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Citation: J Med Discov (2026);11(1):jmd25063; DOI:10.24262/jmd.11.1.25063

Review Article

Research progress on the pathogenesis of myopia

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Abstract Myopia, a globally prevalent refractive error, threatens the visual health of children and adolescents with its increasingly younger and more severe incidence. High myopia can lead to irreversible visual impairment. Clarifying its pathogenesis is crucial for scientific prevention and control. Recent studies have confirmed that myopia is caused by a combination of genetic and environmental factors, and is closely related to retinal dopamine metabolism, scleral hypoxia remodeling, and abnormal choroidal blood flow. This article systematically reviews relevant research progress, elucidating the mechanisms from multiple dimensions, and providing a theoretical reference for clinical prevention and precise treatment.

Keywords: Myopia; Pathogenesis; Retina; Dopamine; Scleral remodeling; Choroidal blood flow

How to cite: Xiuzhe He et al., Research progress on the pathogenesis of myopia. J Med Discov (2026); 11(1): jmd25063; DOI:10.24262/jmd.11.1.25063; Received September 20th, 2025, Revised November 27th, 2025, Accepted December 15th, 2025, Published January 6th, 2026.

According to data from the Global Burden of Disease Study [1], myopia ranks seventh among common diseases worldwide in terms of annual outpatient visits, and the number of people with disabilities (blindness) caused by myopia is second only to cataracts. In my country, myopia is particularly prominent, with about 40% of the population (nearly 600 million people) suffering from myopia, and more than 300,000 people suffering from low vision or even blindness due to complications of high myopia such as posterior staphyloma, choroidal retinal atrophy, and retinal detachment [2]. In some parts of Asia, the prevalence of myopia among young people has reached 80% to 90%, and it is estimated that by 2050, the global myopia population will reach 4.758 billion, accounting for 49.8% of the total population, and the number of patients with high myopia will reach 938 million [1]. At present, a variety of myopia prevention and control methods have been formed in clinical practice, including orthokeratology lens correction, low-concentration atropine intervention, and increased outdoor activities, but due to the complexity of the pathogenesis of myopia, further research is still needed, and etiological treatment still faces huge challenges [3]. This article systematically reviews the key advances in the pathogenesis of myopia, focusing on the interaction and regulatory network of the retina, sclera, and choroid in the development and evolution of myopia, providing a reference for further research in the field of myopia prevention and control.

1 Retinal Regulation Mechanisms

The retina, as the core tissue for sensing visual signals and regulating eye growth, plays a crucial role in the dynamic balance of neurotransmitter metabolism, especially the synthesis and release of dopamine, in the pathogenesis of myopia [4]. Dopamine is an important neuroactive substance in the retina, mainly synthesized and released by

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dopaminergic amacrine cells and inner reticular cells in the inner nuclear layer, and is the main source of retinal catecholamines [9]. Tyrosine hydroxylase plays a rate-limiting role in its synthesis, while 3,4-dihydroxyphenylacetic acid, as its main metabolite, can effectively reflect the release level of retinal dopamine [5].

1.1 Light-Dopamine Pathway

Epidemiological studies as early as 2000 found that the weekly outdoor activity time of children is negatively correlated with the risk of myopia. Children under 10 years of age who have sufficient outdoor exposure have a significantly reduced incidence of myopia, and this effect is independent of the type of outdoor activity, which cannot be replaced by indoor exercise [6]. A randomized controlled trial published in JAMA by He Mingguang's team in 2015 further confirmed [7] that adding 40 minutes of outdoor classes per day to 6-7 year old children resulted in a significantly lower incidence of myopia after 3 years compared to the control group that did not receive the additional outdoor classes. Basic research has clarified the molecular mechanism of this phenomenon: light intensity is linearly correlated with the production and release of dopamine in the retina, and bright light can significantly increase dopamine levels, while dopamine can effectively inhibit excessive eyeball growth [8]. Ji et al. fed 4-week-old mice with green light and white light for 12 weeks respectively and found that mice in the green light group were more prone to developing pathological myopia, and the dopamine content was significantly correlated with the degree of myopia [9]. Animal experiments showed that dim environments can induce form deprivation myopia in chicks and mice, while bright light can reverse this process; if dopamine receptor antagonists are used in the eyeball, the protective effect of strong light on myopia will be significantly weakened, directly confirming that dopamine is a key mediator for regulating myopia in strong light [10].

1.2 Antagonistic Regulation of Dopamine Receptors

Dopamine regulates eye growth and refractive state development through two receptor families, D1 and D2[11]. Among them, D1 receptors (including D1 and D5 subtypes) can activate adenylate cyclase, thereby increasing the content of the second messenger cyclic adenosine monophosphate (cAMP), which is widely distributed in bipolar cells, horizontal cells, amacrine cells, and ganglion cells[12]. D2 receptors (including D2, D3, and D4 subtypes) inhibit adenylate cyclase activity, reduce cAMP levels, and are widely distributed in retinal photoreceptor cells, retinal pigment epithelial cells, and amacrine cells[13]. Some studies have revealed the antagonistic balance between the two types of receptors: giving mice 6 hours of strong light exposure daily can significantly reduce the degree of form deprivation-induced myopia, and this inhibitory effect can be blocked by dopamine receptor antagonists[8]. Ward et al. [14] injected D1 and D2 receptor agonists and antagonists into the vitreous cavity of tree shrews with form deprivation myopia and found that D2 receptor agonists had a significant effect on inhibiting myopia progression, while D1 receptors had little effect. Dong et al. [15] found that injecting the nonspecific dopamine receptor agonist apomorphine into the conjunctiva of guinea pig eyes could effectively inhibit the progression of form deprivation myopia.

2 Mechanism of Scleral Remodeling

The sclera, as the outermost layer of the eyeball wall, directly determines the shape of the eyeball and the length

of the axial length due to its thickness and biomechanical properties. It is an important effector in the process of myopia development[16]. Under normal physiological conditions, scleral fibroblasts secrete a large amount of extracellular matrix components such as type I collagen to maintain the toughness and elasticity of the sclera. However, when myopia occurs, the sclera undergoes structural remodeling, thinning, and decreased collagen content, which eventually leads to abnormal elongation of the axial length[17]. Recent studies have confirmed that scleral hypoxia is the core initiating factor that triggers this series of pathological changes[18].

2.1 Hypoxia-Inducible Factor

Single-cell sequencing technology has found that in the scleral tissue of form deprivation myopia mice, the transformation of fibroblasts into myofibroblasts with low collagen expression is increased. This cell phenotypic transformation process is regulated by the hypoxia-inducible factor signaling pathway[19]. Animal experiments have shown that after inducing myopia in guinea pigs, the expression level of hypoxia-inducible factor 1α protein in their scleral tissue significantly increased, while the expression level of this protein decreased when the myopia symptoms were relieved; whether in short-term or long-term induction of myopia in mice, the upregulation of scleral hypoxia-inducible factor 1α protein expression could be observed [19]. Further intervention experiments showed that injecting anti-hypoxia drugs into the peribulbar region of myopic guinea pigs could effectively inhibit the occurrence of myopia, while reducing the high expression level of hypoxia-inducible factor 1α and alleviating the reduction of collagen content [19]. Genome-wide association analysis and pedigree genetic studies have also found that human myopia susceptibility genes are closely related to the hypoxia-inducible factor 1α signaling pathway, confirming that scleral hypoxia not only exists in animal models, but is also a key pathological factor in the formation of human myopia [20].

2.2 Retina-choroid-sclera signal axis

The blood supply to the sclera mainly depends on the choroid. When myopia occurs, the choroid will become thinner and the blood flow will decrease, resulting in insufficient oxygen and nutrient supply to the scleral tissue, which in turn activates subsequent pathological reactions [21]. Previous studies have shown that when abnormal visual signals are affected by congenital heredity or acquired environment, signals such as intraocular growth factors and neurotransmitters will affect scleral remodeling and cause axial elongation, thereby inducing axial myopia in the retina-choroid-sclera pathway [22]. The specific transmission pathway is as follows: after external myopia-promoting factors such as form deprivation and prolonged close-range eye use are perceived by the retina, the signal is transmitted to the choroid, causing the choroid to become thinner and the blood flow to decrease; due to ischemia and hypoxia, the fibroblasts of the sclera transform into myofibroblasts by upregulating the expression of hypoxia-inducible factor 1α, increasing the phosphorylation level of eukaryotic initiation factor 2α and target of rapamycin, resulting in reduced collagen synthesis and extracellular matrix remodeling, which ultimately leads to changes in eyeball morphology and axial elongation [23]. The discovery of this "retina-choroid-sclera" signal axis clearly reveals the interaction mechanism between different ocular tissues

during the development of myopia, providing a new framework for understanding the pathophysiological process of myopia progression [24].

3 Choroidal Blood Flow Mechanism

The choroid, located between the retina and sclera, is not only the main source of oxygen and nutrients for the outer layer of the retina (especially the macula), but also plays a crucial role in transmitting visual signals from the retina to the sclera. Its blood flow and thickness changes play an important regulatory role in the development of myopia [25].

3.1 Choroidal Thickness and Blood Flow

Clinical studies have found that the choroidal thickness of patients with high myopia is significantly reduced, and the degree of reduction is positively correlated with the severity of myopia [26]. Animal experiments have further confirmed that the choroidal thickness and blood flow in chickens and guinea pigs with form deprivation myopia and lens-induced myopia gradually decrease, and both recover and increase after the removal of myopia-inducing factors, and the trend of change is significantly positively correlated [21, 27, 28]. In human myopia, the number of large and small blood vessels and capillaries in the choroid of high myopia is reduced, the vascular layer is thinned, and the reduction in choroidal blood flow is closely related to the narrowing of the vessel diameter and the hardening of the vessel wall [29]. Furthermore, after the human eye is stimulated by accommodation, the thickness and blood flow of the choroid will be significantly reduced. This phenomenon suggests that the choroidal blood flow perfusion can be used as a rapid predictive indicator of myopia, providing an effective basis for early monitoring of myopia progression [30].

3.2 Neural and Molecular Regulatory Mechanisms of Choroidal Blood Flow

Choroidal blood flow is regulated by both the autonomic nervous system and local molecular signals: the sympathetic nervous system constricts choroidal vessels and reduces blood supply by releasing neurotransmitters such as adrenaline and neuropeptide Y; the parasympathetic nervous system and trigeminal nerve promote vasodilation and increase blood flow by releasing substances such as acetylcholine, vasoactive intestinal peptide, and calcitonin gene-related peptide [31]. In addition, choroidal intrinsic neurons can maintain choroidal blood flow stability when sympathetic regulation is decompensated by releasing neurotransmitters such as neuropeptide Y and calcitonin gene-related peptide [32]. In myopia, these regulatory mechanisms become unbalanced, leading to a reduction in choroidal blood flow, which in turn exacerbates scleral hypoxia and remodeling [33]. For example, after the parasympathetic nerves of chicks are removed, their choroidal diurnal rhythm becomes abnormal, showing thickening during the day and thinning at night. However, the injection of nitric oxide synthase inhibitors can inhibit the thickening of the choroid and the shortening of the axial length, confirming that the parasympathetic nerves participate in the regulation of choroidal function and the occurrence of myopia through the nitric oxide pathway [34].

4 Summary and Outlook

Recent studies have clearly shown that the pathogenesis of myopia is a complex multi-layered regulatory network involving retinal dopamine metabolic imbalance, scleral

hypoxia remodeling, and choroidal blood flow abnormalities [35]. However, existing research still has many shortcomings: First, the mutual regulation mechanism between retinal dopamine and choroidal blood flow has not been fully elucidated, such as how light affects choroidal vasomotor activity through dopamine signals [36]; Second, the specific molecular signaling pathways triggered by scleral hypoxia, such as the interaction between hypoxia-inducible factor 1α and other regulatory factors, still need to be explored in depth [37]. In conclusion, myopia is the result of multiple factors working together, and further research on its pathogenesis is of great significance for the treatment and prevention of myopia.

Acknowledgments

None

Conflict of Interests

None

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