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Association between circadian gene expression amplitude and phase abnormalities and ocular diseases

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Abstract. The biological clock is an internal timing regulation system that exists in almost all organisms, including humans. It plays an important regulatory role in the physiology, behavior, and cognitive functions of organisms. It is one of the important mechanisms for organisms to adapt to the environment, maintain a stable internal environment, and achieve coordination of biological functions. The master controller of the biological clock system is located in the suprachiasmatic nucleus of the brain. Normal operation of the biological clock requires the normal expression of clock genes such as *Bmal1* and *Cry*. Clock and rhythm genes also exist in the retina. Damage to the retinal clock can affect the occurrence and development of retinal diseases and also have an impact on retinal aging. This article reviews the relationship between myopia, diabetic retinopathy, glaucoma, age-related macular degeneration, and abnormalities in clock genes, providing new ideas for the management and treatment of these diseases in clinical practice.

Keywords: Circadian gene, Myopia, Diabetic retinopathy, Glaucoma, Age-related macular degeneration

1. Mechanism of Circadian Rhythms

For their contributions to the discovery of molecular processes governing circadian rhythms, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young were jointly granted the 2017 Nobel Prize in Physiology or Medicine. Circadian rhythms are broadly distributed at the cellular level in a wide range of animals, including bacteria, algae, and vertebrates. These rhythms help these organisms adjust to recurring environmental changes, such as the 24-hour day-night cycle [1]. This environmental variation serves as a major factor influencing circadian rhythms. The central clock regulating biological circadian rhythms is located in the suprachiasmatic nucleus (SCN) which is in the hypothalamus. In mammals, the eyes constitute the only light signal receivers for the SCN. Three different types of photoreceptor cells in the retina—rods, cones, and intrinsically photosensitive retinal ganglion cells (ipRGCs)—are involved in the functioning of this central clock [2].

In mammals, various systems such as endocrine and cardiovascular systems exhibit rhythmicity. Melatonin, for instance, reaches its peak at night and then falls in the presence of light to encourage awakening. It rises before nightfall as a result of lowering light intensity [3]. Blood pressure level rises

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during the morning and decreases at night, which is known as the dipper pattern [4]. The retina also possesses rhythmicity, and ocular physiology is influenced by circadian rhythms. ipRGCs play a crucial role in retinal rhythms. Atypical ganglion cells called ipRGCs play a role in circadian rhythm regulation, pupillary light reflex modulation, and visual development. ipRGCs express melanopsin, allowing them to respond to light signals beyond input from cones and rods [5]. ipRGCs integrate light signals processed and sent by rods and cones and send axons to the SCN and several other locations in the brain [6]. When ipRGCs process light signals, both wavelength and irradiance act as regulatory signals to make sure the circadian rhythm system is in sync with the outside light/dark cycles [7]. Circadian rhythm regulation allows vision to adapt to the alternating day-night cycle (i.e., variations in light intensity) and also regulates the retina's ability to send signals to the circadian rhythm system. Extensive research has been conducted on retinal circadian rhythms within 24 hours, and it is now known that many molecular and cellular processes are controlled by the biological clock. Increasingly more "clock genes" and unique transcriptional-translation feedback pathways have been described in mammals. Although there are some differences, they still adhere to the same basic principles: light signals regulate the expression of numerous rhythm genes.

In summary, the regulation of rhythm gene expression involves two branches: (1) direct transcriptional activation of Clock-Controlled Genes (CCGs) genes due to the cumulative response of clock factors and tissue-specific regulatory factors; (2) indirect effects originating from transcription factors acting as clock targets [8]. Specifically, circadian rhythms rely on transcription factors encoded by genes such as *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1*, and *Cry2*. These clock genes interact through a series of transcription-translation feedback pathways. The CLOCK:BMAL1 heterodimer interacts with clock genes *Period 1-2* (*Per 1-2*) [9] and *Cryptochrome 1-2* (*Cry 1-2*) [10], as well as the E-box enhancers of CCGs, promoting their expression [11]. After the interaction between PER proteins and CRY proteins, they will be transported to the nucleus, where they can interact with the CLOCK:BMAL1 heterodimer, inhibiting its transcription, thereby suppressing their transcription [12]. The second feedback loop involves in REV-ERB proteins and Retinoic acid-related orphan nuclear receptors (RORs). CLOCK:BMAL1 also activates the nuclear receptors *REV-erbα* and *REV-erbβ*, which competitively bind to RORs on the ROR-binding elements (ROREs). The expression of *REV-erbα/β* inhibits the expression of *Bmal1* [13], while *ROr* can promote *Bmal1* expression.

Increased exposure to artificial light sources at night disrupts the organism's biological clock. Existing research indicates that circadian rhythm disruption may increase the risk of cancer, metabolic diseases (such as obesity, and diabetes), neurological disorders (like Alzheimer's disease), psychiatric disorders (such as bipolar disorder, depression, and anxiety), cardiovascular diseases (such as myocardial infarction, arrhythmias), skeletal and muscular diseases, and autoimmune diseases [14]. Variations in light-darkness are an important feature of circadian rhythms. The eyes are the most important photoreceptive organs in the body and are also regulated by circadian rhythms. Changes in light signals or abnormalities in rhythm genes can affect the structure and physiological functions of the eyes. making them an important area of concern.

In the molecular pathways of circadian rhythms, *Bmal1* is a necessary component of the mammalian circadian pacemaker. Deletion of *Bmal1* results in the immediate disappearance of circadian rhythms, impaired activity during light/dark cycles, and decreased activity levels [15]. Meanwhile, in *Bmal1* knockout mice, changes in corneal structure have been observed, including corneal neovascularization, keratinization, and inflammatory responses [16], leading to a significant increase in the incidence of cataracts and corneal inflammation during aging. Additionally, the vitality of photoreceptor cells is significantly reduced [17]. These changes can lead to the occurrence of certain eye diseases. Circadian rhythm regulation in the retina is present in all vertebrates, but significant differences exist in the circadian rhythms of the retina among different taxa and usually within the same species. The understanding of human circadian rhythm control from the viewpoints of genetics, chemistry, and biochemistry will be clarified in this review, along with the connection between aberrant circadian rhythm genes and eye disorders.

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2. Circadian Genes and Eye Diseases

2.1. Circadian Genes and Myopia

Myopia is a common global ocular disease, mainly occurring during childhood and adolescence, characterized by blurry distant vision. Research on children's eye diseases in Anyang found that the annual incidence and progression rates of myopia and high myopia are high among school-age children in China, especially after the third grade, where the incidence of myopia increased from 7.8% in the first and second grades to 25.3% in the fifth and sixth grades, and the incidence of high myopia increased from 0.1% to 1.0% [18]. It is estimated that by 2050, half of the world's population will be myopic [19]. Myopia can be divided into axial myopia and refractive myopia, the former is associated with an excessive axial elongation of the eye, while the latter is associated with an excessive curvature of the cornea or lens [20]. The primary causes of myopia in the majority of cases are contemporary lifestyle choices such as extended near-distance work and little time spent outside. However, genetic factors are also significant. [20].

Meta-analysis has demonstrated that light-dependent retinal signals are important driving factors for refractive errors [21]. Additionally, large-scale GWAS studies have found circadian rhythm genes, such as *CRX*, *PAX4*, and *OTX2* [22], to be associated with the occurrence of refractive errors and myopia in European populations [23]. The irregularities of modern lifestyles promote the development of the disease. Both the axial length of the eye and the thickness of the choroid undergo circadian rhythm changes as myopia develops. While the choroidal thickness changes in the opposite direction, the axial length achieves its highest value in the afternoon and lowest value in the morning. Remarkably, myopic patients show fewer changes in choroidal thickness but larger variations in axial length [24].

Myopic defocus disrupts the rhythmicity of axial length and choroidal thickness in the human eye. The peak values of axial length and choroidal thickness are found to be delayed by roughly 6 and 8.5 hours, respectively, following myopic defocus. These findings suggest that circadian-related regulatory mechanisms play a role in the alterations of biological parameters in the human eye [25]. Mice can develop myopia if the *Bmal1* gene is specifically knocked off in the retina. Compared to control $Bmal1^{-/-}$ and $Bmal1^{+/-}$ mice, the gene knockout mice show elongation of the axial eye length and vitreous cavity. Additionally, these mice exhibit slightly decreased contrast sensitivity, which may manifest as central visual problems in humans [26]. This data implies that the development of myopia in the human eye may be influenced by circadian rhythms and genes. Optical defocus disrupts the rhythmic expression of clock genes in the retina/retinal pigment epithelium cells and choroid. In chick form-deprivation experiments, the rhythmicity of 4 genes (*Opn4m*, *Clock*, *Npas2*, and *Mntr1a*) disappeared, and there were time-phase shifts in the occurrence of some clock genes [27]. Outdoor exposure can inhibit form-deprivation myopia in chicks [28].

Based on the above research, the mechanism that can suppress the development of myopia by increasing outdoor activities for adolescents involves the regulation of circadian gene expression. Additionally, reducing the intensity of artificial light exposure at night while increasing daytime activities can enhance the signal of circadian rhythms, thereby increasing the inhibitory effect of outdoor exposure on myopia [29].

2.2. Circadian Genes and Diabetic Retinopathy

Diabetic retinopathy is a particular type of microvascular complication, with retinal arteriolar dilation possibly being an early physiological marker of microvascular dysfunction [30]. It manifests as damaged retinal vessels, leading to the formation of ischemic areas and capillary leakage, thereby resulting in macular edema [31]. Diabetic retinopathy is a common complication of diabetes which is a major cause of preventable blindness in the adult working population. Its global morbidity is estimated at 22.27%, with the highest prevalence in Africa (39.50%) and North America and the Caribbean (33.30%) [32]. In China, about 40% of diabetic patients suffer from diabetic retinopathy [33]. Globally, there are projected to be 103.12 million patients with diabetic retinopathy by 2045 [32]. According to studies, type 2 diabetic female patients have a higher incidence of diabetic retinopathy than male patients do, while

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male patients also have more severe retinopathy and visual impairment or blindness [34]. Higher blood glucose levels, hypertension, the duration of diabetes, and elevated glycated hemoglobin levels are all associated with the prevalence of diabetic retinopathy.

Abnormal expression of circadian genes has drawn a lot of interest in animal investigations of diabetic retinopathy, and disruption of circadian rhythms may be causally related to the lesion's progression. The expression of multiple clock genes is altered in the retinas of diabetic mice. Although *Bmal1* maintains its rhythmicity, its amplitude is dramatically attenuated. Studies have demonstrated that wild-type male C57BL/6J mice were administered streptozotocin at 3 weeks of age and euthanized after 12 weeks to obtain retinal tissue. The expression amplitude of *Per1* and *Cry1* genes exhibited a clear circadian rhythm increase, while *Per3* lost its rhythmicity [35]. However, in another experiment, male Long Evans rats received streptozotocin injections at 8 weeks of age and were analyzed after 6 weeks, revealing reduced *Per1* expression and elevated *Bmal1* expression in the retina. These findings may be attributed to species or experimental design variations [36].

The disorder of retinal rhythms can also lead to diabetic retinopathy. For instance, *Clock* and *Bmal1* conditional knock-out mice ultimately developed type 1 diabetes. Mice with *Per2* mutations also display symptoms associated with diabetic retinopathy, including acellular capillaries, increased retinal permeability, and progressive retinal vascular dysfunction, along with inadequate endothelial nitric oxide synthase synthesis, upregulation of pro-fibrotic genes, disruption of tight junctions, and decreased adherent junction integrity [37-38]. Research has indicated that fatty acid oxidation damage in diabetic retinopathy may be caused by the disruption of circadian genes and the expression of genes involved in lipid metabolism, which in turn may impact the disease's course [36,39].

Moreover, it is hypothesized that a harmful role for the phase mismatch between internal biological rhythms and retinal metabolic cycles may exist in the development of diabetic retinopathy. It is believed that the phase difference between retinal metabolic pathways and the biological clock governed by light-dark rhythms increases oxidative stress and neural damage, thereby leading to the progression of diabetic retinopathy [40]. Additionally, changes in the retina and retinal clock can also affect the main clock of SCN and its function [41]. In the SCN of diabetic mice, the expression of all circadian genes is reduced [42]. Research has revealed that the phase of *Cry1* expression is delayed, the rhythms of *Cry2* and *Rorβ* vanish in the SCN of diabetic mice, and the reduced production of light-induced clock genes in the SCN can also cause morphological alterations in ipRGC [35]. This can also impact retinal rhythm in turn at the same time.

In conclusion, changing the way circadian genes are expressed may also be a strategy for treating diabetic retinopathy. The *Bmal1* retinal clock system is both a target and an effector in the process of diabetes. Although the expression of *Bmal1* is altered and affects retinal rhythm, the loss of *Bmal1* can improve the pathophysiological condition of the retina in mice with pre-diabetes, so *Bmal1* may serve as a potential therapeutic target for diabetic retinopathy [43]. Additionally, REV-erb agonists can significantly improve lipid and hyperglycemia conditions, thereby alleviating disease progression [44]. Chuanxiong ketone acts on ROR nuclear receptors, establishing a connection with the circadian gene network through the REV-erb/ROR pathway, stabilizing the stability of the feedback pathway, and ultimately improving blood sugar and glucose tolerance, playing a therapeutic role [45]. KL001 can also control blood glucose by stabilizing CRY protein [46].

The interaction between circadian genes and diabetic retinopathy is complex, and choosing different experimental animals and analyzing them at different modeling stages may lead to varied experimental results. Therefore, the effects of diabetic retinopathy on circadian genes may be diverse in different periods. In addition to existing drugs that enhance the expression of circadian genes, it is indispensable to conduct relative research on applying specific frequencies and intensities of light to patients to enhance the expression of circadian genes for therapeutic purposes. Whether circadian genes have a clear impact on the onset of the disease still needs further exploration, which is crucial for the management of subsequent diseases.

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2.3. Glaucoma and Circadian Rhythms

Glaucoma is the second leading cause of blindness worldwide, with higher incidence rates in females and Asians [47]. By 2040, the estimated prevalence of glaucoma is expected to reach 1.118 billion people [48]. Glaucoma is characterized by progressive degeneration of a group of retinal ganglion cells in the optic nerve [49]. Research has largely concentrated on the function of intraocular pressure (IOP), while also taking into account other aspects such as aberrant ocular blood flow and the lamina cribrosa's pressure tolerance, even if the pathophysiology of glaucoma is not entirely known [50]. Risk factors for glaucoma include aging, non-white ethnicity, and a family history of glaucoma [51-53].

It has long been known that intraocular pressure follows a rhythm, peaking at night and falling during the day [54-55]. This rhythmicity depends on circadian genes and the integrity of the circadian clock, with known involvement of *Cry* genes in generating the diurnal IOP rhythm [56]. The iris-ciliary body complex has been shown to express circadian genes, which may regulate intraocular pressure [57-58]. Current research indicates that IOP is driven by the rhythm signals from SCN through cortisol or adrenaline [59]. Translaminar pressure, or the difference in pressure between intracranial and IOP on the papilla of the optic nerve, may cause damage to retinal ganglion cells as IOP. This is one of the pathogenic mechanisms of normal-tension glaucoma, according to certain studies [60]. Similarly to intraocular pressure, intracranial pressure also exhibits rhythmicity [61], peaking at night. Additionally, nighttime blood pressure reduction is a risk factor for progressive visual field loss in glaucoma. But unlike intracranial and intraocular pressure, blood pressure is lowest at night [62], which increases the risk of injury from inadequate ocular perfusion [54].

Few studies have been conducted to determine if circadian gene mutations cause glaucoma or if the condition is caused by changes in circadian gene expression. The prevailing theory still attributes glaucoma to pathological alterations in ocular structures as well as the synergistic impact of specific hereditary and environmental variables. Perhaps intervention in daily behaviors to enhance circadian stability could provide some help in controlling the disease.

2.4. Age-Related Macular Degeneration (AMD) and Circadian Rhythms

Age-related macular degeneration is the leading cause of incurable blindness in the elderly worldwide. Among the global population, Europeans have the highest prevalence worldwide, and as the world's population ages, it is predicted that 288 million people will suffer from AMD by 2040 [63]. Typical signs of AMD include choroidal neovascularization and drusen. Its pathogenesis is proven to be related to the aging of the retinal pigment epithelial cells, oxidative stress, inflammation, immune responses, and changes in lipid metabolism [63-64].

There is limited research on the role of circadian gene abnormalities in the development of AMD, but studies have shown that as age increases, biological rhythms become increasingly disrupted, and the decrease in rhythm amplitude may be the most severe effect of aging on biological rhythms [65-66]. Meanwhile, the impairment of the retinal clock may also be involved in the development of retinal diseases [67]. During aging, changes in retinal rhythms reduce the survival of photoreceptors. Studies have shown that mice with *Bmal1* knockout have a 20-30% reduction in the nuclei of the outer nuclear layer, while mice with *Clock/Npas2* knockout also show a significant reduction in the photoreceptor layer [17].

One of the key pathogenic mechanisms of AMD is oxidative stress [68], and the circadian clock is also necessary for regulating the body's redox reaction [69]. Anomalies in the WNT/β pathway are linked to the development of exudative AMD, and anomalies in *Bmal1* function can cause the downregulation of genes in the WNT/β pathway, which increases the production of lipids [70]. Additionally, *Bmal1* regulates the amounts of reduced FAD and oxidative NADPH [71]. Furthermore, there is a rhythm to the phagocytosis of retinal pigment epithelium cells and the shedding of photoreceptor outer segment discs that is regulated centrally by the SCN and locally by retinal rhythms [71]. Once this rhythm is disrupted, the function and survival of photoreceptors are inevitably affected, and the delayed phagocytosis of retinal pigment epithelial cells leads to the accumulation of substances

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within the cells, which is harmful to both the retinal pigment epithelial cells and eventually the whole retina, thus leading to the occurrence and development of AMD [72-73].

Endogenous neurohormone melatonin is generated by the pineal gland and retina. It is a vital rhythmic hormone in retinal rhythms and has an anti-oxidative stress effect on retinal pigment epithelium cells. It has been found that the level of melatonin is significantly reduced in patients with AMD [74]. Studies have shown that daily administration of melatonin can protect the retina and delay macular degeneration [75]. Additionally, blue light stimulation can affect biological rhythms, thereby disrupting the diurnal secretion rhythm of melatonin. Using blue light-blocking lenses to reduce reactive oxygen species and increase antioxidant enzyme levels can help prevent retinal phototoxicity [76].

The relationship between the pathogenesis of AMD and circadian gene abnormalities is worthy of enough attention. The mainstream treatment approach mainly focuses on delaying progression, such as the use of lutein and anti-angiogenic drugs. Currently, there aren't many therapies that target circadian rhythms; however, as was previously noted, lowering blue light stimulation to safeguard the retina is a workable solution, but further study is needed to determine its therapeutic efficacy.

3. Conclusion

The growth and development of organisms rely heavily on biological rhythms, which also guarantee the timely occurrence of physiological responses in the body. The molecular basis for this is the set of biological rhythm genes, including *Clock*, *Bmal1*, *Cry*, *Per*, and others. Among these, *Bmal1* holds particular significance. The four forms of eye disorders that are covered in this paper are myopia, diabetic retinopathy, glaucoma, and age-related macular degeneration. These diseases are related to abnormalities in rhythm genes. Abnormal expression levels and timing of gene expression can trigger changes in diseases, while diseases can interfere with the expression of rhythm genes in turn. The interaction between eye diseases and gene expression is complex. For these eye diseases, several means of treatment, including medication and physical therapy, were already applied and proven to be effective in increasing rhythm amplitudes and stability. In future research, further exploration of abnormalities in the feedback pathways of biological rhythms and their effects on the occurrence and development of diseases should be conducted. Additionally, drugs targeting biological rhythms could serve as a direction for further drug research and development.

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