Chapter 2

Circadian Regulation of Colon Cancer Stem Cells: Implications for Therapy

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Abstract

The presence of cancer stem cells (CSCs) in colorectal cancer (CRC) has been associated with tumor initiation, metastasis, relapse, and resistance to chemotherapy and radiotherapy. Therefore, a better knowledge of the molecular mechanisms involved in the regulation of CSCs is required to develop treatments that are more effective. Like normal cells, cancer cells contain molecular clocks that generate circadian rhythms in gene expression and metabolic activity. Disruption of circadian rhythms has been linked to increased cancer risk, chemoresistance, and progression in CRC. CSCs also generate rhythms, which could be exploited with a chronopharmacological approach. Although the regulation of the expression of circadian rhythm genes appears to be mediated mainly by transcription–translation feedback loops, the existence of forms of nontranscriptional regulation has been demonstrated. Particularly, microRNAs (miRNA) and SIRT1 are significant players in regulating various aspects of the circadian clock function. Furthermore, miRNA acts as a regulator of cancer progression by regulating the CSC characteristics through SIRT1. These findings led us to hypothesize that there is a circadian rhythm of CSC markers regulated by miRNAs in CRC with SIRT1 acting as a mediator of miRNA activity. The pharmacological regulation of SIRT1, and therefore of the circadian machinery, could result in antiproliferative effects and increased sensitivity to antitumor treatments in CRC.

Keywords: circadian rhythms, cancer stem cells, SIRT1, redox homeostasis, melatonin

1. Introduction

Cancer is a major health burden and one of the leading causes of death worldwide. There are more than 200 known types of cancer, being CRC one of the most common cancers. In men, CRC is the third most common, after lung and prostate cancer. In women, CRC is the second most common cancer behind breast cancer [1].

Cancer begins with the transformation of a normal cell into a tumor cell through a multistage process. In this process, the changes are the result of the interaction between the genetic factors of the patient and external agents, including physical, chemical, or biological agents. Aging is another fundamental factor in the development of cancer. The coming years will see an increase in the total number of cancer cases [2]. This will be caused by the dramatic increase in average life expectancy during the last century in the industrialized world and by the fact that about 5% of the population in the developed countries is predicted to have more than 85 years by 2050 [3].

CRC is an excellent example of the increased cell malignancy with age; according to the Centers for Control and Prevention of Diseases, the incidence rate of CRC increases progressively with age. In 2007, the Surveillance, Epidemiology, and End Results Program registry reported that CRC incidence was 74.5/100,000 in persons aged 50–64 years, 186.0/100,000 in persons aged 65–74 years, and 290.1/100,000 in persons aged ≥75 years [4].

Little is known about the precise biochemical mechanisms responsible for the rise in CRC rates with aging. Some authors have proposed cancer stem cells/stem-like cells (CSCs/CSLCs) as the main factor associated with age-related rise in CRCs [5]. CSCs are a small subpopulation of cells that might play a critical role in CRC progression and resistance to chemotherapy and radiotherapy. Because of these resistances, CSCs play an important role in the processes of tumor recurrence and metastasis [6–8]. Therefore, it is increasingly likely that therapies that specifically target CSCs will be needed for the complete eradication of the tumor [7] because these cells are responsible for the morbidity and mortality associated with this type of cancer [9].

2. CSCs and CRC

CSCs, also known as tumor-initiating cells, were first identified by John Dick in acute myeloid leukemia in the late 1990s. Since then, they have been an intense focus of cancer research. CSCs have recently been identified in several solid tumors, including breast [10], colon [11], head and neck [12], lung [13], pancreas [14], and central nervous system cancer [15]. CSCs are defined as cancer cells that possess characteristics associated with normal stem cells, specifically the ability to self-renew and differentiate into multiple cell types, in particular into all the heterogeneous cell types found in a particular cancer sample [16] (**Figure 1**).

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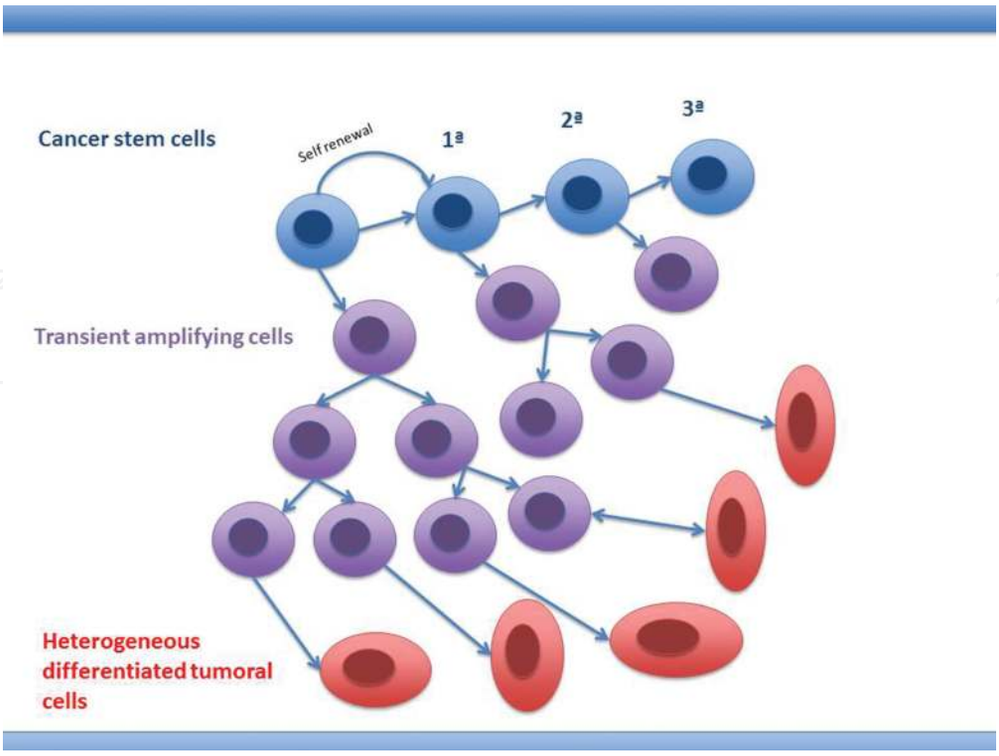

Figure 1. The cancer stem cells (CSCs) theory suggests that tumors grow like normal tissues of the body. In this way, the CSCs are able to both self-renew extensively, copying to them, and to produce the tissue grow (cancer tissue). In this process, the CSCs produce transit amplifying cells that have the capacity to divide a certain number of times, and then, they can differentiate into specialized heterogeneous tumor cells that do not have the skill to divide and therefore do not contribute to tumor growth.

Little is known about the origin of CSCs. Several proposals have been made regarding the origin of CSCs and probably several answers are possible depending on the tumor type and the tumor phenotype. In brief, CSC can arise if there are mutations in a developing stem or progenitor cells, in adult stem cells or adult progenitor cells, or in differentiated cells that acquire stem-like attributes [17]. Some data pointed to adult stem cells as origin of CSC in CRC. In this way, according to the most accepted model of CRC progression [18], four to five mutations in tumor suppressor genes or oncogenes are required and this takes about 8–12 years. As the colonic mucosa is a highly dynamic tissue, the mucosal cells are constantly replaced with cells derived from crypt stem cells. Therefore, only the long-lived cells (stem cells) may serve as reservoirs for accumulation of such mutations and epigenetic modifications.

In CRC, the presence of CSC has been correlated to tumor initiation, progression, metastasis, relapse, and resistance to chemotherapy and radiotherapy. [19]. CSCs have been isolated from CRC and are identified by the expression of specific surface markers and by their functional characteristics: CD44, CD166, CD133, ALDH1 (aldehyde dehydrogenase isoform 1), and ESA (epithelial-specific antigen, also known as EpCAM) [20]. Moreover, CSCs have been involved in the transition from adenoma to carcinoma, and this issue is age-dependent. In addition, an age-related rise in CSC has been observed in normal colonic mucosa and in premalignant adenomatous polyps. Moreover, the CSCs found showed an increased expression of CD44,

CD166, ALDH1, miR-21, and oncogenic miRNA, which suggests a predisposition of the organ to developing colorectal cancer [21]. Another characteristic of CSCs is that they can undergo epithelial–mesenchymal transition [22]. The fact that CSCs are resistant to conventional therapies has important implications in the development of novel strategies, such as CSCs-targeted treatments. It makes sense that eradication of CSCs or, alternatively, the attenuation of their malignant and stemness properties can lead us to achieve more effective therapeutic approaches. Therefore, development of specific CSCs-targeted therapies holds hope for improvement in the survival and quality of life of cancer patients, especially in patients with metastatic disease.

3. Epigenetic phenomena associated with CRC: miRNA regulatory network

Epigenetic processes are potentially reversible genetic modifications that lead to genomic instability and malfunction but that do not involve changes in DNA sequence. Epigenetic changes include (a) altered DNA methylation, (b) chromatin remodeling, and (c) small non-coding RNA (miRNAs). Notable changes in epigenetics have been reported for several age-related diseases, including CRC [23]. miRNAs are a small non-coding RNAs with 18–25 nucleotides found in plants, animals, and some viruses that are involved in RNA silencing and regulation of gene expression at the post-transcriptional level. miRNAs bind to the 3′-untranslated region (3′-UTR) of the protein-coding messenger RNAs (mRNAs). A single miRNA may regulate multiple mRNA targets and these small molecules are predicted to regulate approximately 60% of the human genes [24].

miRNAs are involved in different biological processes, including embryogenesis and the maintenance of stem cell characteristics, cell proliferation, metabolism, and transduction signals as in resistance to cancer treatments, including chemo- and radiotherapy [25, 26]. The presence of certain miRNAs has been associated with tumor development, tumor cell invasion, and cancer metastasis, and they may be of value as biomarkers for tumor detection and prognosis [27]. In addition, evidences show that miRNAs participate as oncogenic or tumor suppressors in the developmental and physiological processes of several human cancers, including CRC.

3.1. miRNA regulatory network in CRC

Approximately 450 unique miRNAs have been associated with CRC. In this disease, the aberrant expression of miRNAs has been associated with initiation and progression of CRC. Of special interest is miRNA involvement in the invasion, migration, and progression of disease through epithelial–mesenchymal transition into metastases. This event occurred due to IL6/STAT3 mediation and/or TP53 inactivation [28]. miRNAs are also involved in resistance to radio-chemotherapy [29].

Furthermore, miRNAs might regulate cell proliferation and apoptosis by targeting mitogen receptor tyrosine kinases and cell cycle regulators, such as cyclin-dependent kinases

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(CDKs), reciprocal miRNA interactions with MYC (v-myc avian myelocytomatosis viral oncogene homolog) and TP53, and by regulating the proapoptotic and antiapoptotic mRNAs [30].

Moreover, due to the altered expression of miRNAs in tumor development, they have been proposed as tissue and circulation biomarkers (blood derivates and feces). They might play a role in the prognostic and predictive diagnosis of CRC [31]. **Table 1** shows the potential roles of miRNA in CRC. Additionally, miRNA-related polymorphisms might disrupt their binding sites, miRNA processing, and expression. In this way, the single-nucleotide polymorphism (SNP) and other genetic abnormalities might be of utility in the study of the risk and prognosis of CRC.

	Role in CRC	miRNA
Oncogene	Proliferation	miR-21, miR-92a, miR-96, miR-135a, miR-135b
	Apoptosis	miR-21
	DNA damage response	miR-155
	Invasion	miR-21, miR-92a
	Epithelial–mesenchymal transition	miR-92a
	Metastasis	miR-224
	Inflammation	miR-224
Tumor suppressor	Proliferation	let-7, miR-7, miR-18a, miR-26b, miR-27b, miR-143, miR-144, miR-145, miR-194, miR-320a
	Apoptosis	miR-26b, miR-34a, miR-194, miR-195, miR-365, miR-491
	Angiogenesis	miR-27b, miR-145, miR-101, miR-126
	Invasion	miR-26b, miR-145, miR-194
	Migration	miR-26b, miR-145, miR-194
Circulatory biomarkers	Diagnosis	miR-21, miR-31, miR-34a, miR-92a, miR-143, miR-145, miR-601, miR-760
	Prognosis/survival	miR-21, miR-124-5p, miR-141, miR-155, miR-182, miR-200c
	Chemotherapy	miR-17-5p, miR-19a, miR-20a, miR-27b, miR-126, miR-130, miR-140, miR-145, miR-192, miR-216, miR-200c

Table 1. MiRNAs described in CRC

MiRNA has also been described with high potential as therapeutic target. According to Schetter et al., the two strategies for miRNA-based therapies are (a) to inhibit oncogenic

miRNAs and (b) to restore tumor suppressor miRNAs. Some preclinical models have shown that both strategies might be effective in the treatment of CRC cancers [29].

3.2. miRNA regulation of CSC in CRC

Many studies have reported that miRNAs are key players in the regulation of CSCs [32]. Bitarte et al. [33] have described that miR-451 is involved in the self-renewal, tumorigenicity, and chemoresistance of CRC stem cells. Up-regulation of miR-451 resulted in reduction of colon sphere formation and growth, inhibition of tumorigenicity in vivo, and sensitization to the active metabolite of irinotecan, SN38. This metabolite might be related to miR-451–mediated down-regulation of cyclooxygenase-2 (COX-2) and WNT (Wingless-type MMTV integration site family) pathway, essential to maintain cell stemness. On the other hand, Bitarte et al. also described that the regulation of expression of ATP-binding cassette (ABCB1) by miR-451 could decrease SN38 resistance.

Moreover, it has been suggested that miR-215 and miR-140 could control the slow proliferation and the chemoresistance of CSCs in the colon. In this respect, Jones et al. [34] described miRNA-215 (miR-215) as a direct transcriptional target of CDX1 in CRC stem cell differentiation. Song et al. [35] suggested miR-215 as molecular modulator of chemoresistance in CSC in CRC. Moreover, Yu et al. [36] have reported that miR-93 suppresses proliferation and colony formation of human CRC stem cells.

4. Circadian rhythms and CSC in CRC

Circadian rhythms are daily rhythms that take the form of a sine wave with high or active and low or quiet periods over the 24-hour clock. Many biological processes are temporally coordinated so that groups of genes called “clock genes” and their products are expressed at different critical times of the day, being likewise coordinated in circadian time [37]. A master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus organizes the circadian system in a hierarchical manner. The SCN receives photic input through direct retinal innervation that initiates gene expression in the SCN [38]. In this way, light exposure synchronizes the SCN clock to solar time, adapting the oscillator to exact 24-hour cycle. The master clock of the SCN communicates day-night information to the rest of the body. The SCN receives light input from the retina and then conveys the photic information into neural or humoral signals. This information is then sent to peripheral circadian clocks that exist in almost all cells of the body and synchronize them to the same phase [39]. Whereas light is the dominant rhythmic signal for the SCN oscillator, the peripheral clocks respond to other environmental signal, such as body temperature, hunger, and hormone secretion cycles, and modify their phase accordingly [40, 41].

4.1. Regulation of circadian rhythms in mammals

In mammals, these daily rhythms are maintained by autoregulatory transcriptional and translational feedback and feed-forward loops (TTFLs) [42]. The core clock genes are BMAL1

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(brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1), CLOCK (circadian locomotor output cycles kaput), PER (period homolog), and CRY (cryptochrome) [41]. BMAL1 heterodimerizes with either CLOCK or NPAS2 (neuronal PAS domain protein 2) and binds to E-box elements in PER (PER1-3) and CRY (CRY1-2) promoter regions and activates their transcription. Upon accumulation in the cytoplasm, PER and CRY proteins translocate to the nucleus where they repress the BMAL1: CLOCK/NPAS2 regulatory complex, thereby shutting down their own transcription. The PER and CRY heterodimers are progressively degraded, allowing the circuit to start again. This negative feedback leads to a cycle in gene expression that takes approximately 24 hours to complete (**Figure 2**) [43].

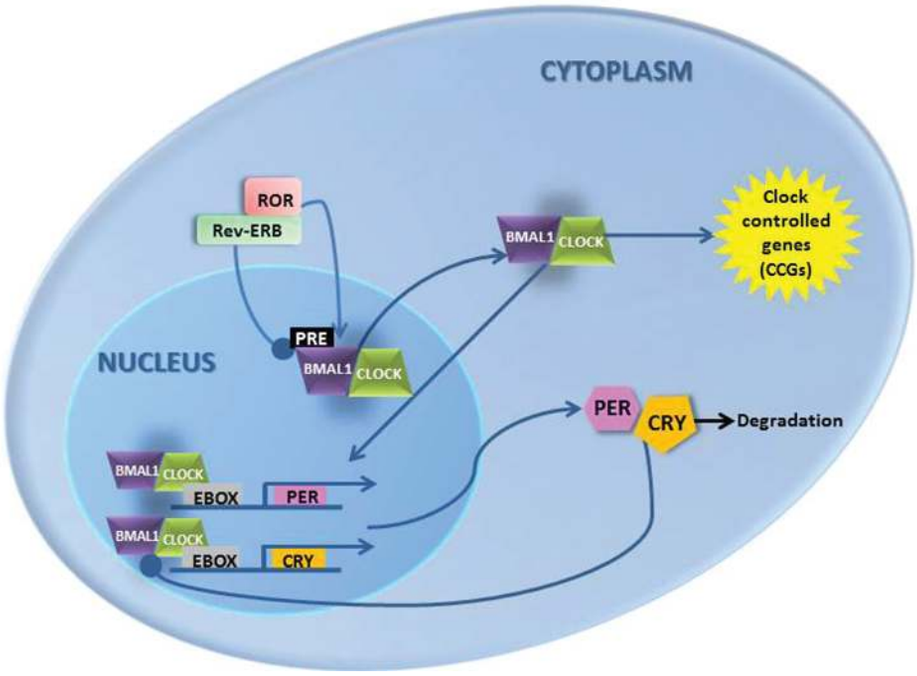

Figure 2. Schematic representation of the core circadian clock. (Adapted from Robinson and Reddy [52]. Copyright ©2014). BMAL1 and CLOCK transcription products translocate to the cytoplasm and dimerize. They then return to the nucleus and bind to E-box regions and promote Period (PER) and Cryptochrome (CRY) transcription. PER and CRY translocate to the cytoplasm, dimerize, and return to the nucleus and inhibit the binding of the CLOCK/BMAL complex. PER and CRY are subsequently degraded. REV-ERB inhibits the transcription of Bmal1, whereas ROR promotes BMAL1 expression. The clock-controlled genes REV-ERBα (REV-ERB) and RORα (ROR) generate additional circadian control by modulating the expression of BMAL1.

Post-transcriptional and post-translational modifications, such as phosphorylation, acetylation, methylation, sumoylation, and ubiquitination, are crucial to the clock molecular mechanism [44]. Post-translational modifications of the proteins of the circuit generate the essential time delay that maintains the period of the cycle at approximately 24 hours. Additional feedback pathways involving nuclear receptors, such as RORα (retinoid-related orphan receptor alpha), REV-ERBα (NR1D1, nuclear receptor subfamily 1, group D, member 1), PPARγ (peroxisome proliferator–activated receptor gamma), and PGC-1α (peroxisome proliferator–activated receptor gamma coactivator 1-alpha) provide further robustness to the circuit [45, 46]. Additionally, these clock genes control numerous target genes (termed clock

controlled genes, CCGs) and they regulate the circadian rhythms of various biochemical and physiological processes [47].

4.2. Redox regulation of circadian rhythms

The possible relation between circadian rhythm and redox state has been long known but it was unclear whether redox oscillations are a driver of the clock or a biomarker of cellular time. The discovery that circadian redox oscillations appear to be conserved throughout evolution, and that circadian oscillations in redox parameters persist in the absence of transcriptional system, has consolidated the interplay between metabolic processes and the molecular clock [48]. In mammals, nearly 10,000 genes are known to be under circadian control [49]. Several studies have investigated circadian oscillations in gene expression in metabolic tissues, including brown fat, liver, and skeletal muscle [50]. Certain metabolic enzymes are rhythmically expressed in the liver, such as aconitase, aldolase 2, enolase 1, ketohexokinase, and succinate dehydrogenase 1 [51]. Since numerous metabolic diseases appear to have a circadian-related dysfunction, it follows that core cellular metabolism and the clock are intimately connected [52].

The redox state of a cell has been shown to be an integral component in the regulation of the molecular clock. DNA binding of NPAS2 and CLOCK is influenced by the redox state of NAD(H) and NHAP(H). NADP inhibits NPAS2:BMAL1 binding to DNA, but, on the other hand, DNA binding is promoted by NADPH. At a ratio of NADP:NADP(H) of over 75% NPAS2:BMAL1 DNA binding increases, whereas below 75% binding decreases [53].

Peroxiredoxins (PRDXs) are a family of antioxidants that help to prevent cellular damage resulting from the production of ROS and work by reducing H_2O_2 to water. Six PRDX isoforms are known (PRDX 1–6), and they are found in different cellular localizations: isoforms 1, 2, 5, and 6 in the cytosol, isoforms 3 and 5 in the mitochondria, isoform 5 in the peroxisome, and isoform 4 in the endoplasmic reticulum [54, 55]. PRDXs could have one or two redox active cysteine residues that bind H_2O_2 forming a sulfenic acid. In mammals, there are five two-Cysperoxiredoxins (PRDX 1–5) and a single one-Cysperoxiredoxin (PRDX 6) [56]. In most cases, a homodimer is formed by a resolving cysteine at the C terminus forming a disulphide bond with the cysteine sulfenic acid. This bond can then be 'resolved' by thioredoxin, enabling further catabolism of peroxide by PRDX [57].

The cycle of PRDX had been shown to follow a circadian rhythm, with two forms of PRDX6 oscillating in antiphase in the liver, emphasizing a role of post-translational modification in circadian rhythmicity [51]. While the core clockwork use TTFLs, many works suggest the redox state of PRDXs is driven by the metabolic state of the cell, but it is independent of transcription [58]. However, the reciprocal influence between the TTFL and the PRDX-based metabolic clock has not fully addressed yet.

4.3. Epigenetic regulation of circadian rhythms by miRNAs

Some miRNAs have regulatory functions contributing to the control over circadian protein expression [59]. The influences of the circadian clock function on miRNA expression or vice

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versa have been well established. Experimental evidence suggests that up to 30% of core clock genes are under the control of miRNA. Recently, miR-132 and miR-219 seem to be directly involved in the clock system and regulate light response [60].

Other studies examine the role of extracellular miRNAs in the regulation of molecular components and modulation of rhythmicity in peripheral cellular clocks. The studies revealed that exposure to miR-142-3p– and miR-494–enriched conditioned medium increases intracellular expression of these miRNAs and results in functional effects in recipient cells [59].

4.4. Circadian rhythms and CRC

In carcinogenesis, the levels of expression of many proteins may be dependent directly or indirectly on the circadian cycle. Investigations on the relation between the circadian clock and DNA damage response have revealed that DNA damage checkpoints, nucleotide excision repair, and apoptosis are appreciably influenced by the clock [61]. Changes in the circadian rhythm of cell division are considered important component in neoplastic transformation. The presence of DNA damage is usually associated with cell cycle arrest for attempted repairs or induction of apoptosis. The mechanism of repair happens before the S-phase of the cell cycle, and although there are post-replication mechanisms for induction of cell cycle arrest, the G1/S checkpoint is usually the most stringent cell cycle checkpoint and this event will take place at night for adjustment of the circadian rhythm [61]. On the other hand, disruptions of the circadian rhythm genes are associated with increased susceptibility to cancers [62].

Some experimental studies have showed the role of the disruption of the molecular clock work in colorectal carcinogenesis and CRC progression [63]. One example is seen in human cancer cells lines when PER1 is overexpressed. In this experiment, it was observed a reduced colony formation and clonogenic expansion, in sensitization to radiation-induced apoptosis, and in altered expression of transcriptional target genes, such as c-MYC and p21 [64]. In contrast, PER2-null mice showed an increase in hyperplasia and neoplasia in response to γ-radiation [65]. In line with this work, restoring CLOCK expression in a human colon adenocarcinoma cell line derived from a primary colon cancer, in response to ionizing radiation, conferred protection against ultraviolet (UV)-induced apoptosis and decreased G2/M arrest [66].

On the other hand, one study that used CRC tumor tissue from patients demonstrated that PER2 expression was higher in well-differentiated cancer cells when compared to poorly differentiated ones. Associations of decreased PER2 levels with patient age, histological grade, TNM (for tumors/nodes/metastases) stage, and expression of nuclear proliferation-related antigen Ki67 were also observed [67]. In addition, down-regulation of PER3 associated with various clinicopathological factors, including tumor location, differentiation, and stage, as well as poorer survival was seen in CRC tissues, thus suggesting an important role in CRC progression [68].

The efficacy of many drugs and the intensity of their effects depend on the time of day when they are administered (chronochemotherapy), and they are therefore associated with the circadian rhythm. The clock acts as a modulator of the pharmacokinetics and pharmacodynamics of chemotherapeutic drugs and of the activity of the DNA-repair enzymes that repair

the DNA damage caused by anticancer drugs [61]. Some studies have demonstrated that chronomodulated chemotherapy has better tolerability and antitumor activity compared with conventional chemotherapy. A good example is the treatment of advanced stage CRC where oxaliplatin is administered in the afternoon and 5-FU and leucovorin are delivered late at night (chronoFLO4) [69]. Other authors have observed that 5-FU administration during the sleeping time before radiotherapy could have an advantage as a chronotherapy and also as a radiosensitizer [70].

4.5. Regulation of stemness by the circadian machinery

Numerous studies are demonstrating the importance of coherent circadian oscillations for a variety of homeostatic functions of tissues. One example is the timed activation and differentiation of stem and progenitor cells, and how perturbation of this temporal coordination leads to pathologies, including obesity and neurological diseases, aging, and cancer [71].

Like normal cells, cancer cells contain molecular clocks that generate circadian rhythms in gene expression and metabolic activity [72]. The circadian rhythms not only regulate the cell cycle in normal differentiated cells but there could also be a functional relation between circadian rhythm gene expression and the intrinsic control of the proliferation of CSCs and progenitor cells in different tissues [73]. In rodents and humans, all the hematopoietic stem and progenitor cells exhibit a predictable circadian variation [74, 75]. Some authors have shown that there is an increase in circadian rhythm gene expression of highly differentiated stem cell cultures. In both cancer and normal cells, a rhythmic nuclear translocation of PER2 and other critical clock proteins is an essential part of a clock timing mechanism based on transcriptional–translational feedback loops and rhythmic chromatin modification [73, 76].

The malignant phenotype depends not only on the characteristics of the cancer cell itself but also on the tumor microenvironment. CSCs have to survive for a long time in the body to generate the highly tumorigenic cells responsible for the clinical manifestations of cancer. During this period, the niche helps to shelter CSCs from different types of insults, such as the immune response and chemotherapy-induced genotoxic stress [77, 78]. This suggests that the niche may also play a protective role for CSCs, thus increasing the risk of cancer. In fact, BMAL1 suppresses cancer cell invasion by blocking the phosphoinositide 3-kinase-Akt-Matrix metalloproteinase-2 (MMP-2) signaling pathway [79]. Other authors have reported circadian oscillations in the levels of MMP-9 [80].

5. SIRT1 and the circadian regulation of CSCs by miRNAs

The silent information regulator (SIRT) 2 family of proteins, known as sirtuins, is a class III of histone deacetylases or NAD+–dependent deacetylases and is conserved from bacteria to humans. The requirement for NAD+ links the activity of sirtuins directly to the metabolic state of the cell, since the deacetylase activity of these proteins is controlled by the cellular NAD+/NADH ratio. There are seven sirtuins (SIRT1–7) in mammals. They have different specific substrates and biological functions and are found in various cell compartments [81].

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The role of sirtuin activation in mammals is to regulate the progression of aging and age-associated disorders, including neurodegeneration, diabetes, cardiovascular diseases, and many types of cancer [82]. The best characterized and well-studied among the human sirtuins is SIRT1. It can be found in the nucleus and in the cytoplasm of the cells [83].

5.1. Sirt1 in cancer biology

SIRT1 is overexpressed in some types of human cancer tissues, such as ovary, liver, breast, stomach, pancreas and prostate, and down expressed in skin cancer. In CRC, SIRT1 is also overexpressed. However, other investigations have revealed pronounced SIRT1 expression in both normal colon and tumor tissues, although its expression is substantially reduced in higher grade CRC tumors [84].

SIRT1 has a dual role in tumorigenesis, where it can function as either a tumor promoter or a tumor suppressor. Its function in malignancy varies with concentration, cellular location, temporal and spatial distribution, and regulation by upstream and downstream factors [85].

The initial connection of sirtuins to cancer was made when SIRT1 was found to deacetylate and repress the activity of the tumor suppressor p53 [86, 87]. SIRT1-mediated deacetylation suppresses the functions of other tumor suppressors, including p73, hypermethylated in cancer 1 (HIC1), E2F transcription factor 1(E2F1, also known as retinoblastoma-associated protein 1), retinoblastoma protein (Rb), and phosphatase and tensin homologue deleted in chromosome 10 (PTEN), thus suggesting that SIRT1 acts as a promoter in tumor development and progression [88–93]. Other reports showed SIRT1 as a downstream of the oncoprotein BCR-ABL tyrosine kinase (Abelson murine leukemia viral oncogene homolog 1), implicated in the development of chronic myelogenous leukemia (CML)-like myeloproliferative disease [94].

Autophagy is a self-degradative process that plays a role by eliminating damaged organelles and misfolded or aggregated proteins through the lysosomal degradation pathway. Autophagy initially serves as a protective process to prevent cancer initiation; however, after neoplastic transformation, it can promote tumor cell survival and maintenance [95]. Autophagy can also affect chemotherapeutic and immunotherapeutic response in cancer cells making it an attractive target for development of anticancer drugs [96, 97]. SIRT1 forms a molecular complex with the genes related to autophagy and autophagosome formation, Atg5, Atg7, and Atg8. Loss of SIRT1 activity results in the acetylation of those factors thus leading to defects in the process of autophagy [98].

Consistent with a tumor-suppressor role, SIRT1 deacetylates and decreases the stability of the oncogene c-MYC [99]. In addition, the activity of SIRT1 can be increased by some tumor-suppressors, for example BRCA1 (breast cancer 1) [99]. SIRT1 exerts anticarcinogenic effects through multiple mechanisms [83]. SIRT1 can counteract various genotoxic insults, including oxidative DNA damage, thereby blocking initiation of carcinogenesis. SIRT1 deacetylates and inhibits proapoptotic p53 and PARP-1 (poly (ADP-ribose) polymerase 1) under stressful conditions, conferring cell survival [86, 100]. SIRT1 is also required for DNA repair processes to maintain genomic stability [101, 102].

SIRT1 inhibits the mediators involved in aberrantly amplified proinflammatory signaling during promotion and progression of carcinogenesis [103–105]. The anti-inflammatory effect of SIRT1 might be achieved by inhibition of several transcription factors related to inflammation, nuclear factor κB (NF-κB), signal transducer and activator of transcription 3 (STAT3), and the c-Jun and fos elements of transcription factor activator protein 1 (AP-1) [106–108]. Mainly through NF-κB and AP-1 pathways, SIRT1 was engaged in macrophage and T-cell activation [105, 109]. SIRT1 also regulates the differentiation and function of iTreg (induced Treg helper cells) [110]. Interestingly, SIRT1 translates metabolic cues during regulation of the immune responses, which would bring new insights into both pathogenesis and potential therapeutic strategies of a variety of immune-related diseases, such as cancer [111].

5.2. SIRT1 and stem cells

SIRT1 is considered an old multifaceted enzyme with an important role in the maintenance of pluripotency in various types of stem cells. Most of the in vivo data suggest that Sirt1 acts in early development as a modulatory molecule on basic developmental processes [112]. In cancer, SIRT1 has been implicated in the regulation of CSCs survival and differentiation. SIRT1 has been found to regulate the growth and survival of leukemia stem cells (LSCs) and confer resistance against chemotherapy [113], stimulate endometrial cell tumor growth through lipogenesis [114], maintain neural stem cells and promote oncogenic transformation [115], and foster hepatocellular carcinoma [116]. As a result, SIRT1 and agents that modulate SIRT1 activity may represent new therapeutic strategies against tumorigenesis.

One of the more intriguing hypotheses about aging and age-related disease is that age-associated phenotypic alterations derive from the inability of resident stem cells to maintain tissue structure and function [117]. This suggests that the aging process could arise from loss or malfunction of self-renewal and/or differentiation potential in adult stem cell populations. SIRT1 has a positive role in stemness by aiding in the silencing of differentiation genes, which suggests new potential explanations of its ability to extend lifespan and to avoid cell and organism senescence [112, 118].

5.3. SIRT1 and miRNAs

Expression of SIRT1 is controlled at multiple levels by transcriptional, post-transcriptional, and post-translational mechanisms under physiological and pathological conditions [119]. Deacetylation activity of SIRT1 can be modulated by multiple regulators. AROS (Active regulator of SIRT1) and DBC1 (deleted in breast cancer 1) are positive and negative regulators of SIRT1, respectively [120, 121].

Emerging evidence indicates that miRNAs are important regulators of SIRT1 expression and activity [119]. In cancer, SIRT1 mediates miR-34a activation of apoptosis by regulating p53 activity. In addition, p53 induces expression of miR-34a which suppresses SIRT1, increasing p53 activity [122]. In CRC, dysregulation of microRNA-34a expression causes drug-resistance to 5-FU in human colon cancer cells through the downregulation of Sirt1 and E2F3 [123, 124].

miRNAs play an important role in proper function and differentiation of human and mouse stem cells. Recently, it has been demonstrated that miR-34a is required for proper differentiation of mouse embryonic stem cells, mouse neural stem cell, and mouse embryonic fibroblasts and that it function in part by targeting SIRT1 and modulating p53 activity [125–127]. Also, the miR-29b-Sirt1 axis regulates self-renewal of mouse embryonic stem cells in response to reactive oxygen species [128]. miR-34a is also a critical regulator of cancer progression by the regulation of CSC characteristics, through SIRT1 as a mediator [129–133], and mainly, through up-regulation of p53/p21 [131].

5.4. SIRT1 as regulator of circadian rhythms

Two independent studies identified SIRT1 as a critical modulator of the circadian clock machinery. Asher et al. [134] observed oscillations in SIRT1 protein levels, and Nakahata et al. [135] demonstrated that SIRT1 activity, and not its protein levels, oscillates in a circadian manner. SIRT1 modulates circadian rhythms by deacetylating histone H3 Lys9 and Lys14 at promoters of rhythmic genes, BMAL1 and PER2. The CLOCK-BMAL1 complex interacts with SIRT1 and recruits it to the promoters of rhythmic genes. While BMAL1 acetylation acts as a signal for CRY recruitment, PER2 acetylation enhances its stability [134]. These findings led to the concept that SIRT1 operates as a rheostat of the circadian machinery, modulating the amplitude of CLOCK-mediated acetylation and consequent transcription cycles [135].

Circadian oscillation of SIRT1 activity suggested that cellular NAD+ levels may also oscillate. In fact, circadian clock controls the expression of NAMPT (nicotinamide phosphoribosyltransferase), a key rate-limiting enzyme in the salvage pathway of NAD+ biosynthesis. The oscillatory expression of NAMPT is abolished in Clock/Clock mice, which results in drastically reduced levels of NAD+. These results imply the existence of an enzymatic/transcriptional feedback loop, wherein SIRT1 regulates the levels of its own cofactor [135]. These results also connect the circadian machinery to cell metabolism [134].

SIRT1 either directly or indirectly can influence the redox property of the cell [136]. In addition to reduce cellular oxidative stress burden, SIRT1 is also regulated by oxidative stress [137]. Since redox homeostasis influence circadian machinery, SIR1 could regulate circadian genes trough redox status of the cell. A recent report suggests that PRDX2 regulates the TTFL oscillation by decreasing the nuclear redox levels and increasing SIRT1 enzymatic activity, although neither a direct interaction between PRX and SIRT1 nor a modulation of SIRT1 intracellular levels by PRX was found [138].

5.5. SIRT1 regulators as new tools for cancer treatment

Recently, multiple research groups have pursued the identification and development of small molecule compounds that modulate sirtuins SIRT1 regulators as new tools for cancer treatment [139]. To date, SIRT1 inhibitors and activators have been described with different effects on cancer [140].

SIRT inhibitors require combined targeting of both SIRT1 and SIRT2 to induce p53 acetylation and cell death, like sirtinol and salermide [139]. Trichostatin A (TSA) and sirtinol induce

p38MAPK- and AMPK-mediated downregulation of survivin and its functional correlation with decreased colon cancer cell viability in vitro [141]. Other salermide-related sirtuin inhibitors show antiproliferative effects in colon cancer cells in vitro, including CSCs [142]. Vorinostat activates p53, but does not require p53 for inducing its anticancer action in CRC [143]. The SIRT1 selective inhibitor Amurensin G may be effective in eliminating colon CSCs and may be applicable to potentiate the sensitivity of colon CSCs to TNF-related apoptosis-inducing ligand (TRAIL) [144].

Studies have shown that the sirtuin activator resveratrol, a polyphenol found in wines has chemopreventive activity against various cancers. In CRC, resveratrol induce apoptosis and suppressed the PI3K/Akt signaling pathway. The combination treatment with resveratrol and 5-FU induced a synergistic enhancement of growth inhibition and apoptosis in colon cancer DLD-1 cells. Interestingly, resveratrol increased the intracellular expression level of miR-34a, which down-regulated the target gene E2F3 and its downstream Sirt1, resulting in growth inhibition [145].

Melatonin is the main secretory product of the pineal gland and plays important roles in several biological functions, including circadian rhythms, sleep, mood, reproductive physiology, and aging diseases [146]. Numerous studies based on animal and clinical data have provided evidence that melatonin reduces the incidence of experimentally induced cancers and may significantly inhibit the growth of some human tumors [147]. Recently, melatonin was confirmed as a novel inhibitor of SIRT1. Melatonin inhibits prostate cancer and osteosarcoma cell growth through SIRT1 inhibition [148, 149]. Interestingly, it was recently reported that melatonin decreases CSCs and dysplastic injuries in colon tissue [150].

6. Concluding remarks

SIRT1 expression correlated with depth of invasion, lymph node metastasis, and TNM stage in CRC. Simultaneously, SIRT1 overexpression predicted a poor overall survival in CRC patients, and SIRT1 is a candidate negative prognostic biomarker for CRC patients [151]. SIRT1 has also been implicated in chemoresistance in CRC patients with [152] or without metastasis [124]. Further investigations aimed at targeting SIRT1 alone or in combination with chemotherapy deserve further attention and may ultimately increase response rates in the treatment of CRC. In this sense, melatonin can significantly amplify the cytostatic and the cytotoxic effects triggered by other compounds or conventional drugs. We are far from having a satisfactory understanding about how and when melatonin exerts its beneficial effects. Melatonin in the nanomolar range induces down-regulation of SIRT1. This finding is of great relevance because there is intense research ongoing to identify nontoxic feasible inhibitors of SIRT1. Melatonin should be evaluated for the management of those cancers where this protein is overexpressed and is functional.

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