Advances in Neuroimmune Biology 4 (2013) 85–96
DOI 10.3233/NIB-130058
IOS Press

Role of Astrocytes in the Immune-Circadian Signaling

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Abstract. The mammalian circadian system controls biological rhythms by means of a central biological clock located in the suprachiasmatic nuclei (SCN) as well as diverse peripheral oscillators located throughout the body. Besides entrainment by the environment, rhythmic nervous and humoral factors are able to stimulate the clock and therefore close a feedback loop that fine-tunes the system. Among such factors, the immune system is clearly regulated by the circadian clock, with both cellular and humoral components experiencing daily rhythms in different tissues. We propose that immune factors are able to modulate the SCN and affect the phase of the oscillator. In addition, taking into account that astrocytes respond to cytokines and chemokines and might also secrete such molecules, as well as express immune-like receptors, we suggest that glial cells of the central nervous system play a key role as an interface between the immune and the circadian systems. The circadian modulation of the immune system opens a new perspective for the understanding of not only the origins of disease but also of physiological regulation of body functions. Conversely, immune factors are now being recognized as clock regulators, and astrocytes provide a link for such communication, adding another role to an increasing list of glial functions.

Keywords: Circadian rhythms, suprachiasmatic nuclei, astrocytes, immune system, cytokines

THE CIRCADIAN SYSTEM

In response to a changing environment, living organisms have developed an internal timing system capable of predicting periodic events, rather than simply responding to them. Indeed, circadian rhythms serve several purposes in physiology. An obvious one is optimization of resources, by temporal allocation of anabolic and catabolic process along the day. In addition, the prediction of a cyclic environment allows to prepare the body in advance by maintaining an adequate metabolic status. Desynchronization of the circadian system has been linked with pathological state, encompassing cellular, humoral, immune and cognitive consequences.

Although biological timing scales might span several orders of magnitude [1], the most studied mechanism is the one that tracks the 24 h cycle by means of a biological clock that, in mammals, has been located in the hypothalamic suprachiasmatic nuclei (SCN) [2, 3]. The cellular and neurochemical nature of the SCN indicate a subdivision between a ventrolateral core and a dorsomedial shell region, which differ in neuropeptide expression, afferent and efferent projections and gene expression [4, 5] (Fig. 1). In addition, these nuclei exhibit a dense presence of astrocytes, as evidenced by glial fibrillary acidic protein (GFAP) expression [6, 7]. Although individual SCN cells maintain robust rhythms in electrical activity and gene expression [8, 9], an adequate synchronization among such cellular oscillators is needed in order to achieve a coherent control of circadian output [10, 11].

Other than this internal synchronization, since circadian rhythms cycle with periods close to, but not exactly of, 24 hours, precise entrainment mechanisms are needed to keep pace with the environment. Probably the most important of such mechanisms is the one that links the SCN to the light-dark cycle, responsible for photic entrainment [12]. Light signaling reaches

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ISSN 1878-948X/13/$27.50

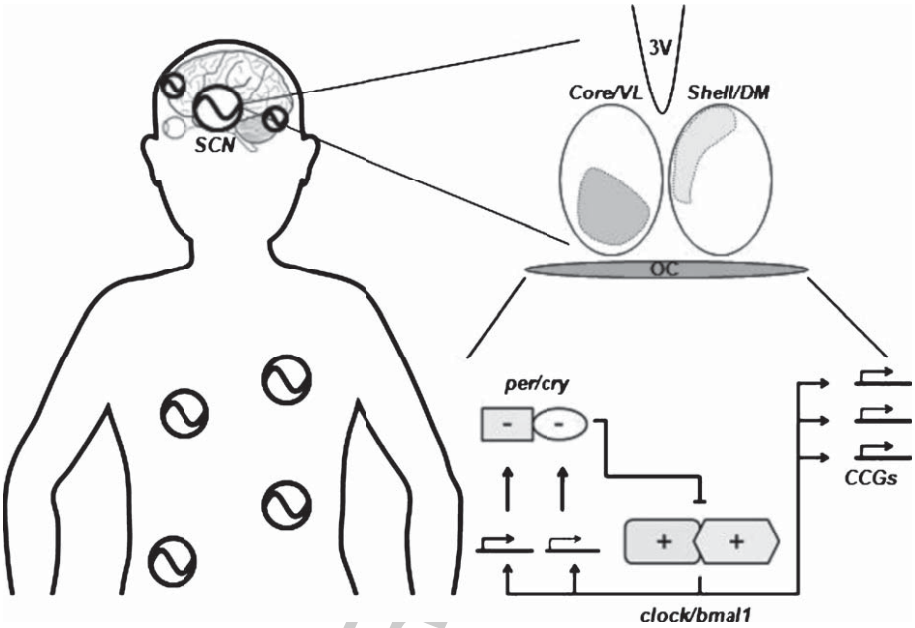

Fig. 1. The SCN as a master oscillator in the brain. Besides circadian clocks located in the brain and throughout the body, the suprachiasmatic nuclei (SCN) are considered the master circadian oscillator that set the pace to biological rhythms. The nuclei exhibit a heterogeneous structure, with a core (ventrolateral region, VL) and a shell (dorsomedial region, DM) with different inputs and outputs. Each pacemaker cell is characterized by a molecular oscillator exemplified by a transcription/translation feedback loop. The output of this circadian loop controls the expression of clock-controlled genes (CCGs), which might include those responsible for neural, humoral and immune communication. OC: optic chiasm, 3V: third ventricule.

the SCN through a direct retinohypothalamic pathway that activates the circadian oscillator and sets the phase of the clock, by interaction of glutamate and ionotropic/metabotropic receptors. Such photic messages are transduced inside SCN cells and ultimately affect the expression and/or post-translational regulation of specific genes.

This molecular circadian clockwork has been characterized in several systems – spanning from flies to mammals - which share many common features, notably a transcription-translation negative feedback loop with transcription factors that activate the expression of clock genes which in turn repress their own transcription [13] (Fig. 1). The key players in mammals include *Clock* and *Bmal1* genes, whose products heterodimerize and interact with E-boxes in the promoters of *Per* and *Cry* genes (as well as with other clock-controlled genes that represent the main molecular output of the clock). In turn, PER and CRY proteins interact and inhibit the activity of CLOCK and BMAL1. The system is regulated and stabilized by other loops which include retinoid-related orphan receptor (ROR) and REV-ERBα, among other accessory proteins which aid in the fine-tuning of the oscillator [14].

In recent decades the role of the SCN has been found to be closely related to circadian oscillators throughout the body, known in an SCN-centered view as "peripheral clocks". Although the first model regarded the SCN as a master clock which is entrained by the environment and thus sets the pace to the rest of the oscillators, recent evidence suggests that peripheral oscillators might be independently regulated by internal or external stimuli (e.g., food availability) and the role of the SCN is to maintain coherency among the different cycles in the body [15, 16]. Autonomous circadian clocks in the cardiovascular, respiratory, hepatic, digestive and immune systems are therefore able to govern local timing mechanisms and, indeed, desynchronization between body rhythms might be considered a sign of disease [17].

It is well known that the immune system is under strict circadian control [18, 19]; however, in recent years our group has focused on the role of immune factors as signaling molecules from the periphery to the central circadian clock. The cellular and molecular pathways for this bidirectional interaction are not completely understood, and in this short review we summarize findings pointing towards a fundamental role of glia in such process.

GLIA AND THE CIRCADIAN CLOCK

Since the nervous system was first described as having two main types of cells, neurons and neuroglia, the latter were considered to play just a role of neuronal support, completely unrelated to the information processing attributed to neurons. As the development of the brain was studied in more detail, it became clear that glial cells are critical for its correct morphological and functional maturation. Glial cells can be divided into microglia, which are derived from erithromyeloid precursors during development, and macroglia, which arises from neuroepithelial stem cells and include astrocytes, oligodendrocytes and NG2 cells. While immune functions in the central nervous system are mainly devoted to microglia, in the last two decades, plenty of information was gathered by neuroscientists around the world supporting the idea of astrocytes playing an active role in both central nervous system maturation and information processing. Today the tripartite synapse, with astroglial cells participating actively in the synaptic process together with presynaptic and postsynaptic neurons, is widely accepted by the scientific community. Astrocyte cells can release and respond to intercellular signaling molecules known as gliotransmitters, they can also modulate the abundance of neurotransmitters in the synaptic cleft by reuptake mechanisms, provide neurons with neurotransmitter precursors and can mechanically modify synapses by changing the neuronal coverage. Gliotransmitters include a large variety of signaling molecules including neurotransmitters (i.e. glutamate, adenosine, ATP and D-serine), cytokines, chemokines, prostaglandins and many more [20, 21]. Each astrocyte can release many different gliotransmitters and communicate with neighboring astrocytes, neurons and other cells through gap junctions, leading to a very complex network of cellular interactions. Thus it is necessary to unveil the specific roles of glial cells in order to have a better understanding of how the nervous system or any of its components work. The circadian system is no exception to this.

When the SCN were identified as a possible location for the central circadian pacemaker, one of the first observations was that these nuclei could be marked just by immunostaining for GFAP [6] due to the dense presence of astrocytes, the most abundant type of glial cells in the brain. The high levels of GFAP expression suggest that astrocytes in the SCN are in a reactive state [6], a common feature of astrocytes responding to inflammation and injury. Interestingly this feature is shared by the intergeniculate leaflet (IGL) [22] an homologous structure in rodents to the primate pregeniculate nucleus. The IGL works as a relay nucleus that allows photic and non-photic stimuli to modulate the SCN and is part of the circadian system [23]. Maturation of the SCN, the IGL and the neuronal tracts connecting them is clearly correlated to glial activity and maturation in both embryonic and postnatal stages [22]. Glial cells are also critical for the development of the retino-hypothalamic tract that connects the SCN directly with the retina.

While our understanding of the role of glia is still limited, it is clear that they play important roles beyond developmental functions. Enough data was gathered in the last few decades showing the importance of glial cells and particularly astrocytes in the functioning of the circadian system (the general role of glial cells in the circadian system has been covered by other articles [24, 25]) and its interactions with other systems (i.e., endocrine and immune systems). The presence of reactive astrocytes in the SCN led researchers to use GFAP expression to investigate if there were circadian rhythms in expression levels or morphology of the GFAP immunoreactivity. It was found in hamsters that GFAP immunoreactivity and morphology in the SCN displayed circadian variations [7]. These results were confirmed later in mice [26, 27] while only daily rhythms (absent in constant conditions) were observed in rats [28]. Since GFAP is expressed only in astrocytes in the adult brain, these data show that astrocytes in the mammalian SCN can display circadian rhythms. The role of circadian variations in GFAP immunoreactivity and astrocyte morphology is hard to assess but it can be related to SCN plasticity. The astrocytic coverage of vasointestinal peptide (VIP) and arginine-vasopressin (AVP) positive synapses in the SCN change during the day with higher coverage during the night for neurons in the core (mostly VIP positive) and increased coverage during the day for the shell region (mostly AVP positive) [29]. Because the SCN core is the area receiving photic input from the retina, changes in astrocytic coverage could be modulating or gating photic input to the SCN and therefore entrainment by light. This is supported by the finding that upon photic stimulation, some glial cells in the SCN are activated as assessed by c-Fos immunoreactivity [30, 31], which could be considered a marker of astrocytic activation [32–35]. It was also reported that lighting conditions in pups affected the number and distribution of GFAP positive cells in the SCN. Autonomous rhythmicity of astrocytes was confirmed using bioluminescent clock-gene reporters that showed circadian expression even after isolating and culturing astrocytes in a dish [36, 37].

Several experiments were carried out to determine the relevance of glia in the SCN *in vivo*. Prosser and cols [38] treated rats with fluorocitrate, an inhibitor of glial metabolism and with octanol, a gap junctional blocker. They were able to show that in both cases circadian rhythms of running-wheel activity were affected. Fluorocitrate induced ultradian rhythmicity and octanol disrupted the rhythms. Bilaterally enucleated hamsters had a shorter average period and broader range of periods when compared to hamsters kept in constant darkness. The only difference found within the SCN was a large decrease in GFAP staining while AVP, VIP, calbindin and Neuropeptide-Y were unaltered [39]. Circadian rhythms of mice lacking GFAP were studied and it was found that GFAP knock-out mice had longer periods and unstable running-wheel activity rhythms under constant light conditions [40]. These results showed that astrocytes play a role in the normal generation of circadian rhythms but details remain unclear.

A few questions are still lacking a definitive answer. Can glial cells be synchronized and do they have pacemaking capabilities? Studying primary astrocyte cultures derived from PER2::LUC transgenic mice, it was shown that they could be entrained by several factors including VIP [41], a neuropeptide that is crucial for the synchrony among neurons of the SCN [37] and a well known anti-inflammatory factor [42]. In fruit flies (*Drosophila melanogaster*) PER protein is expressed rhythmically in both glia and neurons, and flies with PER protein detectable only in glial cells were weakly rhythmic indicating for the first time that glial cells could behave as circadian pacemakers [43]. This result correlates with the finding that flies carrying a null mutation in the ebony gene (expressing a glia-specific enzyme), are arrhythmic [44] but become rhythmic when astrocyte-like glial cells are rescued and express the *ebony* gene. It was also shown that glial modulation of neurons and circadian rhythms in flies depend on intercellular calcium stores [45]. These data showed that astrocyte-like glial cells in the fly could modulate clock neurons and circadian behavior. It is still unclear which signaling pathways are involved or necessary in glial pacemaking capabilities but several candidates are being studied.

Interestingly, astrocyte morphology mediates the interaction between the circadian and endocrine systems. Release of VIP by SCN neurons induce a morphological change in astrocytes surrounding gonadotropin-releasing hormone (GnRH) neuronal cell bodies leading to a change in the neuronal area covered by astrocytes. Decreased coverage is associated with an increased input to the GnRH neurons inducing preovulatory synthesis and release of the neuropeptide [46, 47]. Astrocytes in the SCN could modulate neuropeptide release through similar mechanisms. In such case, these glial cells could gate input signals to the SCN and modulate downstream interactions between SCN neurons (Fig. 2). In addition, astrocytes located in brain areas targeted by SCN outputs could modulate the response of target neurons. Through astrocyte-astrocyte gap junctions and gliotransmision, astrocytes behave as a very complex network that could add plasticity and complexity to the SCN leading to the fine tuning required to orchestrate the timing of the multiple oscillators in the body. There are several signaling molecules that fit as good candidates to test such model, glutamate, PACAP and NPY [48] are the main input signals to the SCN and astrocytes have receptors for all of them plus the capability of modulating extracellular glutamate concentration through uptake and release. Astrocytes have also receptors for GABA, one of the main neurotransmitters within the SCN [49] and for VIP that is critical for both, intra-SCN synchrony and SCN output to other brain areas [37, 49–51]. Other hypothalamic nuclei such as the paraventricular hypothalamic nuclei (PVN) should be studied in this context since they behave as relays to the interaction with other functions including general metabolism, thermal regulation and immune responses.

One of the signaling molecules studied in more detail within the circadian system is extracellular ATP, an important mediator of intercellular interactions in the nervous, vascular and immune systems and it was found to be rhythmic in astrocytic cell cultures, SCN and SCN-derived immortalized cells [52, 53]. Circadian rhythms in extracellular ATP contents are generated by the canonical clock genes, require the inositol-triphosphate pathway, calcium release from internal stores and it is not related to SNARE-dependent vesicular release [53, 54]. This suggests that other ATP releasing mechanisms such as hemichannels could be under the control of the molecular clock. Altogether these data suggest astrocytes might behave as autonomous circadian oscillators under certain conditions and, in addition, these cells can be entrained and affect SCN neuronal activity.

RHYTHMS IN THE IMMUNE SYSTEM: A BIDIRECTIONAL COMMUNICATION

The importance of the circadian system in the regulation of different physiological process can be

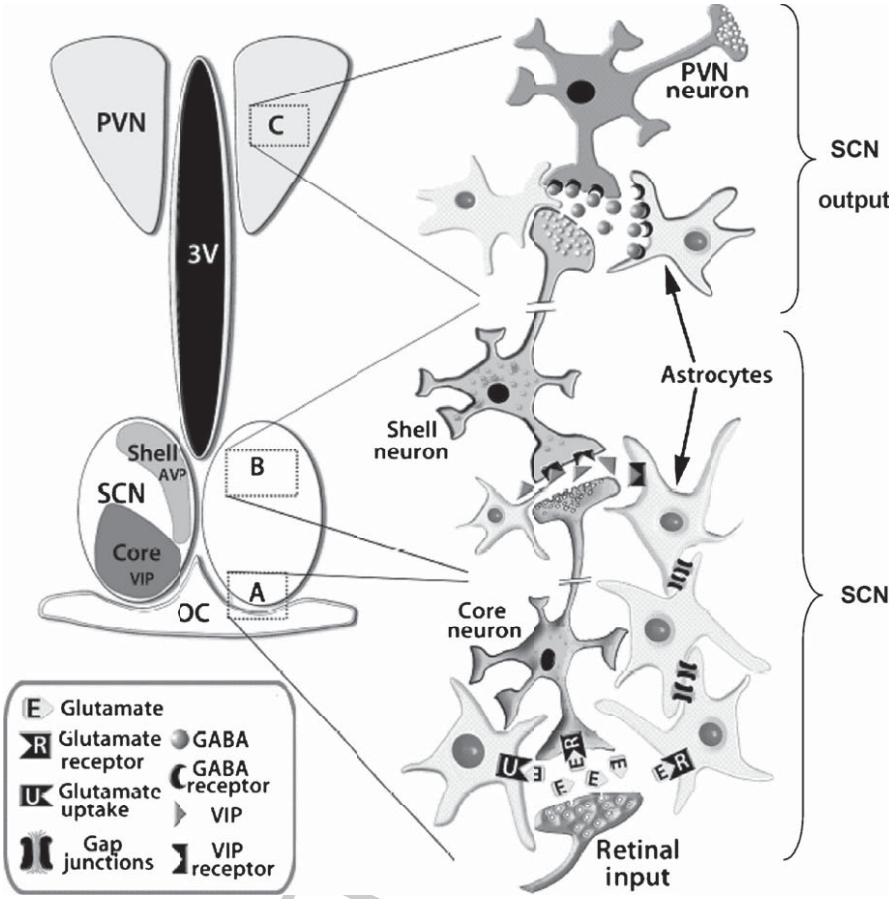

Fig. 2. Hypothetical model for the role of astrocytes in the circadian system. A) Photic signals arrive to the suprachiasmatic nuclei (SCN) from the retina through glutamatergic projections that interact with retinorecipient neurons (black nuclei) within the SCN which express both ionotropic and metabotropic receptors. These interactions can be modulated by astrocytes (grey nuclei) through glutamate uptake, gliotransmitter release and neuronal coverage. B) Sinchrony within the SCN requires both gamma-aminobutyric acid (GABA) and vasoactive intestinal peptide (VIP) signalling, that can also generate a response in astrocytes. Upon activation with VIP, astrocyte morphology and clock gene expression change, modulating the activation of downstream neurons. C) Finally, an output signal from the SCN sets the phase of other nuclei (Paraventricular nuclei, PVN, as an example here) by both, activating neurons and astrocytes in the target brain areas. 3V: third ventricle.

evidenced in a variety of disorders that are influenced by circadian dysfunction. These conditions include sleep disorders, depression, metabolic syndrome, cancer and inflammation [55–60]. The biological clock exerts a very precise control over the immune system, which may be important in the pathological consequences of circadian disruption. The levels of circulating cytokines, immune cells, and hormones that regulate the immune response vary along the time of day [61], and oscillatory expression of clock genes, immune-related receptors and signaling molecules has been described in organs and cells involved in the immunological responses [62–66]. Moreover, the response of the immune system to a wide variety of stimuli is modulated by the circadian clock [63, 67–73] and a number of pathologies that involve inflammatory activation present daily patterns in severity of symptoms, such as rheumatoid arthritis, asthma, Alzheimer's disease and sepsis [74–77], which stress the importance of the circadian control of the immune system. The precise pathways by which the circadian system regulates the immunological variables are not fully understood yet, although there are several evidences suggesting neural, endocrine and molecular cross-communication between the two systems (Fig. 3). Neural circadian control over different oscillating immune parameters could be achieved through PVN neurons. As already mentioned, the PVN acts a circadian relay station governing autonomic inputs to peripheral immune structures such as the thymus, spleen and lymph nodes. Indeed, sympathetic, norepinephrine-mediated, signals reaching the spleen

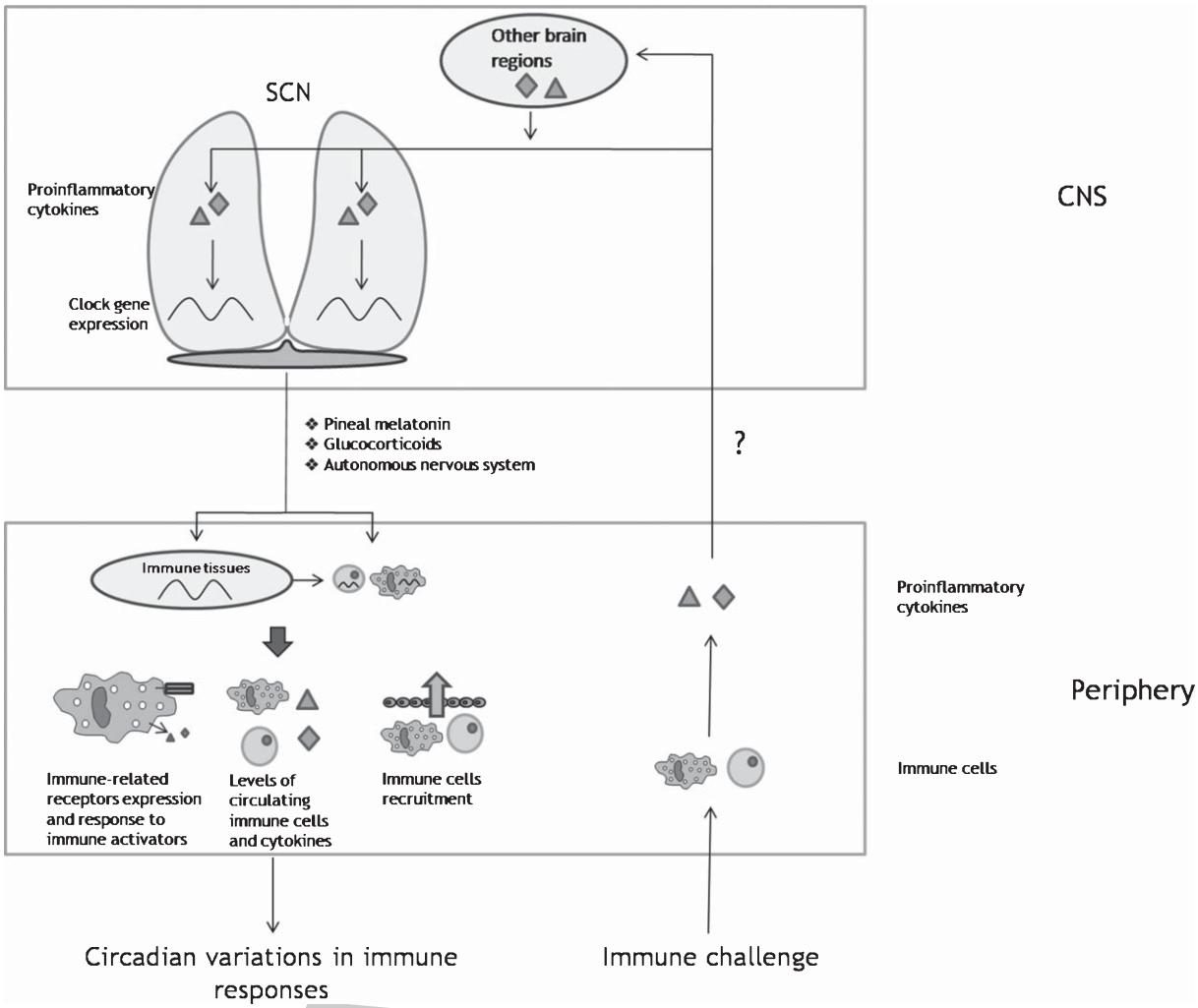

Fig. 3. Bidirectional communications between the immune and the circadian systems. The master circadian clock, located in the suprachiasmatic nuclei (SCN) regulates rhythmic immune function through both endocrine and neural pathways. This might be achieved by setting the circadian clock in tissues and cells from the immune system. These, in turns, control the oscillations in the levels of circulating cytokines and in the number, trafficking, and responsiveness of immune cells which are responsible for circadian gating of the immune response. Conversely, signals of activation of the immune system after a challenge reaches the central nervous system (CNS) through pathways that are not fully characterized yet, and may involve both neural (i.e. vagal) and humoral routes. This information results in increased levels of proinflammatory cytokines in the hypothalamus, and other brain regions, and ultimately leads to an increase of proinflammatory cytokines levels within the SCN. These cytokines produce alterations in clock gene expression and ultimately induce changes in circadian behavioral outputs.

control rhythms in cytokine and cytolytic factors levels in splenocytes and NK cells [78]. Furthermore, circadian control through the autonomic nervous system is responsible for the temporal changes in the localization of different immune cells. Epinephrine was shown to control the rhythms in the levels of circulating CD-8 + T-cells [79], and circadian oscillations in leukocyte recruitment to different tissues was reported to be governed by sympathetic innervations acting on adrenergic receptors [80]. Regarding endocrine parameters, strong circadian control has been described for the pineal hormone melatonin and for glucocorticoids, both of which possess immunomodulatory functions. Indeed, administration of melatonin has been shown to modulate TNF-α serum levels and to drive rhythmic clock gene expression [81, 82] and pro- and anti-inflammatory cytokines in the spleen [83]. Cortisol has been shown to control the levels of circulating naïve T cells [79]. In addition, at a molecular level, several clock genes, such as *Per2-3* [84–86], *Cry* [87, 88], *Bmal1* [62], *Clock* [89] and *Rev-erb*-α [72], have been linked to the modulation of the immune responses,

probably acting through the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) signaling pathway [75, 88–91].

Besides a strong rhythmic modulation in immunological functions and responses, the immune system is able to feedback to the circadian clock (Fig. 3). Pathologies such as Human African trypanosomiasis, sepsis, cancer and Alzheimer's disease, which involve immune and inflammatory activation, have been shown to alter circadian rhythms [92–97]. Furthermore, the administration of proinflammatory factors can act on the molecular clock of different organs and cell types, both in the periphery and within the central nervous system (CNS). *In vitro* studies have shown that the proinflammatory cytokines IFN-α, TNF-α, IL-1β and IL-6 can alter clock gene expression in different peripheral cell types [98–100]. Moreover, cytokine modulation on clock gene expression has also been described in *in vivo* approaches. Chronic infusion of TNF-α and IFN-α impairs clock gene expression in the liver [98, 100], and LPS administration alters clock gene expression in different types of blood cells [101, 102] and suppress *Per1-2* rhythms in the liver [103]. The influence of peripheral immune stimuli can reach the circadian clock in the CNS and alter the master oscillator. Low doses of LPS administered intraperitoneally induce *Per1* expression in the PVN and produce phase shifts in behavioral rhythms [104–106], and, at a higher dose, transiently suppressed *Per2* expression in the SCN [103]. When administered into the SCN region, proinflammatory cytokines induce phase shifts in locomotor activity circadian rhythms [107, 108], suggesting that the effects of peripheral immune stimuli on the master circadian clock could be mediated by the action of these molecules acting at central level. Indeed, the circadian behavioral outcomes of intraperitoneal endotoxin administration were blocked by TNF-α antagonism in the SCN region [107]. In addition, *in vitro* studies have shown that both clock gene expression and electrical activity of SCN cells can be altered by the proinflammatory cytokines IFN-γ, TNF-α [109–111]. Regarding the signaling pathway by which immune molecules could modulate clock gene expression and circadian behavior, there are evidences suggesting the involvement of p38 and NFκB [100, 112]. Moreover, the effects of an immune challenge on the circadian clock are themselves time-dependent. IFN-α repeated dosage leads to inhibition of clock gene expression in peripheral organs (liver and adrenal) and in the SCN, when the cytokine is administered in the day/night, but not in the night/day transition [113]. Phase delays produced by peripheral endotoxin administration occur only when the challenge is given at the beginning of the subjective night [106], and intracerebroventricular (icv) delivery of a proinflammatory cocktail during night produced higher cFos induction in the SCN than during the day [114]. These evidences suggest a complex interaction between the immune and the circadian system, involving proinflammatory cytokines.

ASTROCYTES AS AN IMMUNE-CIRCADIAN INTERFACE

Immune functions in the central nervous system are accomplished by glial cells, particularly microglia and astrocytes, as well as by infiltrating cells such as neutrophils, mast cells and T cells that migrate from periphery in response to proinflammatory signals. Immune surveillance, as well as primary response to immune insults, are mainly mediated by microglia, which constitute the principal immune soldiers within the CNS. However, although microglia is highly specialized to elicit an innate inflammatory response, astroglial cells are also involved in the generation and regulation of proinflammatory signals. Upon activation, astrocytes respond by secreting a wide variety of cytokines (IL-1, IL-6, IL-10, TNF-α), chemokines (CXCL1,2,12, CCL2,5,10,19), gaseous messengers (NO) and altering the uptake of components involved in synaptic transmission [115]. Beyond pathological or inflammatory situations, proinflammatory factors secreted by astrocytes are involved in the regulation of synaptic functioning in physiological conditions. TNF-α secreted by astrocytes increase long-term potentiation and homeostatic synaptic scaling [116, 117] and impairment in learning and memory in interleukin-1 receptor type I knock-out mice was rescued by WT astrocytes transplantation [118].

The evidences showing that astrocytes can respond to immune stimuli and are implicated in circadian regulation led to the hypothesis that these cells are involved in the circadian outcome of an immune activation. Astrocyte activation in the SCN might be induced by proinflammatory cytokines reaching the brain upon peripheral immune activation, or by alterations in endocrine pathways due to inflammatory conditions. For instance, GFAP expression and glial coverage of synapses in the SCN is modulated by adrenal glucocorticods, likely through an indirect pathway, since these nuclei express a relatively low number of glucocorticoid receptors [29, 119]. Since glucocorticoid hormones are upregulated upon immune stimulation,

this might provide a pathway for astroglial activation following peripheral challenges.

Systemic LPS challenges activate NF-κB signaling in the SCN and the phase shifts induced by this endotoxin are also mediated by NF-κB activity [106, 120]. Astrocytes from the SCN express NF-κB, which is activated in SCN glial cell cultures upon treatment with LPS, TNF-α and IL-1α [27] suggesting the modulation exerted by this transcription factor on the circadian clock could have astroglial cells as a cellular substrate in the CNS. SCN glial activation in response to immune stimuli was also evidenced *in vivo*. Upon icv administration of a proinflammatory cocktail, there is an increase in GFAP expression accompanied with astrocytic hypertrophy in the SCN of mice with prevalence in the core region of the nuclei [121].

Activation of astrocytes leads both to morphological changes in the cells and to the secretion of an interesting diversity of signaling molecules. Immune activation in SCN astrocytes leads to alterations in the molecular clock of these cells and to the secretion of TNF-α. This cytokine, in turn, modulates clock gene expression in other cell types and induces behavioral phase-shifts in locomotor activity rhythms (Duhart et al., unpublished data). These findings point to astrocytes acting as cellular mediators of the immune-circadian interaction at the SCN level, recognizing proinflammatory signals, and releasing factors that modify SCN physiology. However, an important role for other brain immune-responsive cells, such as microglia, in the modulation of the circadian clock by the immune system cannot be discarded and might be an interesting topic for future research.

CONCLUDING REMARKS

The nervous and immune systems can hardly be considered as separate entities since there are tight bidirectional interactions in both physiological and pathological states. Neurotransmitters can act as immune modulators and immune factors as neuromodulators, making the distinction between these systems some times unnecessary except for pedagogical reasons. The circadian system is responsible of setting the time for the rest of the body including the so-called peripheral oscillators and all other organs and bodily functions. The immune system is both one of the targets and an input for the biological clock and, as mentioned previously, immune factors could also play a role in its pacemaking properties.

There are many reasons why astrocytes arise as key players in neuroimmune interactions involving the circadian system. They are located and highly reactive in circadian-related structures (SCN, IGL and other), they react to photic stimuli, are capable of releasing many different gliotransmitters relevant for circadian rhythmicity, regulate synaptic plasticity in the SCN and display circadian oscillations of both clock genes and signaling molecules. Although other glial cells might also be playing an important role in this interaction, research involving cells other than astrocytes in the circadian system is on its early stages. Circadian rhythms of clock genes were reported in ependymal cells of the third ventricle but it is still unclear if and how they interact with the circadian system *in vivo*. There is almost no data regarding circadian properties and interactions of microglia and NG2 cells, making these an interest topic of research.

There are still many open questions and, therefore, many experiments to perform. Are glial cells behaving as pacemakers *in vivo* or are they just following neuronal inputs? Is the molecular clock in glial cells required for any of their functions both circadian and non circadian? Are they capable of restoring rhythmicity in arrhythmic animals? This last question was addressed by several researchers finding in flies that having normal clocks in glial (astrocyte-like) cells is enough for some rhythmicity to be displayed. There are now powerful genetic tools available to address these questions in more detail and with higher reliability so it is expected we will have a clearer understanding of the neuroimmune interactions in the mammalian circadian system in the near future. This would certainly help to increase the use of this knowledge in possible chronopharmacological treatments, sleep disorders and circadian dysfunctions including jet-lag, seasonal affective disorders and other.

The circadian modulation of the immune system opens a new perspective for the understanding of not only the origins of disease but also of physiological regulation of body functions. Indeed, the same key players involved in inflammation and defense against infections might serve other purposes, for example in the central nervous system and in metabolic activity. In particular, we have shown that proinflammatory cytokines and chemokines are able to affect the central circadian pacekamer, probably performing a fine-tuning regulation of the phase of the clock. Since astrocytes in the CNS are involved in both immune and circadian modulation, we propose that these cells behave as an interface between both systems, adding another role to an increasing list of glial functions.

ACKNOWLEDGMENTS

Our studies have been funded by the National Research Council (CONICET), the National Science Agency (ANPCyT) and the National University of Quilmes (UNQ).

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