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A broken circadian clock: The emerging neuro-immune link connecting depression to cancer

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ABSTRACT

Circadian clocks orchestrate daily rhythms in many organisms and are essential for optimal health. Circadian rhythm disrupting events, such as jet-lag, shift-work, night-light exposure and clock gene alterations, give rise to pathologic conditions that include cancer and clinical depression. This review systemically describes the fundamental mechanisms of circadian clocks and the interacting relationships among a broken circadian clock, cancer and depression. We propose that this broken clock is an emerging link that connects depression and cancer development. Importantly, broken circadian clocks, cancer and depression form a vicious feedback loop that threatens systemic fitness. Arresting this harmful loop by restoring normal circadian rhythms is a potential therapeutic strategy for treating both cancer and depression.

1. Introduction

Circadian clocks are intrinsic time-keeping mechanisms that enable organisms to anticipate cyclic environmental changes and to resonate with the ~24h periodic oscillation of the earth (Koronowski and Sassone-Corsi, 2021). The central clock in the suprachiasmatic nucleus (SCN) conveys ambient light signals to tissue resident peripheral clocks in order to synchronize internal timing to the external environment (Koronowski and Sassone-Corsi, 2021). Individual cells possess self-sustaining circadian clocks driven by transcription-translation feedback loops. This intricate clock machinery consists of several rhythmically expressed proteins that reciprocally regulate one another (Takahashi, 2017), generating rhythms for numerous clock-controlled genes that regulate multiple physiologic processes (Takahashi, 2017).

Circadian disruption leads to a collapse in systemic homeostasis and causes adverse health outcomes, including cancer, depression, the metabolic syndrome and cardiovascular disease (Ohdo et al., 2019). Of these, cancer has become one of the most threatening diseases to human longevity (Lin et al., 2019). Notably, a significant signature of a variety of cancers is circadian disruption, which in turn contributes to cancer development (Pariollaud and Lamia, 2020) by regulating physiologic events such the immune and endocrine system as well as metabolism (Shafi and Knudsen, 2019).

In cancer patients, depression is a common symptom that facilitates cancer development and impedes effective therapy (Fishbein et al., 2021). Circadian disruption is not only a prevalent feature of depressed patients but also a significant risk factor for depression (Lyall et al., 2018). These findings suggest that the circadian clock is a potential link between depression and cancer. Here we review the fundamental mechanisms of circadian clocks and elucidate the immune and neuro-endocrine pathways that link circadian disruption to both cancer and depression. These data reveal that circadian clocks are potential mechanisms that connect depression to cancer. More investigations on the role of circadian clocks in co-development of cancer and depression will provide new therapeutic strategies based on chronobiology.

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2. Regulation of the circadian clock

Circadian clocks evolved with the Earth's geometric light-dark cycle, developing free-running mechanisms for organisms to anticipate oscillating environmental changes (Pariollaud and Lamia, 2020). This physiological time machine synchronizes internal biological activities to external light signals through neuroendocrine and behavioral mechanisms (Bass and Takahashi, 2010). This process controls diurnal oscillations of vital life-sustaining processes, including immune, endocrine and metabolic activities (Albrecht, 2006). The harmonious operation of circadian clocks is critical for optimal health. In the following section, we provide an overview of the fundamental mechanisms of the circadian clock.

2.1. Molecular clock regulatory mechanisms

2.1.1. Transcription-translation feedback loops

The molecular clock is ubiquitously expressed in most mammalian cells. It is driven by several tightly coupled time-delayed transcription-translation feedback loops (Sancar and Van Gelder, 2021). The primary loop is driven by the transcription activator CLOCK-BMAL1 and its down-stream product PER-CRY that serves as a repressor (Koronowski and Sassone-Corsi, 2021). The secondary loop is controlled by activation and repression of BMAL1 by the retinoid related orphan receptor (ROR) and nuclear receptor subfamily 1 group D (REV-ERB), respectively (Partch et al., 2014). The activity and proteasome degradation of this repressive complex are strictly controlled by post-translational modifications that ensure proper initiation of the next 24 h cycle. Other feedback loops involve DBP, HLF, TEF, E4BP4, DEC1 and DEC2, all of which are transcriptional targets of the CLOCK-BMAL1 heterodimer (Mohawk et al., 2012). These interlocking feedback loops sustain the ~24 h oscillation of core circadian genes and downstream clock-controlled genes, generating 50-80% of the rhythms of protein-encoding genes in both humans and mice (Sancar and Van Gelder, 2021).

2.1.2. Post-translational modification regulates molecular clocks

In addition to transcriptional regulation, molecular clocks are controlled by post-translational modifications (PTM) (Gallego and Virshup, 2007). Circadian PTM regulates important processes such as nuclear entry, protein degradation and protein interactions, guaranteeing the clock to oscillate on a ~24 h period (Gallego and Virshup, 2007). Phosphorylation triggers nuclear translocation and degradation of clock proteins. CK1ε and GSK3 phosphorylate PER and CRY in the cytoplasm to facilitate their translocation into the nucleus (Iitaka et al., 2005). Ubiquitination also controls degradation of clock proteins. For example, F-Box and Leucine Rich Repeat Protein 21 (FBXL21) mediates ubiquitination of CRY to induce proteasome degradation in the cytoplasm. This also protects CRY1 from FBXL3-induced ubiquitination-degradation in the nucleus (Yoo et al., 2013). In addition, acetylation regulates protein interactions. CLOCK acetylates the BMAL1 protein to enhance recruitment of CRY1 to the CLOCK-BMAL1 complex, thus inhibiting transcriptional activity of the complex (Grimaldi et al., 2007).

2.1.3. Metabolic loop controls molecular clocks

Non-canonical metabolic control also plays a pivotal role in generating circadian rhythms. The CLOCK-BMAL1 heterodimer activates rhythmic transcription of nicotinamide phosphoribosyltransferase (NAMPT), which is a rate-limiting enzyme in NAD^+ biosynthesis. Further, the NAD^+ rhythmically regulates sirtuin 1 (SIRT1) activity to deacetylate BMAL1, thus forming a metabolic loop that regulates the circadian clock (Logan and Mcclung, 2019). Even in mammalian red blood cells, circadian rhythms exist in the form of cytoplasmic redox parameters, including peroxiredoxin oxidation–reduction, hemoglobin tetramer-dimer transitions and the NADH/NADP ratio (O'neill and Reddy, 2011). This system indicates a critical auxiliary role of metabolic redox regulation in maintaining circadian rhythms.

In conclusion, the entire circadian clock system is orchestrated in a sophisticated and harmonious manner. The transcription-translation feedback loops are the dominant oscillators that generate circadian rhythms that lead to downstream gene expression or repression. Multiple post-translational modifications of transcription-translation feedback loops serve as fine-turning mechanisms that properly adjust biological clocks. In addition, metabolic loops enable the clock to sense changes in metabolism and independently sustain physiologic rhythms as compensating oscillators. As such, multiple mechanisms cooperate to precisely regulate circadian clocks. (Fig. 1).

2.2. Hierarchical circadian clock system

2.2.1. Necessity of the hierarchical circadian clock system

Auto-regulatory biological clocks universally exist in all light-sensitive life forms, from cyanophyta to humans (Meyers and Malinverno, 2018). Prokaryotic clocks directly sense light signals to regulate cellular activities, whereas multicellular mammals require sophisticated clock systems to transmit environmental light signals to the 10^{12} to 10^{16} cells in the body (Koronowski and Sassone-Corsi, 2021). A hierarchical circadian regulatory system effectively transmits and amplifies external signals to endogenous clocks (Fig. 2). In mammals, exogenous light input is received by the central oscillator in the SCN through the retina and hypothalamic tract. This central oscillator relays time information to peripheral clocks (Schibler and Sassone-Corsi, 2002).

2.2.2. The central clock senses light induced neuronal signals

The SCN of the hypothalamus are central pacemakers generating circadian rhythms in mammals. Animal studies have proven that SCN ablation eliminates circadian patterns of sleep and feeding behaviors as well as plasma corticosterone level (Herzog, 2007). Thus, the central clock is an indispensable part of the circadian clock system. The SCN consist of ~20,000 neurons, each of which possesses an autonomous circadian oscillator. The neurons form a closely coupled intracellular network to ensure they oscillate in a consistent manner. The intrinsic rhythmic period of SCN neurons varies from 22 to 30 h at the single cell level. It is amazing that SCN circuit connectivity is preserved in organotypic slice cultures, as shown by these neurons coordinating to exhibit coherent and robust oscillations (Hastings et al., 2018). In detail, this intracellular coupling probably involves both the synaptic release of GABA and the paracrine secretion of neuropeptides (Hastings et al., 2018). Light signals received by the retina are transduced through neurotransmitter signals such as glutamate and pituitary adenylate cyclase-activating peptide, whereas behavior signals are relayed from brain centers by acetylcholine, neuropeptide Y and serotonin that are associated with sleep-wake regulation and arousal (Deboer et al., 2003). These neuronal signals are sensed by the SCN central clock to regulate widely distributed peripheral clocks.

2.2.3. The central clock regulates peripheral clocks

Peripheral clocks are distributed throughout the body, with clock genes rhythmically oscillating in multiple cells and tissues (Schibler and Sassone-Corsi, 2002). This hierarchical circadian clock system ensures that peripheral clocks controlled by the SCN central clock can accurately adapt to environmental time cues. When the SCN is eliminated as in the *mPer2^{luc}* knock-in mouse model, rhythmic *Per2* expression loses synchronization in a variety of tissues, including the cornea, liver, pituitary, kidney and lung (Yoo et al., 2004).

The SCN control peripheral oscillators through direct and indirect pathways. Directly, neuroendocrine signals synchronize peripheral clocks through sympathetic and parasympathetic pathways. Sympathetic innervation from the SCN to the adrenal gland contributes to rhythmic adrenocorticotropic hormone (ACTH) release (Kalsbeek et al., 2010). Moreover, autonomic nerves from the SCN relay light signals to a peripheral clock in the adrenal gland to control circadian secretion of

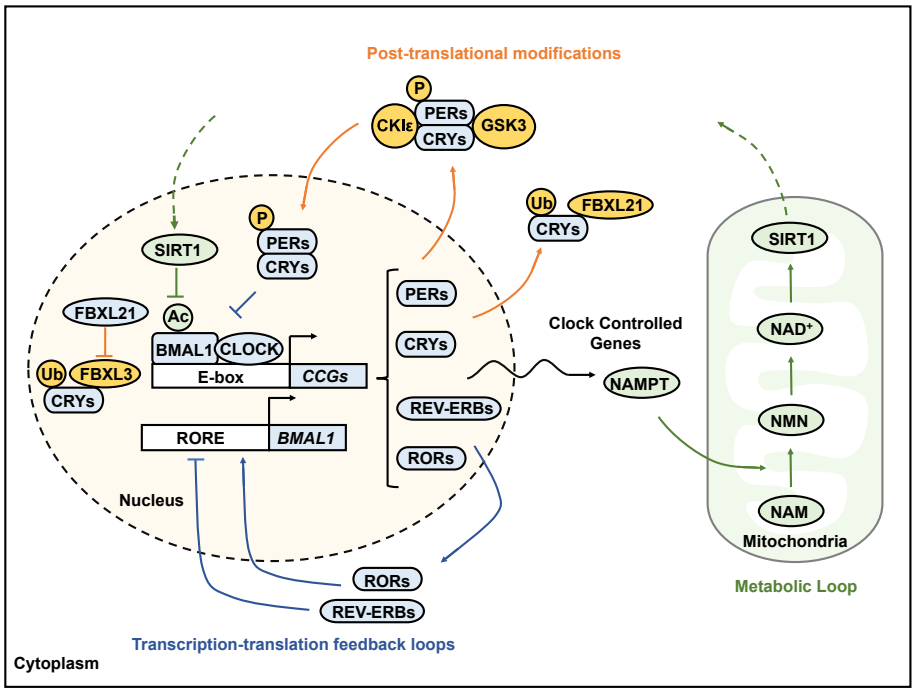

Fig. 1. The three key regulatory mechanisms of the self-autonomous molecular circadian clock: Transcription-translation feedback loops, post-translational modifications and the metabolic loop. Transcription-translation feedback loops drive the mammalian molecular clock. The primary loop is initiated by the CLOCK-BMAL1 heterodimer binding to E-box elements in gene promoters to activate transcription of CCGs such as PER and CRY (Koronowski and Sassone-Corsi, 2021). Post-translational phosphorylation mediated by CKIε and GSK3β promotes the repressive proteins PER and CRY in the cytoplasm to dimerize and translocate to the nucleus (Gallego and Virshup, 2007). In the nucleus, PER-CRY represses transcriptional activity of CLOCK-BMAL1, thus inhibiting its own expression. The secondary loop consists of RORs and REV-ERBs, both of which are transcriptionally regulated by CLOCK-BMAL1. By interacting with RORE in the *BMAL1* promoter, RORs and REV-ERBs activate and repress transcription of BMAL1, respectively (Koronowski and Sassone-Corsi, 2021). FBXL21 causes post-translational ubiquitination of CRY to promote its proteasome degradation in the cytoplasm, while FBXL21 inhibits CRY ubiquitination and degradation by FBXL3 in the nucleus (Hirano et al., 2013). Finally, a metabolic loop also regulates the circadian clock (Logan and Mcclung, 2019). CLOCK-BMAL1 transcriptionally activates expression of NAMPT to catabolize NAM to NMN, which then leads to formation of NAD^+. Further, NAD^+ activates SIRT1 activity to deacetylate BMAL1, thus inhibiting CLOCK-BMAL1 transcriptional functions (Logan and Mcclung, 2019).

Abbreviations: CLOCK, circadian locomotor output cycles protein kaput; BMAL1, brain and muscle ARNT-like 1; CCGs, clock controlled genes; PER, Period; CRY, Cryptochrome; CKIε, casein kinase; GSK3, glycogen synthase kinase-3; RORE, ROR element; RORs, retinoid related orphan receptors; REV-ERBs, nuclear receptor subfamily 1 group D; FBXL21/3, F-Box and Leucine Rich Repeat Protein 21/3; NAMPT, nicotinamide phosphoribosyltransferase; NAM, nicotinamide; NMN, nicotinamide mononucleotide; SIRT1, sirtuin 1.

glucocorticoids adjusting cellular metabolism (Ishida et al., 2005). In addition, glucocorticoids further react with glucocorticoid-response elements that exist in regulatory DNA regions of the core clock genes *Bmal1, Cry1, Per1* and *Per2* (Reddy et al., 2007). This leads to transcriptional activation of clock genes and clock-controlled genes in local tissues.

Indirectly, the central clock entrains peripheral circadian rhythms by regulating daily activity-rest cycles and feed-fasting cycles. The SCN projection to a variety of brain regions to control rhythmic behaviors such as feeding and sleep (Hastings et al., 2018). These physiologic behaviors further rewire local circadian rhythms, and local clocks in turn direct local programs of circadian gene expression. For example, time-restricted feeding in mice resets clock gene *Dbp* expression in liver faster than in the kidneys, heart and pancreas (Damiola et al., 2000). Insufficient sleep in humans significantly disrupts the circadian rhythm of 374 genes in blood cells, including those associated with the circadian clock (*PER1, PER2, PER3, CRY2, CLOCK, NR1D1, NR1D2, RORA*), sleep homeostasis (*IL6, STAT3, KCNV2, CAMK2D*), oxidative stress (*PRDX2, PRDX5*) and metabolism (*SLC2A3, SLC2A5, GHRL, ABCA1*) (Moller-Levet et al., 2013).

In summary, the circadian clock system is sophisticatedly organized in a hierarchical manner. The central clock robustly senses environmental time cues and accurately relays this information to peripheral clocks through direct neuroendocrine pathways and indirect behavioral pathways. As a result, peripheral clocks resonate efficiently with the external environment to ensure optimal fitness.

2.3. Internal and external cues ticking the clock

2.3.1. Importance of internal and external regulation of the circadian clock

The circadian clock is a highly stable but adjustable system. On one hand, one of the most significant features of the circadian clock is self-sustaining, which means that circadian rhythms persist even without external signals (Koronowski and Sassone-Corsi, 2021). Autonomic rhythms enable organisms to predict environmental changes via internal clock mechanisms. On the other hand, intrinsic circadian clocks need to be adjusted by external signals so that internal physiologic processes precisely synchronize with environmental changes. Thus, both endogenous and exogenous factors are indispensable for clockwork regulation (Fig. 2).

2.3.2. Internal signals adjust the circadian clock

The circadian clock is regulated by internal biochemical signals to maintain metabolic and endocrine homeostasis. Some clock genes intrinsically possess promoter elements that integrate intracellular signals (Koronowski and Sassone-Corsi, 2021) emanating from temperature, cyclic adenosine monophosphate (cAMP), NAD^+, heme and glucocorticoids. For instance, daily temperature variation mediates rhythmic binding of Hsf1 to heat shock elements on the *Per2* promoter of mice (Reinke et al., 2008). The SCN relays light input via the retinohypothalamic tract by stimulating cAMP signaling with neurotransmitters. This leads to cAMP response elements on the *PER* promoter to be induced in response to light (Travnickova-Bendova et al., 2002). NAD^+-dependent SIRT1 is recruited to the CLOCK protein. The CLOCK chromatin complex on circadian promoters rhythmically acetylates BMAL1 and H3 Lys 9/Lys (Nakahata et al., 2008). Heme binds to the heme-binding motif on *NPAS2* to sense nitric oxide, which inhibits DNA binding ability of NPAS2-BAML1 heterodimer (Kaasik and Lee, 2004). Glucocorticoids directly bind to the *Per1* promoter to activate its transcription (Conway-Campbell et al., 2010). Overall, internal biochemical signals allow widely distributed circadian clocks to be constantly synchronized to specific physiological conditions.

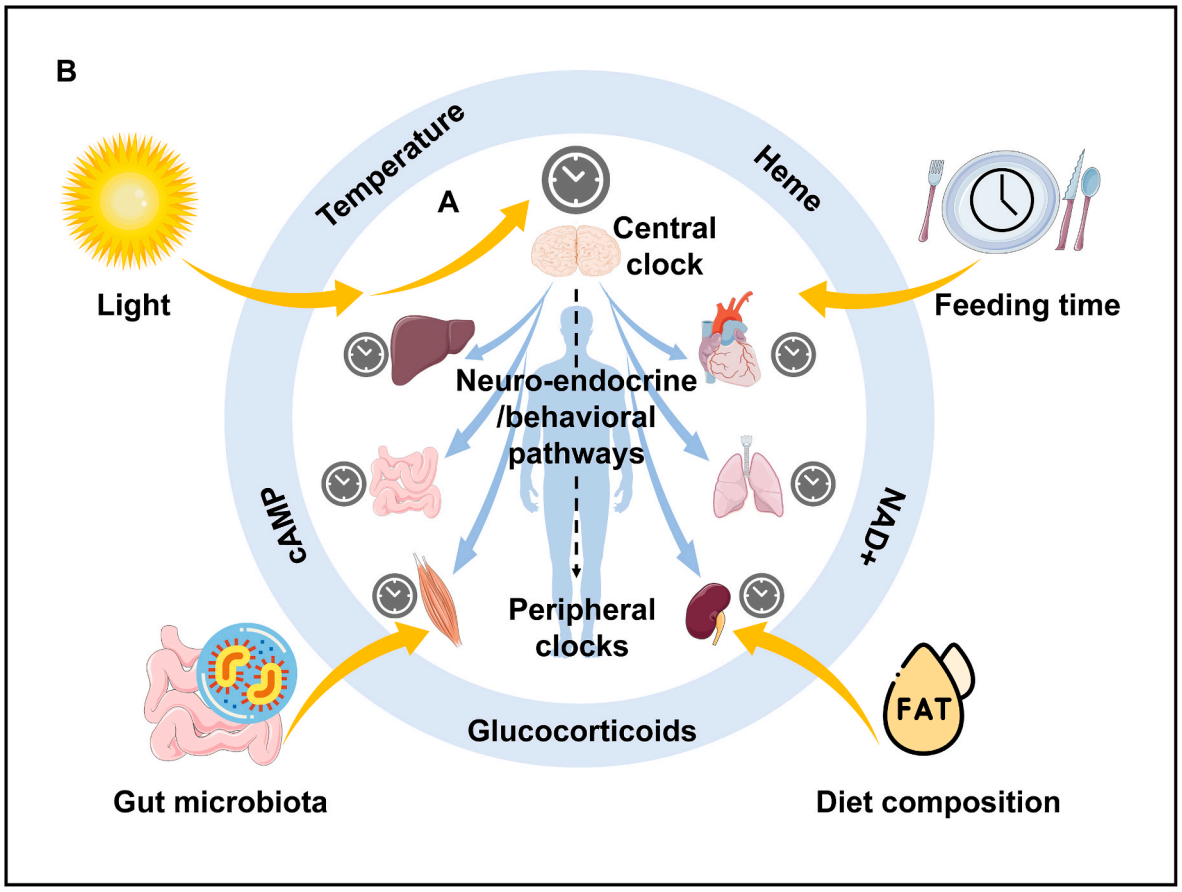

Fig. 2. Regulation of the circadian clock system. A) Hierarchical regulation system of circadian clocks. The central clock (SCN) receives light input via neuronal signaling and relays time information to peripheral clocks distributed from non-SCN brain regions to peripheral tissues through direct and indirect pathways. Directly, neuroendocrine signals synchronize peripheral clocks through both sympathetic and parasympathetic pathways. Indirectly, the SCN regulates daily activity-rest and feed-fasting cycles to synchronize peripheral clocks. B) Internal and external time cues of the circadian clock. The circadian clock is entrained by internal and external signals to harmoniously orchestrate rhythms within the organism as well as to keep pace with changes in the environment. Internal signals include metabolic and endocrine signals, such as temperature, cAMP, NAD^+, heme and various hormones. External signals include light, feeding time, diet composition and gut microbiota. A portion of the elements used in this figure was from Flaticon.com and Smart. servier.com. License: https://creativecommons.org/licenses/by/3.0/deed.en.

2.3.3. External time cues regulate the circadian clock

Light and feeding are the most potent external zeitgebers that trigger circadian rhythm entrainment. In modern industrialized societies, deleterious exposure to light at night is much more prevalent than during previous centuries, leading to circadian rhythm disruption in a large proportion of the world's population (Potter et al., 2016). Even exposure to dim (5 lux) light in the dark phase attenuates amplitude of clock gene *Per* and *Cry* expression in the hypothalamus and liver of mice (Fonken et al., 2013). Feeding time is another critical contributor to circadian clock entrainment. Irregular feeding in mice extensively disrupts circadian gene expression, resulting in aberrant expression patterns of *Bmal1, Per2, Cry2 and Rev-erbα* and *Dbp* in liver, epididymal fat, gastrocnemius muscle and heart (Bray et al., 2013). Patients with night-eating syndrome display disrupted leptin and insulin levels, melatonin and glucose rhythms and attenuated cortisol, ghrelin and insulin oscillation amplitudes (Goel et al., 2009). Importantly, the influence of light and feeding time on circadian rhythms does not exist independently, as detrimental lifestyle inevitably disrupts biological rhythms by exposing humans to abnormal changes in light and eating times.

In addition to lighting and feeding time, whether other environmental cues participate in clock regulation has aroused widespread interest. Diet composition and the gut microbiome are emerging regulators of circadian rhythms. High fat diet (HFD) deregulates the oscillation of core clock genes and downstream clock-controlled genes in liver, adipose tissue and the hypothalamus (Kohsaka et al., 2007). Furthermore, gut microbiota is a potential organizer of the host circadian rhythm. Microbiota rhythmically regulate intestinal epithelial HDAC3 expression to synchronize diurnal oscillations in histone acetylation and gene expression related to lipid uptake and metabolism (Kuang et al., 2019).

The harmonious operation of circadian clocks relies on internal biochemical and external environmental signaling. Endogenous biochemical signals ensure the circadian machinery will operate in a coordinated fashion. Exogenous environmental cues sustained by a healthy lifestyle are fundamental to maintain the circadian clock. Such fitness could face multiple threats once the alignment of internal and external rhythms is impaired.

3. Circadian rhythms and cancer

Circadian disruption is associated with numerous diseases including cancer (Masri et al., 2015). Moreover, circadian rhythm-disrupting behaviors such as light-at-night exposure and shift work correlate with an increase in the incidence of breast, ovarian, prostate, and colorectal cancers (Sancar and Van Gelder, 2021). Reciprocally, patients with altered circadian clocks display poorer prognosis when compared to patients with normal circadian rhythms (Lis et al., 2003). As cancer is

threatening human health, and circadian disruption is increasingly prevalent in modern society and medical care, understanding the role of circadian disruption in cancer development is imperative. Here we discuss present advances in the field of circadian clocks and cancer.

3.1. Cancer contributes to circadian disruption

3.1.1. Cancer is associated with circadian disruption

Circadian disruption is a common characteristic of a variety of tumor tissues. Analysis of the Cancer Genome Atlas depicted changes in clock genes across 32 types of cancer. Most (90.2%) clock-related genes are abnormally expressed in tumor samples of at least one cancer type. For example, *PER1, PER2, PER3* and *RORB* are downregulated in 7-11 cancer types, while *ARNTL2* is upregulated in 9 cancers (Ye et al., 2018). Compared with normal tissues, tumors present significantly fewer genes correlated with clock genes, suggesting impaired circadian output in tumor tissues. Besides genetic alterations, circadian disruption of multiple biological processes has been noted in various types of cancers, including breast, ovarian, prostate, gastric and colon cancers (Sephton and Spiegel, 2003). For example, cancerous states induce disrupted diurnal rhythms in plasma lymphocyte abundance as well as endocrine factors including cortisol, melatonin and prolactin of cancer patients. Further, these hormones modulate immune cell differentiation, trafficking and functions by dictating expression of cytokine and adhesion molecules (Webster et al., 2002). In turn, sustained dysregulation of glucocorticoid rhythms could influence anti-cancer immunity of immune cells (Sephton and Spiegel, 2003).

Rhythm disruptions in cancer patients may not only result from oncogenesis but also from medical interventions including chemotherapies. Patients with breast cancer display decreased daytime light exposure during chemotherapy (Liu et al., 2005), which could lead to circadian disruption. A rodent study demonstrated that administration of the anti-cancer drug paclitaxel alters circadian wheel running behavior, serum corticosterone rhythm, and circadian clock gene expression in the brain and adrenal glands (Sullivan et al., 2022). Thus, cancer is associated with circadian disruption in genetic alterations of circadian genes and physiological changes in endocrine and immune rhythms. In addition, therapeutic interventions also contribute to circadian disruption, suggesting the adverse effect of circadian rhythm dysregulation should be taken into consideration in cancer therapy.

3.1.2. Oncogene expression disrupts circadian clocks

Oncogenes residing in cancer function as modulators of circadian clocks. The MYC family is a group of transcription factors associated with poor prognosis in many types of cancers (Eilers and Eisenman, 2008). For example, oncogenic N-MYC induces REV-ERBα to disrupt expression and rhythmicity of BMAL1 in a neuroblastoma cell line as well as patients (Altman et al., 2015). RAS oncogenes (*HRAS*, *NRAS*, and *KRAS*) are among the most frequently mutated oncogenes in cancer because they possess strong transforming potential (Kimmelman, 2015). HRAS transformation in colon carcinoma cells downregulates *BMAL1* and *PER2* expression and upregulates *CLOCK* and *CRY1* expression (Relogio et al., 2014).

3.1.3. Oncogenic signaling interferes with circadian clocks

Cancer activates multiple oncogenic signaling pathways that interrupt circadian clocks. The mTOR pathway is a frequently dysregulated pathway in many cancers (Janku et al., 2018). Hypoxic tumor microenvironment-induced acidification drives peripheral redistribution of normal perinuclear lysosomes away from perinuclear RHEB in human and murine cell lines. This impedes activity of lysosome-bound mTORC1 that disrupts clock protein translation (Walton et al., 2018). Wnt/β-catenin signaling is critical to cell fate determination and promotes cancer development by regulating the circadian clock. Wnt/β-catenin signaling is dysregulated in $Apc^{Min/+}$ mice. This $Apc^{Min/+}$ alteration destabilizes Per2 in the intestinal mucosa through SCF ubiquitin E3 ligase β-TrCP mediated ubiquitination. This facilitates epithelial neoplastic transformation (Yang et al., 2009).

In summary, cancers disrupt genetic circadian rhythms in gene expression and physiologic rhythms in immune and endocrine oscillations. Cancer chemotherapy is another contributor to circadian disruption in patients, as well as alterations in light exposure. At the molecular level, oncogenes and oncogenic signaling pathways dysregulate the circadian clock. However, the mechanisms by which cancer disrupts circadian clocks remain elusive. Further investigations will help us better understand how cancer and its treatment disrupts circadian clocks.

3.2. Circadian disruption promotes cancer development

3.2.1. Genetic circadian disruption is associated with cancer

Genetic variations in molecular clock lead to circadian disruption and exacerbate cancer development. Circadian gene disruption makes humans susceptible to multiple cancers, including breast, colon, prostate, lung, liver and ovarian cancers (Sullivan et al., 2016). Genetic association analysis has identified a critical role of CRY2 dysregulation in the promotion of non-Hodgkin lymphoma, an effect associated with disrupted immune responses and hematologic system development (Hoffman et al., 2009). In a human colorectal cancer cell line, removal of BMAL1 abolishes the rhythmic pattern of the glycolytic gene *HKDC1* and leads to increased glycolytic activity and colorectal cancer progression (Fuhr et al., 2018). In mice, dysregulation of Per2 promotes growth, cell cycle progression and clonogenic ability of malignant cells to participate in initiation and progression of acute myeloid leukemia (Gery et al., 2005).

3.2.2. Behavioral circadian disruption is associated with cancer

The International Agency for Research on Cancer (IARC) of the World Health Organization listed night-shift work as a possible human carcinogen (Burki, 2019). Shift workers suffer more from prostate, endometrial and breast cancer compared to non-shift workers (Hammer et al., 2015; Viswanathan and Schernhammer, 2009). In a $K\text{-}ras^{LSL\text{-}G12D/+}$ $p53^{flox/flox}$ lung cancer mice model, a chronic shift work schedule accelerated lung tumorigenesis by increasing tumor burden and severity (Papagiannakopoulos et al., 2016). Of note, the negative effects induced by circadian disrupting lifestyles are extensive. For example, irregular mealtime, sleep disruption and mental stress, which are potential contributors to cancer development. Thus, increasing studies are trying to carefully separate the influence of circadian disruption by excluding feeding, sleeping and mental change of experimental subjects (Castanon-Cervantes et al., 2010). This will benefit the search for determining the true effect of circadian disruption on tumorigenesis.

3.2.3. Circadian disruption facilitates cancer by dysregulating immunity

A vital hallmark of cancer is immune deficiency (Hanahan, 2022), which is under the regulation of circadian clocks (Scheiermann et al., 2018). Circadian clock regulates systemic immunity and the tumor immune microenvironment to promote cancer.

Chronic shiftwork induces circadian rhythm disruption in NK cells, resulting in disturbed expression of *Per2* and *Bmal1* and altered rhythmicity of perforin, granzyme B and IFN-γ. These changes lead to a decreased cytolytic function of natural killer cells and accelerated lung tumor growth (Logan et al., 2012). Rorα recruits HDAC that downregulates Acat1/2 and Abca1 to suppress cholesterol elimination and further facilities $CD8^+$ T cell anti-cancer immunity. As such, Rorα dysregulation maintains $CD8^+$ T cells in a dormant status (Lee et al., 2020).

The circadian clock manipulates immune cells in the tumor microenvironment to promote cancer development. Abnormal *CLOCK* expression enhances the self-renewal ability of glioblastoma stem cell and transcriptionally upregulates OLFML3 that recruits immunosuppressive microglia into glioblastomas to aggravate malignancy

(Chen et al., 2020). Chronic jet-lag enhances the CXCL5-CXCR2 axis to promote recruitment of myeloid-derived suppressor cells to nourish an immunosuppressive microenvironment, resulting in cancer-cell dissemination and lung metastasis of breast cancer (Hadadi et al., 2020).

3.2.4. Circadian disruption promotes cancer via endocrine changes

Biological clocks control endocrine activities to support various malignant signatures of cancer. A disrupted circadian rhythm in mice decreases nocturnal secretion of melatonin and leads to down-regulation of carboxylesterase 1 to induce lipid accumulation. This reduces ER stress-related apoptosis and increases intra-tumor androgen synthesis to promote prostate tumor growth (Zhou et al., 2021). Supplementation of human tissue-isolated SK-LMS-1 xenografts with nighttime-collected melatonin-rich blood mitigates metabolic reprogramming of tumor glucose and fatty acid metabolism, leading to inhibited tumor growth and invasion (Mao et al., 2016).

Apart from melatonin, IGF-1 and glucocorticoids are also critical mediators for circadian disruption to promote cancer. Insulin-like growth factor-1 (IGF-1) is reported to be a key regulator of malignant cell growth (Pollak, 2008). Nighttime light induces circadian disruption to continuously elevate IGF-1 to enhance growth of xenografts in nude rats (Wu et al., 2011). As summarized in another review (Greene, 2012), jet lag alters the rhythm of glucocorticoid synthesis and release, which may contribute to tumor growth. However, the role of glucocorticoids in regulating tumor growth remains to be tested in desynchronized animal models.

Overall, cancer plays an important role in circadian disruption, while genetic and behavioral circadian disturbances facilitate tumor development. Present evidence suggests that circadian disruption and cancer development may interact reciprocally to promote one another, yet the causal relationship remains poorly explained. Circadian disruption contributes to the remodeling of immunity and endocrine features that accelerate tumorigenesis. In addition, circadian clocks may facilitate cancer development by regulating other cancer features, including aberrant metabolism status, a dysregulated cell cycle and an enhanced stemness phenotype (Fu et al., 2002; Gu et al., 2012; Li et al., 2021; Zhou et al., 2021). These interactions imply a vital role of circadian clocks in cancer development.

4. A broken circadian clock links depression to cancer

Depression is a frequently observed symptom in various types of cancer. The depressed state of patients leads to deleterious effects for both therapeutic treatments and cancer progression (Wang et al., 2020). Depression is accompanied by circadian rhythm disruption (Fishbein et al., 2021), and dysregulation of circadian rhythms serves as a risk factor for depression (Lyall et al., 2018). These interactive relationships suggest an important role for the broken circadian clock acting as a bridge that connects cancer to depression. Here we elucidate the interactions between depression, cancer and the circadian clock as an intrinsic basis for linking the broken circadian clock to depression and cancer.

4.1. The relationship of cancer and depression

4.1.1. Depression is associated with cancer

Depression is defined as presentation of depressed mood that is characterized by a marked loss of interest or pleasure in most or all activities for at least 2 weeks. Clinical depression is accompanied by at least four other depressive symptoms that include fatigue, appetite disturbance, weight loss, sleep difficulties, memory loss, concentration issues and suicidal thoughts (Chochinov, 2001). In 2008, major depression was ranked as the third cause of global burden of disease and is projected to be ranked the first by 2030 (Malhi and Mann, 2018). Depression is observed in multiple chronic diseases, including cancer, cardiovascular disease, metabolic disorders, inflammatory dysregulation, neurological degeneration (Gold et al., 2020).

Depression is a common symptom in cancer patients (Sullivan et al., 2016). A meta-analysis covering 24 interview-based studies reported that 24.6% (95% CI 17.5–32.4) of cancer patients suffer from at least one depressive episode, including major depression, minor depression or dysthymic disorder (Mitchell et al., 2011). Importantly, cancer patients have two to three times greater incidence of major depression than the general population (Currier and Nemeroff, 2014). It is noteworthy that, cancer and depression often co-exist in the same individual. As cancer patients often suffer from depression (Mitchell et al., 2011), and depression also serves as a risk factor for cancer (Currier and Nemeroff, 2014), the causal relationship between cancer and depression is difficult to determine. Unfortunately, a more detailed reporting of the entire process of disease development is often lacking, so it is challenging to determine whether depression comes first to promote cancer or vice versa. Clearly, more comprehensive and detailed investigations on the entire process of disease development is needed to more fully understand the interactions that are known to occur between cancer and depression. This knowledge would be beneficial to prevent and treat the both diseases.

4.1.2. Depression promotes cancer development

Depression serves as a vital risk factor for cancer. A meta-analysis that included 165 studies revealed that stress-related psychosocial factors are associated with a greater incidence of cancer and in 53 studies there was a higher incidence of cancer mortality (Chida et al., 2008). Furthermore, mental factors are correlated with a higher incidence of lung cancer and poorer survival in breast, lung, head and neck, hepatobiliary and lymphoid cancers (Chida et al., 2008; Cui et al., 2021). Depression aggravates tumorigenesis and synergistically harms overall health during cancer (Cui et al., 2019). It is speculated that depression may enhance cancer progression through physiologic mechanisms, such as immune alterations and neuroendocrine disorders (Miller et al., 2008). Depression facilitates tumor progression by reducing NK cell activity through elevated TNF-α and inhibition of MHC-I and MHC-II expression (Holden et al., 1998). Consistently, epidemiologic studies reveal that hepatobiliary cancer patients with depression display lower NK cell activity, and this is associated with reduced survival rate (Irwin and Miller, 2007). Compared with non-depressed cancer patients, subjects show reduced sensitivity to glucocorticoids and flattened diurnal cortisol levels (Miller et al., 2008). Still, the role of depression in cancer development is poorly understood. As such, further investigation in this field is likely to benefit cancer patients with depressive symptoms.

4.1.3. Cancer contributes to development of depression

Depression and anxiety are contributing to incidence of all-cause cancers (Wang et al., 2020). Depression may arise from cancer pathology, psychological issues or the clinical treatment in cancer patients. Pathologically, many tumor antigens generate abnormal inflammatory signals, predominately IL-6, TNF and C-reactive protein, that promote depression (Mcfarland et al., 2022; Young and Singh, 2018; Yu et al., 2022). Furthermore, tumor-induced inflammatory cytokines can activate indoleamine 2,3 dioxygenase to disrupt tryptophan metabolism that is needed for synthesis of the neurotransmitter serotonin, which plays an important role in inhibiting depression (Bortolato et al., 2017). Psychologically, patients who are faced with a diagnosis of cancer and its treatment usually experience painful emotional reactions that can develop into clinical depression (Carlson, 2022). Moreover, psychosocial factors including perceived burdensomeness and thwarted belongingness mediate depressive symptoms in cancer patients (Tripp et al., 2020). Clinically, therapeutic treatments are potential inducers of depression. For example, cancer patients receiving chemotherapy have 12-18% incidence of developing major depression (Mitchell et al., 2011). Some anti-cancer medications, including radiotherapy, interferon, vincristine and cyproterone, induce depressive mood changes characteristic of depression and often lead to cognitive dysfunction

(Chochinov, 2001; Santos and Pyter, 2018; Sotelo et al., 2014). Overall, cancer contribute to depression in multiple ways. This is why the underlying mechanisms that promote the development of depression in cancer patients should be actively pursued.

In summary, clinical evidence reveals a tight relationship between cancer and depression. Cancer patients tend to suffer from depressive mental states, which further elicits psychological and pathological changes that impair cancer treatment. Cancer also plays an important role in promoting depression.

4.2. The relationship between depression and the circadian clock

4.2.1. Circadian disruption is common in depressed patients

The close relationship between depression and the circadian clock has been recognized since the 1980s. Depressed patients present disturbed circadian rhythms in both physiology and behavior.

Immune and endocrine rhythms are disrupted in depressed patients. For instance, patients with major depression display reduced diurnal oscillations of Leu-11 NK cell abundance and cytotoxicity (Petitto et al., 1992). In addition, depression is often accompanied with increased nocturnal body temperature and decreased plasma thyrotropin levels (Souetre et al., 1988). Moreover, a phase advance and reduction in blood melatonin occurs in depressed patients (Parry and Newton, 2001).

In addition to physiological circadian disruption, depression also impairs behavioral rhythms. One important feature of mood disorders including depression is a disrupted sleep–wake cycle. Indeed, 50–90% of patients with diagnosed depression complain about impairment of sleep quality (Riemann et al., 2001). A fuller understanding of circadian rhythm function in the development of depression will provide a fresh approach for more effective depression interventions.

4.2.2. Circadian disruption promotes depression

Circadian rhythm disruption is not only a symptom but also a potential causal factor for depression. Genetically, the risk of depression is increased in people with a circadian disorder caused by clock gene mutations (*CRY1, NFIL3 or RORC*) that delay the sleep-wake phase (Patke et al., 2017). Physiologically, depression risk is higher in subjects with a biological circadian misalignment, such as an abnormal melatonin onset phase (Kang et al., 2017). Behaviorally, chronic shift-workers are susceptible to various psychiatric disorders such as depression, and long-term shift work for over 20 years results in increased lifetime risk of major depression (Wright et al., 2013). Thus, circadian disruption plays a pivotal role in promoting depression, but the underlying mechanisms are largely unknown.

Genetic changes in the circadian clock play a pivotal role in the development of depression. Analysis of 46 single nucleotide polymorphisms (SNPs) in 8 clock genes revealed a strong association of *BMAL1* and *TIM* with mood disorder (Mansour et al., 2006). This indicates a close link between circadian genes and the development of depressive disorder. The relationship between clock genes and depression has been established in pre-clinical studies. For instance, overexpression of the circadian clock regulator glycogen synthase kinase-3β (GSK3β) in mice leads to a reduction in depression-like behaviors (Prickaerts et al., 2006).

Apart from genetic circadian disruptions, development of depression can also arise from physiologic circadian disruptions, such as the dysregulation of immune responses and neuronal signaling (Mcclung, 2013). For example, exposure to 4-week long term darkness increases murine depressive-like behaviors by elevating the pro-inflammatory cytokine interleukin-6 in plasma and the type 1 interleukin 1 receptor in the hippocampus. This suggests a critical role for cytokine responses in depressive-like behaviors induced by diurnal rhythm disruption (Monje et al., 2011). Harmful exposure to light-at-night induced depressive-like behavior is mediated by the ipRGC-dpHb-NAc neuro signaling pathway that preferentially transfers light signals at night (An et al., 2020). As such, depression is interrelated in multiple dimensions to the circadian clock system.

4.3. Circadian clock at the intersection of cancer and depression

Based on the inter-regulatory relationships within circadian clocks, cancer and depression, we speculate the circadian clock is an important bidirectional link that connects cancer to depression. Cancer disrupts the circadian clock to manifest its influence on depression, while depression dysregulates the circadian clock to affect cancer. Moreover, circadian disruption simultaneously aggravates cancer and depression. As a result, circadian clock, cancer and depression constitute a vicious feedback loop (Fig. 3).

4.3.1. The broken circadian clock is a link between cancer and depression

As one of the most distinctive features of cancer, circadian disruption promotes cancer development through genetic and physiological pathways. Additionally, depression in cancer patients is becoming increasingly prevalent, as shown by a distress rate in cancer patients that is four-times higher than in the healthy population (Yang et al., 2022). Moreover, circadian disruption is a common characteristic of depressed individuals (Lyall et al., 2018). Thus, we propose that cancer and depression converge at the level of the circadian clock to influence one other, indicating linkage of the circadian clock to both cancer and depression. Epidemiologic research shows that flight attendants have a 2-5.7-fold higher likelihood of developing depression, anxiety, fatigue and sleep disorders, as well as a higher prevalence of cancers (Mcneely et al., 2018). A recent meta-analysis involving 39 observational studies concluded that evening chronotypes, characterized as late wake-up timing and more nocturnal activities, is associated with a higher risk of diabetes (OR: 1.30; 95% CI: 1.20, 1.41), cancer (OR: 1.18; 95% CI: 1.08, 1.30) and depression (OR: 1.86; 95% CI: 1.20, 2.88) (Lotti et al., 2022). These findings support our hypothesis by confirming that circadian disruption is associated with both depression and cancer. More importantly, clinical evidence reveals that circadian disruption in cancer patients influences the development of depression. A comparative study involving seventy-eight female breast cancer patients assessed the correlation of sleep-activity patterns and depression inventories (Roscoe et al., 2002). This study showed that circadian rhythm disruption is associated with depression in cancer patients ($r = -0.34$; $P = 0.03$). Moreover, patients with advanced lung cancer who have severe sleep rhythm disruptions display more anxiety and depression than those who maintain normal behavioral rhythms (Hrushesky et al., 2009). These findings suggest that circadian disruption might serve as a link between cancer and depression. However, the fundamental biochemical basis for this circadian clock linkage to depression and cancer remains to be determined.

4.3.2. Cancer breaks the circadian clock to promote depression

Patients with tumors often suffer from mood disorders like depression (Mampay et al., 2021). Cancer may break the circadian clock to dysregulate events that promote depression, such as neuro-inflammation and the hypothalamic-pituitary-adrenal (HPA) axis (Ketchesin et al., 2020).

Cancer may facilitate development of depression by inducing inflammation in both the periphery and brain. Mice with C26 colon adenocarcinoma display increased depressive-like behaviors, as assessed by wheel running, sucrose preference and forced swim tests (Norden et al., 2015). This is related to elevations in neuro-inflammatory IL-1β and IL-6 in the hippocampus (Norden et al., 2015). Sleep disturbances in cancer patients are prevalent (Palesh et al., 2010), and such disturbances induce depressive behaviors by disrupting clock gene expression and clock controlled pro-inflammatory cytokines like IL-6, IL-1β and TNFα (Xing et al., 2021). As such, cancer is likely to promote depression by regulating circadian clock driven inflammatory states.

Cancer patients are reported to have increased plasma cortisol levels that are indicative of a dysfunctional HPA axis. This dysregulation is

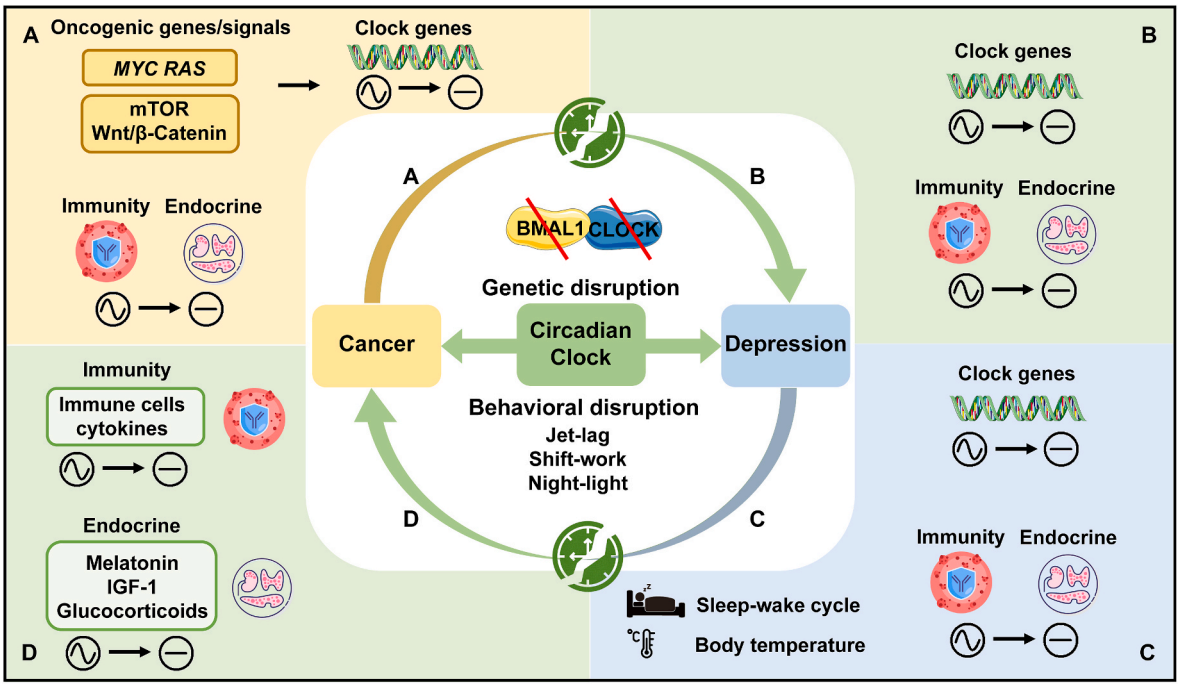

Fig. 3. Theoretical model of the circadian clock-cancer-depression feedback loop. A) Cancer disrupts the circadian clock. Dysregulated circadian genes and physiological rhythms are common in various types of cancer. B) Circadian disruption promotes depression. Circadian disruption mainly promotes depression by immune and endocrine pathways. C) Depression disrupts the circadian clock. Depression is associated with genetic and physiologic circadian disruptions. Depression is often accompanied by genetic disruption of circadian clock genes as well as disturbed physiologic rhythms, including the sleep-wake cycle, body temperature and immunity and hormone secretion (e.g., thyrotropin, cortisol and melatonin). D) Circadian disruption promotes cancer. Circadian disruption promotes cancer via interacting with oncogenes (e.g., MYC and RAS) and oncogenic pathways (e.g., mTOR and Wnt/β-Catenin) and malignancy features (e.g., immunity and endocrine). Parts of the elements used in this figure derived were from Flaticon.com and Smart.servier.com. License: https://creativecommons.org/licenses/by/3.0/deed.en.

positively correlated with the patients' depression state (Jehn et al., 2010). Cancer dysregulates expression of clock genes, including *BMAL1, PER, RORB* and *ARNTL2* (Ye et al., 2018), so circadian clocks serve as a potential link between cancer and depression. Moreover, BMAL1-deleted monkeys show increased depressive behaviors and continuously elevated blood cortisol (Qiu et al., 2019), suggesting an important role for the HPA axis in rhythm disruption and depression. Likewise, genetic Bmal1 deletion in the murine cerebral cortex results in depressive-like behaviors as assessed by the tail suspension test and reduces cortical norepinephrine (Bering et al., 2018). Therefore, cancer might rewire circadian clock controlled HPA rhythm to exacerbate depression. In conclusion, cancer disrupts the circadian clock to modulate physiologic rhythms and these changes further contribute to development of depression.

4.3.3. *Depression rewires the circadian clock to promote cancer*

Depression is associated with higher cancer incidence and poorer cancer prognosis (Currier and Nemeroff, 2014). Depression may disrupt both genetic and behavior circadian clocks to regulate cancer-promoting processes. These include cell proliferation dysregulated metabolism and immune suppression (Sulli et al., 2019).

Chronic mild stress-induced depression remodels murine circadian clock machinery by reducing *Bmal1* and *Clock*, *Per*, *Cry*, *Rev-erbβ* and *Pparα* expression (Calabrese et al., 2016). In addition, major depressive disorder in humans is associated poorer brain rhythms in a variety of genes, including *BMAL1*, *PER1-2-3*, *NR1D1* and *DBP*, compared to healthy controls in mood-relevant brain regions (Li et al., 2013). Further, abnormal regulation of *Bmal1*, *Clock* and other core clock genes have been shown to increase the risk of various malignancies including pancreatic, lung, colorectal and tongue cancer (Jiang et al., 2016; Papagiannakopoulos et al., 2016; Tang et al., 2017; Zeng et al., 2014). For example, *Bmal1* deficiency promotes pancreatic cancer growth, as Bmal1 transcriptionally activates the downstream tumor suppressor pathway by directly binding to the *p53* promoter (Jiang et al., 2016). Absence of *Per2* and *Bmal1* independently promotes glucose/glutamine metabolism, c-Myc activation, and cell proliferation in lung cancer (Papagiannakopoulos et al., 2016).

Other than genetic variation, both activity-rest and sleep-wake cycles also display altered rhythms in individuals with mood disorders (Mcclung, 2007). Disruption of these behavioral cycles are likely to further promote cancer development. Sleep disruption facilitates tumor growth and invasiveness through recruiting immune-suppressive M2 tumor associated macrophages with increased pro-inflammatory TLR4 signaling (Hakim et al., 2014). Thus, depression may indirectly regulate cancer malignant phenotypes by genetically and behaviorally disrupting the circadian clock.

4.3.4. *Disruption of the circadian clock simultaneously facilitates cancer and depression*

Circadian disruption is not merely a link that straddles depression and cancer. Deleterious modern lifestyles, such as jet-lag, shift-work and night-light exposure can directly lead to circadian disruptions. As such, the circadian clock could potently transmit detrimental effects through both directions to promote depression and/or cancer development. Epidemiologic evidence shows that compared with non-shift workers, chronic shift-workers are more susceptible to depression and various types of cancer (Siegel et al., 2017). In a pre-clinical murine study, chronic jet-lag schedule-induced circadian disruption dysregulates diurnal oscillations of M1 and M2 macrophages, the M1/M2 ratio and IL-1β, IL-6 and TNF-α in spleen and tumor tissues, all of which promotes melanoma cell proliferation by reducing expression of the cell cycle inhibitor $p21^{WAF/CIP1}$ (Aiello et al., 2020). Interestingly, central infusion of IL-1β results in significant phase delay in locomotor activity rhythms, which is associated with depression risk (Logan and Sarkar, 2012). Shift-work light schedules disrupt expression of the core clock genes *Per1*, *Per2*, *Rev-erbα*, *Clock* and *Bmal1* in the SCN and mood-controlling

brain regions in the prefrontal cortex, leading to development of depressive-like behaviors (Otsuka et al., 2020). Besides jet-lag and shift-work, circadian disruption by nighttime light also promotes cancer and depression. Night-light exposure modulates metabolism in rats to support tumor growth by upregulating lipogenesis and glucose uptake with decreased blood triglyceride and increased glucose levels (Guerrero-Vargas et al., 2017). Night-light exposure disrupts the rhythm of clock genes in mice locomotor activity and body temperature, as well as depressive-like behaviors (Walker et al., 2020). Collectively, these results from different models support our hypothesis that circadian disruption bidirectionally promotes the development of cancer and depression. This suggests that circadian clock disruption as a promising target for cancer and depression comorbidity.

5. Conclusions and future directions

The past few decades have witnessed major advances in the field of circadian clocks. An understanding of vital disease development and their relationships to biological clocks is becoming increasingly important. The close connection between circadian clock disruption and tumorigenesis has been well established, but the biochemical underpinnings of this relationship are just beginning to be elucidated. Genetic and behavioral disruption of the circadian clock facilitates carcinogenesis by interacting with oncogenic signaling and various physiological processes, especially immune and endocrine activities (Shafi and Knudsen, 2019). Depression is a common symptom in cancer patients, and the depressed population has a higher incidence of cancer (Chida et al., 2008). Currently, links between depression and tumorigenesis are mainly built on immune and neuroendocrine pathways (Miller et al., 2008). Interestingly, depressed individuals often present with disrupted circadian rhythms (Sullivan et al., 2016). Consistently, animal studies further demonstrate that circadian disruption actively participates in the development of depression (Logan et al., 2015). This evidence strongly implicates circadian disruption as a potential neuro-immune link between depression and other adverse health outcomes.

We propose that a broken circadian clock is an important link that connects cancer and depression, especially through immune and endocrine connections. In other words, circadian disruption provides a pathway for cancer and depression to facilitate one another. Moreover, detrimental lifestyles that harm circadian rhythms could turn the clock to be a bidirectional promoter of both cancer and depression. The feedback loop formed by a broken circadian clock, cancer and depression create a vicious circle that adversely affects overall health. This hypothesis helps to explain why depression and cancer comorbidity have a greater deleterious influence than either one alone. Depression and cancer manifest their impact on one another through disruption of the circadian clock system that orchestrates a wide range of genes that regulate essential physiologic processes. Meanwhile, our theory provides a new perspective suggesting that chemical and behavioral interventions that aim to restore a normal circadian clock may reverse the vicious circle whirling around cancer and depression.

Despite these advances, we are far from understanding the complex relationships among circadian disruption, cancer and depression. The initial starting point of the vicious loop around a broken circadian clock, cancer and depression remains a mystery. The direct mechanisms of cancer and depression that influence each other through rewiring the rhythmicity of immune, endocrine, neural, microbiota and other systems remain to be elucidated. As such, developing potent pre-clinical experimental models as well as clinical research approaches is imperative. Importantly, discovery of intervention strategies that arrest the vicious feedback loop by correcting the dysregulated time keepers is urgently needed. The verification of effectiveness and safety of such interventions are necessary.

Author contributions

QL, KS and BC conceived the work. KS and ZUD reviewed the literature and drafted the manuscript. BC and FP reviewed the literature and edited the manuscript. YZ, CW, XZ, JL, HL, BH and KWK edited the manuscript. All authors approved the manuscript for submission.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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