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Chapter

A Molecular Link between the Circadian Clock, DNA Damage Responses, and Oncogene Activation

Yoshimi Okamoto-Uchida, Junko Izawa and Jun Hirayama

Abstract

Circadian clocks enhance the efficiency and survival of living things by organizing their behavior and body functions. There has been a long history of research seeking a link between circadian clock and tumorigenesis. Studies of animal models and human tumor samples have revealed that the dysregulation of circadian clocks is an important endogenous factor causing mammalian cancer development. The core circadian clock regulators have been implicated in the control of both the cell cycle and DNA damage responses (DDR). Conversely, several intracellular signaling cascades that play important roles in regulation of the cell cycle and the DDR also contribute to circadian clock regulation. This review describes selected regulatory aspects of circadian clocks, providing evidence of a molecular link of the circadian clocks with cellular DDR.

Keywords: circadian clock, DNA damage response, DNA repair, oncogenes

1. Introduction

Circadian (derived from Latin "around the day") clocks constitute ubiquitous processes that regulate various biochemical and physiological events occurring with a 24 h periodicity, even in the absence of external cues [1, 2]. Under natural conditions, clocks are entrained to a 24 h day by environmental time cues, most commonly light. Circadian clocks are established in cell-autonomous oscillators, referred to as cellular clocks, which are controlled by a transcription/translation-based negative feedback loop [3, 4]. In humans, the circadian clock generates circadian rhythms in synthesis and release of hormones and cardiovascular activities such as heart rate, blood pressure, and vascular tone [5, 6]. Moreover, immune responses show temporal changes in antibody levels and total number of lymphocytes, which are related to circadian variations [7]. Therefore, dysfunction of the clock can cause a variety of diseases. In particular, it has been reported that the circadian clocks are associated with tumor suppression in vivo, indicative of the theoretical foundations for cancer chronotherapy [8, 9].

At the molecular level, the circadian clocks can be divided into three conceptual components [10, 11]. The first is the pacemaker, dedicated to generating and sustaining circadian rhythms by receiving and integrating signals from external

time cues. The second component is the input which refers to the pathway through which these cues are perceived and act upon the central pacemaker. The third element applies to how the clock affects physiology, which is achieved through the output pathways. In vertebrates, the cellular clocks are comprised of the circadian locomotor output cycles kaput (CLOCK), neuronal PAS domain-containing protein 2 (NPAS2), brain and muscle arnt-like protein-1 (BMAL), period (PER), and cryptochrome (CRY) proteins (**Figure 1A**) [11]. CLOCK or NPAS2 heterodimerize with BMAL to form an active transcription complex that transactivates clock-controlled genes, including *Cry* and *Per*. Once the CRY and PER proteins have been translated, they are translocated to the nucleus, where they inhibit CLOCK(NPAS2):BMAL-mediated transcription through a direct protein-protein interaction. Importantly,

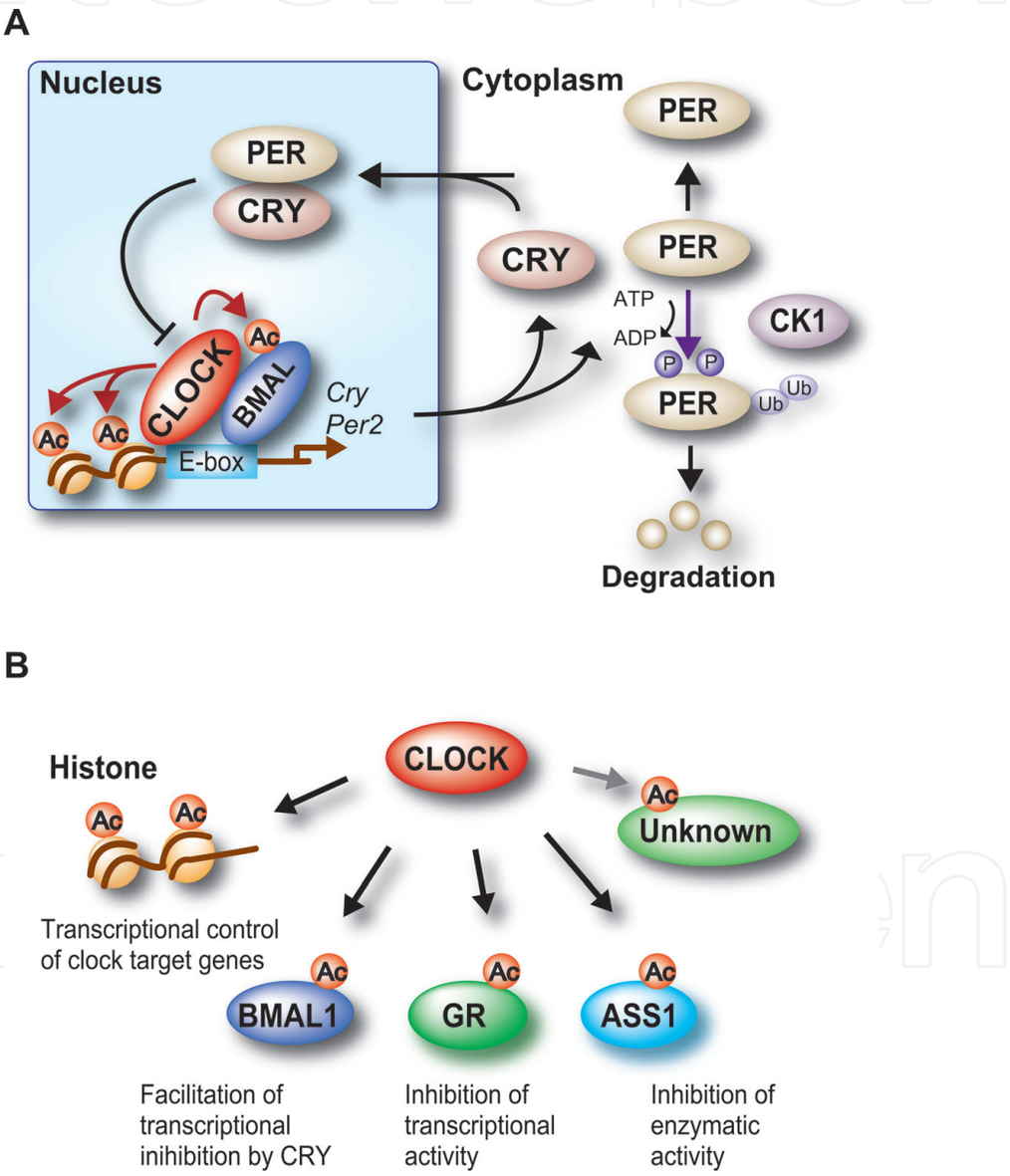

Figure 1.
Molecular mechanisms establishing circadian clocks in vertebrates. (A) Model of the vertebrate cellular clocks. Two basic helix-loop-helix PAS domain-containing transcription factors CLOCK and BMAL constitute the positive elements. When these transcription factors heterodimerize, they bind to E-boxes to drive the transcription of the negative components of the clock, Per and Cry genes. The products of these clock genes then negatively regulate their own expression, setting up the rhythmic oscillations of gene expression that drive the circadian clocks. CLOCK:BMAL complex also regulates clock-controlled genes, whose products mediate the "output" function of the clocks. CK1 phosphorylates PER protein, which is required for ubiquitination of PER and its subsequent degradation. An essential prerequisite for the circadian feedback loop is a short half-life of clock proteins. Thus, CK1-mediated degradation of PER is critical for maintenance of circadian rhythmicity of cellular clock. (B) Schematic representation of the proteins that are acetylated by CLOCK protein.

when active, the CLOCK (NPAS2):BMAL complex stimulates the transcription of many other clock-controlled genes. These genes in turn influence functions external to the oscillatory mechanism itself and mediate the "output" function of the clock. This accounts in part for the presence of circadian rhythms in a variety of physiological processes.

The phenotypes of mice with targeted disruptions of the genes encoding cellular clock's components have revealed direct links between the circadian clock and non-circadian aspects of animal physiology [6, 9]. In particular, these findings argue in favor of a major role played by the circadian machinery in cellular genotoxic stress responses and reveal intriguing links between the DNA damage responses (DDR) pathways and the circadian clocks. In this review, we summarize the evidence and explore the implications of such a link.

2. The relationship between transcriptional regulation of oncogenes and circadian clocks

The disruption of circadian clocks can have a profound effect on animal health and is linked to abnormal development and cancer [6, 9]. Expression of the circadian clock genes has been reported to be dysregulated in human cancers [12]. The circadian transcriptional machinery, cellular clock, has been reported to control expression of tumor suppressors. Thus, the abnormal control of clock genes' expression in cancer cells activates oncogenic signaling pathways by functional inhibition of tumor suppressors, such as ataxia telangiectasia mutated (ATM), p53, p21, and WEE1 [12].

The Wingless-related integration site (Wnt) signaling pathways collectively play important roles in developmental, proliferative, and cell death processes [13]. Mutations in genes encoding the various components of Wnt pathways have been identified that contribute to various types of cancer including hepatocellular carcinoma, pancreatic tumors, ovarian cancer, and breast cancer. Importantly, there are several lines of evidence that suggest the existence of an interaction between circadian clocks and Wnt signaling pathways. Previous study have performed microarray-based screening for circadian genes in several mouse tissues and have constructed a publicly accessible database, by which users can query for finding circadianly regulated genes or for the study of the temporal expression patterns of their genes of interest [14]. Interestingly, in this database, several Wnt signaling pathway genes, such as *Axin2*, *Frizzled3* (*Fzd3*), and *Disheveled* (*Dvl1*), show a circadian pattern of expression, suggesting the possibility that circadian clocks control transcription of Wnt signaling pathway genes. The future study of the connecting routes that link the circadian transcriptional machinery to Wnt signaling pathway will reveal a molecular link between circadian clock deficiency and tumorigenesis.

3. Possible roles of clock proteins in functional regulation of crucial components of DDR pathways

The activities associated with the physiological processes are organized in daily manner: during the daytime, the animal's physiology is given over to the catabolic processes, whereas at night, it concentrates on the anabolic functions of growth, repair, and consolidation [5, 6]. Disrupt, the time-dependent regulation of physiological functions in animals has profound effects on their health. In particular, many studies have provided evidence that disruption of the circadian clocks results

in tumorigenesis [8, 9]. Importantly, mice with mutations in the *Bmal1* gene show premature aging phenotype [15]. In addition, human CLOCK has been suggested to be involved in metastasis of colorectal cancer [16]. These findings implicate the core circadian machinery in the regulation of DDR and the cell cycle. Indeed, the circadian regulators have been demonstrated to interact with crucial components of cellular stress response pathways including the ATM, the checkpoint kinase 2 (Chk2) kinase [17], sirtuin1 (SIRT1) deacetylase [18], and nuclear receptors 19, 20], whereas it has been reported that DNA damage can act as a resetting cue for the mammalian circadian clock [21].

Histone acetyltransferases (HATs) such as CBP/p300 are known to acetylate nonhistone targets and have also been recognized as tumor suppressors [22, 23]. Translocation, amplification, overexpression, or mutation of HAT genes are known to occur in several forms of cancer, and several key cell cycle proteins (including p53 and c-MYC) are known targets of HATs. These observations suggest that HATs can also affect cell proliferation and differentiation in multiple ways, in addition to chromatin remodeling. It was previously reported that a core circadian regulator, CLOCK, has intrinsic HAT activity [24] and further that it acetylates a nonhistone target, the heterodimeric CLOCK-binding partner BMAL (**Figure 1B**) [25]. CLOCK also acetylates the glucocorticoid receptor and the argininosuccinate synthase, negatively regulating the transactivation capacity and the enzymatic activity, respectively [20, 26]. It is conceivable that CLOCK would directly interact with and regulate key DDR regulators, leading to the acetylation of these proteins and thereby modulating their activities (**Figure 1B**).

4. Roles of circadian clocks in regulation of cell cycle

Circadian clock proteins appear to play roles in cell cycle control, acting as tumor suppressors. They control the timing of cell proliferation by transcriptional control of key cell cycle genes such as *Wee1*, *c-Myc*, and cyclin-dependent kinase inhibitor 1d (20 kDa protein, *p20*) [27–29]. In mammals, PER proteins directly interact with ATM and Chk2 proteins, inducing cell growth inhibition, cell cycle arrest, and apoptosis [17]. In addition, it has been also reported that PER1 and PER2 interact with the androgen receptor (AR) or estrogen receptor (ER), respectively, in that PER1 inhibits AR-dependent transcription and PER2 induces ER degradation [19, 30]. These findings support the idea that clock proteins act as key players in the cell cycle by interacting directly with and regulating the functions of the cell cycle regulators.

In zebrafish, the cell cycle is directly regulated by light [31, 32]. Light determines the timing of mitosis (M phase) and DNA synthesis (S phase), establishing a circadian rhythm for cell cycle progression. At the molecular level, cellular clocks establish the circadian expression of the cell cycle genes, zebrafish *Wee1* and *p20* [29, 32]. The Wee-l kinase controls the timing of the G_2/M transition by directly phosphorylating and inhibiting cell division cycle2 (Cdc2)/cyclin B, leading to the suppression of mitotic cell division. In contrast, p20 regulates the G1/S transition of the cell cycle. Thus, the circadian control of these cell cycle regulators could be a mechanism establishing the circadian rhythm of cell cycle. Both cell cycle and circadian clock are endogenous pacemakers, and these mechanisms coexist in most eukaryotic cells and share several conceptual characteristics. The abovementioned findings point to functional links between the cell cycle and circadian clock in different organisms.

5. Posttranslational modifications contributing to both the circadian clock regulation and the cellular DDR

Posttranslational modifications of proteins regulate various biological processes at molecular levels, including gene expression, chromatin remodeling, and protein stabilization. These molecular events have essential roles in appropriately regulating biological phenomena, including development and circadian clock, by maintaining cellular functions, such as proliferation and molecular clocks, respectively. Posttranslational modifications, such as phosphorylation, sumoylation, and acetylation, control the transcriptional activity, subcellular localization, and stability of circadian clock regulators in multiple ways [4, 33]. In particular, the defects in phosphorylating the circadian clock regulators have been implicated in human sleep disorders [34, 35]. It is also well established that posttranslational modifications are vital for the regulation of the cell cycle and DDR. SIRT1 and casein kinase2 (CK2), already identified as responsible factors for posttranslational modifications of clock proteins [18, 36–39], have also been implicated in posttranslational modifications of proteins such as p53, forkhead box class O (FoxO), and E-cadherin that are involved in cellular metabolism, the cell cycle, and DDR [40, 41]. These findings support the hypothesis that the circadian clocks may be linked to other cellular processes, such as cell cycle control and DDR, through shared posttranslational modifications.

6. Studies on light-dependent regulation of zebrafish circadian clock have revealed links of circadian clock with DNA repair and cellular DDR

To guarantee that an organism's behavior remains tied to the rhythms of its environment, the circadian clocks must respond to environmental stimuli to be reset [2, 10]. The main cue for animals is light, which is provided by the day-night cycle. The mammalian route for circadian entrainment by light uses the retinohypothalamic tract, which connects directly to the central clock located in the suprachiasmatic nucleus of the brain [42]. This makes it difficult to analyze the light entrainment mechanisms of the circadian clocks, especially at cellular levels. Zebrafish peripheral cellular clocks display a striking feature as they are directly light responsive [43]. Notably, in the zebrafish-cultured cell lines, oscillations of clock gene expression can be entrained to new light-dark cycle, and expression of clock genes, such as zebrafish *Cryptochrome1a* (*zCry1a*) and *Period2* (*zPer2*), is transactivated by an acute light pulse [44–46]. These observations show that zebrafish cultured cells have the clock components required for a light-induced reset of circadian clock, therefore, providing a valuable tool for the study of general light-dependent regulation of cellular clocks.

Studies using zebrafish-cultured cells have contributed to identification of cellular signaling cascades involved in the light-dependent regulation of cellular clocks [47]. In several organisms, external stimuli are connected to a cell's nucleus via MAPK signaling pathways, such as p38 and extracellular signal-regulated kinase (ERK) [48]. Light has been reported to activate these signaling cascades in zebrafish cells (**Figure 2**) [49]. By a pharmacological approach, it has also been reported that the light-induced ERK activation triggers expression of *zPer2* and *zCry1a* genes, whereas the light-induced p38 activation suppresses it, highlighting a MAPK-mediated cross-regulatory mechanism of the expression of circadian clock genes [49, 50]. Importantly, an increased understanding of the light-dependent cellular clock regulation in zebrafish has suggested intriguing associations of the circadian clock with DNA repair and cellular DDR as described below.

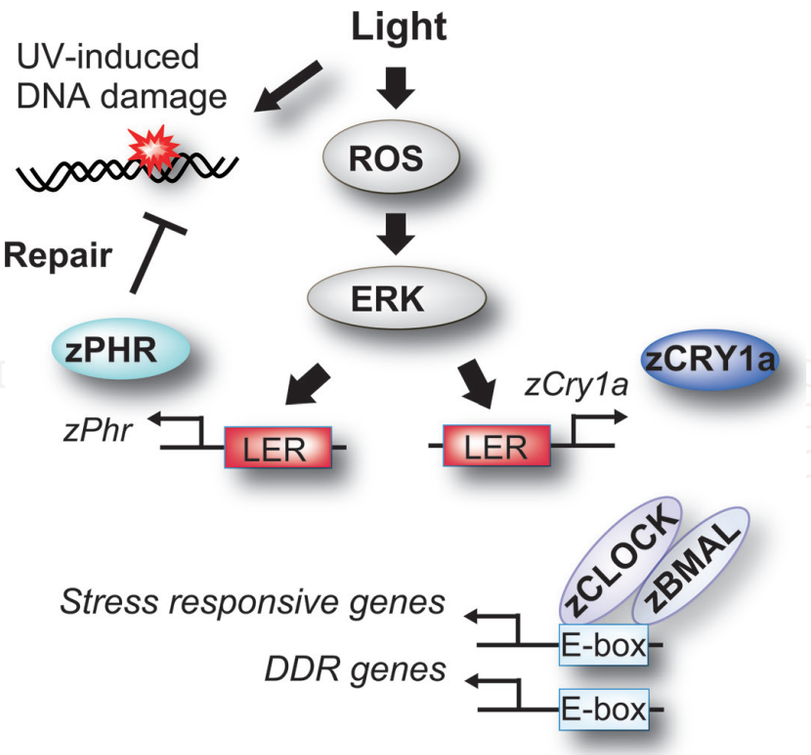

Figure 2.
A proposal model of light signaling pathways involved in shared control of the circadian clock and DNA repair in zebrafish. In a variety of organisms, light induces ROS production. In zebrafish cells, the light-induced ROS stimulate intracellular MAPK/ERK signaling pathway, which transduces photic signal to zCry1a expression. The light-induced zCRY1a interacts directly with the zCLOCK:zBMAL complex and modifies its transcriptional capacity. Notably, the zCLOCK:zBMAL complex regulates the transcription of a variety of genes involved in cellular stress responses and DDR. UV component of sunlight induces DNA damage. Light-induced ROS and activation of MAPK/ERK pathway also induce expression of a DNA repair enzyme, zPHR. The induced zPHR repairs UV-damaged DNA in a light-dependent manner.

7. Shared regulatory pathway for circadian clock and DNA repair in zebrafish

Although solar light has several beneficial uses, including the regulation of circadian clocks, the UV component of solar light is harmful to living cells because it produces cytotoxic and mutagenic lesions in DNA called cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts [(6-4) photoproducts] (**Figure 2**) [51, 52]. Natural selective pressure has forced the development of a self-defense system mediated by photoreactivation. Photoreactivation is the light-dependent DNA repair mechanism mediated by DNA photolyases (PHRs), which bind to and repair the UV-induced DNA damage using visible light as an energy source [53]. Two classes of PHRs have been identified, one specific for CPDs and the other specific for (6-4) photoproducts. Importantly, both the induction of PHRs in response to light and subsequent light-dependent repair of DNA by PHRs are essential for a successful photoreactivation in zebrafish cells [42, 54, 55]. Notably, the expression of the zebrafish *Phr* repairing (6-4) photoproduct (*z64Phr*) is regulated by the same light-induced MAPK cascades as those controlling the expression of the clock genes *zCry1a* and *zPer2* (**Figure 2**) [49]. The light-induced ERK activation triggers the expression of *z64Phr*, whereas the light-induced p38 activation inhibits it. Thus, the light-dependent DNA repair and regulation of the circadian clock are governed by shared regulatory pathways. Both CRYs and PHRs belong to the DNA photolyase/cryptochrome protein family and have highly similar amino acid sequences [42, 55, 56]. Evolutionary studies have shown that the animal CRY proteins functionally diverged first from the CPD photolyase and then further

to generate 64PHR [57]. These facts, together with the observation that *zCry1a* and *z64Phr* share regulatory pathways, strongly indicate an evolutionary link between the circadian clock and DNA repair. Importantly, evolutionary links functionally coupling the circadian clock and DNA repair also have been reported in other organisms. For example, *Neurospora* PRD-4, an orthologue of mammalian Chk2, transduces stress signals into the core circadian clock machinery, contributing the regulation of circadian clock [58]. Additionally, in the diatom *Phaeodactylum tricornutum*, *Phaeodactylum tricornutum* cryptochrome/photolyase family1 (PtCPF1), a novel cryptochrome/photolyase family member, not only repairs UV-induced DNA damage but also acts as a transcriptional repressor of the circadian clock [59].

8. Cellular responses to photooxidative stress are the candidate evolutionary origin of circadian clocks

Cellular reactive oxygen species (ROS) were originally thought to solely act as toxic metabolites because they react with components of DNA, proteins, and lipids and exert oxidative stress. However, ROS are also ideally suited as signaling molecules because they are small and can easily diffuse to short distances within a cell [60]. In addition, mechanisms for ROS production and the rapid removal (such as via catalase) are present in almost all cell types [61]. Much evidence has accumulated indicating significant roles of ROS in circadian clock controls that have resulted in the functional coupling of the circadian clock and DDR. For example, in *Drosophila*, a genome-wide screen identified several redox molecules as essential for the light entrainment of the circadian clock [62]. Similarly, a study in mammals showed that changes in reduced NADPH and NADH levels altered the affinity of the NPAS2:BMAL1 complex for its target DNA *in vitro* [63]. Thus, redox state may be an important determinant of circadian oscillations in mammalian cells. Nuclear factor erythroid-derived 2-like 2 (NRF2) is one of the components involved in the major cellular antioxidant defense pathways [64]. It induces a transcriptional program that maintains cellular redox balance and protects cells from oxidative insults. Importantly, it has been reported in mouse that cellular clock generates circadian rhythm in NRF2 level, which is essential in regulating the rhythmic expression of antioxidant genes involved in glutathione redox homeostasis in the lung [65].

In zebrafish, the transcriptional induction of *zCry1a* and *zPer2* genes has been proposed to be required for the light entrainment of cellular clocks [45, 66, 67]. The light-dependent transcription of *zCry1a* and *zPer2* is controlled through the production and removal of cellular ROS [66, 68]. The light-induced ROS stimulate the intracellular ERK signaling pathway and transduce photic signals to the transactivation of *zCry1a* and *zPer2* (**Figure 2**). Importantly, light increases the intracellular catalase activity by increasing the expression *of catalase*, an event that occurs after the maximum expression of the *zCry1a* and *zPer2* genes has been reached. This increased catalase activity diminishes the light-induced cellular ROS levels, resulting in decreased expression levels of *zCry1a* and *zPer2* genes. These findings provide evidence that ROS induced by light are the second messenger coupling photoreception to the entrainment of the circadian clock in zebrafish and further indicate that cellular responses to photooxidative stress would be the evolutionary origin of circadian clocks.

9. The light entrainment of the circadian clock in zebrafish would reflect a cellular response to photooxidative stress

It is conceivable that the development of circadian clocks is one way to segregate daytime from nighttime processes with light-dark cycles acting as selective forces

[69, 70]. In this scenario, increasing levels of oxygen-free radicals during the daytime may be a decisive factor in relegating the anabolic processes of mitosis, growth, and consolidation to the dark hours. Thus, it is reasonable that cellular signaling cascade mediated by ROS is utilized in the regulation of the circadian clocks and that common regulatory pathways mediate both cellular responses to photooxidative stress and the light-dependent regulation of the circadian clocks (**Figure 2**).

In addition to the photooxidative stress derived from sunlight, the UV component of it is major source of harm to organisms [51, 52]. In zebrafish, the light induces expression of PHRs which repair UV-damaged DNA in a light-dependent manner (**Figure 2**) [49, 71]. Importantly, this light induction of *DNA Phr* expression appears to be mediated by photooxidative stress [68, 72]. These observations are consistent with the idea that photooxidative stress may be utilized as a signal to activate DNA repair enzymes that can protect the organism's DNA from UV-induced damage. The fact that ROS, a well-known inducer of oxidative stress, can activate *zCry1a* transcription in zebrafish cells [66], together with the finding that *zCry1a* and *DNA Phr* are governed by shared light-induced signaling pathways [49], strongly suggests that, at least in zebrafish, the light entrainment of the circadian clock reflects a long-standing cellular response to photooxidative stress (**Figure 2**). The zCRY1a protein interacts directly with the CLOCK (NPAS2):BMAL complexes and regulates its transcriptional capacity [67, 73]. The complexes regulate a variety of key genes involved in cellular stress responses, DNA repair, and cell cycle regulation [14, 74]. Thus, the circadian clock protein zCRY1a may be the key integrator of oxidative stress that controls the core circadian machinery to regulate the transcription of genes responsible for DDR and cell cycle adjustments.

10. Conclusion

Many studies have identified a link between the circadian clock and tumorigenesis [8, 12]. The core of the circadian clock mechanism is the cell-autonomous and self-sustained transcriptional machinery called the cellular clock. Importantly, the cellular clocks have been reported to regulate transcription of tumor suppressors and cell cycle regulators [6, 12]. In addition, circadian proteins appear to play roles in cell cycle control, acting as tumor suppressors [9]. For example, it has been hypothesized that a core circadian regulator, CLOCK, directly interacts with key checkpoint proteins, leading to the acetylation of these proteins and thereby modulating their activities. In support of this idea, *Clock* mutant mice have been reported to be tumor-prone [9].

Cancer chronotherapy relies on the asynchrony that exists in cell proliferation and drug sensitivities between normal and malignant cells [8, 12]. The administration of cancer therapy based on circadian timing has had encouraging results, but still lacks a strong mechanistic foundation. Thus, identification of detailed molecular links between the circadian clocks and tumorigenesis will provide the functional basis of cancer chronotherapy.

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