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REVIEW ARTICLE

Circadian clocks' interactions with oxygen sensing and signalling

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Abstract

In mammals, physiology and metabolism are shaped both by immediate and anticipatory responses to environmental changes through the myriad of molecular mechanisms. Whilst the former is mostly mediated through different acute signalling pathways the latter is primarily orchestrated by the circadian clock. Oxygen is vital for life and as such mammals have evolved different mechanisms to cope with changes in oxygen levels. It is widely accepted that oxygen sensing through the HIF-1 signalling pathway is paramount for the acute response to changes in oxygen levels. Circadian clocks are molecular oscillators that control 24 hours rhythms in various aspects of physiology and behaviour. Evidence emerging in recent years points towards pervasive molecular and functional interactions between these two pathways on multiple levels. Daily oscillations in oxygen levels are circadian clock-controlled and can reset the clock through HIF-1. Furthermore, the circadian clock appears to modulate the hypoxic response. We review herein the literature related to the crosstalk between the circadian clockwork and the oxygen-signalling pathway in mammals at the molecular and physiological level both under normal and pathologic conditions.

KEYWORDS

circadian clocks, daily rhythms, HIF-1, metabolism, oxygen, physiology

1 | INTRODUCTION

1.1 | Circadian rhythms and the molecular clockwork

Rhythmicity represents the changes that occur with a beat-like regularity and are characteristic of many physical and biological phenomena in nature. In living organisms, biological rhythms have a wide spectrum of period lengths, from fractions of a second to several years.[1] The most ubiquitous are biological processes that oscillate with a 24 hours rhythmicity, corresponding to the cyclic environment (eg, daily light-dark cycles) generated by the earth's rotation on its axis.[2] These rhythms often persist in constant conditions (ie, environment devoid of time—cues) with a "free-running" period that slightly deviates from 24 hours and thus is termed "circadian" (from the Latin *circa*, about and *diem*, a day).[3] Hence, circadian rhythms are endogenously driven by a circadian clock and are not a mere response to environmental changes. Circadian clocks are found in most light-sensitive organisms, ranging from unicellular to humans[4] and are, therefore, believed to confer an evolutionary advantage by allowing the organism to anticipate, and act a priori to challenges imposed by the cyclic environment.

Mammals exhibit circadian rhythmicity in a wide variety of behavioural, physiological and metabolic functions, these include activity, food intake, oxygen consumption, hormone secretion and temperature cycles.[5,6] Circadian clocks are present in most cells of mammals and are hierarchically organized. A master clock is present in the suprachiasmatic nucleus (SCN) in the hypothalamus region of the brain and responds to light-dark cycles. It synchronizes peripheral clocks within the rest of the body through a myriad of signalling pathways.[7] The molecular clock functions in a self-sustain and cell-autonomous manner and rely on auto-regulatory transcription-translation feedback loops (TTFLs). The positive arm of the feedback loop involves circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like 1 (BMAL1), which heterodimerize and bind E-box elements (CACGTG) to initiate transcription of rhythmic genes. Amongst these activated genes are *Period1,2,3* and *Cryptochrome1,2* which constitute the negative arm of the feedback loop. Subsequently, PER-CRY complexes accumulate in the nucleus and gradually repress their own transcription by inhibiting CLOCK-BMAL1. Consequently, transcription of *Per*s and *Cry*s declines, PER-CRY protein complexes are degraded by the proteasome, and repression is relieved. Initiation of a new round of transcription by CLOCK-BMAL1 is then followed, and this cycle repeats every ~24 hours (Figure 1). Additional integrated regulatory loops that stabilize the cycle were identified. A well-characterized feedback loop includes the nuclear receptors Reverse strand of the *Erb* gene (REV-ERB) α,β and Retinoic acid-related Orphan Receptors (ROR) α,β,γ that competes on ROR-binding elements (RORE) to regulate *Bmal1* expression and are transcriptionally regulated by CLOCK-BMAL1. Several excellent reviews from recent years provide a detailed depiction of the molecular circadian clock.[6,8-11]

Amongst the many biological processes regulated by the circadian clock, metabolic homeostasis stands out. It is well-established that metabolic control is not just an output of the clock, but also feedback to the molecular clock.[5,12-14] This crosstalk between clocks and metabolism occurs at multiple levels, from cellular through organs to the whole organism, and includes various metabolites and metabolic pathways. In this review, we will focus on the interaction between oxygen, which drives mammalian metabolism, and the circadian clock.

1.2 | Evolution of atmospheric oxygen

Oxygen makes up 21% of the atmosphere and is readily available in most places on earth. This was not the case ~2.5 billion years ago when oxygen was very scarce in the atmosphere, perhaps less than 0.1% of that present today.[15] The source of essentially all oxygen in the atmosphere comes from photosynthesis that enabled the emergence of complex life forms. The earliest producers of oxygen by photosynthesis were cyanobacteria, widely diverse prokaryotes that often thrive as pioneer species in harsh habitats.[16] Notably, cyanobacteria are the simplest organisms and, until recently,[17] the only prokaryotes known to have a circadian clock.[18] Therefore, the most ancient clockwork mechanism has evolved in conjunction with the emergence of oxygen metabolism. Throughout millions of years, the percentage of oxygen in the atmosphere continued to gradually rise from 2% to about 10%-20% presumably because of plants and is believed to reach even 35% before the first extinction.[19] Although the earth experienced fluctuations in oxygen levels across different eras, for the past 350 million years the present 21% oxygen remained stable. The introduction of oxygen into the atmosphere provided a more efficient energy source in the form of aerobic metabolism, which gave rise to eukaryotes.[20] Aerobic metabolism generates more energy, producing 16-18 times more adenosine triphosphate (ATP) per hexose sugar compared to anaerobic metabolism. Consequently, more reactions can occur, new metabolites can be generated and organelle formation and cell compartmentalization are more likely to emerge.[19,21,22] Oxygen permitted larger bodies, enabled the ability to fly, and supported the appearance of first terrestrial vertebrates and mammalian placental species.[19] Thus, it is estimated that oxygen played a critical role in the evolution and natural selection of life on earth.

1.3 | Oxygen uptake and utilization in mammals

For mammals, extracting oxygen from the atmosphere is vital, as without proper oxygenation of tissues cellular functions will falter. Oxygen is absorbed from the atmosphere to the lungs and then into the bloodstream through a pressure gradient.[23] The oxygen content in the air is constant and equal to 21%, however, when it comes to diffusion of gas through solutions, ie, blood, the most important factor is not concentration but partial pressure. At sea level, the partial pressure of oxygen is equal to 160 mm Hg, but once the air is inhaled the oxygen partial pressure is reduced because air is warmed and humidified in the nose and upper respiratory tract. Additional fall in the pressure of oxygen occurs from the trachea to the alveoli in the lungs, mainly because of the alveolar pressure of expired carbon dioxide. Therefore, at sea level the alveolar partial pressure of oxygen drops to ~100 mm Hg,[24] which is the driving force of a diffusion gradient that is formed

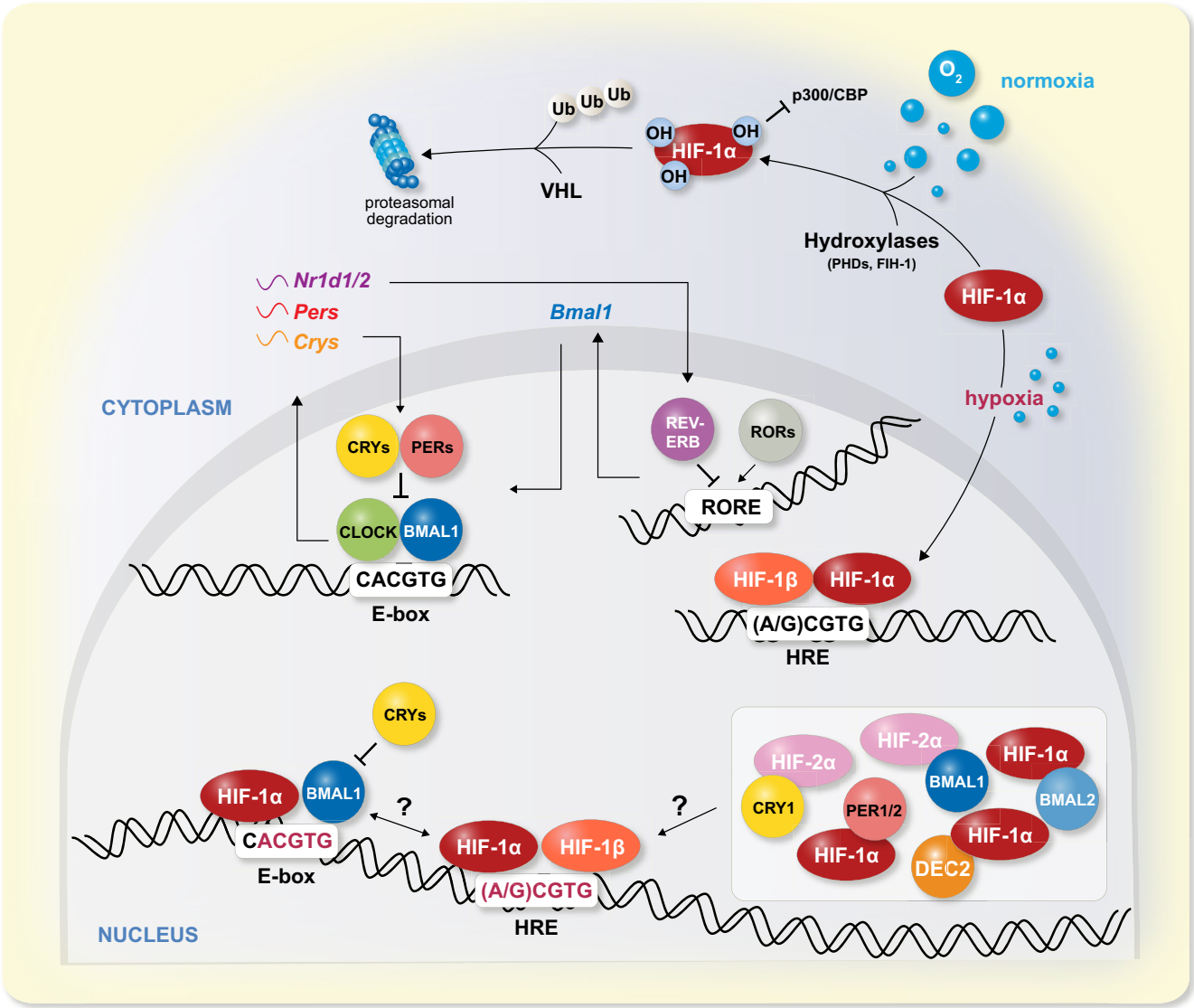

FIGURE 1 HIF-1 and circadian clock signalling pathways, alongside their potential molecular interactions. Under normoxia, hypoxia-inducible factor (HIF-1α) is modified with a hydroxyl group (OH) on two different proline residues by prolyl hydroxylases (PHDs) and consequently binds the Von Hippel-Lindau (VHL) complex, which targets it for degradation through the ubiquitin (Ub) proteasome pathway. Hydroxylation can also occur on asparagine residue through the action of factor inhibiting HIF-1α (FIH-1) protein and inhibits the recruitment of the transcriptional coactivators p300 and CBP. When oxygen levels are low (hypoxia), HIF-1α is protected from degradation and accumulate in the nucleus, where together with HIF-1β it binds to a specific DNA sequence (HRE) to regulate gene expression in response to hypoxia. The molecular circadian clock includes the transcription factors Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-Like 1 (BMAL1) that bind to a specific DNA sequence (E-box) and drive the expression of rhythmic genes. Amongst these genes are *Per1,2,3* (*Pers*) and *Cry1,2* (*Crys*), whose protein products interact with CLOCK-BMAL1 and repress their own transcription. CLOCK and BMAL1 also regulate the transcription of the nuclear receptors REV-ERBα,β (REV-ERBs), encoded by *Nr1d1* and *Nr1d2* respectively (*Nr1d1/2*) and the retinoic acid-related orphan receptors α and β (RORs). REV-ERBs represses whilst RORs activate the transcription of *Bmal1* through the ROR-element motif (RORE) on the DNA. At the bottom, various protein-protein interactions between HIF-1α and HIF-2α and core clock proteins are depicted, yet the functional significance of many of these interactions remains unclear (depicted in "?"). The interaction between BMAL1 and HIF-1α is well documented. BMAL1 and HIF-1α act synergistically to induce transcription from E-box or HRE-driven reporter genes, and they also occupy similar genomic regions that contain both E-box and HRE. The specificity of BMAL1 and HIF-1α interaction on promoter regions that contain either HRE or E-box alone, or both, remains to be explored (depicted in "?"). Finally, CRYs repress transcription driven by BMAL1-HIF-1α

across the alveolar-capillary membrane into the pulmonary blood flow where oxygen partial pressure is lower. Oxygenated blood then returns to the heart through the pulmonary vein and is distributed throughout the body via the cardiovascular system. Throughout this process, the partial pressure of oxygen drops to ~40 mm Hg in

venous blood. The pressure increases when venous blood becomes saturated back with oxygen after passing again through the lungs.[25] It is noteworthy that most laboratories grow cells in culture under ambient oxygen concentration, namely ~21% oxygen, which is way higher than the oxygen tension in the different tissues of the body (eg, the partial pressure of oxygen in the muscle is ~30 mm Hg (~4%), in the liver is ~40 mm Hg (~5%), and in the kidney is ~72 mm Hg (~9%)[26]). Oxygen is carried in the blood mostly by binding to haemoglobin, whereby, *Oxyhemoglobin* and *Deoxyhemoglobin* are the bound and unbound form, respectively. Various factors, such as oxygen partial pressure, pH and carbon dioxide, affect the affinity of oxygen to haemoglobin and facilitate the binding of oxygen to haemoglobin in the lung and its release in the rest of the body.[27]

In summary, oxygen is inhaled and distributed through the body, by the respiratory and cardiovascular systems. An oxygen gradient is formed throughout the body, with different tissues exhibiting different oxygen partial pressures that correspond to their metabolic needs.

1.4 | When oxygen availability is scarce—The cellular response to hypoxia

Hypoxia is a condition in which there is a failure of the tissues, for various reasons, to receive an adequate supply of oxygen.[28,29] This can result from the impaired ability of the lungs to extract oxygen from the air, resulting in lower oxygen partial pressure in both lungs and arterial blood. Such conditions can be caused by reduced oxygen partial pressure in inspired air as experienced during pressurized flights or in high altitude mountain areas, or because of various lung pathologies that are associated with airways obstruction and poor ventilation (eg, chronic obstructive pulmonary disease (COPD), asthma). Cardiovascular defects, which cause a reduction in blood flow (hypoperfusion), can as well lead to an inadequate amount of oxygen reaching the tissues, a phenomenon known as ischemia. Another level at which the body experiences hypoxia is a decrease in the oxygen-carrying capacity of haemoglobin in the blood, as seen, for example, in anaemia. As long as the degree of hypoxia is not too severe, the body may endure long periods of oxygen deficit through numerous physiological and cellular compensatory mechanisms. Once these mechanisms fail to support adequate oxygen supply damage will occur.

At the molecular level, a key oxygen-sensing mechanism that is present in most cells consists of the hypoxia-inducible factor 1 (HIF-1) pathway.[30,31] HIF-1 was first identified as a factor that, in response to hypoxia, increases the transcript levels of the gene encoding for erythropoietin (EPO), a hormone that stimulates red blood cells production.[32] Today, we denote HIF as a complex of two transcription factors named HIF-1α and HIF-1β (ARNT) that bind together in response to hypoxia and regulate the expression of genes that mediate adaptive responses. HIF complex binds to hypoxia response elements (HRE; (A/G)CGTG) in the regulatory regions of target genes involved in cellular metabolism, angiogenesis and cell survival.[33] The HIF heterodimer is formed in response to decreased oxygen levels because of the induced accumulation of HIF-1α. Whilst HIF-1β is constitutively expressed, HIF-1α has a very short protein half-life under normoxia because of its polyubiquitination by the Von Hippel-Lindau (VHL) complex, which targets it to proteasomal degradation. Binding to VHL is achieved by hydroxylation of two proline residues within the oxygen-dependent degradation (ODD) domain of HIF-1α by prolyl hydroxylase domain (PHD) enzymes, which require Fe^{2+} and uses oxygen and α-Ketoglutarate as substrates.[34] However, when oxygen levels are scarce this post-translational modification is inhibited and HIF-1α protein levels build up rapidly. HIF-1α is hydroxylated also on asparagine residue within the C-terminal transactivation domain by factor inhibiting HIF-1 (FIH-1), which prevents the recruitment of the transcriptional co-activators p300 and CBP.[34] Consequently, changes in cellular oxygen concentration modulate both HIF-1α protein stability and transcriptional activity (Figure 1).

2 | CROSSTALK BETWEEN OXYGEN AND CIRCADIAN BIOLOGY UNDER PHYSIOLOGICAL CONDITIONS

2.1 | Daily rhythms in oxygen physiology

Many physiological parameters oscillate throughout the day, amongst others these include rest-activity cycles, metabolic rate and body temperature oscillations. In this section, we will cover the literature related to daily oscillations in related pulmonary and cardiovascular functions. Daily rhythmicity in oxygen consumption was observed in rats and mice.[35-37] These daily changes in respiration are functionally related to rest-activity cycles because of changes in metabolic rate. Unlike wild-type mice, circadian clock mutant mice (eg, *Per1,2*$^{-/-}$ and *Bmal1*$^{-/-}$) fail to show rhythms in rest-activity and oxygen consummation in constant dark suggesting that oxygen rhythmicity is circadian clock-controlled likely through driving rest-activity cycles.[37] Indeed, oxygen rhythmicity is restored when these animals are housed under light-dark cycles or in response to feeding-fasting cycles (ie, time-restricted

feeding), which elicit behavioural rhythms even in clock deficient animals.[37] Along this line, circadian rhythms in breathing were eliminated in SCN-lesioned mice,[38] suggesting that breathing is regulated by the central clock in the brain. Studies in humans under constant routine protocol suggest that the circadian clock may also influence respiratory control independent of behavioural rhythms. Respiration in humans under constant behavioural and environmental conditions exhibited a weak circadian trend,[39] and the respiratory chemoreflex that controls breathing was found to exhibit significant circadian oscillations.[40] Also, a study in rats during a different state of sleep and wakefulness concluded that respiration is not solely dependent on sleep-wake cycles.[41] Whether or not circadian respiration is a mere reflection of sleep-wake cycles or regulated by other rhythmic mechanisms remains an open question as it is extremely challenging to experimentally uncouple these processes.

The cardiovascular system is responsible for the propagation of oxygen throughout the body and is also influenced by rest-activity cycles. Therefore, it is not surprising that heart rate, cardiac contractility and blood pressure display circadian rhythms and are elevated during the active phase.[42,43] In the blood, oxygen transport is carried by red blood cells (RBC). Daily changes in the number of circulating reticulocytes, premature RBC, was reported in rats and mice.[44] The number of circulating RBC also exhibit a daily pattern both in mice and humans.[45,46] Daily rhythms were also observed for erythropoietin,[47,48] the hormone that stimulates RBC production and haemoglobin.[46] Continuous recording of oxygen levels with a telemetry-based oxygen sensor revealed daily oscillations in liver and kidney oxygenation of freely moving animals.[37,49] In tissues, oxygen is devoured by the mitochondria. Oxygen consumption rate (OCR) in cultured cells and isolated mitochondria exhibit ~24 hours rhythmicity.[50,51] These rhythms are abolished when the molecular clock is disrupted.[51-53] Other features of mitochondrial function also fluctuate in a daily manner and are discussed in further detail in relevant reviews.[54,55]

Oxygen uptake and utilization include extraction from inhaled air, delivery through the bloodstream to different tissues, and final utilization by the mitochondria. All of these steps exhibit daily rhythmicity (Figure 2) which appears to be circadian clock-controlled either directly, or indirectly as a result of clock-regulated behavioural rhythms (eg, sleep-active, feeding-fasting).

2.2 | Oxygen as a resetting cue for peripheral clocks

The circadian timing system relies on cyclic cues to remain entrained to the 24-hour daily cycle.[2,56] The central

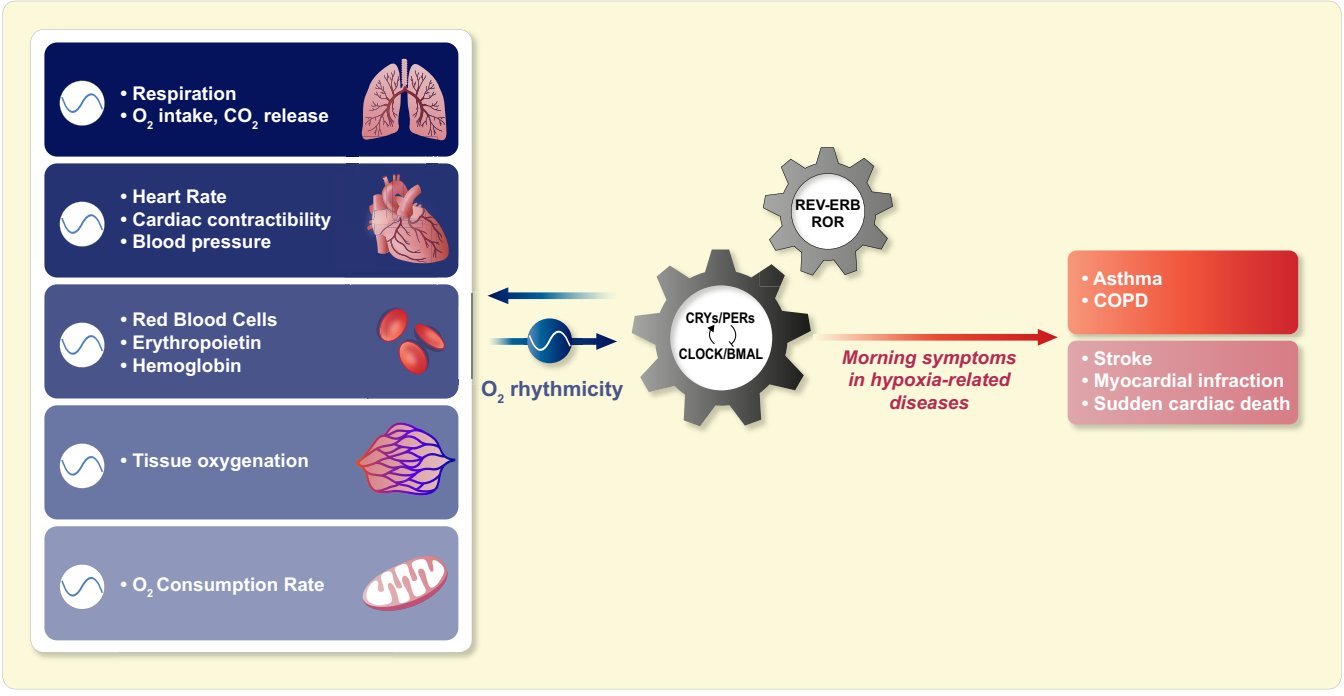

FIGURE 2 The interaction between daily rhythms in oxygen physiology, circadian clocks and day-time prevalence of oxygen-related pathologies. Oxygen uptake and delivery throughout the body is rhythmic at multiple levels. Rhythmic changes in oxygen levels act as a resetting cue for the circadian clock. Clock-driven rhythmicity in oxygen physiology is considered to play a role in the daytime prevalence of hypoxia-related diseases. Chronic Obstructive Pulmonary Disease (COPD)

circadian clock in the brain is entrained by rhythmic environmental timing cues (a.k.a. *zeitgebers*; time givers), primarily light-dark cycles and convey the time to circadian clocks that are present in most cells of the body.[57-59] Time information is communicated to peripheral clocks in the rest of the body through multiple pathways; including neuroendocrine rhythms, body temperature and metabolites.[7,60,61] The SCN maintain phase coherence between organs (ie, keeps organs in a fixed phase relationship),[62] however, peripheral clocks also differentially respond independently to other cues such as food intake, which when presented in antiphase to the light-dark cycle may lead to misalignment between the central and peripheral oscillators.[63-66]

It is primarily through cellular respiration that the body consumes nutrients and oxygen to produce energy and release heat and carbon dioxide. It is notable that peripheral clocks can be entrained by low-amplitude (ie, the difference between peak and through is small) temperature cycles that are equivalent to the circadian body-temperature rhythms.[67,68] Likewise, it was recently demonstrated that peripheral clocks can be entrained by low-amplitude oxygen cycles that are similar to the daily fluctuations in oxygen levels observed in mouse blood and tissues (Figure 2).[49] At the molecular level, HIF-1α emerged as a central communication node between oxygen and the molecular clock as clock resetting (ie, phase synchronization) by oxygen is HIF-1α dependent.[49,53,69] Furthermore, changes in carbon dioxide levels can as well phase shift (ie, advancement or delay of an oscillation along the time axis) the molecular clock in cultured cells.[37] Yet, the identity of the molecules that receive information regarding cellular carbon dioxide levels, let alone transduce it to the clock remains elusive. Interestingly, by imposing restricted daytime feeding in mice, which results in feeding-activity misalignment, it was demonstrated that rhythms in oxygen consumption closely follow activity cycles, whilst rhythms in carbon dioxide release better correlate with feeding cycles.[37]

Overall, the common notion is that peripheral clocks reinforce rhythmic regulation at the tissue level and that they are entrained by SCN-derived signals. It is conceivable that the response of peripheral clocks to food intake is related to multiple time signals entangled together and includes metabolites, temperature, as well as blood gases. Since carbon dioxide is instrumental for acid-base balance in the blood, changes in pH levels might also be included in this conjunction.[70] Overall, it appears that oxygen reset peripheral clocks through HIF-1α and that other blood gases such as carbon dioxide can phase shift the clock.

3 | CROSSTALK BETWEEN OXYGEN AND CIRCADIAN BIOLOGY UNDER PATHOLOGICAL CONDITIONS

3.1 | Day-time prevalence of hypoxia-related diseases

Circadian variations in the airway and cardiovascular functions, as detailed above, might be of relevance to the daytime prevalence of human pathologies that are associated with hypoxic spells. Symptoms of asthma, such as coughing and shortness of breath, worsen overnight and show exacerbation in the early hours of the morning.[71] Sudden death in asthmatic patients also tends to occur during this time.[72] Circadian variations in pulmonary function are suggested to be the underlying reason and involve abnormal or delayed responses to cortisol, adrenaline and melatonin.[73] Rhythmic variations in symptoms also occur in COPD patients and are worsen in the morning hours.[74] Patients who experience morning symptoms are at higher risk for exacerbations, are more likely to use their inhaler and have a higher risk for intubation in the emergency department.[75,76] One of the explanations for morning symptoms observed in asthma and COPD, as well as in smokers, is diurnal variation in peak expiratory flow and forced expiratory volume that dips during early morning hours.[77-80] As a result of the importance of time-of-day in the pathogenesis of airway diseases, treatments of asthma and COPD are now tested to be tailored to the most efficacious time of the day, in what is known as "chronotherapy."[81]

Similar to pulmonary activities, daily fluctuations in cardiovascular parameters are likely to affect the timing of onset, severity and outcome of multiple cardiovascular events.[69,82] Epidemiological data reveal a pattern of early morning onset in stroke, myocardial infarction (heart attack), ventricular arrhythmias and sudden cardiac death.[83] Patients who experienced a heart attack during the morning will mostly have larger infarct size and worse prognosis compared to patients who had a heart attack during other times of the day.[84] The increased probability of cardiovascular events in the morning in susceptible individuals is attributed to the rise in heart rate and blood pressure in those hours. Another contributing factor is the coagulation system that also displays circadian variability, with increased platelet aggregation in the morning hours.[85] Notably, evening intake of the anti-coagulant aspirin turned out to be more efficient for the prevention of cardiovascular events than the standard once-daily late morning intake.[86]

In summary, the incidence and outcome of pulmonary and cardiovascular diseases exhibit circadian rhythmicity, yet the underlying molecular mechanisms are only partially known as detailed below. Given the complex nature of these pathologies, their temporal occurrence is not only related to daily changes in oxygen biology but also to other factors that show daily rhythms such as the immune and inflammatory response.[87,88]

3.2 | The effects of hypoxia on circadian behaviour and physiology

Several studies performed in humans and rodents examined the effect of hypoxic conditions on circadian behaviour, physiology and the molecular clock. Hypoxia was reported to alter daily rhythms in body temperature, locomotor activity and sleep-awake cycles,[89-93] as well as rhythms in the levels of melatonin and cortisol.[94-97] Hypoxic conditions during embryonic life resulted in adult rat offspring with phase advanced activity rhythms and slower adaptation to a new light-dark cycle.[98] Other studies examined the effect of intermittent hypoxia, a protocol with alternating periods of normoxia and hypoxia. This is particularly relevant in the context of sleep apnea, a complex disorder characterized by intermittent pauses of breathing leading to fragmented sleep, and is associated with various metabolic disruptions.[99] Exposure of mice to intermittent hypoxia during the light phase resulted in inversion of daily blood glucose rhythmicity.[100] Moreover, intermittent hypoxia was found to phase-shift clocks in a tissue-dependent manner, leading to inter-tissue circadian clock misalignment.[101]

Oxygen deprivation may also be experienced chronically. This happens for instance to highlanders, such as Tibetan, Andeans and Ethiopians who cope with chronic oxygen deficit through various physiological and genetic adaptations.[102] Interestingly, a recent study suggested that human chronotype, the individual's time-of-day preferences of activities,[103] varies according to altitude.[104] The individual's morning/evening preference is believed to be related to differences in the molecular clock and specifically to its period length.[105,106] It is possible that changes in the partial oxygen pressure at high altitudes contribute to this phenotype.

Mild hypoxia is experienced during air travel in pressurized cabins, in which travellers experience reduced oxygen levels (~15% oxygen).[107] Long-duration transmeridian flights also involve circadian misalignment, known as jet leg.[108] In this regard, exposure of mice to ~15% oxygen before a phase advance shift in the light-dark regimen accelerated their adaptation to the new light-dark schedule.[49] It is noteworthy that the jet lag recovery of HIF-1$\alpha^{-/+}$ mice was not affected by the reduction in ambient oxygen levels,[49] in line with the role of HIF-1α in oxygen-dependent clock resetting, as described above.

Phase synchrony between external time, the SCN clock, and peripheral clocks is considered important for proper coordination of organs functions.[7] Along this line, circadian misalignment has been associated with a wide variety of pathologies. The findings that change in oxygen levels, whether chronic or short-termed, may cause circadian misalignment highlight the central role of oxygen as a resetting agent.

4 | MOLECULAR INTERACTIONS BETWEEN THE HIF PATHWAY AND THE CLOCKWORK

The intricate nature of the molecular clockwork provides various intersection points with the hypoxia signalling pathway (Figure 1). Remarkably, both the hypoxic response and circadian clocks contain proteins from the basic helix-loop-helix (bHLH)- PER-ARNT-SIM (PAS) family, suggesting potential crosstalk between the two. The mammalian bHLH-PAS proteins are an important class of transcription factors that play a role in regulating a variety of developmental and physiological programs.[109] The basic amino acid region and the helix-loop-helix domain (bHLH) serves as a structural dimerization motif for DNA binding. The PAS motif, named after its first characterization in PER, ARNT and SIM proteins,[110] serves as protein interaction, and potentially ligand-binding domain.[111,112] These two interaction surfaces determine pairing combinations between class I proteins, which are tissue-specific or environmentally regulated, and the ubiquitous class II proteins.[113] A relevant example is a heterodimerization between CLOCK (Class I) and BMAL1 (Class II).[114-117] Around the time, the interaction between the bHLH-PAS family members CLOCK and BMAL1 was first identified, the interaction between BMAL1 (a.k.a. MOP3, ARNT3, ARNTL) and HIF-1α (Class I), another family member, was also described using gel shift assays.[118,119] Interaction between HIF-1α and BMAL1 was also recently reported in cell culture.[69] During recent years, HIF-1α was shown to interact with several other clock components, including differentiated embryo-chondrocyte (DEC) 2,[120] PER1[121] and PER2[122] and CRY1 and CRY2.[123,124] Interactions between HIF-1α and BMAL2 (MOP9),[125] and between HIF-2α and BMAL1[118] and CRY1,[124] were also described. It is noteworthy, that these interactions were mostly shown using over expressed and not endogenous proteins, likely because of technical difficulties. Several interactions were shown with endogenous proteins, these include the interaction between HIF1α and PER2 in implanted

tumour cells[126] and in cardiac tissue exposed to hypoxia[127] and between HIF1α and BMAL1 in fibroblasts exposed to cobalt chloride that activates HIF-1α.[123] Co-transfection experiments with luciferase reporters demonstrated that HIF-1α-BMAL1 complexes are transcriptionally active in cells,[53,118,123] and that co-expression of cryptochromes suppresses their transcriptional activity.[123] ChIP-seq analysis done for BMAL1 and HIF-1α further revealed that out of all the sites that bind BMAL1, 20%-30% of the loci are also co-occupied with HIF-1α and are enriched with both HRE ((A/G)CGTG) and E-box (CACGTG) motifs.[69] Notably, PER proteins do not contain bHLH domains and hence do not bind directly to DNA, which led to the suggestion that PERs might interact with HIF-1α to inhibit its transcriptional activity.[110] Two different studies reported contradictory findings, were in one PER2-induced HIF-1 and in the other PER2-inhibited HIF-1 activity.[122,126] The discrepancy might stem from testing different promoter regions or because of the use of over-expressed proteins alongside a reporter assay which is prone to confounding effects.

Out of the loci that were identified to be co-occupied with HIF-1α and BMAL1 were promoters of core clock genes.[69] This suggests that the expression of clock genes can be affected by the hypoxia signalling pathway. Indeed, analysis of brain nuclear fractions from mice exposed to hypoxia showed elevated levels of PER1 and CLOCK.[121] Importantly, the response depended on the time of day the mice were exposed to hypoxia. Hypoxia also induced the expression of *Dec1* and *Dec2*, regulators of the mammalian molecular clock,[128] through functional HRE sites identified in their promoters.[129,130] Another study reported elevated *Per2* expression in isolated cardiac myocytes exposed to hypoxia and increased PER2 levels in cardiac tissues from patients with severe ischemic heart disease.[127] Additionally, treatment with cobalt chloride or overexpressing HIF-1α altered the expression pattern of clock genes.[53,131,132] Finally, the expression of *Cry2* and *RORα* in cultured cells is upregulated upon hypoxia in a HIF-1α-dependent manner.[49] Importantly, HIF-1α does not appear to be an integral part of the core clock oscillator as the clock oscillates perfectly well even in its absence.[49]

Although originally it was proposed that clock proteins do not participate in the response to hypoxia,[133] more recent studies suggest that the hypoxic response is gated by the cellular clock. Mice that were injected at different times of the day with DMOG, used to mimic hypoxia, exhibited rhythmic response in the induction of HIF-1α target genes in their livers.[69] Furthermore, exposure of mice to low oxygen either at the light or at the dark phase revealed that the overall transcriptional response to hypoxia differs throughout the day in a tissue specific manner.[101] Importantly, this effect was largely abolished in *Per1,2*$^{-/-}$ mice, suggesting that the time-dependent response to hypoxia is circadian-clock controlled.[101]

Although recent advancements identified multiple interactions between the circadian clock and the hypoxia signalling pathway (Figure 1), the nature of these interactions at the molecular levels and their functional consequences remain elusive. Future studies are expected to unravel these open questions.

5 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The 2017 and the 2019 Nobel prizes in physiology or medicine were awarded for discoveries that progressed our molecular understanding of circadian clocks and cellular oxygen-sensing, respectively. Remarkably, both systems contain transcription factors from the same family having similar protein domains (ie, bHLH, PAS), and bind to overlapping DNA motifs (ie, E-box, HRE). Despite multiple reports demonstrating protein-protein interactions between clock proteins and HIF-1, it is still largely unknown; (i) whether these interactions are direct or involve large protein complexes, (ii) how and in response to which signals these interactions occur and (iii) what is their biological relevance in vivo.[134,135] For instance, it would be interesting to examine whether the two complexes, CLOCK-BMAL1 and HIF-1α–HIF-1β, bind on adjacent sites on genes' regulatory elements and how they synergize. Notably, the HRE sequence is included within the E-box motif and activated HIF-1 was suggested to drive expression also from E-box containing promoters.[69] Thus, raising the question of whether and which of these sites are occupied by CLOCK-BMAL1 or by BMAL1-HIF-1α, and what factors determine the specificity. In addition, it would be attractive to test whether clock proteins are modified by proline hydroxylation, similar to HIF-1α, in response to changes in oxygen levels. Future studies combining molecular biology and biochemical approaches alongside specific knockout models are expected to shed light on the molecular interplay between these two pathways and their biological relevance.

The crosstalk between oxygen and circadian clocks as observed in mammals on multiple levels and at different stages of life raises the intriguing question of whether this principle is universal and valid for other organisms that harbour a circadian clock, such as plants or cyanobacteria. Namely, do they exhibit oxygen rhythmicity, and can oxygen reset their clocks.

Under pathological hypoxic conditions, the circadian clock system may contribute to the exacerbation of symptoms at a specific time during the day. Currently, we find ourselves in the midst of the global coronavirus diseases

2019 (COVID-19) pandemic, caused by the severe acute respiratory coronavirus-2, and characterized by mild to severe respiratory illness. Time of infection, viral replication, and immune response were recently observed to vary relative to the time of the day,[136,137] further highlighting the interaction between circadian rhythms and hypoxia-related diseases.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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