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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; Aβ, β-amyloid; AF2, Activation function 2; APC, Adenomatous polyposis coli; ARNTL, ary1 hydrocarbon receptor nuclear translocator-like; Bmal1, brain and muscle ARNT-like protein 1; BPD, bipolar disorder; CIN, chromosomal instability; CIMP, CpG island methylator phenotype; CK1d/ε, 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; PP1, protein phosphatase 1; PPARγ, 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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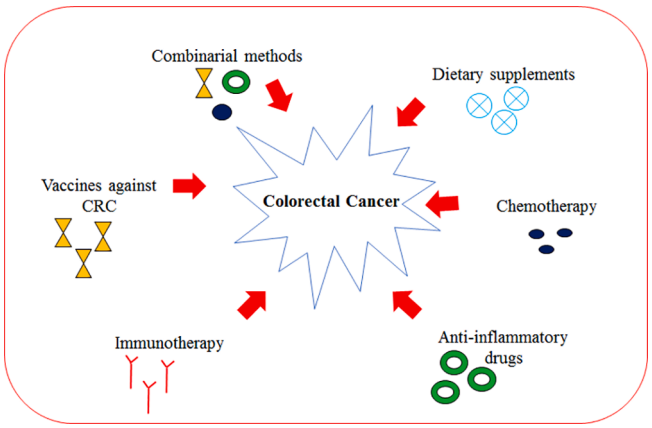

Fig. 1. Different treatment strategies for CRC therapy.

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), ary1 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

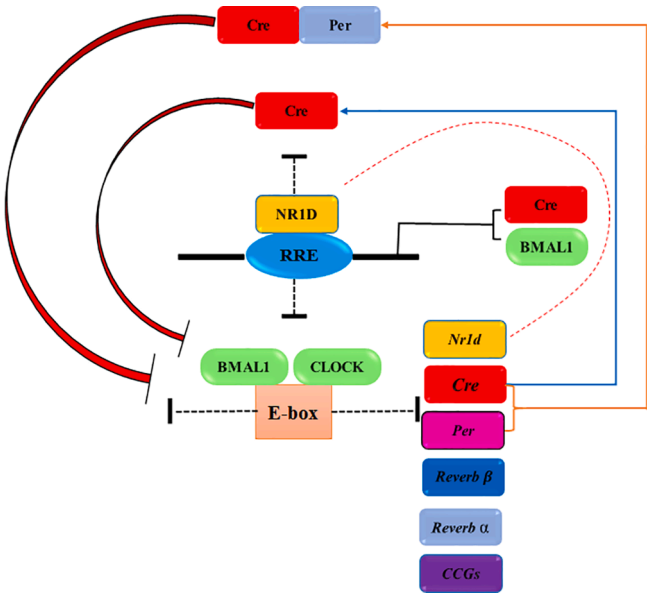

Fig. 2. The transcriptional–translational regulation loop of circadian rhythms. Clock/Bmal1 in the core circadian clock activate genes with E-box elements in their promoters such as clock-controlled genes (CCGs), REV-ERBα transcription factor as well as PER1 and CRY1/2. PER1 and CRY1/2 are involved outside 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 mechanisims, 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, CK1d, CK1δ and CRY2
SAD	Npas2
Bipolar disease	clock
BPD	Timeless gene & Bmal1
DSPD	CRY1, Per3, clock and CK1ε
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 (CK1d/ε) are vital protein kinases for regulation of circadian genes in mammals (Fig. 2). CK1d/ε kinase can phosphorylate and degrade mPer2. The mutation of CK1d 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), CK1δ 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 CK1ε (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 (PPARγ) 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 (Aβ) peptide. Producing and deposition of Aβ 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 Aβ levels by circadian clock. They reported that the loss of central circadian rhythms results in disruption of daily hippocampal interstitial fluid Aβ 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 overexpression 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-erbα, 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 (Mazzoccoli 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). Mazzoccoli et al. approved that an alternation in main clock genes such as Per1, Per2, Rev-Erbα, 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-Erbα, and Dbp was downregulated in CRC tissues. While, the Wee1, c-Myc, and p21 expression is not rhythmic in tumors and normal tissues (Mazzoccoli 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; Mehdizadeh 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, CK1ε/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 rythm 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 G_2-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 (Mehdizadeh 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 WEE-1 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-ERBα

REV-ERBα is a nuclear receptor encoded by NR1D1 gene and belongs to nuclear receptor subfamily 1 group D. REV-ERBα is the main component of circadian clock which acts as a transcriptional repressor. In 1989, REV-ERBα 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-ERBβ, another member of NR1D subfamily, was recognized. As activation function 2 (AF2) is absent in ligand binding domain, REV-ERBα/β is not able to induce gene transcription. On the other hand, REV-ERBα/β acts as transcriptional repressors and prevents gene transcription through recruiting co-repressors nuclear receptor co repressor 1 (NCOR1) and histone deacetylase 3 (HDAC3) (Everett and Lazar, 2014; Kojetin and Burris, 2014). REV-ERBα has a more significant effect in circadian rhythms than REV-ERBβ. It has been shown that circadian rhythms is interrupted in REV-ERBα-deficient mice. Considering the modulatory role of REV-ERBα on circadian rhythm and metabolic genes, REV-ERBα is primarily noticed as a therapeutic target for sleep disorders and metabolic syndrome. Nowadays, investigations indicate the role of REV-ERBα in the pathogenesis of inflammatory diseases and cancers (Wang et al., 2020). REV-ERBα is involved in gastric cancer development and progression. In gastric cancer, the level of REV-ERBα 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-ERBα is worse than patients with high expression of REV-ERBα (Wang et al., 2018). Therefore, REV-ERBα might be considered as a prognosis factor for gastric cancer. Sulli *et al.* indicated that activating REV-ERBα might be considered as a therapeutic target in cancer treatment (Sulli et al., 2018). The advantage of targeting REV-ERBα is an apoptosis induction in cancer cell and not in normal cells. Functionally, REV-ERBα inhibits *de novo* lipid biosynthesis via the suppression of fatty acid synthase and stearoyl-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-ERBα and RORα regulate the BMAL1 expression. BMAL1 deficiency leads to an imbalance in REV-ERBα and RORα expression. REV-ERBα positively regulates p21 promoter which inhibits the cell cycle progression (Karantanos et al., 2014). Disruption in REV-ERBa expression might lead to imbalance in p21 expression (Soták et al., 2013). Moreover, the activation of REV-ERBα suppresses autophagy. Therefore, REV-ERBα 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-ERBA, 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 2Genes symbol	Gene full name	Expression change	Function
BMP7	Bone morphogenetic protein-7	↑	regulates cellular differentiation, proliferation and apoptosis(Shen et al., 2018).
CRKL	Crk-like protein	↓	oncoprotein which contributes cancer cell proliferation, chemoresistance and promoting tumor cell invasion via a Src-dependent pathway(Song et al., 2019).
CXCL1	chemokine (C-X-C motif) ligand 1	↑	as a potential tumor-suppressor gene
DTL	Denticleless E3 Ubiquitin Protein Ligase Homolog	↓	May be involved in cancer development and promotes tumor progression through PDCD4 ubiquitin-dependent degradation(Cui et al., 2019).
EDN1	(Endothelin 1)	↑	Involved in tumorigenesis (Kim et al., 2005).
EMP1	Epithelial Membrane Protein 1	↑	promotes cancer cell growth, invasion, and EMT via MAPK signaling pathway(Liu et al., 2020)
EPAS1	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).
EPHB6	Ephrin type-B receptor 6	↓	Plays a role in tumor invasion and metastasis(Toosi et al., 2018).
GOS2	G0/G1 Switch 2	↑	
GDF15	Growth Differentiation Factor 15	↑	GDF15 may induce the cancer cells proliferation through CyclinD1/CyclinE1 and of p21 down-regulation(Li et al., 2018).
IL8	Interleukin 8	↑	IL-8 signaling stimulates angiogenesis, induces cancer cells proliferation, survival migration(Waugh and Wilson, 2008).
KDM3A	Lysine Demethylase 3A	↓	KDM3A promotes proliferation, survival and migration in cancer cells(Yoo et al., 2020).
KRT17	Keratin 17	↑	KRT17 induces proliferation and invasion of cancer cells via Wnt signaling pathway(Wang et al., 2019b).
LIFR	LIF Receptor Subunit Alpha	↑	LIFR induces cancer cell proliferation, angiogenesis and metastasis(Wu et al., 2018).
PKIA	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 2Genes 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 signalingpathway, 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 O2•− 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-kB 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 (Mazzoccoli 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 tumorgenesis. 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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