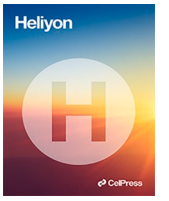
The role of the circadian rhythms in critical illness with a focus on acute pancreatitis

Heliyon 9 (2023) e15335

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

The role of the circadian rhythms in critical illness with a focus on acute pancreatitis

Heather Waddell [a,*,2], Tyler J. Stevenson [b], Damian J. Mole [a,c,1]

[a] Medical Research Council Centre for Inflammation Research, Queen's Medical Research Institute, The University of Edinburgh, Edinburgh, EH16 4TJ, UK
[b] Institute of Biodiversity and Animal Health and Comparative Medicine, College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, G61 1QH, UK
[c] Clinical Surgery, School of Clinical Sciences and Community Health, The University of Edinburgh, Edinburgh, EH16 4SB, UK

ARTICLE INFO

Keywords:
Acute pancreatitis
Circadian rhythms
Critical illness
Immune response
Immune cells

ABSTRACT

Circadian rhythms are responsible for governing various physiological processes, including hormone secretion, immune responses, metabolism, and the sleep/wake cycle. In critical illnesses such as acute pancreatitis (AP), circadian rhythms can become dysregulated due to disease. Evidence suggests that time of onset of disease, coupled with peripheral inflammation brought about by AP will impact on the circadian rhythms generated in the central pacemaker and peripheral tissues. Cells of the innate and adaptive immune system are governed by circadian rhythms and the diurnal pattern of expression can be disrupted during disease. Peak circadian immune cell release and gene expression can coincide with AP onset, that may increase pancreatic injury, tissue damage and the potential for systemic inflammation and multiple organ failure to develop. Here, we provide an overview of the role of circadian rhythms in AP and the underpinning inflammatory mechanisms to contextualise ongoing research into the chronobiology and chronotherapeutics of AP.

1. Introduction

In recent years the incidence of critical illnesses has risen dramatically. Increasing knowledge of circadian rhythms (CRs) and the relationship with critical illness has provided potential new avenues to improve our understanding and treatment of critical illness. There are two linked unknown problems in this field of research, namely 1) how does critical illness disrupt normal CRs, and 2) what is the effect of CRs on the pathobiology and severity of critical illness. This focussed review aims to summarise existing knowledge and draw these two fields together, using acute pancreatitis (AP) as a paradigm of critical illness. AP is a globally important disease, which is increasing in incidence, has a lack of standardised treatments and the chronopathology of AP is largely understudied.

AP is a common inflammatory condition with a high global incidence rate of 34 per 100,000 individuals per year [1]. Over the last 50 years, the global incidence rate has increased by 3.07% across America and Europe, whilst estimates suggest that is has remained stable in Asia. Current studies suggest that this trend is mainly due to biliary disease [2]. AP can be characterised as acute inflammation

* Corresponding author.
E-mail address: H.Waddell@sms.ed.ac.uk (H. Waddell).
[1] Senior author.
[2] Lead contact.

https://doi.org/10.1016/j.heliyon.2023.e15335
Received 26 September 2022; Received in revised form 20 January 2023; Accepted 3 April 2023
Available online 8 April 2023

of the pancreas gland which results in extreme gastrointestinal pain and, in most cases, emergency hospital admission [3]. AP can be caused by many different factors, with gallstone migration and excessive alcohol consumption cited as the two most common causes (Fig. 1). Other identifiable causes include certain prescription medications, viruses, trauma to the pancreas, abdominal surgery, and neurotoxins (scorpion venom). Approximately 10% of cases are idiopathic [4,5]. AP severity is determined using the revised Atlanta classification [6]. This enables clinicians to stratify AP severity into mild, moderate, or severe based on the degree of physiological disruption caused by inflammation. Most (~80%) AP cases are mild, resulting in minimal damage to the pancreas and with a relatively short recovery period [7]. Following recovery from the acute episode, AP is associated with an increased likelihood of developing comorbid diseases, including diabetes, exocrine pancreatic insufficiency and chronic pancreatitis [8]. In some individuals AP is severe, associated with multiple organ dysfunction syndrome (MODS), organ failure and premature death [9,10]. AP onset, regardless of severity, begins with localised inflammation and pancreatic injury which activates an inflammatory cascade and frequently induces systemic inflammatory response syndrome (SIRS) (Fig. 1) [1]. To date, the pathophysiology which underpins AP is complex and the role that the immune system plays in AP disease progression is not clear. Given the clear link between CRs and regulation of inflammation, and the likely impact of inflammation on CRs, exploration of the chronobiology of AP may lead to a better understanding of AP pathophysiology and guide the development of chronotherapeutics [5].

2. The circadian rhythms

Since the start of life on earth, all living organisms follow an approximate 24-hr rhythm, driven by the daily rotation of the Earth's axis [11]. Each axial rotation exposes organisms to daily variation in both temperature and natural light, with the latter known as the light-dark cycle [12]. Additionally, all organisms possess an internal time keeping system, a transcriptional translational feedback loop mechanism referred to as the circadian clock (Fig. 2). The circadian clock's function is to align and adapt internal physiological processes with the external environment [12,13,14]. This aspect of circadian rhythmicity is essential for the survival of many species, given that changes in the external environment influence the availability of food and light resources. CRs are entrained by the external environment to match the light-dark cycle through cues known as zeitgebers or 'timekeepers' [13,14,15]. Established zeitgebers include cues such as light (natural and artificial), nutrient availability, temperature, feeding habits and social interactions, all of which

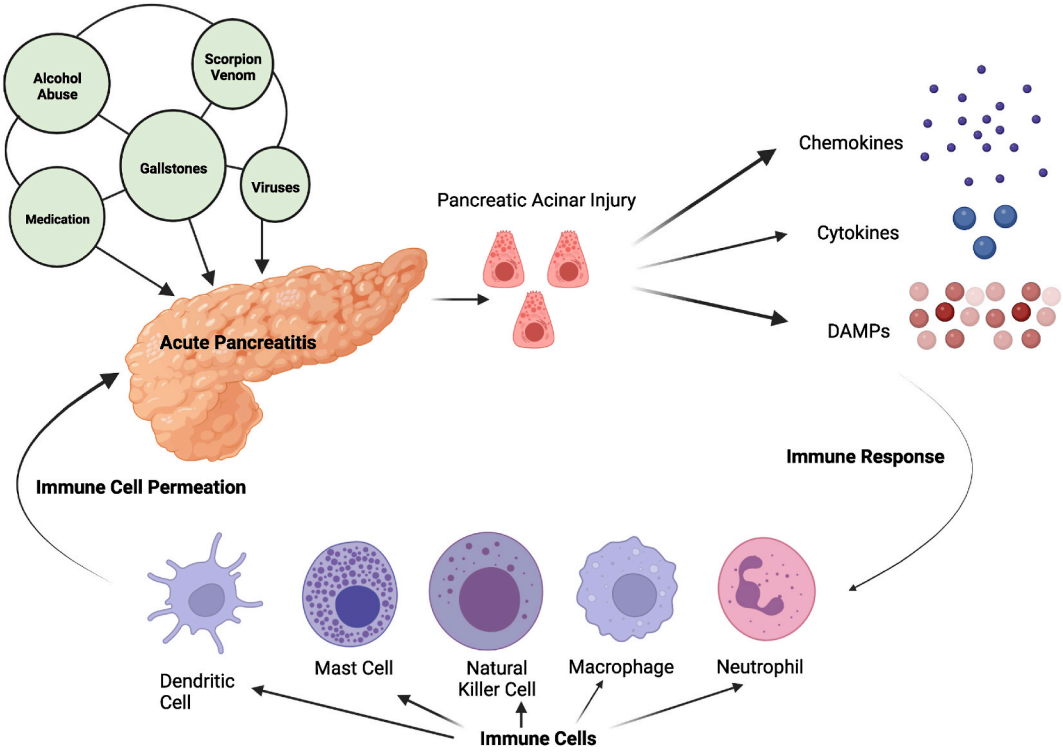


Fig. 1. Schematic of Acute Pancreatitis (AP) mechanisms which involve the immune system.
AP is a common inflammatory disease which normally occurs as a result of gallstones, alcohol abuse and in rare cases medication, viruses, and scorpion venom. AP disease onset begins with injury to the pancreatic acinar cells, which in turn give rise to the release of chemokines (specialised cytokines), cytokines and damage associated molecular patterns (DAMPs). This activates the immune response which responds by sending innate and adaptive cell types to the site of injury to promote tissue repair and necrotic cell clearance. These immune cells include neutrophils, macrophages, natural killer cells, mast cells and dendritic cells. Neutrophil and macrophages make up most of the immune cells recruited, which then permeate through into the pancreas to aid in recovery. Created with BioRender.com.

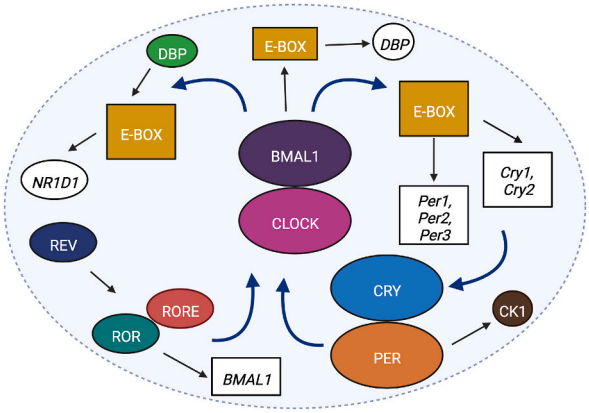


Fig. 2. Schematic showing the molecular circadian clock in mammalian cells.
Transcription and Translation feedback loop begins with CLOCK:BMAL1 transcription factors binding to E-box elements to activate *Per1, Per2, Per3, Cry1* and *Cry2* genes. Protein products produced from this, then work to inhibit their own transcription in the first part of the loop and repress their counterparts. Casein kinase 1 (CK1) is known to phosphorylate PER, resulting in degradation and reduction in PER levels at the start of the day. CLOCK:BMAL1 also mediate the expression of *NR1D1* gene as shown above, through binding with E-box elements. *NR1D1* is then involved in encoding both REV-ERBα/β, which in turn inhibit the production of BMAL1 within the loop. DPB transcription is activated through CLOCK:BMAL1 and E-box elements. This cycle begins at the start of each day spanning across an approximate 24-h period, dependent on the repression of specific core circadian genes from the day before. Created with BioRender.com.

play a key role in the successful circadian entrainment of an organism to its surroundings [16].

The powerhouse of the circadian rhythms, or master clock, is situated within the suprachiasmatic nuclei (SCN) of the brain, which acts to regulate CRs overall by synchronising peripheral circadian clocks [12,15]. Each circadian clock, whether in the SCN or tissues of the body, oscillates autonomously across a 24-hr period, driven by the transcriptional and translational feedback loops (TTFLs), that involve core clock genes [17]. In mammals, the primary circadian clock genes are controlled by the transcription factors CLOCK and BMAL1 that promote the expression of Period *(PER 1/2)* and Cryptochrome *(CRY 1/2)* genes [13,16]. Protein complexes produced from this interaction then inhibit the production of CLOCK and BMAL1 via negative feedback through the activation of PER and CRY [18,19,20]. PER and CRY complete the negative aspect of the feedback loop by repressing further production of themselves, moderated

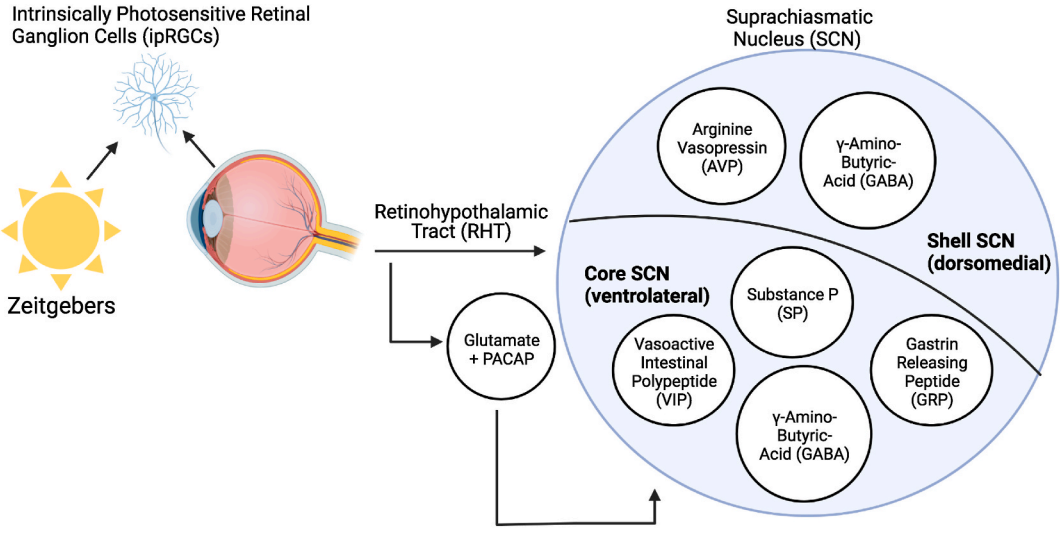


Fig. 3. Schematic showing the pathway, from the intrinsically photosensitive retinal ganglion cells (ipRGCs) to the core SCN.
Light is the primary zeitgeber which provides input signals that the ipRGCs detect, due to the presence of melanopsin. This information is then innervated along the retinohypothalamic tract (RHT) where glutamate and pituitary adenylyl-cyclase activating peptide (PACAP) are activated and increase cellular concentrations of calcium. Transcription of core circadian genes can then be activated by the binding of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB). The core SCN communicates with the shell SCN through neurotransmitters, vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), Substance P(SP) and γ-Amino-Butyric-Acid (GABA). This synchronises the core and shell SCN with the external environment, resulting in a successfully entrained organism with an appropriate period length. Created with BioRender.com.

by PER-timed degradation via casein kinase 1 epsilon. Fine-tuning of the primary loop is achieved by other important circadian genes, including *REV-ERBα, RORα, DBP* and *DEC* [19,21]. These core clock genes within the SCN are responsible for the downstream rhythmic expression of several thousand genes in most organs, tissues, and cells throughout the body (Fig. 2) [17,20].

2.1. SCN core and shell organisation

The SCN can be split into two regions, the ventrolateral core, and the dorsomedial shell which differ in that the ventrolateral core clock gene expression is dependent on external stimuli relevant to entrainment, whilst the dorsomedial shell gene expression maintains a robust 24-h rhythm even in constant darkness. For the SCN core to become coupled with the light-dark cycle, it receives photic input from intrinsically photosensitive retinal ganglion cells (ipRGCs) found in the inner retina which express a photopigment called melanopsin (Fig. 3) [22,23]. Photic information is transmitted from ipRGCs to the core SCN by the retinohypothalamic tract (RHT). Retinal terminals release signalling molecules including the amino acid glutamate and pituitary adenylyl-cyclase activating peptide (PACAP), which activates ionotropic glutamate receptor N-methyl-D-aspartate (NMDA). This in turn causes intracellular calcium ion concentrations to rise, leading to the phosphorylation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB) via protein kinase A (PKA). Transcription of core circadian genes is then initiated through the binding of CREB and cAMP response elements within the Period promoter regions of *PER 1* and *PER 2* [24].

Given that the SCN is comprised of a core and shell, neurons within each are known to communicate to entrain the CRs with the external environment [25,26]. The primary direction of communication has been determined to occur from core to shell, via various neurotransmitters, including vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), substance P (SP) and γ-Amino-Butyric-Acid (GABA) located in the core region (Fig. 3) [27,28]. In addition to these neurotransmitters, most neurons found within the SCN (specifically the shell) demonstrate autonomous oscillations which are controlled by the core circadian genes involved in the TTFL [26,29]. This autoregulatory property was first substantiated by Welsh et al., 1995 who identified that SCN neurons dispersed in culture continued rhythmic expression of core circadian genes with a period distribution of 20 to 30-h. In comparison, SCN neurons cultured using organotypic coronal slices, exhibit a shorter period duration of between 22 and 27-h [30]. Collectively, these findings suggest that communication is necessary to ensure that the core SCN, synchronised mainly by light signals, relays this information to the shell SCN. Without this, the period of the core clock genes and their rhythmic expression would not align with the external environment to phase at the correct time. Therefore, coupling of SCN neurons, within the core and shell, is essential for organisms to optimally express core circadian genes at the correct time of day, following the light-dark cycle, and cascading to control thousands of genes in peripheral tissues [24,29].

2.2. SCN and communication with other brain regions

The two-component structure of the SCN is the primary mechanism which gives rise to CRs. Subsequent research has elucidated that the SCN not only connects the core and shell but innervates other areas of the hypothalamus and brain via efferent nerve projections, which in turn control physiological processes occurring in the periphery e.g., insulin secretion and metabolism [31]. Clear patterns of projection from the SCN can be observed to connect with the medial hypothalamus, medial preoptic area, paraventricular nucleus (PVN), arcuate nucleus, pituitary gland, and dorsomedial hypothalamus [32]. These regions of the brain are involved in the control of downstream homeostatic processes for of most organs of the body, through the secretion of hormones, regulation of the autonomic nervous system and by increasing the sensitivity of peripheral tissues prior to hormonal activation [33].

The areas of the brain which receive projections from the SCN contain specialised neuroendocrine cell populations responsible for the secretion of multiple hormones that are fundamental for health and wellbeing [32]. A key example is the hypothalamic pituitary adrenal (HPA) axis, formed by the interaction between the hypothalamus, pituitary, and adrenal glands. This multifunctional system is directly involved in i) regulating an organism's response to external stressors, ii) impacts on the digestion of food (with dysregulation linked to increased colonic motility), iii) regulation of mood, iv) energy storage and v) immune responses to inflammation [34,35]. The connection between the SCN and HPA axis is not solely anatomical, with the SCN also indirectly controlling the rhythmic expression of a class of steroidal hormones known as glucocorticoids (GCs) produced by the adrenal glands under control of the HPA axis in response to circadian cues and stress [36].

Another key SCN-mediated hormone is corticotrophin realising hormone (CRH) produced within the paraventricular nucleus and partly activated by arginine vasopressin secreted by the shell SCN [37,38]. CRH is synthesised by a group of specialised cells, parvocellular neurosecretory cells, which then are released by the hypophyseal portal system, after passing through the median eminence located at the base of the hypothalamus [34]. Basophils present within the anterior portion of the pituitary, are stimulated to secrete adrenocorticotrophic hormone (ACTH) leading to the production of cortisol, GCs, and adrenal mineralocorticoids [36,39]. Numerous other important hormones, such as somatotrophin (human growth hormone), thyroxine and triiodothyronine (thyroid hormones) are also controlled in part by the SCN. SCN ablation and tracing techniques have shown these hormones to have clear diurnal rhythmicity [34,40]. Collectively, these hormones are necessary for proper organism function, and therefore, when circadian control of these hormone levels becomes abnormal, health declines [41].

2.3. Melatonin and the sleep-wake cycle

The sleep-wake cycle is an important physiological process synchronised to the external light-dark cycle by the hormone melatonin [42]. Melatonin exhibits a clear CR which is controlled by external light signals transmitted along the RHT to the core SCN [43,44].

From this the SCN innervates the pineal gland via an efferent pathway initially from the SCN to the PVN and then to the superior cervical ganglia [45,46,47]. The superior cervical ganglia produce norepinephrine which binds to adrenergic receptors in pinealocytes, stimulating N-acetyltransferase to control the rate of melatonin synthesis [45,46]. Melatonin is then released from the pineal gland into the blood stream to be distributed throughout the body. Melatonin secretion is light controlled, peaking during the night when light levels are diminished and troughing when external light is abundant during the day [42]. As well as controlling the sleep-wake cycle, melatonin has also been identified to play a role in insulin secretion, regulating blood glucose levels, and adapting to seasonal variations in daylight during transition from summer to winter [48].

It is clear that the above hormones are crucial in facilitating numerous biological processes, such as regulation of metabolism, immune system, blood pressure, sleep architecture and the stress response [34,49,50], together emphasising the importance of an entrained SCN for optimum physical and mental health [51,52]. Failure of SCN entrainment due to either intrinsic (disease and inflammation) or extrinsic (irregular light and feeding cues, administration of sedative medication, shift work and jetlag) factors, may exacerbate CR dysregulation and give rise to serious health consequences. For the remainder of this review, we aim to shed light on the impact of inflammation, specifically secondary to acute pancreatitis (AP) on CRs, the potential mechanistic links, and how the CRs may regulate the inflammatory and immunometabolic response to AP.

3. The circadian rhythms and the immune system

When CRs become dysregulated, through either internal or external mechanisms, overall physiological and mental health and well-being are affected [53,54]. Dysregulated CRs have been linked to the development of cancer, depression, diabetes, metabolic disorders, and an increased risk of obesity [55,56]. To date, a precise causality between dysregulated CRs and disease development is unclear. However, research into the mechanisms which link these two areas is addressing this gap in the scientific knowledge. One way in which this is currently being answered is through the investigation of the relationship between the immune system and CRs, given that the immune system is crucial in fighting off infection, by detecting and responding to disease [57].

CRs are increasingly recognised to control various aspects of the immune system in mammals. One key example is enabling organisms to predict changes in their periods of maximum activity, which affects the likelihood of coming into contact with antigens [57]. Additionally, CRs are involved in other aspects pertinent to immune system function, for example migration of immune cells to the site of injury or inflammation, T-cell activation through antigen presentation, proliferation of white blood cells and toll-like receptor (TLR) activation [57,58]. In diseases with an inflammatory basis, like asthma and rheumatoid arthritis, severity of disease varies across the circadian cycle, with the most severe symptoms experienced at night and in the early morning [59,60]. This has partially been attributed to the influence of CRs on the immune system and the timed secretion of rhythmic cellular components [59]. In experimental animals, CR dysregulation, via modelled shift work or jet lag over a long period of time leads to a dysfunctional immune system and susceptibility to disease. An inverted sleep/wake cycle affects the timing of cytokine secretion, and other immune cell function necessary to fend off disease [61].

Most innate and adaptive immune response components exhibit robust CRs [58]. This circadian oscillatory behaviour has been explicitly identified in dendritic cells, macrophages, B lymphocytes, T lymphocytes and natural killer cells, which all contain a molecular circadian clock [62,63]. The molecular clock within these immune cells is thought to regulate inflammatory responses through forming a transient blockade [64,65] by preventing synchronous activation of multiple components of the timed phases of the circadian clock [66]. A key example of clock gene control of inflammatory mediators is *BMAL1* which regulates rhythmic expression of chemokines, specifically chemokine ligand 2 (CCL2) responsible for immune cell recruitment. *BMAL1* impacts on *CCL2* through a protein-protein interaction with polycomb repressive complex 2 (in most immune cells), which it utilises to inhibit *CCL2* gene expression [67]. Genetic deletion of *BMAL1* causes atypical gene expression of *CCL2* in peripheral monocyte and macrophage populations. Other core clock genes, such as *REV-ERBα,* are involved in immune regulation through transcriptional control of inflammatory genes, for example *IL-6* and *CCL2*, via temporary inhibition of gene enhancer regions to prevent gene transcription [64,68].

In addition to clock genes, a second circadian intracellular mechanism exists that enables transient repression of inflammatory mediators, namely glucocorticoid receptors (GRs) [64]. GRs are located within all cell types, including immune cells and act to bind with endogenous GC's secreted from the adrenal gland under the control of the HPA axis and SCN. GR ligation leads to suppression of glucocorticoid response elements located upstream from transcription sites and promote transrepression of numerous innate immune proteins, including key transcription factors such as nuclear factor kappa B (NF-κB) and activator protein 1 [69,70]. Recent studies have investigated this interaction in depth, focusing on the relationship between the molecular clock genes and GR to further elucidate circadian control of immune system components [64,70]. Despite the clock genes having a direct regulatory effect on inflammatory mediator expression, GRs are necessary to activate this temporary inhibitory mechanism which represses inflammatory gene expression. This has been extensively validated in bronchiolar exocrine cells, where genetic intracellular deletion of *BMAL1* gives rise to increased and constant expression of chemokines including *CXCL5* [71]. This is a result of the interaction between *BMAL1* and GR, where the removal of *BMAL1* diminishes GR presence at the genetic locus of *CXCL5*. Collectively, the above evidence suggests that clock genes are required to regulate immune responses, and that interaction between clock components and GRs is fundamental to the activation and suppression of immune cell secretion [70].

3.1. The circadian rhythms, the immune system, and disease

It was first established in the 1960's that the CRs regulate the immune system in response to invading pathogens and control the secretion of pro-inflammatory cytokines involved in the development of inflammation [72]. Since then, the involvement of the CRs in

the immune response has been investigated experimentally in mice using the bacterial endotoxin lipopolysaccharide (LPS) as a model of acute inflammation [72,73]. Mice show an increase in sensitivity to LPS when it is administered at the start of their active phase, and also report a significantly higher mortality rate of 80% compared to 20% mortality when challenged during the rest phase. This indicates that the magnitude of the immune response is CR dependent [58,72]. To date, the precise circadian mechanisms which underpin this observed difference in immune and likelihood of survival are unclear. However, it is reasonable to hypothesise that there is an interaction between several circadian controlled factors which will be discussed below, starting with leukocyte recruitment to peripheral tissues.

Firstly, leukocyte migration into peripheral tissues, is under circadian control [74]. Leukocytes, like many other immune cells, exhibit diurnal variation in cell counts in within the blood stream from where they are available to extravasate to sites of immune recruitment, depending on the internal circadian phase [75,76]. Peak leukocyte migration into peripheral tissues can be observed in mice and other nocturnal species during the active phase [77]. Given that the risk of physical damage and pathogen exposure is increased during this time period, it is reasonable to propose that the ability to rapidly recruit a high leukocyte concentration within tissues will attenuate this by combatting tissue damage and controlling infection [58]. Conversely, high mortality rates in mice exposed to LPS at the start of the active phase may be a result of increased leukocyte infiltration within peripheral tissues. Given that both the expression of chemokines and adhesion molecules, such as intracellular adhesion molecule 1 (ICAM1), are greater during this period, enhanced leukocyte migration may exacerbate tissue damage by flooding peripheral tissues with active leukocytes [78].

Secondly, mice during their active phase demonstrate an increased sensitivity in the detection of and reactivity towards invading pathogens, attributable to an increase in the quantity of specific immune system components [58,79]. These include pattern recognition receptors such as TLRs and other cellular proteins including CD14 and NF-κB [74,80]. Each of these are crucial for innate immune system activation in response to pathogen-associated molecular patterns [81]. Intracellular core clock genes also control rhythmic expression of pattern recognition receptors [82,83]. In mice with a mutated *PER2* gene, when compared to wild-type control mice, *PER2*-mutants showed decreased reactivity and expression of TLR9 on antigen presenting cells [80]. Other TLRs have been shown to exhibit daily oscillations in mRNA expression (including TLR2 and TLR6), in macrophage populations within the spleen suggesting peripheral circadian clock involvement [82]. As well increased pathogenic sensitivity, time of disease onset is also thought to contribute towards disease development.

Thirdly, an effect of time of disease onset similar to that observed by Halberg et al., 1960 in an LPS model is recapitulated in a more complex mouse model of sepsis induced by caecal ligation and puncture (CLP) [84,85]. In the CLP model the circadian *PER2* gene was identified as a potential mechanism by which the severity of sepsis and increased risk of mortality was linked to specific times of the day. Mutation of the *PER2* gene negated the time-of-day sepsis lethality effect exhibited by wild type mice [84,86]. Moreover, *PER2* knockout mice demonstrate greater survival rates and protection against endotoxic shock [87]. Similar effects have been observed in *CLOCK* mutant mice which have reduced overall sepsis mortality rates and a clear loss of the time dependent mortality rates compared to wild type mice [88]. Furthermore, interaction of *PER2* and *CLOCK* proteins affects severity of sepsis. Together, these studies suggest that it is the timed interactions between the clock genes and the clock's ability to function as a whole that dictates the time-of-day risk of mortality and resistance to disease [85].

Less is known about the mechanisms underpinning the involvement of the CRs in human disease, especially those which result in critical illness. However, as previously mentioned, it is widely accepted that numerous diseases of a chronic nature, such as rheumatoid arthritis, bronchial asthma, allergic rhinitis, and cardiovascular disease (myocardial infarction and ischaemic stroke) exhibit a clear exacerbation of symptoms in the early hours of the morning, potentially attributable to CRs [89,90,91]. Recently, this circadian aspect has been investigated in sepsis in human cohorts. Septic shock patients admitted to the intensive care unit exhibited disruption to daily rhythms and in many core clock genes expressed in $CD14^{+}$ monocytes isolated from peripheral blood. Furthermore, the positive regulators of the intracellular monocyte clock, *CLOCK* and *BMAL1*, demonstrated arrhythmic behaviour in the septic patient subgroup, despite antiphase clock components (*NR1D1, CRY1, NR1D2, DBP* and *PER2*) continuing to have rhythmic expression. However, they are significantly dampened in comparison to the healthy control group [92]. This finding has since been validated in other sepsis-based studies in whole blood samples [86,93,94,95].

Overall, the CRs control the immune response through the regulation of immune cell expression, pattern recognition receptors and infiltration of immune cells into peripheral tissues. Dysregulation of the CRs, either globally or within the peripheral clocks, leads to aberrant immune responses which may predispose disease development and concurrently promote disease severity [54].

3.2. Effect of inflammation on CRs

So far, this review has discussed the mechanisms by which the CRs exerts control over the immune system. Next, we discuss how an inflammatory response, especially a severe response as seen during critical illness, affects CRs, and introduce AP as a paradigm of critical illness in which to study CR disruption.

In addition to the presented body of evidence which substantiates circadian regulation of the immune system, the immune system, in turn, also impacts on CRs [57]. This bidirectional relationship has been explored predominantly using LPS as a paradigm of critical illness which, mentioned previously, triggers an acute inflammatory response, and has been found to affect multiple CR components. Intraperitoneal administration of LPS in mice affected circadian regulated activity periods, exhibited by a marked phase delay in activity onset, compared to healthy mice [96]. In rats, intravenous LPS was able to induce temporary repression of core clock genes, such as *PER2* and *DBP*, that are normally rhythmically expressed in the SCN control centre and peripherally within the liver [97]. This suggests that inflammatory diseases have the potential to transiently alter both the master and peripheral clocks during systemic inflammation. When LPS is administered to rat coronal SCN slices, irrespective of peak arginine vasopressin (AVP) expression time, an

increased AVP expression within SCN tissues results [98]. Tumor necrosis factor α (TNF), an essential pro-inflammatory cytokine, involved in the immune response has been identified to suppress *DBP* expression in the SCN by inhibiting the clock genes (CLOCK: BMAL1) from binding with E-box sites which prevents the initiation of *DBP* transcription [57,99]. Regardless of administration route, the above studies collectively demonstrate that the presence of inflammatory disease has the potential to impact on various aspects of the CRs, including both the master pacemaker and peripheral clocks, which in turn may lead to downstream disruption.

3.3. Acute pancreatitis cellular mechanisms

AP disease onset begins with injury to the pancreatic acinar cells which are located within the (usually sterile) pancreas [100]. Intracellular pancreatic enzymes such as amylase, lipase, and proteases contained within the acinar cells are released inappropriately in response to injury and initiate damage the surrounding healthy pancreatic tissue [6]. Moreover, this promotes the development of localised interstitial edema, impairment of pancreatic blood flow and varying degrees of necrosis of the pancreatic parenchyma [101]. During AP onset, calcium ion trafficking from the endoplasmic reticulum to the mitochondria becomes dysregulated which in turn affects mitochondrial ROS production [102]. Oxidative stress, caused by an overproduction of ROS, not only impacts on the endoplasmic reticulum's ability to fold proteins but also impairs lysosomal functioning which results in the secretion of lysosomal proteins (cathepsin B and trypsin) which are fundamental to pancreatic acinar cell death [6,103]. Following this, the contents of the injured acinar cells are extricated, acting as damage-associated molecular patterns (DAMPs). Additionally, other intracellular components, e.g., ATP, chromatin proteins, high mobility group box 1 protein (HMGB1) and histones can trigger immune responses when pathologically displaced into the extracellular space [6,104].

In addition to mitochondrial dysfunction, pro-inflammatory mediators, like TNF-α and interleukin (IL), IL-6 and IL-1 are released, and numerous innate and adaptive immune cells begin to infiltrate the pancreas in response to AP onset [5,10,105]. Known infiltrating

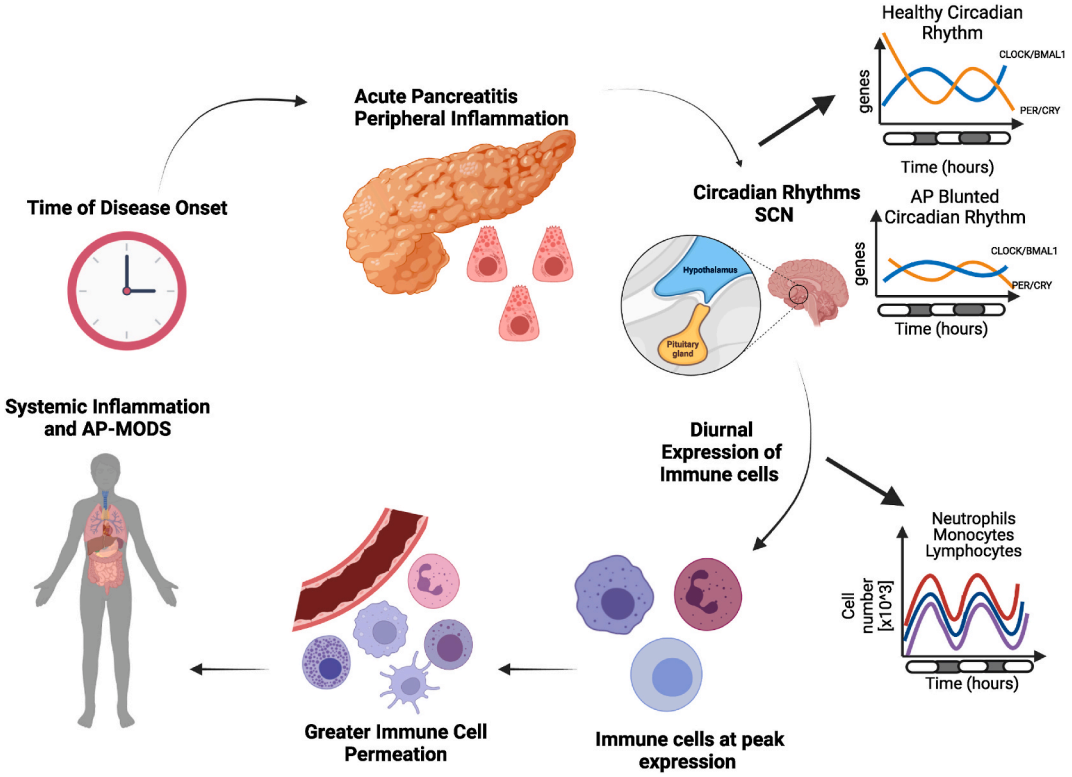


Fig. 4. Schematic of hypothesised mechanism by which Acute Pancreatitis (AP) impacts on the circadian rhythms resulting in altered immune response.

Time of disease onset has been identified, in other models of critical illness, as an underlying factor which can influence the circadian rhythms. In this schematic, we use AP as a paradigm of critical illness. AP onset begins with the resulting pancreatic acinar injury which is fed back to the circadian rhythms through peripheral circadian clocks. We predict that this peripheral inflammation, and in some severe AP cases systemic inflammation, gives rise to blunted circadian rhythm core gene expression, modelled previously in rodents. Research has shown that immune cells, neutrophils, monocytes, and lymphocytes are all expressed in a diurnal manner, dependent on the circadian rhythms. Therefore, if disease onset occurs at peak immune cell expression, for example in neutrophils, between 8:00pm and 2:00am, it may have the potential to cause greater immune cell permeation into the pancreas. Thus, resulting in greater pancreatic injury and healthy tissue damage which can incur systemic inflammation and in severe cases, cause multiple organ dysfunction syndrome (AP-MODS). AP-MODS affects the lungs, kidneys and liver and is associated with increased risk of mortality. Created with BioRender.com.

immune cells include macrophages [106], neutrophils [107,108], dendritic cells [109], natural killer cells [110], B and T lymphocytes [10]. Out of the aforementioned immune cells, it is predominantly neutrophils which infiltrate the pancreas at disease onset followed shortly by macrophage recruitment [111]. After the release of DAMPs, pattern recognition receptors located on the cell surface of various immune cells, such as macrophages, dendritic cells, and B lymphocytes, are activated [112]. This causes the infiltrating immune cells to produce even more inflammatory mediators and in turn recruit other circulating immune cells to the pancreas [10]. The influx of immune cells into the pancreas and inability to sufficiently clear away dead or necrotic cells can, in certain cases, cause further aggravation to the site of injury. This allows accumulation of necrotic pancreatic tissue [108], resulting in persisting localised inflammation and promoting further tissue damage to the surrounding healthy tissue [108,113]. Infiltration of immune cells, including both adaptive and innate types, are therefore important in determining AP severity and disease progression [10].

If systemic inflammation develops secondary to the localised pancreatic inflammation, AP can begin to affect other internal organs. In most AP patients this does not occur, however, approximately 20% of patients will go on to develop organ failure of the liver, lungs, cardiovascular system, and kidneys [1,105]. This scenario warrants critical care and is strongly associated with a fatal outcome, with a 20% mortality rate in severe AP patients admitted to intensive care and high dependency units [7]. Whilst AP has a high incidence and mortality rate, current treatment strategies are limited and focus mostly on supportive management [114].

3.4. Acute pancreatitis and the circadian rhythms

To date, the relationship between AP and CRs is not well understood, with most studies within this area focused on chronic pancreatitis and pancreatic ductal adenocarcinoma [115,116]. Given that AP, induces acute inflammation and presents with a similar disease pathology to LPS and sepsis, it is reasonable to hypothesise that AP will dampen the circadian clock gene transcription and impair internal timekeeping, mediated through systemic inflammation (Fig. 4). The downstream effects of altered circadian core clock gene expression within the pancreas has been investigated. The deletion of both *BMAL1* and *CLOCK* results in a significant depletion of islets of Langerhans, impaired glucose tolerance and a reduction in insulin secretion, which will reciprocally affect glucagon secretion [117]. These all increase the risk of developing diabetes mellitus type II [118,119]. This alteration in circadian gene expression in both the SCN and peripheral tissues may in turn feedback on AP by dysregulating the immune response. There is significant overlap between the pathological mechanisms in AP and those in systemic inflammation from other causes.

Inflammation models e.g., LPS in rodents, alter the time of activity onset and transiently repress core clock gene expression within the SCN and peripheral tissues including the liver [84,86,96,97]. Similar disruptive effects have been observed in models of bacterial sepsis. Disruption to the core clock gene expression and the subsequent timed protein-protein interactions, between *PER2* and *CLOCK*, within peripheral circadian clocks have been identified to increase the likelihood of mortality and severity of disease experienced in mice with sepsis [84,86]. This has not been established in humans, but it has been demonstrated that sepsis alters circadian gene expression within CD-14 positive monocytes. Moreover, septic patients exhibit dampened arrhythmic daily gene expression of the core circadian genes with peripheral blood samples, which is not found in healthy controls [92]. However, as these studies are in the initial stages, the potential widespread disruptive effects are yet to be explored and whether the above side effects of inflammatory diseases are temporary or not.

We speculate that CR dysregulation may impact on AP prognosis, increasing the risk of disease severity and mortality, which has been established in other models of critical illness with an acute inflammatory component [86,94]. Recurrent AP episodes are associated with an increased risk of developing chronic pancreatitis (CP), with approximately 6–13% of AP cases progressing to CP [120]. As part of the CP pathophysiology, pancreatic fibrosis can develop whereby permanent lesions comprised of fibrotic tissue form within the pancreas and begin to disrupt pancreatic function, coupled with exocrine insufficiency. These lesions are the result of continual activation of pancreatic stellate cells [121]. Recently, circadian dysregulation of core circadian genes, *BMAL1*, within the pancreatic clock has been found to increase the likelihood of developing pancreatic fibrosis and exocrine insufficiency [122]. We therefore suggest that progression to CP, from AP, may in part be due to chronic circadian dysregulation of *BMAL1* which has been brought about by the first AP episode. However, further research is justified to examine this novel association.

It is well established that the onset of AP causes adaptive and innate immune cells to be recruited and migrate to the pancreas, where they infiltrate to promote disease recovery by clearing away dead acinar cells [5,6,123]. It is likely that cell infiltration at the start of AP disease onset is dependent on the phase of the CRs, given that CRs affect the availability of circulating immune cells, chemokines and adhesion molecules regulating immune cell trafficking [66,83]. Therefore, individuals who experience AP disease onset at the start of their active phase or at the end of the resting phase, are more likely to undergo greater immune cell infiltration when immune cell expression is at or just after its peak [58,76]. We predict that this will promote a more serious disease course due to the substantial evidence which demonstrates that immune cell infiltration dictates severity of AP, with high infiltration rates associated with severe pancreatic injury, destruction of healthy tissue and increased likelihood of developing persistent systemic inflammation [108,113,123]. Conversely, those who experience AP onset during the active phase and at the start of the rest phase may be protected against severe AP due to lower levels of specific circulating immune cells (Fig. 4).

Empirically, it has been demonstrated in rats that the severity of experimental caerulein acute pancreatitis is dependent on the time of day of induction [124,125]. This has been attributed to the levels of plasma melatonin, which under circadian control, are increased during the rest phase to promote sleep [126]. Melatonin has been established to protect peripheral tissues against damage caused by ROS generation and thus, oxidative stress, which plays a key role in acinar cell death and AP progression [127,128]. It has been reported that melatonin regulates superoxide dismutase (SOD) activity, an intracellular defence mechanism which, under oxidative stress, converts superoxide into both oxygen and hydrogen peroxide [129,130]. Administration of melatonin during experimental AP, attenuates the depletion of SOD and reduces the risk of cellular damage caused by ROS [125,131]. Overall, there is a protective effect

of melatonin in experimental AP, although this has not been tested in naturally occurring clinical AP.

Lastly, it has been well documented that mice in their active phase show increased sensitivity and response to pathogenic invasion, compared to mice in their rest phase, irrespective of the type of invading pathogen [57,132]. This time-of-day dependent immune response has been identified to be an adaptative evolutionary mechanism whereby the CRs have evolved to respond to infectious agents more readily when the risk of encountering a pathogen is at its highest during the active phase. This aligns with the peak temporal expression of numerous immune system components and their respective functions, which have been primed to occur several hours prior to activity onset [57,83]. This circadian control of host immune response has been validated within a multitude of bacterial and viral pathogens, including salmonella enterica, streptococcus pneumoniae, listeria monocytogenes, vesicular stomatitis virus, herpes, and influenza [66,133,134]. Whilst the pathogenesis of AP is different to that of LPS, we hypothesise that the time-of-day host immune response effects are also present in AP and have the potential to influence survival rates and the severity of AP as observed in similar diseases, like sepsis [84,86,135].

4. Conclusions

Mounting evidence demonstrates that CRs are vital to many physiological processes, such as hormone secretion, sleep and wakefulness and the regulation of the immune system. In recent years, the development of many diseases has been associated with the dysregulation of the CRs, therefore, research into these biological rhythms has become a major focal point. It has become increasingly clear that CR dysregulation, via external or internal factors, perpetuates a dysfunctional immune system and predisposes an individual to disease. We propose here that AP is no exception, but this is yet to be supported by robust analysis of empirical data. This review has outlined several biological mechanisms which connect AP with circadian control of the immune system, time-of-day dependent immune cell infiltration moderated by the CRs and CR adaptive evolutionary mechanisms in response to disease. In closing, the elucidation of the reciprocal relationship between CR dysregulation and disease development is fundamental to generate new strategies and treatments for diseases like AP.

5. Limitations of study

This study does not have any limitations as it is a review article and does not contain data.

Funding

HW holds a Doctoral Training Program PhD Studentship funded by the Medical Research Council (UKRI-MRC) ref. 2261490. DJM has a Senior Clinical Fellowship from UKRI-MRC, ref. MR/P008887/1.

Inclusion and diversity

We support inclusive, diverse, and equitable conduct of research.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

No data was used for the research described in the article.

Declaration of interest's statement

The authors declare no competing interests.

Acknowledgements

We would also like to thank Professor Sarah E. Reece and Dr Natalia Bochkina for reviewing this article. Schematics were created using biorender.com under the appropriate student licence.

References

[1] L.P.A. Neyton, X. Zheng, C. Skouras, A. Doeschl-Wilson, M.U. Gutmann, C. Yau, I. Uings, F.V. Rao, A. Nicolas, C. Marshall, et al., Multiomic definition of generalizable endotypes in human acute pancreatitis, bioRxiv (2019), 539569, https://doi.org/10.1101/539569.

[2] J.P. Iannuzzi, J.A. King, J.H. Leong, J. Quan, J.W. Windsor, D. Tanyingoh, S. Coward, N. Forbes, S.J. Heitman, A.A. Shaheen, et al., Global incidence of acute pancreatitis is increasing over time: a systematic review and meta-analysis, Gastroenterology 162 (1) (2022) 122–134, https://doi.org/10.1053/j.gastro.2021.09.043.

[3] A.P. Shah, M.M. Mourad, S.R. Bramhall, Acute pancreatitis: current perspectives on diagnosis and management, J. Inflamm. Res. 11 (2018) 77–85, https://doi.org/10.2147/JIR.S135751.

[4] D.J. Mole, S.P. Webster, I. Uings, X. Zheng, M. Binnie, K. Wilson, J.P. Hutchinson, O. Mirguet, A. Walker, B. Beaufils, et al., Kynurenine-3-monooxygenase inhibition prevents multiple organ failure in rodent models of acute pancreatitis, Nat. Med. 22 (2) (2016) 202–209, https://doi.org/10.1038/nm.4020.

[5] L. Ding, Y. Yang, H. Li, H. Wang, P. Gao, Circulating lymphocyte subsets induce secondary infection in acute pancreatitis, Front. Cell. Infect. Microbiol. 10 (128) (2020) 128, https://doi.org/10.3389/fcimb.2020.00128.

[6] R. Kang, M.T. Lotze, H.J. Zeh, T.R. Billiar, D. Tang, Cell death and DAMPs in acute pancreatitis, Mol. Med. 20 (1) (2014) 466–477, https://doi.org/10.2119/molmed.2014.00117.

[7] P.A. Banks, T.L. Bollen, C. Dervenis, H.G. Gooszen, C.D. Johnson, M.G. Sarr, G.G. Tsiotos, S.S. Vege, Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus, Gut 62 (1) (2013) 102–111, https://doi.org/10.1136/gutjnl-2012-302779.

[8] J. Sand, I. Nordback, Acute pancreatitis: risk of recurrence and late consequences of the disease, Nat. Rev. Gastroenterol. Hepatol. 6 (8) (2009) 470–477, https://doi.org/10.1038/nrgastro.2009.106.

[9] M. Shamoon, Y. Deng, Y.Q. Chen, M. Bhatia, J. Sun, Therapeutic implications of innate immune system in acute pancreatitis, Expert Opin. Ther. Targets 20 (1) (2016) 73–87, https://doi.org/10.1517/14728222.2015.1077227.

[10] C. Peng, Z. Li, X. Yu, The role of pancreatic infiltrating innate immune cells in acute pancreatitis, Int. J. Med. Sci. 18 (2) (2021) 534–545, https://doi.org/10.7150/ijms.51618.

[11] J.O. Early, D. Menon, C.A. Wyse, M.P. Cervantes-Silva, Z. Zaslona, R.G. Carroll, E.M. Palsson-McDermott, S. Angiari, D.G. Ryan, S.E. Corcoran, et al., Circadian clock protein BMAL1 regulates IL-1beta in macrophages via NRF2, Proc. Natl. Acad. Sci. U. S. A. 115 (36) (2018) E8460–E8468, https://doi.org/10.1073/pnas.1800431115.

[12] A.M. Jobanputra, M.T. Scharf, I.P. Androulakis, J. Sunderram, Circadian disruption in critical illness, Front. Neurol. 11 (820) (2020) 820, https://doi.org/10.3389/fneur.2020.00820.

[13] J.S. Takahashi, Transcriptional architecture of the mammalian circadian clock, Nat. Rev. Genet. 18 (3) (2017) 164–179, https://doi.org/10.1038/nrg.2016.150.

[14] T.J. Stevenson, Epigenetic regulation of biological rhythms: an evolutionary ancient molecular timer, Trends Genet. 34 (2) (2018) 90–100, https://doi.org/10.1016/j.tig.2017.11.003.

[15] H. Borrmann, J.A. McKeating, X. Zhuang, The circadian clock and viral infections, J. Biol. Rhythm. 36 (1) (2021) 9–22, https://doi.org/10.1177/0748730420967768.

[16] R. Enoki, S. Kuroda, D. Ono, M.T. Hasan, T. Ueda, S. Honma, K. Honma, Topological specificity and hierarchical network of the circadian calcium rhythm in the suprachiasmatic nucleus, Proc. Natl. Acad. Sci. U. S. A. 109 (52) (2012) 21498–21503, https://doi.org/10.1073/pnas.1214415110.

[17] M. Perelis, B. Marcheva, K.M. Ramsey, M.J. Schipma, A.L. Hutchison, A. Taguchi, C.B. Peek, H. Hong, W. Huang, C. Omura, et al., Pancreatic beta cell enhancers regulate rhythmic transcription of genes controlling insulin secretion, Science 350 (6261) (2015) aac4250, https://doi.org/10.1126/science.aac4250.

[18] T.S. Andreani, T.Q. Itoh, E. Yildirim, D.S. Hwangbo, R. Allada, Genetics of circadian rhythms, Sleep Med. Clin. 10 (4) (2015) 413–421, https://doi.org/10.1016/j.jsmc.2015.08.007.

[19] A. Jagannath, L. Taylor, Z. Wakaf, S.R. Vasudevan, R.G. Foster, The genetics of circadian rhythms, sleep and health, Hum. Mol. Genet. 26 (R2) (2017) R128–R138, https://doi.org/10.1093/hmg/ddx240.

[20] G.E. Duffield, J.D. Best, B.H. Meurers, A. Bittner, J.J. Loros, J.C. Dunlap, Circadian programs of transcriptional activation, signaling, and protein turnover revealed by microarray analysis of mammalian cells, Curr. Biol. 12 (7) (2002) 551–557, https://doi.org/10.1016/s0960-9822(02)00765-0.

[21] J.M. Hurley, J.J. Loros, J.C. Dunlap, Circadian oscillators: around the transcription-translation feedback loop and on to output, Trends Biochem. Sci. 41 (10) (2016) 834–846, https://doi.org/10.1016/j.tibs.2016.07.009.

[22] L.A. Newman, M.T. Walker, R.L. Brown, T.W. Cronin, P.R. Robinson, Melanopsin forms a functional short-wavelength photopigment, Biochemistry 42 (44) (2003) 12734–12738, https://doi.org/10.1021/bi035418z.

[23] M.S. Freedman, R.J. Lucas, B. Soni, M. von Schantz, M. Munoz, Z. David-Gray, R. Foster, Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors, Science 284 (5413) (1999) 502–504, https://doi.org/10.1126/science.284.5413.502.

[24] M. Astiz, I. Heyde, H. Oster, Mechanisms of communication in the mammalian circadian timing system, Int. J. Mol. Sci. 20 (2) (2019), https://doi.org/10.3390/ijms20020343.

[25] R.Y. Moore, M.E. Bernstein, Synaptogenesis in the rat suprachiasmatic nucleus demonstrated by electron microscopy and synapsin I immunoreactivity, J. Neurosci. 9 (6) (1989) 2151–2162, https://doi.org/10.1523/JNEUROSCI.09-06-02151.1989.

[26] S. Varadarajan, M. Tajiri, R. Jain, R. Holt, Q. Ahmed, J. LeSauter, R. Silver, Connectome of the suprachiasmatic nucleus: new evidence of the core-shell relationship, eNeuro 5 (5) (2018), https://doi.org/10.1523/ENEURO.0205-18.2018.

[27] A. Meyer-Spasche, H.D. Piggins, Vasoactive intestinal polypeptide phase-advances the rat suprachiasmatic nuclei circadian pacemaker in vitro via protein kinase A and mitogen-activated protein kinase, Neurosci. Lett. 358 (2) (2004) 91–94, https://doi.org/10.1016/j.neulet.2003.12.114.

[28] R. Aida, T. Moriya, M. Araki, M. Akiyama, K. Wada, E. Wada, S. Shibata, Gastrin-releasing peptide mediates photic entrainable signals to dorsal subsets of suprachiasmatic nucleus via induction of period gene in mice, Mol. Pharmacol. 61 (1) (2002) 26–34, https://doi.org/10.1124/mol.61.1.26.

[29] D.K. Welsh, D.E. Logothetis, M. Meister, S.M. Reppert, Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms, Neuron 14 (4) (1995) 697–706, https://doi.org/10.1016/0896-6273(95)90214-7.

[30] S. Honma, D. Ono, Y. Suzuki, N. Inagaki, T. Yoshikawa, W. Nakamura, K.-i. Honma, Chapter 8 - suprachiasmatic nucleus: cellular clocks and networks, in: Progress in Brain Research, Elsevier, 2012, pp. 129–141, https://doi.org/10.1016/B978-0-444-59427-3.00029-0.

[31] R.M. Buijs, Y.X. Hou, S. Shinn, L.P. Renaud, Ultrastructural evidence for intra- and extranuclear projections of GABAergic neurons of the suprachiasmatic nucleus, J. Comp. Neurol. 340 (3) (1994) 381–391, https://doi.org/10.1002/cne.903400308.

[32] L.J. Kriegsfeld, R. Silver, The regulation of neuroendocrine function: timing is everything, Horm. Behav. 49 (5) (2006) 557–574, https://doi.org/10.1016/j.yhbeh.2005.12.011.

[33] R. Van Drunen, K. Eckel-Mahan, Circadian rhythms of the hypothalamus: from function to physiology, Clocks Sleep 3 (1) (2021) 189–226, https://doi.org/10.3390/clockssleep3010012.

[34] X.W. Lin, I.D. Blum, K.F. Storch, Clocks within the master gland: hypophyseal rhythms and their physiological significance, J. Biol. Rhythm. 30 (4) (2015) 263–276, https://doi.org/10.1177/0748730415580881.

[35] A. Leliavski, R. Dumbell, V. Ott, H. Oster, Adrenal clocks and the role of adrenal hormones in the regulation of circadian physiology, J. Biol. Rhythm. 30 (1) (2015) 20–34, https://doi.org/10.1177/0748730414553971.

[36] A. Kalsbeek, R. van der Spek, J. Lei, E. Endert, R.M. Buijs, E. Fliers, Circadian rhythms in the hypothalamo-pituitary-adrenal (HPA) axis, Mol. Cell. Endocrinol. 349 (1) (2012) 20–29, https://doi.org/10.1016/j.mce.2011.06.042.

[37] G. Aguilera, Y. Liu, The molecular physiology of CRH neurons, Front. Neuroendocrinol. 33 (1) (2012) 67–84, https://doi.org/10.1016/j.yfrne.2011.08.002.

[38] A. Kalsbeek, R.M. Buijs, J.J. van Heerikhuize, M. Arts, T.P. van der Woude, Vasopressin-containing neurons of the suprachiasmatic nuclei inhibit corticosterone release, Brain Res. 580 (1–2) (1992) 62–67, https://doi.org/10.1016/0006-8993(92)90927-2.

[39] J.P. Herman, J.G. Tasker, Paraventricular hypothalamic mechanisms of chronic stress adaptation, Front. Endocrinol. 7 (2016) 137, https://doi.org/10.3389/fendo.2016.00137.

[40] K.J. Tonsfeldt, P.E. Chappell, Clocks on top: the role of the circadian clock in the hypothalamic and pituitary regulation of endocrine physiology, Mol. Cell. Endocrinol. 349 (1) (2012) 3–12, https://doi.org/10.1016/j.mce.2011.07.003.

[41] J.A. Haspel, R. Anafi, M.K. Brown, N. Cermakian, C. Depner, P. Desplats, A.E. Gelman, M. Haack, S. Jelic, B.S. Kim, et al., Perfect timing: circadian rhythms, sleep, and immunity - an NIH workshop summary, JCI Insight 5 (1) (2020), https://doi.org/10.1172/jci.insight.131487.

[42] K. Doghramji, Melatonin and its receptors: a new class of sleep-promoting agents, J. Clin. Sleep Med. 3 (5 Suppl) (2007) S17–S23, https://doi.org/10.5664/jcsm.26932.
[43] R. McCarthy, E.S. Jungheim, J.C. Fay, K. Bates, E.D. Herzog, S.K. England, Riding the rhythm of melatonin through pregnancy to deliver on time, Front. Endocrinol. 10 (2019) 616, https://doi.org/10.3389/fendo.2019.00616.
[44] M. Ma A, H.E. Morrison, Neuroanatomy, Nucleus Suprachiasmatic, StatPearls Publishing, Treasure Island (FL), 2021.
[45] D.J. Skene, J. Arendt, Human circadian rhythms: physiological and therapeutic relevance of light and melatonin, Ann. Clin. Biochem. 43 (Pt 5) (2006) 344–353, https://doi.org/10.1258/000456306778520142.
[46] D.C. Klein, R.Y. Moore, Pineal N-acetyltransferase and hydroxyindole-O-methyltransferase: control by the retinohypothalamic tract and the suprachiasmatic nucleus, Brain Res. 174 (2) (1979) 245–262, https://doi.org/10.1016/0006-8993(79)90848-5.
[47] S. Stevens, Neuroanatomy and neurophysiology, in: Sleep Medicine Secrets, Hanley & Belfus, 2004, pp. 29–37.
[48] J. Arendt, D.J. Skene, Melatonin as a chronobiotic, Sleep Med. Rev. 9 (1) (2005) 25–39, https://doi.org/10.1016/j.smrv.2004.05.002.
[49] U. Albrecht, J.A. Ripperger, Circadian clocks and sleep: impact of rhythmic metabolism and waste clearance on the brain, Trends Neurosci. 41 (10) (2018) 677–688, https://doi.org/10.1016/j.tins.2018.07.007.
[50] H. Borrmann, J.A. McKeating, X. Zhuang, The circadian clock and viral infections, J. Biol. Rhythm. 36 (1) (2021) 9–22, https://doi.org/10.1177/0748730420967768.
[51] W.H. Walker, J.C. Walton, A.C. DeVries, R.J. Nelson, Circadian rhythm disruption and mental health, Transl. Psychiatry 10 (1) (2020) 28, https://doi.org/10.1038/s41398-020-0694-0.
[52] T.A. Bedrosian, R.J. Nelson, Timing of light exposure affects mood and brain circuits, Transl. Psychiatry 7 (1) (2017), e1017, https://doi.org/10.1038/tp.2016.262.
[53] W.H. Walker, J.C. Walton, A.C. DeVries, R.J. Nelson, Circadian rhythm disruption and mental health, Transl. Psychiatry 10 (1) (2020) 28, https://doi.org/10.1038/s41398-020-0694-0.
[54] F. Rijo-Ferreira, J.S. Takahashi, Genomics of circadian rhythms in health and disease, Genome Med. 11 (1) (2019) 82, https://doi.org/10.1186/s13073-019-0704-0.
[55] G. Sulli, M.T.Y. Lam, S. Panda, Interplay between circadian clock and cancer: new frontiers for cancer treatment, Trends Canc. 5 (8) (2019) 475–494, https://doi.org/10.1016/j.trecan.2019.07.002.
[56] I.C. Mason, J. Qian, G.K. Adler, F. Scheer, Impact of circadian disruption on glucose metabolism: implications for type 2 diabetes, Diabetologia 63 (3) (2020) 462–472, https://doi.org/10.1007/s00125-019-05059-6.
[57] R. Dumbell, O. Matveeva, H. Oster, Circadian clocks, stress, and immunity, Front. Endocrinol. 7 (37) (2016) 37, https://doi.org/10.3389/fendo.2016.00037.
[58] C. Scheiermann, Y. Kunisaki, P.S. Frenette, Circadian control of the immune system, Nat. Rev. Immunol. 13 (3) (2013) 190–198, https://doi.org/10.1038/nri3386.
[59] J.E. Gibbs, D.W. Ray, The role of the circadian clock in rheumatoid arthritis, Arthritis Res. Ther. 15 (1) (2013) 205, https://doi.org/10.1186/ar4146.
[60] F. Scheer, M.F. Hilton, H.L. Evoniuk, S.A. Shiels, A. Malhotra, R. Sugarbaker, R.T. Ayers, E. Israel, A.F. Massaro, S.A. Shea, The endogenous circadian system worsens asthma at night independent of sleep and other daily behavioral or environmental cycles, Proc. Natl. Acad. Sci. U. S. A. 118 (37) (2021), e2018486118, https://doi.org/10.1073/pnas.2018486118.
[61] O. Castanon-Cervantes, M. Wu, J.C. Ehlen, K. Paul, K.L. Gamble, R.L. Johnson, R.C. Besing, M. Menaker, A.T. Gewirtz, A.J. Davidson, Dysregulation of inflammatory responses by chronic circadian disruption, J. Immunol. 185 (10) (2010) 5796–5805, https://doi.org/10.4049/jimmunol.1001026.
[62] A.C. Silver, A. Arjona, M.E. Hughes, M.N. Nitabach, E. Fikrig, Circadian expression of clock genes in mouse macrophages, dendritic cells, and B cells, Brain Behav. Immun. 26 (3) (2012) 407–413, https://doi.org/10.1016/j.bbi.2011.10.001.
[63] T. Bollinger, A. Leutz, A. Leliavski, L. Skrum, J. Kovac, L. Bonacina, C. Benedict, T. Lange, J. Westermann, H. Oster, et al., Circadian clocks in mouse and human CD4+ T cells, PLoS One 6 (12) (2011), e29801, https://doi.org/10.1371/journal.pone.0029801.
[64] F. Fagiani, D. Di Marino, A. Romagnoli, C. Travelli, D. Voltan, L. Di Cesare Mannelli, M. Racchi, S. Govoni, C. Lanni, Molecular regulations of circadian rhythm and implications for physiology and diseases, Signal Transduct. Targeted Ther. 7 (1) (2022) 41, https://doi.org/10.1038/s41392-022-00899-y.
[65] M. Comas, C.J. Gordon, B.G. Oliver, N.W. Stow, G. King, P. Sharma, A.J. Ammit, R.R. Grunstein, C.L. Phillips, A circadian based inflammatory response – implications for respiratory disease and treatment, Sleep Sci. Prac. 1 (1) (2017) 18, https://doi.org/10.1186/s41606-017-0019-2.
[66] R. Orozco-Solis, L. Aguilar-Arnal, Circadian regulation of immunity through epigenetic mechanisms, Front. Cell. Infect. Microbiol. 96 (2020), https://doi.org/10.3389/fcimb.2020.00096.
[67] K.D. Nguyen, S.J. Fentress, Y. Qiu, K. Yun, J.S. Cox, A. Chawla, Circadian gene Bmal1 regulates diurnal oscillations of Ly6Chi inflammatory monocytes, Science 341 (6153) (2013) 1483–1488, https://doi.org/10.1126/science.1240636.
[68] J.E. Gibbs, J. Blaikley, S. Beesley, L. Matthews, K.D. Simpson, S.H. Boyce, S.N. Farrow, K.J. Else, D. Singh, D.W. Ray, The nuclear receptor REV-ERBα mediates circadian regulation of innate immunity through selective regulation of inflammatory cytokines, Proc. Natl. Acad. Sci. USA 109 (2) (2012) 582–587, https://doi.org/10.1073/pnas.1106750109.
[69] S. Timmermans, J. Souffriau, C. Libert, A general introduction to glucocorticoid biology, Front. Immunol. 10 (2019) 1545, https://doi.org/10.3389/fimmu.2019.01545.
[70] J. Gibbs, L. Ince, L. Matthews, J. Mei, T. Bell, N. Yang, B. Saer, N. Begley, T. Poolman, M. Pariollaud, et al., An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action, Nat. Med. 20 (8) (2014) 919–926, https://doi.org/10.1038/nm.3599.
[71] J.B. Smith, H.R. Herschman, Glucocorticoid-attenuated response genes encode intercellular mediators, including a new CXC chemokine (*), J. Biol. Chem. 270 (28) (1995) 16756–16765, https://doi.org/10.1074/jbc.270.28.16756.
[72] F. Halberg, E.A. Johnson, B.W. Brown, J.J. Bittner, Susceptibility rhythm to E. coli endotoxin and bioassay, Proc. Soc. Exp. Biol. Med. 103 (1) (1960) 142–144, https://doi.org/10.3181/00379727-103-25439.
[73] R.D. Feigin, J.N. Middelkamp, C. Reed, Circadian rhythmicity in susceptibility of mice to sublethal Coxsackie B3 infection, Nat. New Biol. 240 (97) (1972) 57–58, https://doi.org/10.1038/newbio240057a0.
[74] C. Scheiermann, Y. Kunisaki, D. Lucas, A. Chow, J.E. Jang, D. Zhang, D. Hashimoto, M. Merad, P.S. Frenette, Adrenergic nerves govern circadian leukocyte recruitment to tissues, Immunity 37 (2) (2012) 290–301, https://doi.org/10.1016/j.immuni.2012.05.021.
[75] K. Ella, A. Mocsai, K. Kaldi, Circadian regulation of neutrophils: control by a cell-autonomous clock or systemic factors? Eur. J. Clin. Invest. 48 (Suppl 2) (2018), e12965 https://doi.org/10.1111/eci.12965.
[76] E. Haus, M.H. Smolensky, Biologic rhythms in the immune system, Chronobiol. Int. 16 (5) (1999) 581–622, https://doi.org/10.3109/07420529908998730.
[77] R. Pick, W. He, C.S. Chen, C. Scheiermann, Time-of-Day-Dependent trafficking and function of leukocyte subsets, Trends Immunol. 40 (6) (2019) 524–537, https://doi.org/10.1016/j.it.2019.03.010.
[78] P. Nathan, J.E. Gibbs, G.E. Rainger, M. Chimen, Changes in circadian rhythms dysregulate inflammation in ageing: focus on leukocyte trafficking, Front. Immunol. 12 (2021), 673405, https://doi.org/10.3389/fimmu.2021.673405.
[79] C. Wang, L.K. Lutes, C. Barnoud, C. Scheiermann, The circadian immune system, Sci. Immun. 7 (72) (2022), eabm2465, https://doi.org/10.1126/sciimmunol.abm2465.
[80] A.C. Silver, A. Arjona, W.E. Walker, E. Fikrig, The circadian clock controls toll-like receptor 9-mediated innate and adaptive immunity, Immunity 36 (2) (2012) 251–261, https://doi.org/10.1016/j.immuni.2011.12.017.
[81] D. Li, M. Wu, Pattern recognition receptors in health and diseases, Signal Transduct. Targeted Ther. 6 (1) (2021) 291, https://doi.org/10.1038/s41392-021-00687-0.
[82] A.C. Silver, S.M. Buckley, M.E. Hughes, A.K. Hastings, M.N. Nitabach, E. Fikrig, Daily oscillations in expression and responsiveness of Toll-like receptors in splenic immune cells, Heliyon 4 (3) (2018), e00579, https://doi.org/10.1016/j.heliyon.2018.e00579.

[83] A.M. Curtis, M.M. Bellet, P. Sassone-Corsi, L.A. O'Neill, Circadian clock proteins and immunity, Immunity 40 (2) (2014) 178–186, https://doi.org/10.1016/j.immuni.2014.02.002.

[84] E.L. Heipertz, J. Harper, C.A. Lopez, E. Fikrig, M.E. Hughes, W.E. Walker, Circadian rhythms influence the severity of sepsis in mice via a TLR2-dependent, leukocyte-intrinsic mechanism, J. Immunol. 201 (1) (2018) 193–201, https://doi.org/10.4049/jimmunol.1701677.

[85] J. Poole, G.B. Kitchen, Circadian regulation of innate immunity in animals and humans and implications for human disease, Semin. Immunopathol. 44 (2) (2022) 183–192, https://doi.org/10.1007/s00281-022-00921-z.

[86] M.L. Mul Fedele, C.A. Senna, I. Aiello, D.A. Golombek, N. Paladino, Circadian rhythms in bacterial sepsis pathology: what we know and what we should know, Front. Cell. Infect. Microbiol. 11 (2021), 773181, https://doi.org/10.3389/fcimb.2021.773181.

[87] J. Liu, G. Malkani, X. Shi, M. Meyer, S. Cunningham-Runddles, X. Ma, Z.S. Sun, The circadian clock Period 2 gene regulates gamma interferon production of NK cells in host response to lipopolysaccharide-induced endotoxic shock, Infect. Immun. 74 (8) (2006) 4750–4756, https://doi.org/10.1128/IAI.00287-06.

[88] C.Y. Wang, M.J. Hsieh, I.C. Hsieh, S.S. Shie, M.Y. Ho, J.K. Yeh, M.L. Tsai, C.H. Yang, K.C. Hung, C.C. Wang, et al., CLOCK modulates survival and acute lung injury in mice with polymicrobial sepsis, Biochem. Biophys. Res. Commun. 478 (2) (2016) 935–941, https://doi.org/10.1016/j.bbrc.2016.08.054.

[89] M. Cutolo, Chronobiology and the treatment of rheumatoid arthritis, Curr. Opin. Rheumatol. 24 (3) (2012) 312–318, https://doi.org/10.1097/BOR.0b013e3283521c78.

[90] A. Nakao, Y. Nakamura, S. Shibata, The circadian clock functions as a potent regulator of allergic reaction, Allergy 70 (5) (2015) 467–473, https://doi.org/10.1111/all.12596.

[91] F. Portaluppi, R. Tiseo, M.H. Smolensky, R.C. Hermida, D.E. Ayala, F. Fabbian, Circadian rhythms and cardiovascular health, Sleep Med. Rev. 16 (2) (2012) 151–166, https://doi.org/10.1016/j.smrv.2011.04.003.

[92] G. Lachmann, B. Ananthasubramaniam, V.A. Wunsch, L.M. Scherfig, C. von Haefen, C. Knaak, A. Edel, L. Ehlen, B. Koller, A. Goldmann, et al., Circadian rhythms in septic shock patients, Ann. Intensive Care 11 (1) (2021) 64, https://doi.org/10.1186/s13613-021-00833-5.

[93] C. Acuna-Fernandez, J.S. Marin, M.E. Diaz-Casado, I. Rusanova, B. Darias-Delbey, L. Perez-Guillama, J. Florido-Ruiz, D. Acuna-Castroviejo, Daily changes in the expression of clock genes in sepsis and their relation with sepsis outcome and urinary excretion of 6-sulfatoximelatonin, Shock 53 (5) (2020) 550–559, https://doi.org/10.1097/SHK.0000000000001433.

[94] B. Coiffard, A.B. Diallo, A. Culver, S. Mezouar, E. Hammad, C. Vigne, C. Nicolino-Brunet, F. Dignat-George, K. Baumstarck, M. Boucekine, et al., Circadian rhythm disruption and sepsis in severe trauma patients, Shock 52 (1) (2019) 29–36, https://doi.org/10.1097/SHK.0000000000001241.

[95] K. Rydell-Törmänen, J.R. Johnson, The applicability of mouse models to the study of human disease, in: I. Bertoncello (Ed.), Mouse Cell Culture: Methods and Protocols, Springer, New York: New York, NY, 2019, pp. 3–22, https://doi.org/10.1007/978-1-4939-9086-3_1.

[96] L. Marpegan, M.J. Leone, M.E. Katz, P.M. Sobrero, T.A. Bekinstein, D.A. Golombek, Diurnal variation in endotoxin-induced mortality in mice: correlation with proinflammatory factors, Chronobiol. Int. 26 (7) (2009) 1430–1442, https://doi.org/10.3109/07420520903408358.

[97] K. Okada, M. Yano, Y. Doki, T. Azama, H. Iwanaga, H. Miki, M. Nakayama, H. Miyata, S. Takiguchi, Y. Fujiwara, et al., Injection of LPS causes transient suppression of biological clock genes in rats, J. Surg. Res. 145 (1) (2008) 5–12, https://doi.org/10.1016/j.jss.2007.01.010.

[98] F. Nava, G. Carta, L.W. Haynes, Lipopolysaccharide increases arginine-vasopressin release from rat suprachiasmatic nucleus slice cultures, Neurosci. Lett. 288 (3) (2000) 228–230, https://doi.org/10.1016/s0304-3940(00)01199-x.

[99] G. Cavadini, S. Petrzilka, P. Kohler, C. Jud, I. Tobler, T. Birchler, A. Fontana, TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription, Proc. Natl. Acad. Sci. U. S. A. 104 (31) (2007) 12843–12848, https://doi.org/10.1073/pnas.0701466104.

[100] T. Watanabe, M. Kudo, W. Strober, Immunopathogenesis of pancreatitis, Mucosal Immunol. 10 (2) (2017) 283–298, https://doi.org/10.1038/mi.2016.101.

[101] S.J. Pandol, A.K. Saluja, C.W. Imrie, P.A. Banks, Acute pancreatitis: bench to the bedside, Gastroenterology 132 (3) (2007) 1127–1151, https://doi.org/10.1053/j.gastro.2007.01.055.

[102] A.S. Gukovskaya, S.J. Pandol, I. Gukovsky, New insights into the pathways initiating and driving pancreatitis, Curr. Opin. Gastroenterol. 32 (5) (2016) 429, https://doi.org/10.1097/MOG.0000000000000301.

[103] I. Gukovsky, S.J. Pandol, A.S. Gukovskaya, Organellar dysfunction in the pathogenesis of pancreatitis, Antioxidants Redox Signal. 15 (10) (2011) 2699–2710, https://doi.org/10.1089/ars.2011.4068.

[104] R. Yang, J. Tenhunen, T.I. Tonnessen, HMGB1 and histones play a significant role in inducing systemic inflammation and multiple organ dysfunctions in severe acute pancreatitis, Int. J. Inflamm. 2017 (2017), 1817564, https://doi.org/10.1155/2017/1817564.

[105] P. Fonteh, M. Smith, M. Brand, Adaptive immune cell dysregulation and role in acute pancreatitis disease progression and treatment, Arch. Immunol. Ther. Exp. 66 (3) (2018) 199–209, https://doi.org/10.1007/s00005-017-0495-1.

[106] L. Antonucci, J.B. Fagman, J.Y. Kim, J. Todoric, I. Gukovsky, M. Mackey, M.H. Ellisman, M. Karin, Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress, Proc. Natl. Acad. Sci. U. S. A. 112 (45) (2015) E6166–E6174, https://doi.org/10.1073/pnas.1519384112.

[107] J. Wan, X. Yang, Y. Ren, X. Li, Y. Zhu, A.N. Haddock, B. Ji, L. Xia, N. Lu, Inhibition of miR-155 reduces impaired autophagy and improves prognosis in an experimental pancreatitis mouse model, Cell Death Dis. 10 (4) (2019) 303, https://doi.org/10.1038/s41419-019-1545-x.

[108] F. Sonego, F.V. Castanheira, R.G. Ferreira, A. Kanashiro, C.A. Leite, D.C. Nascimento, D.F. Colon, F. Borges Vde, J.C. Alves-Filho, F.Q. Cunha, Paradoxical roles of the neutrophil in sepsis: protective and deleterious, Front. Immunol. 7 (2016) 155, https://doi.org/10.3389/fimmu.2016.00155.

[109] A.S. Bedrosian, A.H. Nguyen, M. Hackman, M.K. Connolly, A. Malhotra, J. Ibrahim, N.E. Cieza-Rubio, J.R. Henning, R. Barilla, A. Rehman, et al., Dendritic cells promote pancreatic viability in mice with acute pancreatitis, Gastroenterology 141 (5) (2011) 1915, https://doi.org/10.1053/j.gastro.2011.07.033, 19126 e1-14.

[110] I. Lopez-Font, S. Gea-Sorli, E. de-Madaria, L.M. Gutierrez, M. Perez-Mateo, D. Closa, Pancreatic and pulmonary mast cells activation during experimental acute pancreatitis, World J. Gastroenterol. 16 (27) (2010) 3411–3417, https://doi.org/10.3748/wjg.v16.i27.3411.

[111] A. Habtezion, Inflammation in acute and chronic pancreatitis, Curr. Opin. Gastroenterol. 31 (5) (2015) 395–399, https://doi.org/10.1097/MOG.0000000000000195.

[112] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors, Nat. Immunol. 11 (5) (2010) 373–384, https://doi.org/10.1038/ni.1863.

[113] J. Wang, Neutrophils in tissue injury and repair, Cell Tissue Res. 371 (3) (2018) 531–539, https://doi.org/10.1007/s00441-017-2785-7.

[114] J.A. Greenberg, J. Hsu, M. Bawazeer, J. Marshall, J.O. Friedrich, A. Nathens, N. Coburn, G.R. May, E. Pearsall, R.S. McLeod, Clinical practice guideline: management of acute pancreatitis, Can. J. Surg. 59 (2) (2016) 128–140, https://doi.org/10.1503/cjs.015015.

[115] M. García-Costela, J. Escudero-Feliú, J.D. Puentes-Pardo, S.M. San Juán, S. Morales-Santana, S. Ríos-Arrabal, Á. Carazo, J. León, Circadian genes as therapeutic targets in pancreatic cancer, Front. Endocrinol. 11 (2020) 638, https://doi.org/10.3389/fendo.2020.00638.

[116] A. Kessler, S. Weksler-Zangen, Y. Ilan, Role of the immune system and the circadian rhythm in the pathogenesis of chronic pancreatitis: establishing a personalized signature for improving the effect of immunotherapies for chronic pancreatitis, Pancreas 49 (8) (2020) 1024–1032, https://doi.org/10.1097/MPA.0000000000001626.

[117] K. Chan, F.S. Wong, J.A. Pearson, Circadian rhythms and pancreas physiology: a review, Front. Endocrinol. 13 (2022), 920261, https://doi.org/10.3389/fendo.2022.920261.

[118] B. Marcheva, K.M. Ramsey, E.D. Buhr, Y. Kobayashi, H. Su, C.H. Ko, G. Ivanova, C. Omura, S. Mo, M.H. Vitaterna, et al., Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinemia and diabetes, Nature 466 (7306) (2010) 627–631, https://doi.org/10.1038/nature09253.

[119] Z. Novosadova, L. Polidarova, M. Sladek, A. Sumova, Alteration in glucose homeostasis and persistence of the pancreatic clock in aged mPer2(Luc) mice, Sci. Rep. 8 (1) (2018), 11668, https://doi.org/10.1038/s41598-018-30225-y.

[120] D. Sharma, B. Mallick, J. Samanta, V. Gupta, S.K. Sinha, R. Kochhar, Acute-on-Chronic pancreatitis: analysis of clinical profile and outcome, Cureus 13 (4) (2021), e14242, https://doi.org/10.7759/cureus.14242.

[121] C. Jc, R.W. Parks, Chronic pancreatitis—update on pathophysiology and therapeutic approaches, Indian J. Surg. (2020) 1–8, https://doi.org/10.1007/s12262-019-02059-z.
[122] W. Jiang, L. Jin, D. Ju, Z. Lu, C. Wang, X. Guo, H. Zhao, S. Shen, Z. Cheng, J. Shen, et al., The pancreatic clock is a key determinant of pancreatic fibrosis progression and exocrine dysfunction, Sci. Transl. Med. 14 (664) (2022) eabn3586, https://doi.org/10.1126/scitranslmed.abn3586.
[123] C. Peng, Z. Li, X. Yu, The role of pancreatic infiltrating innate immune cells in acute pancreatitis, Int. J. Med. Sci. 18 (2) (2021) 534–545, https://doi.org/10.7150/ijms.51618.
[124] J. Jaworek, S.J. Konturek, R. Tomaszewska, A. Leja-Szpak, J. Bonior, K. Nawrot, M. Palonek, J. Stachura, W.W. Pawlik, The circadian rhythm of melatonin modulates the severity of caerulein-induced pancreatitis in the rat, J. Pineal Res. 37 (3) (2004) 161–170, https://doi.org/10.1111/j.1600-079X.2004.00153.x.
[125] J. Jaworek, J. Szklarczyk, A.K. Jaworek, K. Nawrot-Porabka, A. Leja-Szpak, J. Bonior, M. Kot, Protective effect of melatonin on acute pancreatitis, Int. J. Inflamm. 2012 (2012), 173675, https://doi.org/10.1155/2012/173675.
[126] S. Perreau-Lenz, A. Kalsbeek, M.L. Garidou, J. Wortel, J. van der Vliet, C. van Heijningen, V. Simonneaux, P. Pevet, R.M. Buijs, Suprachiasmatic control of melatonin synthesis in rats: inhibitory and stimulatory mechanisms, Eur. J. Neurosci. 17 (2) (2003) 221–228, https://doi.org/10.1046/j.1460-9568.2003.02442.x.
[127] P.S. Leung, Y.C. Chan, Role of oxidative stress in pancreatic inflammation, Antioxidants Redox Signal. 11 (1) (2009) 135–165, https://doi.org/10.1089/ars.2008.2109.
[128] L. Robles, N.D. Vaziri, H. Ichii, Role of oxidative stress in the pathogenesis of pancreatitis: effect of antioxidant therapy, Pancreat. Disord. Ther. 3 (1) (2013) 112, https://doi.org/10.4172/2165-7092.1000112.
[129] C. Carrasco, A.B. Rodriguez, J.A. Pariente, Effects of melatonin on the oxidative damage and pancreatic antioxidant defenses in cerulein-induced acute pancreatitis in rats, Hepatobiliary Pancreat. Dis. Int. 13 (4) (2014) 442–446, https://doi.org/10.1016/s1499-3872(14)60271-x.
[130] K.H. Jung, S.W. Hong, H.M. Zheng, H.S. Lee, H. Lee, D.H. Lee, S.Y. Lee, S.S. Hong, Melatonin ameliorates cerulein-induced pancreatitis by the modulation of nuclear erythroid 2-related factor 2 and nuclear factor-kappaB in rats, J. Pineal Res. 48 (3) (2010) 239–250, https://doi.org/10.1111/j.1600-079X.2010.00748.x.
[131] M. Esrefoglu, M. Gul, B. Ates, K. Batcioglu, M.A. Selimoglu, Antioxidative effect of melatonin, ascorbic acid and N-acetylcysteine on caerulein-induced pancreatitis and associated liver injury in rats, World J. Gastroenterol. 12 (2) (2006) 259–264, https://doi.org/10.3748/wjg.v12.i2.259.
[132] C. Scheiermann, J. Gibbs, L. Ince, A. Loudon, Clocking in to immunity, Nat. Rev. Immunol. 18 (7) (2018) 423–437, https://doi.org/10.1038/s41577-018-0008-4.
[133] R.S. Edgar, A. Stangherlin, A.D. Nagy, M.P. Nicoll, S. Efstathiou, J.S. O'Neill, A.B. Reddy, Cell autonomous regulation of herpes and influenza virus infection by the circadian clock, Proc. Natl. Acad. Sci. U. S. A. 113 (36) (2016) 10085–10090, https://doi.org/10.1073/pnas.1601895113.
[134] M. Baxter, D.W. Ray, Circadian rhythms in innate immunity and stress responses, Immunology 161 (4) (2020) 261–267, https://doi.org/10.1111/imm.13166.
[135] W. Deng, S. Zhu, L. Zeng, J. Liu, R. Kang, M. Yang, L. Cao, H. Wang, T.R. Billiar, J. Jiang, et al., The circadian clock controls immune checkpoint pathway in sepsis, Cell Rep. 24 (2) (2018) 366–378, https://doi.org/10.1016/j.celrep.2018.06.026.