

REVIEW

Circadian immune circuits

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Immune responses are gated to protect the host against specific antigens and microbes, a task that is achieved through antigen- and pattern-specific receptors. Less appreciated is that in order to optimize responses and to avoid collateral damage to the host, immune responses must be additionally gated in intensity and time. An evolutionary solution to this challenge is provided by the circadian clock, an ancient time-keeping mechanism that anticipates environmental changes and represents a fundamental property of immunity. Immune responses, however, are not exclusive to immune cells and demand the coordinated action of nonhematopoietic cells interspersed within the architecture of tissues. Here, we review the circadian features of innate immunity as they encompass effector immune cells as well as structural cells that orchestrate their responses in space and time. We finally propose models in which the central clock, structural elements, and immune cells establish multidirectional circadian circuits that may shape the efficacy and strength of immune responses and other physiological processes.

Innate immunity and the circadian system

Every 24 h, organisms on Earth receive periodic signals from their environment, such as sunlight or availability of food. Virtually all lifeforms on our planet have evolved mechanisms to synchronize their physiology to these predictable cues (Gerhart-Hines and Lazar, 2015). These variations, known as circadian oscillations, govern most physiological activities (Scheiermann et al., 2018) and are the result of a collection of circadian clocks present in the central nervous system and in peripheral tissues (Dibner et al., 2010). In mammals, the master pacemaker of this network is the central clock located in the suprachiasmatic nucleus (SCN) of the brain, which integrates photic cues and synchronizes peripheral clocks through neural and humoral mediators (Dibner et al., 2010). The time-sensing clockwork is also cell autonomous, as it relies on the presence of a molecular clock expressed in virtually every cell (Reppert and Weaver, 2002), and is composed of a set of clock proteins that generate an autoregulatory transcriptional network with interlocked feedback loops. At the core of this central loop, the transcription factors Bmal1 and Clock form a heterodimer that binds E-box sequences and promotes the expression of its own repressors, whose degradation times establish the ~24-h periodicity (Schibler, 2006).

Clock genes and related transcription factors have been described in all cells of the innate and adaptive immune systems (Silver et al., 2012a; Druzd et al., 2017; Adrover et al., 2019) and directly regulate many aspects of immunity, especially those related with frontline defense by innate immune cells (Scheiermann et al., 2012). However, as innate immune cells are growingly

appreciated to accomplish homeostatic tasks (Aroca-Crevillén et al., 2020; Lavin and Merad, 2013), it is easy to foresee that, in addition to their own molecular clock, they need to integrate signals from a wide variety of sources. For example, circadian clocks in endothelial cells (ECs) control the expression of trafficking factors that influence the migration of leukocytes in the steady state or during inflammation (Scheiermann et al., 2012). Even more intriguing, studies have unearthed circadian connections between the brain and the intestine mediated through a subset of innate lymphoid cells (ILCs; Godinho-Silva et al., 2019b), thereby revealing a role for innate immune cells as mediators of brain-derived circadian signals in tissues. These circadian immune circuits appear ubiquitously (Fig. 1 and Table 1) and may underlie both housekeeping functions and disorders that display strong circadian patterns, including cardiovascular (Gupta and Shetty, 2005; Muller et al., 1985), metabolic (Oh et al., 2019), allergic (Paganelli et al., 2018), and even carcinogenic (Puram et al., 2016).

Here, we summarize evidence highlighting the prevalence and importance of circadian immune circuits, with particular consideration to neural and structural elements in tissues that coordinate with immune cells to orchestrate multiple aspects of circadian physiology and immunity.

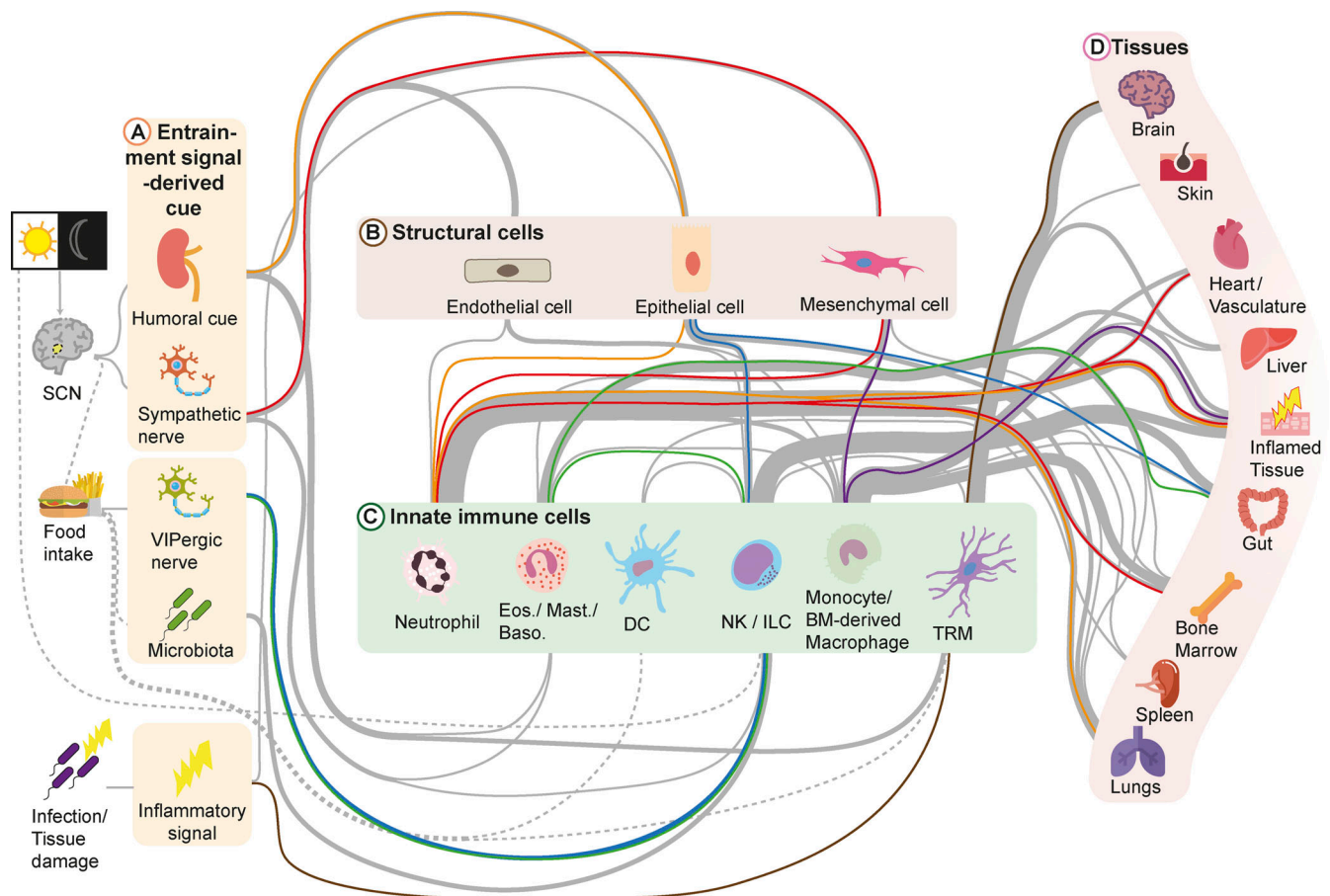
Circadian rhythms in innate immune cells

Almost every hematopoietic and immune cell is subjected to circadian influence by more than one mechanism. In some

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Examples Circadian-Immune circuits

Circuit	Pathway	A	B	C	D	Oscillating Singal	References
—	A-B-C-D					CXCL2/CXCR2, CXCL12/CXCR4	Adrover et al. 2019 Méndez-Ferrer et al. 2008
—	A-B-C-D					CXCL5	Gibbs et al. 2014
—	A-C-C-D		—			IL-5, IL-13	Nussbaum et al. 2013
—	A-C-B-D					IL-22, Reg3γ, Lipid transport	Talbot et al. 2020
—	?-B-C-D	?				Pro-inflammatory cytokines	Hand et al. 2019
—	A-C-D		—			P2Y ₆ receptor, Microglial processes	Takayama et al. 2016

No. of connections

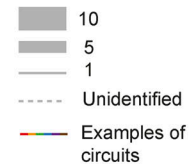


Figure 1. Circadian immune circuits. Circadian regulation of innate immunity requires the coordinated action of at least three compartments: neurons of the SCN (and downstream endocrine organs), structural cells in peripheral tissues, and immune cells. The SCN integrates photic cues, which represent the main entrainment signals; however, the immune system can be also resynchronized by feeding or during infections. In this model, circadian information “flows” through these compartments, forming what we refer to as circadian immune circuits. We organize the distinct compartments of these circuits as those associated with the central clock or other entrainment cues (A), which deliver signals to structural (B) and/or innate immune cells (C) in peripheral organs. The circuits are organized such that structural and innate immune cells reciprocally communicate to orchestrate immune responses or specific physiological events (D). The upper diagram shows a nonexhaustive list of circadian immune circuits identified from the literature, of which some are highlighted by color lines and are referred to in the text and detailed in the lower table. All circuits shown here are detailed in Table 1. Eos, eosinophils; Baso, basophils; TRM, tissue-resident macrophages.

Table 1. **List of reported circadian immune circuits**

Circuit	Pathway	A	B	C	D	Oscillating signal	References
1	A-B-C-D	β -Adrenergic receptors	MCs	Neutrophils	Infected tissue, BM, cardiovascular	CXCL2, CXCR2, CXCL12, CXCR4	Méndez-Ferrer et al., 2008; Adrover et al., 2019
2	A-B-C-D	Glucocorticoid receptors	EpCs	Neutrophils	Infected tissue, lungs	CXCL5	Gibbs et al., 2014
3	A-C-C-D	VIP neurons	—	ILC2s, eosinophils	Gut	IL-5, IL-13	Nussbaum et al., 2013
4	A-C-B-D	VIP neurons	EpCs	ILC3s	Gut	IL-22, Reg3 γ , lipid transport	Talbot et al., 2020
5	B-C-D	—	MCs	Monocytes	Inflamed tissue	Proinflammatory cytokines	Hand et al., 2019
6	A-C-D	Infection	—	Microglia	Brain	P2Y6 receptor, microglial processes	Takayama et al., 2016
7	A-B-C-D	β -Adrenergic receptors, cholinergic signals	MCs	Neutrophils	BM	CXCL12	Méndez-Ferrer et al., 2008; García-García et al., 2019
8	A-B-C-D	β -Adrenergic receptors	ECs	Neutrophils	Inflamed tissue, BM, cardiovascular	Icam-1, Selectins, VCAM-1, CCL2	Scheiermann et al., 2012
9	C-C-D	—	—	Hematopoietic stem cell (HSC)-derived macrophages, neutrophils	Infected tissue	Proinflammatory cytokines	Kiessling et al., 2017
10	C-C-B-D	—	MCs	Neutrophils, HSC-derived macrophages	BM	LXR, CXCL12	Casanova-Acebes et al., 2013
11	C-D	—	—	Neutrophils	Lungs	Lung transcriptome	Casanova-Acebes et al., 2018
12	C-C-D	—	—	Neutrophils, HSC-derived macrophages	Gut, BM	IL-23, G-CSF	Casanova-Acebes et al., 2018
13	C-C-D	—	—	HSC-derived macrophages, eosinophils	Lungs	IL-5, proinflammatory cytokines	Zasłona et al., 2017
14	A-C-D	Glucocorticoids	—	Mast cells	Inflamed tissue	Fc ϵ R1 expression	Nakamura et al., 2016
15	A-C-C-D	Feeding metabolic cues	—	DC, lymphocytes	Infected tissue	IL-12	Hopwood et al., 2018
16	C-D	—	—	DC, lymphocytes	Spleen	TLR expression	Silver et al., 2012b, 2018
17	A-C-D	β -Adrenergic receptors	—	NK cells	Spleen	TNF- α , granzyme B, perforin	Wahle et al., 2001; Logan et al., 2011
18	A-B-C-D	β -Adrenergic receptors	ECs	NK cells	Infected tissue	CXCR4	He et al., 2018
19	A-C-D	Light-derived signals	—	ILC3s	Gut	Epithelial reactivity genes, microbiome composition, lipid epithelial transporters, CCR9	Godinho-Silva et al., 2019b
20	A-C-D	Microbiota/light-derived signals	—	ILC3s	Gut	IL-17, IL-22, NFIL3, ROR γ T	Teng et al., 2019; Wang et al., 2019
21	A-B-C-D	β -Adrenergic receptors	ECs	Monocytes	BM, inflamed tissue	Icam-1, Selectins, VCAM-1, CCL2	Scheiermann et al., 2012
22	C-D	—	—	Monocytes	BM, liver, lungs, infected/inflamed tissues, cardiovascular	CXCR4, CCL2	Chong et al., 2016; He et al., 2018; Nguyen et al., 2013; Huo et al., 2017; Winter et al., 2018; Schloss et al., 2017
23	C-D	—	—	Microglia	Brain	Morphology, purinergic receptors	Hayashi, 2013
24	C-D	—	—	Microglia	Brain	Cathepsin S	Hayashi et al., 2013

Table 1. List of reported circadian immune circuits (Continued)

Circuit	Pathway	A	B	C	D	Oscillating signal	References
25	C-D	Not glucocorticoids	—	Microglia	Brain	IL-1 β , TNF- α , IL-6	Fonken et al., 2015
26	A-C-D	Glucocorticoids	—	Microglia	Brain	Phagocytosis	Choudhury et al., 2020
27	C-D	—	—	KCs	Liver	TLR4 signals	Wang et al., 2018
28	A-C-D	Feeding metabolic cues	—	KCs	Liver	TNF- α	Guerrero-Vargas et al., 2015
29	C-D	—	—	LCs	Skin	IRF7	Greenberg et al., 2020
30	A-C-C-D	Melatonin	—	LCs, lymphoid T cells	Infected tissue	Migration to lymph nodes	Prendergast et al., 2013
31	A-B-D	Glucocorticoids	EpCs	—	Lungs	cell molecular clock	Gibbs et al., 2009
32	A-B-D	LPS treatment	EpCs	—	Lungs	Proinflammatory cytokines, REV-ERBa degradation	Pariollaud et al., 2018
33	A-C-B-D	Microbiota	EpCs	ILC3s	Gut	NFIL3	Wang et al., 2017

instances, a cell-intrinsic clock drives circadian behaviors; however, these are often the result of the coordinated action of several cell types, including those that form part of the tissue architecture. In this section, we summarize the major circadian features of innate immune cells and present them in the broader context of the tissue so as to illustrate the nature and abundance of immune circadian circuits (Fig. 1).

Granulocytes

Neutrophils are characterized by a short lifespan, a feature that may explain their strong circadian patterns (Aroca-Grevillén et al., 2020). Both their numbers in blood and migratory behavior are orchestrated, at least in part, by a cell-autonomous clock (Adrover et al., 2019) in combination with cues originating from tissue-resident or structural cells (He et al., 2018). For example, the circadian trafficking of neutrophils to and from the bone marrow (BM) likely depends on the oscillatory expression of the chemokine CXCL12 (Ella et al., 2016; De Filippo and Rankin, 2018) and its cognate receptor, CXCR4 (Casanova-Acebes et al., 2013), a feature shared with other hematopoietic cells (Lucas et al., 2008; Méndez-Ferrer et al., 2008). Expression of *Cxcl12* is regulated in a circadian manner by direct sympathetic innervation of the marrow and appears to be under direct control of the central clock. This axis critically relies on β 3-adrenergic receptor signaling in mesenchymal cells (MCs) that form the hematopoietic niche (Méndez-Ferrer et al., 2010), resulting in blunted CXCL12 production at daytime in mice (Fig. 1, red circuit; Méndez-Ferrer et al., 2008). Concomitant with this axis, inhibitory cholinergic signals from the parasympathetic nervous system damp the sympathetic tone at night (García-García et al., 2019), altogether establishing a neural mesenchymal circuit that controls neutrophil dynamics in the BM. In addition to MCs, neutrophil dynamics can be controlled by other structural cells, at least during inflammation. In the context of bacterial infections in the lung, for example, expression of *Cxcl5* regulated by the circadian machinery and by glucocorticoids on epithelial cells (EpCs) controls neutrophil recruitment and the magnitude of the response (Fig. 1, orange circuit; Gibbs et al., 2014).

During their brief circulating time (6–10 h in mice), neutrophils undergo oscillations in phenotype and function, a phenomenon referred to as aging (Adrover et al., 2016). These changes are controlled in a cell-intrinsic circadian manner through Bmal1 and CXCR2 and are subjected to light entrainment (Adrover et al., 2019). CXCR4 acts as an internal inhibitor of circadian aging by interfering with CXCR2 signaling in a process that correlates with oscillatory levels of CXCL12 in plasma, suggesting that cell-autonomous and systemic signals contribute to neutrophil aging. This in turn regulates the migratory and toxic properties of circulating neutrophils (Adrover et al., 2019, 2020) and impacts the outcome of infectious, ischemic, and inflammatory responses (Adrover et al., 2019; Zhang et al., 2015). Finally, the finding that neutrophils infiltrate healthy tissues in a circadian manner (Casanova-Acebes et al., 2018) suggests that they could instruct circadian programs in tissues. This intriguing possibility is supported by the finding that neutrophils infiltrating the BM control the circadian activity of hematopoietic niches (Casanova-Acebes et al., 2013), as well as the transcriptional activity in the lungs (Casanova-Acebes et al., 2018), ultimately modulating the migration of hematopoietic stem or metastatic cells, respectively.

The number of eosinophils follow circadian oscillations in blood (Acland and Gould, 1956), and in the intestine, their migration is controlled by an extrinsic circuit involving hormonal cues and type 2 ILCs (ILC2s; Nussbaum et al., 2013). Specifically, food intake generates rhythmic expression of vasoactive intestinal peptide (VIP), which entrains the circadian production of IL-5 and IL-13 by ILC2s and drives the accumulation of eosinophils within tissues (Fig. 1, green circuit; Nussbaum et al., 2013). Together with feeding, independent cues involving adrenal hormones have been long known to entrain fluctuations of eosinophils in blood (Brown and Dougherty, 1956). Thus, a circadian immune-metabolic axis can control immune fluxes and shape specific aspects of tissue homeostasis or disease. For example, the circadian dynamics of eosinophils in blood (Haus and Smolensky, 1999) and lungs (Panzer et al., 2003), the number of circulating low-density eosinophils (Calhoun et al., 1992), and variations of eosinophil-derived GM-CSF (Esnault et al., 2007)

associate with the diurnal onset and clinical manifestations of asthma. Similarly, allergy onset follows circadian patterns in which eosinophils are major cellular effectors and correlates with rhythmic expression of the eosinophil cationic protein (Baumann et al., 2013). In these type 2 as well as in other inflammatory responses, the molecular clock in myeloid cells generally functions to blunt the magnitude of the response (Zasłona et al., 2017).

Mast cells are also major effectors of anaphylactic reactions (Baumann et al., 2015). Expression of tryptase and FcεRI chain and release of prestored histamine, leukotrienes, and proinflammatory cytokines by mast cells are all under circadian regulation and allow temporal gating of mast cell activation and effector functions (Baumann et al., 2013, 2015). Despite the clear circadian patterns of allergy, however, the role of internal versus external clocks in controlling mast cell activation remain poorly defined. Studies in adrenalectomized mice determined that degranulation after an IgE challenge was extrinsically dependent on glucocorticoids, yet the process was shown to additionally require a functional internal clock (Nakamura et al., 2016).

Monocytes, monocyte-derived macrophages, and dendritic cells (DCs)

Monocytes exhibit circadian oscillations in blood counts (He et al., 2018) and in recruitment to tissues, in part mediated by external cues delivered by the sympathetic nerves to ECs (Scheiermann et al., 2012). The release of inflammatory monocytes from the BM is, in contrast, controlled by CCL2-producing MCs (Shi et al., 2011), a cell type that is under strong circadian control (Méndez-Ferrer et al., 2008), suggesting that circadian monocyte release may be regulated through these cells. In the context of inflammation, the molecular clock in local synovocytes (a type of fibroblast) blunts monocyte recruitment and the magnitude of inflammation in arthritis (Fig. 1, violet circuit; Hand et al., 2019). Complementing these extrinsic cues, the intrinsic clock of monocytes controls expression of genes important for their migration. For example, oscillations in CXCR4 regulate their egress from BM (Chong et al., 2016) and homing into the murine liver and lung (Chong et al., 2016; He et al., 2018). Inflammatory, but not patrolling, monocytes show circadian expression of *Ccl2*, which amplifies their migration to infected tissues. *Bmal1* deletion results in exaggerated expression of *Ccl2* and predisposes to septic shock and chronic inflammatory disease (Nguyen et al., 2013). Thus, intrinsic regulation of inflammatory cytokines or their receptors by the circadian clock appears to be generally protective, as also shown in the context of atherosclerosis (Huo et al., 2017; Winter et al., 2018) and myocardial infarction (Schloss et al., 2017).

Monocyte-derived macrophages have been mostly studied in vitro from peritoneal exudates or in vivo in the peritoneum and spleen, where BM-derived macrophages dominate in adulthood (Guilliams et al., 2018). These macrophages display circadian gating in the response against pathogens that is controlled by a *Bmal1*- and *Rev-Erba*-dependent clock (Curtis et al., 2015; Gibbs et al., 2012). For instance, they display rhythmic expression of genes encoding pattern recognition receptors (Keller et al., 2009;

Silver et al., 2018, 2012b) and cytokines (Curtis et al., 2015; Gibbs et al., 2012; Kiessling et al., 2017) or involved in production of reactive oxygen species (Early et al., 2018). Their phagocytic activity is also regulated in a circadian manner, thereby ensuring efficient elimination of pathogens (Kitchen et al., 2020; Oliva-Ramírez et al., 2014) and preservation of tissue homeostasis (A-Gonzalez et al., 2017). The rhythmic changes in phagocytosis appears to be mediated, at least in part, through regulation of the cytoskeletal regulator RhoA by an internal *Bmal1*-dependent clock (Kitchen et al., 2020). Interestingly, inflammatory macrophages express receptors for melatonin (Maestroni et al., 2002), a circadian neurohormone that modulates phagocytosis (Pires-Lapa et al., 2013). Additionally, circadian peaks in mitochondrial dynamics and activity are needed for, and precede, phagocytic activity in macrophages (Wang et al., 2017; Oliva-Ramírez et al., 2014). Interestingly, *Bmal1* is induced upon inflammation and promotes mitochondrial reprogramming, which in turn elicits protective inflammatory responses in the context of infection or cancer (Alexander et al., 2020). Thus, molecular coordination of circadian, metabolic, and immune programs regulates both the timing and type of response in macrophages (Xu et al., 2014; Sato et al., 2014).

Because DCs link innate and adaptive immunity, studies have typically explored DC rhythmicity by observing downstream adaptive responses. For example, morning exposure to helminths generates a more protective response, and ablation of DC-specific *Bmal1* biases the T helper type 1 and 2 response and compromises pathogen clearance (Hopwood et al., 2018). In this case, DC responses are modulated by an intrinsic clock and externally by feeding-derived cues, ultimately regulating the production of T helper 1 cell-type cytokines (Hopwood et al., 2018). DC abundance in the lymph nodes and spleen, a critical parameter to initiate adaptive responses, also features circadian dynamics (Druzd et al., 2017; Silver et al., 2018). It is noteworthy that the peak numbers of DC and T cells align in the lymph nodes, suggesting mechanisms of immune synchronization that optimize adaptive immune responses (Fortier et al., 2011). Likewise, circadian regulation of pattern recognition receptor expression in DCs may have evolved to overlap with higher exposure to pathogens (Silver et al., 2012b, 2018).

Embryo-derived macrophages

Here, we present an overview of representative subsets of tissue-resident macrophages of embryonic origin and emphasize that the circadian biology for many of these highly specialized cells remains unknown.

Microglia, the resident macrophages of the brain, perform highly dynamic tasks that support neural homeostasis; for example, by “pruning” synaptic terminal and producing neurotrophic factors (Wu et al., 2015; Kierdorf and Prinz, 2017), both of which are under circadian influence. Studies focused on microglial morphology revealed circadian patterns in branching through expression of a purinergic receptor (P2Y12R) that was controlled by core clock genes (Hayashi, 2013). This process is relevant to support oscillatory patterns in synaptic strength and spine density and to prevent neuropsychiatric disorders (Hayashi et al., 2014). Intriguingly, this pattern could be inverted upon

exposure to bacterial infection (Takayama et al., 2016), thus uncovering multiple regulatory inputs in microglia (Fig. 1, brown circuit). Expression of cathepsin S, another regulator of synaptic strengthening in the cortex and memory formation (Hayashi et al., 2014), is also under control of the intrinsic microglial clock (Hayashi et al., 2013). External regulators, such as glucocorticoids and noradrenaline, in turn, tune the expression of opsonins and phagocytic receptors, thereby enabling the removal of weak synapses by microglia during the resting phase (Choudhury et al., 2020). Of particular interest for our discussion are the links between circadian oscillations in microglia and neuroinflammatory and cognitive disorders, such as Alzheimer's or Parkinson's disease (Liu et al., 2020; Ni et al., 2019). These patients manifest conspicuous loss of circadian patterns, which in mice is associated with exacerbated inflammatory profiles in microglia that lack core circadian genes. Indeed, an internal clock, rather than extrinsic hormonal cues, appears to control the oscillatory response of microglia to sterile challenges (Fonken et al., 2015). Microglia are therefore both regulators of neuronal synapses and targets of neurohormonal signals, implying important influence of both intrinsic and extrinsic circadian inputs.

Recent proteomic analyses in the murine liver found a strong correlation between the circadian changes in the proteome of Kupffer cells (KCs) and liver physiology (Wang et al., 2018). For example, pathway interactions for KCs and whole-liver proteins were predominantly immune at daytime and metabolic at nighttime. A challenge now is to understand how KCs coordinate with the rest of the tissue to synchronize functional pathways and to define its relevance for organ physiology. KCs isolated from rats subjected to shifts in food intake showed increased production of TNF- α after endotoxin stimulation, again highlighting links of circadian oscillations with metabolism and a general role in limiting inflammation (Guerrero-Vargas et al., 2015). The extent to which the cell-autonomous clock modulates other critical functions of KCs in the liver, such as iron recycling, remains unknown.

Although the skin displays prominent circadian rhythms (Plikus et al., 2015; Sherratt et al., 2019) and is heavily altered in arrhythmic mice lacking *Bmal1* (Welz et al., 2019), little is known about the actual circadian biology of Langerhans cells (LCs), the epidermal macrophages. Global circadian transcriptomic analysis of the skin, however, identified abundant immune-related genes (Geyfman et al., 2012) that suggested circadian regulation of LCs. Consistently, LCs undergo diurnal changes in the subcellular distribution of IFN-sensitive genes in the context of psoriasis, and the absence of *Bmal1* blunted oscillations and exacerbated the IFN-driven response (Greenberg et al., 2020). Interestingly, the antigen-presenting capacity and migration of LCs are extrinsically regulated by the circadian hormone melatonin (Doebel et al., 2017), resulting in defective antigen-specific hypersensitivity reactions in the skin of arrhythmic hamsters (Prendergast et al., 2013). Thus, similar principles of intrinsic and extrinsic circadian regulation, including blunted immune activation by the intrinsic clock, may apply to LCs. Nonetheless, much remains to be learned in order to rigorously substantiate these concepts in

LCs, as well as in multiple other populations of resident macrophages.

ILCs

ILCs are an expanding group of immune cells of the lymphoid lineage that do not express antigen-specific receptors and have functions typically assigned to the innate immune arm, including response to infections, homeostasis, and inflammation. They have different origins, distributions, and functions and are therefore classified in three main groups.

The cytotoxic activity of natural killer (NK), a type 1 ILC, is under the control of both intrinsic, Per2-dependent clock regulation (Arjona and Sarkar, 2006; Liu et al., 2006) and extrinsic neurohormonal signals dependent on the central clock (Liu et al., 2006; Logan et al., 2011). For example, NK cells in the spleen express β -adrenergic receptors (Wahle et al., 2001) that regulate daily variations in TNF- α , granzyme B, and perforin (Logan et al., 2011) but not IFN- γ production, suggesting that additional nonneural cues are necessary to entrain effector functions in NK cells. Disruption of diurnal cycles of rats has major effects in the rhythmic production of inflammatory mediators and cytotoxic activity of NK cells and enhances tumor growth (Logan et al., 2012). Contrasting with the direct regulatory function of circadian cues, the migratory patterns of NK cells into tissues is regulated indirectly by sympathetic nervous system (SNS)-dependent signals that control the molecular clock in ECs (He et al., 2018). An additional, intriguing source of regulation for NK cells is during their lineage specification, through the circadian clock gene *Nfil3*, which in turn is regulated by feeding (Yang et al., 2015). Thus, multiple sources of circadian control dictate different aspects of NK biology.

In contrast to NK cells, type 2 ILCs reside in tissues and respond to parasites and allergens (Vivier et al., 2018). In the small intestine, ILC2s are stimulated by caloric intake through the circadian synchronizer VIP to produce IL-5 and IL-13, thereby regulating eosinophil maintenance in the tissue (Fig. 1, green circuit; Nussbaum et al., 2013). Despite the stark circadian nature of ILC2s, clock-dependent gene expression has not yet been demonstrated, and their influence on the circadian control of other immune cells in relevant tissues, such as alveolar macrophages (Guilliams et al., 2020), remains unexplored. Another particularly interesting aspect of ILCs is the tight connection with local nerves, which in the case of ILC2s have been shown to regulate their activation and effector functions against helminths through neuromedin U (Cardoso et al., 2017), raising the possibility of circadian regulation through this neural-ILC2 circuit.

Recent years have seen a surge of interest in ILC3, a subset of ILCs that critically regulate the intestinal barrier by integrating immune and neural cues (Godinho-Silva et al., 2019a). The regulatory functions of these cells in mucosal integrity appear to be intimately linked with circadian oscillations at different levels. First, a cell-intrinsic REV-ERB α -NFIL3 axis regulates the master transcription factor ROR γ and instructs ILC3 specification (Wang et al., 2019). Second, ablation of *Bmal1* leads to reduced cell numbers in the gut due to defective expression of migratory receptors, causing massive alterations that are specific

to the gut, including impaired epithelial reactivity, dysregulated microbiome, susceptibility to bowel infection, and disrupted lipid metabolism (Godinho-Silva et al., 2019b). Finally, ILC3 oscillations are under the influence of light and prandial cues. Specifically, a neuroimmune circuit involving production of VIP by enteric neurons after feeding represses *Il22* expression by ILC3, in turn favoring lipid absorption through EpCs (Fig. 1, blue circuit; Talbot et al., 2020).

$\gamma\delta$ T cells localize mostly in mucosal areas (in mice) and are specialized in containing pathogen invasion (Palomino-Segura et al., 2020). While their circadian biology remains poorly characterized, their numbers in human blood oscillate during the day (Mazzocchi et al., 2011), possibly regulated by humoral cues triggered by the autonomous nervous system (Suzuki et al., 1997). More recently, the circadian gene clock has been implicated in the direct modulation of *Il23r* expression on $\gamma\delta$ T cells and linked with susceptibility to psoriasis in mice (Ando et al., 2015).

Circadian features of structural immune cells

In addition to immune leukocytes, structural cell lineages within tissues can act as orchestrators of the immune response. Indeed, ECs, EpCs, and MCs embedded within tissues sense danger, provide spatial and temporal guidance for immune cell recruitment (Krausgruber et al., 2020), can store so-called immune memory (Ordovas-Montanes et al., 2020), and are integral elements of the circadian immune circuits discussed herein.

ECs line the inside of blood vessels are therefore key regulators of leukocyte migration to tissues. ECs display marked oscillations in clock genes as well as adhesion receptors and chemokines, which is in line with the circadian adhesion of leukocytes to, and migration through, inflamed vessels (Scheiermann et al., 2012). A puzzling finding was that the oscillatory expression of adhesive and chemotactic genes is out of phase for arteries and veins, despite synchronized expression of their clock genes. Elegant surgical and genetic models revealed a role for NG2-positive mural cells around arteries in sensing SNS signals and instructing circadian adhesion of leukocytes to arteries and adjacent veins (de Juan et al., 2019). Additionally, factors released by myeloid leukocytes such as CCL2 can introduce circadian changes in the adhesive properties of large and small vessels (Winter et al., 2018). Contrasting with this, the EC-intrinsic circadian clock only impacts circadian leukocyte adhesion in venous, but not arterial, vessels (de Juan et al., 2019), a property that may vary across tissues (Kalucka et al., 2020). Finally, surprising new findings suggest that light can entrain metabolic rewiring and elicit cardioprotective responses through *Per2* in ECs (Oyama et al., 2019). These immune- and SNS-driven features in vessels are likely to underlie inflammatory and thrombotic processes in atherosclerosis and other cardiovascular disorders (Winter et al., 2018; de Juan et al., 2019).

MCs include fibroblasts and various types of perivascular cells present in every tissue that control multiple aspects of tissue physiology, including immune and hematopoietic regulation (Stark et al., 2013; Méndez-Ferrer et al., 2010). As discussed above, a prominent role for MCs in the control of circadian

leukocyte dynamics has been best described in the BM (Shi et al., 2011; Méndez-Ferrer et al., 2008). Local SNS innervation and delivery of catecholamines appears to be a common mechanism that regulates circadian immune trafficking; indeed, expression of adrenergic receptors in MCs relays signals locally by modulating expression of chemotactic or adhesive factors such as CXCL12 in the marrow (Méndez-Ferrer et al., 2008). Interestingly, the activity of MCs and their ability to influence hematopoietic trafficking in the BM is additionally regulated by innate immune cells, including medullary-resident macrophages and neutrophils (Casanova-Acebes et al., 2013), revealing reciprocal regulation between MCs and innate immune cells. While the contribution of the intrinsic clock in MCs in immune homeostasis has not been broadly explored, a role for Bmal1 in synovial cells was shown to keep inflammation in check during arthritis (Fig. 1, violet circuit; Hand et al., 2019).

EpCs feature functional clocks in most tissues, although the most relevant immune-circadian analyses have been performed in the intestine (Sládek et al., 2007) and pulmonary airways (Gibbs et al., 2009), both of which manifest marked circadian patterns in basal function and disease manifestation. In the intestine, circadian patterns of EpC function, such lipid transport, are directly regulated by IL-22 secreted by ILC3s and indirectly by feeding and the microbiota (Fig. 1, blue circuit; Talbot et al., 2020). In the lungs, expression of clock genes is largely restricted to club cells, a type of bronchiolar EpC, and is strongly responsive to glucocorticoids (Gibbs et al., 2009). Elegant studies demonstrated that rhythmic expression of the inflammatory gene *Cxcl5* is under direct control of glucocorticoid receptors and Bmal1 in club cells and was responsible for the time-of-day variation in the severity of bacterial infection in the lungs (Gibbs et al., 2014). As shown for other cell types, the intrinsic clock in EpCs appears to be protective by blunting expression of inflammatory gene products, both in basal and inflammatory settings (Pariollaud et al., 2018). Interestingly, inflammatory cytokines induce degradation of the Rev-Erba and exacerbate pulmonary inflammation (Pariollaud et al., 2018), altogether evidencing the existence of multiple regulatory layers and the general protective function of the epithelial clock during immune responses.

Modeling circadian immune circuits

The classical view of circadian biology in mammals posits a hierarchical organization where peripheral clocks in cells and tissues are “enslaved” by the master pacemaker in the SCN (Fig. 2 A; Dibner et al., 2010). In our discussion above, we present examples supporting this prevailing dogma of a hierarchical control of circadian patterns in immune function (Nakamura et al., 2016; Choudhury et al., 2020). We highlight, however, that regulation of immune cells by the central clock is often indirect, i.e., relayed by intermediary cells. These are typically part of the so-called structural system and are increasingly recognized as integral to immune responses (Krausgruber et al., 2020), as also highlighted above. A central theme that arises is that networks composed of multiple signals and cellular intermediaries exist that coordinate immune responses in time and that leukocytes are typically final effector components of the

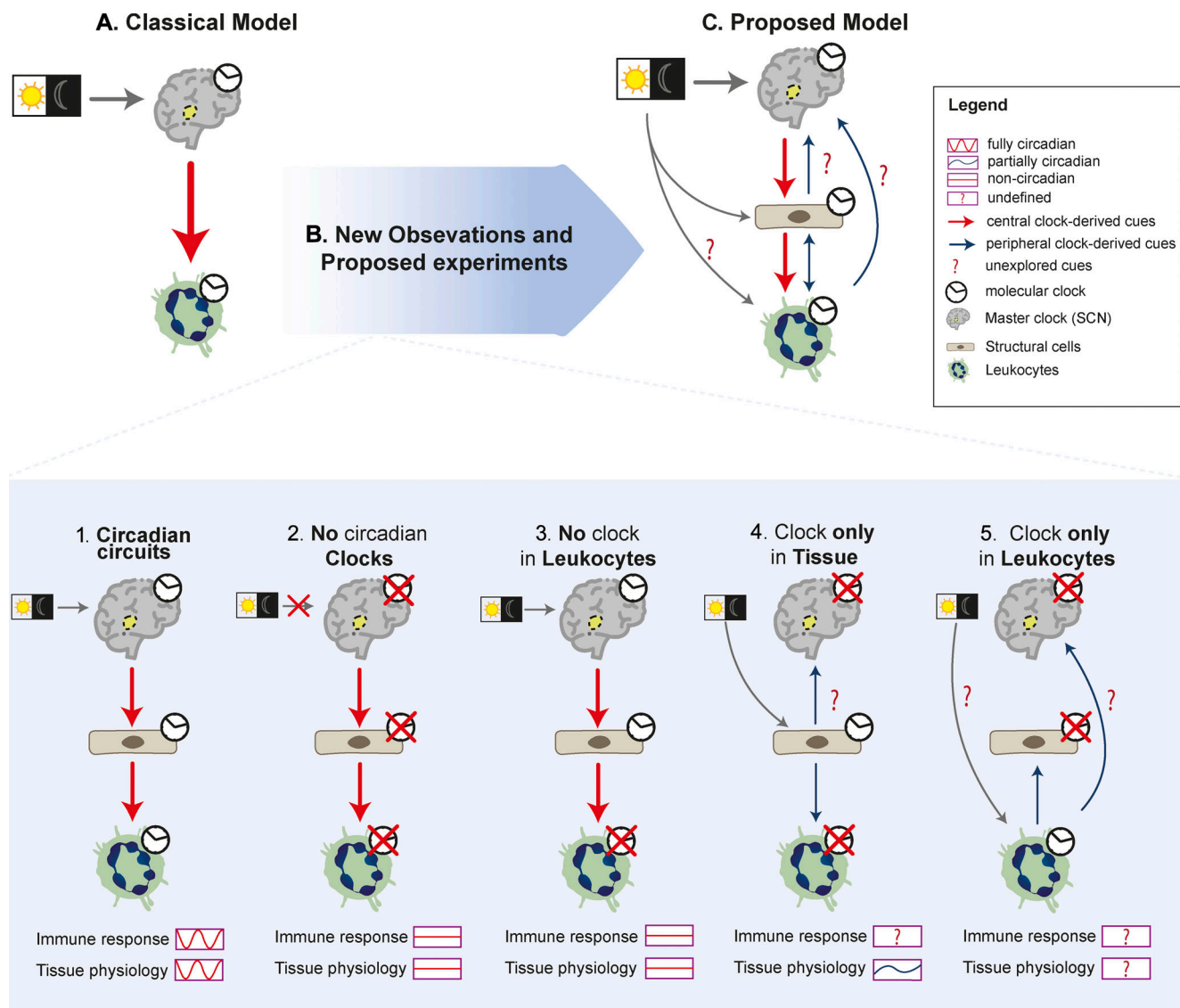


Figure 2. Modeling the architecture of circadian immune circuits. (A) Depiction of the classical model of circadian immune circuits whereby circadian clocks in innate immune subsets are under direct control of the master clock. (B) The model is refined by recent observations that consider at least three elements in the circuit (SCN and structural and immune cells). The presence or depletion of the internal clock in each component of the circuit leads to specific circadian patterns in immune response or tissue physiology. Rescue of a functional clock in specific components in an otherwise arrhythmic mouse (models 4 and 5) will be needed to understand how the circuits are actually organized. (C) Integrating current and future analyses proposed in the text and shown in B will enable building a more accurate model of how these circuits work, including defining whether peripheral clocks sense diurnal changes and deliver circadian cues to the other components of the circuit.

network (see examples in Fig. 1). These networks, which we refer to here as circadian immune circuits, remain only superficially characterized and are important to comprehend key features of innate immunity and tissue physiology.

How are these circuits organized? To address this fundamental question, we resort to multiple experimental models in which the molecular clock of different components of the circuit are disabled (Fig. 2 B). For example, analysis of mice with global clock deficiency demonstrate the importance of circadian regulation in the response to pathogens (Sundar et al., 2015; Majumdar et al., 2017) and organismal physiology (Fig. 2, B.1 and B.2; Kondratova and Kondratov, 2012; Koronowski et al., 2019). However, because these arrhythmic models target all cells, they

cannot be used to tease out the contribution of each separate component of the immune circuits. In contrast, studies in animals in which the molecular clock is targeted in a specific element of the circuit (immune or structural) evidenced that deleting specific clocks in cells along the circuits still causes profound changes in the magnitude and timing of antimicrobial and inflammatory responses, as well as (certain) homeostatic properties of tissues (Fig. 2 B.3; Godinho-Silva et al., 2019b; Gibbs et al., 2014; Nguyen et al., 2013; Kitchen et al., 2020; Adrover et al., 2019). Important insights into these circuits can be also gained by direct analyses of the central clock. Indeed, while a functional clock in the SCN is sufficient to generate circadian rhythms in organismal behavior and in tissues (Sujino

et al., 2003), studies in mice with a genetically ablated central clock demonstrated the existence of peripheral, SCN-independent clocks that could be entrained by light or feeding regimens (Izumo et al., 2014; Husse et al., 2014). In line with these surprising findings, elegant genetic models allowing cell- or tissue-specific rescue of a functional clock in otherwise arrhythmic mice have recently demonstrated that peripheral clocks are sufficient to preserve circadian oscillations in many genes and in organ physiology, autonomously from the SCN (Fig. 2 B.4; Welz et al., 2019; Koronowski et al., 2019). Thus, although much progress has been made in understanding general circadian circuits, we are still far from understanding the fundamental organization of circadian immune circuits. It is unclear, for example, whether and to what extent these circuits are autonomous from the SCN, because no experiments have addressed if clocks in structural or immune cells are by themselves sufficient to support circadian immune responses.

While still hypothetical, the potential for circadian clocks in structural and innate immune cells to sense and generate their own circadian cues can be speculated based on their distinct transcriptional profiles. For instance, a search in public databases (Immgen) reveals that subsets of ILCs, macrophages, neutrophils, mast cells, and EpCs express genes encoding several opsin genes, a family of G protein-coupled receptors that detect light and could render these cells independent of photic cues delivered through the SCN (Fig. 2, B.4 and B.5), as already shown for specific tissues (Buhr et al., 2019; Zhang et al., 2020). Further, because several subsets of innate immune cells, including macrophages, monocytes, and neutrophils, are capable of synthesizing and secreting catecholamines and glucocorticoids (Flierl et al., 2008; Acharya et al., 2020), it is conceivable that they generate neurohormonal signals similar to those used by the central clock to deliver circadian cues to their surrounding tissue. Rescue of functional clocks in immune and structural cells using newly generated mouse models (Welz et al., 2019) should allow exploring the autonomy, directionality, and relevance of the circadian immune circuits proposed herein (Fig. 2 C).

Concluding remarks

We aimed here to present an immunologist's view of how innate immunity and circadian oscillations interact in physiology rather than providing a comprehensive description of circadian immunity, which has been the subject of recent reviews (Scheiermann et al., 2018; Man et al., 2016). We provide an overview of exciting recent findings illustrating that circadian oscillations in peripheral tissues may operate independently of the central clock, that dedicated sensors of light and possibly other environmental cues exist in cells, that multiple cell types coordinate circadian responses, and that innate immune cells can be a source of circadian signals. Integrating these ideas may allow us to better understand how immunity and physiology intersect; for example, the observation that tissue-infiltrating neutrophils entrain circadian oscillations in the lung and the BM (Casanova-Acebes et al., 2018) or that ablation of the molecular clock in these cells blunts diurnal changes in immune responses (Adrover et al., 2019) suggests a remarkable degree

of “circadian autonomy” of innate immunity and its ability to entrain organ physiology. Further, the well-established role of microglia in housekeeping neural connectivity in the brain (Hayashi et al., 2014) and the ability of inflammatory mediators to act directly on the master clock (Kwak et al., 2008) suggest potential roles of immune cells in supporting normal SCN activity, in turn suggesting immune influence in organismal rhythms. We expect that by proposing exploration of multidirectional interactions between circadian oscillations and innate immune cells, including structural cells as essential intermediaries of the circadian immune circuits, we will obtain a better understanding of how these two systems (immune and circadian) orchestrate normal physiology. The proposed studies may additionally enable identification of immune defects as the source of dysregulated circadian oscillations and loss of fitness in tissues in a wide array of pathologies, including those associated with aging.

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