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INVITED REVIEW

Prostate Cancer

Circadian rhythm in prostate cancer: time to take notice of the clock

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The circadian clock is an evolutionary molecular product that is associated with better adaptation to changes in the external environment. Disruption of the circadian rhythm plays a critical role in tumorigenesis of many kinds of cancers, including prostate cancer (PCa). Integrating circadian rhythm into PCa research not only brings a closer understanding of the mechanisms of PCa but also provides new and effective options for the precise treatment of patients with PCa. This review begins with patterns of the circadian clock, highlights the role of the disruption of circadian rhythms in PCa at the epidemiological and molecular levels, and discusses possible new approaches to PCa therapy that target the circadian clock.

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INTRODUCTION

As early as the 18th century, Mairan, a French scientist found that light did not affect the 24-h fluctuation of mimosa leaf activity, revealing the existing potential endogenous rhythms of organisms. Circadian rhythm can help reconcile a large amount of behaviors, physiological processes, and functions in the human body with circadian changes, such as the sleep–wake cycle, feeding, and other autonomic activities, as well as essential physiological activities, such as the maintenance of proper blood pressure, heart rate, basal body temperature, hormone levels, and the normal operation of cell metabolism, cell proliferation, and immune regulation.[1–3] Therefore, unsurprisingly, circadian disruption is associated with poor health status and many diseases, such as aging,[4] inflammation status,[5] degenerative changes in the central nervous system,[6] cardiovascular diseases,[7] metabolic diseases,[8] and cancers,[9] including prostate cancer (PCa).[10]

Generally, the generation, maintenance, and regulation of circadian rhythm physiologically depend on central and peripheral clock systems as well as the coordination of rhythm input and output systems. The central clock generated in the suprachiasmatic nucleus (SCN) plays a leading role in circadian rhythm regulation, cooperating with environmental signals and output systems, such as the autonomic nervous system and the neuroendocrine system.[11,12] As the secondary pacemaker of the circadian rhythm, on the one hand, peripheral clocks are controlled by various signal factors of neurohumoral regulatory systems under the central clock directly or indirectly. On the other hand, they can operate independently of the control of SCN. At the cellular level, the circadian rhythm is a 24-h oscillation consisting of a series of transcriptional and translational regulatory feedback loops. Posttranslational modifications and degradation of clock genes and clock control genes are also involved in maintaining the stabilization of homeostasis, behaviors, and other basic life activities in the human body related to better adaptation to changes in the external environment.[4,13–15]

MOLECULAR REGULATORY MECHANISMS OF THE CIRCADIAN CLOCK

As mentioned above, the generation and maintenance of circadian rhythm are controlled by clock genes and clock control genes. A study has shown that approximately 10% of genes in cells are rhythmically expressed.[16] Circadian genes exert their effects mainly through the transcriptional translational oscillator (TTO), the main part of the classical circadian clock regulation network. TTO primarily consists of two interconnected negative feedback loops. Circadian locomotor output cycles kaput (CLOCK) and its chaperone neuronal per-arnt-sim (PAS) domain-containing protein 2 (NPAS2) form a heterodimer with aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL; also identified in brain and muscle as Arnt-like protein-1, BMAL1) to initiate the transcription of target genes encoding period circadian protein (PER) and cryptochrome (CRY), by directly binding to the E-box enhancer element (the sequence CACGTG) located in its upstream promoter regions in the daytime.[17–19] With the accumulation of PER and CRY proteins, the newly formed PER and CRY protein heterodimers are transferred into the nucleus and in turn interact with CLOCK/BMAL1 heterodimers to suppress their own transcription.[19] At the same time, the levels of CRY and PER proteins are decreased by ubiquitination activity and degradation of several ligases,[20,21] relieving the negative feedback suppression intensity of CLOCK/BMAL1 and ultimately resuming a new TTO cycle. In addition, CLOCK/BMAL1 heterodimers can induce the expression of nuclear receptors Rev-erb α and retinoic acid receptor (RAR)-related orphan receptors (RORs). The combination of Rev-erb α or RORα with ROR binding element (RRE) in the promoter region of *BMAL1* promotes or

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represses *BMAL1* transcription, respectively, which forms the auxiliary loop of TTO.[22,23] Because of these processes, the oscillation cycle of upregulation and downregulation of core circadian rhythm-regulating genes takes approximately 24 h. This oscillation not only endows the transcriptional activity of the CLOCK/BMAL1 heterodimer with a rhythmic characteristic, but also leads to the rhythmical expression of downstream clock control genes, and thus, a circadian rhythm forms.[24] Furthermore, basic leucine zipper proteins, such as D-box binding protein (DBP; the direct target of BMAL1/CLOCK heterodimers), and the repressor E4 promoter-binding protein 4 (E4BP4; the direct target of REV-erb α), can also regulate PER expression via the D-box, further complicating the signal transmission network of the TTO loop.[25,26]

CIRCADIAN CLOCK DISRUPTION AND PCA

PCa is one of the most common cancers in men living in European and American areas and is also the main cause of death.[27] According to the 2022 cancer (CA) estimated statistics, PCa ranks first in the prevalence of male malignant tumors and second in mortality, separately accounting for 27% and 11% in the USA.[28] Although good progress has been made in the treatment of PCa, PCa remains one of the major health threats to men worldwide.[29–31] Despite the relatively high morbidity and mortality, the etiology of PCa is not fully understood. However, according to some migrant studies, Asian Americans had a higher PCa rate than their counterparts living in Asia, indicating the significance of environment, lifestyle, and consequent circadian rhythm disruption in PCa formation.[32–34] More importantly, as an age-related disease, the incidences of benign prostatic hyperplasia (BPH) and PCa increase with age, and the circadian rhythms also deteriorate with age due to many reasons, revealing a possible relationship between the circadian clock and PCa.[4,35] Transurethral plasmakinetic resection of prostate (TUPKP) is one of the most mature management patterns for BPH patients with detailed and comprehensive guidelines,[36,37] while PCa patients need more attention. As a supplement, increasing evidence shows the association between circadian rhythm disruption and prostate carcinogenesis as well.[10] Both exogenous and endogenous factors can induce PCa risk-associated circadian disruption according to a large amount of epidemiological data and many consequent studies, including endogenous factors such as aging and alternations of the endocrine system, as well as changes in night-shift work, sleep patterns, and intermittent fasting as exogenous alterations. **Figure 1** illustrates the possible link among endogenous factors, exogenous factors, circadian rhythm, and PCa.

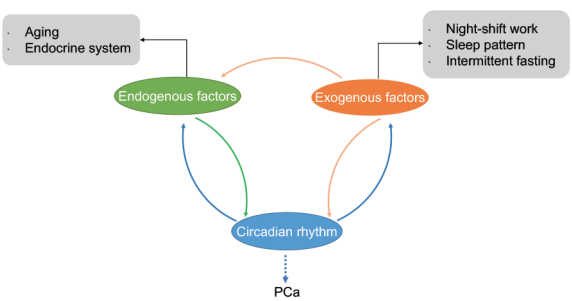

Figure 1: Relationship among exogenous factors, endogenous factors, circadian rhythm and PCa. Changes in endogenous factors and exogenous factors are both involved in the disruption of circadian rhythm, which is potentially related to PCa. Alternations in circadian rhythm also impact endogenous and exogenous factors. In addition, alternations in the lifestyle of exogenous factors, including night-shift work, changes in sleep patterns and intermittent fasting, play a role in aging and endocrine disturbance. PCa: prostate cancer.

Aging is closely tied to the circadian clock. Many studies have suggested that the structure and composition of the SCN are related to age. Compared with young people, the total number and volume of SCN cells decreased in elderly individuals,[38,39] and the composition of SCN also changed, mainly in the decreased expression of arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP).[40–42] In addition, the decrease in γ-aminobutyric acid (GABA) with aging also affects synaptic transmission in the SCN to some extent, which could underlie aging-related SCN dysfunction, resulting in circadian disruption.[43] This was also suggested by the deterioration of the electrical activity rhythmicity of the SCN associated with aging.[44] More remarkably, although the relationship between aging and circadian gene expression has not been directly confirmed, a study found that rhythmic PER expression decreased with aging.[45] In addition, it was reported that aging perhaps inhibited oscillation in circadian gene expression.[46,47] In addition, the circadian rhythm also affects the aging process in turn. Aging experimental animals that received fetal SCN tissue transplantation had a longer life span, while their circadian rhythms were restored.[48] In contrast, experimental animals receiving clock gene knockout showed accelerated aging phenotypes. For example, in addition to the loss of circadian rhythms, BMAL1-deficient mice also developed symptoms of premature aging, such as cataracts and organ shrinkage.[49] Similarly, the life span of *Drosophila* lacking PER was significantly shortened.[50] The interaction between circadian rhythm and aging may be mediated by sirtuin 1 (SIRT1), an nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylase.[4] SIRT1 is significantly elevated in human PCa, acting as an oncogene and epigenetic regulator in tumorigenesis by anti-apoptotic activity.[51,52] It plays a critical role in tumor cell proliferation, invasion, migration, and drug resistance of PCa.[53,54] Therefore, aging and aging-related circadian clock disruption may play an important role in the occurrence and development of PCa.

For the endocrine system, the alterations in melatonin and cortisol mainly contribute to circadian disruption. Rhythmic melatonin release is under the control of SCN and it plays a role in modulating the downstream rhythms of the main circadian clock. For example, endogenous rhythmic release of melatonin is involved in healthy sleep patterns, maintenance of basal body temperature, and physiology of inner retinal photoreceptors.[55,56] Exogenous melatonin supplementation can act as a "chronobiotic" in the treatment of circadian disruption, which was also found to inhibit tumor initiation and growth in animal models and human breast cancer cell lines.[55,57–59] The secretion of total melatonin decreases with age, and the rhythm of melatonin secretion also changes in elderly people compared to younger people.[60–62] Interestingly, a study by Zeitzer *et al.*[63] reported that very healthy older men had a melatonin rhythm similar to that of younger people, which may suggest that normal melatonin rhythms can maintain normal circadian rhythms, and thus protect against diseases, including PCa. Similar to melatonin, cortisol release is regulated by SCN and is involved in the rhythmic expression of downstream clock genes.[64–67] Similarly, changes in cortisol rhythm are age-related, and its disruption has been linked to age-related diseases.[68–71]

In terms of night-shift work, studies on whether night-shift work involving disruption of circadian rhythm is related to an increased PCa risk remain contradictory. For example, a large case-control study by Barul *et al.*[72] found no supportive result for a major role of night-shift work in PCa development. In contrast, another large case-control study conducted by Lozano-Lorca *et al.*[73] suggested that night-shift work could increase PCa risk. Several cohort studies also showed controversial results. For instance, Behrens *et al.*[74] reported increased risks of PCa among men involved in night-shift work, while

Dickerman *et al*.[75] found no significant relation between night-shift work and PCa risk. In general, among large clinical studies published in recent years, six suggested a link between night-shift work and PCa,[73,74,76–79] while 4 studies did not[75,80–82] (**Table 1**). Several previous meta-analyses and systematic reviews did not reach consistent conclusions about night-shift work and PCa risk.[10,83] Among them, the most recent meta-analysis published in 2020 conducted by Rivera-Izquierdo *et al*.[84] reported no association between rotating/night-shift work and PCa, as did another meta-analysis conducted by Dun *et al*.[85] Reasons for these contradictory results may include the following: (1) the lack of a standardized definition of night-shift work and exposure assessment among different studies; (2) it is difficult to keep the baseline levels consistent in the study population, since many other factors, such as sleep–wake cycles, eating habits, and even mood changes could affect the subjects' own circadian rhythms; and (3) each person in those studies had their own circadian rhythm, which was not equally affected by night-shift work. Moreover, some epidemiological studies also showed that changes in sleep patterns, such as sleep with low quality or short duration, were associated with increased risks of PCa.[86,87] However, a systematic review including 16 epidemiological studies did not draw a definite conclusion and suggested that more studies were still needed on the potential impact of circadian disruption and sleep patterns on PCa risk.[88] Furthermore, intermittent fasting seems to regulate the circadian clock and protect against carcinogenesis.[89] A study by Palomar-Cros *et al*.[90] suggested that a prolonged night-time fasting duration might be associated with a lower risk of PCa. Remarkably, a study in *Drosophila* suggested that the longevity extension from fasting was achieved by increasing the expression of several peripheral clock genes that regulate fat metabolism.[91] Fat metabolism was confirmed to play a critical role in PCa, especially in castration-resistant PCa (CRPC).[92] Presumably, we can speculate that fasting may reduce the risk of PCa, and even play a role in CRPC by regulating the circadian rhythm. Changes in the circadian clock can also affect these exogenous factors in reverse. For example, CLOCK deficiency can lead to premature cataracts,[93] which affects melatonin secretion and changes sleep patterns.[94] There is no consensus on the effect of different exogenous factors causing circadian rhythm disruption on PCa risk, which may be due to the existence of many endogenous factors, such as aging and endocrine disturbance mentioned above, which were not covered by previous baseline criteria for epidemiological study populations.

MOLECULAR MECHANISMS OF THE CIRCADIAN CLOCK IN PCA

At the cellular level, when studying exogenous factors in PCa risk, the role of circadian-associated genes in PCa should also be taken into account because they have been shown to probably regulate the influence of night-shift work in breast cancer.[95,96] A variety of epidemiological studies suggested that variants of *CRY1*, *CRY2*, *NPAS2*, *CLOCK*, *PER2*, and *RORA* were associated with increased or decreased PCa risk[97–102] (**Table 2**). Additionally, *CRY2*, *NPAS2*, *RORA*, and *BMAL1* were found to be associated with PCa progression.[103] Several studies based on epidemiological study of prostate cancer (EPICAP, a population-based case–control study in France)[104] showed that *ARNTL*, *NPAS2*, and *RORA* were significantly associated with PCa, especially among night workers, and *RORA* was related to aggressive PCa.[105,106] Under an equilibrated status, circadian genes may regulate and even inhibit tumor progression by regulating DNA repair, and the process of the cell cycle, and ultimately affect cell proliferation.[107] In addition, circadian genes participate in inflammation and tumor immunity[108] (**Figure 2**).

NPAS2 is suggested to play a putative role in c-myc transcriptional inhibition.[109] *NPAS2* is involved in the repair of DNA damage[110] and cell cycle processes by regulating its diverse downstream genes.[111] Until now, there have been few studies on the relationship between *NPAS2* and PCa. A case–control study conducted by Chu *et al*.[97] suggested that the *NPAS2*-variant A allele was related to a decreased PCa risk among men with less insulin resistance than their counterparts. Another large-scale case–control study based on Americans reported the linkage

Table 1: Epidemiological association between night-shift work and prostate cancer

Study	*Study type*	*Shift patterns*	*Participants*	*Conclusions*
Lozano-Lorca *et al*.[73] 2020	Case–control study	Working partly or entirely ≥3 h between 22:00 and 06:00, at least three times per month	465 PCa cases and 410 controls	Night shifts, especially rotating night shifts, could increase PCa risk
Barul *et al*.[72] 2019	Case–control study	Working ≥3 h between midnight and 05:00, ≥3 nights per month for ≥1 year	1904 PCa cases and 1965 controls	Night-shift work was not associated with PCa development
Wendeu-Foyet *et al*.[81] 2018	Case–control study	Shift starting between midnight and 06:00 Shift ending between 21:00 and 02:00 Shift starting before 00:00 and ending after 05:00	819 PCa cases and 879 controls	Night work was not associated with PCa
Behrens *et al*.[74] 2017	Cohort study	A shift including work between 00:00 and 05:00	1757 men	Shift or night work was associated with increased risk of PCa
Åkerstedt *et al*.[82] 2017	Cohort study	Lack of a definite definition of shifts	12 322 male twins	Night work was not significantly associated with PCa
Dickerman *et al*.[75] 2016	Cohort study	Night shifts in either a 2-shift or 3-shift pattern	11 370 twins	Shift work was not significantly associated with PCa risk
Papantoniou *et al*.[79] 2015	Case–control study	Working partly or entirely between 00:00 and 06:00, at least three times per month	1095 PCa cases and 1388 controls	Night-shift work was associated with PCa, particularly for tumors with worse prognosis
Hammer *et al*.[80] 2015	Cohort study	3 ×12 h patterns and 4 ×12 h patterns	12 609 rotating shift workers and 15 219 daytime workers	Both groups of workers had a higher incidence of PCa than the general population
Parent *et al*.[78] 2012	Case–control study	Working between 01:00 and 02:00 for at least 6 months	400 PCa cases and 533 controls	Night work may increase PCa risk
Conlon *et al*.[77] 2007	Case–control study	Lack of a definite definition of shifts	760 PCa cases and 1632 controls	Working full-time rotating shifts may be associated with increased risk of PCa
Kubo *et al*.[76] 2006	Cohort study	Lack of a definite definition of shifts	14 052 men	Rotating-shift was associated with increased risk of PCa

PCa: prostate cancer

Table 2: Genetic association between circadian genes polymorphisms and prostate cancer

Circadian gene	*SNP*	*PCa risk*	*Reference*
NPAS2	*rs895521*, *rs1369481*, *rs2305160*	Decreased	97,98,102
	rs17024926	Increased	
	rs6542993	Increased risk of PCa progression	
BMAL1	*rs7950226*	Increased	98,101
	rs142435152	Associated	
CLOCK	*rs11133373*	Decreased in heterozygous variant	98
CRY1	*rs12315175*, *rs10778534*	Increased	98–100
	rs7297614, *rs1921126*	Associated with fatal PCa	
CRY2	*rs2292912*	Decreased in heterozygous variant	97,98
	rs1401417	Increased	
PER1	*rs885747*	Decreased in heterozygous variant	98
	rs2289591	Increased in heterozygous variant	
PER2	*rs7602358*	Decreased in heterozygous variant	98
PER3	*rs1012477*	Decreased in heterozygous variant	98,100
	rs228697	Decreased	
RORA	*rs17191414*	Associated	101

PCa: prostate cancer; SNP: single nucleotide polymorphism; *NPAS2*: neuronal per-arnt-sim (PAS) domain-containing protein 2; *BMAL1*: aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL, also identified in brain and muscle as Arnt-like protein-1); *CLOCK*: circadian locomotor output cycles kaput; *CRY1*: cryptochrome 1; *CRY2*: cryptochrome 2; *PER1*: period circadian protein 1; *PER2*: period circadian protein 2; *PER3*: period circadian protein 3; *RORA*: retinoic acid receptor (RAR)-related orphan receptor A

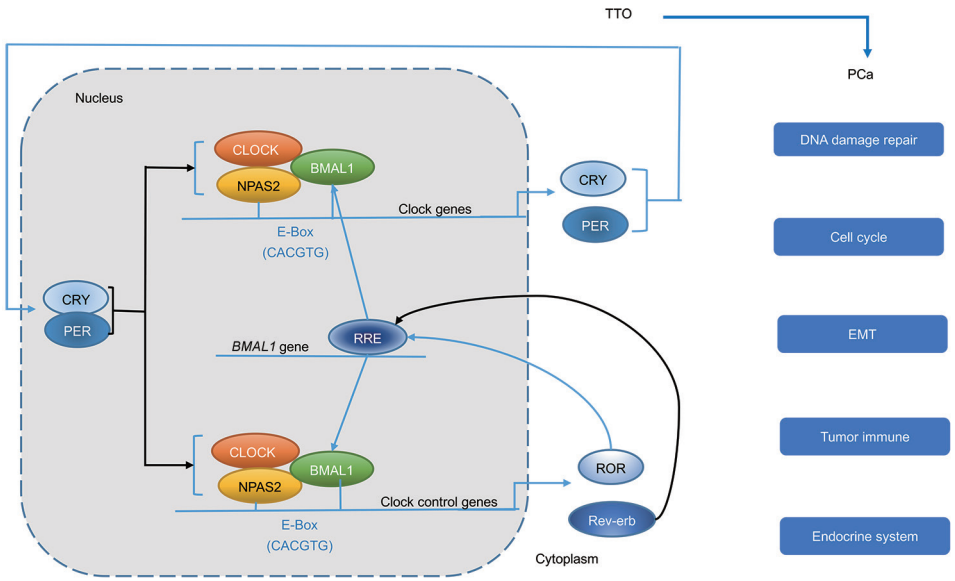

Figure 2: Circadian clock and PCa. The molecular organization of the circadian clock is based on the TTO, which is mainly composed of two negative feedback loops. Through the functions of TTO at the cellular level, the circadian clock eventually plays a role in DNA damage repair, the cell cycle, EMT, and the tumor immune and endocrine system of PCa. The blue arrows represent the positive effect and the black arrows represent the negative effect. TTO: transcriptional translational oscillator; PCa: prostate cancer; CLOCK: circadian locomotor output cycles kaput; BMAL1: aryl hydrocarbon receptor nuclear translocator-like protein 1 (ARNTL, also identified in brain and muscle as Arnt-like protein-1); NPAS2: neuronal per-arnt-sim (PAS) domain-containing protein 2; CRY: cryptochrome; PER: period circadian protein; ROR: retinoic acid receptor (RAR)-related orphan receptors; RRE: ROR binding element; EMT: epithelial-mesenchymal transition.

between *NPAS2* variants and PCa susceptibility as well.[98] Moreover, a new study conducted by Yu *et al.*[102] revealed a potential relationship between *NPAS2* expression and PCa progression. However, *NPAS2* has been regarded as a prognostic biomarker of breast cancer and colorectal cancer,[112,113] the silence of whose expression was reported to promote the proliferation and invasion of colorectal cancer cells,[113] indicating possibly similar roles of *NPAS2* in tumor development, metastasis, and prognosis in PCa.

The expression of *CRY1* is predominantly regulated by *ROR* and *REV-erb*, and *CRY2* is rather directly controlled by the CLOCK/BMAL1 heterodimer.[114] *CRY1* was found to be involved in DNA repair and the cell cycle process of PCa cells[115] and its variants were associated with the prognosis of PCa.[100] Previous studies on the relationship between *CRY2* and PCa risk showed that different variants of *CRY2* corresponded to different PCa risks.[97,98] Currently, although there is only a little direct evidence linking *CRY2* to PCa, studies about thyroid cancer and breast cancer have confirmed that high expression of *CRY2* seems to be a protective factor against cancers.[116,117] More importantly, animal experiments showed that the activation of the CLOCK/BMAL1 heterodimer caused by synchronous ablation of CRY1

and CRY2 could prevent cancer progression and improve prognosis, suggesting that the negative influence of circadian rhythm disruption might be minimized as long as the CLOCK/BMAL1 heterodimer was continuously activated.

PER1 also plays an important role in controlling DNA damage and cell growth, interacting with proteins in cell-cycle pathways as well.[118] Not only was *PER1* regulated by androgen in PCa cells, but overexpression of *PER1* also led to significant growth inhibition and apoptosis in PCa cells.[119] In addition, overexpression of *PER2* was also found to result in a significant inhibition of PCa cell growth and viability,[120] which was related to *mPER2* to an extent, a tumor suppressor gene participating in DNA damage response regulation.[109] For *PER3*, its low expression level stimulates *BMAL1* expression, leading to the activation of the wingless/integrated (WNT)/β-catenin pathway,[121] which is involved in cell proliferation and transcription.[122,123] The epidemiological linkage between PCa risk and variants as well as expression of those circadian genes has been reported in many previous studies.[124]

Furthermore, increasing evidence shows that chronic inflammatory status is involved in prostate carcinogenesis.[125] The disruption of the circadian rhythm may be related to epithelial–mesenchymal transition (EMT) induction and contribute to the formation of a proinflammatory environment at the systemic level and even in the tumor microenvironment (TME) of PCa.[108] For example, the downregulation of *PER2* was related to the expression of EMT-transcription factors (TFs) and increased EMT-specific cellular characteristics.[126] It has been confirmed by many studies about other cancers that circadian rhythm disruption may link EMT to inflammation to favor the dissemination of cancer cells,[108] which may also be one of the molecular mechanisms of prostate carcinogenesis. In addition, intrinsic circadian clock disruption of many immune cell types, such as macrophages, neutrophils, natural killer (NK) cells, T cells, and dendritic cells (DCs), affects immune escape and immune exclusion,[108,127–129] thus affecting the progression of PCa.

On the other hand, owing to the close link between circadian rhythm and the endocrine system, various endocrine hormones are modulated by circadian clocks.[130] Melatonin and cortisol are not only upstream regulators but also downstream targets of the circadian clock. Moreover, androgen levels are also regulated by the circadian clock. Studies *in vivo* have shown that androgen is important for the growth of PCa as well as normal cells.[131,132] Circadian rhythm may affect PCa evolution by regulating androgen and androgen-associated productions.[133,134] Melatonin and cortisol have the capacity for tumor-suppression and immunosuppression. The finding that PCa patients had lower melatonin levels than patients with BPH suggested the potential protective role of melatonin against prostatic disease progression.[135] A low level of melatonin was also reported to be associated with an increased risk of PCa. Mechanistically, melatonin inhibits the accumulation of intracellular lipid droplets, as well as cell proliferation and migration. It also reduces endogenous androgen biosynthesis in CRPC mouse models by upregulating the expression of lipid metabolism-related carboxylesterase 1 (CES1).[136] However, there was also a study that did not support the inhibitory effect of melatonin on PCa.[137] Cortisol is another important endocrine factor for circadian rhythm modulation.[68,138] The inverse relation between the melatonin/cortisol ratio and the presence and stage of PCa indicated the potential synergistic anticancer effects of melatonin and cortisol.[139] Therefore, it is of great significance to understand the specific roles of melatonin and cortisol in the initiation, development, and progression of PCa, which may guide the prevention and treatment of PCa.

TREATMENT TARGETING THE CIRCADIAN CLOCK

There are also circadian changes in drug pharmacokinetics.[140] The use of chronotherapy, a term generally described as using timed dosing to reach optimal therapeutic effects, has achieved good efficacy in cardiovascular diseases.[141,142] When given at different times of the day, many anticancer agents show a 2–10 times variation in drug tolerability in mouse models and the time-related variations in drug tolerance have been confirmed by clinical trials of patients with cancer.[140,143,144] Chronotherapy has shown clear success in PCa outcome and improved management of the disease.[145] In addition to drug therapy, chronotherapy can also be applied to radiotherapy. Morning proton beam therapy for localized PCa was observed to significantly ameliorate the worsening lower urinary tract symptoms, compared with therapy around noon or late afternoon.[146] Drug castration in androgen deprivation therapy (ADT) is also a common treatment for PCa patients. Although patients who lack indications for surgery and radiotherapy are treated with ADT, the majority of patients undergoing ADT therapy will progress to CRPC.[147] Both epidemiological and laboratory studies suggest the importance of lipid metabolism in PCa progression and resistance to endocrine therapy[148] and ADT therapy significantly changed lipid metabolism in patients with PCa.[149] Circadian clock genes are involved in lipid metabolism regulation and variants of circadian genes may be associated with varying serum sex steroid levels.[91,134] Therefore, ADT may aggravate circadian clock disruption and promote the progression of CRPC, and therapy targeting the circadian clock may be a new option for treating CRPC. In addition, cell proliferation regulated by circadian rhythm often shows asynchrony between normal and malignant tissues, which is also one of the theoretical bases for cancer chronotherapy.[107] Despite the lack of specific studies about circadian changes and the corresponding chronotherapeutic plans of these drugs, treatment based on circadian changes in castration drugs may also be an ideal option.

Moreover, treatment strategies that involve gene editing or strict changes to a patient's behavior and lifestyle are clearly not ideal enough for a number of reasons. Exogenous melatonin supplementation may resynchronize the circadian rhythm, helpfully providing a novel way in PCa management.[120] The study of Zhou *et al*.[136] has proven that melatonin therapy inhibits tumor growth and reverses enzalutamide resistance in CRPC animal models with a disruption of circadian rhythm. This may be because melatonin reverses the circadian rhythm disruption aggravated by ADT therapy, thus exerting its therapeutic effect on CRPC. Melatonin was also found to inhibit PCa metastasis in both *in vitro* and *in vivo* models.[150] Employing transgenic adenocarcinoma of mouse prostate mice, Jung-Hynes and colleagues also demonstrated that oral melatonin intake, at human-achievable doses, significantly inhibited PCa tumorigenesis.[151] Notably, in animal models, exogenous melatonin intake was found to inhibit neutrophil migration in a dose-dependent and time-dependent manner.[152] Although a similar pattern has not been found in men with PCa, the amount and timing of exogenous melatonin supplementation should be carefully considered. Other pharmaceutical agents that directly target the circadian clock might also be a new option. For instance, a small molecule named longdaysin was shown to lengthen the circadian period and lead to PER1 degradation by targeting multiple kinases simultaneously.[153] Another small molecule called KL001 was also found to lengthen the period of circadian clock by stabilizing CRY proteins.[154] It is rather predictable that when combined with chronotherapy, these small molecules may have therapeutic potential by restoring the circadian rhythm in many biological processes in the

body. Interestingly, in addition to therapeutic applications, circadian rhythm may help in surveillance of PCa metastasis. Zhu *et al.*[155] found that daily fluctuations in circulating tumor cell (CTC) count peaked during the nocturnal active phase in rodents, confirming that CTC release may also be related to circadian rhythms.

CONCLUSIONS

As described in this review, disruption of the circadian clock strongly influences PCa initiation and development through changes in multiple regulatory pathways, including the cell cycle, EMT, tumor immunity, and the endocrine system. Although a relatively strong relationship between circadian disruption and PCa has been established, more mechanisms of how the circadian clock regulates PCa progression need to be elucidated, such as the exact molecular mechanisms of tissue-specific circadian gene expression and their impacts on prostate tumorigenesis. At the population level, after excluding other related confounding factors, the role of circadian rhythm disruption in the occurrence and development of PCa also needs further exploration. In addition, it is critical to establish reasonable chronotherapeutic strategies, especially ensuring the optimal administration time and schedule. In summary, further research on circadian rhythm could help the prevention and treatment of PCa.

AUTHOR CONTRIBUTIONS

WZZ and QYH proposed the project and wrote the manuscript. DCF revised and supplemented the manuscript. QW and LY supervised the project. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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