



Review

The role of circadian genes in the pathogenesis of colorectal cancer

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ABSTRACT

Colorectal cancer (CRC) is the third most frequent cancer in human beings and is also the major cause of death among the other gastrointestinal cancers. The exact mechanisms of CRC development in most patients remains unclear. So far, several genetically, environmental and epigenetically risk factors have been identified for CRC development. The circadian rhythm is a 24-h rhythm that drives several biologic processes. The circadian system is guided by a central pacemaker which is located in the suprachiasmatic nucleus (SCN) in the hypothalamus. Circadian rhythm is regulated by circadian clock genes, cytokines and hormones like melatonin. Disruptions in biological rhythms are known to be strongly associated with several diseases, including cancer. The role of the different circadian genes has been verified in various cancers, however, the pathways of different circadian genes in the pathogenesis of CRC are less investigated. Identification of the details of the pathways in CRC helps researchers to explore new therapies for the malignancy.

1. Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed malignancy worldwide and counts for about 10% cancer-related death in western countries. The majority of CRCs are not accompanied with hereditary or familial factors (Gao et al., 2017; Siegel et al., 2017). The developed countries' life styles including frequent consumption of red meat, fat, alcohol, and smoking increase the risk of CRC initiation. In

addition, bacterial infection (Eyvazi et al., 2020), heart disease, type 2 diabetes (T2DM), high blood pressure, and obesity are associated with increasing of CRC risk (Hadjipetrou et al., 2017; Obidike et al., 2019). CRC is a heterogeneous disease. The accumulation of several genetic and epigenetic changes in the colon epithelial cells is the main process which drives CRC initiation and progression (Okugawa et al., 2015; Ebrahimi et al., 2020). In adenoma-carcinoma cascade, the inactivation of adenomatous polyposis coli (APC) is the first event which changes the

Abbreviations: AD, Alzheimer's disease; A β , β -amyloid; AF2, Activation function 2; APC, Adenomatous polyposis coli; ARNTL, aryl hydrocarbon receptor nuclear translocator-like; Bmal1, brain and muscle ARNT-like protein 1; BPD, bipolar disorder; CIN, chromosomal instability; CIMP, CpG island methylator phenotype; CK1 δ /e, Casein kinase 1 delta and epsilon; CLK, Clock and Cdc2-like kinase; CLOCk, cycles kaput protein; CRC, Colorectal cancer; CRY1, cryptochrome 1; CRY2, cryptochrome 2; CSNK1E, casein kinase 1-epsilon; DBP, D-box binding protein; Dec1/2, differentiated embryo-chondrocyte expressed genes; DSPD, Delayed sleep phase disorder; FASPD, familial advanced sleep phase disorder; HDAC3, histone deacetylase 3; MSI, microsatellite instability; NCOR1, nuclear receptor co repressor 1; NPAS2, neuronal PAS domain protein 2; PER1, period 1; PER2, period 2; PER3, period 3; PPI, protein phosphatase 1; PPAR γ , peroxisome proliferator-activated receptor gamma; SAD, seasonal affective disorder; SNP, single nucleotide polymorphism; SCN, suprachiasmatic nucleus; T2DM, type 2 diabetes; TIM, Timeless.

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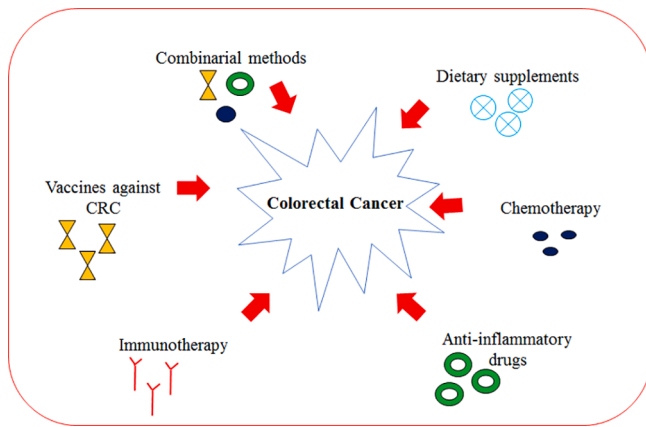


Fig. 1. Different treatment strategies for CRC therapy.

colon normal epithelium to adenoma. Following mutations in KRAS and TP53 genes, progression of adenoma to carcinoma occurs (Maffeis et al., 2019). CRCs are classified into subgroups based on the three principle pathophysiological pathways: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP) (Nguyen and Duong, 2018; Jung et al., 2020).

CIN pathway is responsible for about 80–85% of CRC cases. In this pathway, neoplasia develops from adenomatous polyps due to inactivation of APC gene and finally transforms into adenocarcinomas via additional activating mutations in KRAS gene and inactivation of SMAD4 and TP53 genes (Jung et al., 2020).

MSI happens due to changes in microsatellites following DNA mismatch repair deficiency in MMR genes like MLH1, MSH2, MSH6, and PMS2 (Lynch et al., 2008). CIMP subgroup is described based on CpG island hypermethylation at the promoters of some tumor suppressor genes. MLH1 promoter hyper methylation is common in this type of CRC (Toyota et al., 1999).

The CRC treatment plan composed of a combination of surgery, radiation therapy, chemotherapy and targeted therapy (Fig. 1). The response to surgery in cancers restricted to the wall of the colon is acceptable; however, the metastatic forms are not curable, and the palliative care is suggested to improve life quality and reduce the symptoms. Nowadays, targeted therapy of cancer is highly considered compared with conventional therapies due to its higher efficiency and lower side effects (Razi Soofiyani et al., 2017; RaziSoofiyani et al., 2017; Payandeh et al., 2019).

Circadian rhythms are the basic biological systems in most living creatures which are regulated by circadian clock placed in the suprachiasmatic nucleus in the hypothalamus. The circadian system controls various cellular procedures involved in tumor development like metabolism, DNA damage response, and cell cycle (Evans and Davidson, 2013; Shafi and Knudsen, 2019). Several investigations have demonstrated that interference in circadian rhythms lead to lots of health problems, including metabolic syndrome (Maroufi et al., 2016), cardiovascular dysfunction, immune dysregulation, reproductive problems, sleep disorders fatigue, learning difficulties, cancer progression, and carcinogenesis (Viswanathan et al., 2007; Froy, 2010; Khapre et al., 2010; Sellix and Menaker, 2011; Karantanos et al., 2014). The circadian principal clock pathway genes are circadian locomotor output cycles kaput protein (CLOCK), neuronal PAS domain protein 2 (NPAS2), aryl hydrocarbon receptor nuclear translocator-like (ARNTL), period 1 (PER1), period 2 (PER2), period 3 (PER3), brain and muscle ARNT-like protein 1 (Bmal1), cryptochrome 1 (CRY1), cryptochrome 2 (CRY2), Timeless (TIM), and casein kinase 1-epsilon (CSNK1E).

During the past decades, the association of circadian genes with cancer development has been investigated extensively. For example, a study showed that melatonin, as a circadian rhythms regulator, is associated with cancer susceptibility (Gu et al., 2018). Disruption of

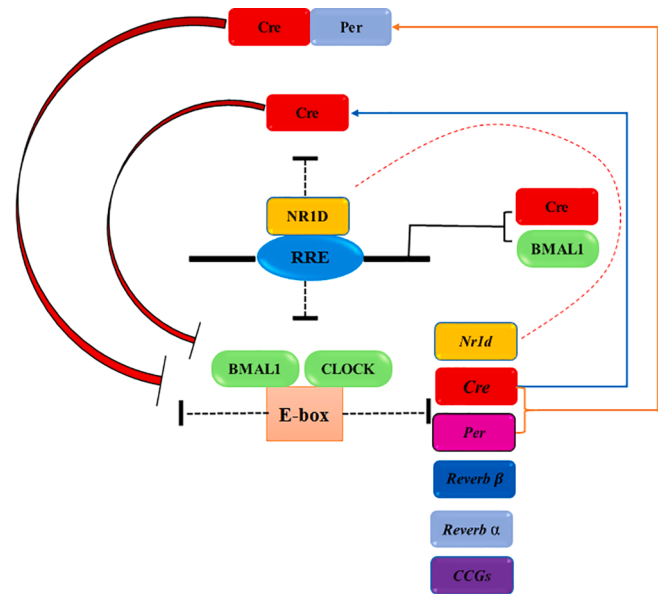


Fig. 2. The transcriptional-translational regulation loop of circadian rhythms. Clock/Bmal1 in the core circadian clock activate genes with E-box elements in their promoters such as clock-controlled genes (CCGs), REV-ERBA transcription factor as well as PER1 and CRY1/2. PER1 and CRY1/2 are involved outside of the core regulatory feedback loop.

circadian rhythm in knock-out mouse and human investigations has been known in a wide range of malignancies, including colorectal, lung, breast, ovarian, and hematologic malignancies in humans (Kettner et al., 2014). Furthermore, it has been shown that changes in CLOCK, PERs, CRYs, and TIMELESS gene expression are frequently associated with related gene methylation and cancer development and progression (Evans and Davidson, 2013). Previous studies indicated the associations of circadian gene expression and clinicopathological features and consequences in CRC. Identification of the details of the pathways in CRC helps researchers to explore new therapies for the malignancy. So, in this review, the association of various circadian genes in CRC development has been reviewed.

2. Circadian genes

Circadian genes are very important and vital group of genes which create an internal time-keeping system in different organisms and affect their behavior. While, exogenous signals like heat and light can affect those genes, most organisms organize their own behavior like mood, cognition, attention (Reppert and Weaver, 2001), metabolism (Green et al., 2008), physiology, such as circulating hormone levels (Lightman, 2016), and body temperature fluctuations into the 24 h solar cycle, using circadian genes. Organisms use circadian genes for adapting to environmental changes by regulating their expression (Choi and Nitabach, 2010; Cui et al., 2018). Circadian genes also affect non-circadian manner of cellular functions (Takahashi, 2017).

The central pacemaker of mammalian circadian clock is located in the suprachiasmatic nucleus (SCN) in the hypothalamus (Hastings et al., 2018). Circadian clocks (rhythm) are controlled by post-transcriptional (Kojima et al., 2011) and post-translational mechanisms, such as phosphorylation which is the major mechanism of post-translational modification processes (Mehra et al., 2009). There is a relation between gene rhythmic transcription and histone modification, transcription binding factor (Fang et al., 2014), chromosome organization (Xu et al., 2016), chromatin conformation (Rijo-Ferreira and Takahashi, 2019), and operation of RNA polymerase II (Pol II) (Koike et al., 2012). A dimer of Bmal1 and Clock is one of the main factors as transcriptional activator for regulating circadian genes (Kurabayashi et al., 2006).

Table 1

The abnormal expression of several circadian genes leads different disorders.

Disorder	Genes
FASPD	Per2, CK1 δ , CK1 ϵ and CRY2
SAD	Npas2
Bipolar disease	clock
BPD	Timeless gene & Bmal1
DSPD	CRY1, Per3, clock and CK1 ϵ
Diurnal preference disorder	Per1, Per2, Per3 and Clock
Hepatic gluconeogenesis	CRY1
Lipid metabolism	PER2
Diabetes, hyperinsulinemia and obesity	Bmal1, Clock, CLK, hCry2, hPer2 and hPer3
Familial forms of breast cancer	hPer1
AD	Bmal1

FASPD: Familial advanced sleep-phase disorder.

SAD: Seasonal affective disorder.

BPD: Borderline personality disorder.

DSPD: Delayed sleep phase disorder.

AD: Alzheimer's disease.

In fact the expression of circadian genes are regulated by D-box binding protein (DBP) (Ripperger and Schibler, 2006), REVERBs/RORs (Ueda et al., 2002), and Clock/Bmal1 (Takahashi, 2017) in the core circadian clock and PER1 and CRY1/2 outside of the core regulatory feedback loop (Lamia et al., 2011). Casein kinase 1 delta and epsilon (CK1 δ/ϵ) are vital protein kinases for regulation of circadian genes in mammals (Fig. 2). CK1 δ/ϵ kinase can phosphorylate and degrade mPer2. The mutation of CK1 δ causes familial advanced sleep phase disorder (FASPD) in humans (Xu et al., 2005). According to Fang et al., the regulation of clock is also done by some of the phosphatases such as protein phosphatase 1 (PP1) (Fang et al., 2007).

Sleep timing and duration can affect the circadian genes. The expression profile of rhythmic genes are different in human blood with sufficient and insufficient sleep (Moller-Levet et al., 2013). According to previous researches, dysregulation of circadian genes and some diseases are associated.

3. The association of circadian genes dysregulation and various diseases such as cancer

The abnormal expression of circadian genes affects different diseases such as sleep disorders, metabolic processes, Alzheimer's, cancer, etc. (Table 1).

The development of seasonal affective disorder (SAD) is created by replacing an amino acid (471 Leu/Ser) in neuronal PAS domain protein 2 (Npas2) (Johansson et al., 2003). A single nucleotide polymorphism (SNP) in the clock gene, in 3' flanking region (3111 T to C), is associated with bipolar disease (Benedetti et al., 2003). Other kinds of SNP have been reported in timeless gene and in Bmal1, associated with bipolar disorder (BPD) (Mansour et al., 2006). In humans, circadian rhythm sleep disorders are created by mutation in circadian clocks. For example, FASPD is associated with missense mutations of CRY2 gene (A260T) (Hirano et al., 2016), CK1 δ gene (T44A) (Xu et al., 2005), and Per2 gene (S662G) (Xu et al., 2007). Delayed sleep phase disorder (DSPD) is another example for circadian rhythm sleep disorders induced by a mutation in specific kind of circadian genes, such as CRY1 (in the 5' splice site of exon 11), Per3, Clock, and CK1 ϵ (Patke et al., 2017). Mutations in Per1, Per 2, Per 3, and Clock result in diurnal preference disorder (Carpen et al., 2006). Wake increasing and reducing rapid and non-rapid eye movement sleep states have been observed in patients with deleted in esophageal cancer (DEC2) gene (He et al., 2009).

Normal circadian physiology can be maintained by a regular daily feeding pattern. The disruption of feeding pattern and daily rhythms are related with metabolic syndrome (Karlsson et al., 2001). Driving transcriptional programs of metabolic pathways is controlled by circadian genes. CRY1 gene suppresses hepatic gluconeogenesis by regulation of

cAMP/CREB signaling pathways (Jang et al., 2016). In humans, the regulation of mitochondrial rate-limiting enzymes and peroxisome proliferator-activated receptor gamma (PPAR γ) by Per 2 control lipid metabolism (Grimaldi et al., 2010). Diabetes, hyperinsulinemia, and obesity can be the results of the mutations of Bmal1, Clock, and Cdc2-like kinase (CLK) and the down-regulation of hCry2, hPer2, and hPer3 (Marcheva et al., 2010; Zhang et al., 2010).

An important factor in Alzheimer's disease (AD) is β -amyloid (A β) peptide. Producing and deposition of A β are associated with AD. Circadian rhythms are changed in AD patients. In these patients, night-time wakefulness and day-time sleep increase (Holth et al., 2019). Therefore, researchers try to find the correlation between AD and circadian genes. Kress et al. tried to determine A β levels by circadian clock. They reported that the loss of central circadian rhythms results in disruption of daily hippocampal interstitial fluid A β oscillations and accelerates amyloid plaque accumulation (Kress et al., 2018). According to another research, in pre-clinical AD, abnormalities in circadian rhythms can be introduced as a biomarker for the disease (Musiek et al., 2018). So, healthy sleep-wake cycle is considered as an interventional factor for preventing AD.

According to oncological studies, there is a relationship between the disruption of circadian genes and increasing of cancer (Fu and Kettner, 2013). These genes have very important roles in DNA repair mechanisms and cellular proliferation, tumorigenesis, and tumor development (Savvidis and Koutsilieris, 2012). For example, BMAL1: CLOCK/NPAS2 dimers regulate several transcriptional factors' expression such as c-Myc which influences the cell cycle progression by regulating the expression of cell cycle-related genes and thus participating in the development of tumors (Soták et al., 2014). Circadian genes also can affect several biological pathways such as apoptosis. It has been shown that Per1 over-expression induces c-Myc and suppresses p21 in response to ionizing radiation. Per1 also blocks the expression of Wee1, CyclinB1, CyclinD1, and CDK1, which leads to a decrease in cancer cell proliferation (Yang et al., 2009). Low expressions of Per1, Per2, and Per3 genes are commonly reported in human cancers (Fu and Kettner, 2013). For example, comparing familial forms of breast cancer and sporadic forms shows that hPer1 gene expression is very low in familial forms. Fu et al. reported that Per2 can directly block the activation of the P53 protein and result in the promotion of tumor development (Fu et al., 2002). Per1 and Per2 have been reported to be associated with the upregulation of Mmp9 and Bax and downregulation of Bcl-2, c-Myc, and p53 in lung, mammary, pancreatic, hepatocellular, and oral carcinoma cell lines (Li, 2019). In another study, the progression of breast cancer has been reported to be correlated with dysregulation of circadian genes, such as CLOCK, PER1, PER2, PER3, CRY2, NPAS2, and RORC (Cadenas et al., 2014). Circadian genes are also involved in tumor immunity. It has been shown that BMAL1 controls the immune system and promotes an anti-inflammatory state. The dysregulation of BMAL1 has been reported in hematologic malignancies such as diffuse large B-cell lymphoma, chronic lymphocytic leukemia, and acute myeloid leukemia. Also, other circadian genes such Per1/2, Cry1/2, Bmal1, Rev-erb α , or Clock dysregulate the immune system, including a reduction in proinflammatory cytokines, cytotoxic receptors, and NK and mast cell activity, and inhibition of B-lymphocyte differentiation (Li, 2019). Furthermore, in shift workers, the disruption of circadian genes at organismal level can increase the risk of cancer (Davis and Mirick, 2006). Therefore, they can be used as a biomarker for early detection of the diseases.

4. Circadian genes and colorectal cancer

The clock genes control the expression of various genes such as cell-cycle regulators, oncogenes, and tumor suppressor genes in the time dependent manner. The clock-controlled genes regulate the timing of cellular basic functions like metabolism, DNA damage repair, and autophagy (Mazzocchi et al., 2012). Also, the circadian system regulates the cell growth and death by affecting transcription/post-

translational modification of critical proteins for DNA replication (Lee, 2006). Disrupted circadian clock may interrupt the cell growth. Circadian disruptions have been known as a risk factor for cancer and enhanced frequency of CRC in night shift workers (Schernhammer et al., 2003). The role of dysregulation of circadian clock in the development and progression of CRC has been indicated by experimental data. The circadian clock role was assessed during transformation in primary colorectal cancer mouse model. This model has shown that the expression of Per2 protein noticeably decreases in the intestinal epithelium of *Apc^{Min/+}* mice, and its circadian rhythm is lost (Yang and Stockwell, 2008). Mazzocchi et al. approved that an alternation in main clock genes such as *Per1*, *Per2*, *Rev-Erb α* , and *Bmal1* and clock-controlled genes such as *Wee1*, *c-Myc*, and *p21* was analyzed in cancerous tissues compared with normal tissues during a day. The rhythmic expression of *Per1*, *Per2*, *Rev-Erb α* , and *Dbp* was downregulated in CRC tissues. While, the *Wee1*, *c-Myc*, and *p21* expression is not rhythmic in tumors and normal tissues (Mazzocchi et al., 2014).

In mice, the mutations of circadian genes modify genes' expression involved in cell-cycle regulation and tumor suppression including *c-Myc*, *Cyclin D1*, *Cyclin A*, *Mdm-2*, *GADD45A*, and DNA damage response. Furthermore, it has been shown that the mutations deregulate and accelerate intestinal polyp formation in *ApcMin/+* mice which increase the neoplastic growth.

4.1. CLOCK gene

At the molecular level, the circadian rhythms are regulated by a set of positive and negative transcription-translation autoregulatory feedback loops. The transcriptional-translational autoregulatory network results in the production of circadian rhythms by oscillating the expression of clock genes every 24 h (Li, 2019). Evidence determines that about 20% of mammalian genes are recognized as clock-controlled. More recently, it has been revealed that circadian clock at the cellular level plays a role in the production and regulation of many processes such as cell cycle, DNA synthesis, and DNA repair (Karantanos et al., 2014; Mehdiadeh et al., 2017a; Fathi et al., 2019). So far, 12 genes including *Per1*, *Per2*, *Per3*, Aryl hydrocarbon nuclear translocator-like receptor (ARNTL or BMAL1), CRY1CRY2, CLOCK, Timeless (TIMN-PAS2), retinoic acid-related orphan nuclear receptor (ROR), nuclear receptor subfamily 1 group D member 1 and 2 (NR1D1 and NR1D2) and casein kinase I epsilon (CSNK1E), REV-ERBs, and differentiated embryochondrocyte expressed genes (Dec) 1/2 have been recognized as core circadian clock genes (Angelousi et al., 2019). Mechanically, BMAL1 in the cytoplasm produces BMAL1: CLOCK or BMAL1: NPAS2 dimers by interacting with CLOCK or NPAS2 proteins through the PAS domain; these dimers increase the expression of clock genes *Per1*, 2, and 3 and *Cry1*, 2 by entering the nucleus and produces a positive feedback loop. When *Per* and *Cry* reach a certain concentration, they act as a suppressor for BMAL1: CLOCK or BMAL1: NPAS2 dimers by creating heteromultimeric complexes and entering the core and reduce its expression level by forming a negative feedback loop (Mohawk et al., 2012; Li, 2019). In the mentioned process, CK1 ϵ/δ and adenosine monophosphate-activated protein kinase (AMPK) regulate the period of the circadian rhythm by controlling the degradation of *Per* and *Cry* proteins. In addition to the mechanisms, *Bmal1*/CLOCK heterodimer increases the expression level of REV-ERBs and RORs genes by translocation to the nucleus and binding to E-boxes in the promoter of these genes. Therefore, CLOCK gene plays an important role in circadian rhythm regulation, and its dysfunction may be involved in CRC pathogenesis. Alhopuro et al. indicated that the CLOCK gene is a MSI target gene in microsatellite unstable colorectal carcinomas. The mutations in CLOCK gene occur in more than half of MSI CRCs. The mutations in CLOCK gene change the cellular response to DNA damage which induces carcinogenesis in the cells. It has been shown that CLOCK gene acts as a tumor suppressor gene and reduces the time of arrest in G₂-M phase in response to ionizing radiation in CLOCK expressing cells (Alhopuro

et al., 2010). Another study showed that the 311 T > C polymorphism in the CLOCK gene is correlated with the high risk of colorectal cancer development in patients (Karantanos et al., 2013).

4.2. PER

The PER gene family consists of three members, including *PER1*, *PER2*, and *PER3* which are the core members of the clock genes. Much evidence shows that in many cancers, the expressions of PER genes decrease during the development of human tumors such as pancreatic cancer, HNSCC, NSCLC, hepatocellular carcinoma, chronic lymphocytic leukemia, melanoma, and colorectal cancer (Mehdiadeh et al., 2017b; Deng and Yang, 2019; Fathi et al., 2020). It has been shown that in patients with colorectal cancer, the decreased *Per1* gene expression is associated with liver cancer metastasis. *PER1* upregulation in human cancer cell lines causes colony formation/expansion reduction and induces the expression of target genes such as *c-MYC* and *p21*. *PER1/2* are involved in ATM-Chk1/Chk2 which are the components of the checkpoint machinery in response to DNA damage and regulated β -catenin (Yang et al., 2009; Panahi et al., 2018). *PER1/2* acts as an oncogene and affects cellular proliferation in CRC. Consecutively, intestinal carcinogenesis might influence clock function due to the destabilization of *PER2* dependent to β -catenin upregulation. On the other hand, in another study, *Per2* gene increased in these patients and rendered better outcomes (Oshima et al., 2011). Studies on the expression of the *Per3* gene revealed that the expression of this gene is dramatically degraded in colorectal cancer. Hong et al., reported that an increase in the expression of *Per3* is associated with increase in the expression of *p53*, *cyclin B1*, *CDC2*, *Bid*, and cleaved-caspases 3/8 and decrease in the expression of *Bcl-2*, resulting in apoptosis, inhibiting cell cycle in G₂/M phase, inhibiting invasion, and cell metastasis in colorectal cancer. In addition, their results implied that miR-103, which is highly expressed in colorectal cancer, may reduce *PER3* expression by targeting this gene and plays a role in the pathogenesis of colorectal cancer by alternating *Per3* expression (Hong et al., 2014). Momma et al. reported that the expression level of *Per1*, *Per2* in human colorectal adenoma is not detectable; however, it is detectable in colorectal carcinoma. The results explained that the expression level of these genes is directly correlated to tumor size and invasion (Momma et al., 2017).

The findings suggest that *Per* family genes play a fundamental role in the progression of colorectal cancer. Nevertheless, there is a necessity to conduct more comprehensive studies to clarify the molecular mechanism of these genes in colorectal cancer.

4.3. Bmal1

Bmal1 is one of the most important clock genes that plays a crucial role in the normal life of organisms. This gene plays a fundamental role in circadian rhythm, heart diseases, aging, immune system diseases, and cancer (Wang et al., 2019a). The gene also plays a critical role in controlling tumor cells apoptosis, cell-cycle promotion, and DNA damage response (Modak and Chai, 2009). Recent studies explain that at the cellular level, *Bmal1* and CLOCK form a dimer that directly influences many genes involved in cell cycle control, apoptosis, cell proliferation, and DNA damage in addition to its role in regulating circadian rhythm. For example, this dimer influences the expression level of *WEE1* and *Cyclin-D1*, the two effective genes in the cell cycle; therefore, defects in the regulation of circadian rhythm bring about a disorder in the cell cycle that is effective in carcinogenesis (Huisman et al., 2016). Several researchers in this field have considered the role of *Bmal1* in colorectal cancer. For example, Zeng and et al. reported that *Bmal1* overexpression reduces the growth and proliferation of colorectal cancer cells and increases the sensitivity of these cells to oxaliplatin. Also, increasing the expression of this gene through the ATM (ATM Serine/Threonine Kinase) signaling pathway inhibits the cell cycle in the G₂ – M phase. *Bmal1* expression levels in patients with colorectal cancer were high;

these patients have longer overall survival than patients with low Bmal1 expression (Zeng et al., 2014). Oshima et al. also reported that an increase in the levels of Bmal1 expression was associated with the possibility of liver metastasis in patients with colorectal cancer and can be a useful predictor of liver cancer metastasis (Oshima et al., 2011). Accordingly, Bmal1 can be more assessed as a potential therapeutic target as well as a diagnostic marker in CRC.

4.4. REV-ERB α

REV-ERB α is a nuclear receptor encoded by NR1D1 gene and belongs to nuclear receptor subfamily 1 group D. REV-ERB α is the main component of circadian clock which acts as a transcriptional repressor. In 1989, REV-ERB α was introduced and nominated regarding its genomic locus on the reverse DNA strand of v-erbA oncogene (Miyajima et al., 1989). About five years later, REV-ERB β , another member of NR1D subfamily, was recognized. As activation function 2 (AF2) is absent in ligand binding domain, REV-ERB α/β is not able to induce gene transcription. On the other hand, REV-ERB α/β acts as transcriptional repressors and prevents gene transcription through recruiting corepressors nuclear receptor co repressor 1 (NCOR1) and histone deacetylase 3 (HDAC3) (Everett and Lazar, 2014; Kojetin and Burris, 2014). REV-ERB α has a more significant effect in circadian rhythms than REV-ERB β . It has been shown that circadian rhythms is interrupted in REV-ERB α -deficient mice. Considering the modulatory role of REV-ERB α on circadian rhythm and metabolic genes, REV-ERB α is primarily noticed as a therapeutic target for sleep disorders and metabolic syndrome. Nowadays, investigations indicate the role of REV-ERB α in the pathogenesis of inflammatory diseases and cancers (Wang et al., 2020). REV-ERB α is involved in gastric cancer development and progression. In gastric cancer, the level of REV-ERB α expression is correlated with clinicopathological features like cancer cells' differentiation, tumor TMN stage, and lymph node metastasis. The outcome of patients with low expression of REV-ERB α is worse than patients with high expression of REV-ERB α (Wang et al., 2018). Therefore, REV-ERB α might be considered as a prognosis factor for gastric cancer. Sulli et al. indicated that activating REV-ERB α might be considered as a therapeutic target in cancer treatment (Sulli et al., 2018). The advantage of targeting REV-ERB α is an apoptosis induction in cancer cell and not in normal cells. Functionally, REV-ERB α inhibits *de novo* lipid biosynthesis via the suppression of fatty acid synthase and stearyl-CoA desaturase, leading to oleic acid deficiency. The circadian system controls the cell cycle through the regulation of p53, p21, cyclin D/B, c-Myc, Wee1, and Mdm2. REV-ERB α and ROR α regulate the BMAL1 expression. BMAL1 deficiency leads to an imbalance in REV-ERB α and ROR α expression. REV-ERB α positively regulates p21 promoter which inhibits the cell cycle progression (Karantanos et al., 2014). Disruption in REV-ERB α expression might lead to imbalance in p21 expression (Soták et al., 2013). Moreover, the activation of REV-ERB α suppresses autophagy. Therefore, REV-ERB α controls cancer cells' development through the repression of cell proliferation, *de novo* lipid synthesis and autophagy, and apoptosis induction in tumor cells (Zhang et al., 2019). Similarly, Soták et al., used a chemically induced CRC model and found that the circadian system of REV-ERB α , PER1, and PER2 is considerably reduced in CRC tissues, whereas the rhythmicity of BMAL1 is entirely eliminated not only in the CRC tissues but also in the adjacent healthy colon tissues as well in tumor bearing mice. These effects clearly support the fact that the deregulation of the circadian rhythmicity is intensely associated with the development of CRC (Soták et al., 2013).

4.5. Timeless

Timeless (TIM) is an evolutionarily conserved circadian system gene which regulates many cellular functions like DNA damage recognition/repair, cell growth, and metabolism. TIM interacts with DNA replication system components to control DNA replication (Agostino et al., 2009).

Table 2

The various genes which are dysregulated following TIM silencing. (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3924353/pdf/1471-2407-13-498.pdf>).

Table 2 Genes symbol	Gene full name	Expression change	Function
<i>BMP7</i>	Bone morphogenetic protein-7	↑	regulates cellular differentiation, proliferation and apoptosis (Shen et al., 2018).
<i>CRKL</i>	Crk-like protein	↓	oncprotein which contributes cancer cell proliferation, chemoresistance and promoting tumor cell invasion via a Src-dependent pathway (Song et al., 2019).
<i>CXCL1</i>	chemokine (C-X-C motif) ligand 1	↑	as a potential tumor-suppressor gene
<i>DTL</i>	Denticless E3 Ubiquitin Protein Ligase Homolog	↓	May be involved in cancer development and promotes tumor progression through PDCD4 ubiquitin-dependent degradation (Cui et al., 2019).
<i>EDN1</i>	(Endothelin 1)	↑	Involved in tumorigenesis (Kim et al., 2005).
<i>EMP1</i>	Epithelial Membrane Protein 1	↑	promotes cancer cell growth, invasion, and EMT via MAPK signaling pathway (Liu et al., 2020)
<i>EPAS1</i>	Endothelial PAS domain-containing protein 1	↑	EPAS1 is the main factor of cell adaptation to hypoxia, regulating the genes expression which involved in tumor angiogenesis, glucose metabolism and resistance to oxidative stress (Mohammed et al., 2011).
<i>EPHB6</i>	Ephrin type-B receptor 6	↓	Plays a role in tumor invasion and metastasis (Toosi et al., 2018).
<i>GOS2</i>	G0/G1 Switch 2	↑	GDF15 may induce the cancer cells proliferation through CyclinD1/ CyclinE1 and of p21 down-regulation (Li et al., 2018).
<i>GDF15</i>	Growth Differentiation Factor 15	↑	
<i>IL8</i>	Interleukin 8	↑	IL-8 signaling stimulates angiogenesis, induces cancer cells proliferation, survival migration (Vaughan and Wilson, 2008).
<i>KDM3A</i>	Lysine Demethylase 3A	↓	KDM3A promotes proliferation, survival and migration in cancer cells (Yoo et al., 2020).
<i>KRT17</i>	Keratin 17	↑	KRT17 induces proliferation and invasion of cancer cells via Wnt signaling pathway (Wang et al., 2019b).
<i>LIFR</i>	LIF Receptor Subunit Alpha	↑	LIFR induces cancer cell proliferation, angiogenesis and metastasis (Wu et al., 2018).
<i>PKIA</i>	CAMP-Dependent Protein Kinase Inhibitor Alpha	↓	PKIA is involved in the control of a wide variety of cellular processes from metabolism to ion channel activation, cell growth and differentiation, gene expression and apoptosis. Importantly, since it has been implicated in the

(continued on next page)

Table 2 (continued)

Table 2 Genes symbol	Gene full name	Expression change	Function
			initiation and progression of many tumors, is involved in the control of a wide variety of cellular processes from metabolism to ion channel activation, cell growth and differentiation, gene expression and apoptosis. Importantly, since it has been implicated in the initiation and progression of many tumors.
PODXL	Podocalyxin Like	↓	Plays a role in cancer cells proliferation, migration, invasion and EMT(Xu et al., 2018).
PTGFR	Prostaglandin F Receptor	↑	PMEPA1 modulates TGF signaling pathway, upregulates E-cadherin protein level- and decreases nuclear localization of catenin, therefore enhances the cell plasticity and growth(Jiménez-Segovia et al., 2019).
RGS20	Regulator Of G Protein Signaling 20	↓	
RHOB	Ras Homolog Family Member B	↑	RhoB can suppress cell growth, survival and metastasis(Huang and Prendergast, 2006)
SOD2	Superoxide dismutase 2	↑	SOD2 plays a role as a O ₂ • ⁻ scavenger and it is known as a tumor suppressor(Kim et al., 2017).
TFPI2	Tissue factor pathway inhibitor 2	↓	TFPI-2 is an plasmin inhibitor and inhibits tumor invasiveness and metastases(Lavergne et al., 2013).
TNFRSF4	TNF Receptor Superfamily Member 4	↓	NFRSF4 activates NF-κB pathway. PI3K/PKB and NFAT pathway are the downstream of TNFRSF4. The main role of TNFRSF4 is to stimulate proliferation/survival and cytokine production of T lymphocytes by activating the mentioned pathways(Gu et al., 2020).

The exact role of TIM in mammals is not fully understood. According to previous studies, TIM is aberrantly expressed in various malignancies, and the expression of TIM is associated with tumor aggressiveness (Bianco et al., 2019; Zhou et al., 2020). The expression analysis of the TIM genes in gliomas and nonglioma tissues obtained at the same time showed that the expression of TIM genes in high-grade glioma tumors was remarkably higher than that of the low-grade gliomas, reinforcing the hypothesis that the disruption of timeless expression may lead to loss of the control of the normal circadian rhythm. Wang et al., demonstrated that TIM expression is associated with glioma progression. Also, the methylation of TIM gene promoter decreased in high stages of glioma (Wang and Chen, 2018). Silencing of TIM attenuated the cell proliferation rate of breast cancer cells and increased the cytotoxic effect of chemotherapy agent via activating the DNA response pathway in the cells (Yang et al., 2010). The expression of various genes are dysregulated following TIM silencing. These genes are provided in Table 2. It

seems that targeting TIM is a promising approach for cancer treatment to enhance the effectiveness of cytotoxicity of chemotherapeutic agents through activating DNA repair system in cancer cells (Kemp et al., 2010).

Wang et al., reported that the TIM expression level was upregulated in colorectal cancer (Wang et al., 2016). TIM expression in colorectal cancer tissues is correlated with TNM stage, lymph node involvement, and MSI (microsatellite instability) (Yang et al., 2010). About 15% of diagnosed CRCs own DNA mismatch repair defects which cause MSI and generate various mutations. The overexpression of TIM in MSI-H and MSI-L in CRC patients may be associated with the tumorigenesis process of CRC and affect appropriate response to adjuvant chemotherapy (Mazzocoli et al., 2011).

5. Conclusion

The circadian system plays a significant role in gastrointestinal physiology, and changes in molecular circadian clock may be involved in colorectal cancer tumorigenesis. The circadian genes/proteins are frequently changed in colorectal malignancies and affect the phenotype of colon neoplastic cells, progression of cancer, survival of patients, and chemotherapy responses. To further understand the mechanisms regulated by the circadian genes and alternation in the genes involved in colorectal carcinogenesis, additional progresses are needed for the identification of the pathophysiological mechanisms of CRC. Therefore, further studies should be performed to shed the light on the effect of circadian genes' alternation in the pathogenesis and progress of CRC. Advances in knowledge suggest promising therapeutic strategies for patients with advanced colorectal cancers.

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.

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References

- Agostino, P.V., Harrington, M.E., Ralph, M.R., Golombek, D.A., 2009. Casein Kinase-1-Epsilon (CK1ε) and Circadian Photoc Responses in Hamsters. *Chronobiol. Int.* 26 (1), 126–133.
- Alhopuro, P., Björklund, M., Sammalkorpi, H., Turunen, M., Tuupainen, S., Biström, M., Niittymäki, I., Lehtonen, H.J., Kivioja, T., Launonen, V., Saharinen, J., Nousiainen, K., Hautaniemi, S., Nuorva, K., Mecklin, J.-P., Järvinen, H., Orntoft, T., Arango, D., Lehtonen, R., Karhu, A., Taipale, J., Aaltonen, L.A., 2010. Mutations in the circadian gene CLOCK in colorectal cancer. *Mol. Cancer Res.* 8 (7), 952–960.
- Angelousi, A., Kassi, E., Ansari-Nasiri, N., Randevara, H., Kaltsas, G. and Chrousos, G., 2019. Clock genes and cancer development in particular in endocrine tissues. *Endocrine-related cancer* 26, R305-R317.
- Benedetti, F., Serretti, A., Colombo, C., Barbini, B., Lorenzi, C., Campori, E., Smeraldi, E., 2003. Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 123B (1), 23–26.
- Bianco, J.N., Bergoglio, V., Lin, Y.-L., Pillaire, M.-J., Schmitz, A.-L., Gilhodes, J., Lusque, A., Mazières, J., Lacroix-Triki, M., Roumeliotis, T.I., Choudhary, J., Moreaux, J., Hoffmann, J.-S., Tourrière, H., Pasero, P., 2019. Overexpression of Claspin and Timeless protects cancer cells from replication stress in a checkpoint-independent manner. *Nat. Commun.* 10 (1) <https://doi.org/10.1038/s41467-019-08886-8>.

- Cadenas, C., van de Sandt, L., Edlund, K., Lohr, M., Hellwig, B., Marchan, R., Schmidt, M., Rahnenführer, J., Oster, H., Hengstler, J.G., 2014. Loss of circadian clock gene expression is associated with tumor progression in breast cancer. *Cell Cycle* 13 (20), 3282–3291.
- Carpen, J.D., von Schantz, M., Smits, M., Skene, D.J., Archer, S.N., 2006. A silent polymorphism in the PER1 gene associates with extreme diurnal preference in humans. *J. Hum. Genet.* 51 (12), 1122–1125.
- Choi, C., Nitabach, M.N., 2010. Circadian biology: environmental regulation of a multi-oscillator network. *Curr. Biol.* 20 (7), R322–R324.
- Cui, H., Wang, Q., Lei, Z., Feng, M., Zhao, Z., Wang, Y., Wei, G., 2019. DTL promotes cancer progression by PDCD4 ubiquitin-dependent degradation. *J. Exp. Clin. Cancer Res.* 38, 350.
- Cui, P., Zhong, T., Wang, Z., Wang, T., Zhao, H., Liu, C., Lu, H., 2018. Identification of human circadian genes based on time course gene expression profiles by using a deep learning method. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 1864 (6), 2274–2283.
- Davis, S., Mirick, D.K., 2006. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. *Cancer Causes Control* 17 (4), 539–545.
- Deng, F., Yang, K., 2019. Current status of research on the period family of clock genes in the occurrence and development of cancer. *Journal of Cancer* 10 (5), 1117–1123.
- Ebrahimi, V., Soleimani, A., Ebrahimi, T., Azargun, R., Yazdani, P., Eyvazi, S., Tarhriz, V., 2020. Epigenetic modifications in gastric cancer: Focus on DNA methylation. *Gene* 742, 144577. <https://doi.org/10.1016/j.gene.2020.144577>.
- Evans, J.A., Davidson, A.J., 2013. Health consequences of circadian disruption in humans and animal models, Progress in molecular biology and translational science. Elsevier 283–323.
- Everett, L.J., Lazar, M.A., 2014. Nuclear receptor Rev-erb α : up, down, and all around. *Trends Endocrinol. Metab.* 25 (11), 586–592.
- Eyvazi, S., Vostakolaei, M.A., Dilmaghani, A., Borumandi, O., Hejazi, M.S., Kahroba, H., Tarhriz, V., 2020. The oncogenic roles of bacterial infections in development of cancer. *Microb. Pathog.* 141, 104019. <https://doi.org/10.1016/j.micpath.2020.104019>.
- Fang, B., Everett, L.J., Jager, J., Briggs, E., Armour, S.M., Feng, D., Roy, A., Gerhart-Hines, Z., Sun, Z., Lazar, M.A., 2014. Circadian enhancers coordinate multiple phases of rhythmic gene transcription in vivo. *Cell* 159, 1140–1152.
- Fang, Y., Sathyanarayanan, S., Sehgal, A., 2007. Post-translational regulation of the *Drosophila* circadian clock requires protein phosphatase 1 (PP1). *Genes Dev.* 21 (12), 1506–1518.
- Fathi, E., Sanaat, Z., Farahzadi, R., 2019. Mesenchymal stem cells in acute myeloid leukemia: a focus on mechanisms involved and therapeutic concepts. *Blood research* 54 (3), 165–174.
- Fathi, E., Valipour, B., Sanaat, Z., Nozad Charoudeh, H., Farahzadi, R., 2020. Interleukin-6, -8, and TGF- β Secreted from Mesenchymal Stem Cells Show Functional Role in Reduction of Telomerase Activity of Leukemia Cell Via Wnt5a/ β -Catenin and P53 Pathways. *Advanced Pharmaceutical Bulletin* 10 (2), 307–314.
- Froy, O., 2010. Metabolism and circadian rhythms—implications for obesity. *Endocr. Rev.* 31, 1–24.
- Fu, L., Kettner, N.M., 2013. The circadian clock in cancer development and therapy, Progress in molecular biology and translational science. Elsevier 221–282.
- Fu, L., Pelicano, H., Liu, J., Huang, P., Lee, C.C., 2002. The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response in vivo. *Cell* 111 (1), 41–50.
- Gao, R., Gao, Z., Huang, L., Qin, H., 2017. Gut microbiota and colorectal cancer. *Eur. J. Clin. Microbiol. Infect. Dis.* 36 (5), 757–769.
- Green, C.B., Takahashi, J.S., Bass, J., 2008. The meter of metabolism. *Cell* 134 (5), 728–742.
- Grimaldi, B., Bellet, M.M., Katada, S., Astarita, G., Hirayama, J., Amin, R.H., Granneman, J.G., Piomelli, D., Leff, T., Sassone-Corsi, P., 2010. PER2 controls lipid metabolism by direct regulation of PPAR γ . *Cell Metab.* 12 (5), 509–520.
- Gu, D., Li, S., Ben, S., Du, M., Chu, H., Zhang, Z., Wang, M., Zhang, Z.-F., Chen, J., 2018. Circadian clock pathway genes associated with colorectal cancer risk and prognosis. *Arch. Toxicol.* 92 (8), 2681–2689.
- Gu, S., Zi, J., Han, Q., Song, C., Ge, Z., 2020. Elevated TNFRSF4 gene expression is a predictor of poor prognosis in non-M3 acute myeloid leukemia. *Cancer Cell International* 20, 1–13.
- Hadjipetrou, A., Anyfantakis, D., Galanakis, C.G., Kastanakis, M., Kastanakis, S., 2017. Colorectal cancer, screening and primary care: a mini literature review. *World J. Gastroenterol.* 23 (33), 6049–6058.
- Hastings, M.H., Maywood, E.S., Brancaccio, M., 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. *Nat. Rev. Neurosci.* 19 (8), 453–469.
- He, Y., Jones, C.R., Fujiki, N., Xu, Y., Guo, B., Holder, J.L., Rossner, M.J., Nishino, S., Fu, Y.-H., 2009. The transcriptional repressor DEC2 regulates sleep length in mammals. *Science* 325 (5942), 866–870.
- Hirano, A., Shi, G., Jones, C.R., Lipzen, A., Pennacchio, L.A., Xu, Y., Hallows, W.C., McMahon, T., Yamazaki, M. and Ptáček, L.J., 2016. A Cryptochrome 2 mutation yields advanced sleep phase in humans. *Elife* 5, e16695.
- Holth, J.K., Fritsch, S.K., Wang, C., Pedersen, N.P., Cirrito, J.R., Mahan, T.E., Finn, M.B., Manis, M., Geerling, J.C., Fuller, P.M., Lucey, B.P., Holtzman, D.M., 2019. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. *Science* 363 (6429), 880–884.
- Hong, Z., Feng, Z., Sai, Z., Tao, S.u., 2014. PER3, a novel target of miR-103, plays a suppressive role in colorectal cancer in vitro. *BMB reports* 47 (9), 500–505.
- Huang, M., Prendergast, G., 2006. RhoB in cancer suppression. *Histology and histopathology*.
- Huisman, S.A., Ahmadi, A.R., IJzermans, J.N.M., Verhoef, C., van der Horst, G.T.J., de Bruin, R.W.F., 2016. Disruption of clock gene expression in human colorectal liver metastases. *Tumor Biology* 37 (10), 13973–13981.
- Jang, H., Lee, G.Y., Selby, C.P., Lee, G., Jeon, Y.G., Lee, J.H., Cheng, K.K.Y., Titchenell, P., Birnbaum, M.J., Xu, A., Sancar, A., Kim, J.B., 2016. SREBP1c-CRY1 signalling represses hepatic glucose production by promoting FOXO1 degradation during refeeding. *Nat. Commun.* 7 (1) <https://doi.org/10.1038/ncomms12180>.
- Jiménez-Segovia, A., Mota, A., Rojo-Sebastián, A., Barrocal, B., Rynne-Vidal, A., García-Bermejo, M.-L., Gómez-Bris, R., Hawinkels, L.J.A.C., Sandoval, P., García-Escudero, R., López-Cabrera, M., Moreno-Bueno, G., Fresno, M., Stamatakis, K., 2019. Prostaglandin F $_{2\alpha}$ -induced Prostate Transmembrane Protein, Androgen Induced 1 mediates ovarian cancer progression increasing epithelial plasticity. *Neoplasia* 21 (11), 1073–1084.
- Johansson, C., Willeit, M., Smedh, C., Ekholm, J., Paunio, T., Kieseppä, T., Lichtermann, D., Pruschak-Rieder, N., Neumeister, A., Nilsson, L.-G., Kasper, S., Peltonen, L., Adolfsson, R., Schalling, M., Partonen, T., 2003. Circadian clock-related polymorphisms in seasonal affective disorder and their relevance to diurnal preference. *Neuropsychopharmacology* 28 (4), 734–739.
- Jung, G., Hernández-Ilán, E., Moreira, L., Balaguer, F., Goel, A., 2020. Epigenetics of colorectal cancer: biomarker and therapeutic potential. *Nat. Rev. Gastroenterol. Hepatol.* 17 (2), 111–130.
- Karantanos, T., Theodoropoulos, G., Gazouli, M., Vaiopoulou, A., Karantanou, C., Stravopodis, D.J., Bramis, K., Lymperi, M., Pektasidis, D., 2013. Association of the clock genes polymorphisms with colorectal cancer susceptibility. *J. Surg. Oncol.* 108 (8), 563–567.
- Karantanos, T., Theodoropoulos, G., Pektasides, D., Gazouli, M., 2014. Clock genes: their role in colorectal cancer. *World Journal of Gastroenterology: WJG* 20, 1986.
- Karlsson, B., Knutsson, A., Lindahl, B., 2001. Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27 485 people. *Occup. Environ. Med.* 58, 747–752.
- Kemp, M.G., Akan, S., Yilmaz, S., Grillo, M., Smith-Roe, S.L., Kang, T.-H., Cordeiro-Stone, M., Kaufmann, W.K., Abraham, R.T., Sancar, A., Ünsal-Kaçmaz, K., 2010. Tipin-replication protein A interaction mediates Chk1 phosphorylation by ATR in response to genotoxic stress. *J. Biol. Chem.* 285 (22), 16562–16571.
- Kettner, N.M., Katchy, C.A., Fu, L., 2014. Circadian gene variants in cancer. *Ann. Med.* 46 (4), 208–220.
- Khapre, R.V., Samsa, W.E., Kondratov, R.V., 2010. Circadian regulation of cell cycle: Molecular connections between aging and the circadian clock. *Ann. Med.* 42 (6), 404–415.
- Kim, T.H., Xiong, H., Zhang, Z., Ren, B., 2005. β -Catenin activates the growth factor endothelin-1 in colon cancer cells. *Oncogene* 24 (4), 597–604.
- Kim, Y., Gupta Vallur, P., Phaëton, R., Mythreye, K., Hempel, N., 2017. Insights into the Dichotomous Regulation of SOD2 in Cancer. *Antioxidants* 6 (4), 86. <https://doi.org/10.3390/antiox6040086>.
- Koike, N., Yoo, S.-H., Huang, H.-C., Kumar, V., Lee, C., Kim, T.-K., Takahashi, J.S., 2012. Transcriptional architecture and chromatin landscape of the core circadian clock in mammals. *Science* 338 (6105), 349–354.
- Kojet, D.J., Burris, T.P., 2014. REV-ERB and ROR nuclear receptors as drug targets. *Nat. Rev. Drug Discovery* 13 (3), 197–216.
- Kojima, S., Shingle, D.L., Green, C.B., 2011. Post-transcriptional control of circadian rhythms. *J. Cell Sci.* 124, 311–320.
- Kress, G.J., Liao, F., Dimitry, J., Cedeno, M.R., FitzGerald, G.A., Holtzman, D.M., Musiek, E.S., 2018. Regulation of amyloid- β dynamics and pathology by the circadian clock. *J. Exp. Med.* 215, 1059–1068.
- Kurabayashi, N., Hirota, T., Harada, Y., Sakai, M., Fukada, Y., 2006. Phosphorylation of mCRY2 at Ser557 in the hypothalamic suprachiasmatic nucleus of the mouse. *Chronobiol. Int.* 23 (1–2), 129–134.
- Lamia, K.A., Papp, S.J., Yu, R.T., Barish, G.D., Uhlenhaut, N.H., Jonker, J.W., Downes, M., Evans, R.M., 2011. Cryptochromes mediate rhythmic repression of the glucocorticoid receptor. *Nature* 480 (7378), 552–556.
- Laverne, M., Jourdan, M.-L., Blechet, C., Guyetant, S., Le Pape, A., Heuze-Vourc'h, N., Courty, Y., Lerondel, S., Sobilo, J. and Iochmann, S., 2013. Beneficial role of overexpression of TFPI-2 on tumour progression in human small cell lung cancer. *FEBS open bio* 3, 291–301.
- Lee, C.C., 2006. Tumor suppression by the mammalian Period genes. *Cancer Causes Control* 17 (4), 525–530.
- Li, H.-X., 2019. The role of circadian clock genes in tumors. *OncoTargets and therapy* 12, 3645.
- Li, S., Ma, Y.-M., Zheng, P.-S., Zhang, P., 2018. GDF15 promotes the proliferation of cervical cancer cells by phosphorylating AKT1 and Erk1/2 through the receptor ErbB2. *J. Exp. Clin. Cancer Res.* 37, 80.
- Lightman, S., 2016. Rhythms within rhythms: the importance of oscillations for glucocorticoid hormones. A time for metabolism and hormones. Springer, Cham, pp. 87–99.
- Liu, Y., Ding, Y., Nie, Y., Yang, M., 2020. EMP1 Promotes the Proliferation and Invasion of Ovarian Cancer Cells Through Activating the MAPK Pathway. *OncoTargets and therapy* 13, 2047.
- Lynch, H.T., Lynch, J.F., Lynch, P.M., Attard, T., 2008. Hereditary colorectal cancer syndromes: molecular genetics, genetic counseling, diagnosis and management. *Fam. Cancer* 7 (1), 27–39.
- Maffei, V., Nicole, L. and Cappellesso, R. 2019. RAS, cellular plasticity, and tumor budding in colorectal cancer. *Frontiers in Oncology*. 9.
- Mansour, H.A., Wood, J., Logue, T., Chowdari, K.V., Dayal, M., Kupfer, D.J., Monk, T.H., Devlin, B., Nimgaonkar, V.L., 2006. Association study of eight circadian genes with bipolar I disorder, schizoaffective disorder and schizophrenia. *Genes, brain and behavior* 5 (2), 150–157.

- Marcheva, B., Ramsey, K.M., Buhr, E.D., Kobayashi, Y., Su, H., Ko, C.H., Ivanova, G., Omura, C., Mo, S., Vitaterna, M.H., Lopez, J.P., Philipson, L.H., Bradfield, C.A., Crosby, S.D., JeBailey, L., Wang, X., Takahashi, J.S., Bass, J., 2010. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature* 466 (7306), 627–631.
- Maroufi, N.F., Farzaneh, K., Alibabdel, M., Zarei, L., Cheraghi, O., Soltani, S., Montazersaheb, S., Akbarzadeh, M., Nouri, M., 2016. Taq1B polymorphism of cholesteryl ester transfer protein (CETP) and its effects on the serum lipid levels in metabolic syndrome patients. *Biochem. Genet.* 54 (6), 894–902.
- Mazzoccoli, G., Panza, A., Valvano, M.R., Palumbo, O., Carella, M., Paziienza, V., Biscaglia, G., Tavano, F., Di Sebastiano, P., Andriulli, A., Piepoli, A., 2011. Clock gene expression levels and relationship with clinical and pathological features in colorectal cancer patients. *Chronobiol. Int.* 28 (10), 841–851.
- Mazzoccoli, G., Paziienza, V., Vinciguerra, M., 2012. Clock genes and clock-controlled genes in the regulation of metabolic rhythms. *Chronobiol. Int.* 29 (3), 227–251.
- Mazzoccoli, G., Vinciguerra, M., Papa, G., Piepoli, A., 2014. Circadian clock circuitry in colorectal cancer. *World journal of gastroenterology: WJG* 20, 4197.
- Mehdizadeh, A., Bonyadi, M., Darabi, M., Rahbarghazi, R., Montazersaheb, S., Velaei, K., Shaaker, M., Somi, M.H., 2017a. Common chemotherapeutic agents modulate fatty acid distribution in human hepatocellular carcinoma and colorectal cancer cells. *BioImpacts: BI* 7 (1), 31–39.
- Mehdizadeh, A., Somi, M.H., Darabi, M., Farajnia, S., Akbarzadeh, A., Montazersaheb, S., Yousefi, M., Bonyadi, M., 2017b. Liposome-mediated RNA interference delivery against Erk1 and Erk2 does not equally promote chemosensitivity in human hepatocellular carcinoma cell line HepG2. *Artif. Cells Nanomed. Biotechnol.* 45 (8), 1612–1619.
- Mehra, A., Baker, C.L., Loros, J.J., Dunlap, J.C., 2009. Post-translational modifications in circadian rhythms. *Trends Biochem. Sci.* 34 (10), 483–490.
- Miyajima, N., Horiuchi, R., Shibuya, Y., Fukushima, S.-I., Matsubara, K.-I., Toyoshima, K., Yamamoto, T., 1989. Two *erbA* homologs encoding proteins with different T3 binding capacities are transcribed from opposite DNA strands of the same genetic locus. *Cell* 57 (1), 31–39.
- Modak, C., Chai, J., 2009. Potential of casein kinase I in digestive cancer screening. *World journal of gastrointestinal oncology* 1, 26.
- Mohammed, N., Rodriguez, M., Garcia, V., Garcia, J., Dominguez, G., Pena, C., Herrera, M., Gomez, I., Diaz, R. and Soldevilla, B., 2011. EPAS1 mRNA in plasma from colorectal cancer patients is associated with poor outcome in advanced stages. *Oncology letters* 2, 719–724.
- Mohawk, J.A., Green, C.B., Takahashi, J.S., 2012. Central and peripheral circadian clocks in mammals. *Annu. Rev. Neurosci.* 35 (1), 445–462.
- Moller-Levet, C.S., Archer, S.N., Bucca, G., Laing, E.E., Slak, A., Kabiljo, R., Lo, J.C.Y., Santhi, N., von Schantz, M., Smith, C.P., Dijk, D.-J., 2013. Effects of insufficient sleep on circadian rhythmicity and expression amplitude of the human blood transcriptome. *Proc. Natl. Acad. Sci.* 110 (12), E1132–E1141.
- Momma, T., Okayama, H., Saitou, M., Sugeno, H., Yoshimoto, N., Takebayashi, Y., Ohki, S., Takenoshita, S., 2017. Expression of circadian clock genes in human colorectal adenoma and carcinoma. *Oncology Letters* 14, 5319–5325.
- Musiek, E.S., Bhimasani, M., Zangrilli, M.A., Morris, J.C., Holtzman, D.M., Ju, Y.-E., 2018. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA neurology* 75 (5), 582. <https://doi.org/10.1001/jamaneurol.2017.4719>.
- Nguyen, H.T., Duong, H.Q., 2018. The molecular characteristics of colorectal cancer: Implications for diagnosis and therapy. *Oncology letters* 16, 9–18.
- Obidike, O.J., Rogers, C.R., Caspi, C.E., 2019. Examining Colorectal Cancer Risk Awareness and Food Shelf Use Among Health Center Patients. *Journal of racial and ethnic health disparities* 6 (5), 1021–1029.
- Okugawa, Y., Grady, W.M., Goel, A., 2015. Epigenetic alterations in colorectal cancer: emerging biomarkers. *Gastroenterology* 149 (1204–1225), e12.
- Oshima, T., Takenoshita, S., Akaike, M., Kunisaki, C., Fujii, S., Nozaki, A., Numata, K., Shiozawa, M., Rino, Y., Tanaka, K., 2011. Expression of circadian genes correlates with liver metastasis and outcomes in colorectal cancer. *Oncol. Rep.* 25, 1439–1446.
- Patke, A., Murphy, P.J., Onat, O.E., Krieger, A.C., Özçelik, T., Campbell, S.S., Young, M. W., 2017. Mutation of the human circadian clock gene *CRY1* in familial delayed sleep phase disorder. *Cell* 169 (2), 203–215.e13.
- Payandeh, Z., Yarahmadi, M., Nariman-Saleh-Fam, Z., Tarhriz, V., Islami, M., Aghdam, A.M., Eyvazi, S., 2019. Immune therapy of melanoma: Overview of the therapeutic vaccines. *J. Cell. Physiol.* 234 (9), 14612–14621.
- Razi Soofiyan, S., Lotfipour, F., Kazemi, T., Mohammad Hoseini, A., Shanehbandi, D., Mohammadnejad, L., Baradaran, B., Hallaj-Nezhadi, S., 2017. Combined Interleukin 12 and Granulocyte-macrophage Colony-stimulating Factor Gene Therapy Synergistically Suppresses Tumor Growth in the Murine Fibrosarcoma. *International Journal of Cancer Management* 10 (10). <https://doi.org/10.5812/ijcm.10.5812/ijcm.8462>.
- RaziSoofiyan, S., Kazemi, T., Lotfipour, F., Mohammadnejad, L., Hallaj-Nezhadi, S., Shotorbani, S.S., Hosseini, A.M., Baradaran, B., 2017. The effects of gene therapy with granulocyte-macrophage colony-stimulating factor in the regression of tumor masses in fibrosarcoma mouse model. *J. Cancer Res. Ther.* 13, 362.
- Reppert, S.M., Weaver, D.R., 2001. Molecular analysis of mammalian circadian rhythms. *Annu. Rev. Physiol.* 63, 647–676.
- Rijo-Ferreira, F., Takahashi, J.S., 2019. Genomics of circadian rhythms in health and disease. *Genome Med.* 11, 1–16.
- Ripperger, J.A., Schibler, U., 2006. Rhythmic CLOCK-BMAL1 binding to multiple E-box motifs drives circadian Dbp transcription and chromatin transitions. *Nat. Genet.* 38, 369–374.
- Savvidis, C., Koutsilieris, M., 2012. Circadian rhythm disruption in cancer biology. *Mol. Med.* 18, 1249–1260.
- Schernhammer, E.S., Laden, F., Speizer, F.E., Willett, W.C., Hunter, D.J., Kawachi, I., Fuchs, C.S., Colditz, G.A., 2003. Night-shift work and risk of colorectal cancer in the nurses' health study. *J. Natl. Cancer Inst.* 95, 825–828.
- Sellix, M., Menaker, M., 2011. Circadian clocks in mammalian reproductive physiology: effects of the "other" biological clock on fertility. *Discovery medicine* 11, 273–281.
- Shafi, A.A., Knudsen, K.E., 2019. Cancer and the circadian clock. *Cancer Res.* 79, 3806–3814.
- Shen, W., Pang, H., Xin, B., Duan, L., Liu, L., Zhang, H., 2018. Biological effects of BMP7 on small-cell lung cancer cells and its bone metastasis. *Int. J. Oncol.* 53, 1354–1362.
- Siegel, R.L., Miller, K.D., Fedewa, S.A., Ahnen, D.J., Meester, R.G., Barzi, A. and Jemal, A., 2017. Colorectal cancer statistics, 2017. *CA: a cancer journal for clinicians* 67, 177–193.
- Song, Q., Yi, F., Zhang, Y., Li, D.K.J., Wei, Y., Yu, H., Zhang, Y., 2019. CRKL regulates alternative splicing of cancer-related genes in cervical cancer samples and HeLa cell. *BMC cancer* 19, 499.
- Soták, M., Polidarová, L., Ergang, P., Sumová, A., Pácha, J., 2013. An association between clock genes and clock-controlled cell cycle genes in murine colorectal tumors. *Int. J. Cancer* 132, 1032–1041.
- Soták, M., Sumová, A., Pácha, J., 2014. Cross-talk between the circadian clock and the cell cycle in cancer. *Ann. Med.* 46, 221–232.
- Sulli, G., Rommel, A., Wang, X., Kolar, M.J., Puca, F., Saghatelian, A., Plikus, M.V., Verma, I.M., Panda, S., 2018. Pharmacological activation of REV-ERBs is lethal in cancer and oncogene-induced senescence. *Nature* 553, 351–355.
- Takahashi, J.S., 2017. Transcriptional architecture of the mammalian circadian clock. *Nat. Rev. Genet.* 18, 164.
- Toosi, B.M., El Zawily, A., Truitt, L., Shannon, M., Allonby, O., Babu, M., DeCoteau, J., Mousseau, D., Ali, M., Freywald, T., 2018. EPHB6 augments both development and drug sensitivity of triple-negative breast cancer tumours. *Oncogene* 37, 4073–4093.
- Toyota, M., Ahuja, N., Ohe-Toyota, M., Herman, J.G., Baylin, S.B., Issa, J.-P.-J., 1999. CpG island methylator phenotype in colorectal cancer. *Proc. Natl. Acad. Sci.* 96, 8681–8686.
- Ueda, H.R., Chen, W., Adachi, A., Wakamatsu, H., Hayashi, S., Takasugi, T., Nagano, M., Nakahama, K.-I., Suzuki, Y., Sugano, S., 2002. A transcription factor response element for gene expression during circadian night. *Nature* 418, 534–539.
- Viswanathan, A.N., Hankinson, S.E., Schernhammer, E.S., 2007. Night shift work and the risk of endometrial cancer. *Cancer Res.* 67, 10618–10622.
- Wang, F., Chen, Q., 2018. The analysis of deregulated expression of the timeless genes in gliomas. *J. Cancer Res. Ther.* 14, 708.
- Wang, J., Li, S., Li, X., Li, B., Li, Y., Xia, K., Yang, Y., Aman, S., Wang, M., Wu, H., 2019a. Circadian protein BMAL1 promotes breast cancer cell invasion and metastasis by up-regulating matrix metalloproteinase9 expression. *Cancer cell international* 19, 182.
- Wang, S., Li, F., Lin, Y., Wu, B., 2020. Targeting REV-ERB α for therapeutic purposes: promises and challenges. *Theranostics* 10, 4168.
- Wang, X., Wang, N., Wei, X., Yu, H., Wang, Z., 2018. REV-ERB α reduction is associated with clinicopathological features and prognosis in human gastric cancer. *Oncology letters* 16, 1499–1506.
- Wang, Y., Cheng, Y., Yu, G., Jia, B., Hu, Z., Zhang, L., 2016. Expression of PER, CRY, and TIM genes for the pathological features of colorectal cancer patients. *Oncotargets and therapy* 9, 1997.
- Wang, Z., Yang, M.-Q., Lei, L., Fei, L.-R., Zheng, Y.-W., Huang, W.-J., Li, Z.-H., Liu, C.-C., Xu, H.-T., 2019b. Overexpression of KRT17 promotes proliferation and invasion of non-small cell lung cancer and indicates poor prognosis. *Cancer management and research* 11, 7485.
- Waugh, D.J., Wilson, C., 2008. The interleukin-8 pathway in cancer. *Clin. Cancer Res.* 14, 6735–6741.
- Wu, H.-X., Cheng, X., Jing, X.-Q., Ji, X.-P., Chen, X.-Z., Zhang, Y.-Q., He, Y.-G., Liu, K., Ye, F., Sun, H.-X., 2018. LIFR promotes tumor angiogenesis by up-regulating IL-8 levels in colorectal cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease* 1864, 2769–2784.
- Xu, Y., Guo, W., Li, P., Zhang, Y., Zhao, M., Fan, Z., Zhao, Z., Yan, J., 2016. Long-range chromosome interactions mediated by cohesin shape circadian gene expression. *PLoS Genet.* 12, e1005992.
- Xu, Y., Padiath, Q.S., Shapiro, R.E., Jones, C.R., Wu, S.C., Saigoh, N., Saigoh, K., Ptáček, L.J., Fu, Y.-H., 2005. Functional consequences of a CK1 δ mutation causing familial advanced sleep phase syndrome. *Nature* 434, 640–644.
- Xu, Y., Pan, Z., Shu, L., Li, Q., 2018. Podocalyxin-like, targeted by miR-138, promotes colorectal cancer cell proliferation, migration, invasion and EMT. *Eur. Rev. Med. Pharmacol. Sci.* 22, 8664–8674.
- Xu, Y., Toh, K., Jones, C., Shin, J.-Y., Fu, Y.-H., Ptáček, L., 2007. Modeling of a human circadian mutation yields insights into clock regulation by PER2. *Cell* 128, 59–70.
- Yang, W.S., Stockwell, B.R., 2008. Inhibition of casein kinase 1-epsilon induces cancer-cell-selective, PERIOD2-dependent growth arrest. *Genome Biol.* 9, R92.
- Yang, X., Wood, P.A., Ansell, C.M., Quiton, D.F.T., Oh, E.-Y., Du-Quiton, J., Hrushesky, W.J., 2009. The circadian clock gene *Per1* suppresses cancer cell proliferation and tumor growth at specific times of day. *Chronobiol. Int.* 26, 1323–1339.
- Yang, X., Wood, P.A., Hrushesky, W.J., 2010. Mammalian TIMELESS is required for ATM-dependent CHK2 activation and G2/M checkpoint control. *J. Biol. Chem.* 285, 3030–3034.
- Yoo, J., Jeon, Y.H., Cho, H.Y., Lee, S.W., Kim, G.W., Lee, D.H., Kwon, S.H., 2020. Advances in Histone Demethylase KDM3A as a Cancer Therapeutic Target. *Cancers* 12, 1098.
- Zeng, Z.-L., Luo, H.-Y., Yang, J., Wu, W.-J., Chen, D.-L., Huang, P., Xu, R.-H., 2014. Overexpression of the circadian clock gene *Bmal1* increases sensitivity to oxaliplatin in colorectal cancer. *Clin. Cancer Res.* 20, 1042–1052.

- Zhang, E.E., Liu, Y., Dentin, R., Pongsawakul, P.Y., Liu, A.C., Hirota, T., Nusinow, D.A., Sun, X., Landais, S., Kodama, Y., 2010. Cryptochrome mediates circadian regulation of cAMP signaling and hepatic gluconeogenesis. *Nat. Med.* 16, 1152.
- Zhang, T., Chen, M., Guo, L., Yu, F., Zhou, C., Xu, H., Wu, B., 2019. Reverse erythroblastosis virus α antagonism promotes homocysteine catabolism and ammonia clearance. *Hepatology* 70, 1770–1784.
- Zhou, J., Zhang, Y., Zou, X., Kuai, L., Wang, L., Wang, J., Shen, F., Hu, J., Zhang, X., Huang, Y., 2020. Aberrantly Expressed Timeless Regulates Cell Proliferation and Cisplatin Efficacy in Cervical Cancer. *Hum. Gene Ther.* 31, 385–395.