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Circadian clock and cancer

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Abstract

Circadian rhythms play a critical role in regulating physiological and behavioral processes, such as the sleep-wake cycle, hormone secretion, and metabolism. These rhythms are controlled by endogenous biological clocks, which are synchronized with environmental cues, primarily the light-dark cycle. Notably, disruption or reprogramming of circadian rhythms is closely associated with cancer initiation, progression, and treatment response. At the molecular level, the dysregulation of core clock genes can disturb normal cellular rhythms, leading to aberrant cell proliferation, impaired DNA repair, altered metabolism, and disrupted immune responses. This review systematically summarizes the pivotal roles and molecular mechanisms of circadian rhythms in tumor development, with a particular focus on strategies to modulate clock genes through behavioral interventions, pharmacological approaches, and gene-editing techniques, highlighting their potential as novel therapeutic strategies and clinical applications in cancer management.

Key words Circadian clock, Cancer, DNA damage response, Metabolic reprogramming, Immunity, Hypoxia signaling, Chronotherapy

Background

Circadian rhythms, also known as the biological clock, are intrinsic timekeeping systems that regulate periodic physiological and behavioral activities, aligning them with the environmental day-night cycle [1]. These rhythms encompass a broad spectrum of biological processes, ranging from gene expression and protein synthesis to cellular metabolism and whole-organism behavior [2].

In mammals, the principal circadian system is the circadian timing system, which comprises a central clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus and peripheral clocks distributed throughout various tissues and organs [2-4]. The SCN synchronizes with environmental cues, primarily light-dark cycles, to coordinate circadian outputs and align oscillators in peripheral tissues with the central rhythm through neural and/or humoral signals [5-7].

Disruption of circadian rhythms has been associated with increased risks of a range of chronic conditions, including diabetes, metabolic disorders, depression, and cardiovascular diseases [8]. Recent epidemiological studies further suggest that circadian misalignment, caused by factors such as jet lag, shift work, insomnia, irregular eating schedules, and nighttime light exposure, is linked to an increased risk of cancer [9-11]. The World Health Organization (WHO) has classified circadian disruption as a probable carcinogen [12-15]. Growing evidence indicates that the dysregulation of circadian clock genes is closely implicated in the initiation and progression of multiple malignancies, including pancreatic, ovarian, prostate, lung, breast, colorectal, and liver cancers, as well as acute myeloid leukemia and osteosarcoma [16-18]. Although the precise mechanisms remain incompletely understood, recent studies have begun to elucidate its molecular impact on hallmark cancer phenotypes and key oncogenic pathways. These effects encompass dysregulated DNA damage responses (DDR), metabolic reprogramming, tumor microenvironment remodeling, and hypoxia adaptation [19-22].

Circadian regulations of biological processes

Most mammalian cells are capable of generating circadian oscillations through cell-autonomous molecular clocks composed of interlocked transcriptional-translational feedback loops (TTFLs) [23]. These rhythms are governed by a core set of clock genes, including circadian locomotor output cycles kaput (*CLOCK*), brain and muscle ARNT-Like 1 (*BMAL1*, also known as *ARNTL*), cryptochrome 1/2 (*CRY1/2*), and period 1/2/3 (*PER1/2/3*) [23,24]. CLOCK and BMAL1 heterodimerize and bind E-box elements in target gene promoters, activating cryptochromes (*CRYs*)

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and periods (*PERs*) transcription. CRY and PER proteins form heterodimers that translocate to the nucleus and inhibit CLOCK/BMAL1 activity, resulting in the formation of a canonical negative feedback loop [25-29].

Beyond the canonical core clock components, additional feedback loops and auxiliary clock genes contribute to the regulation of the circadian network [30]. Proteins of the retinoic acid receptor-related orphan receptor (ROR) family, including RORA, RORB, and RORC, function as transcriptional activators by binding to ROR response elements (ROREs) in the *BMAL1* promoter, thereby pro-moting *BMAL1* transcription and contributing to the positive limb of the circadian regulatory network [31,32]. In contrast, nuclear receptor subfamily 1 group D member 1 (NR1D1, also known as REV-ERBα) and nuclear receptor subfamily 1 group D member 2 (NR1D2, also known as REV-ERBβ), members of the nuclear receptor subfamily, act as transcriptional repressors that compete with RORs for the same binding sites, thereby suppressing *BMAL1* transcription and providing a counterbalancing negative regulatory input to the circadian clock. *REV-ERBa* is rhythmically expressed under the positive control of CLOCK/BMAL1 and negatively regulated by PER and CRY, forming a secondary feedback loop that fine-tunes *BMAL1* expression [33]. A third loop involves D-site binding protein (DBP) and nuclear factor interleukin 3-regulated protein (NFIL3). CLOCK/BMAL1 rhythmically activates *DBP* transcription via E-boxes and chromatin modifications, whereas dynamic binding of CRY1 to the *DBP* promoter delays CLOCK/BMAL1-mediated *DBP* transcription [34,35]. DBP and NFIL3 also bind D-box elements in *RORα/β* promoters, linking D-box and RORE regulatory pathways [36] (Fig. 1). Beyond transcriptional control, accumulating evidence indicates that post-transcriptional and post-translational mechanisms are integral to circadian timekeeping [37]. The

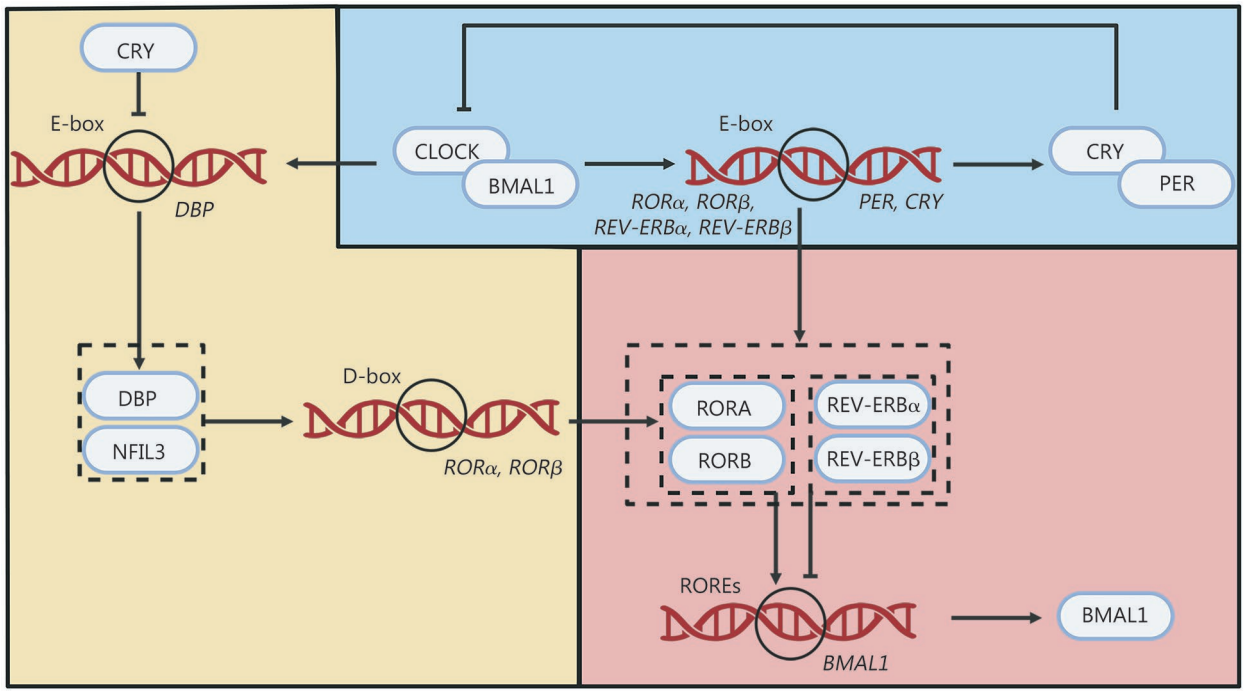

Fig. 1 Schematic representation of the core transcriptional-translational feedback loops of the mammalian circadian clock. CLOCK and BMAL1 form heterodimers that bind to E-box elements in the promoters of target genes, thereby activating the transcription of *PER* and *CRY*, as well as auxiliary clock components including ROR and REV-ERBs, also known as NR1D1/2. PER and CRY proteins subsequently form complexes that translocate into the nucleus and repress CLOCK/BMAL1 transcriptional activity, constituting the core negative feedback loop. ROR family members (RORA, RORB, and RORC) activate *BMAL1* transcription by binding to ROR response elements (ROREs), whereas REV-ERBα/β (NR1D1/2), whose expression is also driven by CLOCK/BMAL1, competitively represses *BMAL1*, providing a counterbalancing negative regulatory input. A third regulatory loop involves DBP and NFIL3, in which CLOCK/BMAL1 rhythmically activates *DBP* transcription via E-box elements, while CRY1-mediated delayed repression shapes its oscillatory expression. DBP and NFIL3 bind to D-box elements in downstream clock-controlled genes, including *RORα/β*, thereby integrating D-box- and RORE-mediated transcriptional programs and regulating circadian output. BMAL1. Brain and muscle ARNT-like 1; CLOCK. Circadian locomotor output cycles kaput; CRY. Cryptochrome; DBP. D-site binding protein; NFIL3. Nuclear factor interleukin 3 regulated; PER. Period; REV-ERBα. Nuclear receptor subfamily 1 group D member 1; REV-ERBβ. Nuclear receptor subfamily 1 group D member 2; RORA. Retinoic acid receptor-related orphan receptor α; RORB. Retinoic acid receptor-related orphan receptor β

abundance and rhythmicity of core clock transcripts, including *PER* and *CRY*, are shaped by regulated mRNA stability and RNA-binding proteins, whereas the stability and turnover of PER and CRY proteins are finely tuned by casein kinase 1 delta/epsilon (CK1δ/ε)-mediated phosphorylation and F-box and leucine-rich repeat protein (FBXL)3/FBXL21-dependent ubiquitin-proteasome pathways, thereby determining clock periodicity and robustness [38]. In summary, multiple overlapping feedback loops involving transcriptional, post-transcriptional, and post-translational regulation confer robust and cell-autonomous rhythmicity to gene expression, metabolism, and physiology. This multilayered regulatory architecture enables an organism to maintain homeostasis in response to daily environmental cycles [4,39,40].

Given the central role of circadian clocks in coordinating fundamental cellular processes, disruption of these tightly regulated TTFL networks can profoundly affect cellular homeostasis and contribute to disease pathogenesis. Importantly, accumulating evidence indicates that these TTFL circuits are not only passive timekeepers but also active regulators of cellular programs governing DDR, immunity, metabolism, and hypoxia-related pathways [41-43]. For example, CLOCK/BMAL1-driven transcriptional oscillations impose temporal control over cell-cycle regulators, including cyclins, cyclin-dependent kinases (CDKs), and checkpoint components, thereby coupling cell division to circadian timing [44]. In parallel, coherent entrainment of TTFL machinery to environmental cues is essential for maintaining robust rhythmic gene expression profiles across tissues [45]. Loss of such temporal coordination can lead to attenuated or arrhythmic oscillations, reflecting a breakdown in circadian organization at the cellular level [43]. These observations underscore the capacity of circadian TTFL networks to shape fundamental cellular states and adaptive responses, providing a mechanistic framework for understanding how circadian disruption may facilitate pathological transformation.

Circadian crosstalk with hallmark mechanisms in cancer

The effects of circadian rhythm disruption on cancer development, progression, and treatment response are due not only to the functional roles of individual clock genes but also from their complex interactions with key cancer-associated pathways, including DDR, metabolic reprogramming, immune regulation, and hypoxia signaling, which collectively reshape the overall tumor environment [46-49] (Fig. 2). These effects help maintain genome stability, control energy use, support immune escape, and adapt to low-oxygen conditions [43,50-52]. This multilayered regulatory architecture not only enhances the adaptive capacity of cancer cells under diverse stress conditions but also provides a theoretical foundation for circadian-based precision interventions (chronotherapy) [53]. It is important to note that some studies mentioned here are not from cancer models, but since these mechanisms are highly conserved under different conditions, their findings still provide valuable insights into the temporospatial regulation of cancer [54].

Circadian clock and DNA damage response

The circadian clock and the DDR pathway are intricately interconnected through bidirectional regulatory mechanisms, which are essential for maintaining genome stability [55]. Here, we explain how core clock components (such as CLOCK, BMAL1, PERs, and CRYs) control DDR pathways such as nucleotide excision repair (NER), homologous recombination (HR), and base excision repair (BER) through transcriptional control, protein interactions, and metabolic changes [56]. DNA damage itself is also a strong signal that can disturb and reshape circadian function and plays a pivotal role in tumor initiation, progression, and therapeutic response (Fig. 3).

Transcriptional regulation of DNA damage response by the circadian clock

Circadian regulation of DDR is a highly organized process that works at the transcriptional, post-translational, metabolic, and systemic levels [46,47,55,57-63]. The most direct mechanism is transcriptional regulation. Consistent with its canonical role in circadian transcriptional control, CLOCK/BMAL1-driven rhythmic regulation extends to key components of the DNA damage response. Among these, the NER factor xeroderma pigmentosum, complementation group A (*XPA*) represents a prototypical example, exhibiting robust circadian oscillation that is dynamically shaped by CLOCK/BMAL1-mediated activation and CRY/PER-dependent repression [56]. Its amplitude is maintained by homologous to the E6-AP carboxyl terminus (HECT) and regulator of chromosome condensation (RCC)1-like domain-containing protein 2 (HERC2)-dependent ubiquitination, which sets peaks and lows of global NER activity [60,62,64-69]. Genome-wide analyses have further revealed that transcription-coupled repair (TCR) efficiency also oscillates with transcription, with repair peaks moving from the 5' end to the 3' end of genes [70]. Similarly, key HR pathway genes, such as RAD51 recombinase (*RAD51*), breast

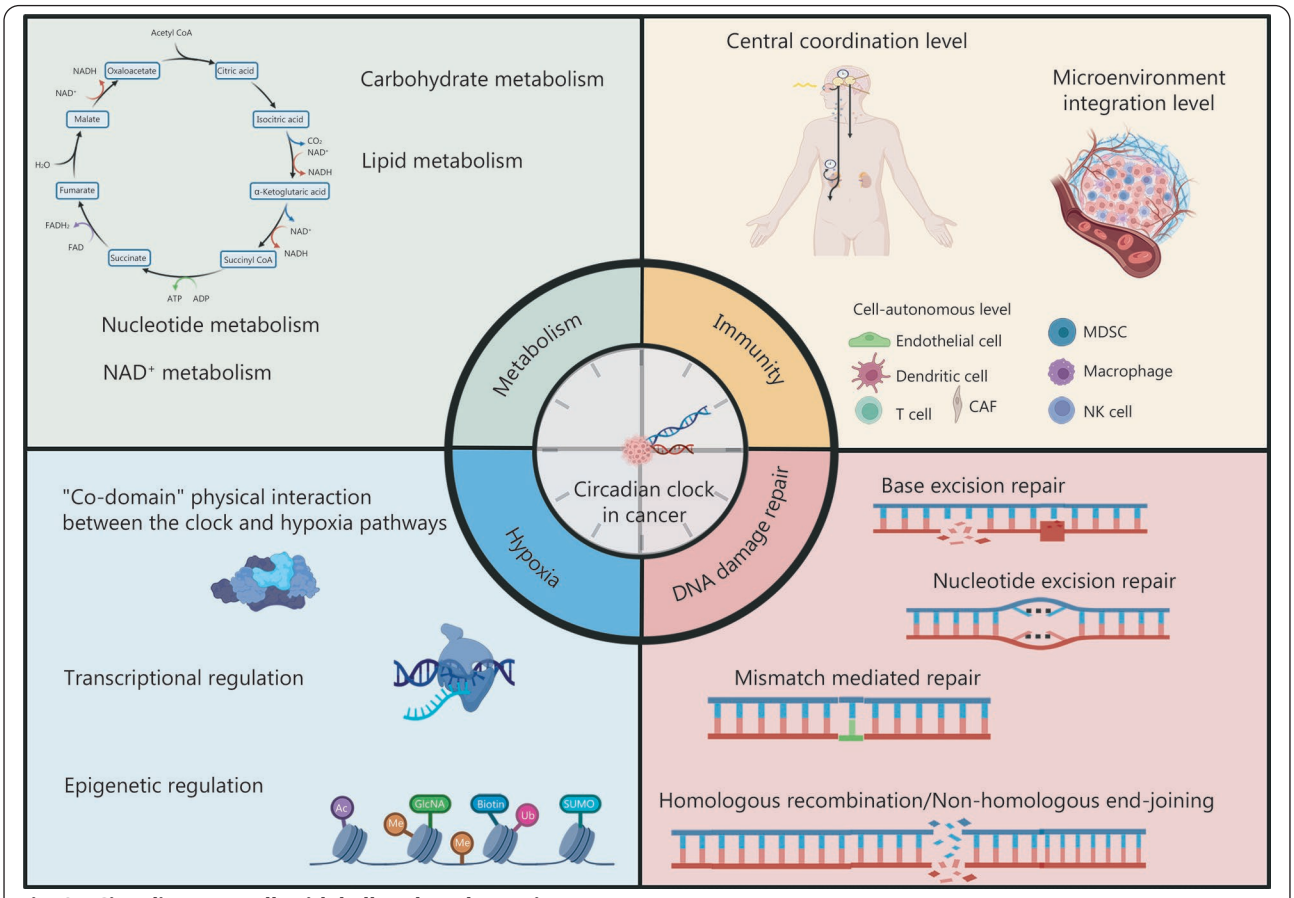

Fig. 2 Circadian crosstalk with hallmark pathways in cancer.
The circadian clock connects key oncogenic processes, including the DDR, metabolism, immunity, and hypoxia signaling. Core clock components rhythmically modulate metabolic homeostasis, genome stability, immune cell function, and hypoxia adaptation, collectively shaping tumor progression and therapeutic response. Ac. Acetylation; ADP. Adenosine diphosphate; ATP. Adenosine triphosphate; CAF. Cancer-associated fibroblast; CoA. Coenzyme A; FAD. Flavin adenine dinucleotide; FADH2. Flavin adenine dinucleotide reduced; GlcNA. N-acetylglucosamine; MDSC. Myeloid-derived suppressor cell; Me. Methylation; NAD^+. Nicotinamide adenine dinucleotide; NADH. Reduced nicotinamide adenine dinucleotide; NK. Natural killer; SUMO. SUMOylation; Ub. Ubiquitination

cancer type 1 susceptibility protein (*BRCA1*), breast cancer type 2 susceptibility protein (*BRCA2*), ataxia telangiectasia mutated (*ATM*), MRE11 double strand break repair nuclease (*MRE11A*), RAD50 double strand break repair protein (*RAD50*), X-ray repair cross-complementing protein (*XRCC*)3, and DNA polymerase delta 2 (*POLD2*), have been confirmed as direct circadian targets [71,72]. In *Drosophila*, the clock gene *ho* (a homolog of *CLOCK*) modulates the nuclear factor erythroid 2-related factor 2 (*NRF2*)/antioxidant response element (ARE) antioxidant pathway and ATM/ataxia telangiectasia and Rad3-related protein (ATR) signaling to reduce reactive oxygen species (ROS) levels at dawn while activating the expression of repair genes at night [73]. Similarly, BER factors including *XRCC1*, 8-oxoguanine DNA glycosylase (*OGG1*), and poly(ADP-ribose) polymerase 1 (*PARP1*), exhibit circadian oscillations [59,60]. PARP1 activity follows the nicotinamide adenine dinucleotide (NAD^+) cycle and peaks during the wake phase [60,74]. Even the choice of non-homologous end joining (NHEJ) and single-strand annealing (SSA) repair may be indirectly affected by the clock through cell cycle control [57]. Core clock genes additionally govern cell cycle checkpoint regulators [e.g., WEE1 G2 checkpoint kinase (*WEE1*) and cyclin-dependent kinase inhibitor 1A (*CDKN1A/p21*)] [43,75] and apoptosis-related genes, thereby coordinating repair and cell fate decisions.

Protein-protein interactions linking the circadian clock and DDR

Beyond transcriptional control, protein-protein interactions play a critical role in fine-tuning circadian and DDR. PER1 interacts directly with ATM kinase and checkpoint kinase 2 (CHK2) to promote checkpoint activation and DNA double-strand break (DDSB) repair [43,57,76]. PER2, via

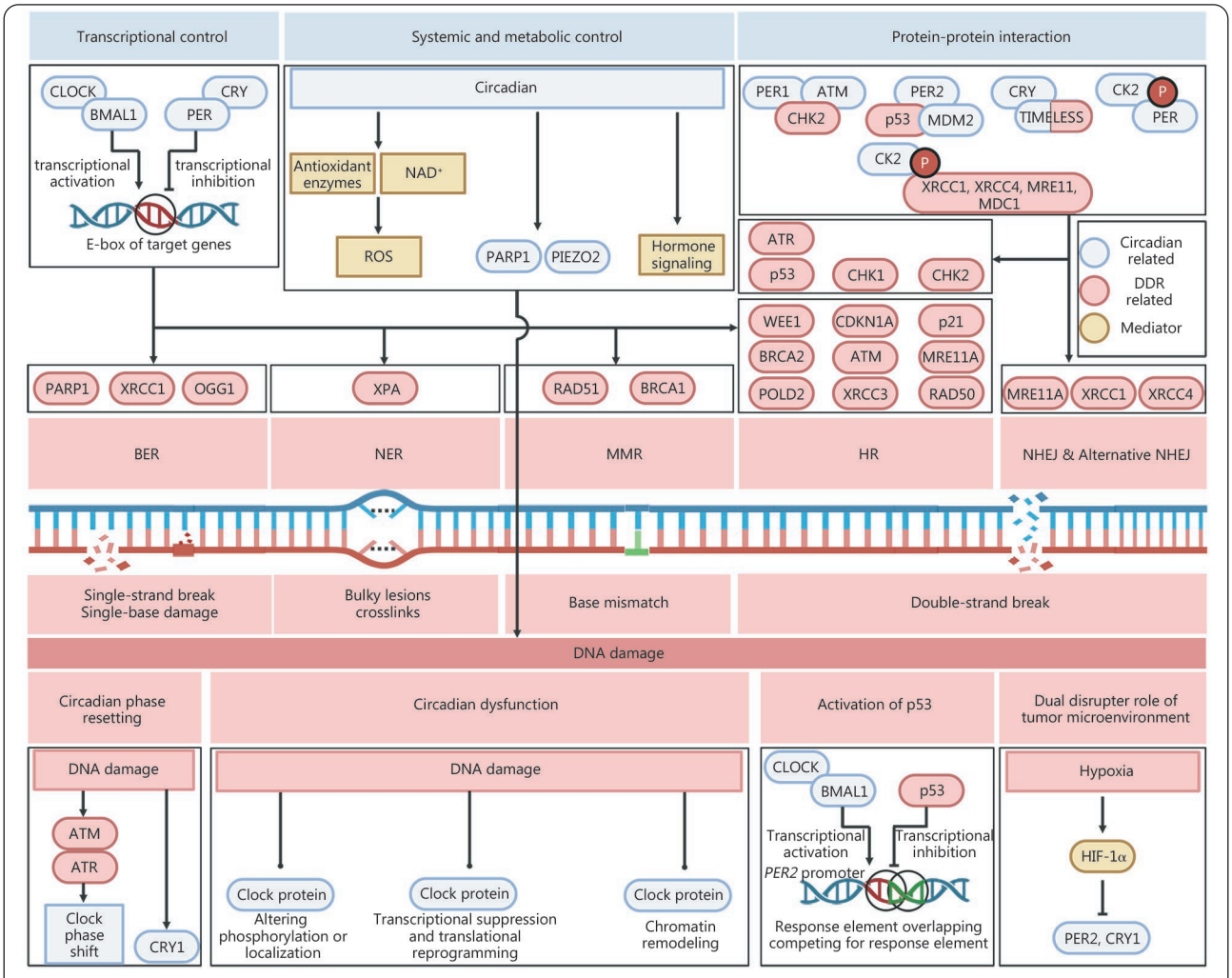

Fig. 3 Circadian clock and DNA damage repair.

The circadian clock regulates multiple DNA repair pathways (including BER, NER, MMR, HR, and NHEJ) through transcriptional control, protein-protein interactions, and systemic/metabolic signaling. CLOCK-BMAL1 and CRY-PER complexes rhythmically modulate *DDR* gene expression (e.g., *XPA*, *RAD51*, and *PARP1*), whereas core clock proteins interact with key DDR regulators such as ATM, ATR, CHK1/2, p53, and XRCC1/MRE11/XRCC4. The circadian control of antioxidant enzymes, NAD^+ metabolism, and hormone signaling further shapes the cellular redox state and repair capacity. DNA damage in turn resets the circadian phase and induces clock dysfunction, influencing p53 activation, hypoxia responses, and tumor microenvironment remodeling. ATM. Ataxia telangiectasia mutated; ATR. Ataxia telangiectasia and Rad3-related protein; BER. Base excision repair; BMAL1. Brain and muscle ARNT-Like 1; BRCA1. Breast cancer type 1 susceptibility protein; BRCA2. Breast cancer type 2 susceptibility protein; CDKN1A. Cyclin-dependent kinase inhibitor 1A; CHK. Checkpoint kinase; CK2. Casein kinase 2; CLOCK. Circadian locomotor output cycles kaput; CRY1. Cryptochrome 1; HIF-1α. Hypoxia-inducible factor-1α; HR. Homologous recombination; MDC. Mediator of DNA damage checkpoint; MMR. Mismatch-mediated repair; MRE11. MRE11 double-strand break repair nuclease; NAD. Nicotinamide adenine dinucleotide; NER. Nucleotide excision repair; NHEJ. Non-homologous end-joining; OGG1. 8-oxoguanine DNA glycosylase; PARP1. Poly (ADP-ribose) polymerase 1; PER. Period; PIEZO2. Piezo-type mechanosensitive ion channel component 2; POLD2. DNA polymerase delta 2; RAD50. RAD50 double-strand break repair protein; RAD51. RAD51 recombinase; ROS. Reactive oxygen species; TIMELESS. Timeless circadian regulator; WEE1. WEE1 G2 checkpoint kinase; XPA. Xeroderma pigmentosum complementation group A; XRCC. X-ray repair cross-complementing protein

its C-terminal domain, binds both p53 and its E3 ligase MDM2 proto-oncogene (MDM2), forming a ternary complex that inhibits p53 ubiquitination and degradation, thus promoting p53-mediated cell-cycle arrest and apoptosis [43,63,77]. CRY1 associates with timeless circadian regulator (TIMELESS) to rhythmically regulate ATR-CHK1 signaling, ultimately influencing the replication stress response, G2/M checkpoint activation [78], and NER efficiency [61,64,68]. TIMELESS itself is a dual-function factor in circadian and DDR processes, peaking during the S/G2 phases to stabilize replication forks and activate checkpoints [78]. Casein kinase 2 (CK2) links clock stability

and repair efficiency by phosphorylating both PER proteins and DDR factors such as XRCC1, XRCC4, MRE11, and mediator of DNA damage checkpoint 1 (MDC1) [79,80].

Metabolic and systemic regulation of circadian-DDR crosstalk

In addition to transcriptional and protein-level regulation, circadian control extends to systemic metabolic processes. The circadian clock orchestrates the activity of antioxidant enzymes [e.g., superoxide dismutase (SOD), catalase (CAT), and glutathione S-transferase epsilon 12 (GSTE12)] [59,73,81] and NAD^+ rhythmicity [74,81] to manage ROS levels, thereby limiting oxidative DNA lesions such as 8-oxo-7,8-dihydroguanine (8-oxoG) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) [59,60,81,82]. BMAL1, for instance, regulates the rate-limiting enzyme glucose-6-phosphate dehydrogenase (G6PD) in the pentose phosphate pathway (PPP) to maintain nucleotide pools and prevent replication stress [83]. Disrupted circadian rhythms cause the loss of ROS oscillations [60], exacerbate oxidative stress, and increase the expression of inflammatory cytokines such as IL-6, creating a positive feedback loop [81,82]. Even magnetic field exposure can perturb downstream circadian-DDR interactions by inducing oxidative stress [84]. In the nervous system, the sleep-wake cycle tightly couples with DNA damage clearance through PARP1 activity [74] and piezo-type mechanosensitive ion channel component 2 (PIEZO2)-mediated gut-brain ultradian signaling [85], whereas sleep deprivation markedly impairs repair capacity. Some studies have reported that Krüppel-like factor (KLF) 9 and other factors link hormone signaling and the circadian clock to regulate the DDR (e.g., enhancing glucocorticoid-induced PER1 expression) [86].

DNA damage-mediated resetting and disruption of circadian rhythms

The interplay between circadian rhythms and the DDR is not unidirectional. DNA damage itself strongly resets circadian function, which has critical implications in cancer biology. Acute DNA damage has been shown to reset circadian phase, as diverse genotoxic insults, double-strand breaks (DSBs), ultraviolet irradiation, and alkylating agents such as methyl methanesulfonate (MMS), can advance or shift clock oscillations through ATM/ATR-dependent signaling pathways [55]. Consistently, DSBs or ultraviolet (UV) exposure induce a phase advance of *PER2* promoter-driven bioluminescent rhythms [55]. Mechanistically, CRY1, a key circadian regulator of homologous recombination, orchestrates the temporal induction of DDR genes following DSBs, sequentially activating early sensors and downstream effectors to ensure repair fidelity [72].

In contrast to the phase-resetting effects of acute damage, persistent genotoxic stress compromises circadian integrity. Chronic exposure to chemotherapeutic agents such as doxorubicin, as well as sustained endogenous stress arising from replication stress or oxidative damage, disrupts clock oscillations through multiple mechanisms [87]. These include prolonged ATM/ATR signaling that alters clock protein phosphorylation or subcellular localization, global transcriptional repression coupled with translational reprogramming in response to DNA damage, and chromatin remodeling events, such as histone eviction, that impair the periodic transcription of core clock genes [87].

Circadian-DDR dysregulation in cancer and therapeutic implications

Such persistent circadian disruption ultimately leads to profound alterations in genome maintenance and contributes to tumorigenesis and therapeutic resistance. The tumor suppressor p53 emerges as a central integrator of this bidirectional crosstalk. PER2 stabilizes p53, whereas accumulated p53 represses *PER2* transcription by competing for a response element overlapping the CLOCK-BMAL1 E-box, resulting in the formation of a negative feedback loop [43,77]. Under conditions of severe or sustained DNA damage, PER2 oscillation is abolished and locked at per-sistently low levels, reinforcing circadian disruption.

Beyond cell-intrinsic signaling, the tumor microenvironment further amplifies circadian-DDR dysregulation. Hypoxia-inducible factor (HIF)-1α activation represses *PER2* and *CRY1* expression [88], whereas hypoxia itself generates DNA lesions, creating a vicious cycle of hypoxia, DNA damage, and circadian disruption in cancer.

Circadian disruption, either from genetic defects, shift work, abnormal light exposure, or environmental stress, breaks this temporal organization, leading to DDR impairment and severe genome instability [47,57,89-92]. Studies have shown that *Per1*/*Per2* double knockout mice exhibit persistent phosphorylated histone H2A.X at serine 139 (γ-H2AX) accumulation and compensatory upregulation of DDR genes (*Atm*, *Atr*, *Prkdc*, *Msh2*, *Msh6*, and *H2afx*), indicating that chronic rhythm disruption induces cumulative damage and sustained DDR activation [93]. Similarly, *Bmal1* deficiency leads to defects in HR, and the accumulation of DSBs [94], and weakened apoptotic responses [47,89]. In hepatocellular carcinoma (HCC), *PER2* and *CRY1* expression is downregulated and phase-shifted, correlating with

abnormal γ-H2AX rhythmicity, potentially through HIF-1α activation and enhancer of zeste homolog 2 (EZH2)-mediated methylation [88]. *Cry1/2* double knockout mice completely lose rhythmic NER activity [55,62,68]. The inhibition of CK2 causes spindle errors and activates the spindle assembly checkpoint (SAC), highlighting its role in maintaining genome stability [79]. Simulated night shift conditions erase the transcriptional rhythms of multiple DDR genes, including *XPA*, excision repair cross-complementation group 6 (*ERCC6*), replication protein A subunit 3 (*RPA3*), *PARP1*, and *RAD50*, and disrupt overall DDR pathway rhythmicity [92]. These cells also exhibit increased DNA damage markers and delayed repair after additional stress. Long-term night shift work is associated with increased cancer risk, which may be linked to the loss of XPA and OGG1 activity, reduced repair efficiency, and increased ultraviolet radiation B (UVB) sensitivity related to CRY2 expression [60,95]. Evidence from skin aging models has demonstrated that the circadian clock orchestrates multiple DNA repair pathways, including NER, BER, HR, translesion synthesis (TLS), and single-strand break repair (SSBR), in coordination with cell-cycle progression, oxidative stress control, and immune regulation [96]. Disruption of this integrated regulatory network has direct pathological consequences, particularly in cancer, where circadian misalignment promotes tumor progression and therapeutic resistance. In oral squamous cell carcinoma, reduced *PER2* expression removes a critical restraint on the 3-phosphoinositide-dependent protein kinase-1 (PDK1)-Akt-mechanistic target of rapamycin (mTOR) axis, enhancing DNA repair capacity and conferring resistance to cisplatin, whereas restoration of *PER2* increases platinum adduct formation and re-sensitizes tumor cells to chemotherapy [96]. In cisplatin-resistant ovarian cancer, expression of *CLOCK* is positively correlated with tumor growth [62]. The robustness of tumor clocks, such as the *Bmal1-Per2* phase relationship, can predict cisplatin sensitivity [91]. Specific *CRY2* mutations (D325H and S510L) increase cell growth by suppressing p53 signaling [97]. Abnormal coupling between the circadian clock and the cell cycle, particularly in embryonic stem cells and certain cancer cells, can facilitate DNA damage tolerance and polyploidy [75].

Collectively, the circadian system establishes a complex framework, encompassing transcriptional regulation, protein interactions, and redox-metabolic integration, that governs the rhythm and efficiency of the DDR. Key hubs such as *XPA* (NER), *CRY1* (HR), *PER2* (p53 stabilization), and p53 itself form the backbone of this network. Disruption of this rhythm destabilizes the axis, leading to genomic instability and reducing the effectiveness of cancer therapy. These insights open new avenues for chronotherapy, which exploits differential rhythmic DDR activity between normal and tumor tissues to optimize drug timing for maximal therapeutic efficacy [64]. Future strategies include small-molecule modulators targeting clock-DDR hubs, such as CRY stabilizers (KL001) to increase HR repair [72], or REV-ERB antagonists (SR8278) and CRY inhibitors (KS15) to increase NER and checkpoint control to improve platinum sensitivity [69,98]. Therapeutic strategies targeting oxidative stress regulation, such as modulation of the NRF2 pathway or melatonin supplementation, have also shown potential benefits [60]. Additional work is required to delineate the tissue- and tumor-specific features of these mechanisms in humans and to evaluate peripheral indicators, including rhythmic changes in DNA repair factors in blood or urinary 8-OHdG excretion, as candidate markers for guiding chronotherapy [82]. Moreover, attention should be given to the reverse regulation of the circadian clock by the DDR, such as DNA damage resetting the clock phase via ATM/ATR signaling [55,87], and its role in rhythm disruption-driven tumorigenesis. Investigating the temporal coupling between the circadian clock and the DDR, as well as epigenetic regulation, will provide broader theoretical perspectives and deeper insights.

Circadian clock and metabolic reprogramming

Metabolic reprogramming is a hallmark of cancer, enabling tumor cells to acquire essential nutrients from nutrient-deprived environments to sustain viability and generate biomass [99]. Compared with normal cells, tumor cells exhibit distinct metabolic features, collectively referred to as cancer metabolic reprogramming [100]. These features include the dysregulated uptake of glucose and amino acids, the utilization of glycolytic and tricarboxylic acid (TCA) cycle intermediates for biosynthesis, and increased nitrogen demand [101]. Within the tumor microenvironment, the nutrient sources available to cancer cells dynamically change during tumor progression, and metabolic reprogramming facilitates proliferation, survival, migration, invasion, and metastasis [102]. Genetic or environmental perturbations disrupting circadian rhythms can lead to metabolic disorders, including hyperleptinemia, hypertriglyceridemia, hepatic steatosis, diabetes, and obesity, highlighting the pivotal role of the circadian clock in maintaining metabolic homeostasis, particularly lipid metabolism [103,104] (Fig. 4).

This intimate clock-metabolism coupling is not merely correlative but involves hierarchical, causal regulatory networks [2,105]. Disruption of core clock components often initiates

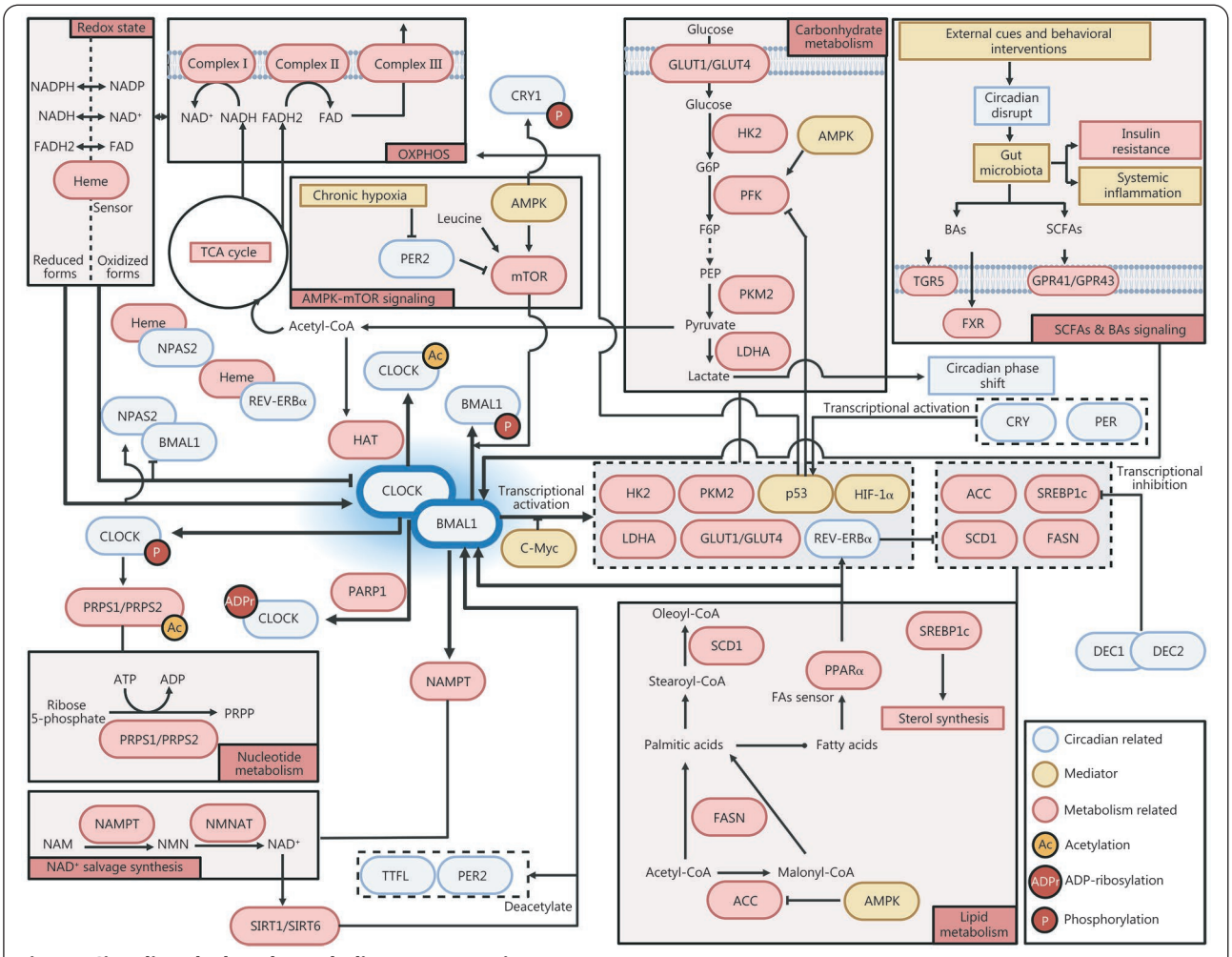

Fig. 4 Circadian clock and metabolic reprogramming.

This schematic illustrates the bidirectional crosstalk between the circadian clock and metabolic reprogramming in tumor cells. The core CLOCK/BMAL1 complex transcriptionally activates key glycolytic genes while modulating oxidative phosphorylation and p53-dependent metabolic balance. Circadian rhythms suppress lipid-producing pathways, whereas metabolic sensors reinforce clock activity. The clock also shapes nucleotide synthesis by allowing oncogenic signals to stabilize key metabolic enzymes. Metabolites provide feedback to tune clock function through redox and cofactor dynamics. Energy- and oxygen-sensing pathways integrate metabolic status with circadian timing, altering protein synthesis and stress responses. External cues further shift peripheral rhythms, influencing inflammation, metabolic health, and tumor progression. ACC. Acetyl-CoA carboxylase; ADP. Adenosine diphosphate; AMPK. AMP-activated protein kinase; ATP. Adenosine triphosphate; Bas. Bile acids; BMAL1. Brain and muscle ARNT-Like 1; CLOCK. Circadian locomotor output cycles kaput; C-Myc. MYC proto-oncogene, bHLH transcription factor; CoA. Coenzyme A; CRY1. Cryptochrome 1; DEC1. Differentiated embryo-chondrocyte expressed gene 1; DEC2. Differentiated embryo-chondrocyte expressed gene 2; F6P. Fructose-6-Phosphate; FAD. Flavin adenine dinucleotide; FADH2. Reduced flavin adenine dinucleotide; FAs. Fatty acids; FASN. Fatty acid synthase; FXR. Farnesoid X receptor; G6P. Glucose-6-Phosphate; GLUT. Glucose transporter; GPR41. G-protein-coupled receptors 41; GPR43. G-protein-coupled receptors 43; HAT. Histone acetyltransferase; HIF-1α. Hypoxia-inducible factor-1α; HK2. hexokinase 2; LDHA. Lactate dehydrogenase A; mTOR. Mechanistic target of rapamycin; NAD. Nicotinamide adenine dinucleotide; NADH. Nicotinamide adenine dinucleotide; NADP. Nicotinamide adenine dinucleotide phosphate; NADPH. Nicotinamide adenine dinucleotide phosphate; NAM. Nicotinamide; NAMPT. Nicotinamide phosphoribosyltransferase; NMN. Nicotinamide mononucleotide; NMNAT. Nicotinamide mononucleotide adenylyltransferase; NPAS2 Neuronal PAS domain protein 2; OXPHOS. Oxidative phosphorylation; PARP1. Poly (ADP-ribose) polymerase 1; PEP. Phosphoenolpyruvate; PER2. Period 2; PFK. Phosphofructokinase; PKM2. Pyruvate kinase M2; PPARα. Peroxisome proliferator-activated receptor alpha; PRPP. Phosphoribosyl pyrophosphate; PRPS1. Phosphoribosyl pyrophosphate synthetase 1; PRPS2. Phosphoribosyl pyrophosphate synthetase 2; REV-ERBα. Nuclear receptor subfamily 1 group D member 1; SCD1. Stearoyl-CoA desaturase 1; SCFAs. Short-chain fatty acids; SIRT. Sirtuin; SREBP1c. Sterol regulatory element-binding protein 1c; TCA. Tricarboxylic acid cycle; TGR5. Takeda G protein-coupled receptor 5; TTFLs. Transcriptional-translational feedback loops

a cascade of metabolic dysregulation, which in turn further destabilizes the circadian system, creating a vicious cycle that promotes oncogenesis. The molecular mechanisms extend beyond transcriptional control to include post-translational modifications, allosteric regulation by metabolites, and dynamic rewiring of signaling hubs in response to circadian and metabolic cues [106,107].

Clock control of metabolic programs

Core clock proteins directly regulate the rhythmic expression of numerous metabolic genes. In mammalian liver tissue, more than 50% of metabolites and 43% of transcripts exhibit circadian oscillations, underscoring the pervasive influence of the clock on metabolic homeostasis [21,108]. Within the context of glucose metabolism, the CLOCK/BMAL1 directly activates glucose transporters (*GLUT*)1/4 and glycolytic enzymes [e.g., hexokinase 2 (*HK2*), pyruvate kinase M2 (*PKM2*), lactate dehydrogenase A (*LDHA*)] [46,109,110] but indirectly suppresses glycolysis and promotes oxidative phosphorylation (OXPHOS) through the regulation of p53 [46]. Circadian control is also particularly pronounced in lipid metabolism. CLOCK/BMAL1 activates REV-ERBα, which represses lipogenic enzymes [fatty acid synthase (*FASN*), acetyl-CoA carboxylase (*ACC*), and stearoyl-CoA desaturase 1 (*SCD1*)] and the core lipogenic transcription factor sterol regulatory element-binding protein 1c (*SREBP1c*) [109,111]. Additional clock-associated factors, such as differentiated embryo-chondrocyte expressed gene (*DEC*)1 and *DEC2*, further suppress lipogenesis by directly binding to the *SREBP1c* promoter [111]. In addition, fatty acid-sensing nuclear receptors also feed back into the circadian clock regulation. Peroxisome proliferator-activated receptor alpha (PPARα) activates *BMAL1* and *REV-ERB* expression, resulting in the formation of a positive feedback loop (PPARα/BMAL1/REV-ERB axis) [111]. Additionally, nucleotide metabolism can also be directly shaped by oncogenic repurposing of core circadian clock components [112,113]. Activated receptor tyrosine kinase (RTK) signaling leads to the phosphorylation of CLOCK (S106) through the extracellular signal-regulated kinase (ERK)-CK2 axis, leading to the dissociation of the CLOCK/BMAL1 dimer. Phosphorylated CLOCK is translocated to the cytoplasm, where acetylation stabilizes the rate-limiting nucleotide synthesis enzymes phosphoribosyl pyrophosphate synthetase 1/2 (PRPS1/2), thereby driving de novo nucleotide synthesis and supporting tumor proliferation [112]. This oncogenic rewiring exemplifies deep pathway integration, whereby an extracellular growth signal (RTK) is transduced through a kinase cascade (ERK-CK2) to post-translationally modify the core clock component CLOCK, thereby spatially relocalizing it from its canonical nuclear transcriptional function to a cytoplasmic, non-canonical role in stabilizing metabolic enzymes [112].

Metabolite feedback on the circadian clock

Metabolites not only are outputs of clock regulation but also act as signaling molecules, modulating clock protein function or cofactor activity to provide feedback on the clock [114,115]. Among these, NAD^+ represents a central molecular interface linking cellular metabolic state to circadian oscillations. In mammalian tissues, NAD^+ levels exhibit pronounced diurnal rhythmicity, primarily driven by the core clock transcription factors CLOCK and BMAL1. The CLOCK/BMAL1 complex directly regulates the transcription of nicotinamide phosphoribosyltransferase (*NAMPT*) by binding to E-box elements in its promoter. As the rate-limiting enzyme of the NAD^+ salvage pathway, the rhythmic expression of NAMPT drives oscillations of intracellular NAD^+, thereby establishing a tightly coupled transcription-metabolism feedback loop [108,116]. NAD^+ oscillations, in turn, activate the NAD^+-dependent protein deacetylases sirtuin (SIRT)1 and SIRT6, which modulate clock protein activity. SIRT1 deacetylates core clock proteins such as BMAL1 and PER2, regulating their stability, subcellular localization, and transcriptional activity [117,118]. Additionally, SIRT1 participates in CLOCK/BMAL1-mediated chromatin remodeling through histone deacetylation, fine-tuning the circadian expression of clock-controlled genes (CCGs) [119]. SIRT6 is recruited to the CLOCK/BMAL1 complex, where it mediates rhythmic acetylation of BMAL1 and cyclic acetylation of histone H3 lysine 9/14 (H3K9/14) at circadian promoters, further influencing gene transcription [120]. Together, SIRT1 and SIRT6 form a bidirectional regulatory hub with NAD^+, tightly coupling the cellular metabolic state with circadian rhythms [108,116,121]. Another key regulator, PARP1, is also under circadian control. Its rhythmic activation can ADP-ribosylate CLOCK, inhibiting CLOCK/BMAL1 DNA binding and thus modulating clock gene transcription. Moreover, DNA damage or excessive PARP1 activation can deplete NAD^+, indirectly suppressing SIRT1 activity, indicating that NAD^+ levels also play a role in DNA damage responses and clock resetting [116]. Furthermore, the NAD^+-SIRT axis collaborates with other energy sensors, such as AMP-activated protein kinase (AMPK), integrating cellular energy status with the circadian timing mechanism to ensure that circadian rhythms are aligned with energy

availability. This highly integrated transcription-metabolism network highlights the pivotal role of NAD^+ as a central hub connecting the circadian clock to cellular metabolism [122].

Alongside NAD^+ metabolism, fluctuations in other metabolites directly impinge on circadian transcriptional control. Acetyl-coenzyme A (CoA), the essential substrate for histone acetylation, directly influences the histone acetyltransferase activity of CLOCK, thereby modulating chromatin accessibility and metabolic gene transcription [110,123]. Cellular redox state serves as another rapid metabolic sensor. The $NAD(P)^+$/NAD(P)H and flavin adenine dinucleotide (FAD)/flavin adenine dinucleotide reduced (FADH2) ratios directly influence CLOCK/BMAL1 and neuronal PAS domain protein 2 (NPAS2)/BMAL1 DNA-binding, with reduced forms promoting binding and oxidized forms inhibiting binding [43,116,124]. Heme also senses redox changes and binds REV-ERB and NPAS2 to regulate clock function [43,125]. The mechanism by which redox states influence clock function involves direct modulation of transcriptional complex activity. For instance, the reduced forms of NADH and FADH2 can allosterically promote the binding affinity of the CLOCK/BMAL1 heterodimer to E-box elements, enhancing the transcription of target genes during metabolic phases associated with reductive power [126]. Conversely, oxidative stress (e.g., an increased $NADP^+$/NADPH ratio) can inhibit this binding. This creates a direct, rapid feedback loop in which the metabolic redox status of the cell fine-tunes the amplitude and phase of circadian transcriptional output, independent of new protein synthesis. This represents a deeply integrated layer of metabolic sensing within the core circadian machinery [124].

Finally, microbial metabolites extend circadian-metabolic coupling to the systemic level. Bile acids and short-chain fatty acids (SCFAs) produced by the gut microbiota signal through nuclear receptors such as farnesoid X receptor (FXR) and takeda G protein-coupled receptor 5 (TGR5) or through G-protein-coupled receptors (GPR41/43), thereby influencing *BMAL1* expression and circadian phase in peripheral tissues [127,128]. This gut-liver-brain axis of circadian communication exemplifies systemic pathway integration. Diurnal variations in gut microbiota composition and function lead to the rhythmic production of SCFAs. These metabolites signal through enteroendocrine cells or enter the circulation to bind receptors on hepatocytes (e.g., FXR) or immune cells, ultimately modulating the expression and phase of core clock genes such as *BMAL1* in distal tissues [127,128]. This pathway directly links environmental/behavioral cues (feeding time and diet composition) to peripheral clock synchronization and metabolic gene expression, providing a mechanistic basis for how timed feeding interventions exert their effects.

Integration of energy-sensing pathways in circadian-metabolic control

The circadian clock can integrate key signaling pathways to regulate cellular energy status, stress responses, and anabolic metabolism [110,129-131]. In this network, the AMPK/mechanistic target of rapamycin (mTOR) axis acts as a central hub. AMPK senses energy and nutrient status, phosphorylating CRY proteins under low-energy conditions to promote degradation and reset the peripheral clock phase [129,130]. Conversely, mTOR, rhythmically regulated by the clock, senses amino acid signals and phosphorylates BMAL1 to control periodic protein synthesis [110]. Notably, the core clock protein PER2 can act as a scaffold to inhibit mTORC1 activity; therefore, the loss of PER2 lifts this inhibition, increasing protein synthesis and driving cell proliferation [110]. Environmental stress responses are tightly coupled to circadian regulation. HIF-1α is linked to hypoxia and metabolic remodeling: its promoter is directly regulated by CLOCK/BMAL1, conferring intrinsic rhythmicity to hypoxic responses [110]. *BMAL1* deficiency reduces HIF-1α stability and transactivation, impairing tumor adaptation to hypoxia [131]. Chronic hypoxia can provide feedback to suppress *PER2* oscillation, resulting in the formation of a destructive positive feedback loop [123,132]. Circadian disruption also perturbs the gut microbiota, activating pattern recognition receptors [Toll-like receptor 4/5 (TLR4/5) and NOD-, LRR- and Pyrin domain-containing protein 3 (NLRP3)] to trigger systemic inflammation and insulin resistance [127]. The HIF-1α-clock interaction is a prime example of pathway cross-talk that mediates metabolic adaptation. Rhythmic HIF-1α expression ensures that hypoxic responses and associated metabolic shifts are optimally timed. However, in tumors, sustained hypoxia disrupts this rhythm by suppressing *PER2*, *BMAL1* loss further destabilizes HIF-1α protein [123,132,133]. This dual disruption uncouples hypoxic signaling from circadian control, leading to a constitutively active, but poorly regulated, glycolytic phenotype.

Circadian metabolic dysregulation in cancer and therapeutic implications

Circadian disruption profoundly reshapes tumor metabolism by uncoupling temporal control from core bioenergetic and biosynthetic programs. Loss of PER/CRY function shifts cellular metabolism toward aerobic glycolysis while

suppressing oxidative phosphorylation, a pattern consistent with the Warburg phenotype [46]. In parallel, oncogenic drivers such as cellular myelocytomatosis oncogene (c-Myc) interfere with BMAL1-driven oscillatory control, disrupting the rhythmic coordination of glucose and glutamine utilization and sustaining continuous anabolic flux to support tumor growth [109,134]. Importantly, the metabolic consequences of circadian misalignment are not uniform across malignancies but depend on tissue context and oncogenic wiring. For example, lung adenocarcinoma preferentially incorporates circulating lactate as a carbon source for the TCA cycle, whereas pancreatic ductal adenocarcinoma relies more heavily on glutamine metabolism [110]. When the circadian clock properly separates metabolic timing, it can distinguish between anabolic and catabolic processes. However, the activation of oncogenes such as *Myc* disrupts this temporal separation, leading to uncoordinated metabolic pathway activation and sustained anabolic metabolism [135]. Circadian regulation of metabolism is not confined to cancer cells but also operates within tumor microenvironment, linking metabolic reprogramming to immune evasion. Myeloid-specific Bmal1 knockout (M-BKO) macrophages polarize toward a protumor M2-like phenotype, with high expression of immunosuppressive genes such as arginase 1 (*Arg1*) and solute carrier family 7 member 8 (*Slc7a8*), and enhanced glycolysis through the mROS-HIF-1α axis [136,137]. These tumor-associated macrophages can suppress interferon gamma (IFN-γ) production by cluster of differentiation 8 positive T ($CD8^+$ T) cells and natural killer (NK) cells [136]. Circadian regulation of metabolism also operates at the systemic level, enabling tumors to impose metabolic alterations on distant organs. In lung [kirsten rat sarcoma viral oncogene homolog (*Kras*)/tumor protein p53 (*Tp53*) mutant] and breast cancer models, inflammatory factors such as IL-6 can remotely reshape hepatic lipid metabolism and insulin signaling rhythms, causing systemic metabolic disruption [109,110,138]. Similarly, colorectal cancer liver metastases can shift clock gene phases in healthy liver tissue through the secretion of factors such as lactate [138]. Metabolic waste from tumors, such as lactate and ammonia, can be recycled as alternative carbon or nitrogen sources, which may also follow temporal patterns [109]. Finally, external cues and behavioral interventions strongly affect the clock-metabolism axis. Nighttime light exposure or shift work suppresses melatonin, disrupts feeding rhythms, and promotes weight gain and tumor risk [108,123]. Feeding itself acts as a strong peripheral time cue: time-restricted feeding (TRF) limits the eating window to the active phase, improving insulin sensitivity, liver lipid metabolism, and bile acid rhythms even without changing caloric intake, thereby restoring metabolic rhythm amplitude and slowing tumor progression [2,108,139-141]. Conversely, high-fat diets (HFDs) or ad libitum feeding disrupt peripheral clocks and disturb the rhythmic expression of metabolic genes [2,142].

In summary, the circadian clock and metabolism form a complex, multilevel, and tightly regulated two-way network centered on key nodes across molecular (CLOCK/BMAL1, NAD^+/SIRT1, MYC), signaling pathway (AMPK/mTOR, HIF-1α), organelle (mitochondria-mROS), and systemic (liver-bile acid axis) levels [43,46,110,125,129-132,136,138]. These findings have important translational implications. Aligning therapeutic interventions with circadian and metabolic rhythms has been shown to enhance the efficacy of conventional chemotherapeutic agents, such as oxaliplatin, while simultaneously reducing treatment-associated toxicity [143]. In parallel, pharmacological targeting of key nodes within the clock-metabolism axis represents a promising strategy, exemplified by REV-ERB agonists (SR9009/SR9011), which suppress lipid metabolism and autophagy to selectively impair cancer cell viability [144], as well as by CK2 or succinate dehydrogenase (SDH) inhibitors that disrupt oncogenic exploitation of circadian machinery or alleviate immune suppression [129,136]. Beyond pharmacological approaches, behavioral modulation of metabolic timing, particularly through TRF, has emerged as a noninvasive intervention capable of restoring metabolic rhythmicity, improving systemic metabolic health, and restraining tumor progression [141]. Looking ahead, further studies are needed to delineate tissue- and tumor-specific features of clock-metabolism interactions, integrate multi-omics strategies to map spatiotemporal metabolic oscillations, and evaluate how manipulation of peripheral clocks or metabolic rhythms can synergize with cancer immunotherapy [113,145]. Rigorous clinical investigations will ultimately be required to validate the efficacy and feasibility of chronotherapy and metabolism-based interventions in patients [146]. Overall, understanding the cross-talk between the circadian clock and metabolism not only reveals new mechanisms of tumor development but also provides a basis for designing innovative rhythm-based therapeutic strategies.

Circadian clock and immunity

The cancer immune cycle comprises 7 principal steps, including the release and presentation of tumor antigens, the priming and activation of effector immune cells, the

trafficking and infiltration of immune cells into the tumor, and ultimately, the elimination of cancer cells. Emerging evidence indicates that the circadian clock plays a gating role across many aspects of the cancer immune cycle [147].

Circadian gating of the cancer immune cycle

Core clock components (BMAL1, CLOCK, PER, CRY, REV-ERB, ROR, etc.) interact with tumor immunity through both innate and adaptive immune pathways. At the level of innate immunity, the clock rhythmically regulates pattern recognition and inflammatory amplification [e.g., via the TLR-IRF/NF-κB axis and the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING)-type I interferon pathway], as well as chemotactic and adhesion signals [C-X-C motif chemokine ligand (*CXCL*)9/10-C-X-C motif chemokine receptor (*CXCR*)3, *CXCL12-CXCR4*, and intercellular adhesion molecule 1 (*ICAM1*)/vascular cell adhesion molecule 1 (*VCAM1*)], thereby influencing dendritic cell (DC) maturation, antigen presentation, and effector cell recruitment [148-153]. Within adaptive immunity, the clock imposes "temporal gating" on lymphocyte differentiation and effector function (e.g., via retinoic acid-related orphan receptor gamma t (RORγt)/T helper 17 cells (Th17), the NFIL3/interleukin (IL)-12-IFN axis, and regulatory T cells (Treg)/forkhead box P3 (FOXP3) and, by coupling to the cell cycle, the DNA damage response, and metabolic pathways, orchestrates immune surveillance, elimination, and homeostasis within the tumor microenvironment (TME) [154-158]. Furthermore, immune checkpoints [programmed cell death protein 1 (PD-1)/ programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3)] and antigen presentation modules [major histocompatibility complex (MHC)/transporter associated with antigen processing (TAP)/beta-2 microglobulin (B2M)] display circadian expression and functional plasticity that are regulated by both clock and metabolic stress nodes (Myc, p53, HIF, AMPK-mTOR, and NAD^+-SIRT1), thereby modulating immune escape thresholds and immunotherapy responsiveness [159-161].

Central and peripheral coordination of immune rhythms

Clock genes operate through a hierarchical regulatory system, integrating central nervous system cues, peripheral immune organs, and the local tumor microenvironment to generate temporally and spatially organized tumor immune surveillance [162,163].

At the systemic level, circadian coordination is imposed by the SCN, which functions as the master pacemaker synchronizing immune rhythms through neuroendocrine and autonomic pathways. The SCN controls cortisol/glucocorticoid oscillations via the hypothalamus-pituitary-adrenal (HPA) axis, affecting lymphocyte mobilization, homing, and effector potential. As a result, exposure to infection or tumor antigens at different times is associated with "different weights" [148,164-170]. Light signals regulate pineal melatonin secretion via the retina-hypothalamus pathway. Melatonin reduces proinflammatory thresholds and influences antigen presentation via metallothionein (MT)1/MT2 and nuclear receptors [167,171,172]. Host cortisol slopes also correlate with immunotherapy outcomes [148,164,169,170].

In addition to central coordination, immune cells themselves harbor autonomous circadian oscillators. Most immune cell types [T cells, B cells, dendritic cells (DCs), macrophages, neutrophils, etc.] express *BMAL1*, *CLOCK*, *PER*, *CRY*, *REV-ERBs*, and *RORs*, enabling the temporally regulated transcription of key immune genes. For instance, BMAL1/PER2 in T cells directly or indirectly modulates programmed cell death 1 (*Pdcd1*, also known as *CD274*)and exhaustion-associated networks, generating phase-specific "functional windows," whereas REV-ERBα in macrophages, via the nuclear receptor corepressor (NCOR)/histone deacetylase 3 (HDAC3) complex, restricts proinflammatory transcription to prevent tissue damage [149,154,155,160,166,173-175].

Circadian regulation also operates within the tumor microenvironment, where endothelial, stromal, and immune components collectively shape spatiotemporal immune dynamics Endothelial cells rhythmically express adhesion molecules such as ICAM-1 and VCAM-1, as well as chemokines including C-C motif chemokine ligand 21 (CCL21), coordinating with lymphatic valve activity to regulate immune cell trafficking, tissue entry, and drainage in a time-dependent manner [154,156,165,166,176,177] (Fig. 5). Oscillations in the CXCL12-CXCR4 and CXCL10-CXCR3 axes further influence the positioning, survival, and effector function of $CD8^+$ T cells, NK cells, and dendritic cells [178-182]. Innate immune pathways are also temporally gated. Complement signaling through complement component 3a (C3a) and complement component 5a (C5a) receptors intersects with circadian control to regulate inflammation, chemotaxis, and phagocytosis, thereby influencing the clearance of immunogenic cell death and the efficiency of antigen cross-presentation [183,184]. In parallel, antigen processing and presentation are subject to clock regulation,

with rhythmic expression of MHC class I and II molecules, TAP transporters, and proteasomal components setting time-dependent thresholds for T-cell activation [150,166,185-188]. Finally, metabolic and microbial cues integrate into this circadian immune network. Metabolic hubs, including *BMAL1*, *HIF-1a*, *PKM2*, and *SIRT1*, integrate lactate and lipid flux to reshape immunosuppressive and effector functions [149,151,171,185], whereas the gut microbiota and its metabolites (e.g., butyrate) establish a cross-organ "gut-immune axis" that coordinates peripheral clocks and immune rhythms [152,157,158,175,184].

Myeloid cell rhythms in tumor immunity

To understand immune cell function during the day-night

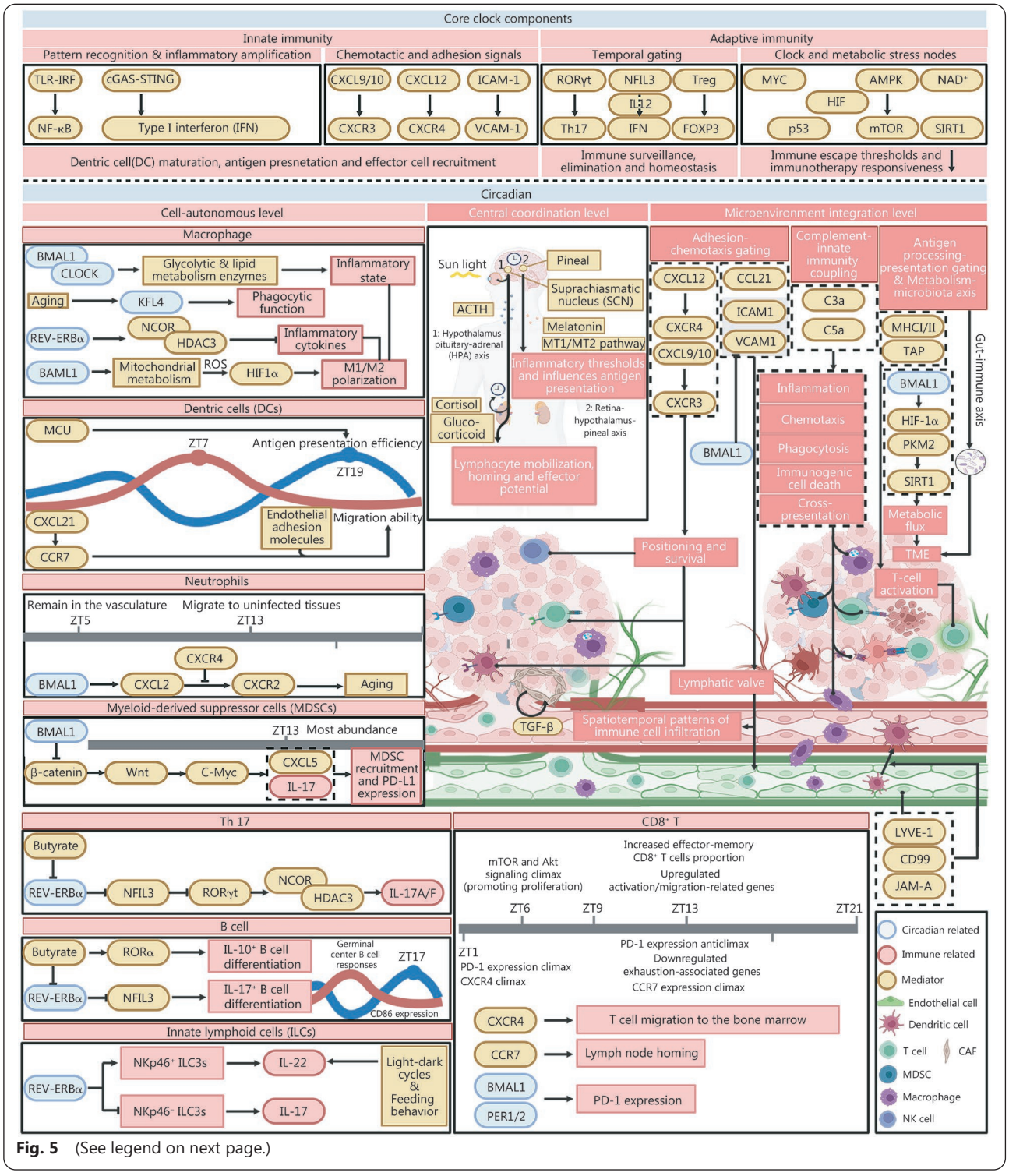

Fig. 5 (See legend on next page.)

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Fig. 5 Circadian clock and immunity.

This schematic summarizes how the circadian clock shapes antitumor immunity through coordinated regulation at the cell-autonomous, central, and microenvironmental levels. Core clock components rhythmically modulate innate and adaptive immune pathways, influencing pattern recognition, inflammatory amplification, chemotaxis, adhesion, antigen presentation, and lymphocyte differentiation. Central pacemaker signals from the SCN synchronize systemic immune rhythms via neuroendocrine and autonomic outputs, whereas local clocks within immune cells regulate activation, migration, and effector functions. In the tumor microenvironment, the rhythmic expression of adhesion molecules, chemokines, complement pathways, and antigen-processing machinery governs the timing of immune cell infiltration, positioning, and cytotoxic responses. Together, these multilayered interactions generate spatial and temporal immune landscapes that influence tumor surveillance, immune escape thresholds, and responsiveness to immunotherapy. ACTH. Adrenocorticotropic hormone; AMPK. AMP-activated protein kinase; BMAL1. Brain and muscle ARNT-like 1; C3a. Complement component 3a; C5a. Complement component 5a; CAF. Cancer-associated fibroblast; CCL21. C-C motif chemokine ligand 21; CCR7. C-C chemokine receptor type 7; $CD8^+$ T cells. Cluster of differentiation 8 positive T cells; CD99. Cluster of differentiation 99; cGAS. Cyclic GMP-AMP synthase; CLOCK. Circadian locomotor output cycles kaput; CXCL. C-X-C motif chemokine ligand; CXCR. C-X-C chemokine receptor; FOXP3. Forkhead box P3; HDAC3. Histone deacetylase 3; HIF. Hypoxia inducible factor; ICAM-1. Intercellular adhesion molecule 1; IFN. Interferon; IL. Interleukin; IRF. Interferon regulatory factor; JAM-A. Junctional adhesion molecule A; KFL4. Kruppel-like factor 4; LYVE-1. Lymphatic vessel endothelial hyaluronan receptor 1; MCU. Mitochondrial calcium uniporter; MDSCs. Myeloid-derived suppressor cells; MHC. Major histocompatibility complex; mTOR. Mechanistic target of rapamycin; MYC. Myelocytomatosis oncogene; NAD. Nicotinamide adenine dinucleotide; NCOR. Nuclear receptor corepressor; NFIL3. Nuclear factor interleukin 3 regulated; NF-κB. Nuclear factor κB; NK. Natural killer; PD-1. Programmed cell death protein 1; PKM2. Pyruvate kinase M2; REV-ERBα. Nuclear receptor subfamily 1 group D member 1; RORγt. RAR-related orphan receptor gamma t; ROS. Reactive oxygen species; SCN. Suprachiasmatic nucleus; SIRT1. Sirtuin 1; STING. Stimulator of interferon genes; TAP. Transporter associated with antigen processing; TGF-β; Transforming growth factor-β; Th17. T helper 17; TLR. Toll-like receptor; TME. Tumor microenvironment; Treg. Regulatory T cells; VCAM-1. Vascular cell adhesion molecule 1; ZT. Zeitgeber time

cycle and the underlying molecular mechanisms, we next focus on how the circadian clock precisely controls the activation, migration, and effector functions of various immune cells, and examine how this rhythmic regulation may affect tumor immune responses and immunotherapy strategies.

Circadian regulation is particularly prominent within the myeloid compartment. Macrophages, dendritic cells, neutrophils, and myeloid-derived suppressor cells all display pronounced daily oscillations in polarization state, migratory behavior, and secretory output. In macrophages, M1/M2 polarization is regulated by circadian clock genes. Loss of *BMAL1* disrupts mitochondrial metabolism, increases ROS levels, stabilizes HIF-1α, and promotes glycolysis and pro-inflammatory cytokine production in macrophages [149]. REV-ERBα represses the expression of inflammatory cytokines such as IL-6 and tumor necrosis factor α (TNF-α) by recruiting the NCOR/HDAC3 complex, and its absence enhances M2 polarization [151,152]. This represents a coherent metabolic-inflammatory circuit. BMAL1 maintains mitochondrial integrity and dampens ROS levels. Its loss leads to metabolic dysfunction (increased glycolysis and mitochondrial ROS), which activates the ROS-HIF-1α axis. HIF-1α then acts as a transcriptional master switch, promoting genes for glycolysis (creating a feedforward loop) and pro-inflammatory cytokines (e.g., IL-1β and IL-6). Thus, the combined disruption of *BMAL1* and *REV-ERBα* rhythms dismantles a coupled metabolic-transcriptional barrier, leading to a constitutively pro-tumorigenic, metabolically dysregulated macrophage phenotype. Aging-associated loss of rhythmic *KLF4* expression abolishes oscillations in the expression of phagocytosis-related genes [glucosylceramidase beta (*GBA*) and ras-related protein rab-3d (*RAB3D*)], leading to disrupted daily phagocytic rhythms [153]. Metabolically, BMAL1/CLOCK regulates the expression of glycolytic enzymes (e.g., *PKM2* and *LDHA*) and lipid metabolism enzymes [e.g., ATP citrate lyase (*ACLY*)], thereby affecting the inflammatory state of macrophages [151]. Dendritic cells likewise exhibit robust circadian regulation that links migration, metabolism, and antigen presentation. The migration and antigen-presenting functions of DCs exhibit clear day-night rhythms. Their migration to draining lymph nodes peaks during the day [zeitgeber time (ZT)7], depending on the CCL21-CCR7 axis and the rhythmic expression of endothelial adhesion molecules [lymphatic vessel endothelial hyaluronan receptor 1 (*LYVE1*), cluster of differentiation 99 (*CD99*), and junctional adhesion molecule A (*JAM-A*)] [176,177]. BMAL1 directly regulates the expression of the costimulatory molecule CD80, affecting T-cell activation [150]. The antigen-processing capacity of DCs is controlled by the rhythmic activity of the mitochondrial calcium uniporter (MCU), with antigen presentation efficiency highest at night (ZT19) [166]. The MCU rhythm provides a direct link between mitochondrial physiology and immune function. High MCU activity at

night increases mitochondrial Ca^{2+} uptake, increasing the oxidative metabolism (TCA cycle and OXPHOS) needed for the energy-intensive process of antigen processing and presentation. This creates a temporal window of enhanced immunogenicity [189,190]. Conversely, low MCU activity during the day limits this capacity. This mechanism ensures that antigen presentation is coupled to the cell's metabolic capacity, which is itself under circadian control, preventing inefficient immune activation during the metabolically suboptimal phase [178,191,192]. Neutrophils are subject to circadian control at the level of lifespan programming and tissue distribution. The "aging" program of neutrophils is regulated by the BMAL1-CXCL2-CXCR2 axis. CXCR2 promotes the aging phenotype (CD62L downregulation and CXCR4 upregulation), whereas CXCR4 inhibits aging by antagonizing CXCR2 signaling [179]. Neutrophils preferentially migrate to uninfected tissues at night (ZT13), enhancing anti-infection capacity, but remain in the vasculature during the day (ZT5), which may promote thromboinflammatory events [179,193]. The rhythmic infiltration of neutrophils also affects local transcriptional programs; for example, 26.7% of rhythmic gene expression in the lung depends on neutrophil infiltration [180]. Circadian control also extends to immunosuppressive myeloid populations. The accumulation of myeloid-derived suppressor cells (MDSCs) shows a circadian rhythm, peaking in the early active phase (ZT16) [162]. *BMAL1* loss activates the Wnt/β-catenin pathway, leading to c-Myc-mediated upregulation of the expression of factors such as *CXCL5* and interleukin 17A (*IL17A*), which promote MDSC recruitment and PD-L1 expression [162]. MDSCs suppress T-cell function through ROS production and *ARG2* expression, and their rhythmic accumulation directly affects the efficacy of immune checkpoint inhibitors [162].

Lymphoid cell rhythms in tumor immunity

Adaptive immune responses are similarly shaped by intrinsic circadian clocks [155-158]. In T cells, clock components regulate differentiation, metabolism, and exhaustion states. The differentiation of Th17 cells is intricately regulated by circadian clock genes at multiple levels. REV-ERBα competitively binds to RORγt target gene promoters and recruits the NCOR/HDAC3 repressor complex, directly suppressing *IL17A*/interleukin 17F (*IL17F*) transcription [152,155]. NFIL3, a key transcriptional repressor, can also bind directly to the GTTACTTAA sequence within the *RORγt* promoter to inhibit its expression [152]. Mechanistically, REV-ERBα expression exhibits diurnal oscillation, increasing during the active phase at night to indirectly promote *RORγt* expression by inhibiting NFIL3, and decreasing during the day, thereby establishing the rhythmic control of Th17 differentiation [152]. The circadian clock further modulates Th17 differentiation by shaping the cytokine milieu. IL-23 receptor expression is rhythmic, influencing the responsiveness of group 3 innate lymphoid cells (ILC3s) and Th17 cells to IL-23 [188]. Microbial metabolites such as butyrate downregulate *NR1D1* (*REV-ERBα*), alleviating NFIL3-mediated repression and reducing $IL\text{-}17^+$ B-cell differentiation [158]. In psoriasis models, local application of the REV-ERB agonist SR9009 significantly ameliorated IL-17-mediated skin inflammation [155]. $CD8^+$ T-cell cytotoxicity is also under direct circadian control. *PDCD1* expression in T cells oscillates, peaking in the early morning (ZT1) and reaching its lowest level in the evening (ZT13), a rhythm dependent on intrinsic *BMAL1* and *PER1/2* genes [154]. Single-cell RNA sequencing revealed that in the evening, the proportion of effector-memory $CD8^+$ T-cell increases, the expression of exhaustion-associated genes [thymocyte selection-associated high mobility group box protein (*Tox*) and lymphocyte activation gene-3 (*Lag3*)] decreases, and the expression of activation/migration-related genes [granzyme B (*Gzmb*) and *Ccl7*] increases [154]. Similarly, T-cell metabolism follows a circadian rhythm. mTOR and AKT signaling are most active at ZT6, promoting glycolysis and oxidative phosphorylation to increase T-cell proliferation [157]. BMAL1 regulates mitochondrial protein acetylation, influencing T-cell metabolic status [157]. Additionally, TCR signaling genes [zeta-chain-associated protein kinase 70 (*ZAP70*) and phosphoinositide 3-kinase (*PI3K*)] are highly expressed at specific time points, indicating that the circadian clock enhances T-cell activation by modulating TCR signaling [166]. T-cell infiltration into tumors clearly exhibits diurnal pattern. In melanoma models, $CD8^+$ T-cell infiltration is significantly greater during the mid-rest phase (ZT9) than during the active phase (ZT21) [166]. This rhythm depends on the circadian function of tumor vascular endothelial cells, endothelial-specific *BMAL1* deletion abolishes rhythmic *ICAM1* expression and eliminates the T-cell infiltration rhythm [154]. The intrinsic clock in tumor endothelial cells drives the rhythmic expression of adhesion molecules (ICAM1). This creates a time-gated "door" in the vasculature. $CD8^+$ T cells, whose chemokine receptors (e.g., CXCR3) may also be rhythmic, can only efficiently adhere and extravasate when this endothelial "door" is open (high ICAM-1 expression). Therefore, the local stromal clock of tumor, not just that of the immune cell, dictates the timing of immune cell entry,

representing a critical microenvironmental checkpoint for chrono-immunotherapy. Lymphocyte migration is further regulated by the rhythmic expression of chemokine receptors. *CCR7* expression peaks at ZT13 in T cells, controlling lymph node homing [156], whereas *CXCR4* expression oscillates under glucocorticoid regulation, with a morning peak promoting T-cell migration to the bone marrow [170]. Collectively, these findings provide a mechanistic basis for chrono-immunotherapy, highlighting the importance of timing in optimizing immune responses. Circadian regulation also extends to humoral immunity, where clock components govern B-cell differentiation, germinal center dynamics, and antibody production. B-cell differentiation is indirectly regulated by circadian clock genes. Butyrate promotes the differentiation of IL-10$^+$ B10 cells by upregulating *RORα*, and reduces IL-17$^+$ B cells by downregulating *NR1D1*, which relieves NFIL3-mediated suppression [158]. After vaccination, the response of follicular helper T (Tfh) cells and germinal center B cells is stronger at night (ZT17), resulting in higher antibody titers[178]. CD86 expression on B-cell surfaces shows rhythmic oscillation, affecting antigen presentation efficiency [166]. In parallel, innate lymphoid cells (ILCs) exhibit intrinsic circadian programs that rhythmically tune their effector functions, tissue residency, and cytokine output. ILC3s exhibit circadian expression of core clock genes, and their IL-22 secretion is modulated by light-dark cycles and feeding behavior [181]. Deletion of *REV-ERBα* results in a reduction in NKp46$^+$ ILC3 numbers and impaired mitochondrial function but increases IL-17 secretion from NKp46$^-$ ILC3s [194]. The circadian clock regulates Th17-cell differentiation via the NFIL3-RORγt axis, with REV-ERBα suppressing *NFIL3* expression and thereby indirectly promoting RORγt activity [152]. Reversing the light cycle can completely shift the IL-17A secretion rhythm of ILCs [195].

Stromal and vascular clocks in the tumor microenvironment

Beyond immune cell-intrinsic programs, circadian regulation is also embedded within the stromal and vascular architecture of the tumor microenvironment, where endothelial and mesenchymal components impose temporal constraints on immune cell trafficking, positioning, and function. Within this compartment, vascular and lymphatic endothelial cells play a central role in shaping spatiotemporal immune dynamics by rhythmically regulating adhesion, transmigration, and lymphatic drainage. Tumor vascular endothelial cells regulate the spatiotemporal patterns of immune cell infiltration through the rhythmic expression of adhesion molecules such as ICAM-1 and VCAM-1 [165]. BMAL1 directly binds to E-box elements in the *Icam1* promoter, and endothelial-specific *Bmal1* knockout abolishes the circadian rhythm of lymphocyte infiltration [154]. Lymphatic endothelial cells rhythmically express *LYVE1*, *CD99*, and *JAM-A*, which cooperate with CCL21 to regulate dendritic cell migration [177]. Mesenchymal stromal cells, particularly cancer-associated fibroblasts (CAFs), further contribute to circadian organization of the tumor microenvironment by rhythmically remodeling the extracellular matrix and mechanical landscape. Under the control of circadian and metabolic cues, CAFs display time-dependent secretion of TGF-β and dynamic regulation of matrix stiffness, creating a "physical circadian barrier" that modulates immune cell motility, tissue penetration, and local antigen accessibility [171,196].

Chrono-immunotherapy and clinical translation

In summary, these cell-specific mechanisms highlight that the circadian clock finely regulates the functional states of various immune cells through multilayered signaling pathways, thereby influencing both the strength and timing of immune responses [163,197,198]. Accumulating mechanistic insights into circadian control of immunity have, in turn, inspired a range of translational strategies with direct clinical relevance. One prominent avenue is chrono-immunotherapy, in which the timing of immune interventions is aligned with endogenous immune rhythms to maximize efficacy. The timing of immune checkpoint inhibitor administration significantly affects therapeutic outcomes. Administering anti-PD-1 therapy in the evening (ZT13 in Mice/Afternoon in humans) enhances CD8$^+$ T-cell activation and cytokine secretion [154]. Clinical data have shown that non-small cell lung cancer (NSCLC) patients receiving nivolumab in the afternoon exhibit markedly longer median progression-free survival than those receiving morning dosing (16.5 vs. 9.8 months) [154,160]. Furthermore, combined anti-CTLA4 and anti-RORα agonist treatment has synergistic antitumor effects [159]. Cellular therapies also benefit from timing optimization; chimeric antigen receptor (CAR)-T cells infused in the evening exhibit a 12.5-fold increase in tumor infiltration and a 50% increase in antitumor efficacy [154]. Vaccine administration time influences immune memory formation, with morning influenza vaccination eliciting superior antibody responses [166]. In addition to treatment timing, circadian biology has opened new opportunities for clock-targeted drug combinations. The REV-ERB

agonist SR9009 suppresses IL-17 secretion and ameliorates psoriasis-like dermatitis [155]. The RORγ agonist LYC-55716 activates *BMAL1* transcription and reduces *PDCD1* expression and is currently under clinical investigation (NCT03396497) [161]. Melatonin modulates immune homeostasis through both membrane receptors (MT1/MT2) and nuclear receptors (RORα/RORγ), with short-term high-dose administration inhibiting the TLR3-p38-JNK-NF-κB pathway [172]. Epigenetic modulators, such as HDAC inhibitors, show synergistic potential when combined with chronotherapeutic approaches [159,199,200]. Advances in circadian immunology have also facilitated the development of predictive models and personalized therapeutic approaches. Circadian gene signatures have emerged as important biomarkers for predicting immunotherapy responses. Patients with low CRS scores exhibit high tumor mutational burdens (TMBs), enhanced immune infiltration, and better responses to immune checkpoint inhibitors (ICIs) [185]. The RORA-HDAC3-DDX3X complex score can predict PD-L1 expression levels and therapeutic responsiveness [159]. Machine learning models based on clock gene features can predict sample collection timing, with patients exhibiting high "evening gene signatures" responding better to ICIs [154]. Additionally, host rhythm markers such as rest-activity rhythms (I<O index) and cortisol slopes can serve as predictors of therapeutic outcomes [201]. The efficacy of chrono-immunotherapy is a direct validation of the underlying causal mechanisms. For example, evening anti-PD-1 administration works because it coincides with the intrinsic trough of PD-1 expression on T cells and the peak of their effector potential, a state governed by the BMAL1/PER2 axis [202,203]. Similarly, an evening CAR-T-cell infusion aligns with the window of maximal endothelial permeability (high ICAM-1 expression) and chemokine-driven recruitment [156]. These are not merely empirical observations but also applications of a mechanistic understanding [154,156,202,203]. In the future, as our understanding of the circadian-immune crosstalk network expands, future directions in tumor immunotherapy will include developing noninvasive rhythm-monitoring technologies, establishing biomarkers for immune rhyth-micity, exploring the synergistic effects of metabolic inter-ventions with chronotherapies, and implementing precision immunotherapies based on circadian profiling. Collectively, these strategies promise to chart a new blueprint for cancer treatment.

Circadian clock and hypoxia signaling

Under conditions of cellular hypoxia, multiple hypoxia-responsive pathways are activated, among which the HIF-mediated pathway is the most prominent. HIF is stabilized under low-oxygen conditions and subsequently regulates the expression of a wide array of target genes involved in angiogenesis, glycolysis, and cell proliferation, thereby enabling cellular adaptation to hypoxic stress [204,205]. In tumors, rapid cellular proliferation coupled with insufficient vascularization frequently results in localized hypoxia (ischemia). HIF activation under these hypoxic conditions not only orchestrates metabolic adaptation but also modulates the expression of circadian clock genes in tumor cells, thereby altering cellular circadian rhythms [206,207]. Conversely, disruption of circadian rhythms can reprogram hypoxia responses, influencing tumor progression and therapeutic outcomes (Fig. 6).

Transcriptional coupling between the circadian clock and HIF pathway

The interaction between circadian clocks and hypoxia signaling pathways plays a pivotal role in tumor initiation and progression, with its molecular basis primarily rooted in the structural homology and functional crosstalk of the core transcription factors from these two pathways. BMAL1 and CLOCK, key activators of the circadian clock, and the hypoxia-inducible factors HIF-1α and HIF-2α belong to the basic helix-loop-helix Per-Arnt-Sim (bHLH-PAS) protein family, providing a structural foundation for the "co-domain" physical interaction between the clock and hypoxia pathways [206,208-213]. Multiple studies have indicated that BMAL1 forms transcriptionally active heterodimers with HIF-2α, while its physical interaction with HIF-1α is markedly enhanced under hypoxia [214-217]. Moreover, CLOCK/BMAL1 directly occupies the *HIF1A* promoter to upregulate its expression, whereas NPAS2/BMAL1 similarly binds and drives HIF-1α-mediated glycolytic programs [218,219]. In glioma stem cells (GSCs), CLOCK-BMAL1 transcriptionally regulates olfactomedin-like 3 (*OLFML3*), indirectly activating HIF-1α, which in turn promotes periostin (*POSTN*) expression and angiogenesis [208]. HIF-1α also reciprocally binds to the *PER2* promoter to increase its circadian amplitude and cooperates with BMAL1/CLOCK at coupled hypoxia response element (HRE)/E-box sites [217,220]. Additionally, PER2 directly interacts with HIF-1α via its N-terminal PAS domain, strengthening HIF-1α binding to HRE; in Caki-2 renal carcinoma cells, this interaction significantly amplifies PER2 transcriptional oscillation, a process dependent on the formation of a PER2-HIF-1α-ARNT ternary complex [216,221]. This PER2- HIF-

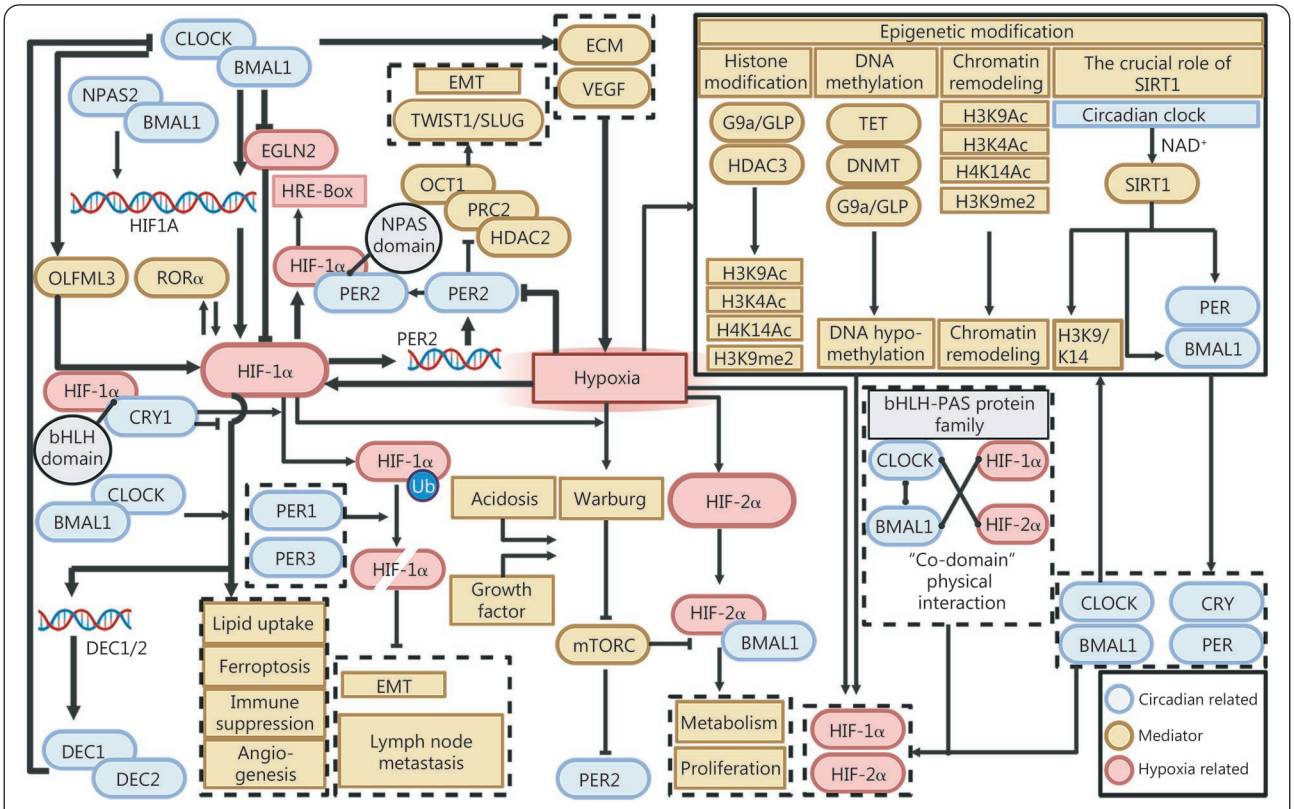

Fig. 6 Circadian clock and hypoxia signaling.

This schematic illustrates the multilayered interactions between circadian timing mechanisms and hypoxia-responsive pathways in tumor cells. Under low oxygen conditions, hypoxia signaling stabilizes key transcriptional regulators that reprogram metabolic, inflammatory, and microenvironmental processes, while simultaneously reshaping circadian oscillations. Conversely, core clock components modulate hypoxia responses through transcriptional feedback, protein-protein interactions, and post-translational regulation, forming reciprocal loops that influence metabolic adaptation, acidosis, angiogenic remodeling, epithelial-mesenchymal transition, and immune suppression. The diagram highlights how this bidirectional network integrates transcriptional, metabolic, and epigenetic cues to coordinate cellular adaptation to hypoxic stress and drive tumor progression. BMAL1. Brain and muscle ARNT-like 1; CLOCK. Circadian locomotor output cycles kaput; CRY. Cryptochrome; DEC. Differentiated embryo chondrocyte expressed gene; DNMT. DNA methyltransferase; ECM. Extracellular matrix; EGLN2. Egl-9 family hypoxia inducible factor 2; EMT. Epithelial-mesenchymal transition; G9a. Euchromatic histone lysine N-methyltransferase 2; GLP. G9a-like protein; H3K4ac. Histone H3 lysine 4 acetylation; H3K9ac. Histone H3 lysine 9 acetylation; H3K9Me2. Histone H3 lysine 9 dimethylation; H4K14ac. Histone H4 lysine 14 acetylation; HDAC. Histone deacetylase; HIF-1α. Hypoxia inducible factor-1α; HIF-2α. Hypoxia inducible factor-2α; HRE. Hypoxia response element; NAD Nicotinamide adenine dinucleotide; NPAS2. Neuronal PAS domain protein 2; OCT1. Octamer-binding transcription factor 1; OLFML3. Olfactomedin like 3; PAS. Per-ARNT-Sim; PER. Period; PRC2. Polycomb repressive complex 2; RORα. Retinoic acid receptor-related orphan receptor alpha; SIRT. Sirtuin; SLUG. Snail family transcriptional repressor 2; TET. Ten-eleven translocation methylcytosine dioxygenase; TWIST. Twist family bHLH transcription factor 1; VEGF. Vascular endothelial growth factor

1α interaction exemplifies a coherent feedforward loop that amplifies both pathways. Hypoxia stabilizes HIF-1α, which then binds and stabilizes the PER2 protein or enhances its transcription. The increased expression of PER2, in turn, strengthens HIF-1α binding to DNA, further potentiating the hypoxic response. This creates a self-reinforcing cycle that can lock cells into a high-HIF/high-PER2 state, promoting traits such as angiogenesis and glycolysis. Disruption of this precise coupling (e.g., *PER2* loss) would not merely dampen oscillations but could skew the hypoxic response, potentially explaining the context-specific pro- or anti-tumor effects of PER2. In contrast, PER1 and PER3 act as brakes on hypoxia-driven transcription by promoting HIF-1α ubiquitination and degradation, thereby modulating protein stability [210,221-224]. CRY1 exerts negative feedback by binding the bHLH domain of HIF-1α to inhibit its transcriptional activity and facilitate HIF-1α degradation via the E3 ubiquitin ligase FBXL3 [225-227]. DEC1 and DEC2 function as nodal cross-talk regulators and are transcriptionally activated by HIF-1α through HRE binding while concurrently repressing BMAL1/CLOCK E-box activity, increasing the complexity of the regulatory network [223,228,229]. These mechanisms are broadly observed across multiple tumor types, including gliomas, renal cell

carcinoma, hepatocellular carcinoma, and oral squamous cell carcinoma, highlighting the direct transcriptional coupling between the circadian clock and hypoxia signaling. Collectively, these molecular couplings extend beyond individual protein-protein interactions, forming a dynamic network through co-occupancy, dimerization, negative feedback, and cross-recruitment. Such molecular-level interactions establish a foundation for subsequent metabolic and epigenetic regulatory processes.

Metabolic and microenvironmental integration of circadian-hypoxia crosstalk

Beyond transcriptional regulation, the crosstalk between the circadian clock and hypoxia signaling profoundly influences cellular metabolism, oxidative stress, pH homeostasis, and the immune microenvironment, collectively driving tumor malignancy [219,220,224,230-235]. The circadian clock modulates NAD^+ levels through the rhythmic expression of NAMPT, thereby regulating SIRT1 deacetylase activity and subsequently affecting HIF-1α stability and function, establishing a metabolic-epigenetic positive feedback loop between NAD^+/SIRT1 and HIF/CLOCK [231]. Hypoxia-induced Warburg metabolism leads to lactate accumulation and microenvironment acidification (pH=6.3–6.6), which disrupts clock oscillations by inhibiting the mTORC1 pathway. Acidosis causes lysosomal dispersion from the perinuclear region to the cell periphery, spatially segregating mTOR from RHEB and suppressing protein translation as well as core clock protein expression (e.g., BMAL1and PER2) [220]. In gliomas, the CLOCK-BMAL1-OLFML3-HIF-1α-LGMN axis promotes microglial infiltration and polarization toward an M2 immunosuppressive phenotype, thereby inhibiting $CD8^+$ T-cell activity; clinical samples show a positive correlation between CLOCK, HIF-1α, and CD206 (an immunosuppressive marker) expression [219]. This axis delineates a sequential signaling cascade from the intrinsic clock of the tumor cell to immune microenvironment reprogramming, which provides a mechanistic explanation for how circadian disruption in tumor cells can have non-cell-autonomous effects, systemically reshaping the tumor immune landscape to favor progression. In clear cell renal cell carcinoma (ccRCC), BMAL1-HIF-2α heterodimers regulate metabolic and proliferative gene networks, resulting in high sensitivity to the HIF-2α antagonist PT2399, with drug efficacy showing diurnal variation (most effective at ZT0) [230]. Additionally, PER3 mediates HIF-1α degradation via the ubiquitin-proteasome pathway, suppressing epithelial-mesenchymal transition (EMT) and lymph node metastasis [224], whereas hypoxia-induced PER2 degradation in breast cancer relieves octamer-binding transcription factor 1 (OCT1)-polycomb repressive complex 2 (PRC2)-HDAC2-mediated transcriptional repression, promoting twist family bHLH transcription factor 1 (*TWIST1*)/snail family transcriptional repressor 2 (*SLUG*) expression and EMT progression [232]. RORα, as a nuclear receptor, engages in bidirectional regulation with HIF-1α, highlighting the potential involvement of nuclear hormone signaling in clock-hypoxia interactions [233]. CLOCK further increase the expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and extracellular matrix (ECM) proteins (e.g., OLFML3 and POSTN), directly shaping the hypoxic microenvironment and immunosuppressive niche [234,235]. These metabolic and microenvironmental interactions not only increase tumor adaptability and invasiveness but also facilitate immune evasion and therapeutic resistance.

Hub regulators in circadian-hypoxia crosstalk

Key hub molecules within the circadian clock-hypoxia signaling network include DEC1/2, PER2, CRY1, BMAL1, mTORC1, and OLFML3, which play central roles depending on tumor type and physiological context. DEC1/2 is transcriptionally activated by HIF-1α and in turn represses circadian and lipid metabolism genes such as *SREBP-1c*, thereby modulating metabolic adaptation in conditions such as alcoholic liver disease and oral cancer [228,236]. *PER2* and *CRY1* exert opposing regulatory effects on HIF activity, with *PER2* acting as a positive modulator and *CRY1* acting as a negative regulator; aberrant expression of either gene disrupts circadian homeostasis and facilitates tumor progression [221,226,227]. BMAL1 stabilizes HIF-1α by transcriptionally repressing prolyl hydroxylase domain 1 (*PHD1*, also known as *EGLN2*), promoting lipid uptake and storage while inhibiting ferroptosis [225]. mTORC1 integrates acidosis and growth factor signaling [e.g., the fibroblast growth factor (FGF)-10-Spry2 axis] to amplify HIF-1α activity during lung development and tumorigenesis [233]. Pathologically, these interactions are closely associated with tumor progression, metastasis, and a poor prognosis in multiple cancers, including glioblastoma, renal cell carcinoma, breast cancer, and oral squamous cell carcinoma. Chronotherapy strategies targeting these hub nodes have shown substantial promise. For instance, timing PT2399 administration according to the BMAL1-HIF-2α oscillation cycle in renal cancer enhances therapeutic efficacy; combining the demethylating agent DAC with the

HIF inhibitor LW6 restores *PER3* expression and suppresses metastasis [224]; and REV-ERB agonist SR9009-mediated BMAL1 inhibition increases glioma radiosensitivity [212]. Future studies should aim to elucidate the real-time dynamics of these pathways within the tumor microenvironment and develop chronopharmacological interventions targeting critical nodes, including: 1) the modulation or disruption of BMAL1/CLOCK/NPAS2-HIF heterodimerization; 2) fine-tuning the PER/CRY regulation of HIF stability and transcriptional complexes; 3) targeting the HIF-DEC axis as a hypoxia-driven circadian inhibitory node; 4) exploiting metabolic-epigenetic interventions via the NAD^+/SIRT1 and ROS-PHD-HIF axes; 5) temporally coordinated targeting of angiogenic factors and ECM remodeling pathways; and 6) identifying circadian-sensitive windows within mTOR and nuclear receptor signaling, such as RORα.

Epigenetic regulation of circadian-hypoxia interactions

In addition, the crosstalk between hypoxia and the circadian clock may also be mediated through epigenetic regulation. Numerous studies have reported that hypoxic conditions reshape the epigenetic landscape, while alterations in the epigenetic environment in turn influence cellular responses to hypoxia [237-241]. Interestingly, the circadian clock is also subject to epigenetic regulation, suggesting that the interplay between hypoxia and the circadian system represents a multilayered and complex regulatory network [52,213,215]. Here, we highlight and discuss this underexplored area. Recent studies have shown that HIF-1α can recruit the histone deacetylase HDAC3 and methyltransferases such as euchromatic histone lysine methyltransferase (EHMT)2, also known as G9a)/EHMT1 [also known as G9a-like protein (GLP)] to regulate histone modifications [e.g., histone H3 lysine 9 dimethylation (H3K9me2) and histone H3 lysine 4 acetylation (H3K4ac)], thereby modulating chromatin accessibility and transcriptional activity [234,238,242]. Moreover, hypoxia inhibits ten-eleven translocation methylcytosine dioxygenase (*TET*) enzyme activity and alters DNA methyltransferase (*DNMT*) expression, leading to genome-wide DNA hypomethylation accompanied by localized hypermethylation, which further affects the expression of HIF pathway-related genes [237,243]. In contrast, core circadian components, such as the CLOCK-BMAL1 heterodimer, regulate the expression of circadian genes by binding E-box elements, and they themselves possess epigenetic regulatory functions. CLOCK exhibits histone acetyltransferase activity, acetylating H3K9 and H3K14 to promote chromatin accessibility [244-246]. The circadian clock also modulates cellular NAD^+ levels, which influence the deacetylase activity of SIRT1, thereby regulating HIF-α stability and transcriptional activity [244,245,247]. Moreover, loss of the clock gene *BMAL1* leads to decreased HIF-1α protein levels, impaired expression of glycolytic genes, and abnormal histone acetylation (e.g., elevated H3K9ac and H4K16ac levels), indicating that the circadian clock shapes hypoxic responses through coupled metabolic and epigenetic mechanisms [248]. Metabolites such as α-ketoglutarate (α-KG), acetyl-CoA, NAD^+, and S-adenosylmethionine (SAM) play central roles in this network, serving both as substrates or cofactors for epigenetic-modifying enzymes and as targets of circadian and hypoxia signaling [243,245,249]. For example, hypoxia-induced lactate accumulation promotes histone lactylation, whereas the circadian clock modulates global acetylation states via the NAMPT-NAD^+-SIRT1 pathway [243,245]. Such cross-regulation among metabolism, epigenetics, and the circadian system is of great importance in tumor microenvironment adaptation, immune evasion, and metabolic disorders [238,247,250]. Taken together, these findings indicate that hypoxia, epigenetics, and the circadian clock form a dynamic interactive network through HIF signaling, clock genes, metabolites, and epigenetic enzymes [such as *DNMTs*, *TETs*, and histone acetyltransferases (*HATs*)/*HDACs*], which orchestrate gene expression, cellular metabolism, and stress adaptation.

In summary, the circadian clock is involved in extensive and intricate interactions with multiple hallmark cancer pathways, including those involved in DNA damage repair, metabolism, immunity, and hypoxia. Notably, these pathways function in a highly interconnected and partially overlapping manner, collectively shaping the dynamic landscape of tumor biology. This systemic interdependence positions the circadian clock as a central hub influencing tumor initiation, tumor progression, and therapeutic response, thereby offering a holistic perspective on the spatiotemporal organization of cancer. Future investigations should aim to delineate the hierarchical interactions and key nodes within this network and apply these insights to develop circadian-based therapeutic strategies that increase the precision and efficacy of cancer treatment.

Role of core circadian genes in cancer

The dysregulation of circadian clock gene expression and disruption of circadian function are closely associated with tumorigenesis [46,251,252]. Numerous circadian genes exhibit differential expression across various types of cancers, and their expression levels are often significantly correlated

with patient prognosis [253-255].

CLOCK/BMAL1

The role of the CLOCK/BMAL1 complex in cancer is highly context-dependent, with its function shifting from tumor-suppressive to tumor-promoting depending on the cancer type, genetic background, and microenvironmental cues [256-258]. On the one hand, this complex acts as a tumor suppressor primarily by maintaining genomic stability, inducing cell cycle arrest and apoptosis, regulating metabolic homeostasis, and enhancing antitumor immunity [94,259-263]. For example, in cell-cycle and apoptosis regulation, BMAL1 is recruited to DDSB through ATM-mediated phosphorylation at Ser183, subsequently recruiting CLOCK to acetylate histone H4, thereby promoting homologous recombination repair in a transcription-independent manner. This mechanism enhances resistance to DNA damage-based therapy in adrenocortical carcinoma [94]. In nasopharyngeal carcinoma [259,260], melanoma [261], tongue squamous cell carcinoma [262], and osteosarcoma [263], BMAL1 induces G2/M arrest and apoptosis by directly repressing CDK5 transcription, activating the p53-p21 pathway and proapoptotic proteins Bcl-2-associated X protein (BAX)/B-cell lymphoma 2 (BCL-2), or recruiting EZH2 to repress the telomerase reverse transcriptase (*TERT*) promoter, thereby suppressing proliferation, migration, and EMT. Its proapoptotic effect in oral squamous cell carcinoma (OSCC) is dependent on autophagy, as ARNTL can increase autophagic activity to activate BAX and suppress BCL-2 expression, thereby reducing proliferation [264]. Moreover, BMAL1 deletion activates the Hippo/Yes-associated protein (YAP) pathway, increasing tumor stem cell self-renewal and disrupting both autonomous and systemic circadian signaling, ultimately promoting tumorigenesis [265]. In tumors with high piwi-like RNA-mediated gene silencing 1 (*PIWIL1*) expression, PIWIL1 inhibits the glycogen synthase kinase 3 beta (GSK3β)-mediated degradation of CLOCK/BMAL1 and the formation of a transcriptional repressor complex, thereby repressing downstream circadian gene expression and disrupting circadian rhythms, which promotes tumor proliferation and invasion [266]. In terms of metabolic regulation, BMAL1 maintains circadian homeostasis through the PI3K-Akt pathway and negative feedback with PER2. Loss or dysfunction of *BMAL1* upregulates c-Myc and reprograms glucose and lipid metabolism, enhancing tumor proliferation and growth [134,267]. In neuroblastoma and ovarian cancer models, silencing *BMAL1* by MYCN proto-oncogene, BHLH transcription factor (MYCN) or DNA methylation disrupts rhythmicity and promotes lipid synthesis, whereas restoring *BMAL1* expression suppresses tumor growth, reduces lipid metabolic activity, and enhances chemosensitivity [268,269]. BMAL1 also plays a role in maintaining stromal homeostasis by transcriptionally activating plasminogen activator inhibitor 1 (*PAI1*). Loss of *BMAL1* promotes the transition toward myofibroblastic cancer-associated fibroblasts (myCAFs) and exacerbates fibrotic remodeling, thereby promoting metastasis [270]. The intestinal epithelial-specific deletion of *CLOCK* genes cooperates with adenomatous polyposis coli (*APC*) mutation through microbiota dysbiosis, metabolic disorders, and barrier disruption to accelerate colorectal cancer initiation and progression [271]. Collectively, the evidence highlights BMAL1 as a key regulator of tumor metabolism and microenvironmental homeostasis. CLOCK/BMAL1 also exerts antitumor effects by modulating the immune microenvironment. Its loss disrupts the central clock-gut microbiota-immune axis, leading to myeloid-derived suppressor cell accumulation, immunosuppression, and colorectal cancer metastasis [265,271]. In melanoma, endothelial BMAL1 regulates the circadian expression of *ICAM1*, while T-cell-intrinsic BMAL1 rhythmically suppresses *PDCD1* expression, together determining the optimal timing for immune checkpoint blockade efficacy [154]. Furthermore, BMAL1 promotes the infiltration of N1-type antitumor neutrophils and maintains the function of PD-L1^{+} regulatory B cells, further restraining tumor progression [272,273]. Taken together, CLOCK/BMAL1 integrates metabolic homeostasis, cell cycle/apoptosis regulation, and immune microenvironment control into a comprehensive tumor-suppressive network, while its loss or dysfunction promotes tumorigenesis at multiple levels.

On the other hand, CLOCK/BMAL1 exhibits tumor-promoting activity in several specific cancer types, including hepatocellular carcinoma, clear cell renal cell carcinoma, breast cancer, colorectal cancer, glioma, lung cancer, prostate cancer, melanoma, and sarcoma [112,230,274-281]. The corresponding mechanisms often deviate from those of classical circadian regulation and instead involve proliferative signaling activation, cytoskeletal remodeling, and invasive behavior, metabolic reprogramming, and modulation of the tumor microenvironment and therapeutic response [112,230,274-281].

At the level of cell-cycle regulation and proliferation, CLOCK/BMAL1 is broadly required for cell proliferation in HCC, where depletion of *BMAL1* or *CLOCK* induces apoptosis via G2/M arrest, p21 upregulation, and Wee1

downregulation, thereby inhibiting growth *in vitro* and *in vivo* [256]. In ccRCC, BMAL1 forms a functional heterodimer with HIF2α to co-occupy chromatin sites and drive oncogenic transcription, promoting tumor progression [230].

Beyond proliferation, CLOCK/BMAL1 contributes to tumor invasion and metastasis through coordinated regulation of EMT, vesicle trafficking, and cytoskeletal dynamics. In breast cancer, BMAL1 activates NF-κB signaling to upregulate matrix metalloproteinase 9 (*MMP9*) transcription and rhythmically activates EMT-related genes in luminal A-type breast cancer, thereby driving invasion, matrix degradation, and metastasis [274,275]. In colorectal cancer, CLOCK/BMAL1 promotes Rab27a-dependent exosome secretion and drives EMT through activation of the mitogen-activated protein kinase (MAPK) and β-catenin/c-Myc signaling axes [276,277]. Similarly, in liver cancer, the CLOCK/BMAL1 complex stabilizes and activates the ras homolog family member A (RHOA)-rho-associated protein kinase (ROCK)-cofilin (CFL) pathway, increasing F-actin polymerization and cytoskeletal remodeling to facilitate migration and invasion [278]. In fibrosarcoma and lung adenocarcinoma, BMAL1 enhances transcriptional activity through Ser42 dephosphorylation, leading to ubiquitin-like with PHD and RING finger domains 1 (*UHRF1*) upregu-lation and reinforcing aggressive tumor phenotypes [279].

A third major oncogenic dimension of CLOCK/BMAL1 lies in metabolic reprogramming, which not only sustains tumor growth but also reshapes the tumor microenvironment. In glioblastoma (GBM), it activates the LDHA-lactate axis to sustain the Warburg effect, and secreted lactate induces M2 macrophage polarization and angiogenesis, resulting in resistance to antiangiogenic therapy [280]. In lung cancer models, sleep deprivation drives persistent CLOCK/BMAL1 activation of acyl-CoA synthetase long chain family member 1 (*ACSL1*) transcription, whereas palmitoyl-CoA promotes CLOCK S-palmitoylation via zinc finger DHHC-type containing 5 (ZDHHC5), resulting in the formation of a positive feedback loop that sustains fatty acid oxidation and tumor stemness [281]. Furthermore, the hyperactivation of CLOCK/BMAL1 stabilizes PRPS1/2 through acetylation, enhancing nucleotide biosynthesis and accelerating tumor proliferation [112].

Finally, CLOCK/BMAL1 influences tumor progression by remodeling the immune microenvironment and shaping therapeutic resistance. In GBM, CLOCK/BMAL1 upregulates legumain (*LGMN*) and *POSTN* expression via the OLFML3-HIF-1α axis, driving immunosuppressive microglial infiltration and angiogenesis, respectively [208,219,257]. In prostate cancer, after enzalutamide treatment, BMAL1 binds along with forkhead box A1 (FOXA1) to new enhancer regions, activating cell-cycle and neuroendocrine-related gene expression and promoting drug resistance [282]. Similarly, in melanoma, *BMAL1* overexpression activates the myocardin-related transcription factor (MRTF)/serum response factor (SRF)-activator protein 1 (AP-1) axis, inducing $Sox9^{high}$ mesenchymal transition and an immunosuppressive microenvironment, thereby reducing anti-PD-1 efficacy [283].

Importantly, the functional consequences of *CLOCK/BMAL1* dysregulation are not uniform across cancers but are profoundly shaped by tissue-specific circadian architecture and lineage-defining transcriptional programs [208,219,257,269,270,277,282-284]. Different organs possess distinct circadian "baseline states" driven by metabolic, hormonal, and immune cues, which are selectively coopted or rewired during malignant transformation [266-268,274,275,282]. As a result, BMAL1 and CLOCK can act through fundamentally different downstream pathways depending on their tissue of origin. For example, *CLOCK/BMAL1* and metabolic nuclear receptors such as hepatocyte nuclear factor (*HNF*)-4α, peroxisome proliferator-activated receptor alpha (*PPARA*)/peroxisome proliferator-activated receptor delta (*PPARD*), nuclear receptor subfamily 1 group H member 4 (*NR1H4*), and nuclear receptor subfamily 1 group I member 3 (*NR1I3*) are strongly coupled in liver- and gut-derived tumors, and disruption of these liver-enriched circadian drivers enhances lipogenesis, bile acid dysregulation, and redox imbalance, uniquely accelerating hepatocarcinogenesis and colorectal tumor progression [284-289]. In contrast, in hormone-responsive tissues such as breast and prostate cancers, CLOCK/BMAL1 is integrated with estrogen receptor 1 (*ESR1*), androgen receptor (*AR*), and *FOXA1* enhancer networks, producing lineage-specific oscillatory programs that influence stemness, endocrine resistance, and metastatic tropism [282,290-294]. Similarly, neural-derived tumors such as gliomas display a distinct dependency on CLOCK/BMAL1-HIF or CLOCK/BMAL1-Myc axes, reflecting the intrinsic oxygen sensitivity and high basal metabolic rate of the brain [208,219,257,269,280]. These variations illustrate that circadian regulation in cancer is not dictated solely by core clock components but emerges from the integration between CLOCK/BMAL1 and tissue-specific transcriptional ecosystems [130,163,270,295]. Moreover, certain malignancies acquire "tissue-specific circadian drivers" that act as oncogenic amplifiers [53,252,296]. Collectively, current evidence underscores that circadian dysregulation in cancer is highly heterogeneous and shaped by tissue identity, metabolic lineage, and oncogenic background, warranting

cancer type-specific circadian therapeutic strategies.

CRYs/PERs

CRYs

The circadian clock genes *CRYs* and *PERs* also play dual roles in cancer, with their functions varying not only across different tumor types but also depending on signaling pathways [97,202,297-303]. CRYs are involved mainly in oncogenic processes through their deep involvement in DNA damage repair and cell cycle regulation [71,72,97,297,304,305]. For instance, in ovarian cancer, *CRY1* is activated by the VEGF/PI3K/Akt pathway, enhancing homologous recombination repair and conferring resistance to PARP inhibitors [71]. In contrast, colorectal cancer predominantly exploits elevated *CRY2* expression to dampen canonical DDR signaling outputs, reducing DNA damage-induced apoptosis and increasing resistance to agents such as oxaliplatin [304,305]. A similar functional outcome is observed in prostate cancer, where *CRY1* upregulation coordinates the expression of DNA repair and cell-cycle-associated genes, supporting sustained proliferation and malignant progression [72,297]. Other studies have reported that *CRY1* overexpression facilitates tumor progression, whereas *PER2* exerts tumor-suppressive effects by regulating the cell cycle and DDR; notably, an imbalance in their expression, particularly a reduced *PER2*/*CRY1* ratio, drives chronic lymphocytic leukemia (CLL) and osteosarcoma and predicts a poor prognosis [306,307]. Collectively, these mechanisms highlight that CRYs, via multiple DDR- and cell cycle-associated pathways, synergistically support tumor growth, invasion, and therapeutic resistance.

Interestingly, numerous studies have identified tumor-suppressive roles for CRYs, mediated primarily by metabolic restraint and transcriptional repression. In metabolic regulation, CRY2, together with the skp1-cullin-F-box protein complex (SCF) ubiquitin ligase complex subunit FBXL3, directly binds c-Myc to promote its ubiquitination and degradation, thereby suppressing glycolysis, proliferation, migration, and invasion [97,298,308]. Post-translational modifications and epigenetic regulation further contribute to CRY-mediated tumor suppression. For example, CRY2 inhibits NF-κB signaling and proliferation, whereas its acetylation diminishes tumor-suppressive activity and protein stability [299]. Moreover, *CRY2* is epigenetically silenced through distinct oncogenic transcriptional programs in a tumor-context-dependent manner. Forkhead box M1 (FOXM1)-DNMT3b and FOXK1-associated corepressor complexes repress *CRY2* expression in breast cancer [309,310], while ubiquitin C-terminal hydrolase L3 (UCHL3)-FOXM1-driven promoter methylation suppresses *CRY2* in esophageal squamous cell carcinoma [311]. This epigenetic silencing attenuates the tumor-suppressive functions of CRY2, thereby facilitating tumor progression. In addition, CRY2 can inhibit CLOCK-BMAL1 transcriptional activity, selectively suppressing glioblastoma stem cell proliferation [312].

PERs

PER family members are more consistently characterized as tumor suppressors across cancer types, acting through coordinated regulation of cell cycle progression, cellular metabolism, and antitumor immunity. Mechanistically, PER2 enhances DNA damage responses and cell cycle restraint by activating the p53-p21 axis, thereby suppressing proliferation in non-small cell lung cancer. Consistently, reduced *PER2* expression in pancreatic and gastric cancers is associated with accelerated cell cycle progression and increased invasive potential [134,300,313]. In parallel, PER1 and PER3 suppress tumor growth by inducing ATM/CHK2-dependent G2/M arrest and apoptosis [301,302,314,315], while in multiple myeloma, PER3 transcriptionally activates glyoxylate reductase 1 homolog (*GLYR1*) to form a GLYR1-PER3 axis that inhibits proliferation, migration, and invasion and promotes apoptosis [316].

Beyond cell cycle control, PER proteins exert broad metabolic regulatory effects that constrain tumor growth and therapy resistance. PER2 inhibits the SIRT2/G^{6}PD-PPP pathway, sensitizing glioblastoma to radiotherapy [317], and suppresses Akt/mTOR signaling by promoting PDK1 degradation, reversing multidrug resistance, and enhancing cisplatin sensitivity [96]. PER2 also cooperates with heat shock protein 70 (HSP70)/Akt to induce cuproptosis, thereby enhancing the antitumor effects of copper ionophores [202]. In parallel, PER1 and PER2 restrain tumorigenesis by suppressing PI3K/Akt signaling and glycolytic metabolism [318,319]. These metabolic functions also extend to MAPK signaling control, as PER2 inhibits JNK/AP-1 activity to limit thyroid cell proliferation, whereas PER3 negatively regulates the mitogen-activated protein kinase kinase (MEK)/ERK pathway to suppress proliferation, migration, and invasion [320,321].

PERs additionally shape the tumor immune microenvironment. PER2 suppresses IκB kinase (IKK)/NF-κB activity and downregulates *CD274* expression, thereby enhancing CD8$^+$ T-cell-mediated cytotoxicity [202]. The restoration of *PER3* similarly promotes antitumor immunity [322,323]. The tumor-suppressive capacity of PERs is further

modulated by epigenetic and post-transcriptional mechanisms, including *PER1* promoter hypermethylation or m^6A modification that reduces transcript stability [324,325], and repression of PER3 by the protein arginine methyltransferase (PRMT)6/PARP1/cullin 4B-RING E3 ligase (CRL4B) complex [326].

Despite their predominantly tumor-suppressive roles, PER proteins can adopt oncogenic or therapy-modulating functions when rewired by specific signaling contexts, treatment pressures, or circadian timing. Under hypoxic conditions, for example, HIF-1α-dependent induction of *PER2* in pituitary adenomas shifts its functional output toward activation of cell cycle-associated genes, thereby promoting tumor growth [327]. Therapeutic stress can similarly reshape PER activity. During cisplatin exposure, PER1 and PER3 exert opposing effects on cell fate, with PER1 favoring survival through antiapoptotic signaling, whereas PER3 enhances drug-induced apoptosis [328]. Metabolically, PER1 forms a complex with PPARγ in gastric cancer to drive circadian *HK2* expression, reinforcing rhythmic glycolysis and contributing to trastuzumab resistance [329]. From a chronological perspective, chronotherapeutic studies further demonstrate that the antitumor efficacy of cisplatin is enhanced when administration coincides with the trough of *PER2* expression [303]. Such functional reversals underscore the bidirectional nature of circadian genes in different genetic and microenvironmental contexts, opening new avenues for therapeutic targeting.

Notably, the roles of *CRYs* and *PERs* in cancer are not uniform but instead display strong cancer-type and tissue-specific heterogeneity shaped by the underlying circadian architecture of each organ. Different tissues exhibit distinct metabolic rhythms, hormonal fluctuations, immune environments, and chromatin landscapes [71,72,305,306,309,312,318,328,329]. As a result, the same *CRY* or *PER* gene can have fundamentally different effects on different malignancies. For example, gastrointestinal and hepatobiliary tumors, which are tightly coupled to nutrient-dependent and bile acid-driven circadian programs, tend to exploit CRY-mediated DDR and PER-mediated metabolic checkpoints to increase proliferation and resistance to oxidative stress [97,300,329]. This complexity highlights the necessity of stratifying therapeutic strategies by cancer type, circadian phase, and genetic background to achieve precise and effective interventions.

Other circadian genes

NR1D1/NR1D2

NR1D1 (*REV-ERBα*) and *NR1D2* (*REV-ERBβ*), members of the nuclear receptor superfamily and core circadian clock components, have complex functions in a variety of cancers, acting either as tumor suppressors or as promoters of tumor progression [144,330-332]. Their activities are jointly regulated by tumor type, molecular background, and microenvironmental cues [332-339].

The tumor-suppressive functions of NR1D1 have been demonstrated across multiple cancer types and arise from its coordinated regulation of DDR, key oncogenic signaling, and antitumor immunity. One central mechanism involves direct interference with DNA repair processes. In breast and ovarian cancers, NR1D1 is recruited to DNA damage sites, where it interacts with PARP1 and prevents the recruitment of repair factors such as SIRT6, phosphorylated Nijmegen breakage syndrome 1 (pNBS1), and BRCA1. This disrupts homologous recombination and NHEJ repair pathways, leading to DNA damage accumulation and enhanced chemosensitivity [330,333,340].

NR1D1 also suppresses tumor growth by restraining major oncogenic signaling pathways in a context-dependent manner. Mechanistically, NR1D1 can attenuate JAK/STAT3 signaling through transcriptional upregulation of suppressor of cytokine signaling 3 (*SOCS3*), leading to G1 cell-cycle arrest and apoptosis in ovarian cancer [341]. In bladder cancer, NR1D1 inhibits the PI3K/Akt/mTOR pathway to suppress proliferation [334]. Pharmacological studies have further revealed that the REV-ERBα agonists SR9011 and SR9009 can inhibit mTOR signaling, repress ATG5 transcription to block autophagic flux, and suppress lipid biosynthesis, selectively inducing cancer cell apoptosis and suppressing tumor growth [144,335,342].

NR1D1 additionally contributes to tumor suppression by shaping the immune microenvironment. It's reported that NR1D1 exerts tumor-suppressive functions by inhibiting NLRP3 inflammasome activation in macrophages, thereby restraining pro-tumorigenic immune signaling in lung cancer [336]. Impaired DNA repair caused by NR1D1 also leads to cytosolic DNA accumulation, which activates the cGAS-STING pathway, triggers type I interferon production, enhances $CD8^+$ T-cell and NK cell infiltration, and strengthens antitumor immune surveillance [343]. In addition, NR1D1 contributes to tumor suppression by regulating metabolism (e.g., inhibiting glycolysis and the pentose phosphate pathway) and cell cycle progression (e.g., repressing cyclin expression) [337,344].

However, in specific contexts, NR1D1 exhibits oncogenic activity. In prostate, liver, and colorectal cancers, NR1D1 forms complexes with bromodomain-containing protein 4 (BRD4)/

p300 coactivators, promoting histone acetylation (H3K27ac) and chromatin accessibility, which directly activate oncogenes in the MAPK/PI3K pathway [e.g., epidermal growth factor receptor (EGFR), KRAS, and Akt], thereby supporting tumor growth and survival [345]. In thyroid cancer, NR1D1 promotes invasion and metastasis through the β-catenin/ZEB1 axis [338].

In contrast, NR1D2 generally displays oncogenic properties across cancers. In neural-derived tumors, NR1D2 couples growth factor signaling with cytoskeletal remodeling and transcriptional activation programs. In glioblastoma, NR1D2 transcriptionally activates AXL receptor tyrosine kinase (*AXL*) to engage PI3K/Akt signaling, thereby promoting proliferation, migration, epithelial-mesenchymal transition, and invasive behavior, while concurrently regulating focal adhesion maturation and F-actin polymerization through AXL-independent mechanisms [346]. This oncogenic circuitry is further reinforced in glioblastoma stem cells, where NR1D2 interfaces with Hippo and Notch signaling by interacting with transcriptional coactivator with PDZ-binding motif (TAZ)/TEA domain family member (TEAD) and recombination signal binding protein for immunoglobulin kappa J region (RBPJ)/Notch intracellular domain 1 (NICD1) complexes, coactivating stemness- and survival-associated oncogenes such as *Myc* and conferring therapeutic resistance [331].

Beyond the central nervous system, NR1D2 similarly drives invasive phenotypes by engaging lineage-specific signaling pathways. In HCC, NR1D2 drives EMT and enhances invasion and metastasis through the Wnt/β-catenin pathway [339]. Pan-cancer analyses have revealed that *NR1D2* is highly expressed in breast, liver, and prostate cancers. By regulating circadian and metabolic genes, it sustains cancer cell survival, while its inhibition enhances chloroquine-induced apoptosis [347]. In melanoma, NR1D1/NR1D2 together support tumor cell survival under conditions of autophagy inhibition by regulating metabolism and the circadian rhythm [332].

Notably, NR1D2 function is strongly dependent on genetic background. In colorectal cancer, NR1D2 regulates cancer stemness in a Tp53-dependent manner, with opposing outcomes dictated by *Tp53* status. In *Tp53*-wild-type tumors, NR1D2 promotes stem-like properties, including expansion of aldehyde dehydrogenase 1 $(ALDH1)^+$ populations and enhanced tumor sphere formation, features associated with poor differentiation and unfavorable prognosis. In contrast, loss of *NR1D2* in *Tp53*-mutant cells paradoxically augments stemness, underscoring a tight functional interplay between NR1D2 and Tp53-mediated transcriptional control [348]. Furthermore, in osteosarcoma cells, NR1D2 cooperates with NR1D1 to suppress NF-κB signaling and maintain extracellular matrix stability, thereby jointly inhibiting tumor progression, indicating that NR1D2 may also exert tumor-suppressive effects under specific conditions [349].

RORA/RORB

RORA and *RORB*, which are members of the nuclear receptor superfamily, predominantly function as tumor suppressors in various cancers [350-353]. Similar to the mechanisms described above, its antitumor effects can likewise be categorized according to coordinated regulation of oncogenic signaling pathways, metabolic reprogramming, immune surveillance, and epigenetic modification.

RORA frequently antagonizes Wnt/β-catenin-driven transcriptional programs that sustain proliferation and invasion [350,354-356]. In gastrointestinal malignancies, RORA promotes β-catenin phosphorylation and represses downstream targets such as cyclin D1(*CCND1*), thereby restraining cell-cycle progression, while its expression is tightly controlled by epigenetic mechanisms including the circGSK3B-EZH2 axis [350]. Similar Wnt/β-catenin suppression is observed in multiple epithelial malignancies, in which RORA directly inhibits β-catenin transcriptional activity and activates tumor-suppressive mediators such as *SPARC* or *SEMA3F*/*p21* [354-356]. Beyond Wnt signaling, other studies have indicated that RORA can increase transcriptional activity via AMPK phosphorylation to upregulate the expression of tumor suppressor genes [357].

Metabolic regulation represents another major axis of RORA-mediated tumor suppression. In squamous and adenocarcinoma contexts, *RORA* is frequently silenced through DNMT1-mediated promoter methylation, which results in derepression of glycolytic regulators such as *SLC2A3* (*GLUT3*), thereby fueling aerobic glycolysis and promoting migratory and invasive behaviors [218]. In ovarian cancer, RORA counteracts the Warburg effect by suppressing key glycolytic enzymes (*HK2* and *GLUT1*) and inhibiting VEGFR2 signaling, thereby limiting angiogenesis and tumor growth [358]. RORA further constrains metabolic stress by repressing mitochondrial complex I subunits [NADH: ubiquinone oxidoreductase core subunit S6 (*NDUFS6*) and NADH:ubiquinone oxidoreductase subunit A11 (*NDUFA11*)], reducing ROS accumulation, and blocking ROS-NF-κB inflammatory signaling, collectively restoring mitochondrial energy homeostasis in HCC [359].

RORA also plays a critical role in shaping the immune microenvironment [159,351,360,361]. In NSCLC, *RORA* expression is positively correlated with immune cell infiltration

(e.g., $CD8^+$ T and B cells) and immune checkpoint genes (*CD274* and *CTLA4*), contributing to anti-tumor immune regulation [351]. Another study found that RORA is highly enriched in liver-resident NK cells (LrNK/ILC1s), where it is essential for maintaining cell survival and effector functions, including IFN-γ production; loss of *RORA* compromises antitumor immunity and accelerates tumor progression [361]. In melanoma, RORA also directly binds the *CD274* promoter and recruits HDAC3-containing corepressor complexes to suppress *CD274* transcription, thereby enhancing $CD8^+$ T cell-mediated cytotoxicity. Consistently, pharmacological activation of RORA using nobiletin synergizes with anti-CTLA-4 immunotherapy to improve antitumor efficacy [159]. Moreover, in gliomas, RORA exerts tumor-suppressive effects by inhibiting the TNF-α/NF-κB pathway under the negative regulation of miR-18a [360].

Within the epigenetic and posttranscriptional modifications, *RORA* expression is frequently attenuated through multilayered regulatory mechanisms. These include DNMT1-mediated promoter methylation, circRNA-EZH2-dependent chromatin repression [218,350], targeting by viral or cellular microRNAs such as EBV-encoded miR-BART5-5p [362], and transcriptional repression via the UBE2T-PBX1 axis [363]. Post-translational modifications further fine-tune RORA stability and activity, with PRMT5-mediated arginine methylation, ITCH-dependent ubiquitination, and UBR5-mediated proteasomal degradation all contributing to reduced RORA abundance in cancer cells [359,364]. Collectively, these mechanisms underlie the frequent downregulation of RORA observed in gastric cancer, nasopharyngeal carcinoma, lung cancer, and other malignancies, where low RORA expression is consistently associated with poor prognosis [218,364,365].

Importantly, *RORA* function remains context dependent. In breast cancer, RORA generally suppresses tumor progression by inhibiting proliferation and invasion, repressing Wnt/β-catenin and NF-κB signaling, downregulating SNAIL, and remodeling the tumor microenvironment [352,366,367]. However, in ER^+ breast cancer, RORA can acquire a protumorigenic role by upregulating aromatase expression, thereby enhancing local estrogen synthesis and fueling hormone-dependent tumor growth [362]. In cutaneous melanoma, *RORA* is regulated by sex hormones, and its polymorphisms influence tumor susceptibility by modulating hormone signaling or transcriptional activity [368]. This duality underscores the necessity of interpreting RORA activity within the framework of tissue lineage, hormonal context, and regulatory landscape.

RORB also functions primarily as a tumor suppressor but has been reported to exhibit oncogenic properties in specific contexts [353,369,370]. In colorectal cancer, RORB activates HMG-box transcription factor 1 (*HBP1*) transcription to suppress Wnt/β-catenin signaling, reducing cancer stem cell self-renewal and tumor formation [369]. In gastric cancer, RORB inhibits Wnt/β-catenin signaling and downregulates the expression of stemness markers [*SOX2* and octamer-binding transcription factor 4 (*OCT4*)] and EMT-related factors (*SLUG* and *TWIST*), thereby suppressing stem-like properties and migration [353]. However, in prostate cancer, *RORB* expression is upregulated and promotes cancer stemness features (e.g., sphere formation and increased $CD44^+/CD133^+$ cell populations), potentially contributing to resistance to castration therapy [370].

Together, accumulating evidence underscores the multiple roles of *NR1D1*, *NR1D2*, *RORA*, and *RORB* in tumor biology and provides an important basis for developing therapeutic strategies targeting these nuclear receptors [144,338,342,344,371]. For example, the use of agonists (SR9009, SR9011, GSK4112, SR1078, and nobiletin) or antagonists (SR8278) can modulate their activity in different contexts to achieve precise anticancer effects [144,372-375]. In addition, regulating the associated signaling axes may offer new strategies for cancer therapy.

Overall, the differential circadian wiring across cancer types and the involvement of tissue-specific drivers highlight the need for chronotherapy approaches that are tailored to the origin of each tumor and its unique circadian physiology. Future studies should systematically map circadian disruptions in a pan-cancer, tissue-resolved manner to identify novel therapeutic windows and combination strategies.

Therapeutic implications of circadian rhythms in cancer management

Principles of cancer chronotherapy

Like most physiological processes, both pharmacodynamics and pharmacokinetics are strongly influenced by circadian rhythms [376]. Pharmacokinetics determines the optimal drug concentration required to balance efficacy and toxicity, and encompasses 4 distinct phases: absorption, distribution, metabolism, and excretion. These processes exhibit circadian oscillations and are governed by the rhythmic expression of drug-metabolizing enzymes and transporters [377,378]. Consequently, harnessing circadian rhythms to improve therapeutic outcomes, particularly in cancer treatment, has become an area of growing interest. Three major approaches to chronotherapy have been widely investigated. The first involves behavioral or environmental interventions to

promote or maintain optimal circadian rhythms ("training the clock"). The second focuses on optimizing the timing of drug administration to maximize therapeutic efficacy while minimizing adverse effects ("timing the drug"). The third employs molecules or drugs that directly modulate core clock genes ("controlling the clock") [53,379,380]. Despite encouraging progress, the clinical translation of these chronotherapeutic principles faces challenges, including interindividual differences in circadian phase, hospital workflow constraints, and the lack of real-time circadian biomarkers [146,381]. Recent studies incorporating wearable devices, physiological rhythm tracking, and computational chronotyping illustrate the potential of personalized time-based interventions [382-385].

Clinical evidendce supporting chronomodulated cancer therapies

Based on phase III randomized clinical trials and meta-analyses, cancer chronotherapy is gradually progressing from conceptual validation to more mature clinical investigations. From a dosing perspective, several colorectal cancer trials have adopted circadian-synchronized sinusoidal infusion patterns for 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and carboplatin [386-390]. By aligning drug delivery with times of maximal host tolerance, these chronomodulated schedules significantly reduced grade III-IV toxicity, including mucositis, diarrhea, and neurotoxicity, and in certain studies enabled a higher dose intensity and resulted in superior objective response rates. Research on lung cancer has demonstrated that administering cisplatin in the evening substantially reduces hematologic and gastrointestinal toxicity without compromising antitumor efficacy [391]. Studies involving endocrine therapy and targeted agents have revealed time-dependent effects as well: nighttime tamoxifen intake improved disease-free survival (DFS) in high-risk early breast patients, and everolimus resulted in differential DFS outcomes depending on the dosing time when combined with tamoxifen [392,393]. The results of ovarian cancer investigations have further revealed that PARP inhibitors alter circadian gene expression and that such perturbations correlate with toxicity and tolerance, highlighting the relevance of chronotherapy in molecularly targeted treatments [394]. In terms of therapeutic outcomes, chronomodulated chemotherapy produces meaningful clinical benefits. Colorectal cancer studies have shown improved response rates, reduced severe toxicity, and, in certain cases, increased resectability rates for initially unresectable disease [386-390]. Nighttime tamoxifen dosing significantly prolonged DFS in selected patients [392]. Evening cisplatin administration reduced toxicity while maintaining efficacy [391]. PARP inhibitor-related circadian disruption correlated with the toxicity burden, supporting the chronotherapeutic optimization of targeted therapy schedules [394].

Collectively, these findings indicate that chronomodulated treatment schedules can confer meaningful clinical benefits, including toxicity reduction and, in some contexts, improved efficacy. However, not all studies have demonstrated robust chronotherapeutic effects [395], emphasizing that therapeutic benefit is highly dependent on appropriate drug selection, dosing patterns, and biological timing.

Challenges and opportunities in circadian oncology

Despite growing clinical and experimental evidence, multiple limitations impede clinical adoption. First, most trials employed fixed, population-level dosing times that overlooked substantial interindividual variability in the circadian phase, likely constraining therapeutic optimization. Second, several trials had modest sample sizes, particularly molecular rhythm substudy cohorts, reducing statistical power. Third, the reliance on complex programmable pumps limits feasibility and accessibility in routine practice. Fourth, the mechanistic links between circadian pharmacokinetics/pharmacodynamics and clinical outcomes remain insufficiently characterized, leaving the causal framework incomplete. Additionally, some early-phase trials utilized overly simplistic delivery patterns that failed to exploit known circadian pharmacology, underscoring the importance of carefully designed chronomodulated regimens. In addition, clinical translation is hindered by the lack of standardized circadian assessment methods, the limited accessibility imposed by high-cost equipment, insufficient awareness among health care professionals, marked heterogeneity in patients' daily rhythms in real-world settings, the complexity of coordinating optimal dosing windows in multidrug regimens, and the absence of time-related labeling within regulatory frameworks. Together, these factors impede the integration of chronotherapy into clinical guidelines and routine oncology practice.

Looking forward, the field is likely to move from fixed-time chronotherapy to precision, individualized chronotherapy. Emerging technologies, including actigraphy, saliva- or blood-based clock gene biomarkers, cortisol/melatonin profiling, and wearable devices, can capture individual circadian phases and amplitudes, enabling patient-specific dosing schedules [396-399]. Digital health tools, artificial intelligence (AI)-based

rhythm modeling, predictive machine learning for toxicity, and integration of multi-omics (e.g., transcriptomics and metabolomics) will further refine precision chronotherapy. The expansion of chronotherapeutic principles to immunotherapy, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, PARP inhibitors, and other targeted agents is expected. Several studies also highlight the importance of stabilizing circadian function itself, as disrupted rest-activity rhythms represent an independent prognostic factor for survival and quality of life, suggesting that circadian-supportive interventions could serve as adjunctive treatments. Overall, despite current limitations, the concept of administering "the right drug to the right patient at the right time" is becoming increasingly tangible. With the convergence of circadian measurement technologies, digital health tools, and precision oncology, chronotherapy is likely to become an indispensable component of future cancer treatment paradigms. Beyond optimizing drug administration timing, therapeutic strategies aimed at circadian entrainment and clock modulation have also begun to attract increasing attention from researchers. The pivotal roles of clock genes in tumor initiation and progression highlight their potential as novel therapeutic targets, while their gatekeeping function in antitumor immunity provides a rationale for developing circadian-based immunotherapies [147]. In the advancement of circadian entrainment therapies, the potential anticancer effects of melatonin across diverse malignancies, including renal, breast, prostate, gastric, pancreatic, and colorectal cancers, have attracted significant interest [400-405]. Additionally, restoring β-endorphin rhythmicity can counteract *CLOCK*/*ACSL1* disruption induced by sleep disturbances, thereby reducing cancer stemness and improving treatment outcomes in patients with lung cancer [281]. Normal β-endorphin oscillation has also been implicated in mitigating ovarian, breast, and bone tumors [406-408]. Controlling the circadian clock through pharmacological interventions has shown considerable promise in therapeutic applications. Compounds such as M47 (a CRY1 destabilizer), KL001 (a CRY stabilizer), KS15 (an inhibitor of CRY-BMAL1 interaction), and REV-ERBα agonists/antagonists have been investigated for their anticancer potential [312,375,409,410]. For instance, compared with monotherapy, the selective targeting of GSCs circadian regulation with REV-ERB or CRY agonists suppresses GSC growth, and the combination of SR9011 and KL001 reduces cell proliferation in a concentration-dependent manner [411]. Notably, accumulating evidence indicates that circadian dysregulation contributes to cancer stem cell maintenance, metabolic plasticity, and epithelial-mesenchymal transition, suggesting that restoring rhythmicity could impair tumor aggressiveness. Moreover, the gut microbiome exhibits robust diurnal oscillations that interact with host circadian pathways to shape tumor immunity and the therapeutic response, suggesting that a potential microbiota-clock-tumor regulatory axis is worthy of future investigation.

In the future, gene-editing strategies targeting circadian genes hold immense promise for cancer therapy. Circadian genes regulate key processes such as immune responses, cell proliferation, metabolism, and hypoxia signaling; precise editing of these genes could enhance immune cell activity and antitumor immunity. Importantly, gene-editing technologies enable the development of personalized therapeutic strategies, allowing for genotype- and pathology-specific modulation of circadian gene expression to achieve optimal therapeutic outcomes. Recent advances, such as clustered regularly interspaced short palindromic repeats (CRISPR)-based high-throughput perturbation screens, single-cell circadian transcriptomics, and machine learning-guided chronotherapeutic optimization are rapidly expanding the toolkit for dissecting tumor-specific rhythmic vulnerabilities. These approaches not only illuminate how cancer cells rewire or suppress the core clock machinery but also provide quantitative frameworks for predicting optimal drug timing at the individual level. Furthermore, tumor-specific mutations in *PER2*, *ARNTL*, *NR1D1* and other core clock genes, together with tissue-dependent clock synchronization mechanisms, underscore the need to understand organ-specific circadian regulation to improve translational relevance and develop precision circadian oncology strategies. Considering patient chronotype, sleep-wake patterns, and circadian robustness will be essential for integrating such strategies into clinical practice and achieving individualized, rhythm-informed cancer therapy.

Together, these advances illustrate that circadian medicine is transitioning from a descriptive discipline into a mechanistically informed and clinically actionable framework for cancer therapy. However, realizing the full potential of circadian-based cancer therapy will require overcoming substantial translational barriers, including the heterogeneity of circadian phenotypes, the absence of standardized monitoring tools, and the complexity of incorporating temporal variables into clinical workflows and regulatory systems. Future efforts should prioritize the development of robust, scalable circadian biomarkers; the harmonization of clinical protocols that incorporate individualized timing; and the design of multidisciplinary translational pipelines that link basic circadian biology with oncology, pharmacology, engineering, and data science. Ultimately, by aligning therapeutic strategies

with the temporal architecture of both the host and the tumor, circadian oncology offers a promising blueprint for improving efficacy, minimizing toxicity, and advancing the next generation of precision cancer therapy.

Conclusion and perspective

Circadian rhythms have emerged as a prominent focus in cancer biology research and play critical roles in tumor initiation, tumor progression, and treatment response. Disruptions of circadian rhythms, whether caused by genetic mutations, environmental factors, or intrinsic tumor signals, profoundly alter key processes such as DNA repair, metabolism, immune surveillance, and the hypoxia response, thereby influencing tumor cell proliferation, immune evasion, and therapeutic sensitivity. These findings not only underscore the central role of circadian rhythms in tumorigenesis but also highlight potential avenues for therapeutic intervention. At the same time, several fundamental questions remain unresolved. For example, how tumor-intrinsic clocks diverge from tissue-of-origin rhythms and why different cancer types display distinct dependencies on clock components such as REV-ERBα/β, RORs, or CRY1 are unclear, indicating unresolved mechanistic heterogeneity across malignancies.

Recent advances have revealed multiple mechanisms through which circadian rhythms impact tumor development. First, the circadian clock regulates extensive gene networks via transcription-translation feedback loops, affecting tumor cell proliferation and metastatic capacity, with dysregulation of core clock genes closely associated with malignancy and a poor prognosis across various cancer types [94,218,312,323,334]. Second, circadian rhythms modulate immune cell migration, cytokine secretion, and antigen presentation, thereby shaping the tumor microenvironment and altering immune recognition and clearance of tumor cells [150,166,173,257]. Moreover, circadian control over metabolic pathways, including lipid synthesis, glycolysis, and redox homeostasis, enables tumor cells to survive under conditions of stress such as hypoxia or nutrient deprivation, further enhancing tumor adaptability and treatment resistance [107,128,134,136].

On the basis of the existing evidence, we propose a unifying conceptual framework, the circadian tumor ecosystem (CTE), that may help guide future research. In this framework, tumor adaptability arises from 3 interlinked rhythmic modules: 1) an intrinsic tumor oscillator (the core clock and its reprogramming), 2) microenvironmental rhythms (rhythmic trafficking or activation of immune and stromal components), and 3) a systemic synchronizing axis (host sleep-wake and feeding cycles, along with downstream hormonal and metabolic mediators).

The purpose of the CTE model is to provide a conceptual basis for selecting optimal therapeutic time windows. When a therapeutic intervention, whether a drug, immunotherapy, or metabolic modulation, aligns with the dominant rhythmic module that remains operative in a given tumor state, treatment efficacy is expected to be maximized. Conversely, in states of clock desynchrony, conventional chronotherapy becomes limited, necessitating a shift toward targeting alternative vulnerabilities.

Despite significant progress, many challenges and unresolved questions remain regarding circadian rhythms in cancer biology. The relationships between circadian disruption and different tumor types or individual variability remain unclear, necessitating more comprehensive and personalized analyses. Additionally, the molecular mechanisms underlying circadian regulation have not been fully elucidated, particularly regarding specific signaling pathways and regulatory networks within tumor cells, and further in-depth molecular investigations are needed. Furthermore, translating circadian modulation into effective clinical interventions remains in its early stages, with optimization of circadian-based strategies in combination with conventional chemotherapy, targeted therapy, or immunotherapy yet to be established.

To enhance clinical translatability, we propose three experimentally testable hypotheses based on the CTE framework. First, tumors that retain partially functional intrinsic oscillators, including those exhibiting hypoxia-induced phase shifts or amplitude dampening, remain sensitive to dosing time. In these tumors, the reprogrammed clock continues to gate DNA damage responses, cell-cycle progression, and metabolic flux. Precision chronotherapy, achieved by optimizing drug administration timing, is therefore predicted to be particularly effective. Experimental and clinical evidence indicate that tumors characterized by hypoxia-induced phase delay, altered PER/CRY dynamics, or heightened DNA damage sensitivity display pronounced dosing-time dependency. Importantly, restoring circadian amplitude or re-aligning tumor-host phase relationships can resensitize these tumors to time-optimized chemotherapy or targeted therapy. Clinically, this strategy aligns with phase III trials demonstrating improved tolerability and efficacy of chronomodulated chemotherapy and endocrine therapy. Within the CTE framework, such benefits are predicted to be maximal when therapeutic delivery coincides with the residual rhythmic vulnerability of the tumor oscillator, thereby maximizing the therapeutic index. Second, a distinct therapeutic opportunity arises in tumors

in which microenvironmental rhythms remain operative, especially those governing immune cell trafficking, antigen presentation, and cytokine signaling. In these CTE states, even when the intrinsic tumor clock is weakened, rhythmic immune surveillance persists. We hypothesize that tumors retaining immune circadian rhythmicity will derive disproportionately greater benefit from immune checkpoint blockade and immunomodulatory therapies administered in a time-matched manner. Experimental studies have demonstrated circadian oscillations in T-cell migration, dendritic cell activation, and immune checkpoint expression, suggesting that immunotherapy efficacy may be gated by host-tumor temporal alignment. This strategy conceptually integrates chronotherapy with immuno-oncology, reframing treatment timing not merely as a pharmacokinetic optimization but as a means to synchronize therapeutic intervention with immune system readiness. Within the CTE model, such tumors are predicted to respond best when treatment aligns with microenvironmental rhythmic peaks rather than tumor-intrinsic clocks alone. Third, a subset of tumors displays profound circadian disruption caused by genetic or epigenetic inactivation of core clock genes such as *PER2*, *ARNTL*, or *NR1D1*, resulting in clock-uncoupled CTE states. In these tumors, conventional chronotherapy is expected to yield limited benefit, as neither tumor-intrinsic nor microenvironmental rhythms are sufficiently coherent to gate therapeutic responses. For these tumors, the CTE framework predicts a shift from time-based intervention toward targeting compensatory vulnerabilities that arise from circadian collapse, particularly metabolic plasticity, redox imbalance, and NAD^+/NADH buffering systems. Accumulating evidence suggests that clock disruption promotes cancer stemness, epithelial-mesenchymal transition, and metabolic rewiring, creating synthetic lethal dependencies that can be therapeutically exploited. Accordingly, metabolic modulators, redox-targeting agents, and pharmacological clock controllers (e.g., CRY or REV-ERB modulators) may serve as alternative entry points. Rather than restoring oscillation per se, these strategies aim to capitalize on the liabilities created by circadian deregulation, offering a rational treatment option for chronotherapy-resistant tumors (Fig. 7).

Future studies should focus on dissecting dynamic circadian networks in tumors, integrating single-cell multi-omics, real-time circadian reporter systems, and high-temporal-resolution sequencing technologies to identify tumor-specific rhythmic

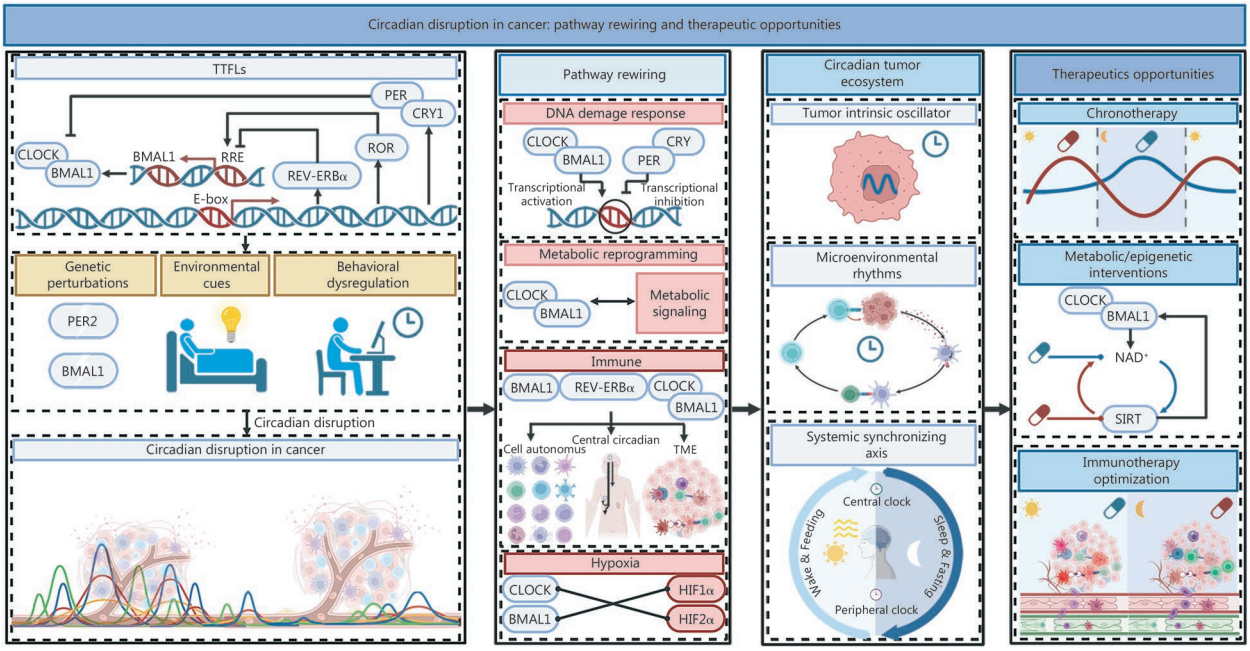

Fig. 7 Circadian disruption in cancer: pathway rewiring and therapeutic opportunities.
This schematic depicts a Circadian Tumor Ecosystem (CTE)-guided framework linking circadian disruption, pathway rewiring, and precision cancer therapy. Genetic, environmental, and behavioral perturbations reprogram core clock-controlled pathways, including DNA damage response, metabolism, immunity, and hypoxia, generating distinct CTE states. Tumors with preserved intrinsic oscillators remain sensitive to precision chronotherapy; those retaining microenvironmental rhythmicity benefit from time-matched immunotherapy; whereas clock-uncoupled tumors exhibit therapeutic vulnerabilities in metabolic and redox pathways rather than time-dependent responses. BMAL1. Brain and muscle ARNT-like 1; CLOCK. Circadian locomotor output cycles kaput; CRY. Cryptochrome; HIF. Hypoxia-inducible factor; NAD. Nicotinamide adenine dinucleotide; PER. Period; REV-ERBα. Nuclear receptor subfamily 1 group D member 1; ROR. Retinoic acid receptor-related orphan receptor; RRE. ROR response element; SIRT. Sirtuin TME. Tumor microenvironment; TTFLs. Transcription-translation feedback loops

vulnerabilities. We propose a mechanistic model in which tumor cells selectively retain or rewire clock-controlled pathways, particularly those linked to hypoxia adaptation, metabolic plasticity, and immune evasion, to create a set of experimentally testable hypotheses regarding tumor-specific "circadian liabilities". Such insights could guide the development of selective pharmacological interventions, including BMAL1-HIF interaction inhibitors, REV-ERB agonists, or CRY stabilizers, while minimizing effects on normal tissue clocks. Combining circadian modulation with immunotherapy represents a promising approach, as circadian rhythms significantly influence immune checkpoint expression, antigen presentation, and T-cell activity, potentially enhancing anti-tumor efficacy and reducing immune-related adverse effects. Personalized chronotherapy strategies, supported by wearable rhythm monitors, biomarker-based phase assessments, and mathematical modeling, could optimize drug administration timing for individual patients. Moreover, genetic and epigenetic interventions targeting clock genes may reconstruct tumor circadian networks, suppress malignant phenotypes, and improve therapeutic responses. Importantly, this review uniquely integrates circadian regulation across metabolism, hypoxia, and immunity into a unified conceptual framework, highlighting cross-pathway crosstalk rarely synthesized in the literature.

Clinically, exploiting circadian rhythms offers a new dimension for precision oncology. By optimizing drug timing, directly targeting clock components, or restoring normal tumor cell rhythms, treatment efficacy can be improved, toxicity can be reduced, and innovative therapeutic strategies can be developed. With advances in systems biology, gene-editing technologies, and AI-driven chronopharmacology, these approaches hold promise for accelerated clinical translation. Overall, the development of time-based cancer therapies has substantial potential to enhance existing treatments and improve survival and quality of life for cancer patients, representing a frontier in oncology research. Moving forward, building a standardized framework for clinical rhythm assessment, harmonizing chronotherapy trial design, and validating tumor-specific circadian biomarkers will be critical steps toward implementing precision "time medicine" in oncology.

Abbreviations

8-OHdG: 8-Hydroxy-2'-deoxyguanosine
8-oxoG: 8-Oxo-7,8-dihydroguanine
α-KG: Alpha-ketoglutarate
γ-H2AX: Phosphorylated histone H2A.X at serine 139
ACC: Acetyl-CoA carboxylase
ACSL1: Acyl-CoA synthetase long chain family member 1
AI: Artificial intelligence
ALDH1: Aldehyde dehydrogenase 1
AMPK: AMP-activated protein kinase
AP-1: Activator protein 1
APC: Adenomatous polyposis coli
AR: Androgen receptor
ARE: Antioxidant response element
ARG1: Arginase 1
ATM: Ataxia telangiectasia mutated
ATR: Ataxia telangiectasia and Rad3-related protein
AXL: AXL receptor tyrosine kinase
B2M: Beta-2 Mmicroglobulin
BAX: Bcl-2-associated X protein
BCL-2: B-cell lymphoma 2
BER: Base excision repair
bHLH: Basic helix-loop-helix
bHLH-PAS: Basic helix-loop-helix Per-Arnt-Sim
BMAL1: Brain and muscle ARNT-Like 1
BRCA1: Breast cancer type 1 susceptibility protein
BRCA2: Breast cancer type 2 susceptibility protein
BRD4: Bromodomain-containing protein 4
C3a: Complement Component 3a
C5a: Complement Component 5a
CAFs: Cancer-associated fibroblasts
CAR: Chimeric antigen receptor
CAT: Catalase
CCGs: Clock-Controlled Genes
CCL21: C-C motif chemokine ligand 21
CCND1: Cyclin D1
CCR7: C-C chemokine receptor type 7
$CD8^+$ T cells: Cluster of differentiation 8 positive T cells
CDK: Cyclin-dependent kinase
CDKN1A: Cyclin-dependent kinase inhibitor 1A
CFL: Cofilin
cGAS: Cyclic GMP-AMP synthase
CK1δ: Casein kinase 1 delta
CK1ε: Casein kinase 1 epsilon
CK2: Casein kinase 2
CLOCK: Circadian locomotor output cycles kaput
c-Myc: Cellular myelocytomatosis oncogene
CoA: Coenzyme A
CRISPR: Clustered regularly interspaced short palindromic repeats
CRL4B: Cullin 4B-RING E3 ligase
CRY: Cryptochrome
CTE: Circadian tumor ecosystem
CTLA-4: Cytotoxic T-lymphocyte associated protein 4
CXCL: C-X-C motif chemokine ligand
CXCR: C-X-C motif chemokine receptor
DBP: D-box binding protein
DC: Dendritic cell
DDR: DNA damage response
DDSB: DNA double-strand break
DDX3X: DEAD-box helicase 3 X-linked
DEC: Differentiated embryo-chondrocyte expressed gene
DFS: Disease-free survival
DNMT: DNA methyltransferase
DSBs: Double-strand breaks
ECM: Extracellular matrix
EGFR: Epidermal growth factor receptor

EMT: Epithelial-mesenchymal transition
ER: Estrogen receptor
ERCC: Excision repair cross-complementation group
ERK: Extracellular signal-regulated kinase
ESR1: Estrogen receptor 1
EZH2: Enhancer of zeste homolog 2
FAD: Flavin adenine dinucleotide
FADH2: Flavin adenine dinucleotide reduced
FASN: Fatty acid synthase
FBXL: F-box and leucine-rich repeat protein
FOXA1: Forkhead box A1
FOXM1: Forkhead box M1
FXR: Farnesoid X receptor
G6PD: Glucose-6-phosphate dehydrogenase
G9a: Euchromatic histone lysine methyltransferase 2
GLP: G9a-like protein
GLUT: Glucose transporter
GLYR1: Glyoxylate reductase 1 homolog
GPR: G-protein-coupled receptor
GSCs: Glioma stem cells
GSK3β: Glycogen synthase kinase 3 beta
GSTE12: Glutathione S-transferase epsilon 12
H3K4ac: Histone H3 lysine 4 acetylation
H3K9me2: Histone H3 lysine 9 dimethylation
HAT: Histone acetyltransferase
HBP1: HMG-box transcription factor 1
HCC: Hepatocellular carcinoma
HDAC3: Histone deacetylase 3
HERC2: HECT and RCC1-like domain-containing protein 2
HFDs: High-fat diets
HIF: Hypoxia-inducible factor
HK2: Hexokinase 2
HNF4α: Hepatocyte nuclear factor 4 alpha
HPA: Hypothalamus-pituitary-adrenal
HR: Homologous recombination
HRE: Hypoxia response element
HSP70: Heat shock protein 70
ICAM-1: Intercellular adhesion molecule 1
ICIs: Immune checkpoint inhibitors
IFN-γ: Interferon gamma
IKK: IκB kinase
IL: Interleukin
IL17A: Interleukin 17A
IL17F: Interleukin 17F
ILC3s: Group 3 innate lymphoid cells
JAM-A: Junctional adhesion molecule A
KLF9: Krüppel-like factor 9
KRAS: Kirsten rat sarcoma viral oncogene homolog
LAG-3: Lymphocyte activation gene-3
LDHA: Lactate dehydrogenase A
LGMN: Legumain
LYVE1: Lymphatic vessel endothelial hyaluronan receptor 1
MAPK: Mitogen-activated protein kinase
MCU: Mitochondrial calcium uniporter
MDC1: Mediator of DNA damage checkpoint 1
MDSCs: Myeloid-derived suppressor cells
MEK: Mitogen-activated protein kinase kinase
MHC: Major histocompatibility complex
MMP9: Matrix metalloproteinase-9
MMS: Methyl methanesulfonate
MRTF: Myocardin-related transcription factor
MT: Metallothionein
mTOR: Mechanistic target of rapamycin
MYCN: MYCN proto-oncogene, bHLH transcription factor
NAD^+: Nicotinamide adenine dinucleotide
NADH: Nicotinamide adenine dinucleotide reduced
NAMPT: Nicotinamide phosphoribosyltransferase
NCOR: Nuclear receptor corepressor
NDUFA11: NADH:ubiquinone oxidoreductase subunit A11
NDUFS6: NADH:ubiquinone oxidoreductase core subunit S6
NER: Nucleotide excision repair
NFIL3: Nuclear factor interleukin 3-regulated protein
NHEJ: Non-homologous end joining
NICD1: Notch intracellular domain 1
NK: Natural killer
NPAS2: Neuronal PAS domain protein 2
NR1D1: Nuclear receptor subfamily 1 group D member 1
NR1D2: Nuclear receptor subfamily 1 group D member 2
NR1H4: Nuclear receptor subfamily 1 group H member 4
NR1I3: Nuclear Receptor Subfamily 1 Group I Member 3
NRF2: Nuclear factor erythroid 2-related factor 2
NSCLC: Non-small cell lung cancer
OCT4: Octamer-binding transcription factor 4
OGG1: 8-Oxoguanine DNA glycosylase
OLFML3: Olfactomedin-like 3
OSCC: Oral squamous cell carcinoma
OXPHOS: Oxidative phosphorylation
PARP1: Poly(ADP-ribose) polymerase 1
PAI1: Plasminogen activator inhibitor-1
PD-1: Programmed cell death protein 1
PDCD1: Programmed cell death 1
PDK1: 3-Phosphoinositide-dependent protein kinase-1
PD-L1: Programmed death-ligand 1
PER: Period
PI3K: Phosphoinositide 3-kinase
PIEZO2: Piezo-type mechanosensitive ion channel component 2
PKM2: Pyruvate kinase M2
POLD2: DNA polymerase delta 2
POSTN: Periostin
PPARα: Peroxisome proliferator-activated receptor alpha
PPARδ: Peroxisome proliferator-activated receptor delta
PPP: Pentose phosphate pathway
PRMT6: Protein arginine methyltransferase 6
PRPS1/2: Phosphoribosyl Pyrophosphate Synthetase ½
RAD50: RAD50 double strand break repair protein
RAD51: RAD51 recombinase
RBPJ: Recombination signal binding protein for immunoglobulin kappa J region
RHOA: Ras homolog family member A
ROCK: Rho-associated protein kinase
ROR: Retinoic acid receptor-related orphan receptor
RORγt: Retinoic acid-related orphan receptor gamma t
ROS: Reactive oxygen species
RPA3: Replication protein A subunit 3
RTK: Receptor tyrosine kinase
SAC: Spindle assembly checkpoint
SAM: S-adenosylmethionine
SCD1: Stearoyl-CoA desaturase 1
SCF: Skp1-cullin-F-box protein complex
SCN: Suprachiasmatic nucleus

SIRT: Sirtuin
SLC7A8: Solute carrier family 7 member 8
SOD: Superoxide dismutase
SREBP1c: Sterol regulatory element-binding protein 1c
SRF: Serum response factor
SSA: Single-strand annealing
SSBR: Single-strand break repair
STING: Stimulator of interferon genes
TAP: Transporter associated with antigen processing
TAZ: Transcriptional coactivator with PDZ-binding motif
TCA: Tricarboxylic acid
TCR: Transcription-coupled repair
TEAD: TEA domain family member
TERT: Telomerase reverse transcriptase
TET: Ten-eleven translocation methylcytosine dioxygenase
TGR5: Takeda G protein-coupled receptor 5
Th17: T helper 17 cells
TIM-3: T-cell immunoglobulin and mucin-domain containing-3
TIMELESS: Timeless circadian regulator
TLS: Translesion synthesis
TLR: Toll-like receptor
TMB: Tumor mutational burden
TP53: Tumor protein p53
Treg: Regulatory T cells
TRF: Time-restricted feeding
UCHL3: Ubiquitin C-terminal hydrolase L3
UHRF1: Ubiquitin-like with PHD and RING finger domains 1
VCAM-1: Vascular cell adhesion molecule 1
VEGF: Vascular endothelial growth factor
WEE1: WEE1 G2 checkpoint kinase
WHO: World Health Organization
XPA: Xeroderma pigmentosum, complementation group A
XRCC: X-ray repair cross-complementing protein
YAP: Yes-associated protein
ZT: Zeitgeber time

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Authors' contributions

ZHW, XPZ, KSW, and JS contributed to conception and were responsible for the whole work. ZHW, ZRD, ASL, and QYL completed the writing and figure making of this review. XPZ, KSW, ZHW, and ZRD provided ideas and assistance. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interest.

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