenous rhythm to an external timing cue	Even though the endogenous period of the internal clocks is slightly different from 24 h, the environmental light/dark cycle can *entrain* them to a 24-h-long day
Free-running period	Period (duration of a full cycle) of the endogenous circadian clock. The free-running period can be observed in the absence of environmental timing cues, i.e., under constant laboratory conditions	The free-running period of human subjects is on average slightly above 24 h
Subjective day/night	Under constant laboratory conditions, subjective day and night correspond to the parts of the cycles equivalent to day and night, respectively	The laboratory mouse is a nocturnal animal, active in the night under a light/dark cycle; thus, under constant darkness conditions, the part of the cycle when the mouse is active will be called the subjective night
SCN	The site of the central circadian clock in mammals located in the anterior hypothalamus	The SCN aligns to the environmental light/dark cycle and in turn controls physiological rhythms, e.g., the rhythmic release of hormones into the blood stream
Phase-shift	Change in the timing of a rhythm, generally following an external timing cue. When the resulting phase is later than the original phase, one will talk of a phase delay; when the resulting phase is earlier than the original phase, one will talk of a phase advance	A light stimulation in the early night (e.g., 8 p.m) moves the onset of the locomotor activity of a mouse from 6 to 7 p.m. (phase delay)

Circadian rhythms are generated by clocks present in most tissues and cell types (Dibner et al. 2010). At the molecular level, these circadian clocks are composed of a number of clock genes including *circadian locomotor output cycles kaput* (*Clock*); *brain and muscle ARNT-like protein 1* (*Bmal1*); *cryptochrome* (*Cry*)*1* and *2*; and *period* (*Per*)*1*, *2*, and *3*, which are involved in an autoregulatory transcriptional–translational feedback loop (Duguay and Cermakian 2009). Additional feedback loops add further levels of complexity, robustness, and a means of regulation to the basic feedback loop. These accessory feedback loops involve other transcription factors such as the orphan nuclear receptors REV-ERB α and β and retinoic acid receptor-related orphan receptor (ROR) α, β, and γ (Duguay and Cermakian 2009). The central pacemaker resides in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus and coordinates rhythms in peripheral clocks through a variety of neuronal, humoral, and behavioral cues (Fig. 1) (Dibner et al. 2010). Peripheral clocks are autonomous but without the SCN, rhythms in individual cells or tissues eventually desynchronize (Nagoshi et al. 2004; Yamazaki et al. 2000; Yoo et al. 2004). Although many cues have been proposed to contribute to the communication between central and peripheral clocks, each tissue seems to respond to a unique set of cues, which are yet to be elucidated in most cases (Dibner et al. 2010).

Many of the cues involved in the communication between circadian clocks are common with immune pathways (e.g., glucocorticoids (GCs) and cytokines). This suggests that immune responses may interfere with circadian clock regulation. Indeed, following an immune challenge, there are notable perturbations in circadian homeostasis. At the same time, rhythmicity in immune mediators is prone to impact on immune responses. Exactly how immune responses and clock mechanisms influence each other is a keen topic of investigation, and the progress toward elucidating these mechanisms will be discussed, with focus on mammals.

Circadian Rhythms in the Immune System

Many immune cell types show daily variations in cell counts in the blood of humans and rodents (Abo et al. 1981; Born et al. 1997; Haus and Smolensky 1999; Lange et al. 2010). This includes T and B lymphocytes, monocytes, macrophages, natural killer (NK) cells, neutrophils, and eosinophils. In addition, the production of various

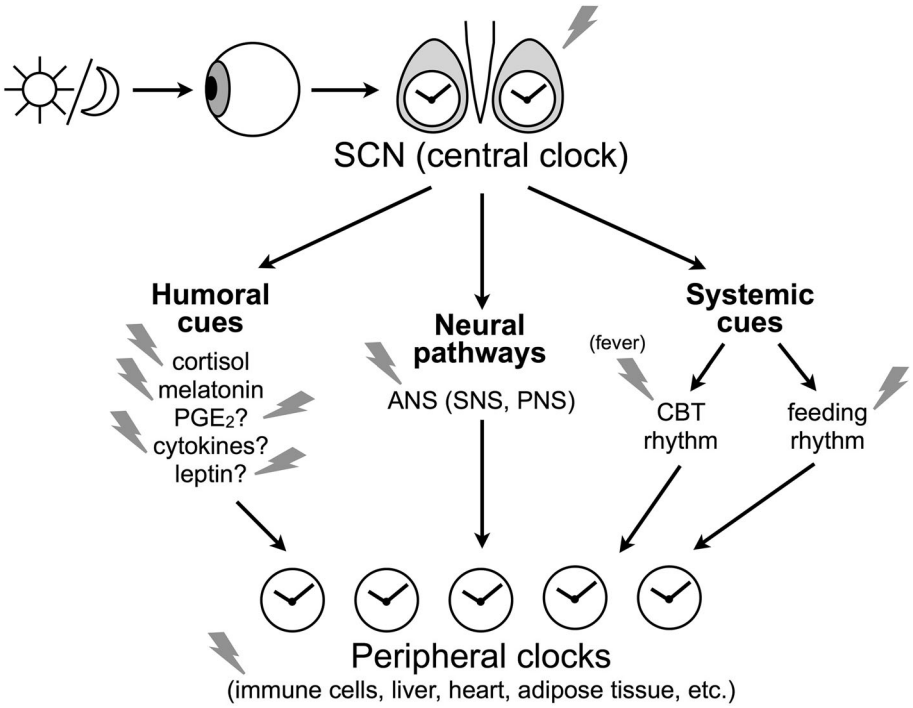

Fig. 1 Organization of the circadian system and mediators affected by inflammation. In mammals, the central circadian clock is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The SCN clock can be entrained by day–night cycles via input from the retina. Many other brain regions and most peripheral tissues have intrinsic circadian clocks. Although these peripheral clocks can drive circadian rhythms on their own, within the organism, their rhythms are coordinated by the SCN central clock. This can occur via different types of rhythmic cues, which can all be controlled by the central clock: humoral cues (such as hormones or cytokines), neural pathways (via the autonomic nervous system: ANS), and systemic cues (such as temperature and feeding rhythms). *Gray lightning symbols* indicate clocks and mediators known to be affected in conditions of immune challenge or inflammation. This scheme is over-simplified in that mediators can also act for the communication between peripheral clocks, or from peripheral clocks back to the central clock or its resetting by light signals. *PGE_2* prostaglandin E_2, *SNS* sympathetic nervous system, *PNS* parasympathetic nervous system, *CBT* core body temperature

cytokines including interleukin (IL)-6, IL-1β, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α is rhythmic in macrophages, T cells, adipose tissue, and spleen (Ando et al. 2011; Bollinger et al. 2011; Keller et al. 2009).

Many of the studies investigating these rhythms were performed under regular light–dark and sleep–wake conditions, making it impossible to tell whether the rhythms are due to the endogenous circadian system or to the cyclic environmental cues. In some studies (Ackermann et al. 2012; Benedict et al. 2007; Born et al. 1997), samples collected from human subjects during a sleep–wake cycle and during a day of sleep deprivation were compared. The data showed that immune variables were differentially regulated by the sleep–wake cycle: some rhythms were very similar in both experimental conditions, indicating little regulation by sleep or wake, and involvement of the circadian system; others were in good part or totally dependent on the sleep–wake cycle. The reader is referred to the literature cited above for more details.

Rhythmic hormones such as cortisol and noradrenaline seem to have a role to play in shaping the rhythm of abundance of immune cell populations. In mice, the daily variations of lymphocyte counts are lost following adrenalectomy (Kawate et al. 1981). In humans, blood counts of $CD4^+$ and $CD8^+$ naive, central memory, and effector memory T lymphocytes drop after cortisol injection (Dimitrov et al. 2009), and conversely, the opposite effect is observed when cortisol levels are pharmacologically reduced or an antagonist of the GC receptor is used (Besedovsky et al. 2014). These data suggest that the decreased numbers of these cells in the morning is due to the high morning cortisol levels. These effects of cortisol on T-cell population rhythms are inversely correlated with the expression of chemokine receptor CXCR4 in these cells, mediating T-cell redistribution (bone marrow homing) in response to cortisol (Besedovsky et al. 2014; Dimitrov et al. 2009). In contrast to the T-cell subsets described above, $CD8^+$ effector T-cell count rise upon noradrenaline injection, which links the normal rise of this subclass of cells in the morning to the high morning noradrenaline levels (Dimitrov et al. 2009). Noradrenaline appears to stimulate demargination from the vascular endothelium via

high chemokine receptor CX3CR1 expression in these cells (Dimitrov et al. 2009). Accordingly, studies in mice showed a daily rhythm of leukocyte recruitment to bone marrow and skeletal muscle (Scheiermann et al. 2012). This rhythm is controlled by the central clock, via the sympathetic nervous system (SNS), which induces a daily oscillation of adhesion molecules and chemokines. In contrast, in rats subjected to constant light conditions (conditions abolishing the rhythms of locomotor activity and catecholamines), the 24-h variations of lymphocyte counts were still observed (Depres-Brummer et al. 1997). The apparent discrepancy could be due to species differences or to the different conditions and measures among the experiments.

The rhythms described above for the levels of immunocompetent cells and cytokines suggest that immune functions may also present a variation across the day and possibly be under the endogenous control of the circadian system itself. Indeed, evidence for the rhythmic regulation of immune functions has begun to be uncovered with the use of mice with mutations in clock genes. For example, mice mutant for the gene *Clock* lose rhythmicity in many immunoregulatory genes (Oishi et al. 1998). *Bmal1*-deficient mice, which lack a functional clock, have lower B-cell counts compared to wild-type (WT) mice, but normal levels of B-cell precursors in the bone marrow, suggesting a defect in B-cell development (Sun et al. 2006).

Recent reports have shown that the function of T lymphocytes is controlled by the circadian system (Bollinger et al. 2011; Esquifino et al. 2004; Fortier et al. 2011; Kirsch et al. 2012). In vitro stimulation with PMA/ionomycin of $CD4^+$ T cells harvested at different times of day showed daily variation in cytokine production (Bollinger et al. 2011) and proliferation (Fortier et al. 2011). While PMA/ionomycin activate cell proliferation by acting on intracellular signalling pathways (intracellular calcium, protein kinase C), other experiments have looked more upstream in T-cell activation pathways, i.e., at the level of the T-cell receptor and antigen presentation to the T cells. When T cells were stimulated through their T-cell receptor using the mitogen concanavalin A (Esquifino et al. 2004) or anti-CD3 T-cell receptor chain antibody (Fortier et al. 2011), rhythms of proliferation were also found. Moreover, immunization of mice using dendritic cells carrying an antigen led to a much stronger antigen-specific activation when injections were administered in the day than in the night (Fortier et al. 2011). Finally, recent data have indicated that the circadian clock in T lymphocyte is key to the development of the T_H17 subtype (Yu et al. 2013). Altogether, these reports show that the response of T lymphocytes to antigen presentation, the subsequent cell expansion and acquisition of effector function, and the differentiation into different T-cell subtypes are all under daily regulation.

While these studies on rhythm in the response to antigen presentation are crucial and may lead to better control of infectious disease as well as more efficient vaccination schemes, the focus of the remainder of the present review will be on the innate immune system, the inflammatory response, and their cross talk with the circadian system. Likewise, over the past decade, many reports have shown an intricate relationship between the circadian system and cells of the innate immune system such as NK cells and macrophages.

The secretion of cytokines (IFN-γ, TNF-α) and cytolytic factors (granzyme B, perforin) by NK cells follows a rhythm in rat and mouse spleens (Arjona and Sarkar 2005; Logan and Sarkar 2012). NK cells express clock genes, and the knockdown of their expression dampens the rhythm of cytolytic factors (Arjona and Sarkar 2008). Similarly, subjecting rats to a repeated jet lag protocol disrupts both clock gene expression and rhythms of cytokine and cytolytic factor secretion by NK cells and reduces their cytotoxicity (Logan and Sarkar 2012). Since the same experimental protocol promoted tumor growth, and given the role of NK cells in tumor surveillance, the authors suggested that disruption of the clock in NK cells may promote tumor development (Logan et al. 2012).

Many articles have delineated a role for the clock in regulating monocyte and macrophage functions. Phagocytic activity of macrophages was shown to vary over the day–night cycle in mice (Hayashi et al. 2007). Also, secretion of cytokines following lipopolysaccharide (LPS) treatment of macrophages in vitro or LPS injection in mice follows a circadian rhythm, with higher secretion of TNF-α, IL-6, and other cytokines in the early subjective night than in the early subjective day (Gibbs et al. 2012; Keller et al. 2009). Notably, this diurnal secretion was shown to be dependent on a functional circadian clock in macrophages (Gibbs et al. 2012). A rhythm in abundance of the REV-ERBα transcription factor, itself controlled by the circadian clock in macrophages, was demonstrated to regulate in a circadian fashion a broad array of genes important for cytokine synthesis and secretion (Gibbs et al. 2012; Keller et al. 2009; Sato et al. 2014). Interestingly, subjecting mice to a chronic jet lag protocol increases the cytokine response to LPS in vivo and in cultured peritoneal macrophages (Castanon-Cervantes et al. 2010).

Recent studies have highlighted the importance of the clock in monocytes and macrophages for the response to pathogens. *Bmal1* gene expression in $Lys6C^{hi}$ inflammatory monocytes was found to be important for their oscillation in numbers, to modulate the recruitment of these cells to the site of *Listeria monocytogenes* infection, and to control the pathogenicity of these bacteria

(Nguyen et al. 2013). Similarly, a time dependence of cytokine response of macrophages to *Salmonella typhimurium* infection was found (Bellet et al. 2013). Moreover, reduced cytokine secretion from macrophages of *Clock* gene mutant mice was observed after LPS treatment of the cells in vitro or after *S. typhimurium* infection of the mice (Bellet et al. 2013).

Daytime Dependence of the Response to Endotoxin Administration

LPS is a molecule of the Gram-negative bacteria's coat that can bind Toll-like receptor 4 (TLR4) on the surface of different cell types (Lu et al. 2008). Binding of LPS to TLR4 leads to the oligomerization of this receptor, the activation of different signalling pathways, and then the upregulation of a large battery of pro-inflammatory cytokines and chemokines (such as IL-1, IL-6, TNF-α, and CCL2) (Rossol et al. 2011). This action of LPS ultimately provokes a strong febrile and systemic inflammatory response (Raetz and Whitfield 2002).

Interestingly, the risk of lethality induced by LPS depends on the time of administration (Halberg et al. 1960; Marpegan et al. 2009). Rodents treated with LPS late in the rest phase have a much higher risk of mortality than those treated during the active phase, which is correlated to the magnitude of pro-inflammatory cytokines induction (Halberg et al. 1960; Kitoh et al. 2005; Marpegan et al. 2009). In mice, time-of-day dependence was observed for lethality following TNF-α injections (Hrushesky et al. 1994) and upon cecal ligation and puncture, an experimental model of sepsis (Silver et al. 2012). A modulation of inflammatory responses across the day also takes place in humans (Petrovsky et al. 1998; Pollmacher et al. 1996). For example, people suffering from sepsis are more likely to die in the early morning (Hrushesky et al. 1994; Sam et al. 2004).

The daily pattern of LPS-induced mortality in rodents is not observed under constant darkness conditions (Marpegan et al. 2009), perhaps due to a loss of the rhythmic upregulation of pro-inflammatory cytokines. One report in humans showed that TNF-α and IL-12 were not rhythmic in subjects kept in constant conditions including sleep deprivation, whereas IL-6 was the only cytokine that maintained its rhythmicity (Lange et al. 2010). These studies suggest the rhythmic responses to LPS are driven by environmental factors. Consistent with an impact of environmental light cues, animals housed in constant light (Carlson and Chiu 2008) or on repeated jet lag conditions (Castanon-Cervantes et al. 2010) are more prone to LPS-induced mortality than animals housed in a regular light–dark cycle. However, in sharp contrast to the studies mentioned above that seem to exclude a direct implication of the circadian clock, *Per2* mutant mice are resistant to endotoxic shock and produce lower levels of pro-inflammatory cytokines (Liu et al. 2006). Further, the time-dependent risk of mortality induced by endotoxin is lost in these mutants. This implies a role for the circadian clock in the severity of an endotoxic shock in mice.

Effects of Endotoxin Administration on Circadian Rhythmicity

As reported in the previous section, there is a clear daily regulation of the inflammatory response to endotoxin administration. Recent research has shown that the converse is also true: circadian rhythms are altered in experimental models of inflammation. For example, clock-regulated behaviors such as sleep–wake cycle, movement, and food intake are all altered by systemic inflammation (Dantzer 2001). In addition, LPS, IL-1, or TNF-α can all phase-shift activity rhythms, but only when animals are treated early in the active phase (Leone et al. 2012; Marpegan et al. 2005).

Studies have shown that inflammation can impact on SCN function. At the molecular level, LPS treatment suppresses the expression of *Per2* and *D-box binding protein* (*Dbp*) in the SCN (Okada et al. 2008). Acute LPS administration induces Fos protein expression in the SCN. While light induces Fos throughout the whole SCN and in particular in the ventro-lateral part of the nucleus, LPS induces Fos only in the dorso-medial part of the SCN, which is reminiscent of the effect of other non-photic treatments (Marpegan et al. 2005). Of note, the effects of inflammation on the circadian system are not only acute. Indeed, LPS challenge in mice can induce long-term (3–4 months) changes on light-induced behavioral phase-shifts and PER2 protein expression in the SCN (O'Callaghan et al. 2012). In another study, LPS was administered chronically (for 2 months), which led to an attenuation of the response of the SCN to light signals (Palomba and Bentivoglio 2008). Notably, all the studies looking at central effects of inflammation have used peripheral LPS treatment. Understanding how the signals reach the SCN will require additional research.

Inflammation also affects clock gene expression in the periphery. LPS administration suppresses the expression of *Per1* and *Per2* in the liver (Okada et al. 2008). LPS-dependent suppression of clock genes in the liver depends on the time of injection (Yamamura et al. 2010). Similarly, in another model of inflammation, the intramuscular injection of turpentine oil in rats, tissue-specific and time-dependent effects on clock gene expression were observed (Westfall et al. 2013). In human subjects, LPS injection suppresses clock gene

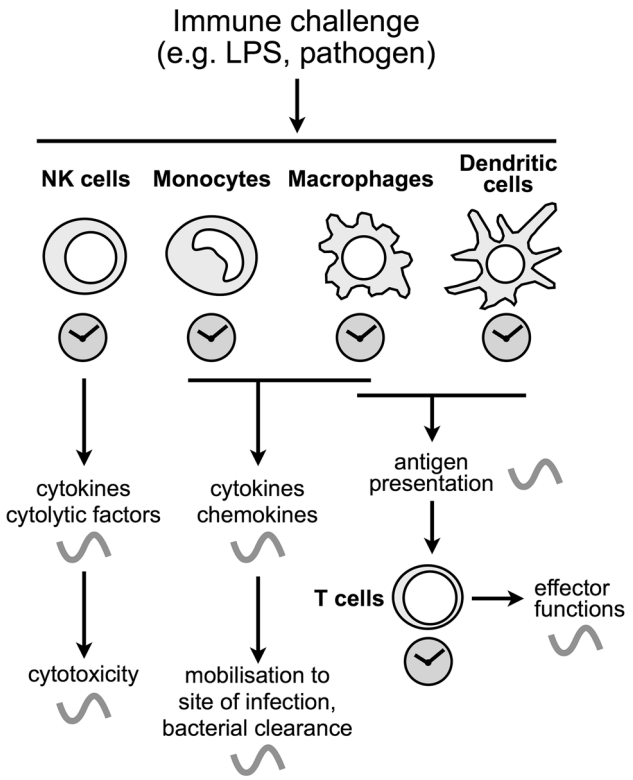

Fig. 2 Circadian rhythms in the immune system. An immune challenge (e.g., infection or treatment with bacterial wall endotoxin lipopolysaccharide: LPS) involves the function of various cell types of the innate immune system (e.g., NK cells, monocytes, macrophages, and dendritic cells) and the adaptive immune system (B and T lymphocytes; only the latter shown here). Components of the molecular circadian clock were found in many of these cell types (symbolized by *gray clock symbols*). Accordingly, studies have illustrated circadian rhythms in the function of these immunocompetent cells (symbolized by *gray rhythm curve symbols*), in particular rhythms in the secretion by these cells of cytokines, chemokines, and cytolytic factors, in the ability to migrate to the site of infection and kill pathogens, and in the effectiveness of the response to antigen presentation and acquisition of effector function by T cells

mRNA levels (Haimovich et al. 2010), while in horses, LPS injection was shown to induce the expression of *Per2* and *Bmal1* (Murphy et al. 2007).

In summary, studies have shown a diurnal regulation of the inflammatory response on one hand and strong effects of inflammation on circadian clocks on the other hand. We propose that immune responses and circadian mechanisms overlap. In particular, the inflammatory response impinges onto pathways and mediators important for the regulation of peripheral clocks (Fig. 1), while circadian clocks and their rhythmic outputs modulate the immune response (Fig. 2). The next sections will describe possible mediators for the cross talk between the innate immune system and circadian clocks. In each case, we will go over the circadian regulation of the mediators and then over their feedback on circadian rhythms.

Cytokines as Mediators of the Immune–Circadian Interaction

Cytokines are the main communication factors of the immune system. Many pro-inflammatory cytokines show a diurnal variation, with peak levels generally observed during the rest phase both in nocturnal rodents (light phase) (Haus and Smolensky 1999) and humans (dark phase) (Guan et al. 2005; Pollmacher et al. 1996). Expression of cytokine receptors can also oscillate. For example, the IFN-γ and IL-1 receptors are rhythmically expressed in the rodent SCN (Beynon and Coogan 2010; Lundkvist et al. 1998; Sadki et al. 2007). Moreover, as mentioned before, the magnitude of the cytokine response to LPS treatment varies over time. Here, for different cytokines, we will go over their daily regulation as well as their known effects on the circadian system.

Tumor Necrosis Factor α

There is a clear bidirectional regulation between *Cry* clock genes and TNF-α. CRY1 can directly reduce the transactivation of the *TNF-α* gene (Hashiramoto et al. 2010). Accordingly, in *Cry1*/*Cry2* knockout (KO) mice, TNF-α levels are higher and the arthritic score is worsened in an induced arthritic experimental model (Hashiramoto et al. 2010). In addition, *Cry* KO mice are sensitized to TNF-α-induced apoptosis through the inhibition of nuclear factor of kappa light polypeptide gene enhancer in B-cell (NFκB) signalling (Lee and Sancar 2011).

Treatment of fibroblasts with TNF-α was shown to inhibit the CLOCK/BMAL1-mediated transactivation of clock genes with E-boxes (Cavadini et al. 2007; Petrzilka et al. 2009). Actually, subcutaneous infusion of TNF-α downregulates a battery of clock genes in the mouse liver (Cavadini et al. 2007). As TNF-α is rhythmically released from NK cells under constant conditions (Arjona and Sarkar 2006), TNF-α might be implicated in the time-dependent regulation of clock gene expression. A modulation of clock gene expression by TNF-α is also observed in human primary rheumatoid synovial cells, but in this case, the effect was proposed to be mediated by PAR bZip transcription factors such as DBP and E4BP4 (Yoshida et al. 2013). This observation in cultured rheumatoid synovial cells may explain the altered clock gene expression in a mouse model of arthritis (Hashiramoto et al. 2010).

TNF-α can also act on the SCN. When injected intracerebroventrically in mice, TNF-α causes a phase delay in locomotor activity rhythms (Leone et al. 2012), while a cocktail composed of TNF-α and IFN-γ activates the expression of the Fos protein in the SCN, differentially according to time of day (Sadki et al. 2007). In vitro, TNF-α

addition to slice preparations leads to an increase in spontaneous firing rate of SCN neurons (Nygard et al. 2009). Moreover, TNF-α phase-shifts PER2 expression rhythms in cultured SCN astrocytes (Duhart et al. 2013). Furthermore, an involvement of TNF-α in the response of the SCN to LPS was suggested: blocking TNF action using a soluble form of its receptor attenuates the response to LPS in the SCN (Leone et al. 2012). Importantly, the TNF-α receptor is expressed in the mouse SCN, with a daily rhythm (Sadki et al. 2007), suggesting a physiological role for this cytokine in regulating the central clock.

Interferon

Depending on the time of IFN-α treatment in mice, different effects are noted on the SCN central clock. Subcutaneous injection at the beginning of the active phase, but not at the beginning of the rest phase, blunts *Per* and *Bmal1* rhythms in the SCN (Ohdo et al. 2001). These changes are accompanied by suppressed locomotor activity and body temperature rhythms. Similarly, continuous administration of IFN-α to mice using a mini-pump reduces CLOCK and BMAL1 protein levels in the SCN and dampens the expression of genes controlled by these transcription factors (e.g., *Per* genes, *Cry1*, *vasopressin*) (Koyanagi and Ohdo 2002). This treatment also reduces the amplitude of the locomotor activity rhythms. As for IFN-γ, its application on SCN slices decreases the spontaneous excitatory postsynaptic activity and chronic treatment blunts *Per1* expression rhythms in SCN culture (Kwak et al. 2008). In addition, IFN-γ phase advances the clock in hamsters upon intracerebroventricular injection in the middle of the day, but not when injected in the middle of the night (Boggio et al. 2003).

IFNs also modify clock gene expression in the periphery. The downregulation of *Clock* and *Bmal1* genes by IFN-α in hepatocytes was attributed to a signal transducer and activator of transcription 1-dependent mechanism (Koyanagi and Ohdo 2002). IFN-α was also found to downregulate *Per1* and *Dbp* genes in the liver (Koyanagi and Ohdo 2002). Interestingly, the rhythmic expression of IFN-α/β receptors in the mouse liver gates the antiviral effect of IFN-α (Koyanagi et al. 2006). Of note though, acute treatment of fibroblasts in culture with either IFN-α or IFN-γ has no effect on the levels of *Per* mRNAs (Cavadini et al. 2007).

IL-6

Evidence is scarcer for a role of IL-6 as a circadian–immune mediator. As mentioned above, IL-6 secretion by macrophages in response to an endotoxin challenge varies with the time of treatment. A similar time dependence was observed when treating whole blood with LPS, and as with macrophages, environmental circadian disruption also increased the IL-6 response in this model (Adams et al. 2013). On the other hand, IL-6 itself might affect on circadian clocks. Indeed, IL-6 was shown to induce the expression of the *Per1* promoter in cultured cells (Motzkus et al. 2002). Following an inflammatory challenge, the suppression of clock gene expression in the liver and heart parallels the induction of IL-6. For example, following turpentine oil injection, maximal IL-6 induction and *Per* mRNA suppression both occur after 8–10 h (Westfall et al. 2013). In this system, IL-6 is the only pro-inflammatory cytokine outside of the site of localized inflammation, suggesting that it may have a role in the effects of turpentine injection on clock genes. However, data argue against a direct causative role of IL-6 in clock gene regulation at least in the liver: it was shown that turpentine-induced suppression of clock genes occurs despite inhibition of IL-6 induction by the IL-1 receptor antagonist and further, in culture, IL-6 has no effect on clock genes in liver-derived cells (Westfall et al. 2013) or in fibroblasts (Cavadini et al. 2007).

Nuclear Factor of κ Light Polypeptide Gene Enhancer in B Cells

NFκB is one of the major transcription factors activated downstream of cytokine and LPS receptors and it is critical for the mounting of an immune response (Vallabhapurapu and Karin 2009). Several recent studies have highlighted various connections between NFκB and molecular clock mechanisms: (1) CLOCK protein binds to NFκB and regulates its transcriptional activity (Spengler et al. 2012). Accordingly, NFκB activation is reduced in *Clock* KO mice (Spengler et al. 2012). (2) In *Cry1*/*Cry2* double KO cells (which are clock-deficient), NFκB activation following TNF-α treatment was weaker than in WT cells (Lee and Sancar 2011). In this case, instead of a direct action of CLOCK on NFκB, the circadian control of NFκB activity is mediated by a circadian regulation of glycogen synthase kinase 3β activity. (3) The effect of *Cry1*/*Cry2* double KO seems to be different in mice than in cells: in these KO mice, a higher cytokine secretion was observed following LPS challenge, and this increased cytokine response can be prevented by blocking the NFκB pathway (Narasimamurthy et al. 2012). In this case, CRY action was not via repression of CLOCK/BMAL1 but through a regulation of adenylyl cyclase activity and protein kinase A-mediated phosphorylation of the p65 subunit of NFκB. (4) Another clock-related transcription factor, RORα, can control cytokine secretion by suppressing the nuclear entry of NFκB and positively regulating the expression of the inhibitor of NFκB, IκBα (Delerive et al. 2001). (5) SIRT1,

a histone deacetylase whose activity varies with a circadian rhythm and that is known to regulate CLOCK/BMAL1 activity, was also demonstrated to impact on NFκB levels (Hwang et al. 2014). (6) Another mechanism seems to involve ubiquitin specific peptidase 2 (USP2) in TNF-α-induced NFκB signalling (Metzig et al. 2011). USP2 is a deubiquitinating enzyme whose mRNA levels oscillate along the day in various organs (Storch et al. 2002; Yan et al. 2008) and has been shown to regulate the clock proteins PER1, CRY1, and BMAL1 (Scoma et al. 2011; Tong et al. 2012; Yang et al. 2012). Thus, a surprisingly wide panel of regulatory mechanisms was found for a circadian regulation of NFκB activity, implicating various clock proteins and clock-controlled enzymes.

The reverse, a regulation of circadian rhythms by NFκB, also exists. At the molecular level, NFκB represses CLOCK/BMAL1-dependent genes (Bellet et al. 2012). For example, *DBP* mRNA is increased in cells KO for the NFκB subunit relB. In the SCN, NFκB is expressed in astrocytes and might mediate the effects of cytokines on central clock rhythms (Leone et al. 2006). For example, inhibition of NFκB activation with sulfasalazine blocks the phase-shifting of the clock that occurs in response to LPS (Marpegan et al. 2005). Finally, mice housed in constant darkness for 4 weeks exhibit depression-like behavior and elevated plasma IL-6. In the same model, clock gene expression is altered in the hippocampus. Interestingly, pharmacological inhibition of NFκB blunts the depression-like behavior, the elevation in IL-6, and the altered clock gene expression (Monje et al. 2011).

Other Possible Humoral Mediators of the Immune–Circadian Interaction

In addition to cytokines, the inflammatory response involves many other circulating molecules, which might act as cues to impact central and/or peripheral clock function.

Leptin

The white adipose tissue releases many molecules into the circulation upon LPS treatment (Fresno et al. 2011). This includes the energy-regulating adipokine leptin. Interestingly, leptin has immunomodulatory effects (Faggioni et al. 2001) and acts as a pro-inflammatory agent (Lago et al. 2007). Like most pro-inflammatory mediators, leptin rises in response to inflammatory signals (Aguilar-Valles et al. 2011; Sarraf et al. 1997) and is critical to the LPS-induced fever response (Harden et al. 2006; Luheshi et al. 1999; Sachot et al. 2004).

Some studies have shown a diurnal rhythm of leptin plasma levels, with a peak in the night in both humans and nocturnal rodents (Kalsbeek et al. 2001). Leptin treatment can strengthen the response of the SCN clock to light in mice (Mendoza et al. 2011). Applied in vitro, leptin phase advances the SCN clock (Prosser and Bergeron 2003) and it modulates the electrical properties of SCN neurons (Inyushkin et al. 2009). Mice lacking a functional leptin gene (*ob*/*ob* mice) have disrupted clock gene expression in both adipose tissue and liver (Ando et al. 2011), and rats with disrupted leptin signalling show tissue-specific alterations of clock gene expression (Motosugi et al. 2011). Even humans fed a high-fat diet have suppressed clock gene rhythms in adipose tissue, which parallels the disrupted leptin rhythms (Tahira et al. 2011). Similarly, in mice, a high-fat diet dampens the rhythmicity of clock gene expression in the adipose tissue, liver, and brainstem (Kaneko et al. 2009; Kohsaka et al. 2007). Although these studies do not show that the inflammatory role of leptin is involved in circadian rhythm regulation, it highlights possible interweaving between circadian rhythms, metabolism, and immune pathways.

Prostaglandin E_2

Prostaglandin E_2 (PGE_2) can be produced in the brain and in the periphery. PGE_2 is critical for the induction of fever in the thermoregulatory centers of the brain (Engblom et al. 2002; Milton and Wendlandt 1970). PGE_2 is also upregulated in the periphery in response to LPS. Kupffer cells in the liver serve as a major source of this peripheral PGE_2 induction (Li et al. 2006). This peripheral PGE_2 induction is thought to contribute to the early cytokine-independent phase of LPS fever (Steiner et al. 2006).

The peripheral induction of PGE_2 may influence peripheral clock gene expression. PGE_2 treatment of mouse fibroblasts in vitro can induce rhythms of clock gene expression (Tsuchiya et al. 2005). *In vivo*, PGE_2 injection can phase-shift clock gene expression rhythms in mouse liver, kidney, and heart, with no effects on central clock-controlled rhythms (Tsuchiya et al. 2005).

Glucocorticoids

Glucocorticoids (GCs) are steroid hormones synthesized in the adrenal gland cortex. The SCN clock is essential, via humoral (hypothalamic–pituitary–adrenal (HPA) axis) and neuronal pathways, for the very robust rhythmicity of GC synthesis and secretion under constant environmental conditions (Son et al. 2011). The local adrenal clock is also critical for the high-amplitude oscillations of this hormone (Oster et al. 2006; Son et al. 2008). GC levels in the circulation are highest in the early active phase (early day in

humans, early night in nocturnal rodents) (Son et al. 2011). In humans, the phase of this rhythm opposes the pro-inflammatory rhythm, which has a peak at night. This is consistent with a well-known anti-inflammatory nature of GCs (Webster et al. 2002). Indeed, numerous studies have shown a role of GCs in regulating various cell types and tissues of the immune system (the reader is referred to Webster et al. 2002, for a review). High levels of GC in the circulation would mainly lead to suppressed immune responses and higher susceptibility to infection. On the contrary, suppression of GC levels would generally lead to exacerbated inflammatory responses (Webster et al. 2002). Consequently, the maintenance of coordinated GC rhythms is essential for health, and many inflammatory diseases are aggravated by abnormal GC rhythms (Carroll et al. 2008; Munck and Naray-Fejes-Toth 1992). For example, the mortality risk in patients with Cushing's syndrome or Addison's disease (with high and low circulating GC levels, respectively) is much higher when GC secretion is arrhythmic (Dallman et al. 2006).

GCs are potently upregulated by both LPS (Konsman et al. 2008) and turpentine oil injection (Turnbull et al. 2003), likely through the activation of the HPA axis by cytokines, in particular IL-6 (Petrovsky et al. 1998). Interestingly, this response to LPS varies across the day: the level of activation of the HPA axis is greater when LPS is administered at the beginning of the rest phase, when endogenous GC levels are low (Pollmacher et al. 1996).

Glucocorticoids (GCs) have also been shown to influence circadian clocks. Binding elements for GC receptors were found in the promoters of the clocks genes *Per1* (Balsalobre et al. 2000; Fukuoka et al. 2005), *Per2* (Cheon et al. 2013; So et al. 2009) and *Rev-erbα* (Torra et al. 2000). Accordingly, GC treatment acutely induces *Per1* and *Per2* expression in cultured cells (Balsalobre et al. 2000; Cheon et al. 2013), in vitro cultured lung slices (Gibbs et al. 2009) and in different organs upon injection in mice (Balsalobre et al. 2000). GCs can synchronize cellular circadian oscillators in vitro and in peripheral tissues in vivo (Balsalobre et al. 2000; Nagoshi et al. 2004; Son et al. 2008). Centrally, GC rhythms are necessary for PER2 protein rhythms in the limbic forebrain (Segall and Amir 2010b). As for the SCN master clock, the absence or low levels of GC receptors in the adult SCN (Balsalobre et al. 2000; Rosenfeld et al. 1993; Segall and Amir 2010b) probably explains the lack of effects of GC injection (Balsalobre et al. 2000; Segall and Amir 2010a) or adrenalectomy (Segall and Amir 2010b) on clock gene expression in the SCN. Overall, GCs are considered as likely candidates for mediating the resetting of the peripheral clocks and they were shown to regulate behavioral resetting, which is thought to be under the control of the SCN (Kiessling et al. 2010). These studies suggest that the differential induction of GCs in response to an immune challenge could impose time- and tissue-dependent regulation of clock gene expression.

In addition to the direct effects on clock genes via the GC receptor, GCs inhibit the action of NFκB by preventing binding to its target genes (Borghetti et al. 2009; Van Bogaert et al. 2010). Given the circadian rhythm of GC levels, this repression of NFκB probably occurs with a circadian rhythm too. Given the known effects of NFκB on clock genes (see above section on NFκB), it is thus possible that GCs, via the regulation of NFκB activity, impose a time dependence on the immune regulation of circadian clock gene expression.

Melatonin

Melatonin is a hormone synthesized and secreted by the pineal gland (Maronde and Stehle 2007). It is produced from serotonin as a result of a two-step synthesis pathway. Modification of serotonin by the enzyme arylalkylamine *N*-acetyltransferase (AA-NAT) is the rate-limiting step. AA-NAT is found at high levels in pinealocytes during the night (both in diurnal and nocturnal animals), and consequently, melatonin synthesis occurs mainly during the night. Melatonin has immunomodulatory effects (Carrillo-Vico et al. 2005), and the literature provides examples of both anti-inflammatory and pro-inflammatory roles, depending on the cell type and conditions (Mauriz et al. 2013). Melatonin influences the diurnal rhythms of leukocyte proliferation, cytokine production, and NK cell activity (del Gobbo et al. 1989; Drazen et al. 2001). In various inflammatory models, melatonin administration was shown to counter inflammation by lowering inducible nitric oxide synthase and cyclooxygenase-1/2 expression, PGE_2 levels, and pro-inflammatory cytokine levels (Mauriz et al. 2013). On the other hand, in a mouse experimental model of arthritis, melatonin administration leads to decreased CRY1 protein and *Cry1* mRNA levels and to worsened symptoms (Bang et al. 2012).

Melatonin was shown to inhibit LPS-induced NFκB activation in a microglial cell line, in turn inhibiting chemokine secretion and promoting the anti-inflammatory role of this hormone (Min et al. 2012). Pineal microglia respond to LPS and express TNF-α following the activation of the NFκB pathway (da Silveira Cruz-Machado et al. 2012). TNF-α then binds its receptor on pinealocytes to negatively regulate *Aanat* gene expression and melatonin production (Carvalho-Sousa et al. 2011). This repression seems to be part of a switch in the source of melatonin, from pinealocytes to immunocompetent cells (Markus et al. 2013). Upon inflammation, NFκB appears to be a key player both for the downregulation of AA-NAT in the pineal (as described above) and for its induction in immune cells, e.g., macrophages, leading to the

secretion of melatonin by these cells (Muxel et al. 2012). Melatonin then acts in an autocrine fashion on macrophages themselves, to increase phagocytic activity. Interestingly, melatonin itself but also corticosterone cooperate to reduce macrophage-borne melatonin production upon recovery from inflammation (Markus et al. 2013). Melatonin and corticosterone also regulate NFκB in the pineal gland: in this organ, NFκB protein levels are rhythmic and melatonin inhibits NFκB activation (Cecon et al. 2010), while stress-induced plasma corticosterone leads to reduced NFκB nuclear levels in the hamster pineal gland (Ferreira et al. 2012).

Other examples exist of interplay between melatonin and GCs. Such an interplay was proposed to contribute to the aggravated morning inflammation in rheumatoid arthritis (RA). Pro-inflammatory cytokines such as IL-6 are upregulated in RA patients during the night and early morning (Cutolo et al. 2006). This nocturnal pro-inflammatory state was associated with increased melatonin levels at night and lower GC levels in the early morning. Indeed, if GC treatment is administered at the maximum pro-inflammatory peak in RA patients, then inflammation is greatly reduced (Jacobs and Bijlsma 2010). More generally, given the regulatory role of melatonin and GCs in inflammation, the interplay between their respective rhythms could contribute to the pro-inflammatory states induced by an acute inflammatory challenge. Given that GCs are time-dependently induced following an inflammatory stimulus, the shift in the balance of these two hormones may create altered pro-inflammatory states, accounting to the time-dependent variation in the immune response.

Coordination of Peripheral Clocks by Core Body Temperature Rhythms and Effects of Fever

The central clock of the SCN drives rhythms in core body temperature, which peaks during the active phase in both humans (light phase) and nocturnal rodents (dark phase). While the SCN network makes this central clock resistant to body temperature daily fluctuations, the body temperature rhythm was proposed to coordinate peripheral clocks (Buhr et al. 2010). Emulated physiological temperature rhythms can maintain rhythmicity of clock gene expression in cell culture and even shift rhythms to a new phase (Brown et al. 2002; Saini et al. 2012), but sudden temperature pulses have the capacity to synchronize cellular oscillators (Brown et al. 2002). This last observation suggests that the rapid change in temperature observed with fever onset could affect the phase of peripheral circadian clocks, or at least provoke a transient alteration of the clock-controlled rhythms in peripheral organs.

Heat-sensing and cold-sensing molecules might be the molecular links between temperature oscillations and clock gene rhythmicity. The expression of several heat-shock proteins (HSPs) is rhythmic in the liver (Kornmann et al. 2007). HSP rhythmicity is driven by heat-shock factor (HSF)1, a transcription factor whose peak DNA-binding activity presents a circadian rhythm in the liver (Reinke et al. 2008). Notably, *Hsf1*-deficient mice have a longer free-running period than WT mice (Reinke et al. 2008). Further, HSF1 is required for the quick synchronization of cells to simulated body temperature rhythms (Saini et al. 2012) or following a quick heat pulse (Tamaru et al. 2011). These results support an earlier study showing that HSF1 is required for resetting *Per2* expression by temperature pulses in cell culture (Buhr et al. 2010). Interestingly, studies have supported a role for HSPs in modulating NFκB response to TNF-α or endotoxin challenge (Liu et al. 2010). The latter observation adds another molecular layer of interplay between clock genes, factors responsive to elevated temperature, and a key factor involved in inflammatory responses.

Other studies have focused on the cold-induced RNA-binding proteins CIRBP and RBM3. These proteins were found to bind the 3′ untranslated region of clock gene and clock-controlled gene mRNAs and to regulate their circadian expression (Liu et al. 2013; Morf et al. 2012). Interestingly, in mouse tissues, mRNAs encoding cold-induced proteins are enriched during the day while mRNAs for HSPs reach peak levels during the night (Kornmann et al. 2007; Liu et al. 2013). This fits well with the circadian rhythm of body temperature in these nocturnal rodents (higher body temperature at night, or active period).

It was shown in both humans (Pollmacher et al. 1996) and rodents (Luker et al. 2000; Sugimoto et al. 1996) that the time of day of endotoxin treatment does not affect the absolute magnitude of fever induction. Similarly, fever induction following turpentine oil injection is relatively independent of the time of treatment (Westfall et al. 2013). In contrast, the local temperature increase in the brain is sensitive to the time of day of endotoxin treatment (Mathias et al. 2000). Despite the time independence of fever magnitude in peripheral tissues, it is possible that the kinetics of fever induction may change according to the time of day of endotoxin challenge. Altogether, the rapid changes in temperature induced by endotoxin treatment may cause time-dependent changes in peripheral clock gene expression. This time dependency might be due to the time-dependent *rate* of fever induction or by variation across the day of the activation of heat- or cold-responsive mechanisms.

Neuronal Connections Within the Immune–Circadian Interaction

An inflammatory challenge in the periphery can directly signal the central febrile mechanisms through both the

sympathetic (SNS) and parasympathetic (PNS) nervous systems (Hori et al. 1995). Likewise, both the SNS and PNS can mediate signals to individual peripheral organs (Esquifino and Cardinali 1994; Hori et al. 1995). This communication loop is gated at several key points by the circadian system and could explain some of the time-dependent effects of the immune response.

LPS imparts an early fever response, which cannot be solely explained by the upregulation of humoral factors. It is possible that the local tissue-specific upregulation of cytokines activate vagal afferents (Mignini et al. 2003), which in turn activate fever pathways in the brain (Watkins et al. 1995). For example, vagal afferents in the liver activate the secretion of noradrenaline in the hypothalamus, induce prostaglandin release, and consequently fever (Sehic and Blatteis 1996). Correspondingly, both IL-1 receptor antagonist and IL-1β were shown to directly interact with vagal afferents (Goehler et al. 1997; Niijima 1996).

The SCN is intimately involved in the neural pathways regulating the immune response. In particular, the SCN is heavily interconnected with the paraventricular nucleus and the arcuate nucleus, two regions involved in peripheral circadian entrainment and immune function (Kalsbeek and Buijs 2002; Kalsbeek et al. 2006). The projections of the SCN to the key febrile centers (e.g., the preoptic anterior hypothalamic area) and the circadian regulation imposed on these centers through circadian factors such as leptin create additional levels of circadian control on immune neuronal signalling (Buijs et al. 2003). Of note though, there has still been no report on the effects of SCN lesion on the inflammatory response.

Autonomic afferents to peripheral organs play a role in the circadian regulation of the immune response. Vagal connections to peripheral immune-regulating tissues inhibit the release of cytokines, thereby controlling the magnitude of the immune response (Borovikova et al. 2000; Czura et al. 2003). One study found that the norepinephrine content in the rat spleen was rhythmic. When connections to the spleen were severed, the rhythms in cytokines and cytolytic factors of splenocytes and NK cells were disrupted along with the rhythmicity of *Bmal1* and *Per2* (Logan et al. 2011). Furthermore, adrenaline treatment on hepatic tissue slices acutely induced *Per1*, while daily treatment entrained liver rhythms in vivo in SCN-lesioned mice (Terazono et al. 2003). Also, vagal afferents were found to be essential for clock gene rhythmicity in the lung (Bando et al. 2007). The PNS and SNS connections to the adrenal gland are particularly important for the regulation of GC secretion (Buijs et al. 2003; Ishida et al. 2005). This is an important connection because as we noted above, GCs are important regulators of both the peripheral circadian response and immune regulation. Interestingly, some of the rhythmic humoral cues described above actually gate the immune-activated autonomic connection. For example, PGE_2 can activate the vagus nerve in the periphery, as there is a large enrichment of PGE_2 receptors on the vagal afferents in the abdominal compartment (Ek et al. 1998).

Conclusion

The dialog between the innate immune response and the endogenous circadian system occurs at multiple levels, due to the large overlap between these systems (Figs. 1, 2). The rhythmicity in cytokines and humoral factors including leptin, PGE_2, GCs, and melatonin can potentially time the immune response. This in turn leads to specific changes in clock-controlled events. Further, the direct neuronal connections from the brain to the periphery may impose fast tissue-specific modifications in circadian clocks in conditions of inflammation. It is likely that no single factor can be coined as "the" mediator of the circadian–immune cross talk alone. Instead, various factors are likely to be involved, in a context- and tissue-dependent manner. Nevertheless, the prominence of the connections between these two key physiological systems underscores the importance of unravelling the mechanism involved. This will allow understanding on how infection and inflammation can affect biological rhythms and vice versa. At the same time, and more broadly, this research will provide a model for the circadian control of physiology. In the context of disease, the diurnal changes in the symptoms of different medical conditions such as RA or sepsis, and the higher incidence of various diseases (e.g., cancer) upon circadian disruption, altogether imply that the research on the reciprocal regulation of circadian clocks and inflammatory pathways will also have important implications for disease understanding and treatment.

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