Role of the circadian rhythm in squamous cell carcinoma: From molecular mechanism to therapy (Review)

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Abstract. Squamous cell carcinoma (SCC) comprises a heterogeneous group of malignancies with distinct molecular characteristics, clinical behavior and therapeutic responses, highlighting the need for personalized treatment strategies. Circadian rhythms regulate fundamental physiological processes, including cell proliferation, metabolism, DNA repair and immune function, and emerging evidence suggests that circadian regulation may influence pathways relevant to SCC biology and treatment response. This review summarizes current knowledge on the role of circadian regulation in SCC, with particular emphasis on lung SCC, focusing on core clock genes, their interactions with oncogenic and immune-related pathways, and their therapeutic implications. We discuss current evidence supporting chronotherapy as a potential component of personalized SCC treatment while addressing important limitations, including the predominance of preclinical studies, limited SCC-specific clinical evidence and extrapolation from other tumor types. Finally, we outline key research priorities for translating circadian biology into clinical SCC management.

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Abbreviations: CAR-T, chimeric antigen receptor-T therapy; CRISPR, clustered regularly interspaced short palindromic repeats; cSCC, cutaneous squamous cell carcinoma; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; HPV, Human papillomavirus; cerSCC, cervix squamous cell carcinoma; ICIs, immune checkpoint inhibitors; KO, knockout; LSCC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma; MDSCs, myeloid-derived suppressor cells; mRNA, messenger RNA; NK, natural killer cell; NSCLC, non-small cell lung cancer; OS, overall survival; OSCC, oral squamous cell carcinoma; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SCC, squamous cell carcinoma; SCN, suprachiasmatic nucleus; TME, tumor microenvironment; UV, ultraviolet

Key words: squamous cell carcinoma, circadian clock, carcinogenesis, chronotherapy

Contents

1. Introduction

Squamous cell carcinoma (SCC) is a prevalent and clinically distinguished form of cancer that arises from the squamous epithelial cells lining multiple organ systems, including the skin, respiratory tract, upper aerodigestive tract and the gastrointestinal tract (1,2). Particularly, cutaneous SCC (cSCC), SCC of the lung (LSCC), of head and neck (HNSCC), of esophagus (ESCC) and of cervix (cerSCC) belong to the most prevalent SCC subtypes and occur more frequently in older people with a long history of smoking, alcohol consumption, and ultraviolet (UV) exposure (3). Infections with one of the 13 carcinogenic human papillomavirus (HPV) genotypes can lead to HNSCC and cerSCC development at an early age (4,5).

Squamous cell carcinoma represents approximately 20% of all diagnosed skin cancers, with an observed increase in incidence rates over the last decades, especially among individuals of European descent in North America, Europe and Asia (6). Notably, cSCC carcinogenesis is strongly influenced by factors like ultraviolet radiation (UVR), epidermal homeostasis and local neuroimmune and endocrine signaling (7-10)

that represent unique and distinctive features from all other SCC types. Although, it is the most common SCC subtype, its mortality rate is lower than SCCs of other organs, such as the lungs. To this day, lung cancer remains the most lethal cancer worldwide (11). LSCC constitutes 30-35% of non-small cell lung cancers (NSCLC) and is associated with chronic smoking. Also it is characterized by a late onset of symptoms frequently resulting in late diagnosis in stage IV with distant metastasis (12,13). In HNSCC, which comprises about 4.5% of cancer diagnoses and deaths per year (4), alcohol consumption and tobacco use increase the risk of developing HNSCC by up to 40-fold compared to non-users. The overall 5-year survival rate is 83% however, it decreases by approximately 50% upon metastasis, marking a shift in prognosis (14). Over 90% of cervical cancer cases are cerSCC, with HPV infection as a primary etiological factor. Similarly, ESCC accounts for roughly 90% of esophageal cancer cases and demonstrates a marked geographic prevalence in Eastern and Central Asia, as well as Eastern and Southern Africa (14,15).

In recent years, advances in high-throughput sequencing and meta-analyses have highlighted a variety of genes and signaling pathways that are central to the initiation and progression of SCC. The main driver genes aberrantly regulated in SCC pathogenesis are TP53, TP63 (1,16,17), FN1 (18,19), TGFB1/TGFBR (18,20), NOTCH1 (1,20), CDKN2A, NFE2L2, PTEN, FGFR (21), CASP8 (22), SOX2 (1), HRAS (20), PIK3CA (1), WEE1 (17) and FOS/FOSL1/FOSL2 (23). Thus, pathways of Mitogen-Activated Protein Kinase and Extracellular Signal-Regulated Kinase (MEK-ERK) and Janus Kinase and Signal Transducer and Activator of Transcription 3 (JAK-STAT3), Phosphoinositide 3-Kinase, Mammalian Target of Rapamycin, and Mitogen-Activated Protein Kinase (PI3K-mTOR/MAPK) and signaling cascades of Notch receptor family (NOTCH) pathways offer potential target for drug development and may serve as prognostic markers.

Past and current therapies involve combinations of surgery, radiotherapy, and chemotherapy, which are primarily used to eradicate local tumors. Metastatic SCC, relapsed SCC, or SCC with initial or acquired resistance to the first-line treatment likely need targeted therapy approaches to overcome the poor prognosis (24,25). The development and increased availability of immune checkpoint inhibitors (ICIs) improved the SCC therapy survival outcome (26). Thus, ICIs are now standard-of-care in a first-line treatment in advanced cSCC (27), LSCC (28), HNSCC (29), ESCC (30), and cerSCC (31) subtypes that are not eligible for curative surgery.

Several factors control the response to immunotherapy, such as tumor type and progression, genetic variations, and the immune status of the patient. More recently, the circadian clock-an internal biochemical oscillator that regulates 24-h cycles of biological, physiological, and behavioral processes in living organisms-has also emerged as an important determinant of response to immunotherapy.

The melanoma outcomes following immunotherapy (MEMOIR) trial demonstrated that those melanoma patients who received at least 20% of infusions with ipilimumab, nivolumab, or pembrolizumab, or a combination thereof after 4:30 pm had significantly worse overall survival (OS) (32). Similarly, in the instance of NSCLC patients who received chemotherapy and the programmed death-ligand 1 (PD-L1) inhibitor durvalumab, late-day infusions were found to be correlated with poorer progression-free survival (PFS) and OS (33). Furthermore, preclinical evidence demonstrates that immune cells infiltrating tumors, especially CD8+ T cells, follow circadian rhythms, indicating the possibility of an immunotherapy treatment time dependence. These observations support the idea that therapeutic timing may be optimized to improve treatment response (34).

SCC represents therefore a biologically related family of cancers that share molecular and pathological features despite arising in different anatomical sites. In addition, SCC remains a major global cancer burden and current therapeutic outcomes require further optimization potentially related daily timing of therapy administration. Circadian rhythms have emerged as important regulators of cancer-related processes across multiple cancer types (35-37), including pathways governing proliferation, apoptosis, metabolism, DNA repair and immune responses. However, despite this growing interest in circadian regulation in cancer, it is important to acknowledge the gap of substantial evidence in SCC. Existing evidence remains fragmented and limited with relatively few high-impact primary studies and reviews in HNSCC (38-40). Accordingly, this review critically evaluates the evidence to date on circadian regulation in SCC, with a particular focus on lung cancer, and identifies areas that require further investigation.

2. System of the circadian clock

The circadian clock is an internal timekeeping system present in nearly every cell of the body, orchestrating various physiological and behavioral processes in alignment with the 24-h day-night cycle (41-43). This includes regulating the timing of sleep, eating, and physiological functions such as hormone release, metabolism, immune response, and cell cycle regulation, in response to external signals like light, temperature, and diet (Fig. 1). These rhythms are driven by an internal biochemical oscillator-the clock complex-which operates autonomously, with tissue specific clocks also known as peripheral clocks (41,44), but synchronizes with the central clock in the nucleus suprachiasmaticus (SCN) (45), a small region in the hypothalamus known as the master regulator of the circadian rhythm, or central clock, in mammals.

The core of this system consists of a series of protein pairs that work through transcriptional and translational feedback loops. The clock complex, which includes CLOCK/NPAS2 and BMAL1 as a dimer activates the CRY and PER expression that then suppresses the activity of the dimer by several mechanisms (Fig. 1). Notably, it was shown that BMAL1 forms a complex with CLOCK in the SCN but is also able to dimerize with NPAS2, a paralog of CLOCK. This happens predominantly in peripheral tissues where NPAS2 is known to be able to compensate for CLOCK loss (45,46). In detail, CRY appears to regulate BMAL1::CLOCK by reducing the phosphorylation levels of CLOCK, which leads to its degradation (47,48). Notably, CLOCK hereby does not directly activate the transcription; rather, it creates a chromatin landscape by rhythmic binding to e-boxes that are located in the core clock genes' promoter regions. This, facilitates the acetylation of histone 3 lysin 9/27 (H3K9, H3K27), thereby enabling the binding of additional transcription factors like

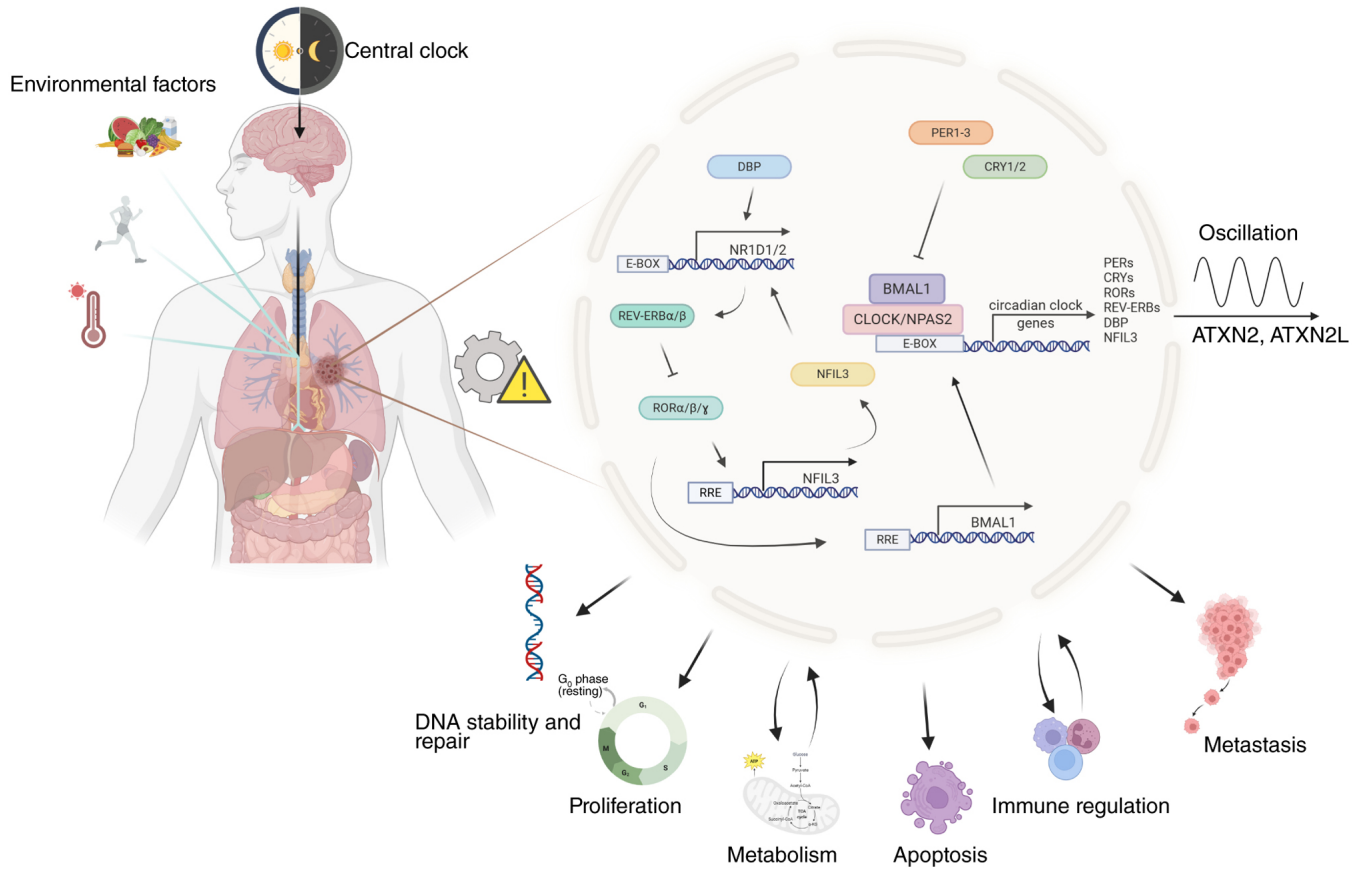

Figure 1. Molecular circadian clock and its systemic influence. The BMAL1::CLOCK/NPAS2 complex activates transcription of fundamental circadian clock genes such as PER, CRY, DBP and NR1D1. Oscillating expression of circadian clock genes is known to be regulated by ATXN2 and ATXN2L. Negative feedback loops involving REV-ERB, ROR and NFIL3 fine-tune circadian oscillations by binding to the corresponding E-BOX, called RRE. Environmental factors such as light, metabolism, temperature and immune signals modulate the clock, which influences cellular processes, mitochondrial activity, immune homeostasis and tumor biology. Disruptions of the clock are linked to metabolic disorders, immune dysfunction and cancer progression Created in BioRender. Meder, L. (2026) https://BioRender.com/faqddmn. BMAL, basic helix-loop-helix ARNT-like 1; CLOCK, clock circadian regulator; ATXN2, ataxin-2; ATXN2L, ataxin-2-like; PER, period circadian regulator; CRY, cryptochrome circadian regulator; DBP, D-box binding PAR bZIP transcription factor; NR1D1, nuclear receptor subfamily 1 group D member 1; NFIL3, nuclear factor, interleukin 3 regulated; REV-ERB, nuclear receptor subfamily 1 group D member, NR1D; ROR, Retinoic related orphan receptor; RRE, ROR response element.

Hepatocyte Nuclear Factor 6 and 4 alpha (HNF6, HNF4A), B-cell Lymphoma 6 (Bcl6) and the induction of oscillating expression (49,50). The competition between transcription factors acting as activators and repressors is important to create oscillation patterns of circadian clock genes. For example, daytime expression of CLOCK genes is generated by morning activation (E-box controlled) and night-time repression (RRE controlled) whereas night-time expression of CLOCK genes is generated by daytime activation (D-box controlled) and morning repression (E-box controlled) (51). These complex matters of E/D box activation and repression processes mentioned before transcriptionally regulate circadian rhythms. Moreover, circadian regulation is tailored to individual tissues (52), enabling a certain degree of circadian autonomy. This autonomy is illustrated by studies using the BMAL1$^{-/-}$ mouse model. Even after BMAL1 loss, circadian rhythms are maintained in liver cells and fibroblasts, suggesting that BMAL1 is relevant for behavioral circadian rhythms but not required for molecular oscillations. Possible mechanisms that sustain the oscillation are the enrichment of ETF transcription factor binding sites and the redox state of peroxiredoxins show a self-sustained oscillation in tissues (53). A recent study has demonstrated that the translational level of oscillation is regulated by spatiotemporal condensation of ataxin-2/ataxin-2 like (ATXN2/ATXN2L) (54). Importantly, studies in other clock entity knockout (KO) model like PER1 -/- show their impact on the circadian rhythm by disrupting the expression of PER2, CRY1 and BMAL1 and dysregulating the peripheral clock genes (55). In PER -/- fibroblasts it was recently shown that PER2 facilitates H2A.Z incorporation which influences chromatin structure and thereby the transcriptional feedback loop and BMAL1 stability (56). Another part of the circadian clock regulation network is REV-ERBs (encoded by NR1D1 and NR1D2) that repress BMAL1 and NPAS2 transcription whereas RORs activate BMAL1 expression (Fig. 1) (57-59). Lastly, D-site binding protein (DBP) and nuclear factor interleukin-3 regulated (NFIL3) are key regulators of circadian gene expression. DBP is known to activate mPer1 transcription (60), whereas the transcriptional regulator NFIL3 links circadian rhythms to metabolic and immune functions (61).

Subsequently, circadian rhythms play a pivotal role in maintaining cellular homeostasis, enabling cells and organs to anticipate and adapt to changes in their environment.

Disruptions to this clock either genetically through genetic mutations or physiologically through lifestyle factors like shift work, or chronic jet lag, have been linked to an increased risk of cancer and promotion of tumorigenesis (62-64). In the context of cancer, circadian dysregulation can lead to altered cell proliferation, impaired DNA repair mechanisms, and immune suppression, creating an environment conducive to tumorigenesis (65).

Mouse models were well established in this field of research and serve as a main experimental model so far. There are four main types: SCN disruption, genetically engineered mice mainly interrupting the circadian genes BMAL1, CLOCK, PER1-3 and CRY1-2, external interruption by light, diet or exercise and models of sleep deprivation (66). These models were integrated into cancer research with results with results verifying that these circadian genes and external factors are involved in tumor development (67-69).

As research continues to uncover links between circadian rhythms and cancer biology, it is becoming increasingly clear that the circadian clock serves as a regulator for maintaining cellular homeostasis and regulating processes critical for cancer development.

3. Role of BMAL1 in cancer

BMAL1 is part of the BMAL1::CLOCK core complex of the circadian clock system and therefore the most studied gene in circadian regulation in SCC and other cancer entities. In general, it is described as a tumor suppressor, but evidence shows that this role is tissue and context dependent.

In NSCLC, including LSCC, BMAL1 expression is significantly reduced in patients with poorer diagnosis and shorter survival. *In vitro* and *in vivo* experiments linked BMAL1 to the well-established oncogenic driver PTEN, confirming that BMAL1 is an upstream regulator of the tumor-suppressive circular RNA circGUCY1A2, which inhibits the PI3K/AKT pathway via PTEN (Fig. 2) (70). Simultaneously, circadian gene regulators have been identified in NSCLC. One example is the regulator gene Y (REGγ) proteasome activator, which promotes BMAL1 degradation through a ubiquitin-independent mechanism, thereby supporting tumor progression (71). BMAL1 has also been observed in ESCC (72) and in OSCC cells as a tumor-suppressor (73,74). In these SCC, increased BMAL expression leads to the upregulation of pro-apoptotic factors such as Bcl-associated protein X (BAX) and Caspase 3, and the downregulation of the anti-apoptotic factors (Bcl-2) (72-74). This is proposed to be due to BMAL modulating dual specificity phosphatase 1 (DUSP1) expression, a regulator of cell cycle and apoptosis, which is also suggested to inhibit ERK phosphorylation within the MAPK pathway (72). Besides the involvement of the PI3K/AKT pathway and MAPK pathway, BMAL-mediated tumor suppression is autophagy-dependent via the AKT/mTOR pathway (Fig. 2) (73,74). Murine xenograft models support these findings, showing reduced tumor volume, weight, and proliferation upon BMAL1 overexpression (72,73).

Aforementioned studies describe BMAL1 as a tumor suppressor however its role alone and within the BMAL1::CLOCK complex, the key regulator of the circadian rhythm, is highly dependent on tissue and type of cancer. This is supported by findings in non-SCC cancers which broaden the BMAL-1 regulated pathways that have not yet been described in SCC. BMAL1::CLOCK studies in hepatocellular carcinoma cell lines, both *in vitro* and *in vivo*, report that loss of the clock leads to downregulation of WEE1, leading to apoptosis and G2/M cell cycle arrest induced by upregulation of p21 (75). Controversially, in pancreatic cancer BMAL1 is significantly downregulated in tumor tissue, correlating with worse survival outcome. BMAL1 murine KO models demonstrated accelerated tumor growth and upregulation of oncogenic pathways like PI3K-AKT and MAPK signaling (76). Beyond its influence on oncogenic pathways, BMAL1 is also a regulator of the oncogene c-MYC. BMAL1 KO in mice leads to increased c-MYC expression whereas a CRY1/2 double KO reduces c-MYC levels. This describes another link between circadian disruption and oncogenic regulation with BMAL1 as the positive arm repressing c-MYC via interaction with β-catenin (Fig. 2) and CRY1/2 as the negative arm promoting c-MYC occurring via the transcriptional control of β-catenin (67). Studies in murine melanoma cell lines revealed that BMAL1 plays a complex role and has context-dependent properties. Loss of BMAL1 in murine and human melanoma cells reduced tumorigenesis, likely due to the downregulation of HIF1α and SOX9. This was confirmed *in vivo*, where the BMAL1 KO reduced tumor growth. However, BMAL1 overexpression did not restore normal function but instead promotes immune resistance, increases tumor growth, and drives a mesenchymal-like, drug-resistant phenotype. This occurs through BMAL1 interaction with myosin heavy chain 9 (Myh9), which enables BMAL1 activate MAL/myocardin-related transcription factor-serum response factor (MRTF-SRF) signaling, a regulation of gene expression linked to cytoskeletal dynamics, cell migration, and differentiation. These findings suggest that BMAL1 may either suppress or promote melanoma progression (77). Another melanoma study revealed that resistance to ferroptosis is linked to fatty-acid binding protein 7 (Fabp7) promoted BMAL1 expression, which in turn suppresses ferroptosis-inducing genes like lysophosphatidylcholine acyltransferase 3 (LPCAT3). Interestingly, cancer cells also induce Fabp7 expression in CD8+ cells, which disrupts their cell-autonomous circadian rhythm, promoting immune exhaustion and apoptosis via p53 stabilization (78).

As the previous study already indicated, not only dysregulation of BMAL1 within the tumor cells but also in immune cells of the tumor microenvironment (TME) influences the tumor progression. A BMAL1 KO in mouse lung alveolar epithelial cells demonstrated that circadian disruption contributes to pulmonary homeostasis disturbances by increased pulmonary neutrophil infiltration. RNA data suggests altered metabolism, extracellular matrix (ECM) remodeling, and rhythmic transcriptome expression alterations (79). In a macrophage-specific BMAL1 KO mouse model of a melanoma, the loss of BMAL1 leads to increased tumor burden, accompanied by mitochondrial dysfunction, elevated oxidative stress, and metabolic reprogramming towards aerobic glycolysis causing succinate accumulation, which in turn stabilizes HIF1α and thereby promotes an immunosuppressive macrophage phenotype. BMAL1 induction in tumor-associated macrophages is driven by inflammatory stimuli and tumor-released factors, highlighting the importance of a functional circadian rhythm

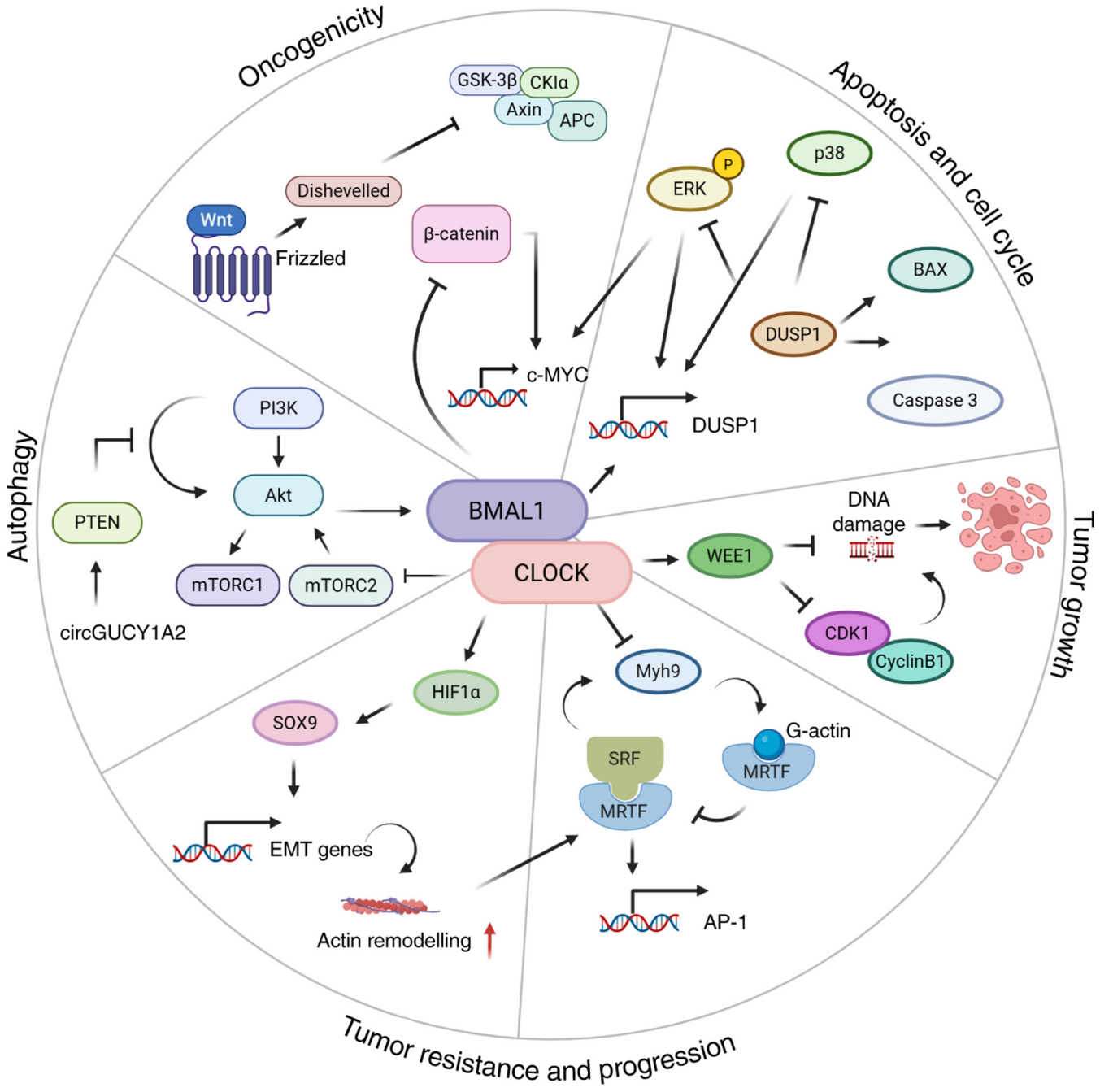

Figure 2. Roles of BMAL1::CLOCK in tumor biology. Described are recently discussed molecular pathways for BMAL1 in cancer regulation. BMAL::CLOCK influences apoptosis and cell cycle, controls tumor growth, tumor resistance and progression, autophagy and oncogenicity through the WNT/b-catenin, PI3K/AKT/mTOR, Myh9/MRTF/SRF and ERK signaling pathways. Created in BioRender. Meder, L. (2026) https://BioRender.com/3r5w6kw. BMAL, basic helix-loop-helix ARNT-like 1; CLOCK, clock circadian regulator; EMT, Epithelial-to-mesenchymal transition; WEE1, nuclear kinase belonging to the Ser/Thr family of protein kinases; CDK1, Cyclin-dependent kinase 1; Myh9, Myosin-9, non-muscle myosin heavy chain IIa; SRF, serum response factor; MRTF, myocardin-related transcription factor; AP-1, activator protein-1; HIF1α, hypoxia-inducible factor 1-subunit alpha; SOX9, SRY-box transcription factor 9; PI3K, phosphoinositide 3-kinases; Akt, serine/threonine kinases, central hubs in the PI3K/AKT signaling pathway; mTORC1/2, mechanistic target of rapamycin complex 1/2; PTEN, phosphatase and tensin homolog; circGUCY1A2, circular RNA of guanylate cyclase 1 soluble subunit alpha-2 (GUCY1A2); GSK-3β, glycogen synthase kinase-3 beta; Axin, critical scaffold proteins that function as negative regulators of the Wnt/β-catenin signaling pathway; APC, adenomatous polyposis coli; CKIα, casein kinase 1 alpha; c-MYC, MYC proto-oncogene, bHLH transcription factor; ERK, extracellular signal-regulated kinases; DUSP1, dual-specificity phosphatase 1; p38, p38 mitogen-activated protein kinase; BAX, BCL2-associated X, apoptosis regulator.

in immune cells for tumor defense (80). Mice with disrupted circadian rhythm, either through BMAL1 or PER1/PER2 KO, are more susceptible to gut inflammation and colorectal cancer. BMAL1 normally regulates IL-33, a cytokine critical for PD-L1+ Breg function, and its dysregulation leads to impaired immune response, increased CD4+T cell apoptosis, and tumor progression (81). A similar effect is observed when investigating the upregulation of NPAS2 in cancer patient samples, associated with tumor progression and poor prognosis (82-85). In lung adenocarcinoma (LUAD) cells, NPAS2 was found to enhance DNA damage repair by stabilizing H2AX messenger RNA (mRNA). This mechanism was

further explored in a NPAS2-deficient tumor xenograft mouse model (84). Additionally, beta-arrestin 1 (ARRB1) was identified in LUAD as a transcription factor of NPAS, facilitating malignant properties and promoting glycolysis, thereby establishing a therapeutic target beyond NPAS itself (86). *In vitro* and *in vivo* studies of prostate cancer and hepatocellular carcinoma have demonstrated that NPAS2 promotes tumor growth by enhancing cell proliferation, inhibiting apoptosis, and driving glycolysis through upregulation of HIF1A and key glycolytic genes (HK2, PKM2, GLUT1, and MCT4) (83,85).

Together, BMAL1, CLOCK, and NPAS2 display context-dependent functions in cancer hallmarks. BMAL1 is mainly an oncogenic suppressor in squamous cell carcinoma, where it regulates apoptosis, autophagy, and oncogenic pathways like PI3K/AKT and MAPK. However, looking into non-SCC cancer studies, it can also contribute to immune resistance through mechanisms such as Myh9 and HIF1α-dependent actin remodeling, as well as polarization of immunosuppressive macrophages. NPAS2, which is often overexpressed in tumors, promotes tumor cell proliferation and glycolytic activity.

4. Role of PER1-3 in cancer

PER1, PER2 and PER3 are described equally in SCC and other cancer entities. Consistently, these studies describe the PER family as tumor suppressors with individual functions in cellular processes and tumor intrinsic immune response. In NSCLC, the expression levels of PER1, PER2, and PER3 are positively correlated and have been reported to be downregulated in tumor tissue compared to normal lung tissue, just like for BMAL1 (87,88). One described mechanism for the downregulation of the PER gene family is described as the hypermethylation of its/their promotor region (89). The loss of PER genes has been associated with aggressive tumor behavior (87,89). In NSCLC, PER expression can restore circadian rhythm through glucose restriction, which activates AMP-activated protein kinase and sirtuin 1 (AMPK-SIRT1) (Fig. 3) (88).

Further analysis of diverse carcinoma patient supports the above findings revealing that PER1 expression was lower in SCC (90) and breast cancer tissues (91). This reduction was associated with decreased survival rate and more advanced tumor stages. *In vitro* and *in vivo* experiments confirmed that PER1 overexpression led to reduced tumor growth through apoptosis and autophagy induction, and by suppressing proliferation and invasiveness (90,91). These effects were linked to the AKT/mTOR pathway (90). A further study identified PER1, like BMAL1, to interact with HIF1α in a feedback loop that promotes ferroptosis (Fig. 3) and thereby inhibits OSCC progression (92).

Similarly, in glioblastoma, PER2 is significantly downregulated in glioma stem cells compared to non-stem glioma cells. PER2 overexpression suppresses tumor stemness and invasion by inducing G0/G1 cell cycle arrest and reduces glioblastoma tumor growth *in vivo*. Its tumor suppressive role may be explained by PER2 suppressing the Wnt/β-catenin pathway, leading to reduced expression of oncogenic factors like c-MYC, MMP2 and MMP9 (93). Additionally, in OSCC and lung adenocarcinoma cells, PER2 expression was negatively correlated with AKT/mTOR signaling, upstream PIK3CA/AKT pathway activity (Fig. 3) (94-96), and multi drug resistance (associated) protein 1 (MDR1, MRP1). Upregulation of PER2 in mice increased effectiveness of chemotherapy (94). Whereas in OSCC upregulation of PER2 seems to enhance the immune system's capacity to combat the tumor and increase its susceptibility to chemotherapy and immunotherapy (94,97,98), the low levels of PER2 expression in ESCC appear to make tumor more vulnerable to DNA-damage and apoptosis, enhancing the effectiveness of cisplatin chemotherapy (99).

To complete the findings for the PER family, PER3 appears to function similarly to PER2. In this study, PER3 mRNA expression was found to be downregulated by hypermethylation in NSCLC, SCC, and other cancer tissues. This downregulation correlated with tumor progression and poor prognosis but could potentially be reversed through demethylation (89). The overexpression of PER3 leads to decreased proliferation and migration while increasing apoptosis (89,39,100-102). Additionally, other cancer entities like prostate cancer show that, downregulated PER3 levels increase BMAL1 expression, which regulates Wnt/β-catenin signaling, promoting cancer stemness and tumor growth (103).

These studies highlight the distinct overlapping roles of PER1-3 tumor suppression. PER1 primarily regulates apoptosis and autophagy, PER2 influences stemness, immune response, and PER3 acts similarly to PER2 but also interacts with BMAL1 and modulates Wnt/β-catenin signaling.

5. Role of REV-ERBα/β in cancer

The nuclear receptors REV-ERBα (NR1D1) and REV-ERBβ (NR1D2) are closely related circadian transcriptional repressors that function as integral components of the molecular clock, regulating metabolism, inflammation, and cell proliferation in a largely overlapping yet tissue-specific manner.

Generally, REV-ERBα (encoded by NR1D1) shows the same trend as the other circadian genes, showing reduced expression in lung cancer in over 80% of LUAD tumor samples. These studies support the finding that reduced expression is associated with cancer by showing that the knockdown of REV-ERBα led to an accumulation of cells in the G2 phase, consequently increased invasion, and upregulation in NFkB signaling (Fig. 4) (104). On a transcriptional level, NR1D1 deficient mice showed increased lung tumor growth, associated with activation of the NLRP3 inflammasome, which promotes tumor growth and epithelial-mesenchymal transition (EMT) (105). In a similar NR1D1 KO mouse model of breast cancer, larger tumors and increased lung metastasis were attributed to reduced cytoplasmic DNA accumulation. This, in turn, was connected to immune infiltration processes, by suppression of cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway signaling which leads to reduced type I interferon (IFN) production and decreased infiltration of CD8+ T cells and NK cells into the tumors (Fig. 4) (106). Similarly, a study of osteoblastoma cells reported involvement of both isoforms, NR1D1 and NR1D2, in inflammatory responses where both mostly redundantly regulate the same target genes. Though upon NR1D1 KO the NFkB pathway (Fig. 4) was upregulated on the one hand, and upon

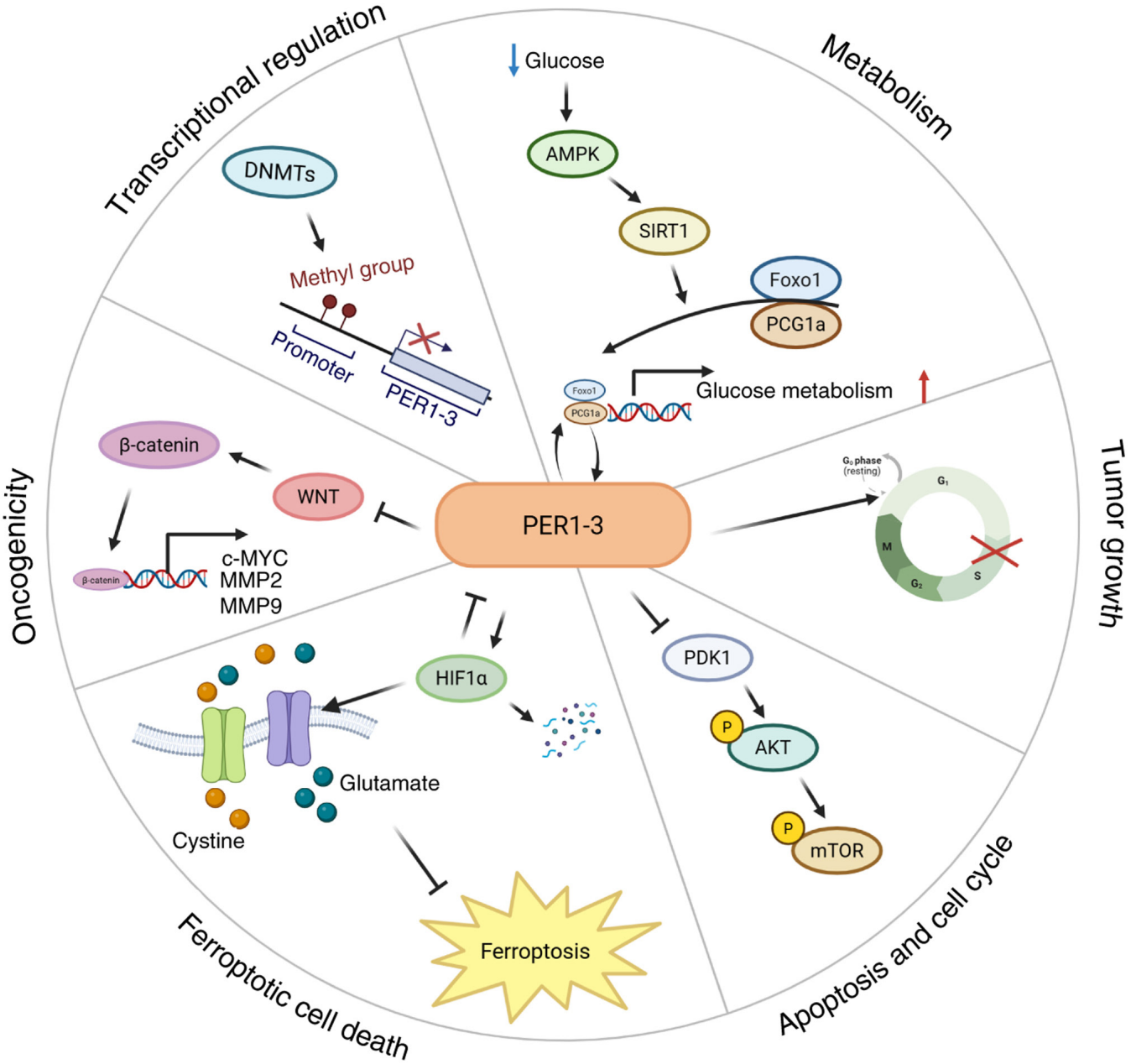

Figure 3. Roles of PER1, PER2 and PER3 in tumor biology. Described are recently discussed molecular pathways for PER1-3 in cancer regulation. PER1-3 modulates glucose metabolism, tumor growth, autophagy/apoptosis and survival, and cell death by ferroptosis, WNT-driven oncogenicity and transcriptional regulation. Created in BioRender. Meder, L. (2026) https://BioRender.com/8tjlj49. PER, period circadian regulator; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; c-MYC, MYC proto-oncogene, bHLH transcription factor; PDK1, pyruvate dehydrogenase kinase 1; HIF1α, hypoxia-inducible factor 1-subunit alpha; Akt, serine/threonine kinases, central hubs in the PI3K/AKT signaling pathway; mTOR, mechanistic target of rapamycin kinase; DNMTs, DNA methyltransferases; AMPK, AMP-activated protein kinase; SIRT1, Sirtuin 1; Foxo1, forkhead box O1; PCG1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha.

NR1D2 deletion on the other hand, genes relevant to ECM components showed downregulation (107). Supporting studies of cervical and esophageal cancer cells report REV-ERBs to be downregulated in patient samples. Activation of REV-ERBα and RORα induced apoptosis in cancer cells, while normal cells were less sensitive highlighting the therapeutic potential of REV-ERBα and RORα agonists in apoptosis (108). This therapeutic role of REV-ERBα was addressed in a recent *in vivo* study of a REV-ERBα and autophagy inhibitor in mouse melanoma xenograft demonstrated a reduction in tumor volume and weight. Although the effects of the drug were confirmed by increased expression of BMAL1 and reduced autophagy (Fig. 4), the authors acknowledges that these effects are likely driven by autophagy (109), only possibly involving REV-ERB (110).

The already mentioned circadian gene RORA was identified in SCC and melanoma as a tumor suppressor (111-113). Under hypoxic conditions, DNMT1-mediated methylation suppresses RORA expression, which in turn increases GLUT3 levels to promote glycolysis and tumor progression (112). In agreement, RORA activation or overexpression was shown to markedly reduce tumor growth and invasiveness in melanoma

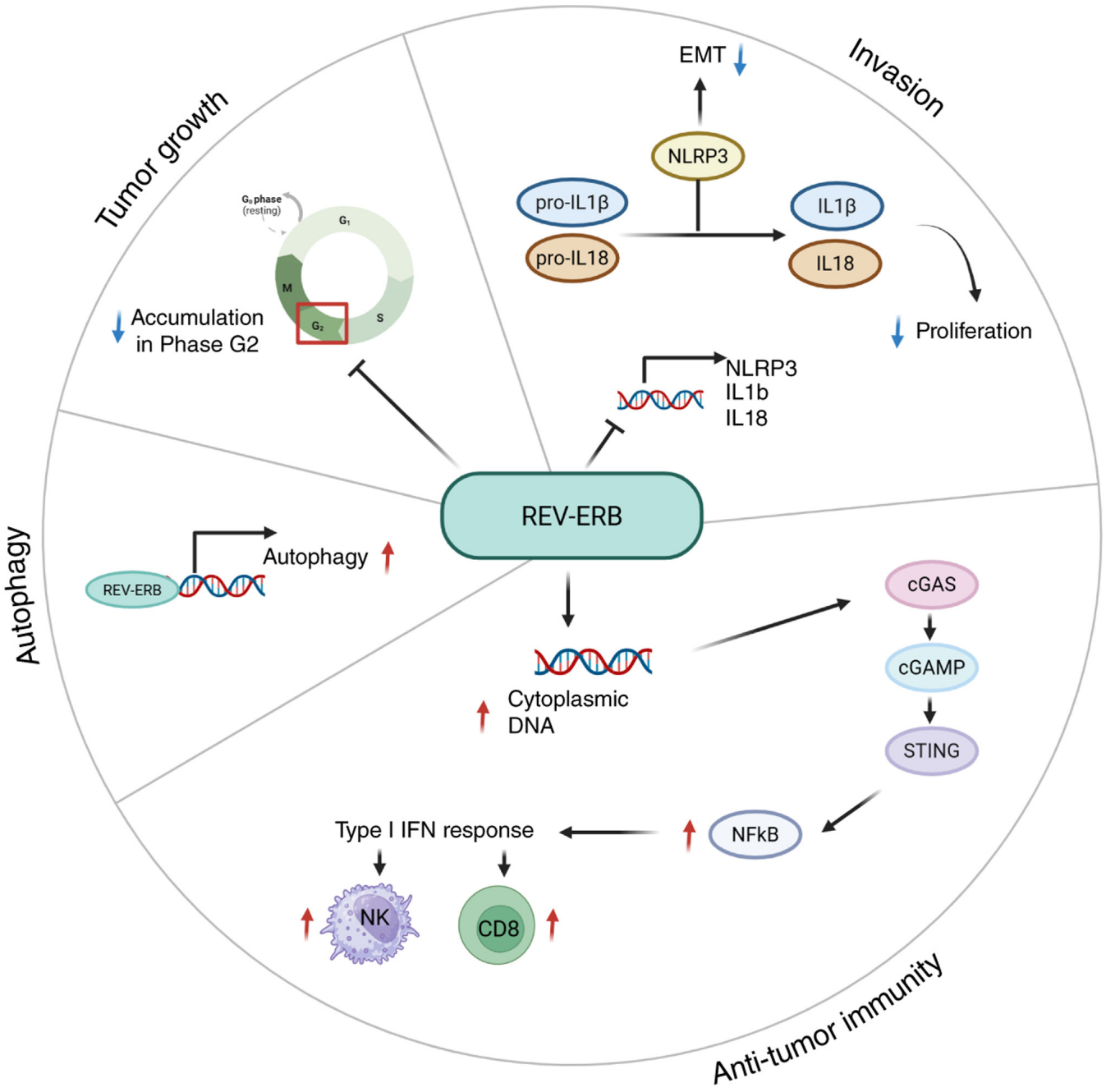

Figure 4. Roles of REV-ERB in tumor biology. REV-ERBs regulates invasion and proliferation by affecting NLRP3 signaling. IL1b and IL18 are upregulated and contribute to NLPR3 signaling and finally to EMT. REV-ERBs regulates antitumor immunity related also to NFkB and type I IFN response. REV-ERBs inhibit DNA repair which upregulates cGAS-cGAMP-STING signaling promoting NFkB and type I IFN signaling. Created in BioRender. Meder, L. (2026) https://BioRender.com/p8eryq3. EMT, Epithelial-to-mesenchymal transition; NLRP3, pyrin domain-containing protein 3; IFN, interferon; REV-ERB, nuclear receptor subfamily 1 group D member, NR1D; IL1β, interleukin-1 beta; IL18, interleukin-18; pro-IL1β, pro-interleukin-1 beta; pro-IL18, pro-interleukin-18; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; STING, stimulator of interferon genes; NK, natural killer cells; CD8, cluster of differentiation 8.

and OSCC *in vivo* models (113). As a result, higher RORA expression in melanoma was correlated with improved prognosis due to the fact that RORA suppresses PD-L1 transcription by forming an inhibitory complex with HDAC3. On the other hand, RORA loss leads to increased PD-L1 levels. Pharmacological activation was used to rescue low RORA expression, resulting in reduced tumor growth, enhanced T cell infiltration, and increased CD8+ T cell cytotoxicity (111).

In summary, while the roles of REV-ERBα/β and RORs in circadian rhythm and cancer are less evident compared to the other described circadian genes, evidence points to tumor-suppressive functions mediated through immune signaling, apoptosis, and autophagy, underscoring their potential as therapeutic targets.

The combined findings from SCC and other cancer types highlight how crucial circadian rhythm genes are for immune modulation and tumor growth. Despite context-dependent effects, several circadian genes, including BMAL1, PER1-3, RORA, and REV-ERBs, display tumor-suppressive roles through regulation of apoptosis, immune modulation, and

metabolic control. The biochemical pathways, such as PI3K/AKT, MAPK, Wnt/β-catenin, and HIF1α signaling connect circadian disturbance to carcinogenesis, providing rising targets for therapeutic intervention. Given the observation of overlapping circadian gene dysregulations across multiple tumor entities, findings from non-SCC cancers may provide a foundation for further research of SCC pathophysiology and treatment. However, current evidence addressing circadian mechanisms in SCC remains fragmented across SCC subtypes. Therefore, findings from non-SCC tumors were introduced to identify candidate targets and pathways that may warrant investigation in SCC. Nevertheless, the interpretation of these studies requires caution since SCC represents genetically, anatomically and functionally a distinct tumor type which characteristics may influence circadian gene function. Finally, finding in this non-SCC cancer should be regarded as hypothesis-generating and not as directly transferable to SCC.

6. Circadian clock in SCC

Several studies on diverse tumor entities have documented a dysregulation of circadian rhythm components and have put forward several of these as prognostic markers for tumor progression and outcome, focusing on the following genes discussed beforehand: BMAL1 (ARNTL), PER1-3, NR1D1/2, CRY1-2 (76,108,114,115) and CLOCK, NPAS2, RORA-C (100,116,117). Importantly, evidence from pan-cancer and multi-omics studies suggests that the circadian system should not be interpreted as a collection of isolated genes but rather as an interconnected transcriptional-translational regulatory network whose coordinated disruption may influence tumor progression, immune modulation and patient outcome (64,118-120). In cSCC, this network is described in environmental factors such as UV and endocrine mediators having direct mechanistic relevance to circadian regulation through skin neuroendocrine pathways (9,10,121). Aforementioned factors are described as very skin specific and applicability to other SCC entities is reduced to hormonal influences such as estrogen levels in women which are described as controversial in HNSCC (122,123). Therefore the current evidence in non-cutaneous SCC, addressing this network-level organization research remains scarce (124), with current studies predominantly focusing on individual clock genes and their associations with clinical-, cancer- or immune-related parameters. Consequently, cited studies in this review summarize the available SCC evidence at the level of the individual circadian genes BMAL1, CLOCK, PER1-3, RORA, REV-ERBα/β, while acknowledging that these observations likely represent elements of a broader circadian regulatory architecture that remains to be characterized in SCC.

Even though evidence is limited, there is equal distribution between genetic focused and immune based studies. SCC studies show increased connection of the circadian clock to immune regulation and infiltration into local tumors. Related studies show circadian genes as markers in lung cancer, where the main players BMAL1, CLOCK, PER1-3, RORA, REV-ERBα/β have been described in LSCC (100,117,119). This validates that these genes can act as prognostic indicators and can be validated through analysis of immune cell infiltrates. For example, a positive correlation was found between CRY2, PER1 and CD4+ T cell infiltration (119). Additionally, PER3 expression in HNSCC has been observed to have a positive correlation with Tregs, CD4+, CD8+, PDCD1, and follicular helper cell infiltration (39). Accordingly, in small cell lung cancer, NR1D2 has been included in an immune-related prognostic model, based on which it has been possible to identify elevated CD56 bright NK cell levels, reduced CD8+ T cell levels, mast cell infiltration, helper T cell infiltration, and increased TGFb signaling associated with EMT (125).

Research linking circadian genes to the involvement in immune recruitment suggests that future studies should interconnect the functionality of circadian genes within the broad network to identify whether general dysregulation of the circadian rhythm is linked to one or multiple joined downstream pathways. To address this, studies should integrate multi-omics with multi-gene circadian gene testing in time-resolved sampling.

7. Circadian clock in cancer therapy

Current SCC treatment guidelines reflect a shift toward novel molecular targets and immunotherapeutic approaches, including ICIs and chimeric antigen receptor-T therapy (CAR-T) (34), in LSCC, ESCC, and HNSCC. All LSCC tumors at stage IV were tested for mutations or fusions of EGFR (exon 18-21), BRAF, ALK, ROS1, RET and NTRK1-3 fusions. These markers were primarily described in NSCLC, where they were most relevant to LUAD and were rarely found in LSCC (126-128). However, since these markers were potentially therapeutically targetable and occasionally altered in some cases of SCC, they remain part of routine testing. These genes are not core circadian genes but may be involved in circadian rhythm regulation. Treatment is adjusted according to the test results and in therapy-naïve SCC patients, PD-L1 expression testing is recommended to guide treatment selection (127). For example, patients with LSCC eligible for EGFR-targeted therapy may receive with EGFR inhibitors such as afatinib or erlotinib. A randomized trial in patients with advanced LSCC directly compared the two inhibitors as a second-line treatment, showing that afatinib significantly improved PFS and OS while maintaining a manageable safety profile (129). Patients who are negative for several mutations or display PD-L1 expression exceeding 50% may receive first line treatment with either PD-1/PD-L1 monotherapy (atezolizumab/cemiplimab/pembrolizumab) or combination immuno-chemotherapy regimens, such as pembrolizumab or nivolumab with ipilimumab. If the score indicates <50% PD-L1 tissue expression, a platin-based chemotherapy with pembrolizumab is suggested (130). To date, randomized trials in LSCC focused on treatment with anti-PD-L1 compound atezolizumab and pembrolizumab, docetaxel, nivolumab targeting anti-PD-1. A clinical trial involving 723 patients with stage IV LSCC without ALK or EGFR mutations compared first-line treatment with Atezolizumab plus chemotherapy vs. chemotherapy alone, demonstrating that the addition of Atezolizumab significantly improved OS (131). First-line chemotherapy combined with Pembrolizumab in metastatic LSCC improved overall survival, progression-free survival, and objective response rates, while maintaining a safety

profile comparable to chemotherapy alone (132). In a cohort of 272 patients with advanced LSCC receiving either nivolumab or docetaxel, nivolumab demonstrated superior overall survival, response rates, and safety; in contrast, treatment strategies in ESCC and HNSCC include radio-chemotherapy and adjuvant or monotherapy with nivolumab, ipilimumab, or cetuximab (133).

HNSCC is classified into oral cavity and laryngeal cancers. In oral cavity cancer, etiological factors such as HPV16, p16, alcohol consumption, and smoking should be considered when planning therapy, whereas in laryngeal cancer these factors are generally not used to guide treatment. Following PD-L1 testing in SCC, pembrolizumab may be used as a monotherapy. In PD-L1-negative cases, EGFR inhibitor cetuximab is administered as a first-line treatment (134-136). Other targets such as mTOR, PI3K, c-MET, RET are also being tested in clinical trials for HNSCC (137). However, in LSCC, targets such as EGFR, ERBB, FGFR, DDR2 demonstrated limited clinical efficacy, with poor response rates in trials. The attempt to target RAS-RAF-MEK, PI3K, AKT with downstream oncogenic potential failed due to cross-reactive toxicity. Therefore, drug development efforts have increasingly targeted dysregulated pathways and molecular alterations beyond the genome. SOX2 amplification in 60-80% of the LSCC is considered undruggable, therefore, the focus lies on its epigenetic chromatin regulators LSD1 and EZH2 which are currently tested in clinical trials (138). The role of circadian rhythm in modulating therapeutic responses has gained increasing attention, as the timing of ICI administration has been linked to treatment efficacy. For instance, in Nivolumab-treated NSCLC patients, the OS was found to be fourfold higher in the patients receiving treatment in the mornings (139). Morning administration similarly improved treatment outcomes with durvalumab (anti-PD-L1) infusions (33).

Additionally, the link between circadian rhythm and ICI modulation was observed at the molecular level. For instance, circadian gene PER2 has been shown to influence the expression of PD-L1. In OSCC, studies have shown that PER2 suppresses PD-L1 expression by binding to the heat shock protein 90, thereby modulating the IKK/NFkB pathway. These *in vitro* studies were further supported by a humanized mouse model, where PER2 upregulation in combination with PD-L1 targeting increased CD8+ cell infiltration and immune defense against the tumor (97). In ovarian tumors patients with a disrupted circadian rhythm (140) and in NSCLC patients (141), low PER2 expression was correlated with increased PD-1/PD-L1 expression and enhanced PI3K/Akt signaling. These alterations may facilitate immune evasion (140) and reduce effectiveness of immunotherapy *in vivo* (141). *In vivo* experiments in NSCLC bearing mice receiving anti-PD-L1 therapy demonstrated smaller tumors were associated with higher BMAL1 and PER2 expression and simultaneously lower PD-1 levels (142). Besides PER2, the circadian gene RORA was found to suppress PD-L1 expression in melanoma by binding to its promoter and forming an inhibitory complex with Histone Deacetylase 3. In contrast, dead-box helicase 3 X-linked (DDX3X) disrupts this inhibitory complex, leading to increased PD-L1 expression and immune evasion (111).

PD-L1 expression is influenced not only by circadian genes at the molecular level but also in a broader immune microenvironment. This study revealed that PD-L1 expression in colorectal cancer cells is regulated by the circadian clock through the influence of Myeloid-suppressor cells (MDSCs). These cells were shown to accumulate in the TME in a rhythmic manner, with a peak in the late afternoon where they exhibit high PD-L1 expression, suppressing CD8+ T cells and thereby reducing anti-tumor immunity (143). Circadian dysregulation increased the recruitment of MDSCs (143) and upregulated the expression of immune checkpoint molecules PD-L1, PD-1, and cytotoxic T-lymphocyte antigen 4 (CTLA4) promoting the immunosuppressive environment (144).

A link between EGFR signaling and circadian rhythm is described in breast cancer where loss of PER3 is associated with increased p-MEK and p-ERK1/2 levels which are part of the downstream cascade activated by EGFR and thereby enhance oncogenesis (145). VEGFR on the other hand was linked to rhythmic expression *in vivo* BMAL KO mice where the VEGFR expression was dampened (146).

While the expression of PD-1, PD-L1, and other immune checkpoints in the TME and therapy resistance is well studied, little is known about the involvement of the circadian rhythm in EGFR and VEGFR signaling. It remains unclear if this gap is crucial to new improvements in SCC treatment since the current focus of therapy has shifted to cell-based therapy, immunotherapy, and chronotherapy.

8. Chronotherapy in cancer treatment

Recent studies have explored usage of the circadian rhythm for therapy. Chronotherapy times drug administration to the patient's internal clock to enhance anti-tumor effects. Such approaches were already researched in clinical trial with radio- and chemotherapy with success. Cis-platin chronotherapy in NSCLC showed less leukopenia and neutropenia with reduced toxicity when the drug was administered early in the morning (120). Same effect was observed in esophageal cancer (147). Clinical trials in HNSCC treatment showed a reduction in severe inflammation and ulceration of the mucous membranes and the reduced toxicity of radiotherapy administered in the morning compared to the evening (148). All these studies suggest that chronotherapy may not always increase the efficacy but it can reduce side effects and toxicity (149). Additionally, several studies support the direct monitoring of circadian rhythm-related gene signatures for diagnostic purposes and prediction of chemotherapy outcomes (99,150,151).

Besides time-dependent chemotherapy, a recent trial evaluated the benefits of timing EGFR tyrosine kinase inhibitors administration (gefitinib, erlotinib, and afatinib) in patients with advanced LSCC has been published. The prospective cohort study concluded that night-time administration reduced side effects, including acne and dry skin, alleviated symptoms such as cough and pain, and lowered the risk of all-cause mortality in patients. However, the pronounced survival benefit was seen only in younger patients (<65 years) (152).

The pioneering trials discussed above, which were recently published, examine the timing of ICI therapy, among other treatment parameters (33,139,153). In the MEMOIR study patients with stage IV diagnosed melanoma were monitored longitudinally during treatment with ipilimumab, nivolumab,

or pembrolizumab, or a combination thereof. Among patients who received more than four infusions, those receiving at least 20% of their treatments after 4:30 pm showed significantly shorter overall survival compared with patients whose infusions were predominantly administered before 3:00 pm (32). A similar observation was made in a single-center retrospective cohort of 82 patients with locally advanced NSCLC treated with second-line durvalumab after chemoradiotherapy. The proportion of durvalumab infusions administered after 3 pm was used to define early versus late treatment. A total of 70 patients received <20% of their infusions after 3 pm and 12 patients received >20% of their infusions after 3 pm. Patients who received ≥20% of their infusions after 3 pm had a significantly shorter PFS and a non-significant trend toward worse OS compared with those who received <20% after 3 pm (33). A 2020 clinical trial enrolled 95 patients with metastatic stage IV NSCLC found that administration of nivolumab before 12:45 pm improved outcomes. The patients were randomly divided into two groups: one receiving nivolumab before 12:45 pm and the other after 12:55 pm. The study found that patients administered nivolumab before 12:45 pm exhibited significantly higher rates of PFS and OS compared to those treated after 12:55 pm, with an 11.3-month increase in PFS and a 34.2-month increase in OS. Additionally, the objective response rate was more than doubled in the morning group. The study's findings, which were observed independent of sex, age, tumor histology, prior treatments, or PD-L1 status, suggest that the circadian clock plays a role in regulating T-cell activity and immune activation (139).

The role of the circadian rhythm in immune activation and effector cell activity was investigated in a mouse model. Tumor-infiltrating immune cells, particularly CD8+ T cells and other innate immune cells, showed circadian oscillations in both number and phenotype, indicating a time-of-day dependency. This finding lent support to the notion that precise timing of CAR-T and ICI therapy holds promise for cancer treatment and reveals the underlying molecular mechanism behind this cancer therapy adjustment (34).

Based on this and other studies linking circadian rhythm with PD-L1 expression (97,140,141,143) and immune processes-including immune cell activation, infiltration, and macrophage-mediated immune suppression (119,125,143,154,155)-the advantage of morning administration likely reflects the clock-dependent activity of immune cells. While the circadian rhythm plays a crucial role in immune cell function and its impact on the TME is increasingly understood, many aspects of its influence on cancer outcomes remain unclear.

Few circadian rhythm-based clinical trials in cancer are registered, and even fewer have published results so far (Table I). Some trials focus on adjusting PD-1 and PD-L1 immunotherapy, predominantly in combination with chemotherapy or radiotherapy. Although OS remains the main outcome, analysis of T-cell infiltration and circadian gene expression are rarely conducted (Table I), despite strong evidence that these factors affect chronotherapy outcomes. Multicentered randomized trials and standardized protocols of treatment timing would strongly support the optimization of cancer treatment and understanding of circadian regulation in the tumor and its microenvironment.

9. Limitations and research strategies

Despite the considerable progress in *in vitro* studies, murine models, and clinical trials performed so far, limitations currently still restrict the interpretation and clinical application of circadian rhythm in SCC. Limitations include for example methodological differences in measuring circadian oscillation *in vivo* and *in vitro*, the understanding between local and peripheral clock *in vitro* and the limited randomized validation in clinical trials.

A present gap in knowledge resides in how the circadian rhythm contributes to SCC initiation and progression. As already known, individuals exposed to chronic circadian disruption (e.g. shift work, jet lag, light pollution) (62-64) are more prone to SCC. The exact mechanisms by which the circadian genes BMAL1, CLOCK, PER1-3, CRY1/2 and REV-ERBs within their framework drive SCC remain mostly unclear. Disruption have been associated with multiple oncogenic pathways, e.g. MEK-ERK and AKT/mTOR (19,51,74,94,97,137,146), yet, their precise interactions remain unclear. This raises the question of whether circadian clock genes are either tumor suppressors or oncogenes in SCC, or whether their role varies by tissue type (77,89,91). Additionally, the interaction between the circadian rhythm and known SCC mutational drivers (1,16-19,21,23) remains poorly understood while additional insight into alterations in metabolism are increasingly recognized in SCC progression. In this metabolic context, the circadian clock is also emerging as a key focus of research (58,80,85), however research is still at early stages, understanding how the circadian clock interacts with main drivers of SCC and how metabolic changes will contribute to understanding the framework of the circadian clock in SCC progression.

Secondly, the role of circadian rhythmicity in SCC therapy is beginning to be explored in cancer clinical trials. Chemotherapy, radiotherapy, and immunotherapy show time-dependent variations in efficacy (32,34,148,153,156). However, randomized clinical trials are needed to clarify how therapy timing affects SCC outcomes and to uncover other variables that modulate treatment response and resistance in a circadian-dependent manner. So far, the clinical trials lack sufficient time sampling that goes beyond timepoints of morning and afternoon treatment and no standardized biomarkers that determine patient 's and potential tumor circadian phase. The integration of such biomarkers into clinical trial design and therapeutic decision-making will be essential for the implementation of personalized chronotherapy and the optimization of circadian-based immunotherapy. Notably, current and further planned chronotherapy trials aim to improve efficacy, reduce side effects and develop personalized treatment schedules.

Thirdly, the connection between central and peripheral clock systems remains poorly understood. The central clock is set by sun light and day-night schedules whereas the peripheral clock in the tissues is independent (Fig. 1). Key questions arising here include whether peripheral clock disruption, independent of the SCN, accelerates SCC progression, and whether epigenetic modifications in clock genes within both the central and peripheral clocks contribute to this progress? Moreover, how do the tumor-intrinsic circadian disruptions affect the peripheral clocks and the TME including all the immune cells? Finding answers to these questions may provide insight on tissue-dependent SCC progression and its connection to the central clock. Additionally,

Table I. Overview of chronotherapy associated clinical trials in cancer treatment.

Trial ID	Cancer entity	Interventions	Primary outcome	Participants	Status	Sponsor/collaborator	Phase	(Refs.)
NCT03793179	NSCLC	Carboplatin, Pemetrexed, Pembrolizumab	OS	600	Active	National Cancer Institute	Phase III	Not published
NCT06882174	NSCLC	Pembrolizumab	Tumor size	58	Not yet recruiting	AHS Cancer Control Alberta	Phase II	Not published
ChiCTR-TRC-14004170	NSCLC	Adjuvant chemotherapy and radiotherapy; neoadjuvant chemotherapy + adjuvant chemotherapy and radiotherapy	Deviation from the scheduling intervention; Dropout rate; PFS rate	420	Recruiting	Cancer Hospital of Sichuan province	Post-market	Not published
JPRN-UMIN000006713	OSCC	Docetaxel, cisplatin	Incidence of Grade 3 or higher neutropenia	50	Completed	Department of Oral and Maxillofacial Surgery, Jichi Medical University	NA	Not published
ChiCTR2400086032	Advanced nasopharyngeal carcinoma	Gemcitabine, Cisplatin; chemoradiotherapy, chemotherapy	3-year recurrence-FSR; OS; PFS	434	Not yet recruiting	Affiliated Cancer Hospital of Guizhou Medical University	Phase III	(165)
NCT04864405	Breast cancer	Endocrine treatment	Endocrine toxicity and tolerability at 12 weeks	247	Completed	Ottawa Hospital Research Institute	Phase IV	(166)
NCT06418139	Non-metastatic triple-negative breast cancer	Pembrolizumab in neoadjuvant chemotherapy or immunotherapy	Residual cancer burden	450	Not yet recruiting	Assistance Publique-Hôpitaux de Paris	NA	Not published
JPRN-UMIN000018215	Colorectal cancer liver metastasis	Hepatic infusion	Efficacy	28	Recruiting	Yokohama City University Hospital	NA	Not published
NCT01693861	Metastatic colorectal cancer	Chemotherapy	Measurement of modified nucleosides, cortisol and 6-sulfatoxymelatonin concentration; Measurement of Clock genes polymorphisms expression	16	Completed	Institut National de la Santé Et de la Recherche Médicale, France	NA	Not published
NCT04735939	Glioma	Radiotherapy	Survival time	80	Recruiting	General Hospital of Ningxia Medical University	NA	Not published
NCT06850766	Glioma	Temozolomide	Adherence to TMZ dose timing protocol	50	Not yet recruiting	Ottawa Hospital Research Institute	NA	Not published

Table I. Continued.

Trial ID	Cancer entity	Interventions	Primary outcome	Participants	Status	Sponsor/collaborator	Phase	(Refs.)
NCT02781792	High grade glioma	Temozolomide	Duration of response; patient treatment compliance as measured by at least 80% compliance with assigned administration time	42	Completed	Washington University School of Medicine	Phase II	(167)

Search was conducted on clinicaltrials.gov and trialsearch.who.int using keywords 'chronotherapy' and 'squamous cell carcinoma'. NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; NA, not available.

it may uncover how tumor-intrinsic circadian rhythms reshape the peripheral clock and TME, including cellular functions, potentially opening new avenues for targeted therapies.

To answer these questions, research employs molecular and genetic approaches, preclinical murine models, as well as translational and clinical research. Bulk and single cell RNA (scRNA) sequencing have been performed in some SCC cancer entities, revealing that circadian gene expression oscillation are disrupted in cancer tissue compared with normal tissue (18,39,125,157). The cancer genome atlas (TCGA) datasets are publicly available for RNA Sequencing, providing a great opportunity for a first in-depth analysis. However, one time sampling in studies of the circadian clock is not sufficient to find pattern of dysregulation or oscillation shifts in circadian gene expression. Since SCC tumors are highly heterogenous compared to other cancer types (17,138,158), scRNA sequencing with time-course sampling would allow the detection of gene expression patterns that are more cell-specific and time-sensitive. Such studies would provide a foundation for target identification in upcoming *in vitro* and *in vivo* studies.

CRISPR/Cas9 knockout, overexpression studies, and gene editing studies are common approaches to investigate the function roles of core circadian genes. Such studies can be conducted in mouse models (53,55,57,146) or different cell types (46,68,78,80). The limitation of CRISPR/Cas9 KO is that knockout gene can affect multiple pathways, making it challenging to attribute observed effects to a specific pathway. Additionally, these studies are not accounting for protein level feedback loops which requires further translational studies to evaluate the circadian framework. CRISPR/Cas9 KO applied *in vitro* settings have the advantage of studying multiple genes at once where mouse models mostly exist as one gene knockout models. Still, *in vivo* models carry the advantage of including the central clock and the SCN which is impossible to re-create in *in vitro* models. In mouse models, day-night cycles are controlled by the light exposure, and further circadian factors can be introduced (Fig. 1) by temperature exposure and food schedules. When studying *in vitro* one is limited to mimicking circadian rhythms through starvation of cells and introduce artificial synchronization where the onset of the circadian rhythm is estimated as soon as fetal bone serum is added to the culture after starvation. Followingly, circadian tumor xenografts models are used to study core circadian oscillations, their effects on cancer progression, and the influence of time-of-day on SCC tumor growth and therapy response (66). Whereas organoid models and SCC cell lines provide *in vitro* systems to study metabolism, proliferation, and drug response in SCC (98,113,159). Analyzing data of any circadian study requires careful selection of housekeeping genes as references (160,161). Interestingly, while oscillation of circadian genes is already present in standard cell culture, organoid cultures appear to maintain the circadian clock even more effectively. Organoids derived from *ex vivo* tissue maintain circadian rhythms for up to three days, with oscillation patterns still detectable even after passaging and in primary structures (162-164). However, questions remain regarding how accurately these *in vitro* models reflect *in vivo* circadian dynamics, particularly within the TME. While organoid cultures offer a more physiologically relevant system than monolayer cell cultures, they still lack systemic cues from the central clock, immune cells, and vascular networks. Additionally, the extent to

which tumor-intrinsic circadian rhythms interact with external signals in these models remains poorly understood. Further research is required to assess how accurately organoid-based circadian studies reflect *in vivo* conditions and whether these models can be optimized to better replicate the complex interactions between central and peripheral clocks in SCC.

Altogether, studying the circadian clock comes with limitations in each given model of research. *In vitro* models enable mechanistical and pathway studies of the circadian genes whereas mouse models benefit from a full framework with central clock system and adaptable external factors that influence the circadian rhythm individually. Clinical trials represent the primary avenue for translating circadian clock research into effective cancer therapies. Early clinical data suggest that the timing of therapy substantially influences SCC progression and patient survival (32,33,148). Still, standardized protocols, consistent timing definitions and sampling and large multicenter randomized clinical trials are needed to provide the necessary therapy validation in SCC (Table I). Most studies evaluate the overall treatment effect rather than the optimization of timing, and few follow-up studies have been conducted. Without follow-up, it is difficult to determine the impact of circadian rhythms on persistent treatment responses at the molecular level, or how patient-specific factors, such as chronotype and lifestyle, influence outcomes.

10. Conclusion

This review highlights the role of circadian disruption on SCC with a focus on LSCC, particularly in immune evasion and treatment response. Current evidence suggests that circadian regulators influence multiple hallmarks of SCC biology and communication within the tumor microenvironment. However, available mechanistic evidence remains fragmented across SCC subtypes and is still largely supported by preclinical studies and selected extrapolation from non-SCC malignancies. With cancer therapy increasingly focused on engaging the patient's immune system, evidence supports that circadian genes regulate key oncogenic pathways in SCC, including immune checkpoint activity and cell-cell interactions within the tumor microenvironment. Rather than representing an isolated therapeutic target, circadian biology may provide a broader framework for understanding temporal variation in treatment susceptibility and immune responsiveness across SCC subtypes. Therefore, chronotherapy may enhance the efficacy of established treatments and supports the development of circadian-directed therapeutic strategies aimed at maximizing patient well-being and survival.

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ME was responsible for investigation (searching and reviewing the literature, data and other evidence; reporting findings for further discussion, analysis, and exchange of ideas), writing, visualization (using data to create charts, graphs or figures), reviewing and editing the manuscript. AMD was responsible for writing, reviewing and editing the manuscript as well as administration with the editorial office. LM was responsible for conceptualization, providing resources (paying for the BioRender and EndNote licenses required for the preparation of the manuscript), writing, reviewing and editing the manuscript and supervised the project. All authors read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

References

1. Guan Y, Wang G, Fails D, Nagarajan P and Ge Y: Unraveling cancer lineage drivers in squamous cell carcinomas. Pharmacol Ther 206: 107448, 2020.
2. National Cancer Institute (NCI): A to Z list of cancer types. NCI, Bethesda, MD, 1980.
3. Dotto GP and Rustgi AK: Squamous cell cancers: A unified perspective on biology and genetics. Cancer Cell 29: 622-637, 2016.
4. Barsouk A, Aluru JS, Rawla P, Saginala K and Barsouk A: Epidemiology, risk factors, and prevention of head and neck squamous cell carcinoma. Med Sci (Basel) 11: 42, 2023.
5. Perkins RB, Wentzensen N, Guido RS and Schiffman M: Cervical cancer screening: A review. JAMA 330: 547-558, 2023.
6. Green AC and Olsen CM: Cutaneous squamous cell carcinoma: An epidemiological review. Br J Dermatol 177: 373-381, 2017.
7. Slominski RM, Raman C, Chen JY and Slominski AT: How cancer hijacks the body's homeostasis through the neuroendocrine system. Trends Neurosci 46: 263-275, 2023.
8. Slominski AT, Kim TK, Janjetovic Z, Slominski RM, Ganguli-Indra G, Athar M, Indra AK, Reiter RJ and Kleszczyński K: Melatonin and the skin: Current progress and perspectives for human health. J Invest Dermatol 145: 1345-1360. e2, 2025.
9. Slominski RM, Chen JY, Raman C and Slominski AT: Photo-neuro-immuno-endocrinology: How the ultraviolet radiation regulates the body, brain, and immune system. Proc Natl Acad Sci USA 121: e2308374121, 2024.

10. Slominski RM, Raman C, Jetten AM and Slominski AT: Neuro-immuno-endocrinology of the skin: How environment regulates body homeostasis. Nat Rev Endocrinol 21: 495-509, 2025.
11. Ervik M, Laversanne M, Lam F, Colombet M, Ferlay J, Filho AM, Bray F: Global Cancer Observatory: Cancer Today. 2024 estimates, version 1.0. International Agency for Research on Cancer, Lyon, France, 2026. Available from: https://gco.iarc.who.int/today. Accessed 12.06.2025.
12. Conti L and Gatt S: Squamous-cell carcinoma of the lung. N Engl J Med 379: e17, 2018.
13. DeMarco C: Squamous cell carcinoma of the lungs: 5 things to know. MD Anderson Cancer Center, Houston, TX, 2023.
14. Abnet CC, Arnold M and Wei WQ: Epidemiology of esophageal squamous cell carcinoma. Gastroenterology 154: 360-373, 2018.
15. Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, Jhingran A, Kitchener HC, Mileshkin LR, Viswanathan AN and Gaffney DK: Cervical cancer: A global health crisis. Cancer 123: 2404-2412, 2017.
16. Gatti V, Fierro C, Annicchiarico-Petruzzelli M, Melino G and Peschiaroli A: ΔNp63 in squamous cell carcinoma: Defining the oncogenic routes affecting epigenetic landscape and tumour microenvironment. Mol Oncol 13: 981-1001, 2019.
17. Campbell JD, Yau C, Bowlby R, Liu Y, Brennan K, Fan H, Taylor AM, Wang C, Walter V, Akbani R, *et al*: Genomic, pathway network, and immunologic features distinguishing squamous carcinomas. Cell Rep 23: 194-212.e6, 2018.
18. Li Q, Wang R, Yang Z, Li W, Yang J, Wang Z, Bai H, Cui Y, Tian Y, Wu Z, *et al*: Molecular profiling of human non-small cell lung cancer by single-cell RNA-seq. Genome Med 14: 87, 2022.
19. Feng B, Wang K, Herpel E, Plath M, Weichert W, Freier K, Zaoui K and Hess J: Prognostic gene signature for squamous cell carcinoma with a higher risk for treatment failure and accelerated MEK-ERK pathway activity. Cancers (Basel) 13: 5182, 2021.
20. Bailey P, Ridgway RA, Cammareri P, Treanor-Taylor M, Bailey UM, Schoenherr C, Bone M, Schreyer D, Purdie K, Thomson J, *et al*: Driver gene combinations dictate cutaneous squamous cell carcinoma disease continuum progression. Nat Commun 14: 5211, 2023.
21. Joshi A, Mishra R, Desai S, Chandrani P, Kore H, Sunder R, Hait S, Iyer P, Trivedi V, Choughule A, *et al*: Molecular characterization of lung squamous cell carcinoma tumors reveals therapeutically relevant alterations. Oncotarget 12: 578-588, 2021.
22. Sarin KY, Lin Y, Daneshjou R, Ziyatdinov A, Thorleifsson G, Rubin A, Pardo LM, Wu W, Khavari PA, Uitterlinden A, *et al*: Genome-wide meta-analysis identifies eight new susceptibility loci for cutaneous squamous cell carcinoma. Nat Commun 11: 820, 2020.
23. Kuonen F, Li NY, Haensel D, Patel T, Gaddam S, Yerly L, Rieger K, Aasi S and Oro AE: c-FOS drives reversible basal to squamous cell carcinoma transition. Cell Rep 37: 109774, 2021.
24. Singh H, Chopra H, Singh I, Mohanto S, Ahmed MG, Ghumra S, Seelan A, Survase M, Kumar A, Mishra A, *et al*: Molecular targeted therapies for cutaneous squamous cell carcinoma: Recent developments and clinical implications. EXCLI J 23: 300-334, 2024.
25. Rodriguez CP: Updates to treatment of recurrent metastatic head and neck cancers. J Natl ComprCancer Netw 22 (Suppl): e245020, 2024.
26. Fitzsimmons TS, Singh N, Walker TDJ, Newton C, Evans DGR, Crosbie EJ and Ryan NAJ: Immune checkpoint inhibitors efficacy across solid cancers and the utility of PD-L1 as a biomarker of response: A systematic review and meta-analysis. Front Med (Lausanne) 10: 1192762, 2023.
27. García-Foncillas J, Tejera-Vaquerizo A, Sanmartín O, Rojo F, Mestre J, Martín S, Azinovic I and Mesía R: Update on management recommendations for advanced cutaneous squamous cell carcinoma. Cancers (Basel) 14: 629, 2022.
28. Vachhani P and Chen H: Spotlight on pembrolizumab in non-small cell lung cancer: The evidence to date. Onco Targets Ther 9: 5855-5866, 2016.
29. American Society of Clinical Oncology (ASCO): FDA approves pembrolizumab for first-line treatment of head and neck squamous cell carcinoma. ASCO, Alexandria, VA, 2024. https://www.asco.org/practice-policy/policy-issues-statements/asco-in-action/fda-approves-pembrolizumab-first-line
30. American Society of Clinical Oncology (ASCO): FDA approves Opdivo in combination with chemotherapy and Opdivo in combination with Yervoy for first-line esophageal squamous cell carcinoma indications. ASCO, Alexandria, VA, 2024. https://www.asco.org/news-initiatives/policy-news-analysis/fda-approves-opdivo-combination-chemotherapy-and-opdivo
31. Colombo N, Dubot C, Lorusso D, Caceres MV, Hasegawa K, Shapira-Frommer R, Tewari KS, Salman P, Hoyos Usta E, Yañez E, *et al*: Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 385: 1856-1867, 2021.
32. Qian DC, Kleber T, Brammer B, Xu KM, Switchenko JM, Janopaul-Naylor JR, Zhong J, Yushak ML, Harvey RD, Paulos CM, *et al*: Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): A propensity score-matched analysis of a single-centre, longitudinal study. Lancet Oncol 22: 1777-1786, 2021.
33. Hirata T, Uehara Y, Hakozaki T, Kobayashi T, Terashima Y, Watanabe K, Yomota M and Hosomi Y: Brief report: Clinical outcomes by infusion timing of immune checkpoint inhibitors in patients with locally advanced NSCLC. JTO Clin Res Rep 5: 100659, 2024.
34. Wang C, Zeng Q, Gül ZM, Wang S, Pick R, Cheng P, Bill R, Wu Y, Naulaerts S, Barnoud C, *et al*: Circadian tumor infiltration and function of $CD8^+$ T cells dictate immunotherapy efficacy. Cell 187: 2690-2702.e17, 2024.
35. Li M, Chen Z, Jiang T, Yang X, Du Y, Liang J, Wang L, Xi J, Lin M and Feng M: Circadian rhythm-associated clinical relevance and tumor microenvironment of non-small cell lung cancer. J Cancer 12: 2582-2597, 2021.
36. Munteanu C, Turti S, Achim L, Muresan R, Souca M, Prifti E, Mârza SM and Papuc I: The relationship between circadian rhythm and cancer disease. Int J Mol Sci 25: 5846, 2024.
37. Pall GS, Melo C, Ortega-Campos SM and Diamantopoulou Z: Designing the perfect strike against cancer: Clocking in with the circadian rhythm. Annu Rev Cancer Biol 10: 157-178, 2026.
38. Rahman S, Kraljević Pavelić S and Markova-Car E: Circadian (De)regulation in head and neck squamous cell carcinoma. Int J Mol Sci 20: 2662, 2019.
39. Jin Y, Wang Z, Huang S, Liu C, Wu X and Wang H: Identify and validate circadian regulators as potential prognostic markers and immune infiltrates in head and neck squamous cell carcinoma. Sci Rep 13: 19939, 2023.
40. Wang C, Liu X, Nov P, Li L, Li C, Liao X, Li L, Du K and Li J: A signature based on circadian rhythm-associated genes for the evaluation of prognosis and the tumour microenvironment in HNSCC. Sci Rep 14: 7594, 2024.
41. Cox KH and Takahashi JS: Introduction to the clock system. In: Circadian Clock in Brain Health and Disease. Engmann O and Brancaccio M (eds). Springer International Publishing, Cham, pp3-20, 2021.
42. Sen A and Hoffmann HM: Role of core circadian clock genes in hormone release and target tissue sensitivity in the reproductive axis. Mol Cell Endocrinol 501: 110655, 2020.
43. Pan X, Mota S and Zhang B: Circadian clock regulation on lipid metabolism and metabolic diseases. Adv Exp Med Biol 1276: 53-66, 2020.
44. Yeung J and Naef F: Rhythms of the genome: Circadian dynamics from chromatin topology, tissue-specific gene expression, to behavior. Trends Genet 34: 915-926, 2018.
45. Hirota T and Fukada Y: Resetting mechanism of central and peripheral circadian clocks in mammals. Zoolog Sci 21: 359-368, 2004.
46. Landgraf D, Wang LL, Diemer T and Welsh DK: NPAS2 compensates for loss of CLOCK in peripheral circadian oscillators. PLoS Genet 12: e1005882, 2016.
47. Xu H, Gustafson CL, Sammons PJ, Khan SK, Parsley NC, Ramanathan C, Lee HW, Liu AC and Partch CL: Cryptochrome 1 regulates the circadian clock through dynamic interactions with the BMAL1 C terminus. Nat Struct Mol Biol 22: 476-484, 2015.
48. Matsumura R, Tsuchiya Y, Tokuda I, Matsuo T, Sato M, Node K, Nishida E and Akashi M: The mammalian circadian clock protein period counteracts cryptochrome in phosphorylation dynamics of circadian locomotor output cycles kaput (CLOCK). J Biol Chem 289: 32064-32072, 2014.
49. Trott AJ and Menet JS: Regulation of circadian clock transcriptional output by CLOCK:BMAL1. PLoS Genet 14: e1007156, 2018.
50. Menet JS, Pescatore S and Rosbash M: CLOCK:BMAL1 is a pioneer-like transcription factor. Genes Dev 28: 8-13, 2014.
51. Ukai-Tadenuma M, Kasukawa T and Ueda HR: Proof-by-synthesis of the transcriptional logic of mammalian circadian clocks. Nat Cell Biol 10: 1154-1163, 2008.

52. Yeung J, Mermet J, Jouffe C, Marquis J, Charpagne A, Gachon F and Naef F: Transcription factor activity rhythms and tissue-specific chromatin interactions explain circadian gene expression across organs. Genome Res 28: 182-191, 2018.
53. Ray S, Valekunja UK, Stangherlin A, Howell SA, Snijders AP, Damodaran G and Reddy AB: Circadian rhythms in the absence of the clock gene Bmal1. Science 367: 800-806, 2020.
54. Zhuang Y, Li Z, Xiong S, Sun C, Li B, Wu SA, Lyu J, Shi X, Yang L, Chen Y, *et al*: Circadian clocks are modulated by compartmentalized oscillating translation. Cell 186: 3245-3260. e23, 2023.
55. Cermakian N, Monaco L, Pando MP, Dierich A and Sassone-Corsi P: Altered behavioral rhythms and clock gene expression in mice with a targeted mutation in the Period1 gene. EMBO J 20: 3967-3974, 2001.
56. Tartour K, Andriani F, Folco EG, Letkova D, Schneider R, Saidi I, Sato T, Welz PS, Benitah SA, Allier C and Padmanabhan K: Mammalian PERIOD2 regulates H2A.Z incorporation in chromatin to orchestrate circadian negative feedback. Nat Struct Mol Biol 29: 549-562, 2022.
57. Ikeda R, Tsuchiya Y, Koike N, Umemura Y, Inokawa H, Ono R, Inoue M, Sasawaki Y, Grieten T, Okubo N, *et al*: REV-ERBα and REV-ERBβ function as key factors regulating mammalian circadian output. Sci Rep 9: 10171, 2019.
58. Adlanmerini M and Lazar MA: The REV-ERB nuclear receptors: Timekeepers for the core clock period and metabolism. Endocrinology 164: bqad069, 2023.
59. Guillaumond F, Dardente H, Giguère V and Cermakian N: Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. J Biol Rhythms 20: 391-403, 2005.
60. Yamaguchi S, Mitsui S, Yan L, Yagita K, Miyake S and Okamura H: Role of DBP in the circadian oscillatory mechanism. Mol Cell Biol 20: 4773-4781, 2000.
61. Kubo M: Diurnal rhythmicity programs of microbiota and transcriptional oscillation of circadian regulator, NFIL3. Front Immunol 11: 552188, 2020.
62. Papagiannakopoulos T, Bauer MR, Davidson SM, Heimann M, Subbaraj L, Bhutkar A, Bartlebaugh J, Vander Heiden MG and Jacks T: Circadian rhythm disruption promotes lung tumorigenesis. Cell Metab 24: 324-331, 2016.
63. Fortin BM, Mahieu AL, Fellows RC, Pannunzio NR and Masri S: Circadian clocks in health and disease: Dissecting the roles of the biological pacemaker in cancer. F1000Res 12: 116, 2023.
64. Morgan MN, Dvuchbabny S, Martinez CA, Kerr B, Cistulli PA and Cook KM: The cancer clock is (Not) ticking: Links between circadian rhythms and cancer. Clocks Sleep 1: 435-458, 2019.
65. Aiello I, Mul Fedele ML, Román F, Marpegan L, Caldart C, Chiesa JJ, Golombek DA, Finkielstein CV and Paladino N: Circadian disruption promotes tumor-immune microenvironment remodeling favoring tumor cell proliferation. Sci Adv 6: eaaz4530, 2020.
66. Wang Y, Guo H and He F: Circadian disruption: From mouse models to molecular mechanisms and cancer therapeutic targets. Cancer Metastasis Rev 42: 297-322, 2023.
67. Liu Z, Selby CP, Yang Y, Lindsey-Boltz LA, Cao X, Eynullazada K and Sancar A: Circadian regulation of c-MYC in mice. Proc Natl Acad Sci USA 117: 21609-21617, 2020.
68. Korkmaz T, Aygenli F, Emisoglu H, Ozcelik G, Canturk A, Yilmaz S and Ozturk N: Opposite carcinogenic effects of circadian clock gene BMAL1. Sci Rep 8: 16023, 2018.
69. Ortega-Campos SM, Verdugo-Sivianes EM, Amiama-Roig A, Blanco JR and Carnero A: Interactions of circadian clock genes with the hallmarks of cancer. Biochim Biophys Acta Rev Cancer 1878: 188900, 2023.
70. Zhao D, Dong Y, Duan M, He D, Xie Q, Peng W, Cui W, Jiang J, Cheng Y, Zhang H, *et al*: Circadian gene ARNTL initiates circGUCY1A2 transcription to suppress non-small cell lung cancer progression via miR-200c-3p/PTEN signaling. J Exp Clin Cancer Res 42: 229, 2023.
71. Kubra S, Zhang H, Si Y, Gao X, Wang T, Pan L, Li L, Zhong N, Fu J, Zhang B and Li X: REGγ regulates circadian clock by modulating BMAL1 protein stability. Cell Death Discov 7: 335, 2021.
72. Wang J, Jia Q, Sun J, Wu S, Wei L and Yao W: Arntl-induced upregulation of DUSP1 inhibits tumor progression in esophageal squamous cell carcinoma by inactivating ERK signaling. Cancer Biol Ther 25: 2408042, 2024.
73. Li H, Li M, Chen K, Li Y, Yang Z and Zhou Z: The circadian clock gene ARNTL overexpression suppresses oral cancer progression by inducing apoptosis via activating autophagy. Med Oncol 39: 244, 2022.
74. Chen K, Li H, Li Y, Yang Z, Luo J and Zhou Z: ARNTL inhibits the malignant behaviors of oral cancer by regulating autophagy in an AKT/mTOR pathway-dependent manner. Cancer Sci 114: 3914-3923, 2023.
75. Qu M, Zhang G, Qu H, Vu A, Wu R, Tsukamoto H, Jia Z, Huang W, Lenz HJ, Rich JN and Kay SA: Circadian regulator BMAL1::CLOCK promotes cell proliferation in hepatocellular carcinoma by controlling apoptosis and cell cycle. Proc Natl Acad Sci USA 120: e2214829120, 2023.
76. Schwartz PB, Nukaya M, Berres ME, Rubinstein CD, Wu G, Hogenesch JB, Bradfield CA and Ronnekleiv-Kelly SM: The circadian clock is disrupted in pancreatic cancer. PLoS Genet 19: e1010770, 2023.
77. Zhang X, Pant SM, Ritch CC, Tang HY, Shao H, Dweep H, Gong YY, Brooks R, Brafford P, Wolpaw AJ, *et al*: Cell state dependent effects of Bmal1 on melanoma immunity and tumorigenicity. Nat Commun 15: 633, 2024.
78. Freitas-Cortez MA, Masrorpour F, Jiang H, Mahmud I, Lu Y, Huang A, Duong LK, Wang Q, Voss TA, Kettlun Leyton CS, *et al*: Cancer cells avoid ferroptosis induced by immune cells via fatty acid binding proteins. Mol Cancer 24: 40, 2025.
79. Zhang Z, Hunter L, Wu G, Maidstone R, Mizoro Y, Vonslow R, Fife M, Hopwood T, Begley N, Saer B, *et al*: Genome-wide effect of pulmonary airway epithelial cell-specific Bmal1 deletion. FASEB J 33: 6226-6238, 2019.
80. Alexander RK, Liou YH, Knudsen NH, Starost KA, Xu C, Hyde AL, Liu S, Jacobi D, Liao NS and Lee CH: Bmal1 integrates mitochondrial metabolism and macrophage activation. Elife 9: e54090, 2020.
81. Liu JL, Wang CY, Cheng TY, Rixiati Y, Ji C, Deng M, Yao S, Yuan LH, Zhao YY, Shen T and Li JM: Circadian clock disruption suppresses PDL1^{+} intraepithelial B cells in experimental colitis and colitis-associated colorectal cancer. Cell Mol Gastroenterol Hepatol 12: 251-276, 2021.
82. Cao XM, Kang WD, Xia TH, Yuan SB, Guo CA, Wang WJ and Liu HB: High expression of the circadian clock gene NPAS2 is associated with progression and poor prognosis of gastric cancer: A single-center study. World J Gastroenterol 29: 3645-3657, 2023.
83. Ma S, Chen Y, Quan P, Zhang J, Han S, Wang G, Qi R, Zhang X, Wang F, Yuan J, *et al*: NPAS2 promotes aerobic glycolysis and tumor growth in prostate cancer through HIF-1A signaling. BMC Cancer 23: 280, 2023.
84. Zhang Y, Chen Y, Huang W, Zhou Y, Wang Y, Fu K and Zhuang W: NPAS2 dampens chemo-sensitivity of lung adenocarcinoma cells by enhancing DNA damage repair. Cell Death Dis 15: 101, 2024.
85. Yuan P, Yang T, Mu J, Zhao J, Yang Y, Yan Z, Hou Y, Chen C, Xing J, Zhang H and Li J: Circadian clock gene NPAS2 promotes reprogramming of glucose metabolism in hepatocellular carcinoma cells. Cancer Lett 469: 498-509, 2020.
86. Wang S, Huang C, Zheng Y, Wu X and Zhong Y: NPAS2, transcriptionally activated by ARRB1, promotes the malignant behaviours of lung adenocarcinoma cells and regulates the reprogramming of glucose metabolism. Clin Exp Pharmacol Physiol 51: e13860, 2024.
87. Liu B, Xu K, Jiang Y and Li X: Aberrant expression of Per1, Per2 and Per3 and their prognostic relevance in non-small cell lung cancer. Int J Clin Exp Pathol 7: 7863-7871, 2014.
88. Li B, Chen Q, Feng Y, Wei T, Zhong Y, Zhang Y and Feng Q: Glucose restriction induces AMPK-SIRT1-mediated circadian clock gene Per expression and delays NSCLC progression. Cancer Lett 576: 216424, 2023.
89. Tang W, Peng W, Zhang H, Zhang Y, Li B and Duan C: Period 3, a tumor suppressor in non-small cell lung cancer, is silenced by hypermethylation. Int J Clin Exp Pathol 11: 120-128, 2018.
90. Yang G, Yang Y, Tang H and Yang K: Loss of the clock gene Per1 promotes oral squamous cell carcinoma progression via the AKT/mTOR pathway. Cancer Sci 111: 1542-1554, 2020.
91. Liu Y, Hao J, Yuan G, Wei M, Bu Y, Jin T and Ma L: PER1 as a tumor suppressor attenuated in the malignant phenotypes of breast cancer cells. Int J Gen Med 14: 7077-7087, 2021.
92. Yang Y, Tang H, Zheng J and Yang K: The PER1/HIF-1alpha negative feedback loop promotes ferroptosis and inhibits tumor progression in oral squamous cell carcinoma. Transl Oncol 18: 101360, 2022.

93. Ma D, Hou L, Xia H, Li H, Fan H, Jia X and Niu Z: PER2 inhibits proliferation and stemness of glioma stem cells via the Wnt/β-catenin signaling pathway. Oncol Rep 44: 533-542, 2020.
94. Zheng H, Yu W, Ren J, Tang H, Li H, Zhang Z, Yin S and Yang K: PER2 binding to PDK1 enhances the cisplatin sensitivity of oral squamous cell carcinoma through inhibition of the AKT/mTOR pathway. Cell Signal 122: 111327, 2024.
95. Chen B, Tan Y, Liang Y, Li Y, Chen L, Wu S, Xu W, Wang Y, Zhao W and Wu J: Per2 participates in AKT-mediated drug resistance in A549/DDP lung adenocarcinoma cells. Oncol Lett 13: 423-428, 2017.
96. Xiong H, Yang Y, Yang K, Zhao D, Tang H and Ran X: Loss of the clock gene PER2 is associated with cancer development and altered expression of important tumor-related genes in oral cancer. Int J Oncol 52: 279-287, 2018.
97. Zhang Z, Sun D, Tang H, Ren J, Yin S and Yang K: PER2 binding to HSP90 enhances immune response against oral squamous cell carcinoma by inhibiting IKK/NF-κB pathway and PD-L1 expression. J Immunother Cancer 11: e007627, 2023.
98. Tang Q, Xie M, Yu S, Zhou X, Xie Y, Chen G, Guo F and Chen L: Periodic oxaliplatin administration in synergy with PER2-mediated PCNA transcription repression promotes chronochemotherapeutic efficacy of OSCC. Adv Sci (Weinh) 6: 1900667, 2019.
99. Redondo JA, Bibes R, Vercauteren Drubbel A, Dassy B, Bisteau X, Maury E and Beck B: PER2 circadian oscillation sensitizes esophageal cancer cells to chemotherapy. Biology (Basel) 10: 266, 2021.
100. Mocellin S, Tropea S, Benna C and Rossi CR: Circadian pathway genetic variation and cancer risk: Evidence from genome-wide association studies. BMC Med 16: 20, 2018.
101. Li Y, Li W, Deng J and Yin M: PER3 promoter hypermethylation correlates to the progression of pan-cancer. Clin Epigenetics 16: 140, 2024.
102. Li Y, Li B, Yang K, Zhu L, Tang H, Huang Y, Deng J and Duan J: PER3 suppresses tumor metastasis of oral squamous cell carcinoma by promoting HIF-1α degradation. Transl Oncol 52: 102258, 2025.
103. Li Q, Xia D, Wang Z, Liu B, Zhang J, Peng P, Tang Q, Dong J, Guo J, Kuang D, *et al*: Circadian rhythm gene PER3 negatively regulates stemness of prostate cancer stem cells via WNT/β-catenin signaling in tumor microenvironment. Front Cell Dev Biol 9: 656981, 2021.
104. Zhang H, Shu R, Liu X, Zhang X and Sun D: Downregulation of REV-ERBα is associated with the progression of lung adenocarcinoma. Ann Transl Med 10: 56, 2022.
105. Kim SM, Jeon Y, Jang JY and Lee H: NR1D1 deficiency in the tumor microenvironment promotes lung tumor development by activating the NLRP3 inflammasome. Cell Death Discov 9: 278, 2023.
106. Ka NL, Park MK, Kim SS, Jeon Y, Hwang S, Kim SM, Lim GY, Lee H and Lee MO: NR1D1 stimulates antitumor immune responses in breast cancer by activating cGAS-STING signaling. Cancer Res 83: 3045-3058, 2023.
107. Cho H, Yun A, Kim J, Park E, Jung JW, Chung S and Son GH: Functional characterization of circadian nuclear receptors REV-ERBα and REV-ERBβ in human osteosarcoma cell cultures. Int J Mol Sci 25: 770, 2024.
108. van der Watt PJ, Roden LC, Davis KT, Parker MI and Leaner VD: Circadian oscillations persist in cervical and esophageal cancer cells displaying decreased expression of tumor-suppressing circadian clock genes. Mol Cancer Res 18: 1340-1353, 2020.
109. Shen W, Zhang W, Ye W, Wang H, Zhang Q, Shen J, Hong Q, Li X, Wen G, Wei T and Zhang J: SR9009 induces a REV-ERB dependent anti-small-cell lung cancer effect through inhibition of autophagy. Theranostics 10: 4466-4480, 2020.
110. Palomba M, Vecchio D, Allavena G, Capaccio V, De Mei C, Scarpelli R and Grimaldi B: Identification of a dual autophagy and REV-ERB inhibitor with in vivo anticancer efficacy. J Med Chem 67: 349-379, 2024.
111. Liu D, Wei B, Liang L, Sheng Y, Sun S, Sun X, Li M, Li H, Yang C, Peng Y, *et al*: The circadian clock component RORA increases immunosurveillance in melanoma by inhibiting PD-L1 expression. Cancer Res 84: 2265-2281, 2024.
112. Yao W, Shang L, Wang Y, Xu L, Bai Y, Feng M, Jia X and Wu S: DNMT1-driven methylation of RORA facilitates esophageal squamous cell carcinoma progression under hypoxia through SLC2A3. J Transl Med 22: 1167, 2024.
113. Wang M, Zeng R, Zheng S and Qian Y: Retinoic acid receptor-related orphan receptor alpha and synthetic RORα agonist against invasion and metastasis in tongue squamous cell carcinoma. Biochem Biophys Res Commun 733: 150421, 2024.
114. Aroca-Siendones MI, Moreno-SanJuan S, Puentes-Pardo JD, Verbeni M, Arnedo J, Escudero-Feliu J, García-Costela M, García-Robles A, Carazo Á and León J: Core circadian clock proteins as biomarkers of progression in colorectal cancer. Biomedicines 9: 967: 967, 2021.
115. Aye L, Wang Z, Chen F, Xiong Y, Zhou J, Wu F, Hu L and Wang D: Circadian regulator-mediated molecular subtypes depict the features of tumor microenvironment and indicate prognosis in head and neck squamous cell carcinoma. J Immunol Res 2023: 9946911, 2023.
116. Berkel C and Cacan E: A majority of circadian clock genes are expressed in estrogen receptor and progesterone receptor status-dependent manner in breast cancer. J Biosci 49: 80, 2024.
117. Zhang H, Liu R, Zhang B, Huo H and Song Z: Advances in the study of circadian genes in non-small cell lung cancer. Integr Cancer Ther 21: 15347354221096080, 2022.
118. Liu Z, Yu K, Zheng J, Lin H, Zhao Q, Zhang X, Feng W, Wang L, Xu J, Xie D, *et al*: Dysregulation, functional implications, and prognostic ability of the circadian clock across cancers. Cancer Med 8: 1710-1720, 2019.
119. Yang Y, Yuan G, Xie H, Wei T, Zhu D, Cui J, Liu X, Shen R, Zhu Y and Yang X: Circadian clock associates with tumor microenvironment in thoracic cancers. Aging (Albany NY) 11: 11814-11828, 2019.
120. Li J, Chen R, Ji M, Zou SL and Zhu LN: Cisplatin-based chronotherapy for advanced non-small cell lung cancer patients: A randomized controlled study and its pharmacokinetics analysis. Cancer Chemother Pharmacol 76: 651-655, 2015.
121. Lamnis L, Christofi C, Stark A, Palm H, Roemer K, Vogt T and Reichrath J: Differential regulation of circadian clock genes by UV-B radiation and 1,25-dihydroxyvitamin D: A pilot study during different stages of skin photocarcinogenesis. Nutrients 16: 254, 2024.
122. Kranjčević JK, Čonkaš J and Ozretić P: The role of estrogen and estrogen receptors in head and neck tumors. Cancers (Basel) 16: 1575, 2024.
123. Langevin SM, Grandis JR and Taioli E: Female hormonal and reproductive factors and head and neck squamous cell carcinoma risk. Cancer Lett 310: 216-221, 2011.
124. Ao Y, Zhao Q, Yang K, Zheng G, Lv X and Su X: A role for the clock period circadian regulator 2 gene in regulating the clock gene network in human oral squamous cell carcinoma cells. Oncol Lett 15: 4185-4192, 2018.
125. Xie Q, Chu H, Yi J, Yu H, Gu T, Guan Y, Liu X, Liang J, Li Y and Wang J: Identification of a prognostic immune-related signature for small cell lung cancer. Cancer Med 10: 9115-9128, 2021.
126. Farago AF and Azzoli CG: Beyond ALK and ROS1: RET, NTRK, EGFR and BRAF gene rearrangements in non-small cell lung cancer. Transl Lung Cancer Res 6: 550-559, 2017.
127. Regence - Medical Policy Manual: Targeted genetic testing for selection of therapy for non-small cell lung cancer (NSCLC). Genetic Testing, Policy No. 56, 2026.
128. Rolfo C and Raez L: New targets bring hope in squamous cell lung cancer: Neurotrophic tyrosine kinase gene fusions. Lab Invest 97: 1268-1270, 2017.
129. Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, Göker E, Georgoulias V, Li W, Isla D, *et al*: Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): An open-label randomised controlled phase 3 trial. Lancet Oncol 16: 897-907, 2015.
130. Langer T: Leitlinienprogramm Onkologie: Prävention, Diagnostik, Therapie und Nachsorge des Lungenkarzinoms: Version 2.2. Office des Leitlinienprogrammes Onkologie, Berlin, Deutschland 2023 (In German). Available from https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Lungenkarzinom/Version_2/LL_Lungenkarzinom_Langversion_2.2.pdf. Accessed 11.06.2025.
131. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, Daniel D, McCune S, Mekhail T, *et al*: Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): A multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 20: 924-937, 2019.

132. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, *et al*: Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 379: 2040-2051, 2018.
133. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, *et al*: Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373: 123-135, 2015.
134. Porschen R, Fischbach W, Gockel I, Hollerbach S, Hölscher A, Jansen PL, Miehlke S, Pech O, Stahl M, Vanhoefer U, *et al*: S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus. Z Gastroenterol 61: 701-745, 2023 (In German).
135. Langer T: Leitlinienprogramm Onkologie: S3-Leitlinie Larynxkarzinom, 2019 (In German). https://www.leitlinien-programm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Larynxkarzinom/Version1.1/LL_Larynxkarzinom_Langversion_1.1.pdf. Accessed 10.06.2025.
136. Leitlinienprogramm Onkologie: S3-Leitlinie Mundhöhlenkarzinom, 2021 (In German). https://www.leitlinienprogramm-onkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Mundhoehlenkarzinom/Version_3/LL_Mundhoehlenkarzinom_Langversion_3.0.pdf. Accessed 10.06.2025.
137. Li Q, Tie Y, Alu A, Ma X and Shi H: Targeted therapy for head and neck cancer: Signaling pathways and clinical studies. Signal Transduct Target Ther 8: 31, 2023.
138. Lau SCM, Pan Y, Velcheti V and Wong KK: Squamous cell lung cancer: Current landscape and future therapeutic options. Cancer Cell 40: 1279-1293, 2022.
139. Karaboué A, Collon T, Pavese I, Bodiguel V, Cucherousset J, Zakine E, Innominato PF, Bouchahda M, Adam R and Lévi F: Time-dependent efficacy of checkpoint inhibitor nivolumab: results from a pilot study in patients with metastatic non-small-cell lung cancer. Cancers (Basel) 14: 896, 2022.
140. Wang Z, Wang H, Guo H, Li F, Wu W, Zhang S and Wang T: The circadian rhythm and core gene Period2 regulate the chemotherapy effect and multidrug resistance of ovarian cancer through the PI3K signaling pathway. Biosci Rep 40: BSR20202683, 2020.
141. Dai Y, Tian X, Ye X, Gong Y, Xu L and Jiao L: Role of the TME in immune checkpoint blockade resistance of non-small cell lung cancer. Cancer Drug Resist 7: 52, 2024.
142. Guo X, Qin L, Wang X, Geng Q, Li D, Lu Y and Jiang H: Chronological effects of immune checkpoint inhibitors in non-small cell lung cancer. Immunology 174: 402-410, 2025.
143. Fortin BM, Pfeiffer SM, Insua-Rodríguez J, Alshetaiwi H, Moshensky A, Song WA, Mahieu AL, Chun SK, Lewis AN, Hsu A, *et al*: Circadian control of tumor immunosuppression impacts efficacy of immune checkpoint blockade. Nat Immunol 25: 1257-1269, 2024.
144. Wu Y, Tao B, Zhang T, Fan Y and Mao R: Pan-cancer analysis reveals disrupted circadian clock associates with T cell exhaustion. Front Immunol 10: 2451, 2019.
145. Liu Y, Wu Z, Li Y, Zhang J, Gao Y, Yuan G and Han M: PER3 plays anticancer roles in the oncogenesis and progression of breast cancer via regulating MEK/ERK signaling pathway. J Chin Med Assoc 85: 1051-1060, 2022.
146. Ma Z, Jin X, Qian Z, Li F, Xu M, Zhang Y, Kang X, Li H, Gao X, Zhao L, *et al*: Deletion of clock gene Bmal1 impaired the chondrocyte function due to disruption of the HIF1α-VEGF signaling pathway. Cell Cycle 18: 1473-1489, 2019.
147. Focan C, Kreutz F, Longrée L, Graas MP, Moeneclaey N, Demolin G and Focan-Henrard D: Interest of chronotherapy in multidisciplinary management of œsophageal and gastric cancers. Pathol Biol (Paris) 55: 181-185, 2007 (In French).
148. Marcu LG: Circadian rhythm-based cancer therapy in randomised clinical trials. Expert Rev Anticancer Ther 24: 29-39, 2024.
149. Chang L, Li L, Li W, Jiang M, Jv Y, Wang L, Hou Y, Long Q and Yu S: Research on radiotherapy at different times of the day for inoperable cervical cancer. Int J Clin Pharmacol Ther 54: 856-864, 2016.
150. Zhou R, Chen X, Liang J, Chen Q, Tian H, Yang C and Liu C: A circadian rhythm-related gene signature associated with tumor immunity, cisplatin efficacy, and prognosis in bladder cancer. Aging (Albany NY) 13: 25153-25179, 2021.
151. Chi H, Yang J, Peng G, Zhang J, Song G, Xie X, Xia Z, Liu J and Tian G: Circadian rhythm-related genes index: A predictor for HNSCC prognosis, immunotherapy efficacy, and chemosensitivity. Front Immunol 14: 1091218, 2023.
152. Ok O, Lee M, Kim N, Cho J, Hong SY, Nam MS, Yi MS, Oh D, Ahn JS, Kang D and Hong JH: Efficacy on symptoms and mortality day vs. night administration of EGFR-TKIs for advanced non-small cell lung cancer. Support Care Cancer 32: 645, 2024.
153. Landré T, Karaboué A, Buchwald ZS, Innominato PF, Qian DC, Assié JB, Chouaïd C, Lévi F and Duchemann B: Effect of immunotherapy-infusion time of day on survival of patients with advanced cancers: A study-level meta-analysis. ESMO Open 9: 102220, 2024.
154. Wang C, Barnoud C, Cenerenti M, Sun M, Caffa I, Kizil B, Bill R, Liu Y, Pick R, Garnier L, *et al*: Dendritic cells direct circadian anti-tumour immune responses. Nature 614: 136-143, 2023.
155. Li J, Luo P, Liu Y, Fang Y, Wang L and Jiang A: Circadian rhythms in tumor regulation: Impacts on tumor progression and the immune microenvironment. Explor Res Hypothesis Med 10: 135-139, 2025.
156. Rosenberg AJ, Perez CA, Guo W, de Oliveira Novaes JM, da Silva Reis KFO, McGarrah PW and Price KAR: Breaking ground in recurrent or metastatic head and neck squamous cell carcinoma: Novel therapies beyond PD-L1 immunotherapy. Am Soc Clin Oncol Educ Book 44: e433330, 2024.
157. Hu ML, Yeh KT, Lin PM, Hsu CM, Hsiao HH, Liu YC, Lin HY, Lin SF and Yang MY: Deregulated expression of circadian clock genes in gastric cancer. BMC Gastroenterol 14: 67, 2014.
158. Li B, Cui Y, Nambiar DK, Sunwoo JB and Li R: The immune subtypes and landscape of squamous cell carcinoma. Clin Cancer Res 25: 3528-3537, 2019.
159. Gong X, Tang H and Yang K: PER1 suppresses glycolysis and cell proliferation in oral squamous cell carcinoma via the PER1/RACK1/PI3K signaling complex. Cell Death Dis 12: 276, 2021.
160. Kosir R, Acimovic J, Golicnik M, Perse M, Majdic G, Fink M and Rozman D: Determination of reference genes for circadian studies in different tissues and mouse strains. BMC Mol Biol 11: 60, 2010.
161. Giri A and Sundar IK: Evaluation of stable reference genes for qPCR normalization in circadian studies related to lung inflammation and injury in mouse model. Sci Rep 12: 1764, 2022.
162. Fujii M and Sato T: Somatic cell-derived organoids as prototypes of human epithelial tissues and diseases. Nat Mater 20: 156-169, 2021.
163. Lee S and Hong CI: Organoids as model systems to investigate circadian clock-related diseases and treatments. Front Genet 13: 874288, 2022.
164. Yamada RG and Ueda HR: The circadian clock ticks in organoids. EMBO J 41: e110157, 2022.
165. Jin F, Li Y, Chen Y, Song J, Wang Y, Gong X, Li Y, Long J and Wu W: Chrono-chemotherapy combined with IMRT in locoregionally advanced nasopharyngeal carcinoma: A prospective randomized study. J Clin Oncol 44 (Suppl): S6113, 2026.
166. Savard MF, Ibrahim M, Saunders D, Pond GR, Ng TL, Awan AA, Sehdev S, Alqahtani N, Vandermeer L, MacDonald F, *et al*: A pragmatic, multicenter, randomized trial comparing morning versus evening dosing of adjuvant endocrine therapy (REaCT-CHRONO Study). NPJ Breast Cancer 11: 49, 2025.
167. Damato AR, Katumba RGN, Luo J, Atluri H, Talcott GR, Govindan A, Slat EA, Weilbaecher KN, Tao Y, Huang J, *et al*: A randomized feasibility study evaluating temozolomide circadian medicine in patients with glioma. Neurooncol Pract 9: 193-200, 2022.

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