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REVIEW

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Circadian-driven transcriptional programs govern metastatic progression

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ABSTRACT Circadian rhythms orchestrate 24-h oscillations in gene expression to govern diverse physiologic functions. Mounting evidence suggests that circadian disruption, resulting from aberrant light exposure, shift work, or genetic mutations in core clock genes (e.g., *BMAL1* and *PER2*), promotes tumorigenesis and progression by dysregulating proliferation, apoptosis, cell cycle progression, metabolic reprogramming, and senescence. Critically, the circadian clock exerts spatiotemporal control over the tumor microenvironment, a dynamic ecosystem central to metastatic efficiency. This review synthesizes emerging mechanisms underlying circadian regulation of tumor microenvironment (TME) components during the metastatic cascade: 1) extracellular matrix (ECM) dynamics. Circadian oscillation of matrix metalloproteinases remodels collagen alignment at invasive edges. 2) Stromal crosstalk. Rhythmic secretion of cytokine by cancer-associated fibroblasts or macrophages gates intravasation efficiency on circulating tumor cells. 3) Immune-extravasation axis. Diurnal variations in endothelial adhesion molecules (ICAM-1/VCAM-1) regulate CTC extravasation, synchronized with neutrophil infiltration peaks. In this review how circadian perturbations (e.g., jet lag-induced cortisol spikes or CRY1 knockout) alter cytokine networks (TGF-β/IL-6), hypoxia responses, and metabolic symbiosis within the TME were dissected. This work unveiled chronotherapeutic targets to disrupt metastasis timing by integrating recent single-cell RNA-seq and intravital imaging data. However, details regarding the molecular mechanisms underlying TME have not been established. We anticipate that upcoming research will deepen our comprehension of these complex interactions, facilitating the creation of novel strategies for cancer therapy.

KEYWORDS Circadian clock; tumor metastasis; TME; cancer therapy

Introduction

The central circadian clock resides in the suprachiasmatic nuclei (SCN) in mammals, where the central circadian clock regulates and synchronizes peripheral clocks across various tissues and organs[1]. The circadian clock operates through a fundamental transcription–translation negative feedback loop (TTFL) on the molecular scale. Aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL, also referred to as BMAL1) and circadian locomotor output cycles kaput (CLOCK) form a positive feedback loop by interacting with E-box enhancer elements during the daytime, thereby inducing the transcription of inhibitory genes, such as period

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(*PER1*, *PER2*, and *PER3*) and cryptochrome (*CRY1* and *CRY2*). PER and CRY proteins assemble into complexes that translocate into the nucleus at night, where PER and CRY inhibit the transcriptional activity of the CLOCK/ARNTL heterodimer. In addition, PER and CRY proteins are degraded *via* β-TrCP and FBXL3, which are E3 ligase complexes. This process leads to a gradual reduction in PER and CRY protein levels. As a result, the negative feedback inhibition is lifted, allowing CLOCK and BMAL1 to regain transcriptional activity. This restoration initiates a new transcriptional cycle, which begins afresh the following morning. The second regulatory loop of the circadian system involves CLOCK/ARNTL (BMAL1)-driven transcription of REV-ERBα/β (NR1D1/2) and retinoic acid-related orphan receptors (RORs), which are key nuclear receptors modulating rhythmic gene expression. BMAL1 expression is inhibited by REV-ERBα/β and activated by RORs, ensuring dynamic circadian rhythm control[2]. The third feedback loop includes the proline-rich and acidic amino acid-rich basic leucine zipper (PAR-bZIP), which involves activators, like albumin D-element-binding protein (DBP), thyrotrophic embryonic factor (TEF), and hepatic leukemia factor (HLF). It also features the transcription repressor known as nuclear factor interleukin 3-regulated (NFIL3, also referred to as E4BP4). These factors compete for binding to the D-box element, thereby modulating the transcription of downstream target genes (**Figure 1**)[3].

Early clinical evidence suggests that factors disrupting circadian rhythms, including light at night (LAN) and night-shift work, correlate with a higher cancer risk[4]. These disturbances have been connected to the promotion of tumor metastasis in breast[5] and colorectal cancer (CRC)[6]. Rather than solely a direct result of the tumor, tumor development and dissemination are profoundly influenced by the complex tumor microenvironment (TME) in which the tumor originates, invades, and spreads[7]. The TME can support and hinder tumor progression, which contributes to extracellular matrix (ECM) remodeling and tumor support involving endothelial cells (ECs) and mesenchymal cells[8]. The TME is vital in each stage of metastatic progression, including edge invasion, intravasation, circulation, extravasation, and colonization in the secondary organs[9]. The TME also significantly affects metastasis processes by influencing immune evasion and suppression, promoting angiogenesis, and epithelial-to-mesenchymal transition (EMT), all of which contribute to tumor progression and spread[9]. Circadian disruption results in remodeling of tumor-associated immune cells in tumor tissues, which involves changes in the temporal dynamics and switching of M1 and M2 macrophage populations, thus accelerating tumor progression[10]. Our previous studies have primarily emphasized the roles of various circadian disruption models in tumorigenesis[11], as well as the differential effects on the tumor and the microenvironment during metastasis[12]. This review comprehensively focuses on how the circadian clock influences tumor metastasis through different stages of metastasis, which is integral to the invasion-metastasis cascade and drives cancer progression through the multistep process.

Clinical relevance between circadian disruption and tumor metastasis

Circadian rhythms have been shown in previous studies and reports to be associated with various types of cancers. Circadian disruption was categorized as a Group 2A carcinogen by the International Agency for Research on Cancer (IARC) as early as 2007[13]. The interference effect of nocturnal shift schedules, nighttime illumination, and social time misalignment, which exhibit irregular patterns of melatonin secretion, are positively linked to the tendency toward breast cancer, prostate cancer, and CRC[14,15]. Despite growing interest, clinical data on how circadian disruption influences tumor metastasis are still scarce. Melatonin and cortisol metabolism fluctuates by means of the interrelationship between the sleep-wake cycle and the internal biological clock. Of note, circadian disruption may reverse melatonin and cortisol rhythms[16]. An abnormal early-night peak in cortisol levels occurs in patients with advanced breast cancer (ABC) that is strongly associated with disease-free survival (DFS)[17]. In addition, circadian disruption promotes fatigue[18] and depression[19], which are significantly associated with increased metastasis and shorter survival. The differential regulation of clock genes in primary and metastatic tumors of cancer patients has been thoroughly studied.

A meta-analysis was conducted involving 36 studies involving 7,476 cancer patients to assess the prognostic impact of clock gene expression regulators of cellular functions, like cell cycle control, DNA repair, and apoptosis[20]. Downregulation of PER1 and PER2 is strongly correlated with poor tumor differentiation, advanced TNM stages, increased metastasis, and shorter overall survival (OS), highlighting the potential role as key prognostic markers and regulators in cancer progression. To explore the association of circadian disruption in endocrine-associated tumors, Kuo and his team[21] found that the promoters of BMAL1, PER1, PER2, and CRY1 exhibit hypermethylation in breast cancer samples. Moreover, BMAL1 and PER2 were relevant to metastasis of lymph nodes[21].

Furthermore, upregulation of circadian regulatory genes, such as *CLOCK, PER1-3, CRY2, NPAS2, and RORC*, has an active role in survival without metastasis, suggesting a prognostic value in breast cancer. Notably, circadian clock functionality was preserved in slow growth, localized behavior, and non-metastatic tumors but disappeared in aggressive phenotypes, like ER^+ and $HER2^+$ breast cancer[22]. Whole-exome sequencing was used to compare mutations of genes between primary tumor tissues and liver metastases in CRC and analysis *via* KEGG pathways revealed a significant enrichment of mutations in genes associated with the circadian clock[23].

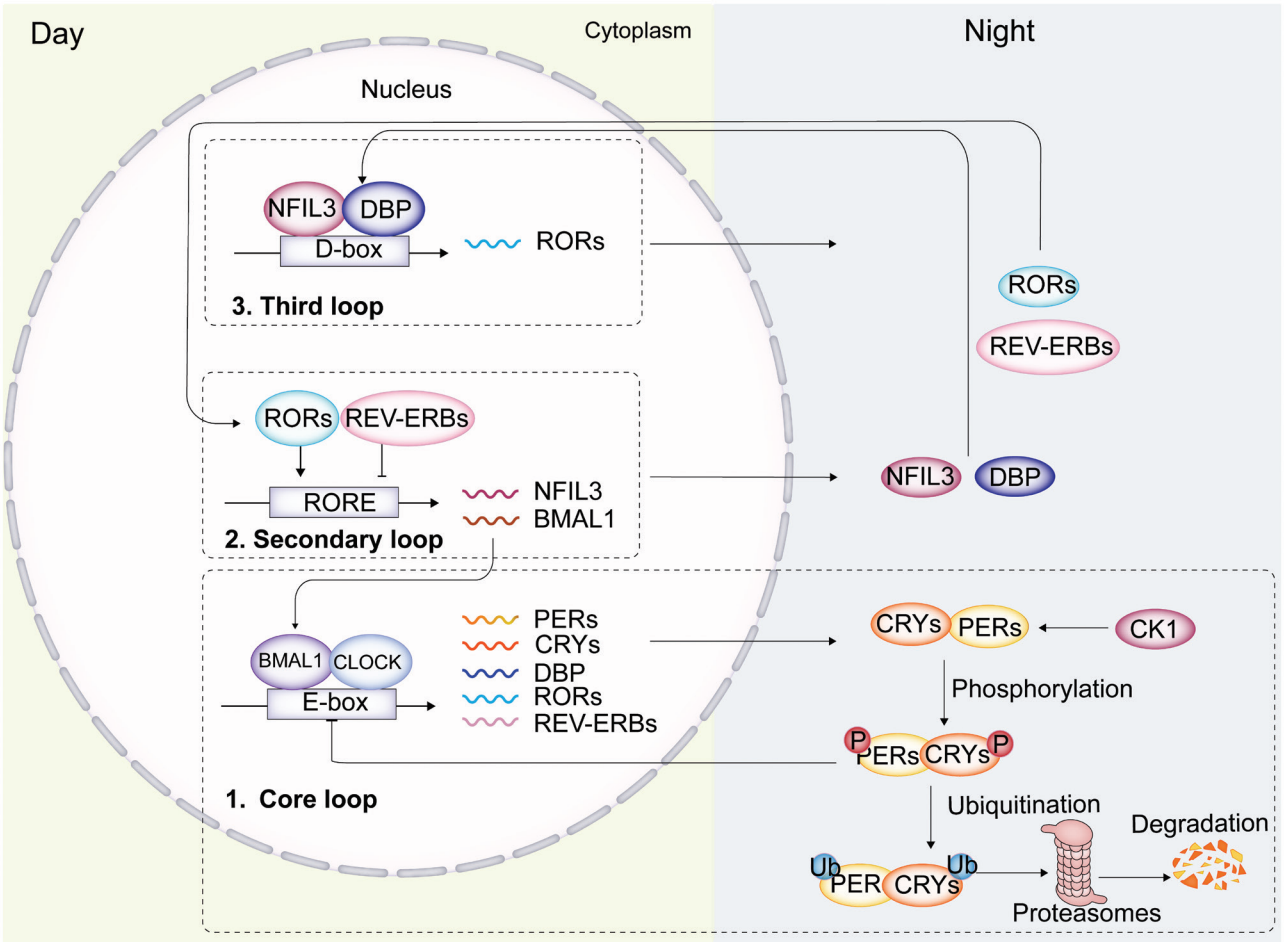


Figure 1 The TTFL of circadian rhythm. The circadian clock is organized around the TTFL composed of three interlocked regulatory loops that coordinate rhythmic gene expression across the day–night cycle. **1. Core feedback loop:** During the daytime, the heterodimeric transcription factors, CLOCK and BMAL1, bind to E-box elements in the nucleus, activating the transcription of core CLOCK genes, including *PERs* and *CRYs*, as well as CLOCK-controlled genes, such as *DBP*, *RORs*, and *REV-ERBs*. Newly synthesized PER and CRY proteins accumulate in the cytoplasm during the night, where CK1 phosphorylates PER proteins, regulating the stability and timing of nuclear entry. Phosphorylated PER/CRY complexes translocate into the nucleus and inhibit CLOCK/BMAL1-mediated transcription. Subsequently, PER and CRY proteins are ubiquitinated and degraded by the **proteasome**, thereby relieving negative feedback and allowing a new circadian cycle to begin. **2. Secondary feedback loop:** In the secondary feedback loop, CLOCK/BMAL1-driven transcription induces the nuclear receptors, REV-ERBs and RORs, which competitively bind to same ROREs in the promoters of circadian genes. Through RORE-dependent mechanisms, REV-ERBs repress whereas RORs activate BMAL1 transcription, thereby stabilizing oscillatory amplitude and phase. Beyond regulating core clock components, RORE-mediated signaling contributes to the phase-aligned expression of downstream clock-associated regulators, including NFIL3, providing a temporal connection between the secondary feedback loop and D-box-dependent circadian output. **3. Third feedback loop:** The loop involves DBP and NFIL3, which competitively bind to D-box elements to regulate rhythmic transcription of downstream clock-controlled genes, thereby contributing to circadian output that is temporally coordinated with ROR-mediated regulation. BMAL1, brain and muscle ARNT-like protein1; CK1, casein kinase 1; CLOCK, circadian locomotor output cycles kaput; CRYs, cryptochromes, CRY1, CRY2; DBP, d-element-binding protein; NFIL3, nuclear factor interleukin 3; PERs, period circadian regulators, PER1, PER2, PER3; RORs, retinoic acid receptor-related orphan receptors, RORα, RORβ, RORγ; RORE, ROR response element; REV-ERBs, nuclear receptor subfamily 1 group d members, REV-ERBα, REV-ERBβ; TTFL, transcription–translation feedback loop.

Further studies compared clock gene expression in primary CRC, colorectal liver metastases (CRLMs), and liver tissue. The level of *PER1*[24] and *PER3* expression was negatively related to the number of CRLMs, whereas, BMAL1[24], BMAL2[25], and CLOCK facilitated CRC metastasis. An opposing relationship was identified between expression of BMAL1 and

distant tumor metastasis in patients with nasopharyngeal carcinoma[26]. TIMELESS is a conserved protein that maintains circadian oscillations of mammals and controls cellular metabolism[27]. Overexpression of TIMELESS has been strongly associated with poor clinical outcomes in human cervical cancer. Specifically, elevated levels of TIMELESS correlates with increased lymphovascular space involvement, which has a vital role in cervical cancer metastasis and progression. REV-ERBα, part of the nuclear hormone receptor group, inhibits tumor and lymph node metastasis in human gastric cancer[28]. Moreover, a reduction in HLF expression has a correlation with early progression and metastatic spread in patients with NSCLC[29].

In summary, the connection between clock genes and tumor metastasis appears to be tissue-specific and context-dependent, and differs across various types of tissues. However, transcriptional clock genes act as factors inhibiting tumor metastasis, whereas the CLOCK/BMAL1 complex acts as a promoter of metastasis in the majority of human cancers, suggesting a vital role in transcriptional activities (**Table 1**). Dysregulation of circadian oscillations can cause tumor metastasis and influence clinical outcomes. The circadian clock and metastasis present opportunities to enhance therapeutic strategies. Combining compounds that modulate clock gene activity with first-line therapies, such as chemotherapy, radiotherapy, or immunotherapy, could improve therapeutic efficacy. This approach not only enhances tumor control but also reduces resistance to conventional treatments, offering a novel and personalized strategy for managing cancer.

Circadian clock mechanisms underlying tumor metastasis

The spread of cancer occurs as tumor cells develop mechanisms to avoid immune detection and invade the circulatory system. Tumor metastasis involves the following five stages: edge invasion; intravasation; circulation; extravasation; and colonization in the distant organ[9]. In this section, we will first elaborate on the roles of circadian rhythms in immune suppression and angiogenesis, which will be followed by a discussion of how circadian rhythms influence the TME at each stage of metastasis.

Circadian rhythm and immune suppression

A pivotal aspect of malignant tumor progression is the ability to evade and suppress the host immune system. This process is always accomplished by suppressing various effector immune cells, or more commonly, by stimulating immunosuppressive cells, including myeloid-derived suppressor cells (MDSCs). MDSCs inhibit immunosurveillance by inhibiting antigen presentation, suppressing T cell activation, altering macrophage polarization, and reducing NK cell cytotoxicity[30]. The circadian clock inherently modulates the action and functionality of immune cells[31]. LAN, a method used to induce circadian disruption, promotes the recruitment of $CD11b^+Ly6G^{high}CD11b^+CD49d^+$MDSCs, thereby fostering an immunologic inhibitory surrounding[32]. Chronic jet lag (CJL) also promotes the recruitment of MDSCs by establishing an immunosuppressive environment through the CXCL5-CXCR2 signaling pathway in bone marrow metastases and breast cancer lung metastases[33]. In addition, CJL impairs NK cell cytotoxicity and suppresses CD122 transcription, thereby further promoting tumor progression[34,35].

In addition to light disruption, inhibition of clock gene oscillation contributes to the abnormal immune landscape in gliomas, which features high PD-L1 and CTLA-4 expression[36]. The positive feedback loop gene, *BMAL1*, correlates positively with $CD4^+$ T cell and neutrophil penetration, and dendritic cells (DCs), indicating anti-tumor activity[37]. The negative feedback loop genes (*PER2* but not *PER1*), which are transcribed by the BMAL1/CLOCK complex, are pivotal in forming a microenvironment that suppresses tumor progression that is characterized by the accumulation of collagen and the presence of cancer-associated fibroblasts (CAFs)[38]. Similarly, the nuclear receptors and retinoic acid-related orphan receptors (*RORα* and *RORγ*) have an important role in immune suppression. RORα has a major role in preserving cholesterol balance in $CD8^+$ T cells through suppression of the NF-κB-mediated transcriptional regulation by altering the status of T cells from dormant-to-cytotoxic[39]. Moreover, *RORα* inhibits activation of proliferative target genes in fibroblasts through the Wnt/β-catenin pathway[40]. RORγ is a key transcription factor that promotes innate immune activation, including the differentiation and function of $CD4^+$Th17 and $CD8^+$Tc17 cells[41], and simultaneously alleviating immune suppression by inhibiting T regulatory cell (Treg) development and reducing the expression of co-inhibitory receptors on tumor-reactive lymphocytes[42]. Immune suppression has a crucial role in tumor initiation and growth. The above studies indicated that most clock genes inhibit tumor metastasis by reshaping immune cell activity. These findings suggested a link between circadian rhythms and immune suppression, highlighting the significant impact on tumor progression (**Figure 2**).

Circadian rhythm and angiogenesis

Angiogenesis has a key role in invasive tumor expansion, metastasis, and deregulation of dormancy in second organs[43]. Some evidence has indicated that regulation of cellular circadian clock machinery can occur directly and indirectly through angiogenic processes. Peripheral circadian regulators within the vasculature are broadly presented in the ECs, vascular smooth muscle cells (VSMCs), and pericytes[44]. Recent studies by Teleanu and colleagues[43] have revealed the

Table 1 CLOCK gene expression across various cancer types

Name	Cancer type	Model	Type	Metastatic endpoint	Effect on cancer	References
BMAL1	CRC	Human tissue	mRNA	Liver metastasis	Increased metastasis of liver	24
	CRC	Mouse model	Protein	-	Longer OS	112
	Nasopharyngeal carcinoma	Human tissue	Protein	Distant metastasis	Decreased tumor distant metastasis	26
BMAL2	CRC	Human tissue	mRNA	Liver metastasis	Increased metastasis of liver	25
TIMELESS	Breast cancer	Human tissue/cell lines	mRNA	-	Shorter MFS	22
	Cervical cancer	Human tissue	Protein	Pelvic lymph node metastasis	Increased metastasis of pelvic lymph nodes, shorter DFS	113
PER1	Breast cancer	Human tissue/cell lines	mRNA	-	Longer MFS	22
	CRC	Human tissue	mRNA	Liver metastasis	Decreased metastasis of liver	24
PER2	Breast cancer	Human tissue	Protein	Lymph node metastasis	Increased metastasis of lymph nodes	21
	Breast cancer	Human tissue/cell lines	mRNA	-	Longer MFS	22
PER3	Breast cancer	Human tissue/cell lines	mRNA	-	Longer MFS	22
	CRC		mRNA	Liver metastasis	Decreased metastasis of liver	114,115
CRY2	Breast cancer	Human tissue/cell lines	mRNA	-	Longer MFS	22
REV-ERBα	Gastric cancer	Human tissue	Protein	-	Decreased metastasis of tumor and lymph nodes	28
RORC	Breast cancer	Human tissue/cell lines	mRNA	-	Longer MFS	22
NPAS2	Breast cancer	Human tissue/cell lines	mRNA		Longer MFS	22
HLF	NSCLC	Human tissue/ xenograft model	mRNA/protein	Distant metastasis	Decreased tumor distant metastasis	29

OS, overall survival; DFS, disease-free survival; MFS, metastasis-free survival; CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

functional impact of elevated BMAL1 expression in VSMCs. Takaguri et al.[45] reported that BMAL1 partially mediates the proliferative response of VSMCs to platelet-derived growth factor-BB (PDGF-BB) through the ERK signaling pathway. The circadian disruption influences pro-angiogenic factors as well, which oscillate in a circadian pattern, including vascular endothelial growth factor (VEGF), bFGF, IGFBP and EGF[46]. Yasuniwa[47] used tumor-bearing mice under constant light (LL) and showed a decreased level of VEGF, revealing that circadian disruption led to inhibited angiogenesis and elevated levels of various pro-angiogenic factors. The amount of VEGF in tumor tissue exhibited a stronger expression peak at nighttime compared to the daytime in a carcinogen-induced mouse sarcoma model[48]. Circadian genes serve as pro-[49] and anti-angiogenic factors[50]. PER2 regulation is context-dependent and varies across different tumor types and models. RORα exhibits an anti-angiogenic phenotype, whereas BMAL1 acts as a pro-angiogenic factor under tissue ischemia and can directly bind to the VEGF gene promoter, thereby modulating the VEGF gene promoter activity[51,52]. Overall, circadian genes are deeply involved in tumor angiogenesis and the regulatory effects vary depending on the tumor type and model (**Figure 2**).

Circadian and invasive edge

The invasive edge refers to the interface between the tumor bulk and the surrounding normal parenchyma, where malignant cells penetrate the basement membrane and begin to infiltrate nearby tissues. Tumor cells display substantial molecular

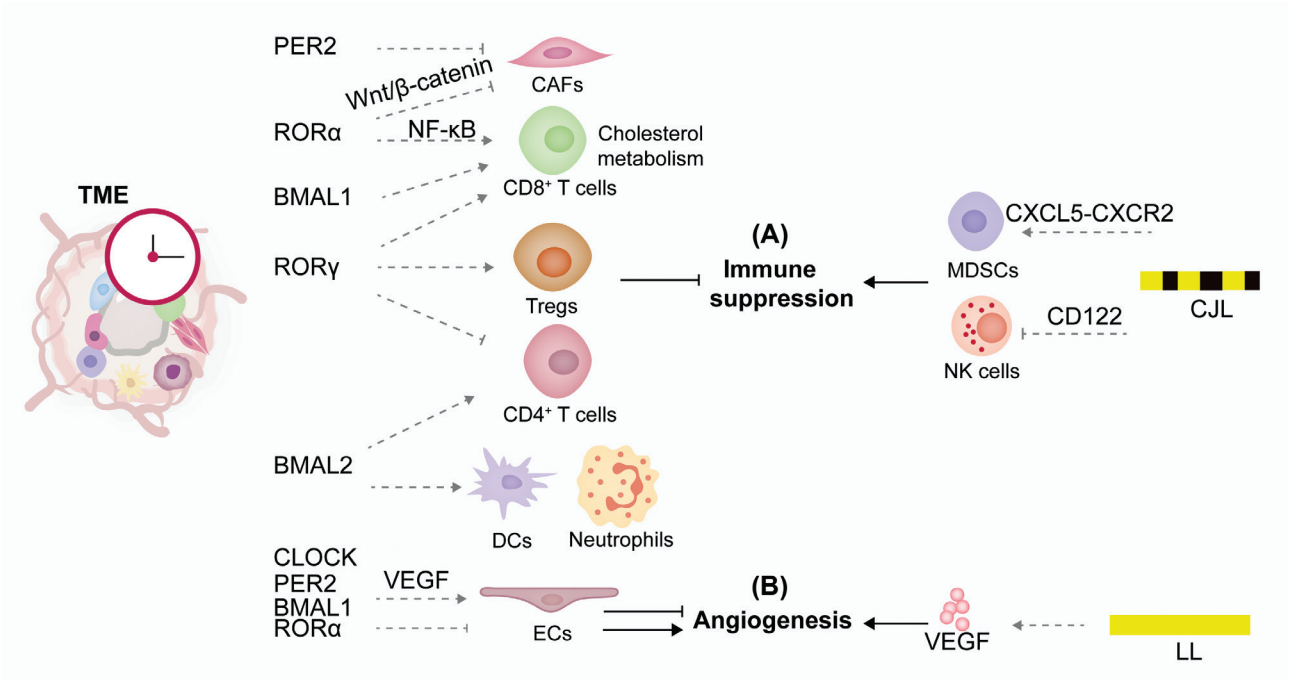


Figure 2 Circadian clock-specific TME that affects immune suppression and angiogenesis. Schematic illustration of how circadian clock components modulate immune suppression and angiogenesis in the TME. (A) **Circadian regulation of immune suppression.** Core clock genes, including *BMAL1*, *BMAL2*, *CLOCK*, *PER2*, *RORα*, and *RORγ*, influence the differentiation, function, and metabolic state of multiple immune cell populations within the TME. Circadian regulation affects CAFs, $CD8^+$ T cells, $CD4^+$ T cells, Tregs, DCs, and neutrophils, thereby shaping immunosuppressive signaling pathways, such as NF-κB and metabolic processes, including cholesterol metabolism. In parallel, circadian disruption, exemplified by CJL, promotes the accumulation and suppressive activity of MDSCs through the CXCL5–CXCR2 axis and impairs NK cell function *via* altered CD122 signaling, collectively enhancing immune suppression. (B) **Circadian regulation of angiogenesis.** Circadian clock components, including CLOCK, BMAL1, PER2, and RORα, regulate angiogenic processes by modulating VEGF signaling in ECs. Disruption of circadian rhythms, such as exposure to LL, enhances VEGF-driven angiogenesis, thereby facilitating tumor vascularization. BMAL1, brain and muscle ARNT-like protein1; BMAL2, brain and muscle ARNT-like protein2; CAFs, cancer-associated fibroblasts; CJL, chronic jet lag; CXCL5, C-X-C motif chemokine ligand 5; CXCR2, C-X-C motif chemokine receptor 2; DCs, dendritic cells; ECs, endothelial cells; LL, constant light; MDSCs, myeloid-derived suppressor cells; NK cells, natural killer cells; PER2, period circadian regulator 2; RORα/γ, retinoic acid receptor-related orphan receptor alpha/gamma; TME, tumor microenvironment; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor.

diversity and phenotypic adaptability within this area, involving reorganization of the cytoskeleton, enhanced expression of matrix-degrading enzymes, such as matrix metalloproteinases (MMPs), modified adhesion properties, and induction of EMT. These invasive front cells exhibit high motility and aggressiveness and are widely recognized as the precursors driving tumor dissemination and relapse.

The EMT represents one of the earliest stages of primary tumor invasion, a phenotypic shift that facilitates tumor cell migration and subsequent entry into the circulatory system[53]. Core circadian transcription factors have a dual role in EMT formation, both promoting and inhibiting EMT formation. BMAL1 can reduce the migratory and invasive capabilities of U87MG[54], lung cancer, and glioma cells[55] *via* blocking the PI3K-Akt-MMP-2, MMP9 pathways, a classical pathway of EMT. Furthermore, *BMAL1* inhibits intracellular ROS-induced EMT *via* TGF-ß signaling[56]. The expression of TGF-β pathway-related genes, including *TGF-β1*, *SMAD3*, *SMAD4*, and *SMAD7*, fluctuates according to circadian rhythms. Among these genes, *SMAD4* enhances invasiveness and chemosensitivity of pancreatic ductal adenocarcinoma (PDA) cells[57]. Conversely, overexpression of BMAL1 enhances the metastatic potential of some tumors. For example, BMAL1 overexpression promotes breast cancer cell metastasis by upregulating MMP9 expression[58]. *CLOCK* has been shown to enhance EMT in CRC and is markedly correlated with late-stage TNM classification and lymphatic metastasis[6]. Moreover, *CLOCK and BMAL1* regulate the RHOA–ROCK–CFL signaling axis, thereby modulating F-actin/G-actin turnover and facilitating the proliferation, migration, and invasion of cancer cells[59]. However, *PER2* serves as a transcript co-repressor to suppress the expression of EMT in breast epithelial and tumor

cell lines *via* recruited polycomb proteins (EZH2, SUZ12, and HDAC2) to octamer transcription factor 1 (OCT1) binding sites of the TWIST1 and SLUG promoters[60]. Above all, these findings indicate that circadian regulation at the invasive edge is context-dependent, varying across tumor types and models.

Moreover, cancer stem cells (CSCs), defined by self-renewal, differentiation, and invasive capabilities, are promoted by EMT and hypoxic conditions[61-63]. There are also strong associations between circadian and CSCs. Chronic circadian disruption (CRD) leads to an increase in the population of breast CSCs. In these cells, particularly in aldehyde dehydrogenase (ALDH)-positive cells, clock genes fail to exhibit rhythmic expression. This observation implies that clock gene activity may be suppressed within CSCs[33]. With respect to clock genes, the CLOCK/BMAL1 heterodimer participates in maintaining glioma stem cells (GSCs) and immunosuppression *via* the enhanced transcription of olfactomedin-like3 (OLFML3), a newly identified chemokine that attracts microglia and suppresses immune responses[64]. A CLOCK-OLFML3-HIF1α-legumain (LGMN)-CD162 signaling axis has been identified in glioblastoma multiforme (GBM), highlighting the role in driving intratumoral immune suppression in the TME[65]. Application of REV-ERB agonists (SR9009 and SR9011) specifically promote CSC differentiation[66], impair the GSC maintaining an undifferentiated state together with self-renewal ability, and cause cell-cycle arrest with apoptosis in GBM[67]. *PER2* and *PER3* negatively regulate breast cancer stemness[68] and prostate cancer stem cells, respectively[69]. Taken together, positive feedback of the CLOCK/BMAL1 heterodimer may be crucial for CSC maintenance, while negative feedback of genes may inhibit cancer stemness (**Figure 3**).

Circadian rhythm and intravasation

In addition to developing an invasive phenotype in primary tumors, the critical phase in the metastatic cascade is the process of blood vessels into the bloodstream, which is known as intravasation[70]. Tumor associated macrophages (TAMs) are within the TME. Increasing evidence suggests that TAMs promote tumor progression by means of various mechanisms, primarily by facilitating intravasation[71]. Therefore, we will elucidate the functions of the circadian clock on TAMs in this chapter.

First, TAMs are positioned to blood vessels, assisting cancer cells in entering the bloodstream through intravasation[72]. Some studies have suggested that circadian regulates macrophage secretion and polarization. The study of Sun et al.[73] revealed that macrophages are increased in CRD tissues and further aggravate the risk of cancer. CRD enhanced tumor progression by altering or reversing the day-night cycles of M1 and M2 macrophages in a model of melanoma, along with concentrations of cytokines in spleen and tumor tissues[74]. Moreover, the cell movement and phagocytosis of macrophages are inversely correlated with levels of *BMAL1*, suggesting that clock genes regulate some aspects of immunity[75]. Furthermore, *BMAL1* directly modulates the transcriptional function of *NRF2*, antioxidative function involved in the regulation of IL-1β in macrophages and drives pro-inflammatory and oncogenic signals[76]. It has also been reported that *BMAL1* retains mitochondrial oxidative metabolism, while reducing oxidative stress to regulate HIF-1α activity, and specific *BMAL1* knockout in TAMs facilitates an immunosuppressive TME[77]. With respect to negative clock loops, REV-ERBα, an orphan nuclear receptor, suppresses macrophage inflammatory responses by directly regulating CCL2 expression[78]. *RORα* has a vital role in regulating macrophages by decreasing the pro-inflammatory cytokines release *in vivo*[79]. It is unclear how the circadian rhythm modulates macrophages during tumor intravasation. Further research is needed to address whether the circadian rhythm hijacks tumor cell intravasation into circulation by regulating resident or myeloid macrophage recruits (**Figure 4**).

Circadian rhythm and circulation

Metastasis is an inherently inefficient process, as fewer than 0.01% of disseminated tumor cells successfully establish colonies at distant sites to form clinically detectable metastases, a process that is dependent on the circulatory system[9]. During dissemination, the platelets release TGF-β and platelet-derived growth factor (PDGF) to protect CTCs against shear stress and immune attacks[80]. CTC counts fluctuate with the circadian rhythm in multiple myeloma (MM) patients, peaking in the latter half of the night, indicating a potential preference for dissemination into peripheral circulation during rest[81]. A study using *in vivo* fluorescent flow cytometry revealed that CTC counts are higher during early stages in prostate cancer compared to advanced stages and exhibit a peak at the onset of the night within a 24-h cycle[82].

Platelets also display a 24-h rhythm in aggregation and adhesion under the control of CLOCK genes. The enforced 20-h rest/activity cycle rhythms peaked with respect to platelet aggregation and adhesion with leukocytes and endothelial cells[83]. Under CRD conditions, platelets and immunoglobulin (IgM and IgE) counts are reduced[84]. Taken together, future investigations are warranted to fully elucidate the mechanisms underlying circadian clock-mediated regulation of CTC trafficking (**Figure 4**).

Circadian rhythm and extravasation

Extravasation of CTCs is a tightly regulated, multistep process requiring dynamic interactions between tumor cells and the vascular endothelium. Recent studies indicate that these interactions are temporally gated by the circadian clock, which coordinates endothelial adhesion, vascular tone, and barrier permeability. The compact structure of

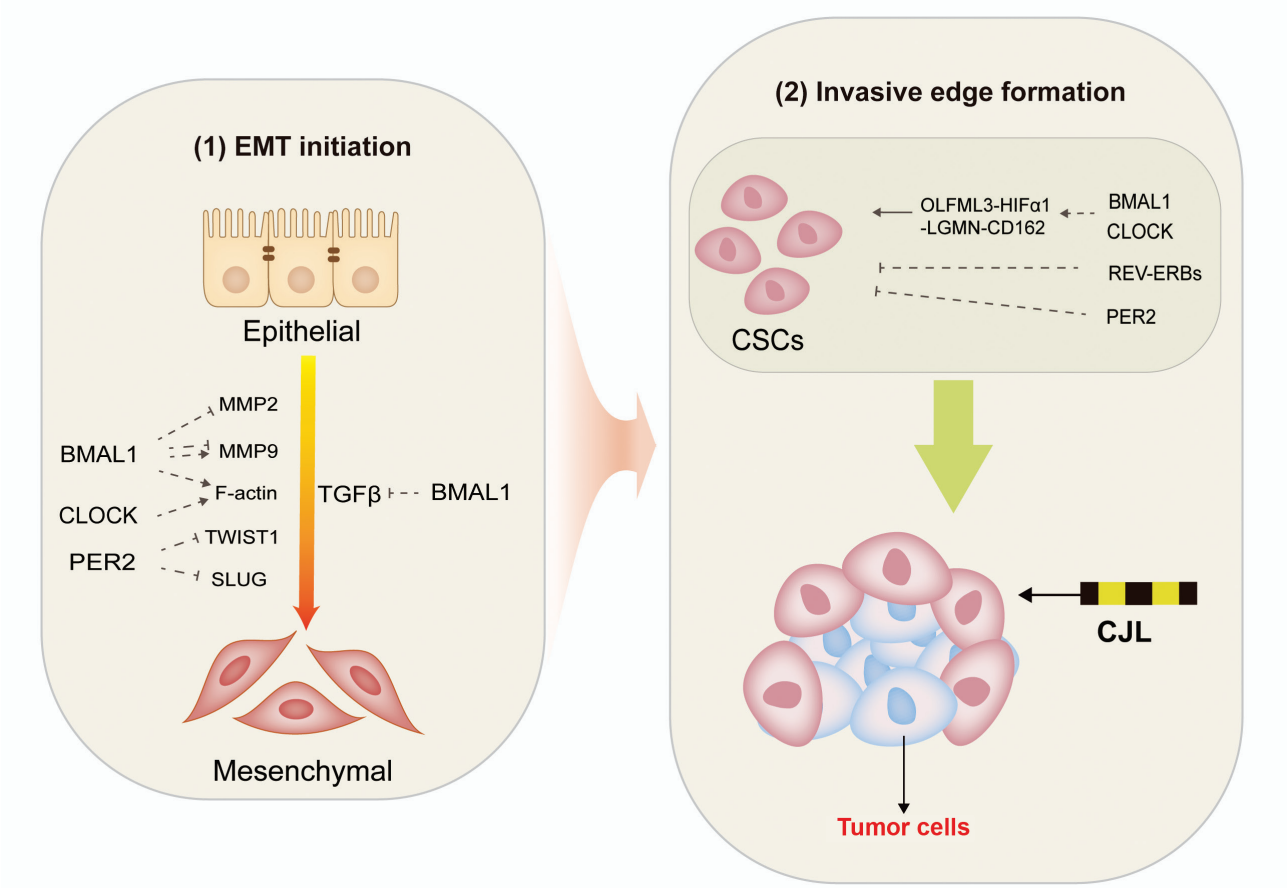


Figure 3 Circadian clock-specific TME that affect invasive edge. Schematic illustration of the context-dependent roles of circadian clock components in regulating tumor invasion at the invasive edge. **(1) EMT initiation:** At the early stage of tumor invasion, core circadian regulators, including **BMAL1, CLOCK, and PER2**, participate in EMT initiation. This process is associated with increased **MMP2/9** expression, altered **F-actin** dynamics, and regulation of EMT-related transcription factors **(TWIST1** and **SLUG)**, together with **TGF-β-related signaling**, thereby facilitating the transition from epithelial-to-mesenchymal phenotypes. **(2) Invasive edge formation:** At the invasive edge, circadian regulation is associated with the CSC-like states and collective invasive behavior. The CLOCK/BMAL1 axis has been implicated in promoting invasive phenotypes through downstream signaling modules (e.g., OLFML3–LGMN–CD162), whereas negative-feedback clock components, such as REV-ERBs and PER2 are associated with the modulation of stemness-related properties. External circadian perturbation, such as CJL, may further influence tumor cell behavior at the invasive edge. BMAL1, brain and muscle ARNT-like protein 1; CLOCK, circadian locomotor output cycles kaput; CJL, chronic jet lag; EMT, epithelial–mesenchymal transition; MMP2/9, matrix metalloproteinase 2/9; PER2, period circadian regulators 2; REV-ERBs, nuclear receptor subfamily 1 group D; SLUG, snail family transcriptional repressor 2; TGFβ, transforming growth factor beta; TWIST1, twist family bHLH transcription factor 1.

capillary endothelial walls contributes to organ-specific patterns of metastasis[85]. Circadian disruption, such as occurs in sleep deprivation (SD), impairs endothelial function *via* dysregulation of the nitric oxide (NO)-dependent vasodilatory pathway in mice and humans[86]. Core CLOCK genes, including *BMAL1* and *PER2*, are positively associated with NO production and inversely related to endothelial nitric oxide synthase (eNOS) expression[87], suggesting that rhythmic control of endothelial activation is integral to vascular homeostasis.

At the molecular level, adhesion molecules, such as ICAM-1 and VCAM-1, exhibit circadian oscillations under the regulation of CLOCK and BMAL1, thereby influencing the timing and efficiency of tumor cell attachment to the endothelium[88,89]. Likewise, circadian variation in eNOS activity and NO release modulates vascular relaxation and permeability, creating time-dependent windows that may favor or hinder tumor cell extravasation[90,91]. In specific vascular niches, such as the blood–brain barrier (BBB), clock-controlled expression of efflux transporters and tight

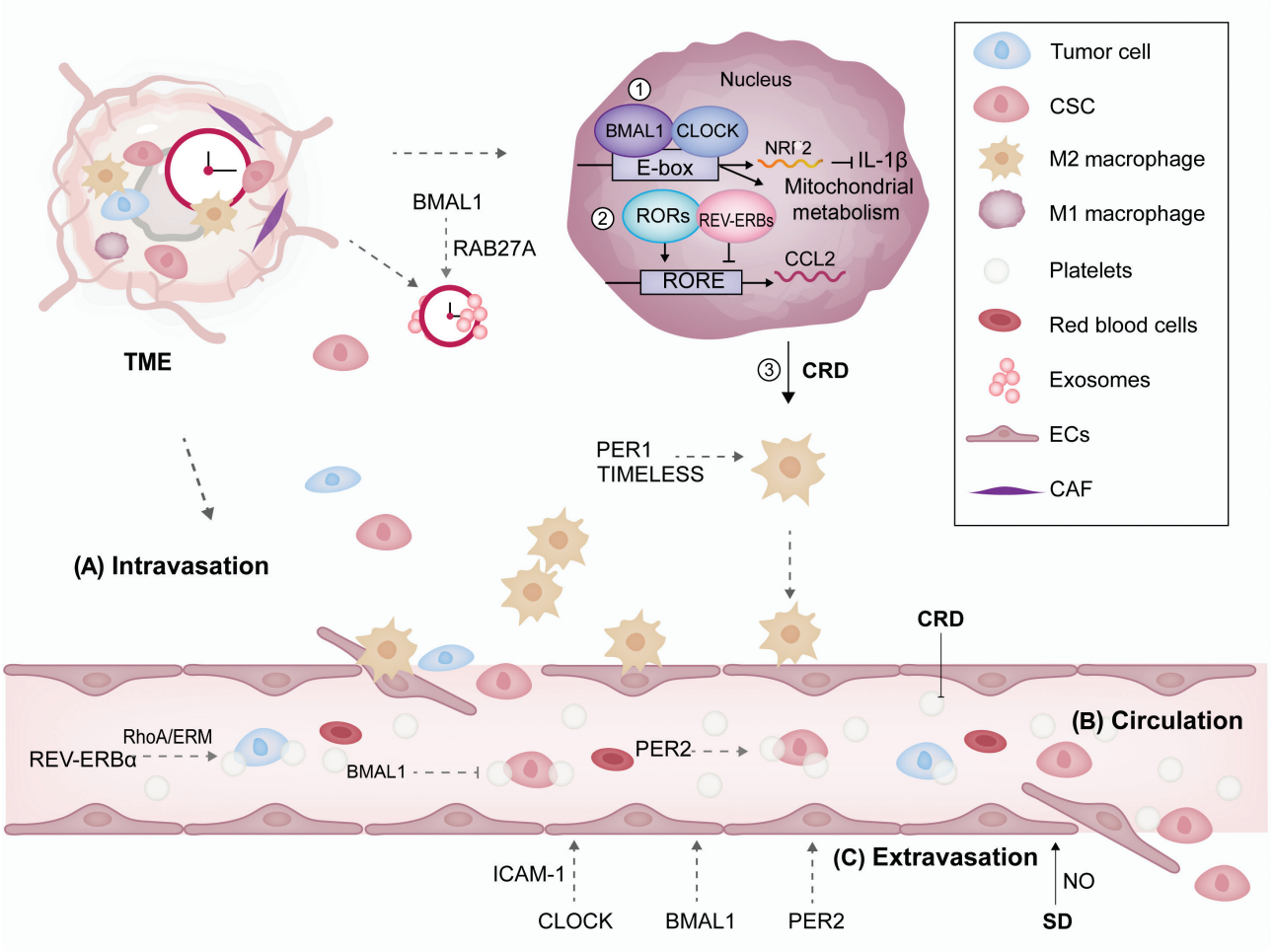


Figure 4 Circadian clock-specific TME that affect intravasation, circulation, and extravasation. Schematic illustration of how circadian clock components regulate key steps of tumor cell dissemination, including intravasation, circulation, and extravasation, through interactions with the TME, exosome-mediated communication, and CRD. (A) **Intravasation.** ① The CLOCK/BMAL1 heterodimer activates the expression of *NRF2*, thus inhibiting secretion of IL-1β in macrophage. The CLOCK/BMAL1 heterodimer binds to the E-box to maintain the mitochondrial metabolism of macrophage homeostasis. ② *RORα* induces the expression of *CCL2*, while *REV-ERBα* inhibits *CCL2* in macrophages. ③ CRD promotes the transition of M1 macrophages to M2 macrophages. (B) **Circulation.** During circulation, disseminated tumor cells are exposed to a dynamic vascular environment under conditions of circadian disruption. Circadian clock components, including BMAL1, PER2, and REV-ERBα, are associated with the regulation of tumor cell interactions with endothelial cells, platelets, and immune cells within the bloodstream, which together influence tumor cell survival and behavior during circulation. (C) **Extravasation.** Circadian clock genes, including *CLOCK*, *BMAL1*, and *PER2*, regulate endothelial activation and barrier function during extravasation. Rhythmic modulation of adhesion molecules, such as ICAM-1, together with NO signaling, influences tumor cell arrest and transmigration across the endothelium. SD and CRD exacerbate endothelial dysfunction, facilitating tumor cell extravasation into distant tissues. BMAL1, brain and muscle ARNT-like protein 1; CAF, cancer-associated fibroblast; CLOCK, circadian locomotor output cycles kaput; CRD, circadian rhythm disruption; CSCs, cancer stem cells; CCL2, C-C motif chemokine ligand 2; ECs, endothelial cells; ICAM-1, intercellular adhesion molecule 1; IL-1β, interleukin-1 beta; NO, nitric oxide; NRF2, nuclear factor erythroid 2-related factor 2; PER1/2, period circadian regulators 1/2; RAB27A, RAB27A member RAS oncogene family; REV-ERBα, nuclear receptor subfamily 1 group D member 1; RORs, retinoic acid receptor-related orphan receptors; SD, sleep disruption; TME, tumor microenvironment.

junction proteins shapes rhythmic changes in barrier permeability, acting as a temporal gate for metastatic invasion[92]. Furthermore, pericytes, which reinforce microvascular stability, harbor intrinsic circadian clocks that synchronize with endothelial rhythms to maintain barrier integrity and regulate neurovascular coupling[93].

Taken together, these findings support the view that cancer extravasation is temporally regulated by endothelial and perivascular clocks that control adhesion, NO signaling, and barrier function. While the mechanistic links connecting the circadian phase with platelet activation, cytokine release, and endothelial–tumor communication remain to be clarified[88] (**Figure 4**).

Circadian rhythm and exosomes

Tumor-derived exosomes, small extracellular vesicles (EVs) secreted by the primary tumor, educate the environment to facilitate formation of the cancer premetastatic niche (PMN). It remains unclear whether EVs, which contain exosomes, facilitated intercellular communication among tissues and exhibit modulation in the circadian rhythm. Khalyfa and his research team[94] observed that plasma exosomes undergo significant modifications when exposed to periodic alterations in environmental lighting. More recently, Yeung[95] suggested that modulation of the rhythmic transcript and protein abundance by the circadian clock indirectly results in the time-specific loading of proteins into small EVs, revealing how exosomes facilitate temporal synchronization between and across different tissues. Moreover, *BMAL1* has been shown to regulate Rab27a expression at the transcriptional level. Rab27a is a crucial molecule involved in exosome secretion, thereby promoting CRC metastasis[96]. In agreement with this finding, Fekry et al.[97] emphasized that exosome secretion and cargo loading exhibit circadian rhythmicity, linking extracellular vesicle dynamics to temporal regulation of tumor development. Because this is a growing area of research, greater focus should be directed toward understanding how circadian rhythms promote the secretion of tumor-derived EVs.

Circadian rhythm and cell cycle regulation

Even if successfully seeded to distant organs, cancer cells must defy angiogenic, cellular, and immune dormancy to guarantee survival and expansion[98]. In the above sections, we have listed angiogenesis and immune suppression under circadian control. We will specifically introduce the cell cycle crosstalk with the circadian clock in this section (**Figure 5**).

Numerous parallels are shared among the circadian regulatory system and cellular division process as biological rhythms within dividing cells with each featuring alternating periods of activation and suppression. Studies show that circadian rhythms impact all steps in the cell division process. For example, during the G1 period, REV-ERBα and RORα facilitate the course of the cellular division process *via* suppress the transcription of $p21^{cip1}$[99]. In contrast, PER1 and TIMELESS hinder the G1-S transition by linking up with ATM and CHK2, leading to stagnation of the cell cycle[100]. CRY1 facilitates the course of the cell cycle by suppressing the special kinase (WEE1), regulating the G2-M checkpoint, which promotes entry into mitosis[101]. In addition, CRY1 aids in the cycle course by repressing WEE1, a kinase responsible for controlling the G2-M checkpoint, thus facilitating entry into mitosis.

The heterodimer of CLOCK and BMAL1 influences the rhythmic transcription of WEE1 and WEE2, effectively managing cell cycle arrest[101]. It has been proposed that the CLOCK–BMAL1 heterodimer influences cell cycle progression by regulating cyclin B1 expression, particularly during the G2/M transition[102]. Conversely, various analyses have revealed that CRY1 limits mitosis by influencing the G2-M transition through mediation of ATM, ATR, and CHK1. This regulation occurs *via* the interaction with the TIMELESS (TIM) in a manner governed by regulating circadian rhythms[103]. Based on the literature discussed above, circadian regulators are critically involved in modulating G1/S and G2/M phase transitions of the cell cycle with the effects varying depending on the context and the phase of the circadian rhythm.

External intervention and CLJ induced disruption of rhythmic expression patterns of the clock and cyclin genes in the liver, resulting in elevated levels of *CcnA2* in tumors, as well as a reduction in $p21^{WAF/CIP1}$ expression, all of which cause a proliferative phenotype[74]. A study in U2OS cells showed that chronic circadian desynchrony (CCD) [serial 8-h advances of the dexamethasone (dex) treatment cycle every 2 d], a substitution of CJL, displayed upregulation of G1/S phase transition genes, including Myc and *cyclin D1/3*, accompanied by enhanced phosphorylation of the retinoblastoma protein by CDK4/6 with increased G1-S progression[104]. With respect to clock genes, the anti-tumor effect of BMAL1 in GBM is associated with reduced migratory and invasive capacities that is mediated by decreased cyclin B1 expression[54]. PER1[105] and PER2[106] are of vital importance in controlling the cell cycle process and ensuring equilibrium between cell proliferation and apoptosis by influencing the cyclin/CDK/CKI network involved in the cell cycle[107]. SR9011, an REV-ERB agonist, impedes breast cancer cell proliferation by targeting cyclin A (CCNA2) and arresting the cell cycle prior to the mitotic phase[108]. In summary, circadian–cell cycle interactions critically shape tumorigenic potential through complex regulatory mechanisms that likely contribute significantly to the effects of diurnal disruption on tumor progression. New research aims to connect these molecular insights to the mechanisms underlying tumor cell proliferation driven by circadian disruption, providing a clearer understanding of the role in cancer progression.

Perspective

The circadian clock regulates 24-h circadian rhythms of numerous physiologic activities through modulation of

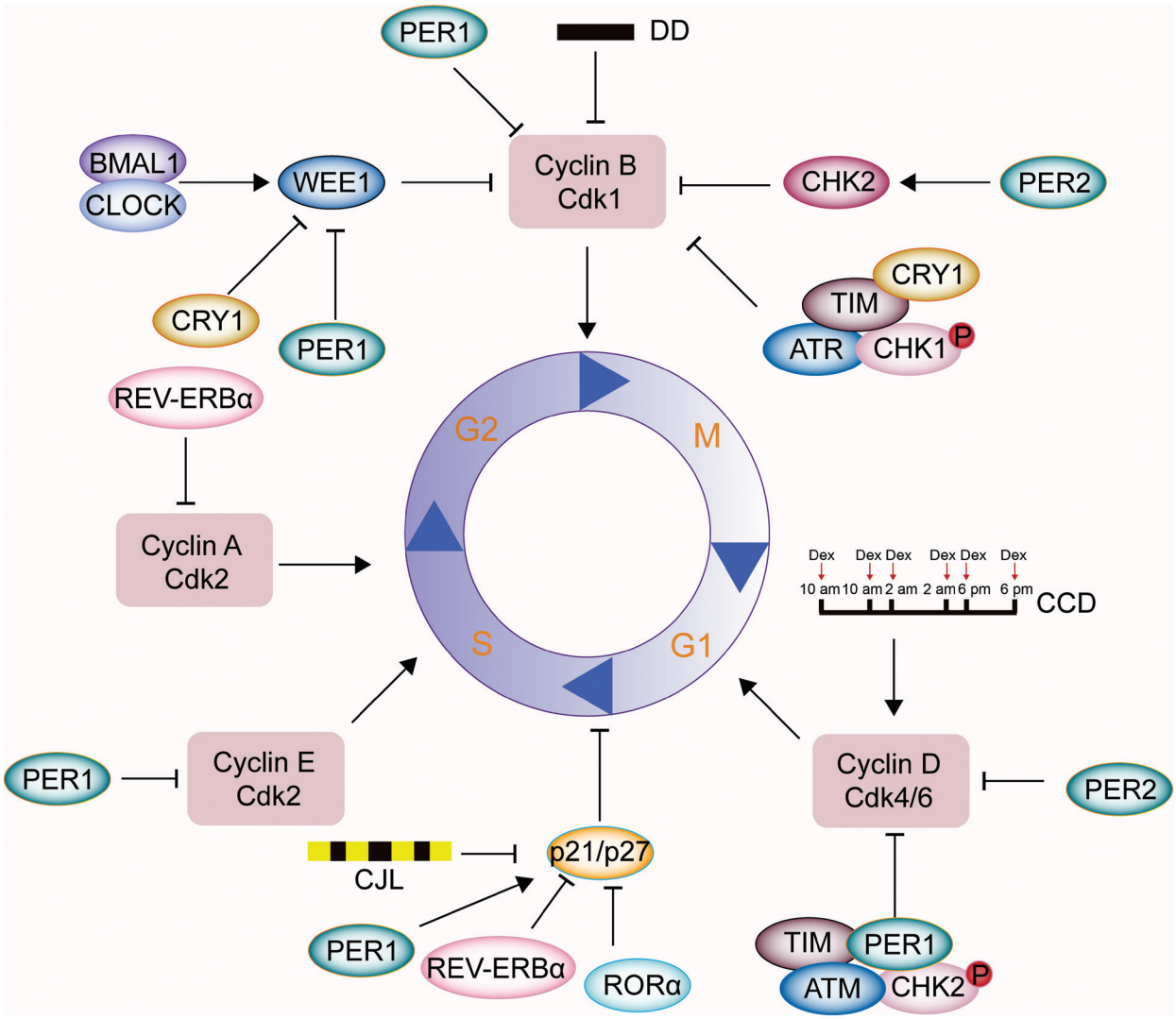


Figure 5 Circadian clock cell-cycle crosstalk on tumor metastasis. Schematic illustration of the interactions between circadian clock components and cell-cycle regulators controlling transitions through G1, S, G2, and M phases. **G1 phase:** Cell-cycle entry is governed by cyclin D–Cdk4/6. Under CCD, cyclin D–Cdk4/6 activity is modulated with PER2 shown as an inhibitory regulator. p21/p27 act as checkpoint mediators at the G1/S boundary and are influenced by PER1, REV-ERBα, RORα, and CJL. These interactions collectively regulate progression toward the S phase. **S phase:** Progression through S phase involves cyclin E–Cdk2 and cyclin A–Cdk2 complexes. PER1 is linked to cyclin E–Cdk2 regulation, while REV-ERBα modulates cyclin A–Cdk2 activity, contributing to S-phase control. **G2 phase:** Transition into mitosis is coordinated by cyclin B–Cdk1. BMAL1/CLOCK regulate WEE1, which in turn modulates cyclin B–Cdk1 activity. CRY1 and PER1 influence WEE1, further integrating circadian control at the G2 checkpoint. **M phase and G2/M checkpoint:** Circadian components intersect with DDR pathways, including PER2–CHK2, CRY1–TIM–ATR–CHK1, and PER1–TIM–ATM–CHK2, which modulate cyclin B–Cdk1-dependent mitotic progression. External cues, such as DD are depicted as additional modulators at this stage. ATR, ATR serine/threonine kinase; ATM, ATM serine/threonine kinase; BMAL1, brain and muscle ARNT-like protein1; CCD, chronic circadian disruption; CDK, cyclin-dependent kinase; CHK1/2, checkpoint kinase1/2; Cdk1/2/4/6, cyclin dependent kinase 1/2/4/6; CLOCK, circadian locomotor output cycles kaput; CRY1, cryptochrome1; CJL, chronic jet-lag; DD, constant dark; PER1/2, period circadian regulator1/2; RORα, retinoic acid receptor-related orphan receptorα; REV-ERBα, nuclear receptor subfamily 1 group d member; TIM, timeless; WEE1, G2 checkpoint kinase.

gene expression. Disruption of circadian rhythms appears to be involved in tumor metastasis, potentially through dysregulation of key biological processes, such as cell growth, tissue homeostasis, metabolism, and response to stimuli. Tumor metastasis is heavily influenced by the complex and dynamic TME where the tumor develops, invades,

and spreads. Highly plastic cancer-resident stem cell populations occupying these specialized TMEs are strongly influenced by local niche signals to facilitate invasion and metastasis. Tumor-associated immune cells, stromal niches, and CSCs display robust and self-automatic rhythmic oscillations under the control of the circadian clock. Herein we discuss the diverse circadian clock signals that support the TME in the context of different stages of tumor metastasis from primary tumors to distant organs, encompassing invasion, intravasation, circulation, extravasation, cell cycle progression, immune response, and angiogenesis. We outline recent advances that suggest circadian disruption that may influence tumor metastasis and offer potential avenues for therapeutic intervention.

Although epidemiologic and experimental studies have firmly established the association between circadian disruption and tumor metastasis, the molecular intricacies within the TME remain inadequately elucidated. To better illustrate the chronobiology reporting standards in circadian research, we have summarized relevant guidelines from previous studies and presented the guidelines in **Figure 6**. This review synthesizes current evidence on how circadian disruption-mediated through environmental perturbations (chronic jet lag/CJL, light-at-night/LAN, long days/LL, constant darkness/DD, and shift work/SD) and core clock gene dysregulation-orchestrates metastatic dissemination *via* TME remodeling. For example, BMAL1 suppresses the migratory and invasive potential of U87MG, lung, and glioma cancer cells[55]. In contrast, *BMAL1* facilitates breast cancer cell metastasis by upregulating MMP9 expression[58]. Core clock components exhibit context-dependent metastatic regulation, necessitating lineage-specific analysis. Given the context-dependent nature of circadian regulation, the effects of core clock genes on tumor progression appear to vary across experimental models, temporal paradigms, and tumor backgrounds. Differences in sampling time, cell or animal models, and the intrinsic metabolic or

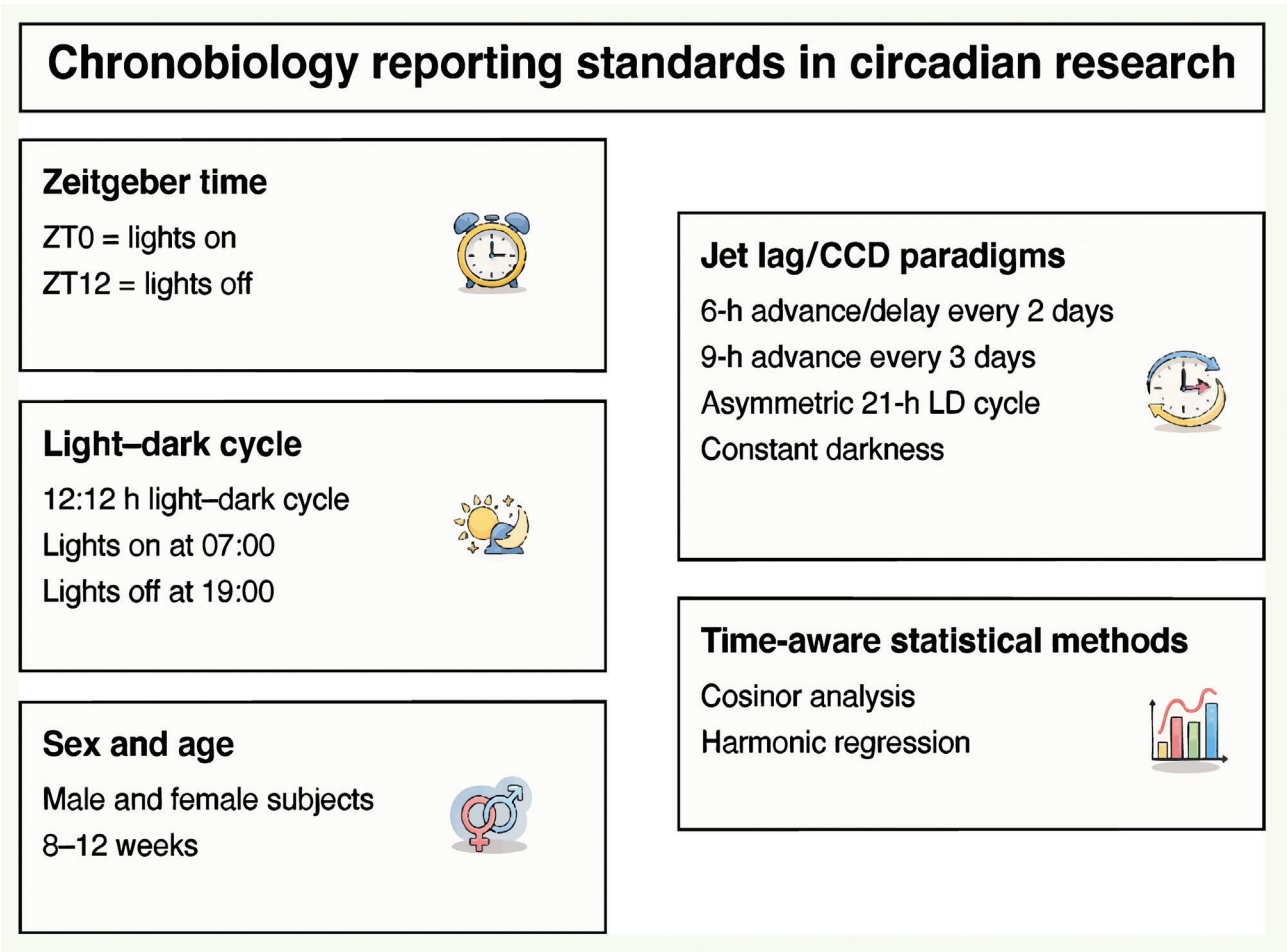


Figure 6 Chronobiology reporting standards in circadian research. Schematic overview of key methodologic parameters that should be reported in circadian studies, including Zeitgeber time definition, light–dark cycle conditions, gender and age of experimental subjects, jet lag or chronic circadian disruption paradigms, and time-aware statistical methods.

immunologic characteristics of each tumor type may underlie the observed inconsistencies among studies. Future work should therefore focus on delineating tumor- and stage-specific mechanisms by which circadian genes influence cancer behavior, as well as developing standardized time-resolved experimental designs to improve the comparability and reproducibility of circadian oncology research[109].

However, regulation of circadian clock cells in the TME has not been fully discussed, which leaves critical knowledge gaps in TME chronobiology. For example, how do central SCN clocks entrain pericyte-endothelial oscillators-especially when pericyte ablation extinguishes endothelial rhythms? The diurnal activity peaks of CAFs, platelets, and tumor-derived exosomes remain unmapped. Neutrophil TEM peaks at ZT14, yet CAF-collagen remodeling timing is unknown.

Moreover, the metastasis-phase-specific roles remain unclear. Clock control over circulating CTC clusters during vascular transit requires intravital imaging validation. To advance this field, we propose spatiotemporal multi-omics, as follows: combining time-series scRNA-seq with circadian proteomics of TME components (e.g., ECM-bound TIMP1 diurnal turnover); microfluidic TME-on-Chip, mimicking rhythmic interstitial flow to test chronopharmacology; and stromal-targeted chronotherapy, exploiting CDK4/6 inhibitor efficacy windows aligned with CAF activation cycles. While circadian regulation of TME dynamics is recognized as a metastasis "gatekeeper," resolving the molecular spatiotemporal map of stromal-tumor interactions will unlock chronotherapeutic strategies-potentially halting metastasis through time-targeted disruption of TME remodeling.

In the pharmacologic domain, several small-molecule modulators targeting core circadian regulators are currently under exploration. Representative examples include the BMAL1-targeting compound [core circadian modulator (CCM)], which binds to the PAS-B domain of BMAL1 to fine-tune transcriptional activity and suppress tumor growth in experimental models[110] and the CRY1-selective molecule. M47, which destabilizes CRY1 and has been shown to prolong lifespan in p53-knockout tumor-prone mice[111]. In addition, the REV-ERB agonists, SR9009 and SR9011, have been reported to modulate circadian and metabolic pathways in preclinical studies[66], although limited pharmacologic specificity and regulatory restrictions constrain translational applicability. While most of these compounds remain in early mechanistic stages, continued progress in clock-directed pharmacology is expected to expand therapeutic opportunities in circadian-based precision oncology. Despite increasing evidence linking circadian disruption to cancer progression and therapeutic response, standardized clinical frameworks for time-dependent sampling or chronotherapy trials remain lacking. Current oncology studies rarely report biological sample timing, treatment delivery phase, or patient chronotype, underscoring the need for harmonized chronobiology guidelines. Future efforts should aim to establish practical recommendations for biospecimen collection windows (e.g., CTCs or plasma biomarkers) and explore feasible time-stratified or time-randomized clinical trial designs for chemotherapy and immunotherapy. Developing such translational standards will be essential for integrating circadian principles into precision oncology.

In summary, numerous studies have explored how clock genes may regulate the TME, suggesting a potential role in tumor metastasis. However, details regarding the molecular mechanisms underlying these remain open. We expect that corollary studies will deepen our comprehension of these complex interactions, facilitating the creation of novel strategies for cancer therapy.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived the structure of the manuscript: Jie Wang, Hao Pan, Yu Wang.
Contributed figures: Hao Pan, Xuan Wang.
Wrote the paper: Jie Wang, Hao Pan, Xuan Wang, Yiwen Huang, Hejin Lai, Yizhou Liu.
Revised the paper: Yu Wang, Ning Pu and Zhimin Fei.

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