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Understanding the significance of Biological Clock and its impact on cancer incidence

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Abstract

The circadian clock is an essential timekeeper that controls, for humans, the daily rhythm of biochemical, physiological, and behavioral functions. Irregular performance or disruption in circadian rhythms results in various diseases, including cancer. As a factor in cancer development, perturbations in circadian rhythms can affect circadian homeostasis in energy balance, lead to alterations in the cell cycle, and cause dysregulation of chromatin remodeling. However, knowledge gaps remain in our understanding of the relationship between the circadian clock and cancer. Therefore, a mechanistic understanding by which circadian disruption enhances cancer risk is needed. This review article outlines the importance of the circadian clock in tumorigenesis and summarizes underlying mechanisms in the clock and its carcinogenic mechanisms, highlighting advances in chronotherapy for cancer treatment.

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8. Author Contributions

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The authors declare that they do not have any conflict of interest.

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Keywords

Biological Clock; Cancer; Molecular mechanisms; Chronotherapy; Metabolism

1. Introduction

As organisms have evolved, they have synchronized their biological processes to the daily light/dark cycle. Nearly all living organisms have an inherent time-keeping mechanism, an endogenous clock that synchronizes and controls their daily biological processes. The daily oscillations directed by endogenous clocks are circadian rhythms, one of the essential characteristics of all living organisms [1]. In mammals, a circadian timing system generates and regulates circadian rhythms with a central pacemaker located in a hypothalamic structure called the suprachiasmatic nucleus (SCN) in the central nervous system [2]. Circadian oscillators, known as peripheral oscillators, are located in all most all tissues of an organism. Together with these, a central clock generates circadian rhythms in the hypothalamic *SCN* of the brain, which constantly synchronizes with environmental cues and controls the various clocks through circadian output pathways [3, 4]. Since this endogenous time-keeping system is close to, but not precisely, 24 h, it must be synchronized to the 24-hour day on a regular basis. The circadian rhythms govern various biological functions, such as sleeping and awakening, rest and activity, cognitive performance, blood pressure, metabolic processes, body temperature, hormone secretions, and immune responses [5–7] (Fig 1). Circadian rhythms are necessary for the *organism's* well-being and survival, and their disruption can lead to pathological conditions, including cancer (Fig 1). In the twenty-first century, the incidence and mortality of cancer have increased in essentially all countries [8]. People have irregular work shifts in the modern lifestyle, including working longer weekly hours, changing their transitions from day to night, and spending more time on activities such as electronic media. This prolonged light exposure, which results in disruption in circadian rhythmicity and has led to altered expression of clock genes, may increase abnormalities in DNA damage, cell metabolism, cell proliferation, and apoptosis, which can contribute to cancer development and progression [9, 10]. However, mechanistic understanding of cancer risk and its association with the circadian clock is incomplete. Therefore, this review discusses recent developments in mechanisms of circadian rhythms and their effects on signaling pathways related to cancer development and progression. At the molecular level, we further explore the future directions required to understand clock disruptions and their role in tumor initiation and progression.

2. Circadian Clock

The circadian time-keeping mechanism has three components: the central pacemaker, the input, and the out pathways [11] (Fig 2). Over the past four decades, the focus has been on identifying the structures that contain the circadian pacemaker. In 1972, the suprachiasmatic nucleus (SCN) in mammals was identified as the brain's circadian clock [12]. The SCN, which acts as a core pacemaker to regulate the cycle of rhythms throughout the body, consists of ~15,000 neurons located in the basal hypothalamus, dorsal to the optic chiasm on both sides of the third ventricle [13–15]. Other clocks reside in peripheral organs,

including the skin, lungs, liver, and kidneys. Core clock genes regulate both clocks (central and peripheral). Light and dark periods have substantial effects on the behavioral and physiological functions of mammals. On exposure to excessive light, the retina is activated and transmits signals to the SCN. It converts signals from the external environment to tissues through the autonomic nervous and endocrine systems, synchronizing circadian rhythms and oscillations. The SCN pacemaker generates self-sustaining, cell-autonomous circadian oscillations that directly or indirectly control the oscillations in the expression of various circadian clock genes [11]. Additional discoveries show separate clocks in the eyes and pineal glands of lower vertebrates such as reptiles, fish, and birds [16, 17]; in the eyes of marine mollusks [17]; and in the lateral neurons of *Drosophila* [18]. Thus, circadian clocks are usually found in neural or neuronal structures, and the brain SCN clock provides standard time for the peripheral clocks. The output pathways within the circadian system are responsible for the expression of circadian rhythms in hormonal (e.g., secretion of melatonin, cortisol, luteinizing hormone, and thyroxine), behavioral (e.g., locomotor activity and rhythms of feeding), neural (e.g., action potentials and rhythmic neuronal activity), and physiological (e.g., temperature and sleep-wake cycles) functions [19]. Thus, to keep the organism healthy, an interactive network of the master clock and peripheral clocks regulates various physiological and homeostatic functions.

2.1 Molecular Regulation of the Circadian Clock

Circadian rhythms are produced by genetically-determined biological clocks [20]. In the mammalian core clock, the circadian oscillations function in a cell-autonomous manner, generated by circadian clock genes, such as Clock and Bmal1; *period genes (*Per3, Per2, and Per1*);* and cryptochrome genes (Cry2 and Cry1) [21]. These clock genes provide an auto-regulatory network with transcriptional-translational feedback loops that include genetic transcription of clock genes and the post-translational activities of “clock proteins” [20, 22, 23]. Their transcriptional activity peaks during the day and is inhibited at night by repressors Per and Cry [24]. In addition to the core clock genes, other genes are involved in the circadian gene network through clock elements, including E-boxes (5’-CACGTG-3’), ROR/REV-ERB (retinoic acid receptor-related orphan receptor/reverse erythroblastosis virus), and ROR response elements (ROREs) [25–27]. The transcriptional repressors (REV-ERBα/REV-ERBβ) and activators (RORα/RORβ/RORγ) bind to ROREs, and then REV-ERBα and RORα directly regulate the circadian expression of core clock genes (Bmal1, Clock, Cry1, and Npas2) via RORE [27]. These other pathways in the circadian gene network add robustness to the molecular clock mechanism [26], which involves at least two large, interconnected feedback loops [21, 22]. Positive regulators of the loop drive the clock. The proteins of CLOCK (circadian locomotor output cycles kaput) (or neuronal PAS-domain protein [NPAS2], mainly expressed in the forebrain), and Bmal1 (brain and muscle ARNT-like protein 1) heterodimers form the positive limb of the feedback loop [28, 29]. The three-period genes and two cryptochrome genes, which form the negative limb of the feedback loop, act as the primary initiators of the circadian rhythm [30]. The CLOCK/Bmal1 heterodimer initiates the transcription by binding to the E-box cis-elements in the promoter regions of Per3, Per2, Per1, Rorb, Rora, Rorc, Rev-Erba, and Rev-Erβ [3, 27]. Accumulation of the Cry and Per proteins results in the Per/Cry repressor complex and its nuclear translocation from the cytoplasm. Upon entry into the nucleus, the Per/Cry

complex binds to CLOCK-Bmal1 at the E-box and suppresses its transcriptional activity by recruiting a SIN3-histone deacetylase complex (SIN3-HDAC) [31]. The time delay in the transcription-translation-based feedback loop within the clock generates daily oscillations with variations in clock genes and their protein products that indicate various forms of the circadian cycle. The amplitude of circadian oscillations is maintained by a cyclic proteolytic degradation of the repressors Per/Cer complex. The degradation/stability level of the Cry and Per proteins is necessary to set the period of the clock. Casein kinase 1 epsilon (CK1ε) and casein kinase 1 delta (CK1δ) phosphorylate PER proteins, which can lead to their ubiquitination by βTrCP and proteasomal degradation (26S proteasome) [21]. Similar to Per, Cry proteins are polyubiquitinated by FBXL3, targeting them for proteasomal degradation. Both Cry1 and Cry2 are targeted for ubiquitination. AMPK1 and Cry2 phosphorylate Cry1 by a subsequent dual-specificity Tyrosine Phosphorylation-Regulated Kinase 1A (DYRK1A)/Glycogen Synthase Kinase 3β (GSK-3β) cascade [32–35]. Collectively, these molecular events control the transcriptional feedback and allow the CLOCK-Bmal1 activator complex to start a new transcriptional cycle [36]. RORs and Rev-Erbs are transcribed during the subjective day, and their protein products regulate the transcription of Bmal1. REV-ERB and ROR proteins, which compete for the ROR regulatory element (RRE) binding sites of the Bmal1 promoter region, activate and repress the transcription of Bmal1 [37]. The circadian clock is regulated through a distinct set of transcriptional regulatory factors, and modifications of critical components of clock-regulatory factors contribute to cancer phenotypes (Fig 3).

2.2 Circadian Clock Dysfunction Promotes Cancer

Circadian clock disruption is caused by various factors, including genetic, environmental, and internal factors [38]. Defects or disruption in normal circadian functioning and altered levels of clock gene expressions can increase the risk of prostate cancers, breast cancers, ovarian cancers, colorectal cancers, endometrial cancers, non-Hodgkin's lymphoma, pancreatic cancers, osteosarcomas, head and neck squamous cell carcinomas, acute myeloid leukemia, and hepatocellular carcinomas (HCCs) [10, 39–43] (Table 1). Such alterations in the circadian system are risk factors for tumor incidence and may accelerate the progression of existing tumors. Circadian regulation can be a prerequisite for maintaining host defenses to prevent cancer [10]. Since circadian genes control the expression of genes, including cell cycle genes, tumor suppressor genes, and genes encoding caspases and transcription factors, they are involved in cancer-associated biological pathways [44]. Endocrine and metabolic hormones exhibit rhythmicity, and the levels of these hormones reciprocally influence circadian rhythms. Defects in this communication may lead to hormone-related pathological conditions, such as breast and endometrial cancers. This is evident by the higher prevalence of breast cancers and other malignancies for those who have been night-shift workers [45, 46]. Another line of evidence, which indicates an association of disrupted circadian functioning and development of breast cancer, comes from analysis of breast tumor tissues, which express lower levels of period genes, Per1 *and* Per2, than normal breast tissue [40, 47, 48]. Also, in HCCs, Bmal1 heterodimerizes with Neuronal PAS domain protein 2 (NPAS2) to facilitate NPAS2-mediated survival of cancer cells [49]. Polymorphisms in the circadian clock genes are associated with an elevated risk of cancer. For example, polymorphisms in the NPAS2 gene are associated with a higher risk of breast cancer [50]; NPAS2, Per1, and

Per2 are associated with gastric cancer [51]; and CLOCK1 is related to the development of colorectal cancers [52]. As determined for a Spanish population, eating dinner before nine pm is associated with a lower risk of prostate and breast cancers [53]. Further, excess artificial light can cause a disruption in circadian rhythm, which can disturb sleep; delayed sleep may contribute to obesity, leading to cancer. Together with smoking, obesity accounts for 30% of cancer incidence [54].

Studies with transgenic models of cancer reveal the impact of tumors on circadian rhythms. After γ-radiation of mice with thymocytes deficient in the mPer2 gene, the mice develop more tumors, and there is less apoptosis of tumor cells. γ-Radiation induces the core circadian genes. Thus, for mice, the Per2 gene regulates the circadian rhythm by controlling DNA damage-responsive pathways [44]. In p53−/− and KrasG12D mutant mice, the mutation in Per2 accelerates the initiation and progression of lung tumors [102]. Further, for KrasG12D mutant mice, deletion of *Bmal1* promotes lung turnorigenesis, and mutation of Cry2 drives the development of aggressive lymphomas in EμMyc models [103]. Bmal1 mutant mice develop lymphomas, along with liver and ovarian tumors [104]. Similar results are observed for mice lacking Cry1 and Cry2 [104]. For mice, liver and breast cancers cause alterations in the expression of the core clock genes, Clock, Per2, Rev-erbα, and RORγ, suggesting that dysregulation from physiological oscillations results in inflammation, oxidative stress and polyploidy.

Similarly, for mice, alterations in RORγ lead to the development of T-cell lymphomas [105]. Therefore, disruption of circadian clock genes promotes cancer progression in rodents and humans (Table 1). However, further studies are needed to understand the connection between circadian rhythms and cancer incidence.

2.3 Post-translational Modifications and Cancer Risk

The precision of the circadian clock mechanism is controlled by multiple post-translational modifications (PTMs), including sumoylation, phosphorylation, ubiquitination, and acetylation [106, 107]. PTMs control the core circadian clock dynamics, facilitated by the regulation of localization, activity, and degradation pathways of components implicated in controlling the feedback loop of core clock proteins [3]. A cyclic regulation of transcriptional activity of clock proteins is necessary for the maintenance of daily oscillations of these proteins and 24-h functioning of the clock. To maintain circadian oscillatory movement, the clock proteins, Bmal1, CLOCK, Per, and Cry, undergo modifications, including phosphorylation, acetylation, sumoylation, ubiquitination, methylation, and poly-ADP-ribosylation catalyzed by specific enzymes [108]. However, there is limited information on the PTMs of these proteins and their role in cancer pathogenesis. This review focuses on understanding the various PTMs from the perspective of carcinogenesis. Several studies have illustrated the importance of PTMs in the cellular machinery for promoting cancer dormancy. For example, the transcription repressors, Stra13 and Sharp-1, undergo sumoylation to mediate cellular growth arrest and inhibit myogenic differentiation, respectively [109, 110]. Another transcription repressor, DEC1 (differentiated embryo-chondrocyte expressed gene 1 protein), potentially involves sensing light signals from the environment [111]. DEC1 regulates the mammalian circadian rhythms

by suppressing Bmal/CLOCK activity in a histone deacetylase-dependent and -independent mechanism [69, 111, 112].

Additionally, DEC1 undergoes proteasomal degradation by USP17 ubiquitin protease to regulate the DNA damage response, which is implicated in the prevention of cancer development [113]. Sumoylation is a reversible PTM mediated by small ubiquitin-related modifier protein (SUMO), like the ubiquitin pathway [114–116]. Abnormal gene expression of BMAL1 in SUMO-deficient mice suggests the importance of sumoylation in regulating the Bmal1 circadian expression and controlling the core circadian clock [117]. These circadian clock genes coordinate various cell functions and help slow tumor growth [118]. As a clock regulator, DEC1 represses the CLOCK-Bmal1 heterodimer-mediated promotor activity via recruiting HDAC1 [26], thus feeding-forward regulation of circadian rhythms.

In MCF-7 breast cancer cells, sumoylation of DEC1 increases the suppression of Bmal1-CLOCK-mediated transcriptional activity via recruiting HDAC1 [119]. Thus, PTMs of DEC 1 appear to exert a substantial effect on regulating circadian transcription factors and mediating the effects in gastric cancers, non-small cell lung cancers, and breast cancers during their development [120–123]. Several hormone-related cancers are associated with disruptive circadian rhythms. For example, abnormal estrogen receptor α (ERα) signaling forms the basis of the development and progression of breast cancers [124]. Sumoylation of CLOCK results in elevated ERα transcriptional activity and thus mediates the estrogen signaling pathway [125]. This sumoylation is promoted by treatment with estradiol. The direct involvement of CLOCK via PTM in modulating hormone-related tumorigenesis underlies the advantages in manipulating the CLOCK-ERα-mediated signaling pathway [125]. Also, CLOCK exhibits intrinsic histone acetyltransferase (HAT) activity, leading to acetylation of specific non-histone proteins, which are most likely responsible for cell cycle regulation and thus linking the circadian clock and carcinogenesis [126]. In sum, PTMs provide an additional level of control of the circadian system based on regulating the transcriptional activity of core clock proteins. These processes appear to be susceptible to pharmacological interventions for cancer treatment. Nevertheless, it is necessary to understand the key mechanisms associated with PTMs and their pathways to develop the drugs to treat cancers.

3. Chromatin Remodeling and Cancer

Regulation of the circadian clock machinery is primarily based on a complex gene expression program, which involves dynamic changes in chromatin structure. Regulation of circadian machinery is achieved through chromatin remodeling and epigenetic control, resulting from modifications to gene expression rather than to changes in DNA sequence [127]. Chromatin structure, regulated through specific proteins, is necessary for synchronizing gene expression in cells, tissues, and organs. Environmental and extracellular signals cause alterations in chromatin structure [128]. These include disruption of DNA-histone interactions through the formation of DNA-loops and sliding nucleosomes; regulation by multiple-protein chromatin remodeling complexes, such as the limitation-switch (ISWI) family; switching to defective/sucrose non-fermentable (SWI/SNF); histone deacetylation (NuRD/CHD) of the inositol 80 (INO80) family; and Mi-2/nucleosome

remodeling [129]. These proteins, which are chromatin structure-regulating proteins, are controlled by ATP-dependent, histone-modifying enzymes and chromatin-remodeling enzymes [130]. These families include one or two distinct SW12/SNF2-type catalytic ATPases and multiple associated subunits [127] (Table 2). The SWI/SNF complex comprises twelve to fifteen subunits, including catalytic ATPase subunits (BRM [SMARCA2] or BRG1 [SMARCA4], alternate subunits [BAF47, BAF250, BAF200, BAF170, and BAF155]) and other accessory subunits. The SWI/SNF family of the chromatin remodeling complex regulates cell death, cell cycle, genomic instability, and DNA repair [131]. Analysis of the genome in human cancers reveals mutated or inactivated genes encoding SWI/SNF proteins [132, 133]. Further, as determined by whole-exome sequencing of 24 HCCs, chromatin regulators are the most mutated genes [134]. In various cancers, the principal subunits of the SWI/SNF complex, ARID1A (BAF250A) and ARID1B (BAF250B), are most frequently mutated (Table 2). In eukaryotic cells, ISWI (Imitation SWItch) has a conserved role in chromatin remodeling [89, 135, 136]. and its complexes are essential for nuclear functions, including regulation of DNA replication transcription and repair and maintenance of chromosome structure [137–140]. The role of ISWI family genes in tumor suppression is evident because mutations in the subunits of the ISWI complex are associated with various types of human cancers (Table 2) and promote tumor aggressiveness [141]. As chromatin remodelers, the Mi-2NuRD/CHD family proteins contribute to the regulation of genomic stability and are associated with various cancers; however, the mechanistic role of these family remodelers in cancer remains poorly understood (Table 2). These proteins share similar features in their capacity to bind nucleosomes, recognize histone modifications, and regulate ATPase activity. The processes and proteins implicated in regulating chromatin structure maintain DNA transcription, synthesis, replication, repair response, and chromatin stability [142]. Dysfunctions of these regulatory elements are associated with perturbations in the transcription of genes involved in tumor growth.

Dysregulation of chromatin remodeling machinery causes an increase of epigenetic abnormalities, leading to the initiation and progression of cancer. Histone variants can profoundly modify chromatin organization and functioning, which control DNA-template-based processes and functions [161]. The capacity of histone variants to facilitate chromatin deposition and provide epigenetic information for biological functioning makes them essential in developmental and differentiation processes. In cancers, the dysregulation of histone variants, employing depletion, overexpression, or mutation, contributes to their pathophysiological roles [162]. Histone deacetylases (HDACs) mediate higher-order chromatin changes in ovarian cancer cells and DNA damage-induced responses.[163].

Further, chemical modifications of histone H3 acetyl K9 and histone H3 trimethyl K4 correlate with altered gene expression for cervical cancer specimens and with poor prognosis of patients [164]. A histone isoform, Hist2h2ac (histone H2A type 2-C), involved in cell proliferation and differentiation, is altered in 17% of breast cancers and likely contributes to the dysregulation of targeted genes [165]. CHD1L is a chromatin remodeler that promotes metastasis and progression of HCCs and has therapeutic applications [166]. Further, liver-specific deletion of histone deacetylase 3 (HDAC3) results in HCCs, and the nuclear receptor corepressor 1 (NcoR1)-HDAC3-Rev-Erb complex formation regulates the circadian control of gene expression [167, 168].

NAD^+-dependent SIRT 1 is a modulator of circadian clock machinery (Fig. 4). SIRT1 deacetylates various histone and non-histone targets, including clock proteins Bmal1 and Per2, which modulate clock function and expression of clock-controlled genes [169, 170]. Similar to SIRT1, AMPK (metabolic sensor), which regulates NAD^+, has been linked to clock function by targeting the Cry and Per proteins [171]. SIRT1 deacetylates another non-histone target, the enzyme, AceCS1, which synthesizes acetyl-CoA, resulting in the cyclic synthesis of acetyl-CoA and thus oscillating the availability of acetyl groups for global acetylation [172]. AceCS1 is acetylated at its Lys661 residue. SIRT1 regulates the HAT activity of CLOCK. Circadian changes of chromatin properties by H3K4me3 are necessary for the regulation of circadian genes. SIRT1 deacetylates MLL1, which is responsible for H3K4me3 and circadian genes [173]. Regulation of SIRT1 activity, a critical circadian change of chromatin properties, indicates that histone H3 Lys9 and Lys14 on circadian promoters and Bmal1 are targets of SIRT1 [169]. Accumulating evidence implicating the importance of chromatin remodelers in the development and progression of cancers has established the core chromatin proteins as therapeutic targets. It is encouraging to find, in various cancers, the involvement of chromatin regulators globally and locally. This situation warrants further investigation of epigenetic changes within tumors and evaluation of their potential in driving the development and progression of tumors.

4. The Circadian Clock in Cancer Cell Metabolism

The cross-talk between the circadian and metabolic systems is of significance. In healthy cells, an intimate association between metabolism and circadian rhythms is required to maintain physiologic homeostasis. Metabolic processes regulated by the circadian clock include gluconeogenesis, glycolysis, glycogen synthesis, glucose transport, and cholesterol metabolism [6, 38]. A misalignment between internal and external environments leads to disruption of circadian rhythms, associated with increased metabolic impairments and incidence of cancer [6, 174–177]. Since individual mammalian tissues cannot generate self-sustained metabolic rhythms, circadian metabolite oscillation is expected to affect the rhythmic expression of metabolic and clock genes. Metabolic signaling to the circadian pacemaker exerts an effect on these processes. The nutrients reset circadian and peripheral clocks. The peripheral clocks indirectly control the Warburg switch by regulating the expression of tumor suppressors and oncoproteins. Thus, the central nervous system and peripheral organs contribute to body homeostasis by regulating various metabolic and physiological responses [7, 8, 178, 179]. Previously, the focus has been on what foodstuffs we eat, but now there is a shift from what we eat to when we eat, i.e., meals' frequency and circadian timing. Shifting food availability through restricted feeding of animals entrained to a standard light-dark schedule resets clock gene expression in the peripheral tissues [180]. Further, jet lag causes extensive changes in the expression of molecular clock genes and levels of metabolites.

Due to the induction of metabolic changes in rats, excessive exposure to constant light can lead to larger tumors than exposure to a standard light: dark cycle [181]. For mice, chronic jet lag leads to non-alcoholic fatty liver disease through metabolic disruptions in the liver [104]. In rodents and humans, the phases of liver lipogenesis and leptin concentrations in plasma are altered, reset with the timing of meals [182, 183]. This alteration in the

nutritional and hormonal signals due to change in feeding times synchronizes peripheral clocks to the underlying metabolic rhythms. Thus, peripheral and central clocks are profoundly affected by meal timing and nutrients. Mice fed with a high-fat diet at the incorrect circadian time exhibit altered clock gene expression as well as behavioral perturbations [184] and accelerated weight gain compared with animals fed at their appropriate circadian time [185], suggesting that signals from metabolic pathways to the circadian pacemaker are transduced via dietary fats, which engage nutrient-responsive machinery. The dietary nutrients are linked to the clock pathway by nuclear hormone receptors and their cofactors. Exposure to a high-fat diet influences the metabolome and circadian transcriptome due to perturbation in Bmal1 and recruitment of PPAR (peroxisome proliferator-activated receptor) γ. For mice, deletion of PPARγ co-activator 1α (PPARGC1α) causes defects in body temperature regulation, locomotor activity, and metabolic rate because PPARGC1α has a circadian expression pattern in metabolic tissues [186]. Moreover, under nutrient-deprived conditions, the circadian rhythm is altered through phosphorylation of Per and Cry1 by a nutrient sensor, AMPK [171, 187]. Hepatocyte nuclear factor 4 α (HNF4α) is highly expressed in human HCCs. Increased expression of BMAL1 in HNF4α-positive HCCs inhibits tumor growth [188]. These results indicate that metabolic oscillators provide a mechanism of circadian timekeeping in addition to the already described transcription feedback loop, which serves as a conserved model of the circadian oscillator.

In general, cancer cells are distinct from normal cells and have specific metabolic characteristics. Therefore, perturbations in molecular clock machinery would change the metabolism homeostasis and energy balance in peripheral organs, favoring tumor progression and initiation. Cancer-associated metabolic abnormalities are characterized by higher NADPH levels, lower TCA cycle activity, and more remarkable fatty acid synthesis [189, 190]. Tumors typically have elevated levels of glycolytic metabolism, driven by various oncogenes, tumor suppressors, and transcriptional regulatory factors. Other regulators of metabolism, including the mTOR and P13K/AKT pathways, c-Myc, Ras, and nuclear hormone receptors, are also associated with circadian rhythms. Activation of the P13K/Pdk1/AKT pathway promotes the glycolytic program in cancer cells and affects the pace of the circadian clock [191]. Under low oxygen conditions, hypoxia-inducible factor-1(HIF1α and HIF1β) is involved in the cellular response to regulate gene expression, and HIFs bind to the hypoxia response element (HRE). Through transcriptional and post-translational mechanisms, the circadian clock enforces a circadian rhythm on HIF-1α for the rhythmic gene expression of hypoxia-dependent genes [192, 193]. In cancer cells, HIF-1α is also activated by low oxygen levels, which contributes to elevated glycolysis by regulating the circadian clock genes *Rora, Cry,* and *Per2* [194, 195]. Oxygen levels control cellular respiration in a circadian manner, but how disruption of this metabolic rhythm drives tumor progression is unknown. There is a potential role of mTOR complexes, TORC1 and TORC2, in controlling the circadian machinery. mTORC1 is affected by cellular acidification, which deactivates mTORC1-dependent control of translation, resulting in suppression of clock regulators such as Per2, Bmal, and CLOCK [8]. Linked to mTOR activity, the circadian metabolic clock is rhythmic and follows food intake [196]. The RAS/MAPK pathway is active in various tumor types, and its activity modulates circadian rhythms through

impairment of Bmal1/CLOCK activity. PI3 kinase (PI3K), an essential component of the RAS signaling pathway, is involved in the glucose metabolism of cancer cells [197, 198]. These results warrant further investigations to examine the cellular energy levels, amino acids, and growth factors sensed by the P13 kinase, mTOR, and RAS/MAPK pathways. This information will be helpful for therapeutic targeting for cancer.

MYC-MAX, a heterodimer of essential helix-loop-helix transcription factors, binds to the canonical E-box to drive rhythmic transcription of genes [199, 200]. In cancer cells, c-MYC supports cell proliferation and growth by regulating glycolytic, lipogenic, and mitochondrial genes to balance the regular loss of glucose as a mitochondrial substrate. c-MYC disrupts circadian clock function through E-box-dependent and -independent mechanisms [201]. Elevated expression of MYC is coupled with the expression of negative regulators of the clock, such as PERI, PER2, CRY1, and REV-ERBα, which suppress Bmal1 expression by binding to E-box sequences [174, 202]. The complex of c-MYC and MIZ1 inhibits Bmal1 expression, providing evidence for directly inhibiting the Bmal1 promoter (E-box independent) by forming transcriptionally repressive MYC-MIZ1 complexes [201]. By repressing the circadian clock, MYC/MIZ regulates cell proliferation and glucose and glutamine utilization [174, 201, 202]. In addition, in various cancers, the MondoA/MLX pathway is implicated in nutrient sensing, lipogenesis regulation, and glutaminolysis [203] (Fig. 5). There is a limited understanding of the relationship between the circadian clock and the nutrient-sensing pathway of MondoA. MYCN, a member of the MYC family, could alter the clock by activating NR1D1. In neuroblastomas, elevated expression of NR1D1 is associated with a poorer prognosis than that for neuroblastomas with lower expression [174, 202] (Fig. 5). However, the MYC superfamily may interfere with the circadian clock through various mechanisms to regulate gene expression programs that control cell proliferation and cellular metabolism. Since we lack a molecular understanding of clock proteins in the regulation of metabolism in multiple cancers, future studies should assess circadian disruption and its influence on cancer metabolism.

4.1 Role of Sirtuins in Metabolic Rhythms and Cancer Risk

Sirtuins, nicotinamide adenine dinucleotide (NAD^+)-dependent histone deacetylases (HDACs), are implicated in numerous physiological functions, including metabolic control and cancer. There are seven mammalian sirtuins, SIRT1-SIRT7. Among the seven, three (SIRT1, SIRT3, and SIRT6) are functionally associated with control of the circadian clock and regulate cyclic outputs in response to metabolic cues [204–206]. SIRT1 localizes between the cytoplasm and the nucleus, whereas SIRT6 is exclusively localized in the nucleus and SIRT3 in the mitochondria [207]. These three sirtuins, through different mechanisms, coordinate the clock machinery. CLOCK-mediated chromatin remodeling and metabolic output are regulated by SIRT1 [208]. SIRT1, an energy and nutrition sensor activated by various stimuli such as low ATP, low nutrition, and exercise, converts cellular metabolites and nutrient signals to the circadian clock [209]. The nutrient-dependent activation of SIRT1 regulates Bmal1 expression and controls the expression of peptides and cofactors [170]. SIRT1 is implicated in energy metabolism by targeting PGC-1α in the SCN [210] (Fig. 6). Further, SIRT1 may be essential for the process of carcinogenesis, as it targets several acetylated proteins, including those for Wnt signaling, MYC, p53, and

FQF. At present, there are contradictory ideas relating to the role of SIRT1 either as a tumor promoter or suppressor [211–214]. When SIRT1 acts as a tumor promoter, it reduces p53-mediated apoptosis and negatively regulates p53-induced cellular senescence [213], leading to uncontrolled cell division and the development of tumors. In addition, SIRT1-mediated deacetylation of p53 and forkhead box 03 alpha (Foxo3a) induces cell survival rather than apoptosis, which is favorable for tumor cells, leading to enhancing tumor growth [215]. SIRT1 regulates cell fate and stress response in mammalian cells and promotes cell survival by inhibiting apoptosis [101]. SIRT1 may also contribute to the nutrition of cancer cells, leading to enhanced growth and cellular survival [215]. Furthermore, SIRT1 has oncogenic activity, and the SIRT1 protein is highly expressed in breast cancer tissues. [216]. Further, crosstalk between SIRT1 and MYC oncogenic signaling regulates drug resistance of the FLT3 receptor in acute myeloid leukemia (AML) [217]. On the other hand, transgenic SIRT1 mice show a lower level of DNA damage and lower expression of p16 (Ink4a), an inhibitor of CDK4, suggesting that SIRT1 acts as a tumor suppressor through chromatin regulation and DNA repair. Further, SIRT1-transgenic mice have a lower chance of developing sarcomas and spontaneous carcinomas than wild-type mice. Thus, SIRT1 is involved in tumor suppression in metabolic syndrome-associated cancers [218]. Furthermore, SIRT1 deacetylates β-catenin, which leads, for APC min/+ mice, to reduce colon cancer development [219]. Similar to SIRT1, SIRT6 forms a complex with CLOCK: Bmal1 and regulates gene expression in a circadian manner, but its target genes are different. Chromatin recruitment of CLOCK/Bmal1 and SREBP1 controlled by SIRT6 regulates lipid and carbohydrate metabolic pathway genes [220]. Although SIRT3 regulates fatty acid oxidation and glucose oxidation rates in an NAD^+-dependent manner (Fig. 6), it acts as a regulator of aerobic glycolysis for energy production (Fig. 6) [221]. Low expression of SIRT3 correlates with the upregulation of HIF-1α target genes, and overexpression of SIRT3 suppresses glycolysis and proliferation in breast cancer cells [222, 223]. This indicates that genomic partitioning of these sirtuins (SIRT1, SIRT6, and SIRT3) contributes to differential control of circadian metabolism (Fig. 6). Alterations in the circadian clock by sirtuins generate robust metabolic yields in various organs and likely drive tumor progression. However, understanding the mechanisms by which sirtuins regulate tumor progression is necessary for developing suitable sirtuin-based therapeutic approaches for cancer.

5. Cell Cycle: Clock Genes and Cancer

A prominent feature of cancer cells is uncontrolled cell proliferation, which can be connected to the machinery of the circadian clock [224]. The cell cycle comprises a sequence of events leading to DNA duplication and the division of cells. Of the four phases, two are considered critical: the S phase, in which the cell duplicates its DNA, and the M (mitosis) phase, in which the cell divides. These two stages are preceded by growth phases G1 and G2. The cellular interphase is comprised of G1 and S, followed by G2 [225]. G0 represents the quiescent state wherein cells are in the non-dividing (somatic) phase. The cells may enter in G1 phase after exposure to environmental stimuli, such as growth factors [226] (Fig. 7). The cell cycle phases are regulated by the circadian clock [227–229]. However, the bond between the cell cycle and circadian rhythms is not evident. The expressions of β-catenin, c-Myc, and Mdm2 (oncogenes); CCND1, CCNB,

and CCN1(cyclins); and Cdk4, Wnt3, and Tcf4 (cell-cycle regulators) are controlled by the circadian clock [104, 230] (Fig.7). Cell cycle progression depends on subsequent and transient activation of CDKs (cyclin-dependent kinases) forming complexes with CCNs (cyclins) such as CCND/CDK4–6 (G1), CCNE/CDK2 (G1/S transition), CCNA/ CDK2 (S), CCNA/CDK1 (S/G2 transition), and CCNB/CDK1 (M) [231, 232]. The CCN/CDK activity is inhibited across the cycle either by CDK inhibitors (CKI-P16, P27, and P21) or by phosphorylation by a kinase. Phosphatases such as CDC25A–B–C activate CCN/CDK [233, 234]. In response to DNA damage, these activators or inhibitors are involved in DNA repair and delay cell cycle progression by regulating cell cycle proteins and directly interacting with clock proteins or checkpoint proteins. The clock-controlled genes *NONO*, *p20*, and *p21* are involved in the G1-S transition. NONO regulates the expression of the CDK inhibitor *p16* at the G_1–S transition by regulating the PER protein. Another clock gene, Per1, is involved in checkpoint 2 (CHK2) and the ataxia-telangiectasia–mutated (ATM) signaling pathways. The G_1–S transition is inhibited by the circadian genes Per1 and Timeless (*TIM*) through interaction with ATM and CHK2, causing cell-cycle arrest [56]. Circadian clock mechanisms affect proliferating cells in the cell cycle by controlling the expression of *Weel,* which regulates Cdc2, transitioning from the G2 to the M-phase of the cell cycle [235]. In mammals, CLOCK/Bmal1 or Bmal1/NPAS2 regulates the anti-mitotic kinase Wee1 [105, 235, 236]. Per1, requiring p53, stabilizes c-Myc and alters transcription of Cdc2, Ccnb1, and Wee1. In tumor cells, deletion of Per1 affects the regulatory component of the cell cycle [56, 97]. Deregulation of c-Myc, a regulator of cell-cycle progression, is common in lymphoproliferative cancers [237]. In Per2 mutant mice, c-Myc transcription is elevated, and it downregulates the expression of CLOCK and BMAL1. c-Myc, phosphorylated by Cry2, recruits FBXL3-E3 ligase and promotes its degradation and ubiquitination; in the absence of Cry2, un-ubiquitinated cMyc enhances the incidence of lymphoma [238]. The pivotal tumor suppressor p53 controls multiple cell cycle checkpoints and regulates Per2 expression by blocking CLOCK: Bmal1 [239]. In Per2-mutated mice, c-Myc is upregulated, and p53 is downregulated, which leads to a general dysregulation of the cell cycle [236]. Overall loss of Per2 can lead to alterations in p53 function, thereby accelerating tumorigenesis and suggesting that similar clock mechanisms inhibit tumorigenesis or increase tumor progression depending on the clock genes involved. Hence, in cancer cells, it is essential to determine alterations of CLOCK: BmalL1-dependent genes in response to the activation of oncogenic Myc or failure of p53 expression. Additional studies are required to comprehend the functions of the cell cycle in various cancers mediated by circadian disruption.

6. Chronotherapy for Cancer

Chronotherapy for cancer involves optimal timing of drug delivery based on individual circadian times, which can improve treatment tolerability and efficacy of anti-cancer medications [240]. Since a chronomodulated chemotherapy approach has treated various cancers, some researchers believe that, in the coming years, chronotherapy will be employed as an advantageous therapeutic option for cancer and other diseases [241–247]. Although normal cells usually display well-synchronized circadian variations within a tissue, tumor cells often have disrupted circadian rhythms, becoming a hallmark of cancer. This escape from circadian control allows for increased cellular proliferation [248] and may be linked

with lesser sensitivity to anti-cancer drugs [249]. Although cancer chronotherapy relies on strong circadian rhythms in healthy tissues, efforts must be made to minimize clock disruptions. The application of chronotherapy to treat gastrointestinal and gynecological cancers showed an excellent response [250]. Recently, Li et al. demonstrated that the REV-ERBα and Bmal1 regulatory transcription loop could enhance the acceptability of chemotherapy. Circadian timing is especially relevant for anti-cancer drugs, often utilized at maximally tolerated doses and responsible for severe toxicities [251]. Mormont and Levi [252] showed that cancer patients exhibit altered circadian rhythms based on the tumor stage and that the same dose of the chemotherapeutic drug becomes fatally toxic only when administered at certain times.

In contrast, at other times, a 10-fold increase in dose was tolerated. Adler et al. found, however, that circadian timing may not always allow the safe application of high doses [253]. Hence, a current clinical challenge lies in reducing their life-threatening and dose-limiting side effects. In addition to reducing the toxicity, the side effects of increasing the dose intensity could also be decreased by chronotherapy. After patients with colorectal carcinomas received chronomodulated 5-fluorouracil, leucovorin daily for 14 days at 04:00 hours, and oxaliplatin at 16:00 hours for four days every 14 days, there was an improvement in cancer treatment, as evident by less toxicity and increased median survival of 50% [243]. The lower toxicities arising from treatment chronomodulation may be explained by different molecular statuses of healthy cells over the 24-h span, protecting them from the drug effect at particular times of the day. A Phase III clinical trial in Europe with 278 patients showed, relative to the conventional treatment group, no beneficial effect of chronotherapy after dosing with leucovorin, fluorouracil, and oxaliplatin. Close to traditional administration, there was a beneficial trend for chronotherapy for men, decreasing their risk of death by 25% but increasing mortality by 38% for women [254, 255]. These studies suggest the need for individualization of drug combinations and the timing of chemotherapy to improve treatment outcomes, considering factors such as patient gender, chronotype, and genetic background. Indeed, clinical trials show that proper chemotherapy timing lowers the toxicities of anti-cancer drugs. However, chronotherapy is not consistently beneficial for treating cancer. Therefore, mechanism-based studies are necessary to understand the potential of a chronotherapeutic approach for cancer treatment.

7. Conclusions and Future Directions

In this review, we have discussed recent reports and developments that support the idea that cell metabolism, the cell cycle, and chromatin remodeling regulate the circadian clock. Disruption of these regulatory pathways can affect tumor growth. Despite efforts for understanding the molecular mechanisms of the role of the circadian clock in cancer progression, challenges remain. These reports suggest that inherited genetic mutations cause only 8-10% of all cancers; however, an unhealthy lifestyle is a significant risk factor. Disruption of the circadian cycle by environmental factors, including nighttime work, jetlag, and nighttime light exposure, increases cancer risk. Therefore, more studies on light exposure and lifestyle interventions combining food, physical activity, nutrition, and sleep are needed to reduce cancer incidence. In addition, investigations are required to examine the relationship between circadian rhythm disruption and other confounding

factors, including diet choices, smoking, alcohol consumption, and exposure to radiation and other carcinogens. Properly regulated, rhythmic metabolism can contribute to cancer prevention.

In several cancers, circadian metabolic pathways are deregulated. SIRT1, which exists as a complex with CLOCK, is involved in circadian clock-mediated metabolism. Metabolic regulation of the circadian clock controls the acetyltransferase activity of CLOCK and the counterbalancing deacetylase activity of SIRT1. NAD^+ metabolism has a close relationship with SIRT1, glycolysis (metabolism), and the clock. However, no evidence has demonstrated that SIRT1 is the link between clock-mediated cancer and NAD^+ availability. Furthermore, research is needed to realize how, in cancers, circadian rhythms influence NAD^+ levels and their interaction with SIRT1. Nevertheless, SIRT1 should be considered a target for therapeutics. A more extensive understanding of the cellular and molecular connections between circadian rhythm and cancer cell metabolism offers new therapeutic strategies for cancer.

Circadian genes regulate diverse components of physiology. Circadian endocrine perturbations are linked with higher concentrations of sex hormones, facilitating the development of cancers. Disruption of the central clock affects the peripheral clocks in various tissues, which can be involved in tumorigenesis and cancer progression. Thus, there is a need to assess the impact of circadian factors on tumorigenesis in a tissue- and tumor type-specific and age-dependent manner. Disruption of the cell cycle linked to clock proteins may interfere with DNA repair, increasing cancer risk. However, the role of the circadian clock in cell cycle regulation remains relatively unexplored. Finally, the circadian function is based on a complex gene expression program, which involves dynamic changes in chromatin structure. The molecular mechanism of clock-controlled chromatin remodeling that responds to environmental stimuli has yet to be determined. Growing evidence indicates that chromatin-modifying enzymes and chromatin remodelers are deregulated in human cancers. However, further understanding is needed regarding how histone modifications and chromatin remodeling complexes are involved in malignancy. These changes provide promising targets for treating human cancers. However, previous studies or clinical trials of chronochemotherapy have not shown significantly increased efficacy for cancer patients relative to conventional therapies. Therefore, a better understanding of chronotherapy could benefit cancer patients.

In conclusion, the circadian clock is a unique system. In cancers, the clock genes regulate various signaling pathways, including cell cycle, chromatin remodeling, metabolism, cell proliferation, cell death, and DNA damage repair. These interlinking processes require mechanistic insights at the molecular and cellular levels that will help develop treatment strategies. Deregulation of circadian homeostasis stimulates cancer initiation and development and is associated with inadequate anticancer treatments; however, restoring normal circadian rhythmicity reduces tumor growth in tumor models.

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Abbreviations

ARID1A	AT-rich Interactive Domain 1A
AMPK	AMP-Activated Protein Kinase
BMAL1	Brain and Muscle ARNT-like Protein-1
CDK4/6	Cyclin-Dependent Kinase 4/6
Cdkn1a	Cyclin-Dependent Kinase Inhibitor 1A
CK1δ	Casein Kinase 1 Delta
CLOCK	Circadian Locomotor Output Cycles Kaput
CRY1/2	Cryptochrome
CK1ε	Casein Kinase 1 Epsilon
Dyrk1A	Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A
FBXL3	F-Box and Leucine-Rich Repeat Protein 3
GSK-3β	Glycogen Synthase Kinase -3 Beta
HDACs	Histone Deacetylases
HIF-1α	Hypoxia-inducible Factor 1-Alpha
HRE	Hypoxia Response Element
HIF	Hypoxia Inducible Factor
KrasG12D	Kras Mutation, and the Single-Site Mutation G12D
NPAS2	Neuronal PAS Domain Protein 2
NR1D1	Nuclear Receptor Subfamily 1, Group D, Member 1
PGC-1alpha	Peroxisome Proliferator-Activated Receptor-Gamma Coactivator-1alpha
PERK	Protein Kinase RNA-like Endoplasmic Reticulum Kinase
PER1/2/3	Period1, Period2, Period3
ROR	Retinoic Acid Receptor-Related Orphan Receptor

SCN	Suprachiasmatic Nucleus

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Highlights

- The endogenous circadian clock regulates various daily physiological and behavioral rhythms.
- Circadian rhythm disruption (e.g., irregular work shifts and frequent travel across time zones) increases cancer initiation and progression risk.
- Understanding the relationship between cancer and the circadian clock offers possibilities for new and effective cancer treatments and would help develop chronotherapeutic approaches to overcome cancer progression.

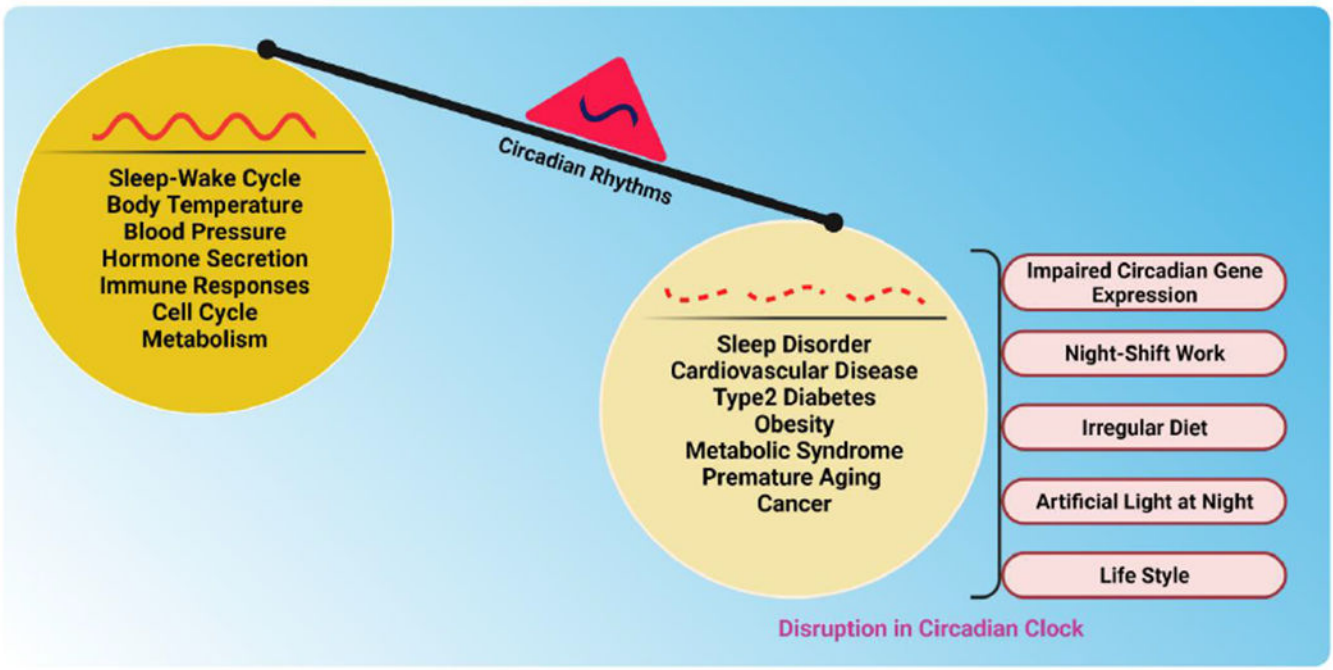

Figure 1. Circadian disruption and its impact on major biological processes.

The breaking of circadian tolerance or disbalance in the circadian clock results in the outbreak of several diseases. The prime factors that play in a disbalance circadian clock are artificial light during day or night, unbalanced diet, work-life balance, and unbalanced lifestyle. (Created with BioRender.com)

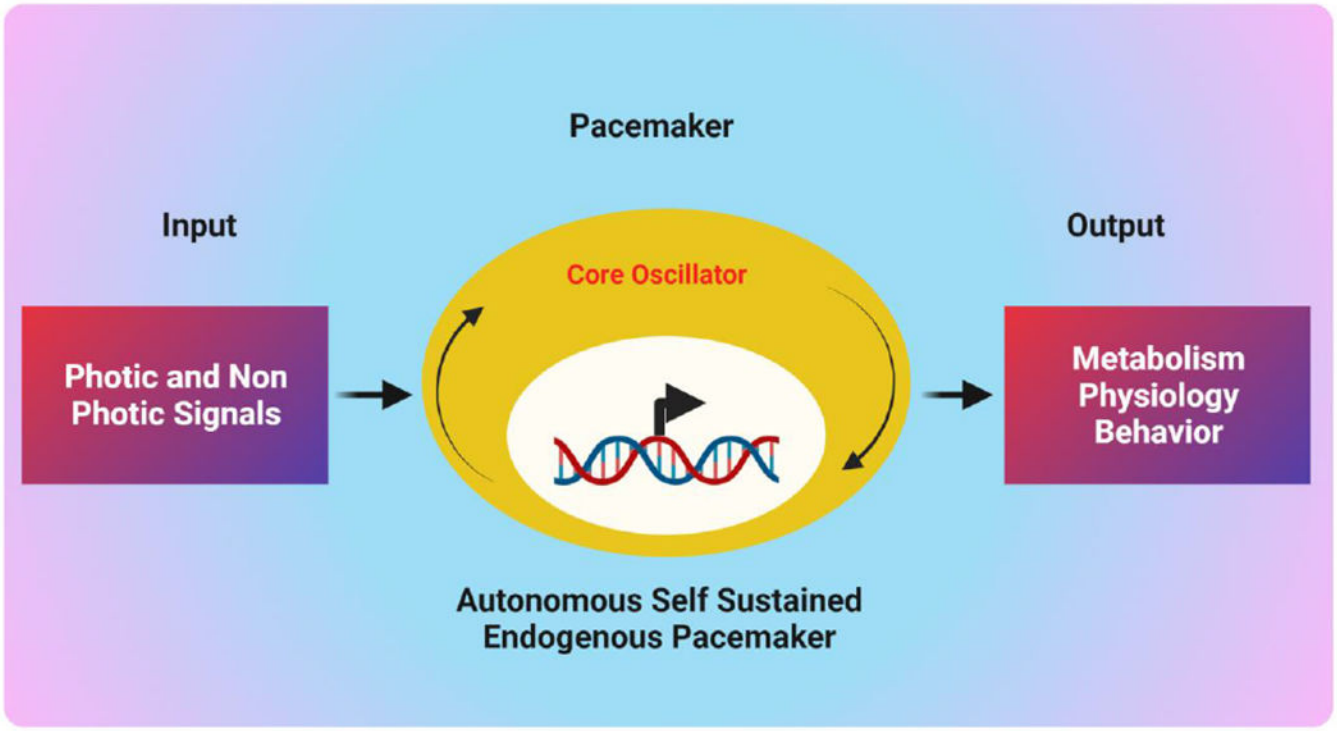

Figure 2. Biological timekeeping system.

The circadian timing system is central to the organization of bodily functions. The input pathway receives environmental cues (hormone secretion, light, and temperature) and attunes the oscillator. The central oscillator generates rhythmicity by processing environmental inputs. The output pathways that generate rhythmic processes include various physiological processes, metabolic pathways, and neuronal functions. (Created with BioRender.com)

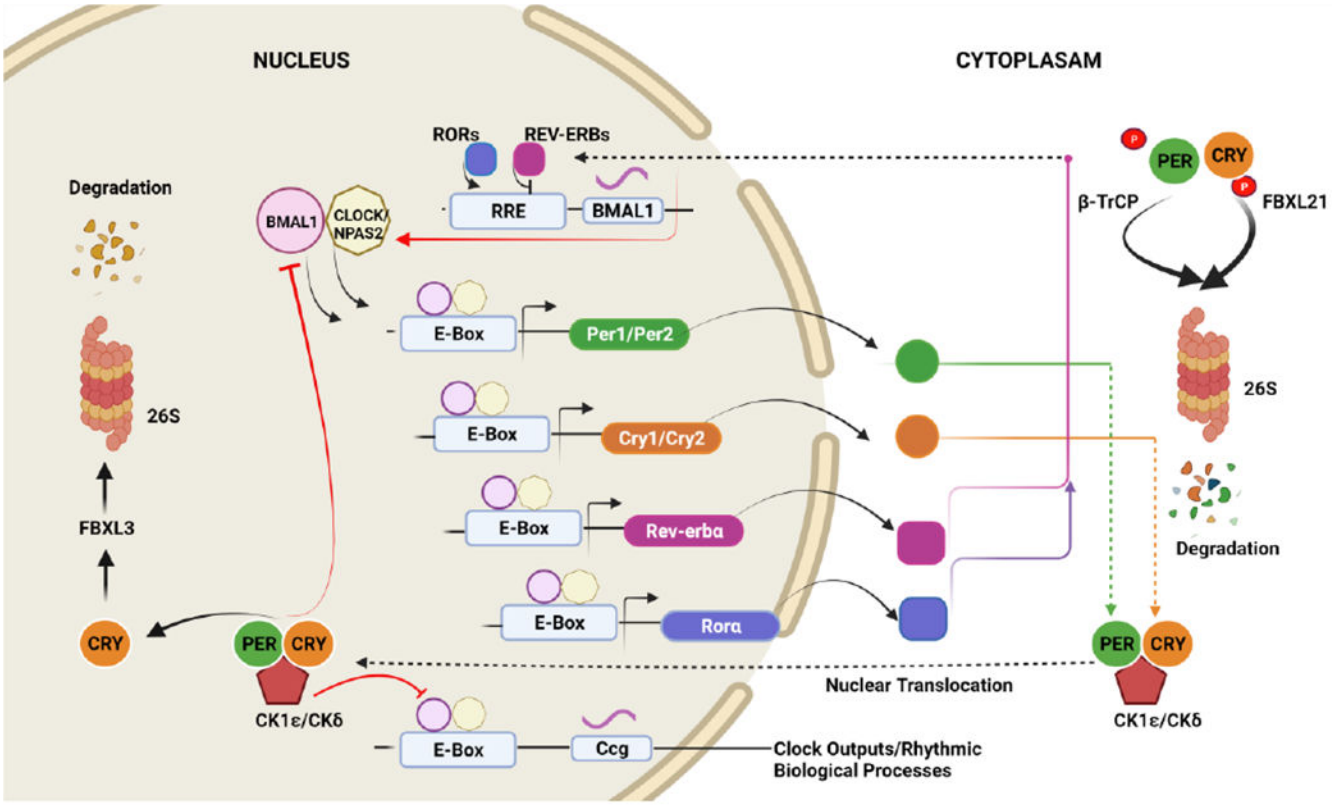

Figure 3. Molecular design of the mammalian daily clock.

The core molecular clock is comprised of positive regulators (Bmal1 and CLOCK) and negative regulators (cryptochrome (Cry 1/2) and period-Per1/2). The protein clock Bmal1 heterodimerizes with CLOCK/NPAS2 to initiate the transcription of target genes through E-boxes present in the promoter region of target genes, resulting in the expression of Per (green circles) and Cry (orange circles) genes. Per and Cry dimerizes and translocates to the nucleus after being phosphorylated by casein kinase 1 epsilon (CK1ε) and casein kinase 1 delta (CK1δ), respectively, and repress their transcription. The Per and Cry proteins inhibit the expression of Bmal1 and CLOCK, creating the core negative feedback loop. In turn, CLOCK-Bmal1 generates another negative feedback loop that upregulates the negative transcription of REV-ERB proteins and negatively regulates Bmal1 transcription, and RORα binding to RORE elements increases the expression of Bmal1. Additionally, Per and Cry genes are regulated by proteins such as AMP-activated protein kinase (AMPK) and CK1ε/δ by phosphorylation and subsequent degradation. This phosphorylation targets Per genesfor polyubiquitination by βTrCP and, similarly, Cry1/Cry2 are phosphorylated by the Fox- proteins, FBXL3 and FBXL21, directing them to ubiquitin-mediated proteasomal degradation. Collectively, these feedback loops trigger circadian oscillations and subsequently regulate the circadian expression of downstream clock-controlled genes (CCGs). (Created with BioRender.com)

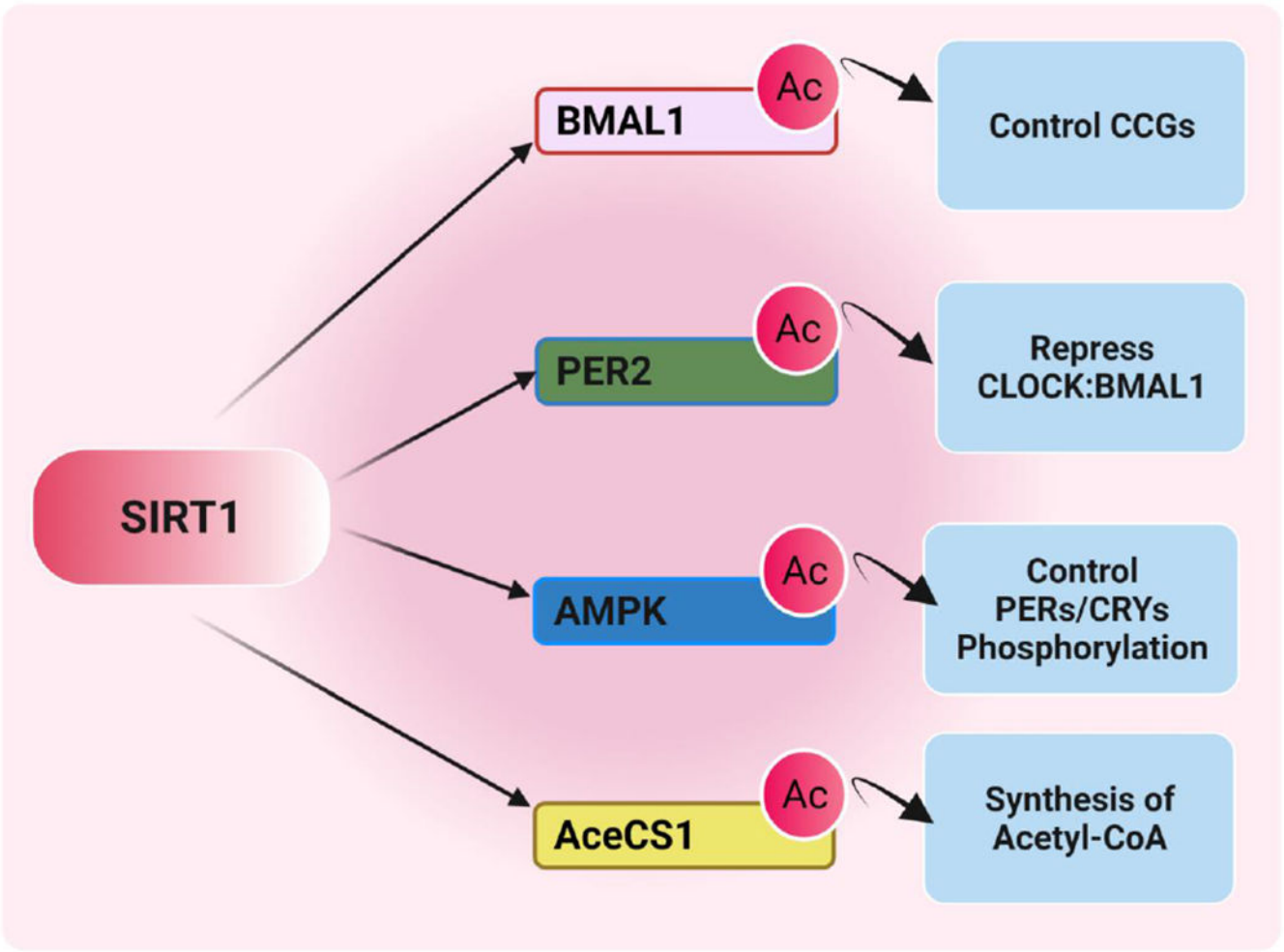

Figure 4. The role of SIRT1 in deacetylation of various non-histone targets.

SIRT1 is an NAD^+-dependent lysine deacetylase that deacetylates different histone and non-histone targets. SIRT1 deacetylates the core circadian transcription factor Bmal1 and core repressor Per2 to modulate CCG expression and a clock function. Similar to SIRT1, AMPK (metabolic sensor) is implicated in regulating NAD^+, which has been associated with clock function by targeting CRY and PER proteins. Another non-histone target is the enzyme acetyl-CoA synthetase 1 (AceCS1). The synthesis of acetyl-CoA is activated by deacetylation of SIRT1, providing acetyl groups globally for acetylation reactions. (Created with BioRender.com)

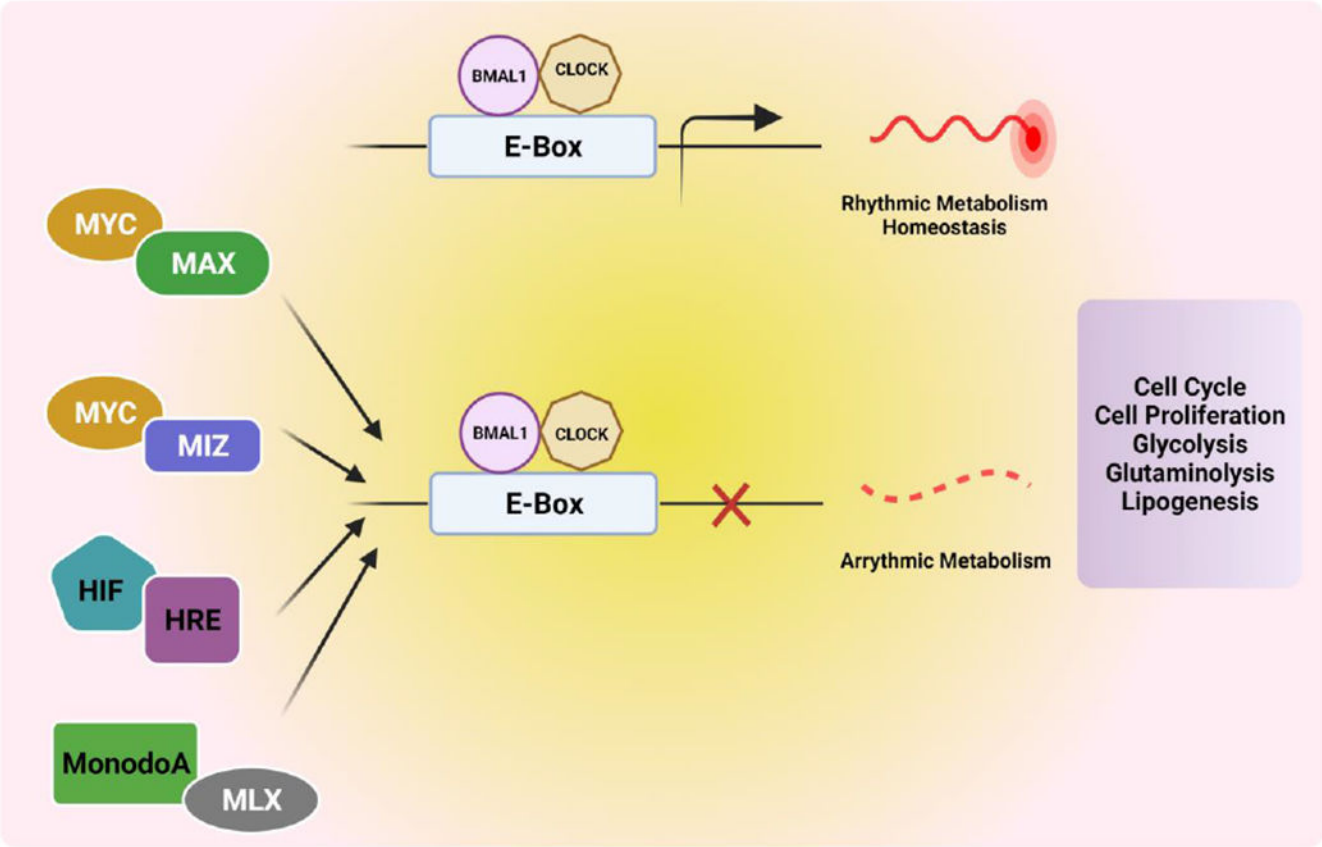

Figure 5. The circadian clock and its interplay with oncogenes and tumor suppressors.

An outline of the critical pathways of tumor suppressors and oncogenes and their role in dysregulation of the circadian clock. The MYC-MAX heterodimer is a dimer of primary helix-loop-helix transcription factors and binds to the E-box engaged by CLOCK-Bmal1. High expression of oncogenic MYC disrupts the circadian clock and its rhythmic metabolism. Dimerization of MYC with MAX inhibits oscillation of the clock and rhythmic metabolism by engagement of the promoter region of Bmal1. MonodoA/MLX is also an E-box binding transcription factor that regulates tumor metabolism by transcriptionally uniting with CLOCK: Bmal1 activity. HRE (hypoxia response element) is an E-box-like sequence bound by HIF under low oxygen conditions and regulated by the CLOCK-Bmal1 complex. It can lead to the expression of glycolysis-related genes. These oncogenes and tumor suppressors regulate pathways involved in the cell cycle, cell proliferation, glycolysis, glutaminolysis, and lipogenesis. (Created with BioRender.com)

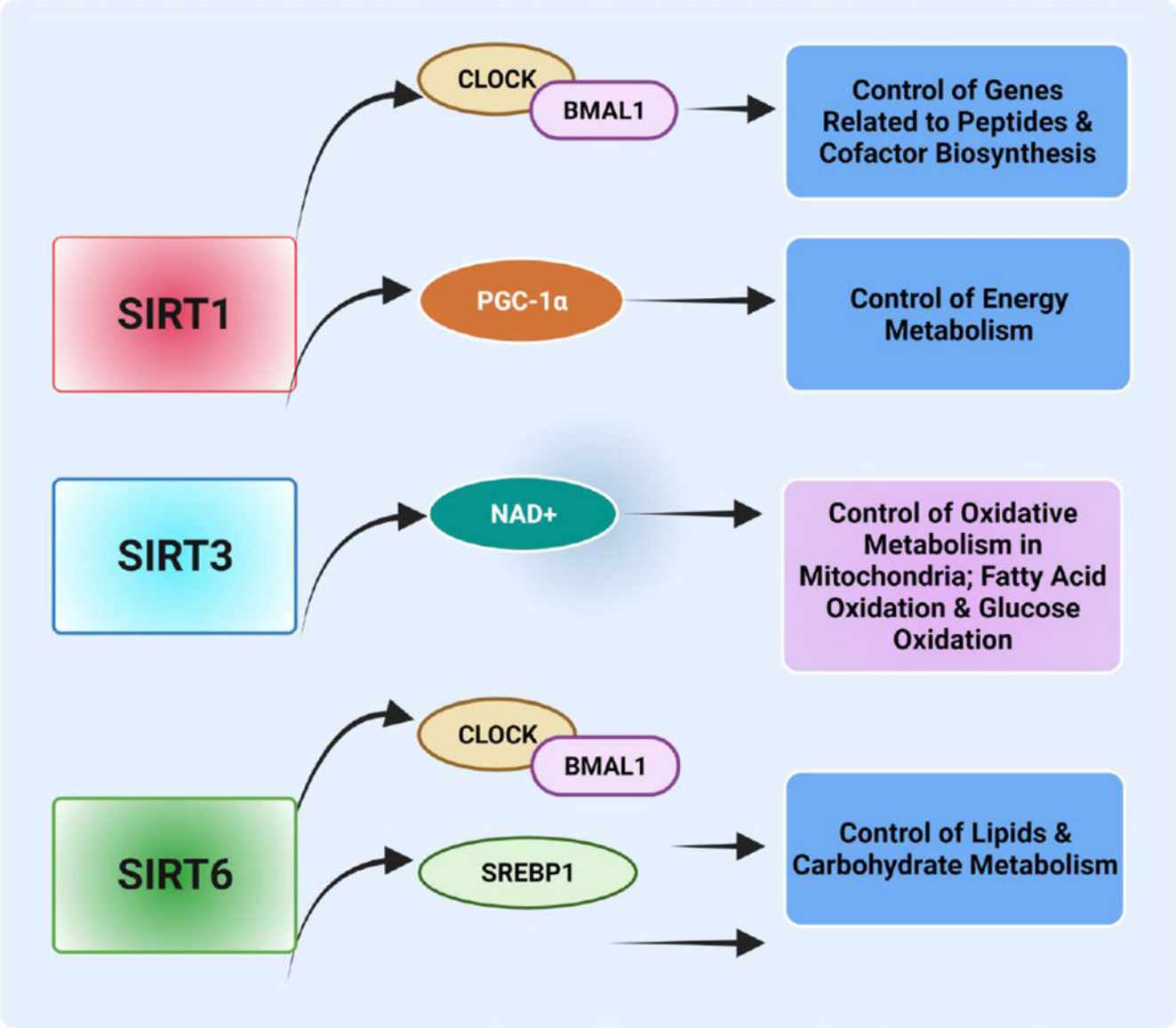

Figure 6. The role of sirtuins in controlling the circadian clock and energy metabolism.

Sirtuins are regulators of energy homeostasis. SIRT1 regulates genes related to the synthesis of peptides and cofactors by controlling CLOCK/Bmal1 circadian transcription factors. The nutrient-dependent activation of SIRT1 regulates energy metabolism by influencing Bmal1 expression through PGC-1α in the suprachiasmatic nucleus. Deacetylation of mitochondrial oxidative enzymes by SIRT3 controls mitochondrial oxidative metabolism. Regulation of chromatin recruitment of CLOCK/Bmal1 via SIRT6 through SREBP1 regulates lipid and carbohydrate metabolism genes. (Created with BioRender.com)

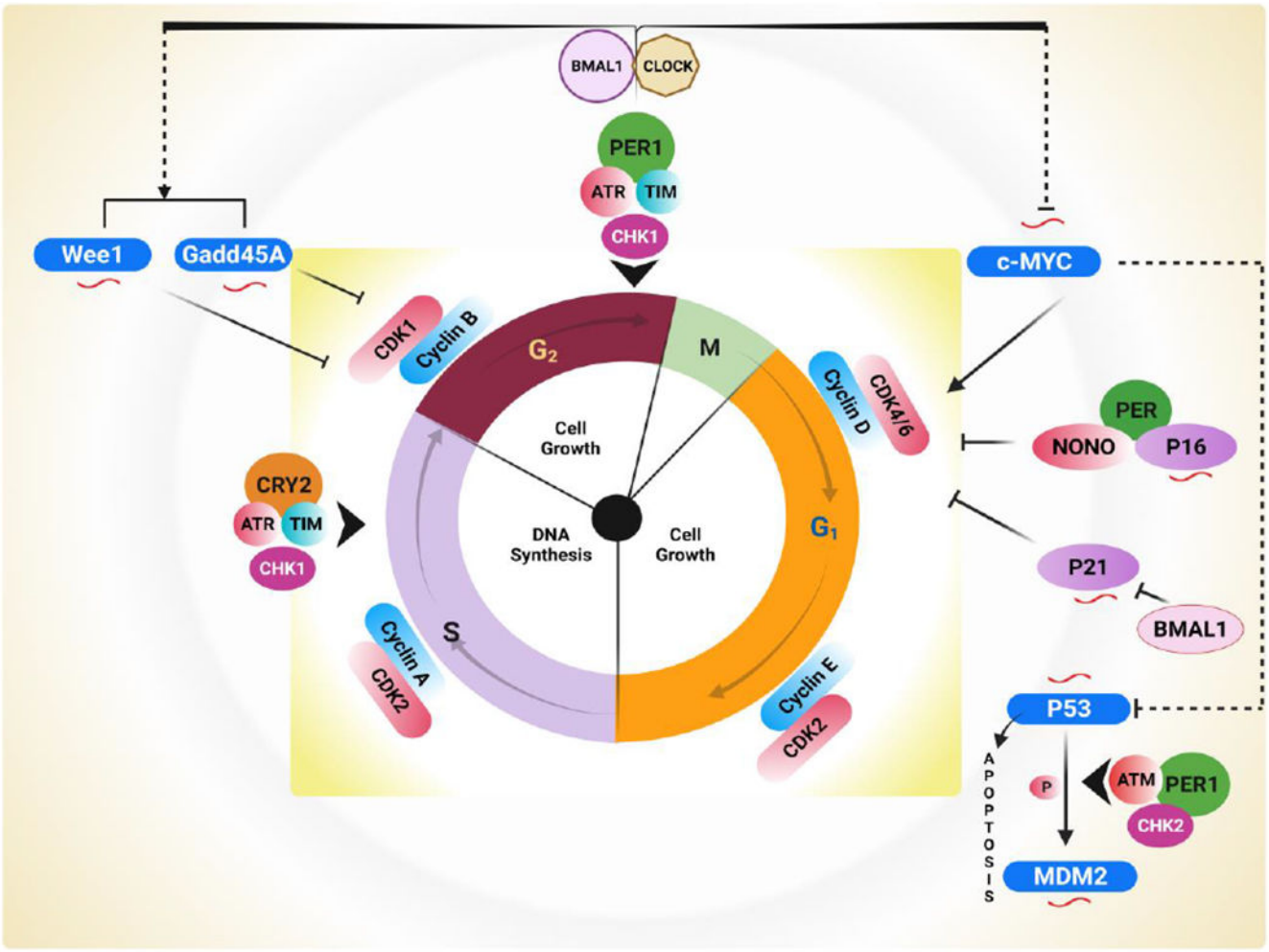

Figure 7. The cell cycle and its molecular interaction with the circadian clock:

The cell cycle, comprised of several stages regulated by CDK/Cyclin complexes, is involved in the control of the progression of cells. CLOCK transcriptionally governs the expression of Wee1 and Gadd45A proteins. Bmal1, through the CDK1/Cyclin B complex, is involved in the inhibition of the G2/M transition of the cell cycle. Further, activation of the c-Myc oncogene promotes the expression of Cyclin D and cell proliferation. Transcription of the tumor suppressor genes p21 and p16 is under circadian control through checkpoints G1 and G1/S. The circadian output effector NONO connects to p16 and promotes transcription with the association of Per. Another CDK inhibitor, p21, is negatively regulated by BMal1. In addition, the interaction between p53 and Per results in increased activation of p53 target genes, including p21 and mdm2, which are regulated by the ATM–Per1–CHK2 complex. In contrast, ATR–Chk1–CRY–TIM pathways regulate the early response to DNA damage by interacting with Cry and Per clock proteins during the S phase and G2/M checkpoints. NONO: Nuclear RNA II binding protein or GADD45A; p54nrb; Growth Arrest; and DNA Damage inducible 45; TIM: Timeless mammalian protein; CHK2: Checkpoint kinase 2; CHK1: Checkpoint kinase 1; ATR: Ataxia telangiectasia and rad3-related; ATM: Ataxia-

telangiectasia mutated. Circadian clock-regulated cell cycle genes are symbolized by (). (Created with BioRender.com)

Table 1.

Deregulated Clock Genes in Cancers

Type of Cancer	Deregulated Clock Genes	References
Breast Cancer	*Bmal1, Clock, Tim, Cry1, Per1, Cry2, Per2, Per3, Npas2*	[39, 40, 46, 48, 55–57]
Colorectal Cancer	*Per1, Per2, Per3, Clock, Npas2, Tim*	[58–64]
Colon Cancer	*Per2*	[9, 65]
Diffuse large B-cell Lymphoma	*Clock, Bmal1*	[66]
Endometrial Cancer	*Per1, Per2, Per3, Cry1*	[45, 67, 68]
Esophageal Cancer	*Dec1, Dec2, Per, Cry*	[69]
Glioma	*Cry1, Per1, Per2, Per3, Cry2,*	[70–72]
Gastric Cancer	*Cry1 Per2*	[73]
HNSCC (Head and Neck Squamous Cell Carcinoma)	*Cry1, Per1, CKIε, Per2, Per3, Bmal1, Cry2, Bmal1, Tim*	[74–77]
Hepatocellular Carcinoma	*Cry2, Per1, Per3, Per2, Tim*	[78, 79]
Leukemia (Acute Lymphocytic Leukemia; Chronic Lymphocytic Leukemia, & Chronic Myeloid Leukemia)	*Per3, Cry2, Clock, Per1, Cry1, CKIε, Per2, Bmal1*	[74, 80–83]
Lung Cancer	*Per1, Per2, Per3, Clock*	[60, 84–87]
Malignant Pleural Mesothelioma	*Per1, Per3, Npas2, Bmal1, Cry2, Rev-erbα, Rev-erbβ, Tim*	[88–90]
Non-Hodgkin's Lymphoma	*Cry2, Npas2, Bmal1*	[70, 91, 92]
Osteosarcoma	*Per2, CK1ε*	[88, 93]
Ovarian Cancer	*Clock, Bmal1, Cry2, Cry1, Per2, Per3, Per1, CK1ε.*	[94–96]
Pancreatic Cancer	*Per2, Bmal1, Cry1, Cry2, Per1, Per3, CK1ε, Clock, Dec1, Tim*	[56, 97–99]
Prostate Cancer	*Cry1, Bmal1, Cry2, Clock, Per2, Per1, Per3, Npas2, CK1ε,*	[100, 101]

Table 2.

Dysregulation of chromatin remodelers in various types of cancer.

Chromatin Remodeler	Types of Tumors	References
SWI/SNF	Breast cancer; Renal cancer; Stomach adenocarcinoma; Ovarian serous cystadenocarcinoma; Uterine corpus endometrioid carcinoma; Stomach adenocarcinoma; Cholangiocarcinoma; Melanoma	[110, 143–147]
ISWI	Uterine corpus endometrioid carcinoma; Melanoma; Lung cancer; Prostate adenocarcinoma; Stomach adenocarcinoma; Adenocarcinoma; Cholangiocarcinoma	[110, 148–153]
Mi-2/NuRD	Melanoma; Colorectal adenocarcinoma; Stomach adenocarcinoma; Prostate cancer; Endometrial cancer; Uterine serous carcinomas; Uterine corpus endometrioid carcinomas; Head and neck squamous cell carcinoma; Lung cancer; Bladder urothelial carcinoma; Pancreatic cancer.	[109, 110, 148, 151, 153–160]