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The Role of Circadian Rhythm Disruption in Prostate Cancer Development: Epidemiological, Molecular, and Therapeutic Perspectives

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Abstract. Circadian rhythm disruption has been increasingly recognized as a critical factor in the development and development of prostate cancer. Through a comprehensive examination of epidemiological evidence, molecular pathways, and experimental studies, circadian misalignment is shown to influence key biological processes that regulate hormone production, DNA repair, and immune function, all essential to maintaining cellular homeostasis. Disruptions in circadian rhythms can lead to altered gene expression, impacting pathways associated with tumour development. Epidemiological data reveal an elevated risk of prostate cancer in individuals with irregular circadian patterns, such as shift workers, further reinforcing the link between circadian dysregulation and cancer risk. Molecular studies have identified potential therapeutic targets within circadian- regulated pathways, offering new opportunities for intervention. Therapeutic approaches aimed at restoring circadian alignment may not only prevent prostate cancer but also improve treatment outcomes by enhancing the effectiveness of current therapies. Understanding the character of circadian rhythms in prostate cancer opens new avenues for prevention and treatment strategies that could ultimately improve patient prognosis. This paper delves into the strong link between circadian rhythm disruption and prostate cancer. Based on the comprehensive analysis of the basic concept of circadian rhythm, the characteristics of prostate cancer, and the epidemiological evidence, molecular mechanism, experimental studies and potential therapeutic targets associated with the two, it is concluded that circadian rhythm disorder plays a crucial role in the occurrence and development of prostate cancer, which provides a new perspective and direction for the prevention and treatment of prostate cancer.

Keywords: Circadian rhythm disruption, prostate cancer, molecular mechanisms, tumour development.

1. Introduction

Prostate cancer is a major global health concern. As a common malignant tumour in the male urogenital system, prostate cancer is one of the major diseases that threaten the life and health of men worldwide. There are 1.41 million new cases of prostate cancer and 375,000 deaths due to disease every year in the world, making it the second most common tumour in the world. The high incidence and mortality of prostate cancer brings huge expenses to families and a heavy burden on society. Understanding the

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underlying mechanisms of prostate cancer occurrence and progression is essential for developing effective prevention and treatment strategies.

Circadian rhythm is defined as the physiological, behavioural, and biochemical changes that an organism exhibits over a period of approximately 24 hours and is a natural, intra- organism process that regulates the sleep- wake cycle and approximately repeats. It is controlled by circadian clock genes and their regulatory networks, and is endogenous, heritable, and environmentally sensitive. From the sleep-wake cycle to hormone secretion, cell metabolism, and more, the circadian rhythm plays a key role in maintaining the normal function of the body. The circadian system serves as a biological clock mechanism that aligns an organism's internal state with environmental changes[1].The mechanism of the human biological clock can be divided into a central clock and a peripheral clock, and the central biological clock is located in the suprachiasmatic nucleus of the hypothalamus, which is a brain nucleus called the suprachiasmatic nucleus in the brain. Peripheral circadian clocks are regulated through neural and endocrine signalling to synchronize with the environment. Peripheral circadian clocks are found in various tissues and organs, including the prostate. In recent years, more and more studies have shown that circadian rhythm disorders are closely related to the occurrence and development of a variety of diseases.

This review aims to comprehensively examine the critical link between circadian rhythm disruption and the development of prostate cancer. By exploring epidemiological characteristics, molecular mechanisms, and recent experimental studies, we aim to provide ins light into how circadian rhythm dysregulation contributes to the onset and progression of prostate cancer. Additionally, this review seeks to highlight potential therapeutic targets and strategies that leverage the regulation of circadian rhythms, providing new ways to prevent and treat the prostate cancer.

2. The association between circadian rhythm and prostate cancer

The connection between circadian rhythm and prostate cancer has been explored extensively, with numerous epidemiological studies demonstrating an increased risk of prostate cancer among individuals who work night shifts or maintain irregular lifestyles. For many years, all living beings, including humans, had an internal biological clock that allowed them to adapt to the diurnal cycle and find the rhythm of life. Working night shifts may cause disruption of the biological clock, affecting our hormone secretion, immune function and cell metabolism, thereby promoting the development of prostate cancer.

2.1. Circadian rhythm influences melatonin levels in relation to prostate cancer

Melatonin is an indoleamine primarily synthesized by the pineal gland, as well as other organs in smaller amounts [2]. It plays a key role in regulating circadian rhythm and sleep- wake rhythm and has the functions of regulating circadian rhythm and antioxidant. Studies have found that the decrease in melatonin levels at night is related to the development of prostate cancer. Melatonin may exert anti-tumour effects by inhibiting tumour cell proliferation, inducing apoptosis, and modulating immune function.

2.2. Circadian rhythm affects prostate cancer by affecting metabolism

Disrupted circadian rhythms both directly and indirectly lead to aberrant epigenetic modifications result in cell proliferation and cancer [3].Circadian regulation of physiology and behaviour is necessary for healthy living. A growing body of epidemiological and genetic evidence suggests that disruption of circadian rhythms is associated with metabolic disorders. At the molecular level, the circadian clock operates through a complex network of interrelated transcriponal-translaonal feedback loops[4].Clock proteins regulate metabolism through the following two pathways: firstly, clock proteins act as transcription factors to directly regulate the expression of rate- limiting enzymes and metabolism-related nuclear receptors of some metabolic key steps, and secondly, they act as coregulators of metabolism- related nuclear receptors to activate or inhibit their transcriptional activity. Although the regulation of metabolic pathways by clock proteins leads to circadian oscillation, the metabolites produced can in turn affect the expression of circadian clock genes, which in turn affects circadian clocks.

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In- depth study of the interaction between circadian clock and metabolism may provide new treatment options for the treatment of certain metabolic disorders. Epidemiological studies support the association between metabolic syndrome and the development of prostate cancer. Although the underlying biological mechanisms remain unelucidated, in vitro and animal studies have shown that metabolic syndrome can promote tumour proliferation, cell mitosis, distant metastasis, and drug resistance through adaptive mechanisms such as intracellular steroids and adipogenesis. Changes in hormone levels such as testosterone, leptin, and adiponectin in people with metabolic syndrome can promote prostate cancer.

Prostate cancer development and mortality rate: a review of diet and lifestyle factors. Poor lifestyle, such as lack of sleep, not eating on time, lack of exercise, etc., may also lead to circadian rhythm disruptions, which can increase the risk of prostate cancer[5]. For example, a high- fat, high- ca Lorie diet may interfere with the expression of circadian clock genes and affect the normal physiological function of the prostate.

3. Molecular mechanism of circadian genes influencing prostate cancer

Circadian genes play a crucial role in regulating various biological processes, and their dysregulation has been closely associated with the advancement of prostate cancer. Key circadian genes, such as CLOCK, BMAL1, PER, and CRY, are involved in remain the circadian rhythm, which governs the cell cycle, DNA repair, metabolism, and apoptosis. When these genes malt unction or are abnormally expressed, it can lead to circadian rhythm disruption, which in turn promotes tumour progression by influencing processes like tumour cell proliferation, invasion, and resistance to apoptosis. Understanding the molecular mechanisms through which circadian genes influence prostate cancer provides insights into potential therapeutic strategies targeting circadian rhythms.

3.1. CLOCK gene

The first is the core genes of circadian rhythm and its role in prostate cancer. One is the CLOCK gene: the CLOCK gene is one of the core genes of the circadian clock, which is a gene that encodes a protein, which is involved in circadian rhythm regulation and is expressed in prostate cells. Studies have shown that mutations or abnormal expression of the CLOCK gene may be related to the occurrence and progression prostate cancer. CLOCK proteins regulate processes such as cell cycle, metabolism, and gene expression by interacting with other circadian clock gene products.

Studies have shown that mutations or abnormal overexpression of the CLOCK gene may contribute to the advancement and progression of prostate cancer. Altered CLOCK gene expression has been associated with improved tumour cell proliferation, reduced apoptosis, and enhanced metastatic potential. It is thought that the disruption of the CLOCK gene's normal regulatory activity may promote the unchecked growth of prostate cells by interfering with the precise timing of cell division cycles. Moreover, its interaction with other circadian- related proteins modulates the expression of several genes that are crucial for maintaining cellular homeostasis, such as those involved in DNA damage repair, metabolic control, and stress responses [6]. Dysregulation of the CLOCK gene can thus impair these protective mechanisms, creating a permissive environment for tumour growth and survival.

3.2. BMALl, PER, and CRY genes

BMAL1, PER, CRY are also important components of the biological clock. In prostate cancer, their dysfunction may lead to circadian rhythm disruptions, which in turn affect the proliferation, apoptosis, and invasion of tumour cells [7]. For example, downregulation of the expression of the BMAL1 gene may promote the growth and metastasis oppo state cancer cells. The third is gene expression and cell cycle regulation: circadian rhythm genes influence the proliferation and division of prostate cells by regulating the expression of cell cycle- related genes. Normal circadian rhythms help maintain the stability of the cell cycle, while disrupted circadian rhythms may lead to cell cycle dysregulation and promote the proliferation of tumour cells. This is followed by DNA damage repair and apoptosis. Circadian rhythm disruption may affect DNA damage repair mechanisms and apoptosis pathways, thereby contributing to the development of prostate cancer. For example, aberrant expression of

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circadian clock genes may lead to reduced activity of DNA repair enzymes, making tumour cells more sensitive to DNA damage. At the same time, circadian rhythm disruption may also inhibit apoptosis, allowing tumour cells to survive and proliferate.

Circadian genes, including CLOCK, BMAL1, PER, and CRY, play a significant role in regulating crucial cellular processes such as cell cycle, DNA repair, metabolism, and apoptosis. Dysregulation of these genes can lead to disruptions in circadian rhythms, contributing to the advancement and progression of prostate cancer. Abnormal expression of circadian genes has been linked to increased tumour proliferation, impaired DNA repair, and reduced apoptosis, creating a favourable environment for cancer growth.

4. Potential therapeutic targets

First, circadian genes present a promising therapeutic target for prostate cancer treatment. By regulating the expression or function of circadian genes, it is expected to become a new strategy and direction for the treatment of prostate cancer. For example, the use of small molecule compounds or gene therapy to restore the normal expression and function of circadian clock genes may inhibit the growth and metastasis of tumour cells. This is followed by the application of melatonin and other modulators. Melatonin supplementation or other circadian rhythm modulators have a potential role in the prevention and treatment of prostate cancer. Melatonin can regulate the biological clock, enhance immune function, inhibit tumour cell proliferation and induce apoptosis. Other modulators, such as caffeine and resveratrol, have also demonstrated anti- tumour potential in various studies. Lastly, the field of chronotherapy offers insights into improving chemotherapy outcomes by aligning drug administration with the body's circadian rhythms [7]. Administering chemotherapy during periods when tumour cells are most sensitive can enhance treatment efficacy and reduce toxicity to normal cells, potentially lowering side effects.

5. Challenges and future research directions

In terms of research challenges, there are still some challenges in studying the relationship between circadian rhythm disorders and prostate cancer. Firstly, the complexity of the circadian rhythm mechanism in prostate cancer makes it difficult to conduct in-depth research. Secondly, the lack of effective clinical research evidence limits the application of circadian rhythm in the prevention and treatment of prostate cancer [8]. In addition, accurately assessing an individual's circadian status and developing personalized prevention and treatment plans for different populations remain challenges to be addressed. Future research can focus on several key areas: First, in- depth exploration of the molecular mechanisms linking circadian rhythms to prostate cancer, with the goal of identifying new therapeutic targets and biomarkers. Second, conducting large- scale clinical studies to verify the effectiveness of circadian rhythm interventions in the prevention and treatment of prostate cancer. Third, analysing the impact of circadian rhythm disorders on the occurrence and development of prostate cancer by combining multi- omics technology more comprehensively [9-10]. Finally, developing innovative methods for monitoring and intervening in circadian rhythms is crucial for advancing personalized medicine in this context.

6. Conclusion

Circadian rhythm disorders are closely related to the occurrence and development of prostate cancer. Working night shifts, changes in melatonin levels, lifestyle factors, and more can all contribute to circadian rhythm disruptions, which in turn increase the risk oppo state cancer. The abnormal expression of circadian genes, DNA damage repair mechanism and apoptotic pathway are important molecular mechanisms for circadian rhythm disorders to promote the development of prostate cancer. Experimental studies and animal models provide strong evidence for the relationship between circadian rhythm and prostate cancer, as well as ideas for potential therapeutic targets. However, several challenges remain in current research, and further in- depth studies along with clinical validation are necessary. Moving forward, a deeper understanding of the relationship between circadian rhythms and

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prostate cancer holds the potential to offer new strategies and approaches for the prevention and treatment of prostate cancer.

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