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A circadian based inflammatory response – implications for respiratory disease and treatment

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Abstract

Circadian clocks regulate the daily timing of many of our physiological, metabolic and biochemical functions. The immune system also displays circadian oscillations in immune cell count, synthesis and cytokine release, clock gene expression in cells and organs of the immune system as well as clock-controlled genes that regulate immune function. Circadian disruption leads to dysregulation of immune responses and inflammation which can further disrupt circadian rhythms. The response of organisms to immune challenges, such as allergic reactions also vary depending on time of the day, which can lead to detrimental responses particularly during the rest and early active periods. This review evaluates what is currently known in terms of circadian biology of immune response and the cross-talk between circadian and immune system. We discuss the circadian pattern of three respiratory-related inflammatory diseases, chronic obstructive pulmonary disease, allergic rhinitis and asthma. Increasing our knowledge on circadian patterns of immune responses and developing chronotherapeutic studies in inflammatory diseases with strong circadian patterns will lead to preventive measures as well as improved therapies focussing on the circadian rhythms of symptoms and the daily variation of the patients' responses to medication.

Keywords: Immune system, Circadian clock, COPD, Allergic rhinitis, Asthma

Introduction

Jürgen Aschoff traced back the interest in biological rhythms to the Greek poet Archilochus of Paros (ca. 680–640 BC) who wrote "recognize which rhythms govern man" (Aschoff 1974). More than 2500 years later biological rhythms are known to 'govern' many aspects in human behaviour, physiology, metabolism, disease symptoms and response to treatment in a rhythmic fashion with the circadian clock as time-keeper.

The circadian clock ensures that the processes it regulates recur every day at the most optimal times of the day for the functioning and survival of the organism in a coordinated manner (Dibner et al. 2010). Disturbance of circadian rhythms due to, for example, shift-work (Kecklund and Axelsson 2016), circadian disorders or dysregulation of rhythmicity (McHill and Wright 2017; Morris et al. 2016; Kadono et al. 2016; Gamaldo et al. 2014; Dickerman et al. 2016) increase the morbidity risk of cardiovascular disease (Reutrakul and Knutson 2015), metabolic disease (Arble et al. 2010) and cancers (Levi and Schibler 2007). Recent work has shown that disruption of the circadian clock leads to dysregulation of immune responses which underlie the pathophysiological basis of disease, suggesting an important regulatory role of the circadian system. This relates to daily oscillations in the number of circulating innate and adaptive immune cells, cytokine and chemokine levels and expression of adhesion molecules that are integral components of the immune response (reviewed in (Labrecque and Cermakian 2015; Nakao 2014; Scheiermann et al. 2013; Cermakian et al. 2013; Cermakian et al. 2014)). Overall, multiple studies suggest that pro-inflammatory activity is elevated during rest and induces sleep whereas anti-inflammatory mediators are induced upon awakening and inhibit sleep (Bryant

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et al. 2004; Krueger 1990; Krueger et al. 2001; Kubota et al. 2001; Kubota et al. 2001; Kubota et al. 2001; Kushikata et al. 1999; Krueger 1987; Kubota et al. 2000). Interestingly, both symptom intensity and response to treatment of many illnesses, including autoimmune or inflammatory diseases, vary across the 24-h day (Smolensky et al. 2007; Smolensky et al. 2012; Buttgereit et al. 2015). For this reason, chronotherapy which entails optimal timing of administration of treatments for disease aims to ensure that effectiveness is maximized whilst any toxic side effects are minimised (Smolensky et al. 2016).

In the context of inflammation, it is crucial that we increase our understanding of the circadian patterns of immune responses and how they are regulated by the central and peripheral clocks to enable discovery of chronotherapeutic approaches for optimal timing of therapies and even preventive measures for inflammatory disease, allergies and infections. This descriptive review focuses on the relationship between circadian clocks and the immune system and inflammatory diseases and discusses the potential for developing new therapeutic approaches. We discuss the urgent need of bridging all the fundamental knowledge established in chronobiology with disease to develop novel translational strategies that take time of day into account.

How is entrainment achieved in circadian rhythms?

Periodic environmental changes in, for example, light intensity, temperature, food availability and predator pressure amongst many others have led to the evolution of biological clocks in most species (Daan 1981). Circadian clocks continue to oscillate in the absence of time cues but, in this scenario, their period is not equal to 24 h. Instead, they display rhythmicity characterized by their individual endogenous circadian period, τ, which is circa 24 h but not necessarily exactly 24 h. In the presence of an external synchronizer, called *Zeitgeber* (from German *Zeit* "time" and *Geber* "giver" (Aschoff 1951; Aschoff 1958)) with a period T, τ is adjusted daily to equal T (Pittendrigh 1981). In addition, a stable and distinctive phase angle difference between the *Zeitgeber* and the circadian clock results (Daan 2000; Hirschie Johnson et al. 2003). This process of synchronization of circadian clocks to the external *Zeitgebers* is called entrainment. For the purposes of this review, entrainment will refer to the central clock aligning to the external time cues, while synchronization will refer to the alignment of the central and peripheral clocks relative to each other.

The light-dark cycle due to the rotation of the Earth with a period T of 24 h is a very reliable signal organisms use to entrain circadian rhythms. Light is the most important *Zeitgeber* for many organisms (Pittendrigh 1981; Daan 2000; Aschoff 1960; Beersma et al. 2009). The specific properties characterizing the light signal that will contribute to entraining the circadian clock of an organism, e.g. duration of light and dark signals (Comas et al. 2006; Comas et al. 2007), light intensity (Boulos 1995), spectral composition (Boulos 1995; Revell et al. 2005; van de Werken et al. 2013; Cajochen et al. 2005) or twilight duration (Comas and Hut 2009; Aschoff and Wever 1965; Boulos et al. 2002; Boulos and Macchi 2005; Roenneberg and Foster 1997), will determine the robustness of entrainment. Other time cues, particularly food availability, have been proven to be potent synchronizers as well (Dibner et al. 2010). In mammals, the suprachiasmatic nucleus (SCN) located in the hypothalamus at the base of the brain is the 'master circadian clock' that generates and regulates the body's circadian rhythms and synchronizes them to the environmental 24-h light-dark cycle.

In addition to the master clock, peripheral clocks are found in virtually all individual cells in the body where they coordinate cellular processes – most notably within organs and other tissues including spleen, lymph nodes and different cells of the immune system (e.g. macrophages, monocytes, neutrophils or natural killers) (Keller et al. 2009; Boivin et al. 2003; Bollinger et al. 2011). All peripheral clocks are synchronized daily and coordinated by the SCN via the hypothalamic pituitary adrenal (HPA) axis and the autonomic nervous system (ANS) (Dibner et al. 2010; Nader et al. 2010; Kalsbeek et al. 2012). Peripheral clocks can also be synchronized and even uncoupled from the SCN by, for example, food availability or temperature (Brown et al. 2002; Mistlberger and Marchant 1995; Damiola 2000; Stokkan et al. 2001; Comas et al. 2014). However, in mammals the SCN is the only component of the circadian system that receives light input to maintain circadian synchronization with other peripheral clocks (Bell-Pedersen et al. 2005) (Fig. 1).

A molecular circadian clock is ticking in each of our cells

The mammalian molecular clock machinery is present in virtually all cell types including immune cells (see reviews for detailed descriptions of the molecular clock machinery (Labrecque and Cermakian 2015; Papazyan et al. 2016; Herzog et al. 2017; Partch et al. 2014; Takahashi 2017; Stojkovic et al. 2014)). In brief, it is composed of a set of proteins that generate two interlocking auto-regulatory transcription-translation feedback loops (TTFLs) (Fig. 2). For clarity reasons, we will use italics when we refer to genes and capital letters when we refer to proteins throughout the text. The main loop is composed of a positive and a negative arm. Circadian Locomotor Output Cycles Kaput (CLOCK), or its paralog NPAS2(DeBruyne et al. 2006), and brain and

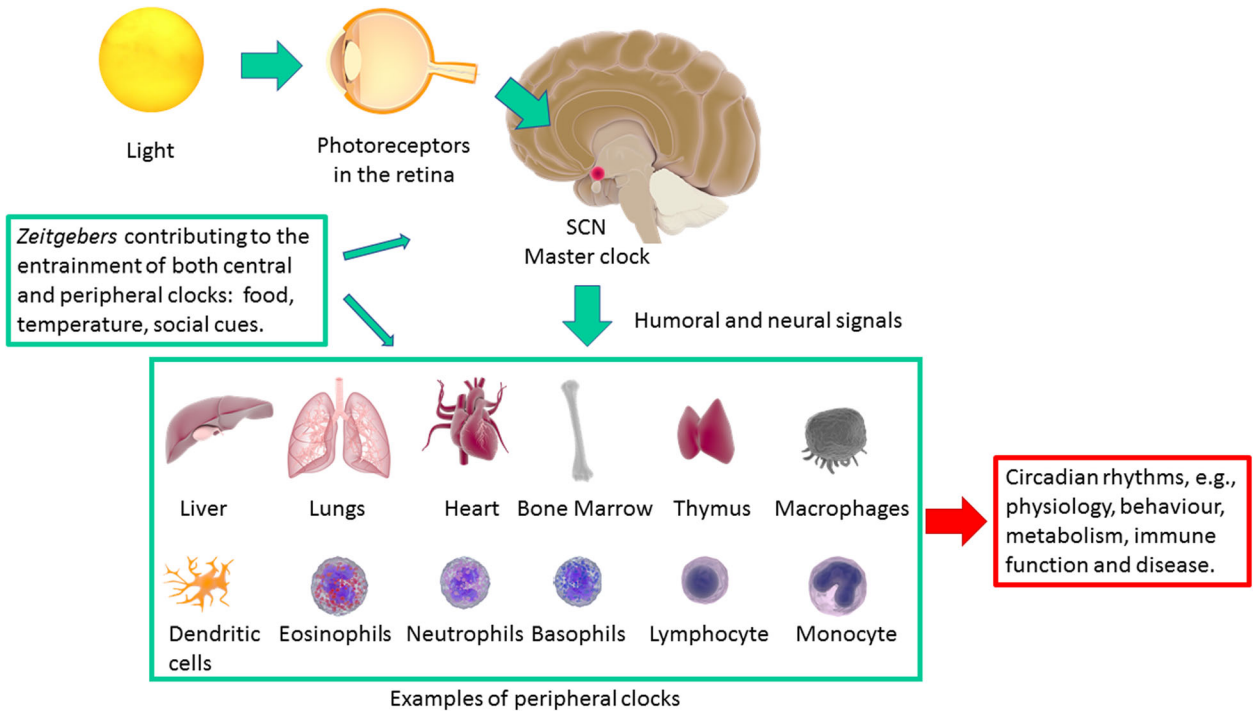

Fig. 1 Light input is received daily by specialized photoreceptor cells in the retina, the intrinsically photosensitive retinal ganglion cells (ipRGCs) and transmitted via the retino-hypothalamic tract to the central clock located in the suprachiasmatic nucleus (SCN) entraining it to the external light dark cycle(Gooley et al. 2001). Then, the SCN synchronizes all tissues and cells via humoral or neural signals maintaining coordination with each other. Besides this synchronization, each tissue and cell has its own molecular clock, the peripheral clocks. *Zeitgebers* other than light, such as food, temperature or social cues, can entrain/synchronize or strenghten the robustness of entrainment/synchronization of both the SCN and peripheral clocks. This will result in the temporal organization of the many functions and behaviours that oscillate daily in most organisms on the planet

muscle ARNT-like protein 1 (BMAL1) proteins are part of the positive arm of the loop. The CLOCK/BMAL1 heterodimer binds to E-box sequences in the promoters of the clock controlled genes regulating the timing of their expression around 24-h. CLOCK/BMAL1 also regulate the transcription of the negative components of the loop that will repress their own activity thereby closing the feedback loop, e.g., *Period* (*Per1, Per2, Per3*) and *Cryptochrome* (*Cry1, Cry2*). PER and CRY proteins heterodimerize and are phosphorylated by CASEIN KINASES 1 δ and ε (CK1δ and CK1ε) which targets them for translocating back into the nucleus where they directly bind to the BMAL1/CLOCK complex, disrupting it and repressing its actions. E3 ligase complexes will then target PER/CRY for ubiquitylation which will lead to degradation by the proteasome. As PER/CRY are degraded and their levels decline, repression of BMAL1/CLOCK will decrease and a new cycle will start. ROR-α and REV-ERB-α proteins conform a second adjoining loop binding to ROREs motifs found on the promoter of *Bmal1* activating or repressing its transcription respectively. What distinguishes the circadian clock feedback loop from any other feedback loops is that it takes about 24 h to be completed. This is achieved through, for example, protein phosphorylation, ubiquitylation, or SUMOylation that will tag proteins for e.g. trafficking or degradation creating delays in the 24 h feedback loops.

Importantly, the transcription of about 2-10% of mammalian genes, from different murine and human tissues or cells, are regulated by the molecular circadian clock (and these include genes related to immune response pathways as well as genes associated with inflammatory lung diseases (see examples and reviews (Partch et al. 2014; Logan and Sarkar 2012; Oishi et al. 2003; Sukumaran et al. 2011; Zhang et al. 2014a; Möller-Levet et al. 2013a; Akhtar 2002)). The percentage of proteins oscillating in mammalian tissues are as high as 20%(Mauvoisin et al. 2014; Reddy et al. 2006; Deery et al. 2009). This suggests that not only transcription but other mechanisms such as post-transcription, translation, post-translational

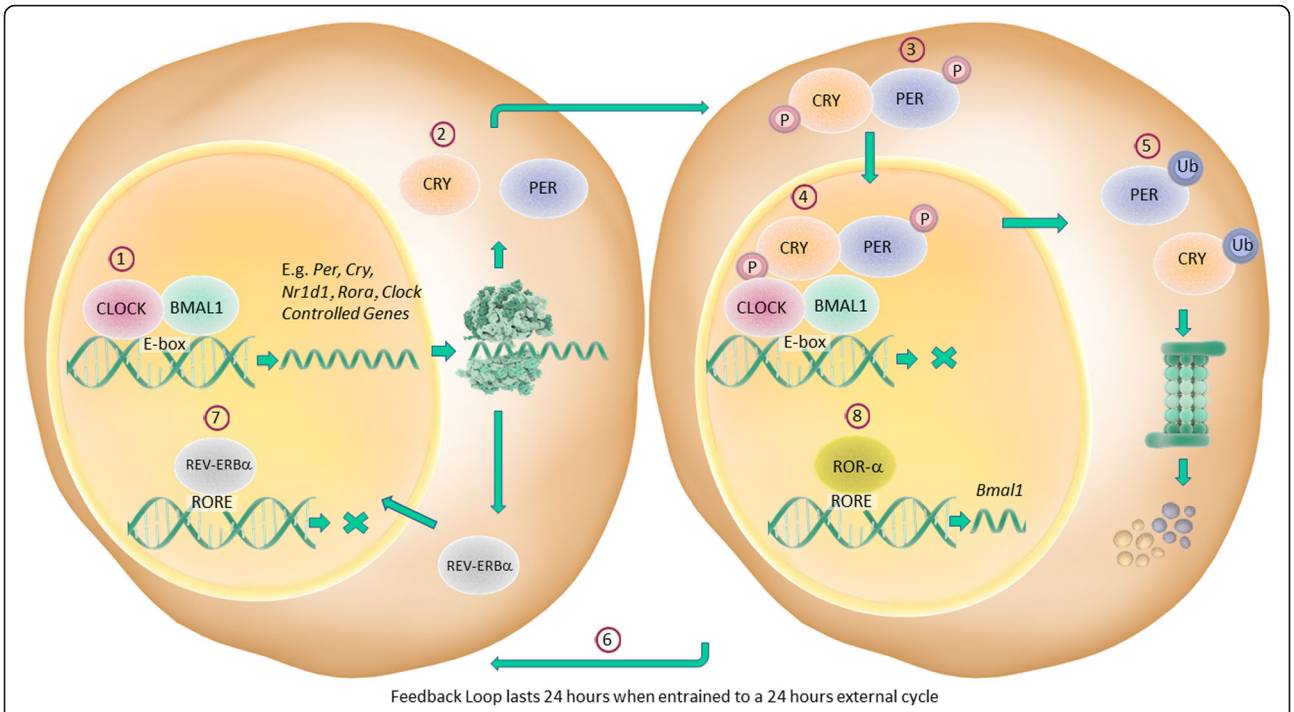

Fig. 2 Scheme representing the same mammalian cell, e.g. SCN cell, showing the molecular circadian clock sequence of events that under normal entrainment conditions in nature, lasts 24 h. ① CLOCK and BMAL1 proteins form a heterodimer which activates the transcription of genes encoding other core components of the loop: e.g. *Cryptochrome* (*Cry1 and Cry2*), *Period* (*Per1 and Per2*), *Nr1d1* (REV-ERB-α protein) or *Ror-α*. CLOCK and BMAL1 also regulate the transcription of the so-called clock controlled genes. Among these genes there are key factors in processes intimately related to immune response.② *Cry* and *Per* mRNAs are translated into CRY and PER proteins with levels increasing during the night and form a heterodimer. ③CK1δ and CK1ε phosphorilate CRY and PER proteins allowing their translocation into the nucleus. ④ In the nucleus, the CRY/PER heterodimer represses the BMAL1/CLOCK activity thereby inhibiting their own transcription. ⑤ CRY and PER proteins are ubiquinated leading to their degradation via the 26S proteosome. ⑥ CRY and PER levels decrease and with it their repression over BMAL1/CLOCK, allowing for a new cycle to start again and the completion of the 24-h feedback loop. BMAL1/CLOCK also regulate the expression of the nuclear receptors *Nr1d1* (⑦ REV-ERB-α protein) and *Ror-α* (⑧ ROR-α protein) which will, in turn, repress or activate *Bmal1* transcription

modifications are oscillating or contributing to the circadian patterns of behaviour, physiology and metabolism.

There is a circadian variation in immune function

The immune system has as a primary function to protect against potentially harmful foreign bodies and disease. The innate component of the immune system comprises skin, all mucosal membranes, phagocytic cells (monocytes, neutrophils, eosinophils, macrophages and basophiles) and natural killer T-cells (NK). It is considered a first line of defence against foreign bodies and it also has a critical role in the activation and regulation of adaptive immunity (Iwasaki and Medzhitov 2015). This component is semi-specific, non-adaptable, non-plastic and has no 'memory'. In contrast, the adaptive component of immunity comprising B and T lymphocytes are adaptable, plastic and have 'memory'. Immune cells of both innate and adaptive immunity become activated and are recruited to sites of infection or injury in the process of inflammation (Riera Romo et al. 2016; Bennett et al. 2017; Ward and Rosenthal 2014). Although beneficial, this inflammatory response can become over expressed leading to diseases and autoimmune disorders (Barnes 2008; Lien et al. 2012; Rose 2016).

Many cells and tissues of the immune system have been shown to have clocks that regulate many of their functions. In mammals, circadian clock genes oscillate in the spleen, lymph nodes, thymus, jejunum, macrophages, NK cells and CD4+ T cells (Keller et al. 2009; Bollinger et al. 2011; Alvarez and Sehgal 2005; Froy and Chapnik 2007; Arjona and Sarkar 2005; Arjona and Sarkar 2006). In fact, about 8% of the expressed genes in mice peritoneal macrophages show circadian variation, including genes involved in the regulation of pathogen recognition and cytokine secretion (Keller et al. 2009). A recent microarray study on the human blood transcriptome from sampled around the clock shows that the number of oscillating transcripts decreases and other genes are either up-, or down-regulated when subjects are sleep deprived, and genes associated with immune system amongst the most affected genes (Möller-Levet et al. 2013b). Whilst this suggests variations throughout the day in immune function, acute responses to infection or response to allergen exposure, future work is still needed to confirm a

causal link between underlying rhythms in immunity and the clock mechanism and functional outcomes.

It has been known since the 1960s-70s that the mortality rate of mice exposed to the bacterial endotoxin lipopolysaccharide (LPS) greatly varies depending on time of exposure (Halberg et al. 1960; Shackelford and Feigin 1973; Feigin et al. 1969; Feigin et al. 1972). In mice, a LPS challenge given at the end of the rest time results in a mortality rate of 80%. When the challenge is given in the middle of the active time the mortality rate is only 20%(Halberg et al. 1960). Similarly, bacterial infection has been shown to lead to higher mortality when initiated during the rest period (Shackelford and Feigin 1973). More recently, these results were confirmed and extended showing that exposing mice to LPS at the end of their rest period or beginning of the active period resulted in a stronger cytokine response and NF-κB activation compared with LPS exposure starting during the active period or beginning of the rest period (Marpegan et al. 2009; Gibbs et al. 2012; Nguyen et al. 2013; Spengler et al. 2012). Similar results have been obtained in humans using the LPS challenge both in vivo injecting LPS to healthy volunteers (Alamili et al. 2014) and in vitro exposing blood samples obtained at different times of the day from volunteers to LPS (Petrovsky et al. 1998; Rahman et al. 2015). The greatest response of the immune system in terms of cytokine release occurs during the rest and early active periods. However, this also implies that the risk of immune-related illnesses, such as, sepsis, allergies and uncontrolled immune reactions are more likely to occur during the late rest period and early active period.

Allergic reactions are initiated with antigen specific IgE production and fixation of IgE to FcεRI receptors on mast cells and basophils (Stone et al. 2010). Importantly mast cells, eosinophils and basophils display circadian oscillations of clock gene expression as well as circadian gene expression and release of their mediators following IgE-mediated activation (Baumann et al. 2013; Wang et al. 2011; Ando et al. 2015; Baumann et al. 2015). Several recent studies have shown that the circadian clock regulated the daily rhythms in IgE/mast cell-mediated allergic reactions. For example, *Per2* mutant mice have a decreased sensitivity to the corticosteroid dexamethasone inhibition of the IgE-mediated degranulation in bone marrow-derived mast cells (Nakamura et al. 2011). Furthermore, anaphylactic reactions to an allergen challenge display a time of day dependent variation in wild-type mice which disappears in *Per2* mutant mice exhibiting a strong reaction at all times throughout the cycle (Nakamura et al. 2011). This could be due to the disrupted circadian clock that specifically results from the *Per2* mutation (Spoelstra et al. 2014; Albrecht et al. 2001; Chong et al. 2012; Xu et al. 2007) compromising the mice's response to dexamethasone as well as to an allergen challenge and its consequent anaphylactic reaction. Another possibility is that PER2 protein has a clock-independent role in allergic reactions as most clock proteins have in different processes and pathways (Yu and Weaver 2011). The authors hypothesized that *Per2* could be regulating the rhythmic secretion of glucocorticoids or gating the glucocorticoid responses of mast cells to specific times of the day. It could also be a combination of clock-dependent and, –independent roles. Loss of clock function due to other factors also leads to disrupted responses to allergic reactions. For example, *Clock* gene mutation in mast cells leads to disruption of temporal variations in IgE mediated degranulation in mast cells associated with loss of temporal regulation of FcεRI expression and signalling (Nakamura et al. 2014). Collectively, these studies suggest that not only proper functioning of the immune system is regulated by circadian clocks but also allergies have a strong circadian component.

In turn, inflammation can also affect the circadian clock and the pathways it regulates such as metabolism and sleep-wake cycle (Bellet et al. 2013; Jewett and Krueger 2012; Lundkvist et al. 2002; Lundkvist et al. 2010). The circadian firing rhythms of the SCN neurons as well clock gene expression in the SCN is differentially affected by various cytokines, i.e. IFN-γ, TNF-α, IFN-α as well as the LPS challenge (Lundkvist et al. 2002; Kwak et al. 2008; Nygård et al. 2009; Okada et al. 2008). Furthermore, the effect of cytokines or LPS on clock gene expression in the SCN and peripheral clocks of rodents such as liver, heart or spleen, temperature or locomotor activity will vary depending on the time of day at which cytokines are administered (Duhart et al. 2013; Ohdo et al. 2001; Koyanagi and Ohdo 2002; Yamamura et al. 2010; Westfall et al. 2013; Marpegán et al. 2005; Leone et al. 2012; Boggio et al. 2003). Similarly in humans, LPS injection causes a suppression of clock genes e.g. *Clock, Cry1,2, Per1,2,3, Csnk1ε, Ror-α* and *Rev.-erb-α* in peripheral blood lymphocytes, neutrophils and monocytes (Haimovich et al. 2010).

Marpegan and colleagues suggested that immune responses may be acting as a synchronizing signal for the clock in a similar way to light that advances and delays circadian rhythms depending on time of day at which they administered (Marpegán et al. 2005). Immune responses could be acting as disrupting circadian clock signals instead. Chronic inflammation achieved by weekly injecting LPS to mice for 2 months leads to a decreased response of the SCN to light 7 days after the last LPS injection; however, the SCN response to light was restored 30 days after the last LPS injection (Palomba and Bentivoglio 2008).

As for potential mechanisms by which the immune system interacts with the molecular clock there are a few of studies so far. Cavadini and colleagues showed that TNF-α inhibits CLOCK-BMAL1 function by interfering with E-box mediated transcription leading to downregulation of expression of clock-controlled genes with E-boxes in their promotor (Cavadini et al. 2007). Petrzilka and colleagues extended this work and showed that TNF-α requires p38 mitogen-activated protein kinases (MAPK) and/or calcium signalling to upregulate expression of several core clock genes but it can downregulate *Dbp* (clock controlled gene) expression independently from p38 but requires calcium signalling (Petrzilka et al. 2009). And Bellet and co-workers showed that the RelB subunit of NF-kB interacts with BMAL1 protein and represses the circadian expression of *Dbp* (Bellet et al. 2012*)*. Overall, these studies provide clues to understand the cross-talk between the circadian and immune systems in inflammatory diseases. Further research should be directed at understanding the potential mechanisms by which the immune system gives time cues to the circadian system, both in health and in acute and in chronic inflammation.

The central clock regulates immune function

The central clock, located in the SCN, is thought to regulate aspects of immune responses. For instance, the SCN has been shown to regulate clock gene expression, oscillations in cytokines and cytosolic factors in NK cells and splenocytes in rats via the noradrenergic system (Logan et al. 2011). A lesion in the SCN leads to loss of the time of day dependence in passive systemic anaphylactic reaction in mice as well as loss of daily variations of cytokines (Nakamura et al. 2014). It has been shown that conditional ablation of *Bmal1* in T and B cells does not affect cell differentiation or their function suggesting a regulatory role of the central clock since circadian gating of IL-2 is preserved in *Bmal1*-deficient cells (Hemmers and Rudensky 2015).

The circadian regulation of the immune response is likely to be an integration of signals from the central clock and the peripheral clocks found in immune cells and organs as well as sites of infection. A very good example of this integration is the recent work by Gibbs and colleagues (Gibbs et al. 2014). They showed that the inflammatory response of the mouse lung to LPS has a daily rhythm peaking in the rest period which is regulated by both peripheral and central clocks. Thus, both the epithelial club cells (Clara) clock and the central clock through systemic glucocorticoid signals of adrenal origin, regulate the circadian oscillation of the CXCL5 chemokine which, in turn, drives the circadian oscillation of neutrophil recruitment to the lung. Disruption of the central or Clara cell clocks, i.e. ablation of *Bmal1* in the Clara cells or adrenalectomy, leads to the disruption of circadian oscillation of CXCL5 and, in consequence, of the neutrophil recruitment to the lung. These experiments demonstrate the importance of central-peripheral clock interaction in mediating lung immune responses.

As for cortisol and melatonin, outputs of the central clock, control the circadian oscillation of the number of circulating T cells in humans (Dimitrov et al. 2009; Besedovsky et al. 2014). Melatonin regulates daily rhythms of core clock gene transcription factors, *Bmal1* and *Per1* expression in the spleen and a pinealectomy (the surgical removal of the pineal gland which produces melatonin) abolishes these rhythms (Prendergast et al. 2013). Melatonin is thought to have an immuno-modulatory role that can either be pro or anti-inflammatory however the mechanism is still unclear. Different studies showing the actions of endogenous and exogenous melatonin on the immune system have been reviewed elsewhere (Carrillo-Vico et al. 2005; Carrillo-Vico et al. 2013; Ren et al. 2017). Nevertheless it is worth mentioning the review by Carrillo-Vico and co-authors suggesting that melatonin may act as an immune buffer, whereby it may act as an immune stimulant under immune suppressive conditions and as an anti-inflammatory agent under conditions of exacerbated inflammation (Carrillo-Vico et al. 2013). If true, then interest in the potential for melatonin as a therapeutic with immune-modulatory properties will significantly increase in the future.

Peripheral clocks regulate immune function

Many cells and organs that are part of the immune system have been shown to display circadian oscillations in clock gene expression and function. Table 1 shows examples of immune system components displaying oscillations in number of cells and/or functionality. Toll-like receptors (TLRs) are proteins expressed on the surface of many cells and within endosomes and play a role in pathogen recognition and consequent activation of the innate immune system. The expression levels of TLRs display significant circadian oscillations in the mouse jejunum (Froy and Chapnik 2007). The levels of TLRs start to rise during the second part of the active phase and peak during the rest period which is probably when unwanted bacteria have reached the jejunum. Silver and colleagues demonstrated in mice that the expression of TLR9 in macrophages and B cells display circadian rhythmicity (Silver et al. 2012). The TLR9 circadian rhythm has functional consequences. For example, the time of day at which sepsis was experimentally induced in mice determines sepsis severity and mortality. This also coincides with the time of day when

Table 1 Examples of circadian rhythms in the immune system and the correspondent peaks and troughs of these oscillations

Organism	Oscillating component	Peak	Trough	Ref.
Mouse	Number of Ly6Chi monocyte in blood and spleen	ZT4-ZT8	ZT12-ZT24	(Nguyen et al. 2013)
Mouse	Circulating total leukocyte counts	ZT5	ZT13	(Scheiermann et al. 2012)
Mouse	Circulating HSCs and their progenitors	ZT5	ZT17	(Mendez-Ferrer et al. 2008)
Mouse	Number of LSK cells per ml of blood	ZT5	ZT13	(Mendez-Ferrer et al. 2008; Lucas et al. 2008)
Mouse	Activation of NF-κB	ZT6	ZT18	(Spengler et al. 2012)
Mouse	TNF-α and IL-6 secreted by spleens harvested around the clock and stimulated with LPS	CT8	CT20 (TNFα) CT16 (IL-6)	(Keller et al. 2009)
Mouse	Abundance of B cells and macrophages in the spleen	CT8	CT16	(Keller et al. 2009)
Mouse	Cytokine responses to LPS IL-1β, IL-6, MCP-1 and MIP1alpha	ZT11	ZT19	(Marpegan et al. 2009)
Mouse	TLR9 mRNA in macrophages	ZT11	ZT3	(Silver et al. 2012)
Mouse	Cytokine responses to LPS: IL-6, IL-12, CCL5, CXCL1 and CCL2	ZT12	ZT0	(Gibbs et al. 2012)
Mouse	Recruitment of leukocytes from the blood to tissues	ZT13	ZT5	(Scheiermann et al. 2012)
Mouse	ICAM1 protein abundance in muscle	ZT13	ZT5	(Scheiermann et al. 2012)
Mouse	Ccl2 mRNA abundance in cremasteric endothelial cells	ZT13	ZT1	(Scheiermann et al. 2012)
Mouse	CXCR4 expression in bone marrow LSK cells	ZT13	ZT5	(Lucas et al. 2008)
Mouse	TLR9 mRNA and protein abundance in the spleen	ZT19	ZT7	(Silver et al. 2012)
Mouse	Phagocytic activity of neutrophils	ZT20	ZT8	(Hriscu 2004)
Mouse	CXCL12 content in bone marrow extracellular fluids	ZT21	ZT9	(Mendez-Ferrer et al. 2008)
Human	Counts of peripheral monocytes	12:00 am	8:00 am	(Born et al. 1997)
Human	Counts of peripheral Lymphocytes, B-cells, T-cells, T-helper, T-suppressor	2:00 am-3:00 am	11:00 am	(Born et al. 1997)
Human	Circulating eosinophils	4:00 am	12:00 pm	(Haus and Smolensky 1999)
Human	Circulating lymphocytes	12:00 am-4:00 am	8:00 am	(Haus and Smolensky 1999)
Human	Counts of peripheral NK	11:00 am-6:00 pm	2:00 am	(Born et al. 1997)
Human	$CD4^+$ T helper, $CD8^+$ cytotoxic T cells: naïve, central memory, effector memory	1:31 pm-2:41 pm	2:00 pm	(Dimitrov et al. 2009)
Human	Effector $CD8^+$ T cells	3:34 pm	3:00 am	(Dimitrov et al. 2009)
Human	Circulating monocytes	8:00 pm	8 am	(Haus and Smolensky 1999)
Human	HSC / progenitor cells in peripheral blood	8:00 pm	8:00 am	(Lucas et al. 2008)
Human	Circulating neutrophils	8:00 pm	8:00 am	(Haus and Smolensky 1999)

Note that in animal research, time of day does not correspond to "clock-time" but it is instead relative to the time of day at which lights are turned on and off in the animal facilities. Thus, ZT stands for *Zeitgeber* Time and ZT0 corresponds to the time of day when lights are turned-on and if mice are in a LD12:12 (12 h of light and 12 h of dark) ZT12 corresponds to time of day when lights are turned-off. If animals are in constant conditions (normally constant dark, but it could be constant light) then CT is used instead of ZT. CT stands for Circadian Time and CT0 corresponds to the time of day when animals start their resting time (as if lights were turned-on) and CT12 corresponds to the time of day when their activity time starts (as if lights were turned off). In the human studies that we have listed here, the authors provide "clock-times"

TLR9 inflammatory response is elevated, i.e. mid-dark period (Silver et al. 2012). Another example of circadian variation in innate immunity occurs in the spleen and NK cells of rats where transcripts of IFN-γ, granzyme B, perforin and TNF-α display circadian oscillations peaking at the end of the active phase and beginning of rest phase coinciding with the cytolytic activity of splenic NK cells (Arjona and Sarkar 2005; Arjona and Sarkar 2006; Arjona et al. 2004). Adaptive immune responses are also circadian regulated. The circadian clock in lymphocytes regulates their migration through lymph nodes which show a daily variation peaking at the beginning of the active phase in mice with a trough at the end of the active phase. Genetic disruption of T-cell clocks abolishes this rhythm (Druzd et al. 2017). The authors argue that the time of day of generation of the adaptive response as well as the numbers of cells present in the lymph node, are crucial in the regulation of the strength of the adaptive immune responses (Druzd et al. 2017; Moon et al. 2007). This idea is in agreement with Silver and colleagues work who showed that vaccinating mice with a TLR9 ligand as the adjuvant at the time of day when TLR9 was more responsive (active

phase) led to an improved adaptive immune response 4 weeks later compared to animals vaccinated at other times (Silver et al. 2012).

It is interesting that the timing of peaks and troughs of function or number of immune cells do not necessarily coincide despite all components being part of the coordinated immune response. A plausible hypothesis to explain the function of differentially gating the timing of different immune system components may be to avoid an excessive simultaneous immune response to a threat that may prove detrimental for the organism (Man et al. 2016). On the other hand, hosts and parasites have evolved to exert selective pressure onto the other whilst the environment exerts pressure on both (Martinez-Bakker and Helm 2015). The host coordinate immune responses to times of day when exposure to threats are more likely to happen. Bacteria may, in turn, increase growth dependent on the host's circadian rhythms (Bellet et al. 2013). Bellet and colleagues infected mice with *Salmonella enterica serovar Typhimurium* at two timepoints, 4 h after beginning of active time and 4 h after resting time, and showed bacteria clearance 72 h after infection was greater 4 h after beginning of active time. The authors subsequently found that the antimicrobial peptide lipocalin-2 levels in the gut was higher during the day than during the night, which suppressed the growth of resident microbiota during the day. However, *Salmonella* is lipocalin-2 resistant allowing a window for Salmonella to increase outgrowth during the day when there is less competition with other microorganisms compared to night time (Bellet et al. 2013). Thus, despite the lack of proof that Salmonella has its own circadian clock it still takes advantage of circadian variations in levels of lipocalin-2 in its host.

In conclusion and as illustrated in Fig. 1, the coordination of the immune system oscillatory function is regulated at different levels, the master clock level as well as peripheral clock levels. This secures an optimization of the timing of the immune response around the clock so that it is most effective against threads to the organism and causes the least damage to the host organism. Dysregulation of the clock will cause disease as we will describe in the next section.

Dysregulation of the clock leads to a dysregulated immune response

Numerous experiments have shown that altering the period and/or amplitude of rhythm of the master clock in the SCN and/or peripheral clocks in organs such as the liver and lungs, result in dysregulation of the immune response. This has been demonstrated under conditions of shift- work where feeding/fasting and sleep/wake cycles are uncoupled from the master and peripheral clocks, with lesion of the SCN (which destroys the master clock), with aging and with the generation of mutant mice or knock-out/knock-down mice for clock proteins involved in pro and anti-inflammatory responses.

Pro-inflammation

In rodents exposed to simulated shift-work with work and feeding during the day, which corresponds to their usual rest and fasting period, and inactivity and fasting at night (usual active feeding period), there is an uncoordinated inflammatory response to LPS challenge, resulting in elevated cytokine levels and increased mortality (Castanon-Cervantes et al. 2010; Adams et al. 2013; Guerrero-Vargas et al. 2015). Interestingly, if feeding time is restricted to the night time and normal active phase then the immune response is not dysregulated when undergoing LPS challenge. The TNF-α and IL-6 inflammatory cytokine levels remain at a similar level to control (ad libitum feeding and activity) rats. In contrast, when animals not subjected to simulated shift-work are restricted to feeding in the day time (the normal resting period), the immune response is also dysregulated with elevated TNF-α and IL-6 levels (Guerrero-Vargas et al. 2015). These data suggest that feeding is a stronger *Zeitgeber* than light in keeping the immune system synchronized and undisturbed. In this context, the gut microbiome is increasingly being implicated in playing a role in chronic inflammation. It has recently been proposed that a desynchronization between sleep, circadian and feeding/fasting cycles, such as that which occurs during shift-work, may promote alterations in gut microbiota leading to chronic inflammation (Reynolds et al. 2017). This research, however, is relatively new and requires further extensive examination (Phillips and Comas 2017). A different method to induce circadian disruption is by lesion of the SCN master clock (Moore and Eichler 1972; Stephan and Zucker 1972). Similar to simulated shift-work, bilateral lesions of the SCN in rats leads to a dysregulated immune response with significantly higher levels of cytokines after exposure to LPS compared to controls (Guerrero-Vargas et al. 2014). Aging has also been shown in rats to dysregulate the circadian clock by decreasing the amplitudes of oscillation of clock genes and cytokine mRNA. This in turn resulted in a chronic state of inflammation with loss of the inflammatory response to an LPS challenge (Fonken et al. 2016). Circadian disruption can also be induced by mutation or knocking down different clock genes. This has resulted in decreased levels of cytokines suggesting a pro-inflammatory role for these clock genes. For example, mutation or knocking down *Per2* resulted in decreased levels of granzyme B (Arjona and Sarkar 2006), perforin proteins (Arjona and Sarkar 2006), IFN-γ (Arjona and Sarkar 2006; Arjona and Dk 2006; Liu et al. 2006) and IL-1β (Liu et al. 2006). In accordance with these studies, *Per2* mutant mice are

more resistant to the LPS challenge compared to wild types (Liu et al. 2006). A reduction of cytokine production (in response to the LPS challenge or *Salmonella Typhimurium* infection) is observed in macrophages from *Clock* mutant mice (Bellet et al. 2013). This is in agreement with the finding that CLOCK protein activates the NF-κB pathway leading to upregulation of cytokines (Spengler et al. 2012).

Anti-inflammation

When a different set of clock genes are compromised then inflammation increases suggesting that other clock proteins have *anti-inflammatory* roles. This has been shown with deletion of *Ror-α* in mice which leads to abnormal immune responses such as hyper responsive macrophages producing higher levels of cytokines in bronchoalveolar lavage fluids after LPS challenge (Sidman et al. 1962; Kopmels et al. 1990; Trenkner and Hoffmann 1966; Stapleton et al. 2005; Dzhagalov et al. 2004). Macrophages from *Rev.-erb-α*$^{-/-}$ mice and from LysM-*Bmal*$^{-/-}$ mice (mice that lack *Bmal1* in their macrophages, monocytes and neutrophils) show loss of circadian gating and constitutively elevated levels of IL-6 in response to the LPS challenge (Gibbs et al. 2012). Two more studies show the important role of BMAL1 protein in inflammation. *Bmal1*$^{-/-}$Lys-MCre mice are more susceptible to LPS challenge compared to wild type mice with decreased survival. Interestingly, deletion of MiR-155 which represses *Bmal1* leads to a reduced inflammatory response to the LPS challenge (Curtis et al. 2015). Thus, this work suggests that *Bmal1* has an important anti-inflammatory role which is relevant not only at the protein level but also at the miRNA regulation level. Knocking down or silencing *Cry1* and *Cry2* also leads to increased inflammation (Narasimamurthy et al. 2012; Hoffman et al. 2009). Whether we can assign definitive anti or pro-inflammatory roles to specific clock genes still requires more work. The effects observed so far for each clock protein may be cell-specific, immune function-specific (e.g. innate vs adaptive) or even species specific.

These studies highlight the need for further research exploring the mechanistic links between circadian clock function and inflammation. However, the available data does provide a framework for continuing translational research in chronotherapy to more effectively manage acute and chronic inflammation.

Circadian rhythms in respiratory inflammatory disease

It is quite clear that the stronger responses of the immune system occur from the second half of the rest time and the first hours of the activity time. Thus, in humans, immune responses are stronger in the second half of the night and early morning hours. These are the times when inflammation is exacerbated and symptoms and mortality rates are highest (Buttgereit et al. 2015; Smolensky et al. 2015). In parallel, timed therapies that decrease inflammation during the night and early morning hours has proven to be more successful than untimed therapy (Smolensky et al. 2007; Buttgereit et al. 2015; Smolensky et al. 2015). Below we discuss these concepts in the context of several common respiratory inflammatory diseases.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD), is the fourth highest cause of death globally (GOLD, 2016). Like other chronic diseases, it is largely caused by preventable risk factors (cigarette smoking and noxious air-borne particles). COPD is a systemic disease with significant extrapulmonary effects that contribute to morbidity and mortality. Its pulmonary component is characterised by airflow limitation which is not fully reversible and is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases (GOLD, 2016). A patient suffering from COPD may have persistent inflammation, increased mucus secretion (chronic bronchitis) and narrowing and destruction of their small airways (small airways disease) and/ or they may have destruction of the lung alveoli resulting in emphysema. COPD symptoms vary throughout the day. While some patients report worsening of their symptoms (cough, shortness of breath and phlegm) in the early morning upon awakening, others complain of nocturnal symptoms, most commonly wheezing, shortness of breath and cough which also cause sleep disruption (Kessler et al. 2011; Price et al. 2013; Lange et al. 2014; Agusti et al. 2011; Stephenson et al. 2015; Jen et al. 2016; Partridge et al. 2009; Espinosa de los Monteros et al. 2012; Kuyucu et al. 2011; Kim et al. 2012; Decramer et al. 2013; Roche et al. 2013; Roche et al. 2013; Miravitlles et al. 2014; Tsai et al. 2007).

Lung cells have their own molecular circadian clocks that coordinate tissue-specific functions and responses to environmental stimuli (Sukumaran et al. 2011; Gibbs et al. 2009; Oishi et al. 1998). This results in circadian oscillations in many common lung function indices (e.g. forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (Agusti et al. 2011; Spengler and Shea 2000)). These normal circadian oscillations in airway calibre may be partly responsible for nocturnal COPD exacerbations and worsening hypoxia (Agusti et al. 2011; Tsai et al. 2007) however, the impact appears to be much greater in asthmatics (Tsai et al. 2007; Brenner et al. 2001), perhaps because of airway hyperresponsiveness (the ability of airways to contract too much and too easily). Although the underlying basis

of airway hyperresponsiveness is unknown, the excessive circadian variations in airway calibre could be due to changes in the contractile properties of airway smooth muscle, inflammation (Kraft et al. 1996), neural activity or changes in lung mechanics during sleep (Irvin et al. 2000). Given that several studies have found that critically ill COPD patients are more likely to die at night and that this is attributable to COPD exacerbations, there is a clear role of the clock in adverse outcomes (Tsai et al. 2007; Martin 1990; Petty 1988; McNicholas and Fitzgerald 1984; Tirlapur 1984; Kimura et al. 1998; Chaouat et al. 2001). Nevertheless early morning symptoms and night time symptoms remain one of the adverse outcomes of COPD, particularly in more severe cases (Partridge et al. 2009). Importantly, a recent study showed that COPD patients that report both or either nocturnal or early morning symptoms have poorer health compared with patients who do not have a worsening of symptoms at specific times of day (Stephenson et al. 2015). This could potentially be used as a biomarker of disease status and there is scope for developing chronotherapeutic approaches for these patients to cover the times of day with worsening symptoms. Very little is known about circadian changes in lung function or disease activity in COPD or why nocturnal symptoms are associated with poorer outcomes. Perhaps research in this area will translate to future clinical benefit.

Additionally, and in the context of this review, several studies have found a potential mechanism connecting disruption of lungs circadian clock, inflammation and COPD (Yao et al. 2015; Hwang et al. 2014; Rajendrasozhan et al. 2008). Importantly, levels of the deacetylase SIRT1 are reduced in COPD patients, as well as in smokers and in mice exposed to cigarette smoke (Yao et al. 2015; Hwang et al. 2014). Furthermore, SIRT1 regulates both central and peripheral circadian clocks (Masri and Sassone-Corsi 2014). A decrease in SIRT1 levels in COPD patients, smokers and mice exposed to cigarette smoke results in increased acetylation of BMAL1 leading to an increased BMAL1 protein degradation and, in consequence, to a molecular clock dysregulation and an increased inflammatory response is observed (Yao et al. 2015; Hwang et al. 2014). To confirm the role of BMAL1 in lung inflammation, Hwang and colleagues studied mice carrying a targeted deletion of *Bmal1* in lung epithelium and they observed that these mice also suffer from increased inflammatory response to cigarette smoke which is not reduced when mice are treated with a SIRT1 activator (Hwang et al. 2014). The authors concluded that both BMAL1 protein as well as its regulation by SIRT1 must have a key role in lung inflammation in COPD patients and smokers (Hwang et al. 2014).

Apart from cigarette smoke (Yao et al. 2015; Hwang et al. 2014; Vasu et al. 2009; Gebel et al. 2006), other environmental factors such as respiratory infections or even chronic jet-lag can lead to dysregulation of the lung circadian clock leading to increased lung inflammation. Sundar and co-workers showed mice with chronic exposure to cigarette smoke combined with infection of influenza A virus altered lung clock gene expression and increased lung inflammation as well as emphysema. The same experiment performed on *Bmal1* Knockout mice resulted in increased lung inflammation and pulmonary fibrosis (Sundar et al. 2015). Disruption of circadian rhythms in mice using a chronic jet-lag protocol for 4 weeks leads to disruption in lung physiology and lung clock gene expression (Hadden et al. 2012). Evidence from a study which investigated the effect of chronic exposure to real-life ambient air particles showed that pollution leads to circadian clock gene expression disruption in the lungs of rats as well as increased lung and systemic inflammation and oxidative stress (Song et al. 2017). These animals were housed in the Haidian district of Beijing which has characteristically high levels of polluted air due to heavy traffic.

The specific pathways regulated by the circadian clock that influence COPD are not clear yet. However, several recent publications have demonstrated that if the circadian clock controlled expression of genes is unregulated, it may lead to pulmonary disease. Disruption of the circadian clocks regulation of Nrf2 expression in mouse lungs leads to chronic pulmonary diseases including COPD, asthma, idiopathic pulmonary fibrosis and cancer (Pekovic-Vaughan et al. 2014). Sukumaran and co-workers showed in rats lungs that genes associated with COPD display circadian oscillations and that some of these oscillating genes are potential COPD drug targets i.e. Myristoylated Ala-rich PKC substrate (*Marcks*) and Adrenergic β2 receptor (*Adrb2*) (Sukumaran et al. 2011). Similarly, Zhang and colleagues listed drugs that are indicated to treat COPD and that target genes that oscillate (Zhang et al. 2014b). Disentangling the molecular pathways that contribute to emphysema and bronchitis in COPD patients regulated by the circadian clock will permit the development of novel chronotherapeutic approaches.

Allergic rhinitis

Allergic rhinitis (AR) is increasing worldwide with current prevalence rates of between 10% and 30%. The prevalence is particularly high in developed countries (Bousquet et al. 2008; Mullol et al. 2008). AR is an immune system-mediated upper airway hypersensitivity to environmental allergens. It is characterized by respiratory tissue inflammation, mucus gland hyperactivation and blood vessel dilation. In people suffering from AR,

the allergen triggers early and late phase reactions that are mediated by a series of inflammatory cells and mediators. The early phase occurs immediately after allergen exposure and the late phase develops 8 to 12 h after allergen exposure. The most common symptoms of AR are sneezing, itching, rhinorrhoea, nasal congestion, and post-nasal drip. The symptoms of the late phase are similar to the early phase, but with more severe congestion (Stull et al. 2009; Hansen et al. 2004).

A daily rhythm in allergic symptoms has been known since the 1960s (Reinberg et al. 1963; Reinberg et al. 1969). Symptoms often intensify overnight and are worst upon wakening, displaying a "morning attack" (Smolensky et al. 2007; Smolensky et al. 2015; Long 2007; Gelfand 2004; Smolensky et al. 1995; Reinberg et al. 1988). Due to the time at which symptoms intensify, AR symptoms often disrupt sleep (Craig et al. 2008; González-Núñez et al. 2013; Santos et al. 2006). This may lead to daytime fatigue, interfering with daily activities, including the capability to work or study and overall quality of life (Stull et al. 2009; González-Núñez et al. 2013; Santos et al. 2006; Bousquet et al. 2013; Walker et al. 2007; de la Hoz et al. 2012; Blanc et al. 2001). Work and school absenteeism and decreased productivity at work due to AR are associated with substantial economic costs, ranging between 2 and 5 billion US dollars (Blaiss 2010; Lamb et al. 2006; Roger et al. 2016). Importantly, the upper airway obstruction that characterizes AR is a risk factor for sleep disordered breathing events, such as apnoeas, hypopneas and snoring in adults and children (Long 2007). AR patients have daily rhythms of salivary melatonin that have a decreased amplitude, baseline and peak levels, as well as lower amplitude of salivary cortisol daily rhythm and delayed peak compared to healthy controls (Fidan et al. 2013). The reason for the lower robustness of these rhythms is unknown but may be due to sleep disruption and/or as a consequence of inflammation. It is also unclear if these disrupted rhythms further worsen inflammation and allergy.

Mouse nasal mucosa has a functional circadian clock and its response to glucocorticoids is dependent on the time of day (Honma et al. 2015). This daily rhythm in hypersensitivity to allergens contributes to the daily rhythms observed in AR (Nakamura et al. 2011; Nakamura et al. 2014; Nakamura et al. 2014; Nakamura et al. 2016). For example in children exposed to an allergic challenge at 6 am, more nasal secretions are produced than when exposed at 3 pm (Aoyagi et al. 1999). Furthermore, the commonest allergen for patients suffering from AR is house dust mite. The greatest allergen challenge occurs from the bedding exposure to dust mite during time in bed during the night which coincides with the worst time for the circadian clock to deal with allergen challenge.

In the context of chronotherapy, Reinberg and colleagues tested whether H1 receptor antagonists were more effective at 7 am compared to 7 pm and found that evening administration was more effective (Reinberg 1997). Importantly, whilst corticosteroid nasal sprays have been shown to effectively treat allergic symptoms, they also interfere with the nasal circadian clock. From a mechanistic perspective, studies have shown that endogenous glucocorticoids regulate clock gene expression by binding directly onto the promoter of clock genes (*Per1, Per2 and Rev.-erb-α*) (Cheon et al. 2013; Yamamoto et al. 2005) and that administration of prednisolone induces *Per1* expression, affecting normal clock function (Fukuoka et al. 2005; Koyanagi et al. 2006). However, the disruption of clock function by prednisolone can be reduced, simply by changing the time of day at which it is administered (Koyanagi et al. 2006). Therefore, the questions arise, what is the best chronotherapeutic strategy to maximise treatment effectiveness? And does it have to minimally disrupt the nasal mucosa circadian clock? Based on their work in mice, Honma and colleagues proposed that the best time to administer intranasal corticosteroids to treat AR is when they disrupt the nasal clock least, which corresponds to early evening for humans (Honma et al. 2015). The authors argued that this timing corresponds to the same time at which aerosol corticosteroid is most efficient to treat asthma and that repeated disruption of circadian clocks leads to other health issues or worsens previous conditions (Honma et al. 2015). Nakamura's work, on the other hand, suggested that the best time to treat allergies was at the time the circadian clock was most susceptible to be disrupted, which is during the night in humans and during the day in mice (Nakamura et al. 2016). They showed that treating with dexamethasone at a time of day that resulted in increasing PER2 levels and reducing FcεRI signalling in mast cells or basophils resulted in suppression of IgE mediated allergic reactions in a mouse model of AR. Furthermore, dexamethasone did not decrease the allergic reactions in both *Clock*-mutated or *Per2*-mutated mast cells. They further hypothesized that reduction of FcεRI signalling depends on PER2 upregulation by glucocorticoids (Nakamura et al. 2016). Even though it appears as a very promising chronotherapeutic approach it is important to understand the long-term consequences of upregulating PER2 by glucocorticoids and thus disrupting the circadian clock in a chronic disease such as AR. Understanding the circadian patterns of allergic response and its regulation by the central and peripheral clocks, specifically in humans will enable discovery of preventive measures which utilise chronotherapy to treat AR patients.

Asthma

Asthma is a chronic inflammatory disease of the lungs that affects approximately 334 million people worldwide (Global

Asthma report, 2014). It is characterized classically by hypersensitivity to environmental antigens which leads to inflammation driven by IgE-dependent mechanisms, constriction and obstruction of the airways. However, non-allergic asthma phenotypes are also common. Asthma shares a lot of characteristics with allergic diseases, including genetic risk factors (Bousquet et al. 2000). Asthma episodes, as well as asthma exacerbations, are more prone to happen during the night and early morning compared to other times of the day both in adults and in children (Smolensky et al. 2007; Reinberg et al. 1988; Turner-Warwick 1988; Smolensky and D'Alonzo 1997; Hoskyns et al. 1995; Jarjour 1999; Bohadana et al. 2002; Litinski et al. 2009). One of the first studies involving 3000 asthma patients found that asthma episodes during washout from regular maintenance asthma treatment occurred 70-fold more frequently between 4 am and 5 am compared to 2 pm-3 pm (Dethlefsen and Repges 1985). Death from severe asthma attacks is also known to mostly occur during the night or early morning (Smolensky and D'Alonzo 1997; Cochrane and Clark 1975).These times coincide with the times at which lung function is reduced and inflammation and airway hyperreactivity is increased (Spengler and Shea 2000; Kraft et al. 1996; Jarjour 1999; Martin et al. 1991; Hetzel and Clark 1980; Gervais et al. 1977; Bonnet et al. 1991; Panzer et al. 2003; Kelly et al. 2004).

Studies with asthmatics using sleep deprivation protocols have shed some light on the partial contribution of sleep and of circadian variation to airway calibre and lung function. Ballard and colleagues studied pulmonary function in asthmatic patients during a sleep deprived night and a normal sleep night (Ballard et al. 1989). They observed that lower airway resistance increases during the night, regardless of whether asthmatic patients sleep or not, but the rate of increase is two-fold higher if patients are allowed to sleep compared to sleep deprivation, implying that sleep itself increases lower airway resistance. However, decrements in forced expired volume in 1 s (FEV_1) were not significantly different between the sleeping night and the sleep deprived night (Ballard et al. 1989). Using the same protocol, another group found that in asthmatics, nocturnal bronchoconstriction occurred both in the sleep and sleep-deprived nights but the morning values of peak expiratory flow (PEF) were higher after the awake night and the absolute and percentage falls in PEF were greater in the sleep night, suggesting the contribution of sleep to nocturnal bronchoconstriction (Catterall et al. 1986). Furthermore, the amplitude of PEF variation in asthmatics is greater compared to non-asthmatics, indicating an exaggeration of daily variation in airway calibre in asthmatics during the night (Hetzel and Clark 1980). However, the Hetzel study showed that sleep deprivation does not improve the overnight fall in PEF, suggesting that it is the circadian variation in pulmonary function, rather than sleep, causing the PEF fall in asthmatics (Hetzel and Clark 1979). The overnight decrease in PEF is related to greater severity of daytime asthma (Martin et al. 1990). Similarly, the time of day at which an asthmatic is undergoing an allergen challenge will have an impact in the chances of developing a late asthmatic response, being higher in the evening compared to the morning (Mohiuddin and Martin 1990).

Nocturnal worsening of asthma has also been associated with nocturnal increases in lung inflammation. For example, analysis of bronchoalveolar lavage fluid from asthmatic patients showed that patients with nocturnal asthma had higher leukocytes count, specifically eosinophils and neutrophils, at 4 am compared to 4 pm, whereas in asthmatic patients without nocturnal episodes, there was no difference between these two time-points. When comparing both groups of patients, there was a significant difference between them at 4 am but not at 4 pm (Martin et al. 1991). Therefore, day time leukocytes count were similar between groups but the difference was attributable to the number of immune cells found during the night. These results were confirmed in other studies with a comparable protocol looking at neutrophils, macrophages and CD4+ cells (Kraft et al. 1996; Kraft et al. 1999) as well as when comparing non-asthmatic controls to nocturnal asthmatic patients (Mackay et al. 1994; Oosterhoff et al. 1995). Another study also showed a higher blood concentration of eosinophils at 4 am compared to 4 pm in nocturnal asthmatics (Calhoun et al. 1992). Furthermore, the night fall in PEF was positively correlated with change in neutrophils and eosinophils, further indicating a relationship between nocturnal inflammation and decline of pulmonary function in nocturnal asthmatics (Martin et al. 1991). Another study investigated FEV_1 and sputum inflammatory cells in mild asthmatics at 4 pm and 7 am resulting in similar findings to the previous studies, that is, lower FEV_1 at 7 am with higher numbers of sputum inflammatory cells compared to 4 pm timepoint (Panzer et al. 2003).

Studies on bronchial hyperreactivity in asthmatic patients in the 1970s have also shown a clear daily variation. Gervais and colleagues exposed asthmatic patients to a bronchial challenge with house dust in an otherwise allergen-shielded room. They measured airway calibre using FEV_1 15 min after house dust inhalation at 8 am, 3 pm, 7 pm and 11 pm and showed that the strongest response occurred at 11 pm whilst the weakest response occurred at 8 am (Gervais et al. 1977). In addition, the effects of histamine and methacholine on airways responsiveness were tested on patients with mild

asthma with night time symptoms at different times of the day and night. Airway hyperresponsiveness as measured by the dose required to cause a 20% decline in FEV1 ($PC_{20}FEV_1$) was greater when the challenges occurred in the middle of the night (3-5 am) compared with daytime (Bonnet et al. 1991). A recent review has confirmed that the circadian variation of bronchial hyperreactivity to different agents in asthma is more profound during the night, except to cold dry air, which shows a peak in the afternoon (Jarjour 1999). Interestingly, this review also found that the amplitude of circadian oscillation of airway hyperreactivity correlated with the amplitude of pulmonary function oscillation. The greater the decline of pulmonary function during the night in asthmatics, the greater the increase of night time airways hyperreactivity in asthmatic patients (Jarjour 1999).

The impairment of lung function at night and early morning also correlated with the expression of several core clock genes. A recent study by Ehlers and colleagues studied the expression pattern of multiple core clock genes in respiratory tract of mild/moderate and severe asthmatic patients (Ehlers et al. 2017). They found reduced expression in 6 core clock genes (including *Bmal1* and *Per2*) and higher expression of *Clock* gene in asthmatics patients (mild-moderate and severe) when compared to controls. Similarly, another study found higher gene expression of *Arntl2* (a paralog of Bmal1) and lower of *Per2* in severe asthmatics when compared to mild asthmatics and healthy donors (Fajt et al. 2015). This suggests a relationship These findings are supported by a recent longitudinal study that demonstrated the association of insomnia and risk of developing asthma in approximately 18,000 participants (Brumpton et al. 2017).

In the context of treatment, similar to COPD, genes associated with asthma display circadian oscillation patterns of expression in rats lungs and some of these genes may represent asthma drug targets i.e. Selectin P (*Selp*), Adenosine A2a receptor (*Adora2a*), Hepatocyte growth factor (*Hgf*), Myristoylated Ala-rich PKC substrate (*Marcks*) and Adrenergic-2 receptor (*Adrb2*) (Sukumaran et al. 2011) using chronotherapy. Research on the circadian patterns of disease as well as on potential to use chronotherapy on both asthma and allergic rhinitis has been accumulating for decades (Smolensky et al. 2007). As always, more research needs to be undertaken in order to apply chronotherapy in asthma but it is one of the most promising diseases to take advantage of time of day to significantly improve therapeutic results.

Conclusion

In recent years, mounting evidence has demonstrated that the immune system displays circadian oscillations (see reviews (Labrecque and Cermakian 2015; Nakao 2014; Scheiermann et al. 2013; Cermakian et al. 2013; Cermakian et al. 2014)). Pro-inflammatory cytokines are elevated during rest time and anti-inflammatory cytokines are elevated during activity time. Organisms display stronger immune responses during the rest period and early active period as compared to other times of the day. Oscillations in immune function are observed in immune challenges (such as LPS challenge or bacterial infection) as well as in disease, including autoimmune and inflammatory diseases. Although the precise mechanism by which the circadian clocks regulate immune function are unclear, there is a clear role for both central and peripheral clocks in regulating the immune response. For example, the SCN regulates the recruitment of leukocytes to tissues and regulates clock gene expression in immune system tissues and cells as well as oscillations in cytokine production. Furthermore, immune function is also regulated through SCN-mediation of hormones (cortisol, melatonin). Peripheral clocks found in many cells and tissues, including those composing the immune system, also regulate circadian oscillations of immune functions. Overall, the interplay between circadian physiology and disease is complex and is further complicated by the bi-directional nature of these systems. Thus, not only does the circadian clock regulate immune function but inflammation will in turn affect the circadian clock and the pathways it regulates. Altogether, the interaction and inter-regulation of the circadian and immune systems seems to be directed at optimizing immune responses around the clock.

In respiratory diseases, signs and symptoms as well as severity show circadian variability across the 24-h cycle. Specifically, obstructive airways diseases and allergic rhinitis demonstrate increased inflammation and disease severity at night. Consequently, exposure to inflammatory insults at night also has greater effects. Altogether, evidence suggests that inflammatory diseases may be response to chronotherapy to improve disease control due to circadian clock control of symptoms and exacerbations. If medicine is evolving towards a more personalized approach this will certainly be an aspect to consider. Chronotherapy into clinical trials studies with existing and new drugs are needed to test whether outcomes can be improved in inflammatory diseases when therapy is administered at different times of day. Assessing circadian periodicity in humans in field studies are also required to understand the influence on pathophysiological processes and therapies. Overall, a better understanding of the circadian clock regulation of the immune system will improve the understanding of the pathophysiology of inflammatory disease and this could lead to development of more effective chronotherapeutic strategies.

Abbreviations
Adora2a: Adenosine A2a receptor; *Adrb2*: Adrenergic β2 receptor; ANS: Autonomic nervous system; AR: Allergic rhinitis; BMAL1: ARNT-like protein 1; CK: Casein Kinases; CLOCK: Circadian Locomotor Output Cycles Kaput; COPD: Chronic obstructive pulmonary disease; Cry: Cryptochrome; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; *Hgf*: Hepatocyte growth factor; HPA: Hypothalamic pituitary adrenal; LPS: Lipopolysaccharide; MAPK: p38 mitogen-activated protein Kinases; *Marcks*: Myristoylated Ala-rich PKC substrate; NK: Natural Killer T-cells; PEF: Peak expiratory volume; Per: Period; SCN: Suprachiasmatic nucleus; *Selp*: Selectin P; TLRs: Toll-like receptors; TTFLs: Transcription-translation feedback loops

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