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 with the ~24h periodic oscillation of the earth (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 (Shaft 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 downstream 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 (Itakaka 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-tuning 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 10^15-10^16 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^NAM PTM, 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.

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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 glucocorticoids. For instance, daily temperature variation mediates 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 catalyze NAM to NMN, which then leads to formation of NAD⁺. Further, NAD⁺ activates SIRT1 activity to deacetylate BMAL1, thus inhibiting CLOCK-BMAL1 transcriptional func-
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 \( \text{Per} \) and \( \text{Cry} \) 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 \( \text{Bmal1}, \text{Per2}, \text{Cry2} \) and \( \text{Rev-erba} \) and \( \text{Dbp} \) 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 microbiota 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 chemotherapy. 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 (Ellers 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 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 disrupted in ApcMin/+ mice. This ApcMin/+ 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 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 KrasLSL-G12D/+; p53fox/fox lung cancer mice model, a chronic shift work schedule accelerated lung tumorogenesis 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 tumorgenesis.

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 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 immune-suppressive microglia into glioblastomas to aggravate malignancy.
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.
can also arise from physiologic circadian disruptions, such as the dysregulation of immune responses and neuronal signaling (Mcclung, 2006).

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 (Soutcro et al., 1989). 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 (Frickaerts 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 (Meclung, 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 another, 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
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). 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).} Depression is associated with higher cancer incidence and poorer cancer prognosis (Currier and Nemeroff, 2014). Depression may disrupt clock machinery by reducing processes. These include cell proliferation dysregulated metabolism and c-Myc activation, and cell proliferation in lung cancer (Jiang et al., 2016; Papagiannakopoulos 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.

4.3.3. Depression rewrites the circadian clock to promote cancer

Depression is associated with higher cancer incidence and poorer cancer prognosis (Carrier 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-erhβ and Pparu expression (Calabrese et al., 2016). In addition, major depressive disorder in humans is associated poorer blood cortisol rhythms in a variety of genes, including Bmal1, Per1-2-3, NRI1D1 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 p21WAF/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-erhβ, 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 (Guerro-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 (Shafl 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

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References

Aiello, I., Fedele, M.L.M., Roman, F., et al., 2020. Circadian disruption promotes tumor-immune microenvironment remodeling favoring tumor cell proliferation. Sci. Adv. 6 (42) https://doi.org/10.1126/sciadv.aaz4530.
Albrecht, U., 2006. Orchestration of gene expression and physiology by the circadian clock. J. Physiol. Paris 100 (5–6), 243–251. https://doi.org/10.1016/j.jphysparis.2007.05.004.
Altman, B.J., Hsieh, A.L., Sengupta, A., et al., 2015. MYC disrupts the circadian clock and metabolism in cancer cells. Cell Metab. 22 (6), 1009–1019. https://doi.org/10.1016/j.cmet.2015.09.003.
An, K., Zhao, H., Miao, Y., et al., 2020. A circadian rhythm-gated subcortical pathway for nighttime-light-induced depressive-like behaviors in mice. Nat. Neurosci. 23 (7), 869–880. https://doi.org/10.1038/s41593-020-0640-8.
Bass, J., Takahashi, J.S., 2010. Circadian integration of metabolism and energetics. Science 330 (6009), 1349–1354. https://doi.org/10.1126/science.1195027.
Bering, T., Carstensen, M.B., Wortwein, G., et al., 2018. The circadian oscillator of the cerebral cortex: molecular, biochemical and behavioral effects of deleting the arntl clock gene in cortical neurons. Cerebr. Cortex 28 (2), 644–657. https://doi.org/10.1093/cercor/bhw406.
Bortolato, B., Hyphantis, T.N., Valpione, S., et al., 2017. Depression in cancer: the many biobehavioral pathways driving tumor progression. Cancer Treat Rev. 52, 58–70. https://doi.org/10.1016/j.ctrv.2016.11.004.
Bray, M.S., Ratcliffe, W.F., Grenett, M.H., et al., 2013. Quantitative analysis of light-phase restricted feeding reveals metabolic dysynchrony in mice. Int. J. Obes. 37 (6), 843–852. https://doi.org/10.1038/ijo.2012.137.
Burki, T.K., 2019. Night shift work and breast cancer. Lancet Oncol. 20 (7), e352. https://doi.org/10.1016/S1470-2045(19)30383-3.
Calabrese, F., Savino, E., Papp, M., et al., 2016. Chronic mild stress-induced alterations of clock gene expression in rat prefrontal cortex: modulatory effects of prolonged laridazole treatment. Pharmacol. Res. 104, 140–150. https://doi.org/10.1016/j.phrs.2015.12.025.
Trigg, D.A., Mihajlovic, V., Fretz, K., et al., 2020. Quality of life, depression, and psychosocial mechanisms of suicide risk in prostate cancer. Can Urol Assoc J 14 (10), E487-E492. https://doi.org/10.5489/cuaj.6310.

Visswannathan, A.N., Schernhammer, E.S., 2009. Circulating melatonin and the risk of breast and endometrial cancer in women. Cancer Lett. 281 (1), 1–7. https://doi.org/10.1016/j.canlet.2008.11.002.

Walker 2nd, W.H., Borniger, J.C., Gaudier-Díaz, M.M., et al., 2020. Acute exposure to low-level light at night is sufficient to induce neurological changes and depressive-like behavior. Mol. Psychiatr. 25 (5), 1080–1093. https://doi.org/10.1038/s41380-019-0480-4.

Walton, Z.E., Patel, C.H., Brooks, R.C., et al., 2018. Acid suspends the circadian clock in hypoxia through inhibition of mTOR. Cell 174 (1), 72–87 e32. https://doi.org/10.1016/j.cell.2018.05.009.

Wang, Y.H., Li, J.Q., Shi, J.F., et al., 2020. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol. Psychiatr. 25 (7), 1487–1499. https://doi.org/10.1038/s41380-019-0595-x.

Walker 2nd, W.H., Borniger, J.C., Gaudier-Díaz, M.M., et al., 2020. Acute exposure to low-level light at night is sufficient to induce neurological changes and depressive-like behavior. Mol. Psychiatr. 25 (5), 1080–1093. https://doi.org/10.1038/s41380-019-0480-4.

Walker 2nd, W.H., Borniger, J.C., Gaudier-Díaz, M.M., et al., 2020. Acute exposure to low-level light at night is sufficient to induce neurological changes and depressive-like behavior. Mol. Psychiatr. 25 (5), 1080–1093. https://doi.org/10.1038/s41380-019-0480-4.

Walton, Z.E., Patel, C.H., Brooks, R.C., et al., 2018. Acid suspends the circadian clock in hypoxia through inhibition of mTOR. Cell 174 (1), 72–87 e32. https://doi.org/10.1016/j.cell.2018.05.009.

Wang, Y.H., Li, J.Q., Shi, J.F., et al., 2020. Depression and anxiety in relation to cancer incidence and mortality: a systematic review and meta-analysis of cohort studies. Mol. Psychiatr. 25 (7), 1487–1499. https://doi.org/10.1038/s41380-019-0595-x.

Walker 2nd, W.H., Borniger, J.C., Gaudier-Díaz, M.M., et al., 2020. Acute exposure to low-level light at night is sufficient to induce neurological changes and depressive-like behavior. Mol. Psychiatr. 25 (5), 1080–1093. https://doi.org/10.1038/s41380-019-0480-4.

Yang, M., Zhang, Z., Nice, E.C., et al., 2022. Psychological intervention to treat distress: an emerging frontier in cancer prevention and therapy. Biochim. Biophys. Acta Rev. Canc. 1877 (1), 188665. https://doi.org/10.1016/j.bbcan.2021.188665.

Yang, X., Wood, P.A., Amnell, C.M., et al., 2009. Beta-catenin induces beta-TrCP-mediated PER2 degradation altering circadian clock gene expression in intestinal mucosa of ApcMin/+ mice. J. Biochem. 145 (3), 289–297. https://doi.org/10.1093/jb/mvn167.

Ye, Y., Xiang, Y., Ozguc, F.M., et al., 2018. The genomic landscape and pharmacogenomic interactions of clock genes in cancer chronotherapy. Cell Syst 6 (3), 314–328 e2. https://doi.org/10.1016/j.cels.2018.01.012.

Young, K., Singh, G., 2018. Biological mechanisms of cancer-induced depression. Front. Psychiatr. 9, 209. https://doi.org/10.3389/fpsyt.2018.00209.

Yu, S., Li, W., Tang, L., et al., 2022. Depression in breast cancer patients: immunopathogenesis and immunotherapy. Cancer Lett. 536, 215648 https://doi.org/10.1016/j.canlet.2022.215648.

Zeng, Z.L., Lao, H.Y., Yang, J., et al., 2014. Overexpression of the circadian clock gene Bmal1 increases sensitivity to oxaliplatin in colorectal cancer. Clin. Cancer Res. 20 (4), 1042–1052. https://doi.org/10.1158/1078-0432.CCR-13-0171.

Zhou, L., Zhang, C., Yang, X., et al., 2021. Melatonin inhibits lipid accumulation to repress prostate cancer progression by mediating the epigenetic modification of CES1. Clin. Transl. Med. 11 (6), e449. https://doi.org/10.1002/ctm2.449.