

# The Role of Circadian Clock Genes in Critical Illness: The Potential Role of Translational Clock Gene Therapies for Targeting Inflammation, Mitochondrial Function, and Muscle Mass in Intensive Care

Joanna Poole\* and David Ray<sup>†,‡,1</sup> 

\*Anaesthetics and Critical Care, Gloucestershire Royal Hospital, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK, <sup>†</sup>NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford, UK, and <sup>‡</sup>Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK

**Abstract** The Earth's 24-h planetary rotation, with predictable light and heat cycles, has driven profound evolutionary adaptation, with prominent impacts on physiological mechanisms important for surviving critical illness. Pathways of interest include inflammation, mitochondrial function, energy metabolism, hypoxic signaling, apoptosis, and defenses against reactive oxygen species. Regulation of these by the cellular circadian clock (BMAL-1 and its network) has an important influence on pulmonary inflammation; ventilator-associated lung injury; septic shock; brain injury, including vasospasm; and overall mortality in both animals and humans. Whether it is cytokines, the inflammasome, or mitochondrial biogenesis, circadian medicine represents exciting opportunities for translational therapy in intensive care, which is currently lacking. Circadian medicine also represents a link to metabolic determinants of outcome, such as diabetes and cardiovascular disease. More than ever, we are appreciating the problem of circadian desynchrony in intensive care. This review explores the rationale and evidence for the importance of the circadian clock in surviving critical illness.

**Keywords** circadian, chronotherapy, intensive care, critical care, inflammation, acute respiratory distress syndrome, ventilator-associated lung injury, therapy, brain injury, multiorgan failure, critical illness, mitochondria, inflammasome, immunomodulation, cytokines, acute kidney injury, epigenetic

*The only reason for time is so that everything doesn't happen at once.*

—Albert Einstein

The regular 24-h environmental cycle generated by the planet's rotation has driven the evolution of intrinsic biological timing mechanisms in virtually all life forms on the Earth. In mammals, circadian clocks

orchestrate daily rhythms in biology and behavior, such that most physiological systems are regulated in a time-of-day-dependent manner (Dibner et al., 2010; West and Bechtold, 2015; Bass and Lazar, 2016). Please see Figure 1. for summary of pertinent critical care physiology regulated by circadian 'clock' genes.

The core cellular circadian pacemaker in mammals oscillates with a 24-h period and is driven by a transcriptional-translational negative feedback loop, with

1. To whom all correspondence should be addressed: David Ray, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford OX3 7LE, UK; e-mail: david.ray@ocdem.ox.ac.uk.

JOURNAL OF BIOLOGICAL RHYTHMS, Vol. 37 No. 4, August 2022 385–402

DOI: 10.1177/07487304221092727

© 2022 The Author(s)



Article reuse guidelines: [sagepub.com/journals-permissions](https://sagepub.com/journals-permissions)

positive transcriptional regulators BMAL1/CLOCK promoting expression of repressors *Period* (*Per1/2*), *Cryptochrome* (*Cry1/2*), *Nr1d1*, and *Nr1d2* (REVERB $\alpha/\beta$ ) (King et al., 1997; Becker-Weimann et al., 2004; Brown and Doyle, 2020) and activators such as RORs (RORa, RORb, and ROR $\gamma$ s). The core clock transcription factors act through clock-controlled genes to regulate multiple aspects of cellular function in a cell- and tissue-specific manner.

Both energy metabolism and immunity are strongly regulated by the circadian clock, shaping physiological and immune responses based on the time of day. Because of the pervasive nature of the clock within our biology, altered circadian rhythmicity has been recognized as a characteristic feature and/or contributing factor to numerous diseases states, with clear implications for diagnosis and treatment (Allada and Bass, 2021).

The circadian clockwork regulates all major cell types and pathways in the immune system, from differentiation, trafficking, and local cell-based responses (Scheiermann et al., 2018). Our group was the first to define the role of specific clock components in shaping immune and inflammatory responses to challenges (Gibbs et al., 2012, 2014; Kitchen et al., 2020) and how inflammatory signals acutely re-set circadian circuits via the rapid selective degradation of specific core proteins of the circadian clockwork (Pariollaud et al., 2018). In addition, energy metabolism is profoundly affected by timed feeding and fasting events, and also by the internal circadian machinery, affecting lipogenic and lipolytic cycles in the liver, and adipose, as one example (Hunter et al., 2020). In the context of critical illness, the influence of the endogenous circadian clock, plus the altered, and typically circadian disruptive, intensive care environment act together to drive physiology and pathophysiological responses. Here, we review why targeting circadian clock genes, for example, with the REVERB agonist SR9009 and others, may be of benefit for patients in intensive care.

In the context of the stress imposed by critical illness, there are some additional considerations. These include the role of the circadian clock in driving cycles of mitochondrial fission and fusion, thereby determining the cellular bioenergetic status. Here, the cellular clock drives a circuit involving the mitochondrial master regulator PGC1 $\alpha$ , through REVERB $\alpha$  (L. Sun et al., 2021). In addition, inflammation-driven HIF1 $\alpha$  stabilization may affect circadian function through heterodimerization with the core clock protein BMAL1; HIF1, and BMAL1 are homologous as bHLH-PAS domain proteins (Peek et al., 2017; Adamovich et al., 2017). These connections suggest that critical illness may provide a rather specific cellular environment to re-wire circadian regulatory networks, with therapeutic implications.

## INTENSIVE CARE ENVIRONMENT

Intensive care is characterized by high nursing ratios and active support of organ failure using artificial scaffolds of tissue function—for example, ventilators are used to facilitate gas exchange and blood filtration supports the poor renal function.

Whatever the reason for intensive care admissions, such as infection, major surgery, or trauma, admissions are typically complicated by ongoing inflammation, lack of homeostasis, metabolic derangement (Singer, 2017), and repeated nosocomial infection secondary to an acquired immune dysfunction (Ward et al., 2008). The most basic cell functions—such as that of ATP generation (Singer, 2017) and pH regulation—are lost (Al-Jaghbeer and Kellum, 2015), necessitating artificial intervention, until such time normal tissue and cell function is resumed.

Throughout intensive care admission, the initial often hyperinflammatory human phenotype in sepsis or trauma is followed by immune paresis (Nakamori et al., 2021), classically mediated by programmed cell death of T cells via the programmed death ligand pathway (PD1), which has been extensively described in COVID-19 patients (Venet et al., 2021). Although there are obvious ways to suppress inflammatory overactivity, such as the use of steroids, these do less for the immune paresis that often follows infection (Nakamori et al., 2021). However, there are many ways to modulate immunity and the body uses them in vivo—one such pathway is regulation, and especially suppression, of cellular circadian clock proteins (Coiffard et al., 2019). It has been shown in human patients in the intensive care unit that initial inflammatory insults—for example, bacterial infection—cause an initial loss in the expression of clock-related genes (Lachmann et al., 2021) in circulating immune cells. One mechanism for this is described below.

Alarmins and antigens, such as lipopolysaccharide (LPS), cause a profound suppression of clock proteins, for example, BMAL1 (Curtis et al., 2015; Diaz et al., 2020). This is mediated partly via upregulation of miRNA-155 (Curtis et al., 2015)—a small noncoding RNA produced in response to DAMPS (damage-associated molecular patterns), alarmins (molecules that signal cell “danger”), LPS, IL-6, and other toxins. This miRNA is well known to potentiate macrophage function and acts mechanistically to stabilize TNF $\alpha$  (Bala et al., 2011). However, it seems that human and murine BMAL1 transcripts both have binding sites for miRNA-155 and are inhibited by it (Curtis et al., 2015). Thus, it seems an evolutionary adaptation to suppress BMAL1, and thereby other clock genes such as CRY and PER in the setting of cell stress—as it is seen in immune cells of septic (Lachmann et al., 2021) as well as heavily injured trauma patients (Coiffard et al., 2019). In mice, experimental BMAL1 knockout

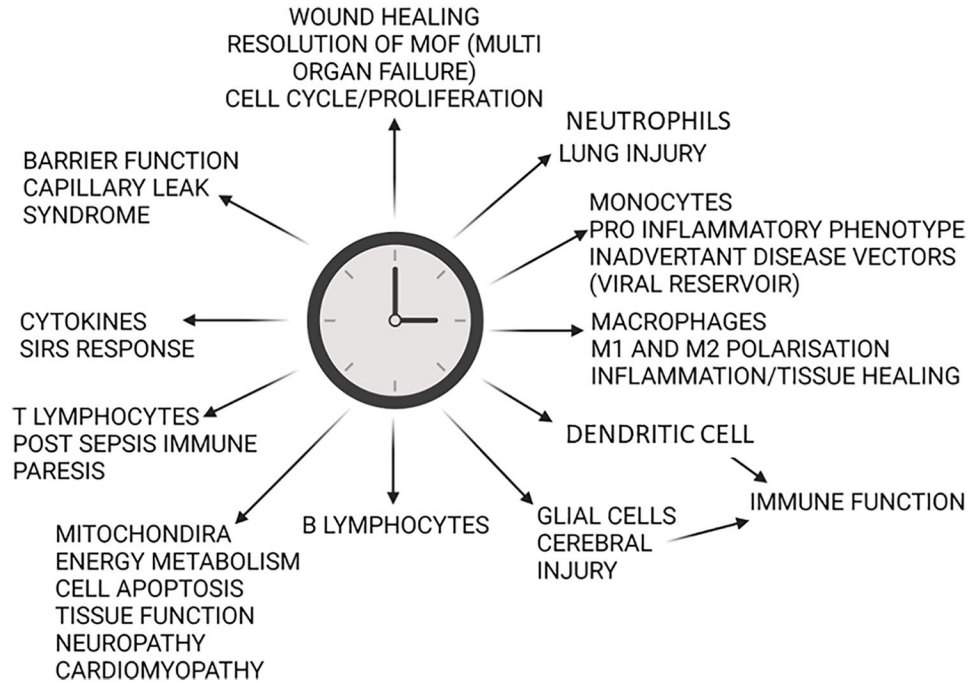


Figure 1. Summary of points of control exerted by the circadian clock relevant to patient physiology in intensive care.

provides a survival advantage in streptococcal pneumonia infection (Kitchen et al., 2020), mediated by improved phagocytic activity and immune cell recruitment (Kitchen et al., 2020), providing experimental evidence that the regulation of clock components has an effect on sepsis responses.

Urinary and serum melatonin and its precursors or metabolites have grossly abnormal circadian oscillations in human patients admitted to intensive care (Oldham et al., 2016). Furthermore, physiological parameters such as core body temperature and the “normal” circadian architecture of blood pressure variation are shown to be disturbed in multiple analyses of human intensive care patients (Chan et al., 2012).

It is not surprising that in very sick individuals, circadian rhythms are disturbed. However, recovery of externally measured circadian factors such as body temperature, heart and respiratory rate, and blood pressure appears to coincide with recovery from the disease state itself (Davidson et al., 2021). What is less clear, as there are no longitudinal studies of circadian biomarkers or gene transcripts throughout human intensive care stays, is when the cell clock resumes normality, and whether this affects disease trajectory. So far there is just evidence that on admission to intensive care, clock gene transcripts are much reduced in expression, and disordered in rhythm (Coiffard et al., 2019; Lachmann et al., 2021; Lazreg et al., 2013) at least in sepsis and trauma. One study shows that in neurologically injured patients (who may therefore have damage to the suprachiasmatic nucleus and other parts of the circadian system), clock genes are impaired

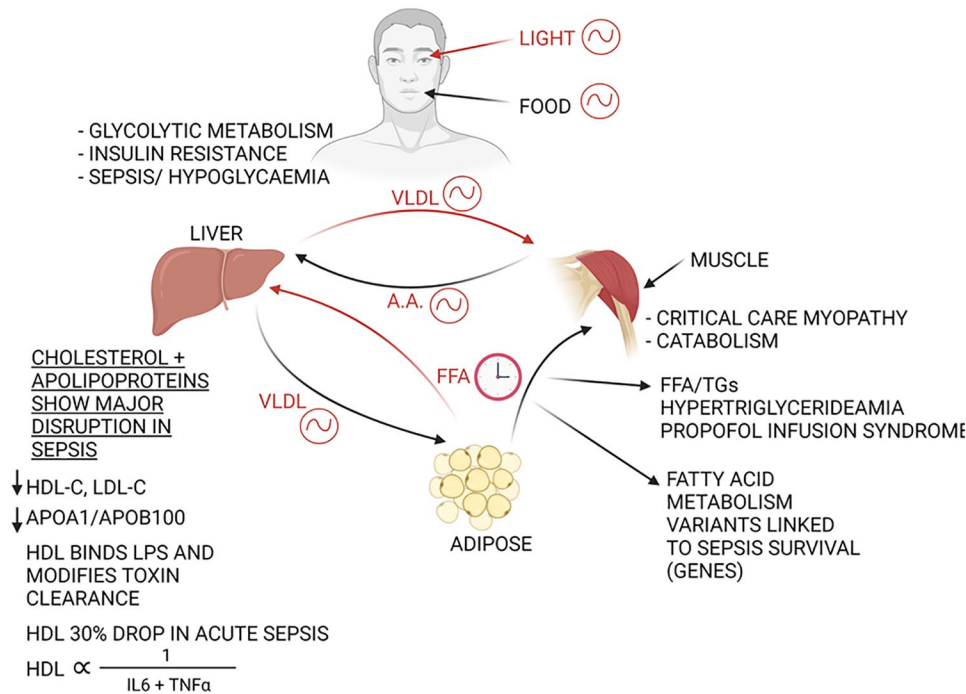
for at least 1 week after admission (Diaz et al., 2020). What we do not know is whether clock gene regulation remains disordered at discharge.

Investigation is complex, because the effects of the cell clock are often tissue-specific, and many of the output pathways are affected by the state of the patient and confounded by the environment. For example, melatonin production from the pineal gland is regulated both by the central clock in the suprachiasmatic nucleus, but also suppressed by light, and so ambient lighting in the intensive care unit can affect melatonin measurements.

Light-dark therapy has thus far had extremely limited success in RCTs (randomised control trials), and this disappointment probably represents the extremely deranged inner milieu of physiology and biochemistry in extremis, thus will not be discussed in detail. Several trials have been done and do not appear to reduce important outcomes like delirium (Simons et al., 2016; Smonig et al., 2019). It is also worth noting other environmental cues to circadian entrainments, such as feeding duration, in intensive care are often continuous (Stroud et al., 2003) rather than episodic, and thus anticipated to blunt circadian entrainment with the environment.

### CIRCADIAN DISRUPTION IN SEPSIS

Sepsis is defined as a dysregulated immune response to infection (Singer et al., 2016). It can lead to multiorgan failure (MOF) and a requirement for



**Figure 2.** Summary of circadian points of control over energy metabolism relevant to intensive care. The disruption to light and food entrainment mechanisms is central to the disruption in physiology seen. The precise coordination or lipid metabolism between the liver, muscle, and adipose, which is essential for health adaptation to rest and active periods, is both clock-regulated and also subject to direct regulation by inflammatory signaling in critical illness. Abbreviation: LPS = lipopolysaccharide; FFA = Free Fatty Acid; TGs = Triglycerides; VLDL = Very Low Density Lipoprotein; HDL-C = High Density Lipoprotein Cholesterol; LDL-C = Low Density Lipoprotein Cholesterol.

organ support. Mortality is as high as 50% (Bauer et al., 2020).

One of the features of septic shock is a high cytokine burden (Osuchowski et al., 2006); predictive of early mortality (Remick et al., 2005). Two such mediators, which also serve as useful biomarkers, are IL-6 (Song et al., 2019) and TNF $\alpha$  (Leon et al., 1998; Osuchowski et al., 2006). Other influential cytokines in this setting are IL-1b (Danielski et al., 2020) (produced by the NLRP3 inflammasome), IFN $\gamma$  (Miles et al., 1994), and IL-18 (Mierzchala-Pasierb et al., 2019).

The cytokine storm can be followed by immunosuppression in the form of a “compensatory anti-inflammatory response” (Ward et al., 2008) coined as CARS (Osuchowski et al., 2006), predisposing to nosocomial infection. There is evidence these proinflammatory cytokines are targets for circadian clock proteins; for example, REVERB represses TNF $\alpha$  expression levels in mice (Lewis et al., 2018), and IL6 has been regarded as the most circadian cytokines, under REVERB control (Gibbs et al., 2012).

With respect to CARS—the immunosuppressive phase of sepsis, one pathway is mediated by TNF $\alpha$  (Zheng et al., 1995), and another by PD-1 (programmed death ligand), reviewed recently for immunotherapy (Liu and Li, 2017). Both of these cause T-cell death, contributing to immune dysfunction (Liu and Li, 2017).

There is now evidence from preclinical animal models that the circadian clock plays a role in the “checkpoint” regulating the PD1 (Deng et al., 2018). In this animal model (Deng et al., 2018), BMAL1 deficiency increased lethality from sepsis; this was mediated by higher levels of lactate-induced PD-1 expression, which was linked to T-cell apoptosis and MOF. Lethality was abrogated in the presence of anti-PD-1 antibodies (Deng et al., 2018). Furthermore, lactate has emerged as a useful biomarker for the severity of septic shock (Singer et al., 2016; Lee and An, 2016). Also intriguingly in the above study (Deng et al., 2018) was the demonstration that BMAL1 deficiency allowed increased PKM-2 glycolytic flux, leading to higher lactate. In the same study, inhibition of PKM-2 also reduced mortality and reduced PD-1 expression. Moreover, PKM-2-induced glycolysis has been shown to directly affect the NLRP-3 inflammasome (Xie et al., 2016), which has been reviewed here (Danielski et al., 2020) as a driver of sepsis outcomes, further strengthening the mechanistic links.

Thus, the clock has a role to play in both reducing proinflammatory cytokines and reducing immune suppression in sepsis. This fits the trend noted in animals and human patients, that there is early and late death in sepsis (Xiao et al., 2006; Daviaud et al., 2015), either from proinflammatory MOF or nosocomial superinfection (Daviaud et al., 2015).



There are other interesting circadian features in sepsis; as early as 1960, Halberg et al (1960) appreciated a time-of-day-dependent lethality to inhaled endotoxin. More recently, the Ray group showed that a mouse model BMAL1 knockout (Kitchen et al., 2020) had improved mortality in *Streptococcal pneumonia*, secondary to improved macrophage motility and phagocytic function. Since then, a further mouse model has demonstrated that there is a time-of-day-responsive lethality to septic insult (Lang et al., 2019), irrespective of the myeloid clock being present, and mortality increased three times if kept in constant dark. This shows that there is more than one regulatory cue affecting this time-of-day response. Constant dark appears to be a mammalian cue for hibernation and stupor (Lee, 2007), promoting enzymes involved in the metabolism of fat (Zhang et al., 2006).

This would appear to be an unhelpful adaptation in the acute stages of sepsis, where it has been shown to increase the lethality of sepsis in a mouse model (Geiger et al., 2021), perhaps as early responses are dominated by a glucose requirement, rather than the mobilization of lipids.

In summary, it would therefore appear the interplay of light, feeding, myeloid clocks, and inflammation is complicated and requires further elucidation. The use of clock-related pathways as targets appears promising in animal models and requires human phase 1 safety trials.

### CIRCADIAN DISRUPTION IN VASCULAR DISEASE

Cardiovascular events are a common source of admission and cause of death in intensive care (Cook et al., 2021). Post cardiac arrest care takes place in the unit, and a period of cardiac “stunning” is common (Laurent et al., 2002). A comprehensive review of the pathophysiology of postresuscitation syndrome is here (Neumar et al., 2008), including ischemia-reperfusion mechanisms, metabolic reprogramming, and autonomic/adrenergic remodeling.

What we see in animal experiments of clock gene manipulation following cardiac arrest is that the presence of an intact clock process is protective in the setting of cardiac ischemia (Hu et al., 2019)—BMAL1 is integral to the healthy fusion-fission maintenance of mitochondria (E. Li et al., 2020). Circadian clock gene knockout models predispose to dilated cardiomyopathy (Ingle et al., 2015) and accelerated age-related dilated cardiomyopathy (Young et al., 2014), not dissimilar to the cardiomyopathy seen in other mitochondrial sources of cardiac pathology such as chemotherapy-induced, in which doxorubicin (Chatterjee et al., 2010) causes changes and damages

mitochondria (Yin et al., 2018), or hereditary (Friedreich’s ataxia) cardiomyopathy (Hanson et al., 2019), a disease where mitochondria are directly damaged by dysfunctional frataxin and subject to enhanced oxidative stress.

Furthermore, there is a significant circadian association to autonomic regulation of cardiac rhythm, with sympathetic input shown to increase the morning risk of ventricular fibrillation (Hayter et al., 2021). Temporal changes in autonomic output are also responsible for a time-of-day susceptibility to QT-prolonging drugs such as the antibiotic levofloxacin (Kervezee et al., 2016).

It has also been shown in vivo that BMAL1 knock-out significantly increases micro and macrovascular risks by altering endothelial function and intimal hyperplasia (Bhatwadekar et al., 2017). The phenotype seen is described as a mimic of diabetic vascular changes. Plaque remodeling in coronary artery disease was also recently shown to be influenced by BMAL1 activity (Zhu et al., 2018). In coronary artery disease, the ROS protective effects of active BMAL1 conveyed protection. This is in contrast to the beneficial effects seen with BMAL1 loss in *Pneumococcal pneumonia*, where the absence of BMAL1 allows augmented inflammatory action.

There has been previous interest in time-of-day-related outcomes in cardiac surgery, noted in aortic valve replacement in human patients (Montaigne et al., 2018). Here, afternoon surgery improved both postoperative troponin release and other clinical outcomes. This does match the circadian pattern of inflammation in humans (peaking in the morning) (Smolensky et al., 2015). A meta-analysis (Fudulu et al., 2021) in several thousands of patients failed to replicate this finding. However, it is worth noting that outcomes already vary by the individual center (Soppa et al., 2019) (the aortic valve study was in a single center), and also that an arbitrary afternoon cutoff of 12:00 may not capture the full circadian range of response. With respect to translational approaches, the REVERB agonist SR9009 when given early after ischemia, in mice, improved ischemia-perfusion-related remodeling and cardiac function (Reitz et al., 2019). In addition to REVERB agonists, attention is currently being applied to the development of ROR $\alpha$  ligands for cardiovascular disease, for example, they are overexpressed in acute myocardial infarction (Meng et al., 2021).

### CLOCK GENES AS TARGETS FOR LUNG INJURY

The lungs are a key tissue supported in intensive care; in the United Kingdom, invasive ventilation can only occur in the intensive care unit. Inflammation in

the lungs is circadian (Nosal et al., 2020), as has been noted particularly in asthma (Durrington et al., 2014) and also in physiological circadian variation in myeloid trafficking (Druzdz et al., 2014).

Ventilator-induced lung injury (Dreyfuss and Saumon, 1998) is a phenomenon in which invasive ventilation directly damages the lungs, irrespective of the underlying condition. There are few epidemiological studies as it is difficult to differentiate from the primary condition (such as pneumonia or acute respiratory distress syndrome); however, in a study of 332 patients, 24% were seen to develop lung injury in the first 5 days of admission (Gajic et al., 2004). Ventilator-associated lung injury (VALI) is known to be a cause of iatrogenic mortality because in a landmark RCT of the lung-protective ventilation strategy, mortality was reduced significantly in those with low tidal volumes (Acute Respiratory Distress Syndrome Network et al., 2000). Later studies have confirmed lower tidal volumes are associated with lower levels of cytokine release (Parsons et al., 2005), such as TNF $\alpha$  (Chiumello et al., 1999) or IL-1 $\beta$  (Dolinay et al., 2012). VALI consists of pressure (Kolobow et al., 1987), volume (Carlton et al., 1990), or hyperoxia (Helmerhorst et al., 2017)-induced trauma to the integrity of lung architecture (Ware, 2013) leading to edema (Carlton et al., 1990), tissue destruction (Ware, 2013), and thus impaired gas exchange. The release of alarmins and cytokines causes systemic inflammation (Parsons et al., 2005) and contributes to MOF (Jaecklin et al., 2010; Chiumello et al., 1999; Plötz et al., 2004). Strategies to reduce VALI are therefore of great interest. Some of the aforementioned pathways that mediate ventilation-induced lung damage have been shown to be affected by clock gene agonists such as REVERB agonists, for example, the NLRP3 inflammasome (Wang et al., 2018). Targeting REVERB may be an option to combat the inflammasome activation seen as part of ventilation-induced lung injury (Liu et al., 2019; Dolinay et al., 2012).

Furthermore, TNF $\alpha$  is implicated in VALI with evidence that the blockade of TNF $\alpha$  is protective (Proudfoot et al., 2018; Bertok et al., 2012). A phase II human trial of anti-TNF $\alpha$  was stopped due to being underpowered (Ryan et al., 2020); however, this was recent, and so far no further human trials have been published. TNF $\alpha$  mediates its actions mainly through the NF $\kappa$ B pathway (Liu et al., 2000; Zhang et al., 2017), and REVERB agonists have been shown to target this intracellular cascade, for example by binding to p65 at its promoter in macrophages (Wang et al., 2018). In addition, REVERB agonists were found to improve mortality and reduce cytokine levels in non-alcoholic steatohepatitis, a disease process with prominent NF $\kappa$ B action (Griffett et al., 2020).

Hyperoxia can drive lung damage, an effect mediated by activation of the JNK/ERK-3 pathway (Li et al., 2007). This pathway can be targeted by REVERB, by transcriptional repression through the NCoR-HDAC3 repressor complex (Zhang et al., 2002; Yin and Lazar, 2005).

A late effect of ventilator-induced lung injury and acute respiratory distress syndrome (ARDS) is pulmonary fibrosis (Albert et al., 2019; Marshall et al., 1998; Cabrera-Benítez et al., 2012, 2014). Mechanical trauma to lung tissue resulting from forced ventilation in mice results in the epithelial-to-mesenchymal transition, through the actions of TGF (Cabrera-Benítez et al., 2012). Fibroblast changes cause increased collagen deposition (Tsukui et al., 2020). Fibrosis directly contributes to mortality (Cabrera-Benítez et al., 2014). REVERB agonists have been shown to protect against fibrosis in an animal model of lung fibrosis (Cunningham et al., 2020). They are also protective with respect to the epithelial-to-mesenchymal transition (Wang et al., 2021), as an inflammatory response, and reduce morbidity, and mortality in an animal model of smoke-induced lung damage (Wang et al., 2021).

Further underlining the role of the clock genes in lung injury, murine experiments demonstrate that the severity of VALI is gated by BMAL1—high tidal volumes are less traumatic in a BMAL1 knockout (Felten et al., 2018) mouse. The loss of BMAL1 was associated with less neutrophil ROS production in response to ventilator injury.

In a rat model, the REVERB agonist SR9009 rescued many of the deleterious changes induced by high ventilator tidal volumes (Li et al., 2014). The tidal volumes used in these experiments were vastly outside the clinical range, 10–40 mL/kg—in humans the “safe” range is 6–8 mL/kg (Acute Respiratory Distress Syndrome Network et al., 2000), so it is impressive to see this degree of reduction. Corresponding parameters include reduced leukocyte egress and reduced TNF $\alpha$  (Li et al., 2014).

Furthermore, tissue susceptibility to stress in the lung has circadian regulation according to a study demonstrating that the oxidative stress response pathways NRF-2/glutathione affected the degree of lung fibrosis developed in response to bleomycin (Cunningham et al., 2020). The authors found that the NRF-2 pathway caused the altered redox state/glutathione reserves that affected the time-of-day response to bleomycin. BMAL1 is shown to bind to an important E-box on the NRF-2 gene (Q. Sun et al., 2021). BMAL1, together with NRF-2, is a key coordinator of oxidative responses in cells (Chhunchha et al., 2020).

Another factor in indirect injury in invasive ventilation is the loss of intercostal and diaphragmatic

muscle mass, which affects weaning from the ventilator (Nakanishi et al., 2019) and may reflect the wider myopathy that occurs in the critically ill (van Gassel et al., 2020). REVERB agonists can affect skeletal muscle oxidative and functional capacity (Woldt et al., 2013; Amador et al., 2018) and so may find an application in this context. Indeed, REVERB doping has been proposed in elite sports (Davies et al., 2019). REVERB may prevent muscle atrophy, so preserving muscle mass (Mayeuf-Louchart et al., 2017). This is an intriguing prospect for intensive care patients who suffer from profound muscle wasting (Koukourikos et al., 2014), despite calorie-calculated feeding (Stroud et al., 2003). Moreover, muscle biopsies in critically ill patients demonstrate “bioenergetic failure” in the sense there is a loss in ATP concentrations that correlates with the degree of protein loss (Puthuchery et al., 2018). This is a very important area in intensive care because in addition to ventilator weaning (Nakanishi et al., 2019), it affects survivors postdischarge (Owen et al., 2019).

### CLOCK GENES AS TARGETS IN SUBARACHNOID HEMORRHAGE

Circadian pathways influence the extent of brain damage in subarachnoid hemorrhage. They also predict recovery (Davidson et al., 2020). Furthermore, changes in circadian rhythm have been shown in neurocritical care to predict the development of an intracranial pressure spike 24 h in advance (Nogueira et al., 2017). In addition, both cryptochromes (Nogueira et al., 2017) and heme oxygenase directly influence the degree of inflammation and neuronal survival in subarachnoid hemorrhage (Li et al., 2018). Heme oxygenase is mentioned given it is a key enzyme in the degradation of heme, is increased locally in hemorrhagic situations as erythrocytes leave the intravascular space, and is also circadian (Li et al., 2018).

Subarachnoid hemorrhage remains a desperate condition; one-third of patients die within 3 months, while over half never fully recover (Andersen et al., 2019). Management is mainly limited to preventing further bleeding via intravascular coiling or neurosurgical clipping (Highton and Smith, 2013), the use of a calcium channel antagonist to limit vasospasm and further ischemia (Pickard et al., 1989) and supportive care (Highton and Smith, 2013).

Following the initial bleed, calcium channel antagonists are used to reduce further cerebral ischemia (Pickard et al., 1989)—defined as areas of cerebral infarction within 6 weeks of the initial bleed but not

related to it directly (Vergouwen et al., 2010). There appears to be more than one mechanism of damage, for example, microthrombosis (Suzuki et al., 1990) in the symptomatic area, evident at autopsy in human patients, and endothelial dysfunction (Frijns et al., 2006), as well as toll-like receptor activation, which predicts the outcome in human patients (C. Ma et al., 2015), inflammasome activation in murine models (Greenhalgh et al., 2012), neuronal and glial toxicity in cell culture and animal models (Regan and Panter, 1993; Rosen and Frumin, 1979), and impaired mitochondrial function/mitophagy (Youn et al., 2021) evident in human CSF (cerebrospinal fluid) samples.

Following subarachnoid hemorrhage, one of the issues central to delayed cerebral ischemia is toxicity from hemoglobin (Suzuki et al., 2003); under physiological conditions, it produces free radicals (Reeder et al., 2004) that oxidize and damage cell lipids, proteins, and DNA (Marnett et al., 2003). Moreover, it induces a form of cell death in neurons called ferroptosis (Bai et al., 2020), only recently described (J. Li et al., 2020), and free heme that is toxic to mitochondria (Mercer et al., 2011).

The extent of bleeding in subarachnoid hemorrhage predicts mortality (van der Steen et al., 2020). In cell culture, heme directly induces cell death (Regan and Panter, 1993), recently confirmed as neuronal ferroptosis (Bai et al., 2020). Inhibition of ferroptosis reduces mortality in an animal model of subarachnoid hemorrhage (Li et al., 2017). Injection of blood, or heme, into the subarachnoid space evokes focal epileptogenesis and symptoms of delayed cerebral ischemia (DCI) in animal models (Rosen and Frumin, 1979). Moreover, chelation of heme reduces DCI in rabbits (Arthur et al., 1997) and primates (Horky et al., 1998), and higher levels of CSF ferritin (an endogenous iron-binding protein) are protective against DCI in human patients (Suzuki et al., 2003). Interestingly, haptoglobin genotype affected functional outcomes in humans (Kantor et al., 2014) after subarachnoid hemorrhage (Kantor et al., 2014)—haptoglobins provide important CSF heme scavenging (Galea et al., 2012). Chelation therapy failed in a phase II human trial for the main endpoint (outcome at 3 months) but was shown to be safe. One issue in the trial was that just 30% of patients received therapy within 12 h—where the animal benefit had been seen to depend on an early window of administration. One issue in patients is time-to-treatment is delayed by diagnosis and presentation (when patients seek medical attention/or are found), time to scan, scan reporting, appropriate referral, surgical intervention, and availability of research personnel for recruitment and administration of drug/placebo, yet cellular damage may occur before this intervention can take place.



REVERB agonists have been shown to have protective effects on ferroptotic injury (Guo et al., 2021). Furthermore, they can assist in improved mitochondrial functional capacity (Woldt et al., 2013) and turnover (L. Sun et al., 2021). Therefore, targeting REVERB may prove an attractive option, in the event that higher potency, and more specific agents emerge from drug discovery programs. There are very few reports of REVERB therapies in neurological preclinical or clinical studies; yet, recent interest in the circadian regulation of disease is taking shape. Stroke infarct size has significant circadian variability and is now under great scrutiny for improving outcomes and secondary prevention of injury (Lo et al., 2021).

Clock pathways therefore represent a truly exciting prospect for the management of critical care neurological conditions. Pathways affected by clock genes are often redox/mitochondrial-related, unsurprising given their origin as phase mediators of UV light toxicity and energy metabolism.

Some impressive studies now suggest that the failure of translation of animal-to-human neuroprotective therapies is an inevitable consequence of administering the intervention to people at the wrong circadian phase, thereby leading to failure in clinical studies (Esposito et al., 2020).

### CLOCK GENES AS TARGETS IN ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is a spectrum of renal disease defined by standardized criteria, based on creatinine changes and/or urine output (Makris and Spanou, 2016). Mortality in intensive care is high, exceeding 50% (Pickkers et al., 2021). In addition to this, organ support with renal replacement therapy is expensive, costing hundreds to thousands of dollars a day (Srisawat et al., 2010). It requires 1:1 nursing and is therefore labor-intensive. It also requires invasive venous access, which risks infection (Atilla et al., 2016).

A recent review encapsulates the pathophysiology of AKI (Makris and Spanou, 2016). Of particular importance is the activation of immune receptors on the glomerular endothelium (Radi, 2018). This leads to local inflammation and also microthrombosis, the occlusion of capillaries by small clots (Chang, 2018)—which reduces oxygen supply to tissues; renal tissue hypoxia is associated with AKI and can be measured directly in animals (Iguchi et al., 2019) and noninvasively in human patients. (Silverton et al., 2021)

In addition to these observations, metabolic deficits have been seen in AKI, for example, abnormal fission and fusion of mitochondria (Brooks et al., 2009; Yan et al., 2020). In particular, the abnormal fission

may be driven by dynamin-related protein 1 (DRP-1) (Perry et al., 2018). Mitochondrial biogenesis is driven by PGC-1 $\alpha$  (Goffart and Wiesner, 2003; Jornayvaz and Shulman, 2010), and PGC-1 $\alpha$  dysregulation is seen in models of AKI development (Fontecha-Barriuso et al., 2020), with increased expression improving outcomes (Tran et al., 2011). Similarly, NAD<sup>+</sup> deficiency is seen in AKI (Poyan Mehr et al., 2018). Supplementation of NAD<sup>+</sup> is successful in improving creatinine levels in human phase 1 trials (Poyan Mehr et al., 2018). The protective effect of NAD<sup>+</sup> on mitochondrial function is mediated by Sirtuin 3 (Lombard et al., 2011; Fan et al., 2021).

Because the clock gene REVERB can affect mitochondrial dynamics via the NRF-2 pathway (Goffart and Wiesner, 2003; Eichenfield et al., 2016; Li et al., 2021; L. Sun et al., 2021). It may be an attractive target either for renal protection (prior to a planned insult such as major surgery [Prowle et al., 2021], or contrast dye [Lei et al., 2018]) or for reducing the severity of AKI in intensive care. REVERB agonists increase mitochondrial oxidative capacity in skeletal muscle, but their role in the kidney has not been explored.

Therefore, this is a translational opportunity for a condition that currently requires time and expensive organ support where there are no published studies on REVERB agonists in the context of sepsis-induced AKI, or to reduce perioperative AKI.

### CIRCADIAN DISRUPTION AND IMMUNOMETABOLISM

For a summary of the metabolic pathways regulated by the circadian clock, please see Figure 2. Early in the systemic inflammatory response, there is a “glycolytic switch”—seen in initially activated neutrophils (Sadiku et al., 2021), macrophages (Yu et al., 2020), B cells (Doughty et al., 2006), proinflammatory T cells (Chapman et al., 2020), and microglia (Cheng et al., 2021). Therefore, metabolic regulation of inflammation is gaining traction (Soto-Herederó et al., 2020). Inhibiting glycolytic changes appears to modify mortality in mice with septic shock—mediated via PMK-2 (Deng et al., 2018). This is logical when considering the effects of glycolysis on proliferation, cell activity, and the production of proinflammatory cytokines (Van Wyngene et al., 2018), which correlate with the severity of septic shock (Leon et al., 1998; Song et al., 2019). The liver transcriptome and proteome are profoundly regulated by the circadian clock (Droin et al., 2020; Weger et al., 2021), with BMAL1 driving changes in carbohydrate (Ma et al., 2016) and lipid metabolism (Zheng et al., 2016). Circadian disruption, such as that produced by shift-work (Sharma et al., 2017) or continuous feeding



(Hutchison et al., 2019) (ubiquitous in critical care), predisposes to impaired glucose tolerance. Glucose intolerance is a poor prognostic factor in sepsis (Bingham et al., 1980) and was noted as early as the 1970s (Bingham et al., 1980) to be associated with a state of hyperglucagonemia, reflecting a “metabolic energy deficit.” Hyperglucagonemia and high glucose cause inhibition of a number of intermediate cell pathways including sirtuins and PGC-1 $\alpha$  (Vieira et al., 2013). PGC-1 $\alpha$  and the related mitochondrial regulator genes are prognostic factors for the outcomes after intensive care admission (Huang et al., 2021), and are heavily involved in mitochondrial fission-fusion homeostasis (Jornayvaz and Shulman, 2010), critical for the regulation of oxidative phosphorylation relevant for sepsis survival (Singer, 2017; Nedel et al., 2021). Interestingly, inhibition of aerobic metabolism is protective against sepsis-induced AKI in some animal models (Tan et al., 2021).

One of the other key developments in critical care is the acknowledgment that immune paresis is seen in patients (Ward et al., 2008), leading to nosocomial secondary infections, such as ventilator-associated pneumonia, intravenous line infections, and opportunistic infection (Ward et al., 2008). This immune paresis is related to the loss of T lymphocyte function (Kühlhorn et al., 2013), with enhanced T-cell apoptosis (Monneret et al., 2016) (secondary to TNF $\alpha$  (Zheng et al., 1995) and increased levels of programmed death ligand—PD-1 (Liu and Li, 2017)]. Specific T lymphocyte subsets, such as Treg cells, have a special role in sepsis recovery—sepsis is a biphasic disease, with either early or late mortality (Nedeva et al., 2019).

Early Treg cell metabolism is glycolytic (Chapman et al., 2020)—the Warburg effect shunting substrate into advanced proliferation and cell division, with the GLUT 1 transporter prominently expressed (Macintyre et al., 2014). However, in the passage of days, metabolism begins to favor fatty acid/glutamine substrate oxidation, and differentiation of pro-resolution T lymphocytes (Kominsky et al., 2010; Arts et al., 2017).

This metabolic polarization matched to function is also reflected in the glycolytic inflammatory M1 macrophage phenotype and the fatty acid-favoring anti-inflammatory/tissue regenerating M2 macrophage (Arts et al., 2017). Closely coordinated with these metabolic needs is the acute suppression of mitochondrial respiration in illness (Singer, 2014; Carré et al., 2010; Singer, 2017).

Moreover, a small number of case reports (Wischmeyer and San-Millan, 2015) have shown that the recovery of fatty acid beta-oxidation after critical illness matches quality-of-life outcomes, such as the ability to exercise. Other studies show that muscle quality and mitochondrial deficits per-

sist after intensive care which influences rehabilitation (Owen et al., 2019).

The importance of fatty acid metabolism in sepsis became important when a seminal paper identified that defects in fatty acid beta-oxidation in children dictated survival from sepsis in pediatric critical care (Wong et al., 2009). There, gene variations in PGC-1 $\alpha$ , a master regulator of PPAR, fatty acid oxidation, and mitochondrial biogenesis (mitochondria and fatty acid oxidation are twinned) underpinned survival.

Immunometabolic work has shown that fatty acid beta-oxidation is especially important in promoting the M2 macrophage phenotype (Arts et al., 2017), encouraging wound healing and tissue regeneration. It is also the favored pathway in slightly older (i.e. T cells that are several days post-TCR activation) Treg cells (Kempkes et al., 2019), which have an anti-inflammatory function. REVERB has been shown to affect cellular fatty acid metabolism in muscle (Amador et al., 2018), but actions on energy substrate utilization in immune cells remain unexplored.

The metabolic and effector function changes underpin and explain the clinical picture seen in sepsis—acute hyperinflammation with early death (Daviaud et al., 2015)—excessive innate immunity (being the immune response that does not require pre-exposure, requiring neutrophils, macrophages, etc., versus adaptive immunity, which is an acquired response directed by B and T), or protracted immune paresis/inappropriate tolerance, nosocomial infection, and late death (Daviaud et al., 2015). Clearly, the circadian control of energy metabolism and thereby regulation of effector function of immune cells represents an exciting breeding ground for novel therapeutic targets.

Briefly, cholesterol metabolism also influences immunity (Sharma et al., 2019), for example, a dramatic reduction in HDL is seen in sepsis (Morin et al., 2015), with actions of bacterial products including LPS (Liu et al., 2015). Inhibition of a cholesterol transporter significantly improves sepsis survival (Trinder et al., 2021) and is under clock control (D. Ma et al., 2015).

## CONCLUSION

Spatiotemporal regulation of the transcriptome of the liver at least has been elegantly illustrated (Droin et al., 2020). The circadian clock helps provide a “metronome” for coordinating metabolism (Weger et al., 2021), hypoxic/oxidative stress (Cunningham et al., 2020; O’Connell et al., 2020), and immune function (Guo et al., 2019), to provide

the best “setting” for response to external triggers (Lang et al., 2019).

Holistic coordination of the transcriptome at a 3D chromatin level has been missing from the management of diseases in intensive care. These patients have dysregulated immune systems (Osuchowski et al., 2006), mitochondrial failure (Singer, 2017), and aggressive muscle loss (Nakanishi et al., 2019). Immunomodulation in critical care has been controversial (Young and Marsh, 2018), with only recently steroids and Tocilizumab being licensed for COVID-19 (RECOVERY Collaborative Group et al., 2021; Abani et al., 2021). However, steroids are associated with muscle atrophy (Hasselgren et al., 2010). There are no currently licensed treatments to improve mitochondrial function in intensive care (Kozlov et al., 2011).

REVERB manipulation and therapeutic targeting of other clock-related pathways represent a truly ground-breaking opportunity to improve multiple axes of illness, and further studies in this area may clarify why current light-related trials have failed to succeed (Simons et al., 2016). Although REVERB targets have currently the most diverse usage in preclinical models, other clock-related gene targets exist. For example, CRY stabilizers prevent the degradation of CRY, and their use in *Drosophila* appears to be life-extending and beneficial under starvation conditions (Solovev et al., 2021), although there are limited publications regarding studies in inflammatory illness. ROR modulators appear to have more preclinical usage than CRY stabilizers at present, especially in relation to autoimmune disease. They have been recently reviewed elegantly (Ladurner et al., 2021). The RORs have different tissue expressions; ROR $\alpha$  is present predominantly in organs, while ROR $\gamma$  is lymphatic (Ladurner et al., 2021); these different isoforms may provide nuanced targeting of cellular pathways. ROR $\alpha$  has proven a target in LPS-associated septic shock in mice (Hams et al., 2021), as well as surviving bacterial infection following severe burns injury, in rodents (Ito et al., 2018). RORs are heavily intertwined with lipid metabolism and homeostasis (Jetten et al., 2018), which has made them a focus for diabetes for example, although the immediate critical care implications are unclear. They have also been recently reviewed in the treatment of myopathies (Welch and Flaveny, 2017), which is highly pertinent to the catabolic, cachexic state of seriously unwell patients as mentioned throughout this review.

The unlicensed use of these drugs as performance enhancers (Davies et al., 2019) raises the issue of how to enhance “performance” in the critically ill. The

early phase of clinical trials of new, circadian clock therapeutics is now urgently needed.

## ACKNOWLEDGMENTS

DWR MRC program grant MR/P023576/1; Wellcome Trust (107849/Z/15/Z).

## CONFLICT OF INTEREST STATEMENT

The author(s) have no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## ORCID iD

David Ray  <https://orcid.org/0000-0002-4739-6773>

## REFERENCES

- Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, Abbott A, Abdallah N, Abdelaziz A, Abdelfattah M, et al. (2021) Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 397:1637-1645.
- Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, and Wheeler A (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 342:1301-1308.
- Adamovich Y, Ladeux B, Golik M, Koeners MP, and Asher G (2017) Rhythmic oxygen levels reset circadian clocks through HIF1 $\alpha$ . *Cell Metab* 25:93-101.
- Albert RK, Smith B, Perlman CE, and Schwartz DA (2019) Is progression of pulmonary fibrosis due to ventilation-induced lung injury? *Am J Respir Crit Care Med* 200:140-151.
- Al-Jaghbeer M and Kellum JA (2015) Acid-base disturbances in intensive care patients: etiology, pathophysiology and treatment. *Nephrol Dial Transplant* 30:1104-1111.
- Allada R and Bass J (2021) Circadian mechanisms in medicine. *N Engl J Med* 384:550-561.
- Amador A, Campbell S, Kazantzis M, Lan G, Burris TP, and Solt LA (2018) Distinct roles for REV-ERB $\alpha$  and REV-ERB $\beta$  in oxidative capacity and mitochondrial biogenesis in skeletal muscle. *PLoS ONE* 13:e0196787.

- Andersen CR, Presseau J, Saigle V, Etminan N, Vergouwen MDI, and English SW (2019) Core outcomes for subarachnoid haemorrhage. *Lancet Neurol* 18:1075-1076.
- Arthur AS, Fergus AH, Lanzino G, Mathys J, Kassell NF, and Lee KS (1997) Systemic Administration of the iron chelator deferiprone attenuates subarachnoid hemorrhage-induced cerebral vasospasm in the rabbit. *Neurosurgery* 41:1385-1392.
- Arts RJW, Gresnigt MS, Joosten LAB, and Netea MG (2017) Cellular metabolism of myeloid cells in sepsis. *J Leukoc Biol* 101:151-164.
- Atila A, Doğanay Z, Çelik HK, Tomak L, Günel Ö, and Kılıç SS (2016) Central line-associated bloodstream infections in the intensive care unit: importance of the care bundle. *Korean J Anesthesiol* 69:599-603.
- Bai Q, Liu J, and Wang G (2020) Ferroptosis, a regulated neuronal cell death type after intracerebral hemorrhage. *Front Cell Neurosci* 14:591874.
- Bala S, Marcos M, Kodys K, Csak T, Catalano D, Mandrekar P, and Szabo G (2011) Up-regulation of MicroRNA-155 in macrophages contributes to increased tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) production via increased mRNA half-life in alcoholic liver disease. *J Biol Chem* 286:1436-1444.
- Bass J and Lazar MA (2016) Circadian time signatures of fitness and disease. *Science* 354:994-999.
- Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, and Adam D (2020) Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019—results from a systematic review and meta-analysis. *Crit Care* 24:239.
- Becker-Weimann S, Wolf J, Herzel H, and Kramer A (2004) Modeling feedback loops of the mammalian circadian oscillator. *Biophys J* 87:3023-3034.
- Bertok S, Wilson MR, Morley PJ, de Wildt R, Bayliffe A, and Takata M (2012) Selective inhibition of intra-alveolar p55 TNF receptor attenuates ventilator-induced lung injury. *Thorax* 67:244-251.
- Bhatwadekar AD, Beli E, Diao Y, Chen J, Luo Q, Alex A, Caballero S, Dominguez JM II, Salazar TE, Busik JV, et al. (2017) Conditional deletion of *bmal1* accentuates microvascular and macrovascular injury. *Am J Pathol* 187:1426-1435.
- Bingham HG, Dahn M, Bouwman D, and Kirkpatrick J (1980) The sepsis-glucose intolerance riddle: a hormonal explanation. *Plast Reconstr Surg* 65:388. [https://journals.lww.com/plasreconsurg/Fulltext/1980/03000/The\\_sepsis\\_glucose\\_intolerance\\_riddle\\_\\_A\\_hormonal.101.aspx](https://journals.lww.com/plasreconsurg/Fulltext/1980/03000/The_sepsis_glucose_intolerance_riddle__A_hormonal.101.aspx).
- Brooks C, Wei Q, Cho S-G, and Dong Z (2009) Regulation of mitochondrial dynamics in acute kidney injury in cell culture and rodent models. *J Clin Invest* 119:1275-1285.
- Brown LS and Doyle FJ III (2020) A dual-feedback loop model of the mammalian circadian clock for multi-input control of circadian phase. *PLoS Comput Biol* 16:e1008459.
- Cabrera-Benítez NE, Laffey JG, Parotto M, Spieth PM, Villar J, Zhang H, and Slutsky AS (2014) Mechanical ventilation-associated lung fibrosis in acute respiratory distress syndrome: a significant contributor to poor outcome. *Anesthesiology* 121:189-198.
- Cabrera-Benítez NE, Parotto M, Post M, Han B, Spieth PM, Cheng W-E, Valladares F, Villar J, Liu M, Sato M, et al. (2012) Mechanical stress induces lung fibrosis by epithelial-mesenchymal transition. *Crit Care Med* 40:510-517.
- Carlton DP, Cummings JJ, Scheerer RG, Poulain FR, and Bland RD (1990) Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. *J Appl Physiol* 69:577-583.
- Carré JE, Orban J-C, Re L, Felsmann K, Iffert W, Bauer M, Suliman HB, Piantadosi CA, Mayhew TM, Breen P, et al. (2010) Survival in critical illness is associated with early activation of mitochondrial biogenesis. *Am J Respir Crit Care Med* 182:745-751.
- Chan M-C, Spieth PM, Quinn K, Parotto M, Zhang H, and Slutsky AS (2012) Circadian rhythms: from basic mechanisms to the intensive care unit. *Crit Care Med* 40:246-253.
- Chang JC (2018) TTP-like syndrome: novel concept and molecular pathogenesis of endotheliopathy-associated vascular microthrombotic disease. *Thromb J* 16:20.
- Chapman NM, Boothby MR, and Chi H (2020) Metabolic coordination of T cell quiescence and activation. *Nat Rev Immunol* 20:55-70.
- Chatterjee K, Zhang J, Honbo N, and Karliner JS (2010) Doxorubicin cardiomyopathy. *Cardiology* 115:155-162.
- Cheng J, Zhang R, Xu Z, Ke Y, Sun R, Yang H, Zhang X, Zhen X, and Zheng L-T (2021) Early glycolytic reprogramming controls microglial inflammatory activation. *J Neuroinflammation* 18:129.
- Chhunchha B, Kubo E, and Singh DP (2020) Clock protein *Bmal1* and *Nrf2* cooperatively control aging or oxidative response and redox homeostasis by regulating rhythmic expression of *Prdx6*. *Cells* 9:1861.
- Chiumello D, Pristine G, and Slutsky AS (1999) Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 160:109-116.
- Coiffard B, Diallo AB, Culver A, Mezouar S, Hammad E, Vigne C, Nicolino-Brunet C, Dignat-George F, Baumstarck K, Boucekine M, et al. (2019) Circadian rhythm disruption and sepsis in severe trauma patients. *Shock* 52:29-36. [https://journals.lww.com/shockjournal/Fulltext/2019/07000/Circadian\\_Rhythm\\_Disruption\\_and\\_Sepsis\\_in\\_Severe.5.aspx](https://journals.lww.com/shockjournal/Fulltext/2019/07000/Circadian_Rhythm_Disruption_and_Sepsis_in_Severe.5.aspx).
- Cook DJ, Webb S, and Proudfoot A (2021) Assessment and management of cardiovascular disease in the intensive care unit. *Heart* 108:397-405.
- Cunningham PS, Meijer P, Nazgiewicz A, Anderson SG, Borthwick LA, Bagnall J, Kitchen GB, Lodyga M, Begley N, Venkateswaran RV, et al. (2020) The circadian clock

- protein REVERB $\alpha$  inhibits pulmonary fibrosis development. *Proc Natl Acad Sci U S A* 117:1139-1147.
- Curtis AM, Fagundes CT, Yang G, Palsson-McDermott EM, Wochal P, McGettrick AF, Foley NH, Early JO, Chen L, Zhang H, et al. (2015) Circadian control of innate immunity in macrophages by miR-155 targeting Bmal1. *Proc Natl Acad Sci U S A* 112:7231-7236.
- Danielski LG, Giustina AD, Bonfante S, Barichello T, and Petronilho F (2020) The NLRP3 inflammasome and its role in sepsis development. *Inflammation* 43:24-31.
- Daviaud F, Grimaldi D, Dechartres A, Charpentier J, Geri G, Marin N, Chiche J-D, Cariou A, Mira J-P, and Pène F (2015) Timing and causes of death in septic shock. *Ann Intensive Care* 5:16.
- Davidson S, Villarroel M, Harford M, Finnegan E, Jorge J, Young D, Watkinson P, and Tarassenko L (2020) Vital-sign circadian rhythms in patients prior to discharge from an ICU: a retrospective observational analysis of routinely recorded physiological data. *Crit Care* 24:181.
- Davidson S, Villarroel M, Harford M, Finnegan E, Jorge J, Young D, Watkinson P, and Tarassenko L (2021) Day-to-day progression of vital-sign circadian rhythms in the intensive care unit. *Crit Care* 25:156.
- Davies SR, Chan BKH, Moawad M, Garrett TR, Brooker L, and Chakrabarty R (2019) Production of certified reference materials for the sports doping control of the REV-ERB agonist SR9009. *Drug Test Anal* 11:257-266.
- Deng W, Zhu S, Zeng L, Liu J, Kang R, Yang M, Cao L, Wang H, Billiar TR, Jiang J, et al. (2018) The circadian clock controls immune checkpoint pathway in sepsis. *Cell Rep* 24:366-378.
- Diaz E, Diaz I, del Busto C, Escudero D, and Pérez S (2020) Clock genes disruption in the intensive care unit. *J Intensive Care Med* 35:1497-1504.
- Dibner C, Schibler U, and Albrecht U (2010) The mammalian circadian timing system: organization and coordination of central and peripheral clocks. *Annu Rev Physiol* 72:517-549.
- Dolinay T, Kim YS, Howrylak J, Hunninghake GM, An CH, Fredenburgh L, Massaro AF, Rogers A, Gazourian L, Nakahira K, et al. (2012) Inflammasome-regulated cytokines are critical mediators of acute lung injury. *Am J Respir Crit Care Med* 185:1225-1234.
- Doughty CA, Bleiman BF, Wagner DJ, Dufort FJ, Mataraza JM, Roberts MF, and Chiles TC (2006) Antigen receptor-mediated changes in glucose metabolism in B lymphocytes: role of phosphatidylinositol 3-kinase signaling in the glycolytic control of growth. *Blood* 107:4458-4465.
- Dreyfuss D and Saumon G (1998) Ventilator-induced lung injury. *Am J Respir Crit Care Med* 157:294-323.
- Droin C, Kholtei JE, Halpern KB, Hurni C, Rozenberg M, Muvkadi S, Itzkovitz S, and Naef F (2020) Space-time logic of liver gene expression at sublobular scale. *bioRxiv*. doi:10.1101/2020.03.05.976571.
- Druz D, de Juan A, and Scheiermann C (2014) Circadian rhythms in leukocyte trafficking. *Semin Immunopathol* 36:149-162.
- Durrington HJ, Farrow SN, Loudon AS, and Ray DW (2014) The circadian clock and asthma. *Thorax* 69:90-92.
- Eichenfield DZ, Troutman TD, Link VM, Lam MT, Cho H, Gosselin D, Spann NJ, Lesch HP, Tao J, Muto J, et al. (2016) Tissue damage drives co-localization of NF- $\kappa$ B, Smad3, and Nrf2 to direct Rev-erb sensitive wound repair in mouse macrophages. *eLife* 5:e13024.
- Esposito E, Li WT, Mandeville E, Park J-H, Şencan I, Guo S, Shi J, Lan J, Lee J, Hayakawa K, et al. (2020) Potential circadian effects on translational failure for neuroprotection. *Nature* 582:395-398.
- Fan H, Le J-W, Sun M, and Zhu J-H (2021) Sirtuin 3 deficiency promotes acute kidney injury induced by sepsis via mitochondrial dysfunction and apoptosis. *Iran J Basic Med Sci* 24:675-681.
- Felten M, Teixeira-Alves LG, Letsiou E, Müller-Redetzky H, Kramer A, Maier B, and Witzenth M (2018) The severity of ventilator-induced lung injury is regulated by the clock gene Bmal1 in myeloid cells. *Eur Respir J* 52:PA4305.
- Fontecha-Barriuso M, Martin-Sanchez D, Martinez-Moreno JM, Monsalve M, Ramos AM, Sanchez-Niño MD, Ruiz-Ortega M, Ortiz A, and Sanz AB (2020) The role of PGC-1 $\alpha$  and mitochondrial biogenesis in kidney diseases. *Biomolecules* 10:347.
- Frijns CJM, Kasius KM, Algra A, Fijnheer R, and Rinkel GJE (2006) Endothelial cell activation markers and delayed cerebral ischaemia in patients with subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 77:863-867.
- Fudulu DP, Dimagli A, Dixon L, Sandhu M, Cocomello L, Angelini GD, and Benedetto U (2021) Daytime and outcomes after cardiac surgery: systematic review and metaanalysis, insights from a large UK database review and post-hoc trial analysis. *Lancet Reg Health Eur* 7:100140.
- Gajic O, Dara SI, Mendez JL, Adesanya AO, Festic E, Caples SM, Rana R, St Sauver JL, Lymp JF, Afessa B, et al. (2004) Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med* 32:1817-1824. [https://journals.lww.com/ccmjournal/Fulltext/2004/09000/Ventilator\\_associated\\_lung\\_injury\\_in\\_patients.1.aspx](https://journals.lww.com/ccmjournal/Fulltext/2004/09000/Ventilator_associated_lung_injury_in_patients.1.aspx).
- Galea J, Cruickshank G, Teeling JL, Boche D, Garland P, Perry VH, and Galea I (2012) The intrathecal CD163-haptoglobin-hemoglobin scavenging system in subarachnoid hemorrhage. *J Neurochem* 121:785-792.
- Geiger SS, Traba J, Richoz N, Farley TK, Brooks SR, Petermann F, Wang L, Gonzalez FJ, Sack MN, and Siegel RM (2021) Feeding-induced resistance to acute lethal sepsis is dependent on hepatic BMAL1 and FXR signalling. *Nat Commun* 12:2745.
- Gibbs JE, Blakley J, Beesley S, Matthews L, Simpson KD, Boyce SH, Farrow SN, Else KJ, Singh D, Ray DW, et al. (2012) The nuclear receptor REV-ERB $\alpha$  mediates circadian regulation of innate immunity through selective



- regulation of inflammatory cytokines. *Proc Natl Acad Sci U S A* 109:582-587.
- Gibbs JE, Ince L, Matthews L, Mei J, Bell T, Yang N, Saer B, Begley N, Poolman T, Pariollaud M, et al. (2014) An epithelial circadian clock controls pulmonary inflammation and glucocorticoid action. *Nat Med* 20:919-926.
- Goffart S and Wiesner RJ (2003) Regulation and co-ordination of nuclear gene expression during mitochondrial biogenesis. *Exp Physiol* 88:33-40.
- Greenhalgh AD, Brough D, Robinson EM, Girard S, Rothwell NJ, and Allan SM (2012) Interleukin-1 receptor antagonist is beneficial after subarachnoid haemorrhage in rat by blocking haem-driven inflammatory pathology. *Dis Model Mech* 5:823-833.
- Griffett K, Bedia-Diaz G, Elgendy B, and Burris TP (2020) REV-ERB agonism improves liver pathology in a mouse model of NASH. *PLoS ONE* 15:e0236000.
- Guo D-K, Zhu Y, Sun H-Y, Xu X-Y, Zhang S, Hao Z-B, Wang G-H, Mu C-C, and Ren H-G (2019) Pharmacological activation of REV-ERB $\alpha$  represses LPS-induced microglial activation through the NF- $\kappa$ B pathway. *Acta Pharmacol Sin* 40:26-34.
- Guo L, Zhang T, Wang F, Chen X, Xu H, Zhou C, Chen M, Yu F, Wang S, Yang D, et al. (2021) Targeted inhibition of Rev-erb- $\alpha/\beta$  limits ferroptosis to ameliorate folic acid-induced acute kidney injury. *Br J Pharmacol* 178:328-345.
- Halberg F, Johnson EA, Brown BW, and Bittner JJ (1960) Susceptibility rhythm to *E. coli* endotoxin and bioassay. *Proc Soc Exp Biol Med* 103:142-144.
- Hams E, Roberts J, Bermingham R, and Fallon PG (2021) Functions for retinoic acid-related orphan receptor alpha (ROR $\alpha$ ) in the activation of macrophages during lipopolysaccharide-induced septic shock. *Front Immunol* 12:647329.
- Hanson E, Sheldon M, Pacheco B, Alkubeysi M, and Raizada V (2019) Heart disease in Friedreich's ataxia. *World J Cardiol* 11:1-12.
- Hasselgren P-O, Alamdari N, Aversa Z, Gonnella P, Smith IJ, and Tizio S (2010) Corticosteroids and muscle wasting: role of transcription factors, nuclear cofactors, and hyperacetylation. *Curr Opin Clin Nutr Metab Care* 13:423-428.
- Hayter EA, Wehrens SMT, Van Dongen HPA, Stangherlin A, Gaddameedhi S, Crooks E, Barron NJ, Venetucci LA, Neill JSO, Brown TM, et al. (2021) Distinct circadian mechanisms govern cardiac rhythms and susceptibility to arrhythmia. *Nat Commun* 12:2472.
- Helmerhorst HJF, Schouten LRA, Wagenaar GTM, Juffermans NP, Roelofs JJTH, Schultz MJ, de Jonge E, and van Westerloo DJ (2017) Hyperoxia provokes a time- and dose-dependent inflammatory response in mechanically ventilated mice, irrespective of tidal volumes. *Intensive Care Med Exp* 5:27.
- Highton D and Smith M (2013) Intensive care management of subarachnoid haemorrhage. *J Intensive Care Soc* 14:28-35.
- Horky LL, Pluta RM, Boock RJ, and Oldfield EH (1998) Role of ferrous iron chelator 2,2'-dipyridyl in preventing delayed vasospasm in a primate model of subarachnoid hemorrhage. *J Neurosurg* 88:298-303.
- Hu J, Xue Y, Tang K, Fan J, Du J, Li W, Chen S, Liu C, Ji W, Liang J, et al. (2019) The protective effects of hydrogen sulfide on the myocardial ischemia via regulating Bmal1. *Biomed Pharmacother* 120:109540.
- Huang W, Wang X, Zhang H, Wang G, and Liu D (2021) Prognostic significance of the fission1/parkin ratio for sepsis: a prospective cohort study. *Front Med* 8:642749.
- Hunter AL, Pelekanou CE, Adamson A, Downton P, Barron NJ, Cornfield T, Poolman TM, Humphreys N, Cunningham PS, Hodson L, et al. (2020) Nuclear receptor REVERB $\alpha$  is a state-dependent regulator of liver energy metabolism. *Proc Natl Acad Sci U S A* 117:25869.
- Hutchison AT, Regmi P, Manoogian ENC, Fleischer JG, Wittert GA, Panda S, and Heilbronn LK (2019) Time-restricted feeding improves glucose tolerance in men at risk for type 2 diabetes: a randomized crossover trial. *Obesity* 27:724-732.
- Iguchi N, Lankadeva YR, Mori TA, Osawa EA, Cutuli SL, Evans RG, Bellomo R, and May CN (2019) Furosemide reverses medullary tissue hypoxia in ovine septic acute kidney injury. *Am J Physiol Regul Integr Comp Physiol* 317:R232-R239.
- Ingle KA, Kain V, Goel M, Prabhu SD, Young ME, and Halade GV (2015) Cardiomyocyte-specific Bmal1 deletion in mice triggers diastolic dysfunction, extracellular matrix response, and impaired resolution of inflammation. *Am J Physiol-Heart Circ Physiol* 309:H1827-H1836.
- Ito I, Kobayashi M, Finnerty CC, Herndon DN, and Suzuki F (2018) Antibacterial resistance of severely burned mice treated with an ROR $\alpha$  selective inverse agonist. *J Immunol* 200:114.19.
- Jaeklin T, Otulakowski G, and Kavanagh BP (2010) Do soluble mediators cause ventilator-induced lung injury and multi-organ failure? *Intensive Care Med* 36:750-757.
- Jetten AM, Takeda Y, Slominski A, and Kang HS (2018) Retinoic acid-related orphan receptor  $\gamma$  (ROR $\gamma$ ): connecting sterol metabolism to regulation of the immune system and autoimmune disease. *Curr Opin Toxicol* 8:66-80.
- Jornayvaz FR and Shulman GI (2010) Regulation of mitochondrial biogenesis. *Essays Biochem* 47:69-84.
- Kantor E, Bayir H, Ren D, Provencio JJ, Watkins L, Crago E, Horowitz MB, Ferrell RE, Conley YP, and Alexander SA (2014) Haptoglobin genotype and functional outcome after aneurysmal subarachnoid hemorrhage: clinical article. *J Neurosurg* 120:386-390.
- Kempkes RWM, Joosten I, Koenen HJPM, and He X (2019) Metabolic pathways involved in regulatory T cell functionality. *Front Immunol* 10:2839.
- Kervezee L, Gotta V, Stevens J, Birkhoff W, Kamerling I, Danhof M, Meijer JH, and Burggraaf J (2016) Levofloxacin-induced QTc prolongation depends on

- the time of drug administration. *CPT Pharmacomet Syst Pharmacol* 5:466-474.
- King DP, Zhao Y, Sangoram AM, Wilsbacher LD, Tanaka M, Antoch MP, Steeves TDL, Vitaterna MH, Kornhauser JM, Lowrey PL, et al. (1997) Positional cloning of the mouse circadian clock gene. *Cell* 89:641-653.
- Kitchen GB, Cunningham PS, Poolman TM, Iqbal M, Maidstone R, Baxter M, Bagnall J, Begley N, Saer B, Hussell T, et al. (2020) The clock gene *Bmal1* inhibits macrophage motility, phagocytosis, and impairs defense against pneumonia. *Proc Natl Acad Sci U S A* 117:1543-1551.
- Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, and Joris M (1987) Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. *Am Rev Respir Dis* 135:312-315.
- Kominsky DJ, Campbell EL, and Colgan SP (2010) Metabolic shifts in immunity and inflammation. *J Immunol* 184:4062-4068.
- Koukourikos K, Tsaloglidou A, and Kourkouta L (2014) Muscle atrophy in intensive care unit patients. *Acta Inform Med* 22:406-410.
- Kozlov AV, Bahrami S, Calzia E, Dungal P, Gille L, Kuznetsov AV, and Troppmair J (2011) Mitochondrial dysfunction and biogenesis: do ICU patients die from mitochondrial failure? *Ann Intensive Care* 1:41.
- Kühlhorn F, Rath M, Schmoedel K, Cziupka K, Nguyen HH, Hildebrandt P, Hünig T, Sparwasser T, Huehn J, Pötschke C, et al. (2013) Foxp3<sup>+</sup> regulatory T cells are required for recovery from severe sepsis. *PLoS ONE* 8:e65109.
- Lachmann G, Ananthasubramaniam B, Wunsch VA, Scherfig L-M, von Haefen C, Knaak C, Edel A, Ehlen L, Koller B, Goldmann A, et al. (2021) Circadian rhythms in septic shock patients. *Ann Intensive Care* 11:64.
- Ladurner A, Schwarz PF, and Dirsch VM (2021) Natural products as modulators of retinoic acid receptor-related orphan receptors (RORs). *Nat Prod Rep* 38:757-781.
- Lang V, Ferencik S, Ananthasubramaniam B, Kramer A, and Maier B (2019) Susceptibility rhythm to bacterial endotoxin in myeloid clock-knockout mice. *bioRxiv*. doi:10.1101/766519.
- Laurent I, Monchi M, Chiche J-D, Joly L-M, Spaulding C, Bourgeois B, Cariou A, Rozenberg A, Carli P, Weber S, et al. (2002) Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 40:2110-2116.
- Lazreg TB, Gribaa M, Naiija O, Bougattas N, Saad A, Saiid R, and Dogui M (2013) Clock genes expression in intensive care unit patients. *Biol Rhythm Res* 44:663-673.
- Lee CC (2007) Constant darkness is a mammalian biological signal. *Cold Spring Harb Symp Quant Biol* 72:287-291.
- Lee SM and An WS (2016) New clinical criteria for septic shock: serum lactate level as new emerging vital sign. *J Thorac Dis* 8:1388-1390.
- Lei R, Zhao F, Tang C-Y, Luo M, Yang S-K, Cheng W, Li X-W, and Duan S-B (2018) Mitophagy plays a protective role in iodinated contrast-induced acute renal tubular epithelial cells injury. *Cell Physiol Biochem* 46:975-985.
- Leon LR, White AA, and Kluger MJ (1998) Role of IL-6 and TNF in thermoregulation and survival during sepsis in mice. *Am J Physiol-Regul Integr Comp Physiol* 275:R269-R277.
- Lewis AJ, Zhang X, Griepentrog JE, Yuan D, Collage RD, Waltz PK, Angus DC, Zuckerbraun BS, and Rosengart MR (2018) Blue light enhances bacterial clearance and reduces organ injury during sepsis. *Crit Care Med* 46:e779-e787.
- Li E, Li X, Huang J, Xu C, Liang Q, Ren K, Bai A, Lu C, Qian R, and Sun N (2020) BMAL1 regulates mitochondrial fission and mitophagy through mitochondrial protein BNIP3 and is critical in the development of dilated cardiomyopathy. *Protein Cell* 11:661-679.
- Li H, Wang C, Hu J, and Tan J (2014) A study on circadian rhythm disorder of rat lung tissue caused by mechanical ventilation induced lung injury. *Int Immunopharmacol* 18:249-254.
- Li J, Cao F, Yin H, Huang Z, Lin Z, Mao N, Sun B, and Wang G (2020) Ferroptosis: past, present and future. *Cell Death Dis* 11:88.
- Li L-F, Liao S-K, Ko Y-S, Lee C-H, and Quinn DA (2007) Hyperoxia increases ventilator-induced lung injury via mitogen-activated protein kinases: a prospective, controlled animal experiment. *Crit Care* 11:R25.
- Li Q, Han X, Lan X, Gao Y, Wan J, Durham F, Cheng T, Yang J, Wang Z, Jiang C, et al. (2017) Inhibition of neuronal ferroptosis protects hemorrhagic brain. *JCI Insight* 2:e90777.
- Li Q-Q, Li L-J, Wang X-Y, Sun Y-Y, and Wu J (2018) Research progress in understanding the relationship between heme oxygenase-1 and intracerebral hemorrhage. *Front Neurol* 9:682.
- Li Y, Feng Y-F, Liu X-T, Li Y-C, Zhu H-M, Sun M-R, Li P, Liu B, and Yang H (2021) Songorine promotes cardiac mitochondrial biogenesis via Nrf2 induction during sepsis. *Redox Biol* 38:101771.
- Liu H, Gu C, Liu M, Liu G, Wang D, Liu X, and Wang Y (2019) Ventilator-induced lung injury is alleviated by inhibiting NLRP3 inflammasome activation. *Mol Immunol* 111:1-10.
- Liu H, Sidiropoulos P, Song G, Pagliari LJ, Birrer MJ, Stein B, Anrather J, and Pope RM (2000) TNF- $\alpha$  gene expression in macrophages: regulation by NF- $\kappa$ B is independent of c-Jun or C/EBP $\beta$ . *J Immunol* 164:4277.
- Liu L, Zhou L, Li Y, Bai W, Liu N, Li W, Gao Y, Liu Z, and Han R (2015) High-density lipoprotein acts as an opsonin to enhance phagocytosis of group A streptococcus by U937 cells. *Microbiol Immunol* 59:419-425.
- Liu Q and Li C-S (2017) Programmed cell death-1/programmed death-ligand 1 pathway: a new target for sepsis. *Chin Med J (Engl)* 130:986-992.
- Lo EH, Albers GW, Dichgans M, Donnan G, Esposito E, Foster R, Howells DW, Huang Y-G, Ji X, Klerman

- EB, et al. (2021) Circadian biology and stroke. *Stroke* 52:2180-2190.
- Lombard DB, Tishkoff DX, and Bao J (2011) Mitochondrial sirtuins in the regulation of mitochondrial activity and metabolic adaptation. *Handb Exp Pharmacol* 206:163-188.
- Ma C, Zhou W, Yan Z, Qu M, and Bu X (2015) Toll-like receptor 4 (TLR4) is correlated with delayed cerebral ischemia (DCI) and poor prognosis in aneurysmal subarachnoid hemorrhage. *J Neurol Sci* 359:67-71.
- Ma D, Liu T, Chang L, Rui C, Xiao Y, Li S, Hogenesch JB, Chen YE, and Lin JD (2015) The liver clock controls cholesterol homeostasis through Trib1 protein-mediated regulation of PCSK9/low density lipoprotein receptor (LDLR) axis. *J Biol Chem* 290:31003-31012.
- Ma X, Zhou Z, Chen Y, Wu Y, and Liu Y (2016) RBP4 functions as a hepatokine in the regulation of glucose metabolism by the circadian clock in mice. *Diabetologia* 59:354-362.
- Macintyre AN, Gerriets VA, Nichols AG, Michalek RD, Rudolph MC, Deoliveira D, Anderson SM, Abel ED, Chen BJ, Hale LP, et al. (2014) The glucose transporter Glut1 is selectively essential for CD4 T cell activation and effector function. *Cell Metab* 20:61-72.
- Makris K and Spanou L (2016) Acute kidney injury: definition, pathophysiology and clinical phenotypes. *Clin Biochem Rev* 37:85-98.
- Marnett LJ, Riggins JN, and West JD (2003) Endogenous generation of reactive oxidants and electrophiles and their reactions with DNA and protein. *J Clin Invest* 111:583-593.
- Marshall R, Bellingan G, and Laurent G (1998) The acute respiratory distress syndrome: fibrosis in the fast lane. *Thorax* 53:815-817.
- Mayeuf-Louchart A, Thorel Q, Delhay S, Beauchamp J, Duhem C, Danckaert A, Lancel S, Pourcet B, Woldt E, Boulinguez A, et al. (2017) Rev-erb- $\alpha$  regulates atrophy-related genes to control skeletal muscle mass. *Sci Rep* 7:14383.
- Meng H, Ruan J, Tian X, Li L, Chen W, and Meng F (2021) High retinoic acid receptor-related orphan receptor A gene expression in peripheral blood leukocytes may be related to acute myocardial infarction. *J Int Med Res* 49(6):3000605211019663. doi:10.1177/03000605211019663.
- Mercer AE, Copple IM, Maggs JL, O'Neill PM, and Park BK (2011) The role of heme and the mitochondrion in the chemical and molecular mechanisms of mammalian cell death induced by the artemisinin antimalarials. *J Biol Chem* 286:987-996.
- Mierzchala-Pasierb M, Krzystek-Korpacka M, Lesnik P, Adamik B, Placzowska S, Serek P, Gamian A, and Lipinska-Gediga M (2019) Interleukin-18 serum levels in sepsis: Correlation with disease severity and inflammatory markers. *Cytokine* 120:22-27.
- Miles R, Paxton T, Dries D, and Gamelli R (1994) Interferon-gamma increases mortality following cecal ligation and puncture. *J Trauma* 36:607-611.
- Monneret G, Gossez M, and Venet F (2016) Sepsis in PD-1 light. *Crit Care Lond Engl* 20:186-186.
- Montaigne D, Marechal X, Modine T, Coisne A, Mouton S, Fayad G, Ninni S, Klein C, Ortmans S, Seunes C, et al. (2018) Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-erb $\alpha$  antagonism: a single-centre propensity-matched cohort study and a randomised study. *Lancet* 391:59-69.
- Morin EE, Guo L, Schwendeman A, and Li X-A (2015) HDL in sepsis—risk factor and therapeutic approach. *Front Pharmacol* 6:244-244.
- Nakamori Y, Park EJ, and Shimaoka M (2021) Immune deregulation in sepsis and septic shock: reversing immune paralysis by targeting PD-1/PD-L1 pathway. *Front Immunol* 11:3912.
- Nakanishi N, Oto J, Ueno Y, Nakataki E, Itagaki T, and Nishimura M (2019) Change in diaphragm and intercostal muscle thickness in mechanically ventilated patients: a prospective observational ultrasonography study. *J Intensive Care* 7:56.
- Nedel WL, Kopczynski A, Rodolphi MS, Strogulski NR, De Bastiani M, Montes THM, Abruzzi J Jr, Galina A, Horvath TL, and Portela LV (2021) Mortality of septic shock patients is associated with impaired mitochondrial oxidative coupling efficiency in lymphocytes: a prospective cohort study. *Intensive Care Med Exp* 9:39.
- Nedeva C, Menassa J, and Puthalakath H (2019) Sepsis: inflammation is a necessary evil. *Front Cell Dev Biol* 7:108.
- Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RSB, Geocadin RG, Jauch EC, et al. (2008) Post-cardiac arrest syndrome. *Circulation* 118:2452-2483.
- Nogueira AB, Nogueira AB, Veiga JCE, and Teixeira MJ (2017) Hypothesis on the role of cryptochromes in inflammation and subarachnoid hemorrhage outcome. *Front Neurol* 8:637.
- Nosal C, Ehlers A, and Haspel JA (2020) Why lungs keep time: circadian rhythms and lung immunity. *Annu Rev Physiol* 82:391-412.
- O'Connell EJ, Martinez C-A, Liang YG, Cistulli PA, and Cook KM (2020) Out of breath, out of time: interactions between HIF and circadian rhythms. *Am J Physiol-Cell Physiol* 319:C533-C540.
- Oldham MA, Lee HB, and Desan PH (2016) Circadian rhythm disruption in the critically ill: an opportunity for improving outcomes. *Crit Care Med* 44:207-217. [https://journals.lww.com/ccmjournal/Fulltext/2016/01000/Circadian\\_Rhythm\\_Disruption\\_in\\_the\\_Critically\\_Ill\\_24.aspx](https://journals.lww.com/ccmjournal/Fulltext/2016/01000/Circadian_Rhythm_Disruption_in_the_Critically_Ill_24.aspx).
- Osuchowski MF, Welch K, Siddiqui J, and Remick DG (2006) Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. *J Immunol* 177:1967-1974.
- Owen AM, Patel SP, Smith JD, Balasuriya BK, Mori SF, Hawk GS, Stromberg AJ, Kuriyama N, Kaneki M,

- Rabchevsky AG, et al. (2019) Chronic muscle weakness and mitochondrial dysfunction in the absence of sustained atrophy in a preclinical sepsis model. *eLife* 8:e49920.
- Pariollaud M, Gibbs JE, Hopwood TW, Brown S, Begley N, Vonslow R, Poolman T, Guo B, Saer B, Jones DH, et al. (2018) Circadian clock component REV-ERB $\alpha$  controls homeostatic regulation of pulmonary inflammation. *J Clin Invest* 128:2281-2296.
- Parsons PE, Eisner MD, Thompson BT, Matthay MA, Ancukiewicz M, Bernard GR, and Wheeler AP, and the NHLBI Acute Respiratory Distress Syndrome Clinical Trials Network (2005) Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med* 33:1-6. [https://journals.lww.com/ccmjournal/Fulltext/2005/01000/Lower\\_tidal\\_volume\\_ventilation\\_and\\_plasma\\_cytokine.1.aspx](https://journals.lww.com/ccmjournal/Fulltext/2005/01000/Lower_tidal_volume_ventilation_and_plasma_cytokine.1.aspx).
- Peek CB, Levine DC, Cedernaes J, Taguchi A, Kobayashi Y, Tsai SJ, Bonar NA, McNulty MR, Ramsey KM, and Bass J (2017) Circadian clock interaction with HIF1 $\alpha$  mediates oxygenic metabolism and anaerobic glycolysis in skeletal muscle. *Cell Metab* 25:86-92.
- Perry HM, Huang L, Wilson RJ, Bajwa A, Sesaki H, Yan Z, Rosin DL, Kashatus DF, and Okusa MD (2018) Dynamin-related protein 1 deficiency promotes recovery from AKI. *J Am Soc Nephrol* 29:194-206.
- Pickard JD, Murray GD, Illingworth R, Shaw MD, Teasdale GM, Foy PM, Humphrey PR, Lang DA, Nelson R, Richards P, et al. (1989) Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British aneurysm nimodipine trial. *BMJ* 298:636-642.
- Pickkers P, Darmon M, Hoste E, Joannidis M, Legrand M, Ostermann M, Prowle JR, Schneider A, and Schetz M (2021) Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Med* 47:835-850.
- Plötz FB, Slutsky AS, van Vught AJ, and Heijnen CJ (2004) Ventilator-induced lung injury and multiple system organ failure: a critical review of facts and hypotheses. *Intensive Care Med* 30:1865-1872.
- Poyan Mehr A, Tran MT, Ralto KM, Leaf DE, Washco V, Messmer J, Lerner A, Kher A, Kim SH, Khoury CC, et al. (2018) De novo NAD(+) biosynthetic impairment in acute kidney injury in humans. *Nat Med* 24:1351-1359.
- Proudfoot A, Bayliffe A, O'Kane CM, Wright T, Serone A, Bareille PJ, Brown V, Hamid UI, Chen Y, Wilson R, et al. (2018) Novel anti-tumour necrosis factor receptor-1 (TNFR1) domain antibody prevents pulmonary inflammation in experimental acute lung injury. *Thorax* 73:723-730.
- Prowle JR, Forni LG, Bell M, Chew MS, Edwards M, Grams ME, Grocott MPW, Liu KD, Mcllroy D, Murray PT, et al. (2021) Postoperative acute kidney injury in adult non-cardiac surgery: joint consensus report of the Acute Disease Quality Initiative and PeriOperative Quality Initiative. *Nat Rev Nephrol* 17:605-618.
- Puthuchery ZA, Astin R, Mcphail MJW, Saeed S, Pasha Y, Bear DE, Constantin D, Velloso C, Manning S, Calvert L, et al. (2018) Metabolic phenotype of skeletal muscle in early critical illness. *Thorax* 73:926-935.
- Radi ZA (2018) Immunopathogenesis of acute kidney injury. *Toxicol Pathol* 46:930-943.
- RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, et al. (2021) Dexamethasone in hospitalized patients with covid-19. *N Engl J Med* 384:693-704.
- Reeder BJ, Svistunenko DA, Cooper CE, and Wilson MT (2004) The radical and redox chemistry of myoglobin and hemoglobin: from in vitro studies to human pathology. *Antioxid Redox Signal* 6:954-966.
- Regan RF and Panter SS (1993) Neurotoxicity of hemoglobin in cortical cell culture. *Neurosci Lett* 153:219-222.
- Reitz CJ, Alibhai FJ, Khatua TN, Rasouli M, Bridle BW, Burris TP, and Martino TA (2019) SR9009 administered for one day after myocardial ischemia-reperfusion prevents heart failure in mice by targeting the cardiac inflammasome. *Commun Biol* 2:353.
- Remick DG, Bolgos G, Copeland S, and Siddiqui J (2005) Role of interleukin-6 in mortality from and physiologic response to sepsis. *Infect Immun* 73:2751-2757.
- Rosen AD and Frumin NV (1979) Focal epileptogenesis after intracortical hemoglobin injection. *Exp Neurol* 66:277-284.
- Ryan J, Bayliffe AI, McAuley DF, Yeung J, Thickett DR, Howells PA, O'Donnell C, Vassallo AM, Wright TJ, McKie E, et al. (2020) A nebulised antitumour necrosis factor receptor-1 domain antibody in patients at risk of postoperative lung injury: a randomised, placebo-controlled pilot study. *Eur J Anaesthesiol* 37:1014-1024.
- Sadiku P, Willson JA, Ryan EM, Sammut D, Coelho P, Watts ER, Grecian R, Young JM, Bewley M, Arienti S, et al. (2021) Neutrophils fuel effective immune responses through gluconeogenesis and glycogenesis. *Cell Metab* 33:411-423.e4.
- Scheiermann C, Gibbs J, Ince L, and Loudon A (2018) Clocking in to immunity. *Nat Rev Immunol* 18:423-437.
- Sharma A, Laurenti MC, Dalla Man C, Varghese RT, Cobelli C, Rizza RA, Matveyenko A, and Vella A (2017) Glucose metabolism during rotational shift-work in healthcare workers. *Diabetologia* 60:1483-1490.
- Sharma NK, Ferreira BL, Tashima AK, Brunialti MKC, Torquato RJS, Bafi A, Assuncao M, Azevedo LCP, and Salomao R (2019) Lipid metabolism impairment in patients with sepsis secondary to hospital acquired pneumonia, a proteomic analysis. *Clin Proteomics* 16:29.
- Silverton NA, Lofgren LR, Hall IE, Stoddard GJ, Melendez NP, Van Tienderen M, Shumway S, Stringer BJ, Kang W, Lybbert C, et al. (2021) Noninvasive urine oxygen



- monitoring and the risk of acute kidney injury in cardiac surgery. *Anesthesiology* 135:406-418.
- Simons KS, Laheij RJF, van den Boogaard M, Moviat MAM, Paling AJ, Polderman FN, Rozendaal FW, Salet GAM, van der Hoeven JG, Pickkers P, et al. (2016) Dynamic light application therapy to reduce the incidence and duration of delirium in intensive-care patients: a randomised controlled trial. *Lancet Respir Med* 4:194-202.
- Singer M (2014) The role of mitochondrial dysfunction in sepsis-induced multi-organ failure. *Virulence* 5:66-72.
- Singer M (2017) Critical illness and flat batteries. *Crit Care* 21:309.
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM, et al. (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315:801-810.
- Smolensky MH, Portaluppi F, Manfredini R, Hermida RC, Tiseo R, Sackett-Lundeen LL, and Haus EL (2015) Diurnal and twenty-four hour patterning of human diseases: Cardiac, vascular, and respiratory diseases, conditions, and syndromes. *Sleep Med Rev* 21:3-11.
- Smonig R, Magalhaes E, Bouadma L, Andreumont O, de Montmollin E, Essardy F, Mourvillier B, Lebut J, Dupuis C, Neuville M, et al. (2019) Impact of natural light exposure on delirium burden in adult patients receiving invasive mechanical ventilation in the ICU: a prospective study. *Ann Intensive Care* 9:120.
- Solovev IA, Shaposhnikov MV, and Moskalev AA (2021) Chronobiotics KL001 and KS15 extend lifespan and modify circadian rhythms of *drosophila melanogaster*. *Clocks Sleep* 3:429-441.
- Song J, Park DW, Moon S, Cho H-J, Park JH, Seok H, and Choi WS (2019) Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: a prospective controlled study according to the Sepsis-3 definitions. *BMC Infect Dis* 19:968.
- Soppa G, Theodoropoulos P, Bilkhu R, Harrison D, Alam R, Beattie R, Bleetman D, Hussain A, Jones S, Kenny L, et al. (2019) Variation between hospitals in outcomes following cardiac surgery in the UK. *Ann R Coll Surg Engl* 101:333-341.
- Soto-Herederó G, Gómez de Las Heras MM, Gabandé-Rodríguez E, Oller J, and Mittelbrunn M (2020) Glycolysis—a key player in the inflammatory response. *FEBS J* 287:3350-3369.
- Srisawat N, Lawsin L, Uchino S, Bellomo R, Kellum JA, and BEST Kidney Investigators (2010) Cost of acute renal replacement therapy in the intensive care unit: results from the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Crit Care Lond Engl* 14:R46-R46.
- Stroud M, Duncan H, and Nightingale J (2003) Guidelines for enteral feeding in adult hospital patients. *Gut* 52:vii1-vii12.
- Sun L, Tian H, Xue S, Ye H, Xue X, Wang R, Liu Y, Zhang C, Chen Q, and Gao S (2021) Circadian clock genes REV-ERBs inhibits granulosa cells apoptosis by regulating mitochondrial biogenesis and autophagy in polycystic ovary syndrome. *Front Cell Dev Biol* 9:2079.
- Sun Q, Zeng C, Du L, and Dong C (2021) Mechanism of circadian regulation of the NRF2/ARE pathway in renal ischemia-reperfusion. *Exp Ther Med* 21:190.
- Suzuki H, Muramatsu M, Kojima T, and Taki W (2003) Intracranial heme metabolism and cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 34:2796-2800.
- Suzuki S, Kimura M, Souma M, Ohkima H, Shimizu T, and Iwabuchi T (1990) Cerebral microthrombosis in symptomatic cerebral vasospasm. *Neurol Med Chir (Tokyo)* 30:309-316.
- Tan C, Gu J, Li T, Chen H, Liu K, Liu M, Zhang H, and Xiao X (2021) Inhibition of aerobic glycolysis alleviates sepsis-induced acute kidney injury by promoting lactate/Sirtuin 3/AMPK-regulated autophagy. *Int J Mol Med* 47:19.
- Tran M, Tam D, Bardia A, Bhasin M, Rowe GC, Kher A, Zsengeller ZK, Akhavan-Sharif MR, Khankin EV, Saintgeniez M, et al. (2011) PGC-1 $\alpha$  promotes recovery after acute kidney injury during systemic inflammation in mice. *J Clin Invest* 121:4003-4014.
- Trinder M, Wang Y, Madsen CM, Ponomarev T, Bohunek L, Daisely BA, Julia Kong H, Blauw LL, Nordestgaard BG, Tybjaerg-Hansen A, et al. (2021) Inhibition of cholesteryl ester transfer protein preserves high-density lipoprotein cholesterol and improves survival in sepsis. *Circulation* 143:921-934.
- Tsukui T, Sun K-H, Wetter JB, Wilson-Kanamori JR, Hazelwood LA, Henderson NC, Adams TS, Schupp JC, Poli SD, Rosas IO, et al. (2020) Collagen-producing lung cell atlas identifies multiple subsets with distinct localization and relevance to fibrosis. *Nat Commun* 11:1920.
- van der Steen WE, Marquering HA, Ramos LA, van den Berg R, Coert BA, Boers AMM, Vergouwen MDI, Rinkel GJE, Velthuis BK, Roos YBWEM, et al. (2020) Prediction of outcome using quantified blood volume in aneurysmal SAH. *AJNR Am J Neuroradiol* 41:1015-1021.
- van Gassel RJJ, Baggerman MR, and van de Poll MCG (2020) Metabolic aspects of muscle wasting during critical illness. *Curr Opin Clin Nutr Metab Care* 23:96-101. [https://journals.lww.com/co-clinicalnutrition/Fulltext/2020/03000/Metabolic\\_aspects\\_of\\_muscle\\_wasting\\_during.8.aspx](https://journals.lww.com/co-clinicalnutrition/Fulltext/2020/03000/Metabolic_aspects_of_muscle_wasting_during.8.aspx).
- Van Wyngene L, Vandewalle J, and Libert C (2018) Reprogramming of basic metabolic pathways in microbial sepsis: therapeutic targets at last? *EMBO Mol Med* 10:e8712.
- Venet F, Cour M, Rimmelé T, Viel S, Yonis H, Coudereau R, Amaz C, Abraham P, Monard C, Casalegno J-S, et al. (2021) Longitudinal assessment of IFN-I activity and

- immune profile in critically ill COVID-19 patients with acute respiratory distress syndrome. *Crit Care* 25:140.
- Vergouwen MDI, Vermeulen M, van Gijn J, Rinkel GJE, Wijdeveld EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, et al. (2010) Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies. *Stroke* 41:2391-2395.
- Vieira E, Marroquí L, Figueroa ALC, Merino B, Fernandez-Ruiz R, Nadal A, Burris TP, Gomis R, and Quesada I (2013) Involvement of the clock gene *Rev-erb alpha* in the regulation of glucagon secretion in pancreatic alpha-cells. *PLoS ONE* 8:e69939.
- Wang Q, Sundar IK, Lucas JH, Muthumalage T, and Rahman I (2021) Molecular clock *REV-ERB $\alpha$*  regulates cigarette smoke-induced pulmonary inflammation and epithelial-mesenchymal transition. *JCI Insight* 6:e145200.
- Wang S, Lin Y, Yuan X, Li F, Guo L, and Wu B (2018) *REV-ERB $\alpha$*  integrates colon clock with experimental colitis through regulation of *NF- $\kappa$ B/NLRP3* axis. *Nat Commun* 9:4246.
- Ward NS, Casserly B, and Ayala A (2008) The compensatory anti-inflammatory response syndrome (CARS) in critically ill patients. *Clin Chest Med* 29:617-625.
- Ware LB (2013) Autopsy in ARDS: insights into natural history. *Lancet Respir Med* 1:352-354.
- Weger BD, Gobet C, David FPA, Atger F, Martin E, Phillips NE, Charpagne A, Weger M, Naef F, and Gachon F (2021) Systematic analysis of differential rhythmic liver gene expression mediated by the circadian clock and feeding rhythms. *Proc Natl Acad Sci U S A* 118:e2015803118.
- Welch RD and Flaveny CA (2017) *REV-ERB* and *ROR*: therapeutic targets for treating myopathies. *Phys Biol* 14:045002.
- West AC and Bechtold DA (2015) The cost of circadian desynchrony: evidence, insights and open questions. *Bioessays* 37:777-788.
- Wischmeyer PE and San-Millan I (2015) Winning the war against ICU-acquired weakness: new innovations in nutrition and exercise physiology. *Crit Care Lond Engl* 19:S6-S6.
- Woldt E, Sebt Y, Solt LA, Duhem C, Lancel S, Eeckhoutte J, Hesselink MKC, Paquet C, Delhay S, Shin Y, et al. (2013) *Rev-erb- $\alpha$*  modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. *Nat Med* 19:1039-1046.
- Wong HR, Cvijanovich N, Allen GL, Lin R, Anas N, Meyer K, Freishtat RJ, Monaco M, Odoms K, Sakthivel B, et al. (2009) Genomic expression profiling across the pediatric systemic inflammatory response syndrome, sepsis, and septic shock spectrum. *Crit Care Med* 37:1558-1566.
- Xiao H, Siddiqui J, and Remick DG (2006) Mechanisms of mortality in early and late sepsis. *Infect Immun* 74:5227-5235.
- Xie M, Yu Y, Kang R, Zhu S, Yang L, Zeng L, Sun X, Yang M, Billiar TR, Wang H, et al. (2016) PKM2-dependent glycolysis promotes NLRP3 and AIM2 inflammasome activation. *Nat Commun* 7:13280.
- Yan Y, Ma Z, Zhu J, Zeng M, Liu H, and Dong Z (2020) miR-214 represses mitofusin-2 to promote renal tubular apoptosis in ischemic acute kidney injury. *Am J Physiol Ren Physiol* 318:F878-F887.
- Yin J, Guo J, Zhang Q, Cui L, Zhang L, Zhang T, Zhao J, Li J, Middleton A, Carmichael PL, et al. (2018) Doxorubicin-induced mitophagy and mitochondrial damage is associated with dysregulation of the PINK1/parkin pathway. *Toxicol in Vitro* 51:1-10.
- Yin L and Lazar MA (2005) The orphan nuclear receptor *Rev-erb $\alpha$*  recruits the N-CoR/histone deacetylase 3 corepressor to regulate the circadian *Bmal1* gene. *Mol Endocrinol* 19:1452-1459.
- Youn DH, Kim Y, Kim BJ, Jeong MS, Lee J, Rhim JK, Kim HC, and Jeon JP (2021) Mitochondrial dysfunction associated with autophagy and mitophagy in cerebrospinal fluid cells of patients with delayed cerebral ischemia following subarachnoid hemorrhage. *Sci Rep* 11:16512.
- Young A and Marsh S (2018) Steroid use in critical care. *BJA Educ* 18:129-134.
- Young ME, Brewer RA, Peliciari-Garcia RA, Collins HE, He L, Birky TL, Peden BW, Thompson EG, Ammons B-J, Bray MS, et al. (2014) Cardiomyocyte-specific *BMAL1* plays critical roles in metabolism, signaling, and maintenance of contractile function of the heart. *J Biol Rhythms* 29:257-276.
- Yu Q, Wang Y, Dong L, He Y, Liu R, Yang Q, Cao Y, Wang Y, Jia A, Bi Y, et al. (2020) Regulations of glycolytic activities on macrophages functions in tumor and infectious inflammation. *Front Cell Infect Microbiol* 10:287.
- Zhang J, Kaasik K, Blackburn MR, and Lee CC (2006) Constant darkness is a circadian metabolic signal in mammals. *Nature* 439:340-343.
- Zhang J, Kalkum M, Chait BT, and Roeder RG (2002) The N-CoR-HDAC3 nuclear receptor corepressor complex inhibits the JNK pathway through the integral subunit *GPS2*. *Mol Cell* 9:611-623.
- Zhang Q, Gupta S, Schipper DL, Kowalczyk GJ, Mancini AE, Faeder JR, and Lee REC (2017) *NF- $\kappa$ B* dynamics discriminate between TNF doses in single cells. *Cell Syst* 5:638-645.e5.
- Zheng L, Fisher G, Miller RE, Peschon J, Lynch DH, and Lenardo MJ (1995) Induction of apoptosis in mature T cells by tumour necrosis factor. *Nature* 377:348-351.
- Zheng Z, Kim H, Qiu Y, Chen X, Mendez R, Dandekar A, Zhang X, Zhang C, Liu AC, Yin L, et al. (2016) *CREBH* couples circadian clock with hepatic lipid metabolism. *Diabetes* 65:3369-3383.
- Zhu M, Tang H, Tang X, Ma X, Guo D, and Chen F (2018) *BMAL1* suppresses ROS-induced endothelial-to-mesenchymal transition and atherosclerosis plaque progression via BMP signaling. *Am J Transl Res* 10:3150-3161.