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REVIEW

The Role of Scleral Changes in the Progression of Myopia: A Review and Future Directions

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Abstract: This review article comprehensively examines the alterations in scleral collagen fibers and the extracellular matrix (ECM) during myopia progression, with a particular focus on the scleral hypoxia theory and inflammatory mechanisms. It delves into key signaling pathways, including the matrix metalloproteinase - 2 (MMP-2) pathway, hypoxia - inducible factors (HIF-1α and HIF-2α) pathways, and the Wnt signaling pathway. By elucidating the intricate relationships between these signaling pathways, this article highlights the latest advancements in myopia prevention and control strategies that target the sclera. Moreover, it provides novel insights into the molecular mechanisms underlying scleral remodeling and explores their potential therapeutic applications for effectively managing myopia progression.

Keywords: sclera, myopia, signaling pathways, surgical methods

Introduction

In recent years, myopia has emerged as a significant global public health concern. Epidemiological studies on the prevalence of high myopia predict that by 2050, the global incidence of high myopia will increase approximately fivefold, potentially affecting nearly one billion individuals worldwide.[1] Despite the availability of various corrective measures, including spectacle lenses, orthokeratology, and refractive surgeries, 34.6% of high myopia patients experience irreversible visual impairment due to associated complications.[2] These complications encompass a range of serious conditions, such as retinal detachment, glaucoma, cataract, macular degeneration, and scleral staphyloma.[3] Although the exact pathogenesis of high myopia remains elusive, a growing body of evidence has elucidated the critical role of reduced scleral collagen fiber diameter and structural defects in the progression of myopia. This review aims to comprehensively summarize the current understanding of the relationship between scleral structural alterations and myopia progression. Additionally, it explores potential therapeutic strategies targeting the sclera to decelerate myopia development, thereby offering insights into future research directions and clinical interventions.

Structure and Biomechanics of the Sclera

In emmetropic eyes, the sclera forms an approximately spherical structure with a vertical diameter of around 24 mm. The Tenon's capsule, situated between the sclera and conjunctiva, imparts a looser consistency to the posterior scleral structure and facilitates the transmission of extraocular muscle forces to the sclera. Type I collagen fibers (COL-1) constitute the major component of the sclera, with mesenchyme interspersed between cellular adhesions and collagen fibrils. Collagen not only dictates the scleral rigidity but also maintains the dynamic equilibrium of other ocular structures through its robust, constantly remodeling framework.[4] The extracellular matrix (ECM), rich in collagen fibers, ultimately determines the biomechanical properties of the sclera.

Scleral morphology exhibits adaptive changes during accommodation for objects at varying distances. While age-related factors influence these alterations, emerging evidence strongly implicates scleral morphological changes in the progression of

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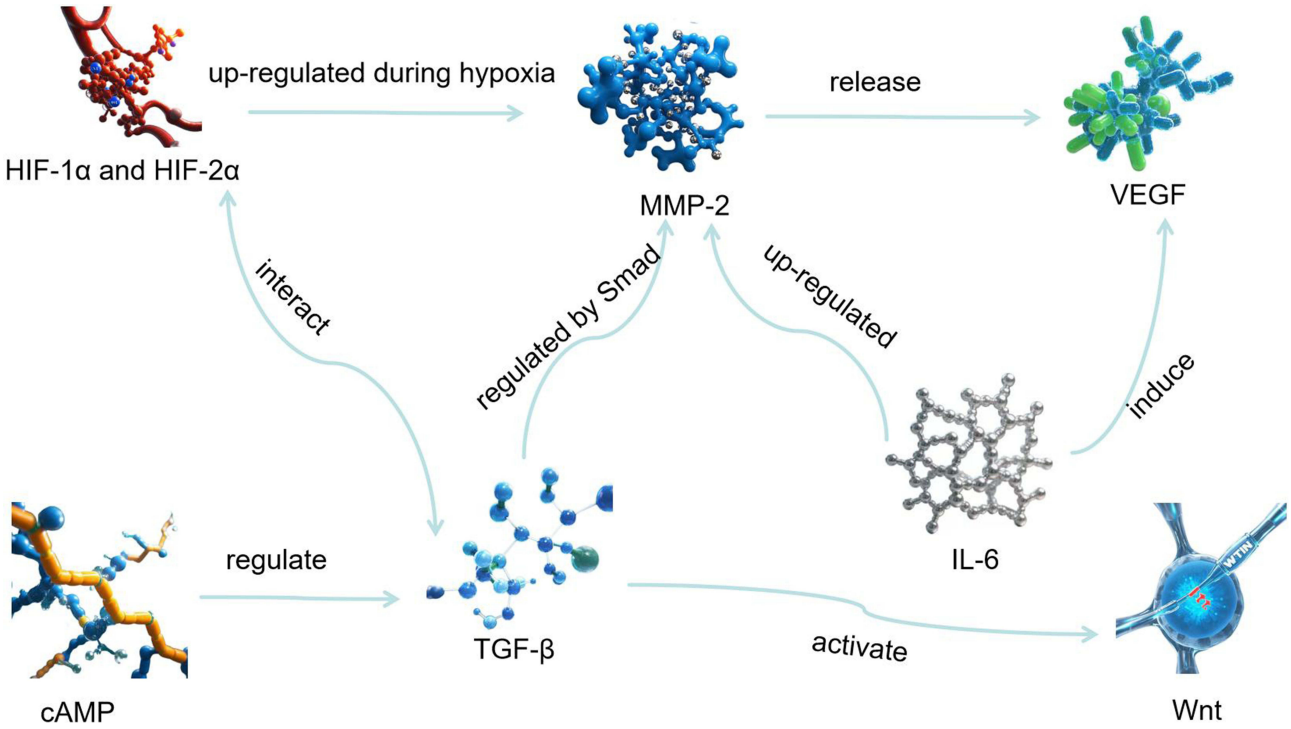

Figure 1 illustrates the interrelationships among various pathways.

myopia.[5] In experimental myopia models, researchers have observed that axial elongation is accompanied by thinning of both the posterior and anterior sclera, with the latter correlating significantly with increasing axial length.[6] Sun et al demonstrated that an increase in small-diameter collagen fibers within the scleral outer layer, coupled with reduced fibroblast activity, leads to decreased COL-1 synthesis.[7] Concurrently, the progression of myopia is associated with a decline in ECM protein content and GAG side chains. Clinically, myopic patients not only exhibit increased axial length but also a deeper vitreous cavity.

Recent advancements in scleral epigenetics have expanded our understanding of myopia pathogenesis. For instance, EFEMP1, a key regulator of the ECM, modulates collagen and proteoglycan levels upon overexpression, thereby altering the ECM architecture.[8] Ikeda et al further revealed that mechanical force-induced knockout or inhibition of scleral PERK and ATF6 genes can effectively control axial elongation, suggesting their critical roles in myopia progression.[9]

The retinal-scleral cascade signaling pathway elucidates that during ametropia development, blurred visual signals originating from the retina are transmitted to the retinal pigment epithelium and choroid, ultimately triggering scleral remodeling.[10] This remodeling process is characterized by decreased collagen synthesis, enhanced collagen degradation, reduced collagen fiber content, increased fibroblast-to-myofibroblast transdifferentiation (FMT) and alterations in fiber diameter.[11] Liu et al reported decreased expression of the transcription factor YES-associated protein (YAP), a key regulator of the ECM signaling pathway, across various myopia models.[12] ECM stiffness modulates YAP accumulation, subsequently reducing COL1A1 expression in fibroblasts and ultimately impairing COL-1 production. GAG and all-trans retinoic acid (atRA) are integral components of the retinal-scleral cascade signaling pathway. Brown et al demonstrated that oral administration of atRA in mice induced scleral changes analogous to those observed in form deprivation myopia models, accompanied by significant biomechanical alterations, while the levels of sGAG remained relatively unchanged.[13] These modifications lead to ECM remodeling, resulting in decreased scleral tensile strength and increased permeability.[14]

Collectively, these findings underscore the complex interplay between collagen fibers, ECM components, and diverse signaling pathways during scleral remodeling. Current theories on myopia progression predominantly focus on scleral hypoxia and inflammatory responses. This review systematically synthesizes and analyzes the molecular mechanisms and

interconnections of relevant pathways, and provides an overview of sclera-targeted myopia prevention and control strategies, thereby offering novel perspectives for myopia management.

Mechanisms Related to Scleral Remodeling

HIF - 1α and HIF - 2α Pathways

Lin et al reported that glycolysis and lactic acid production were elevated under scleral hypoxia conditions.[15] Moreover, increased glycolytic activity and lactic acid accumulation have been implicated in the development of myopia. Currently, the scleral hypoxia theory is widely recognized as one of the key mechanisms underlying axial elongation. Scleral hypoxia triggers the thinning and remodeling of the scleral ECM. Single-cell RNA sequencing of the sclera has revealed the activation of several critical signaling pathways, including the hypoxia signaling pathway, eIF2 signaling pathway, and mTOR signaling pathway. Local administration of anti-hypoxia eye drops has been shown to counteract the activation of these pathways and effectively control myopia progression.[16]

Notably, the hypoxia signaling pathway has been extensively studied, with key factors such as hypoxia-inducible factor 1α (HIF-1α) and hypoxia-inducible factor 2α (HIF-2α) being central to its investigation. In mouse models, knockout of HIF-1α led to the development of hyperopia in form deprivation-induced myopia. This pathway also involves the presence of FMT and alterations in ECM receptors, leading to the proposed mechanism of "myopia-sclera hypoxia dependence, regulation of fibroblast differentiation, and ECM remodeling".[17]

In human scleral fibroblasts exposed to hypoxic conditions, significant upregulation of HIF-1α, LAMA4 expression, and p38 phosphorylation levels was observed. PCR analysis further demonstrated enhanced expression of miR-150-5p. Overexpression of miR-150-5p suppressed LAMA4 content, inhibited the expression of COL1A1 and TIMP-2, and promoted MMP2 expression. Conversely, LAMA4 knockout inhibited COL1A1 and TIMP-2 expression while increasing MMP2 expression through suppression of the p38 MAPK signaling pathway.[18] These findings have elucidated the molecular mechanism of the HIF-1/ miR-150-5p/ LAMA4/ p38 MAPK axis in pathological myopia.

In addition to its genetic implications, HIF-1α also mediates environmental interactions. Notably, HIF-2α exhibits a distinct expression pathway compared to HIF-1α. HIF-2α upregulation promotes matrix metalloproteinase - 2 (MMP-2) expression, whereas scleral knockout of HIF-2α inhibits MMP2 upregulation and the decrease in COL1α1 content, effectively suppressing form deprivation-induced myopia. In contrast to scleral HIF-1α knockout, form deprivation-induced MMP-2 levels remained unchanged.[19] However, it is important to note that knockout techniques in animal experiments carry the risk of compensatory gene activation, thereby limiting their translational potential.[20]

VEGF Pathway

The Vascular Endothelial Growth Factor (VEGF) pathway plays a crucial role in various physiological and pathological processes. In the context of scleral changes, its mechanism encompasses multiple aspects, including the regulation of angiogenesis, transduction of hypoxia signals, and imbalance in ECM metabolism.[21]

Mounting evidence has demonstrated a strong correlation between the development of myopia, particularly axial myopia, and scleral hypoxia. Hypoxia-inducible factors (HIF-1α/HIF-2α) are key regulators in this process. They can activate the transcription of the VEGF pathway, predominantly upregulating the expression of VEGF-A165. This upregulation subsequently promotes angiogenesis and alters vascular permeability.[22]

In experimental myopia models, scleral hypoxia appears to exacerbate local metabolic reprogramming via the HIF-VEGF pathway. For instance, it stimulates the expression of key glycolytic enzymes, such as Enolase 2 (ENO2) and Triosephosphate Isomerase 1 (TPI1), which leads to the accumulation of lactic acid. Additionally, through histone lactylation (eg, H3K18la), it regulates gene expression. Ultimately, these events induce FMT and ECM remodeling, enhance the contractility of fibroblasts, reduce the synthesis of COL-1, and increase the activity of matrix metalloproteinases (MMPs). The heightened MMP activity further degrades the ECM, resulting in scleral thinning and axial elongation.[23]

While the direct role of VEGF in myopia development still awaits more robust experimental validation, its angiogenic properties in hypoxic conditions are likely to indirectly impact ECM homeostasis by modifying the scleral microcirculation. For example, VEGF-A165 may modulate the mechanical signal perception of fibroblasts via the integrin-Focal Adhesion Kinase (FAK) pathway. Alternatively, it may collaborate with other growth factors, such as Transforming

Growth Factor-β (TGF-β), to regulate the equilibrium between MMPs and Tissue Inhibitors of Metalloproteinases (TIMPs), thereby intensifying the disruption of the scleral structure.[24]

Notably, anti-VEGF therapy has been extensively applied in the treatment of retinopathy. However, its potential in controlling myopia remains to be fully explored. Future research should focus on developing targeted intervention strategies that specifically address the sclera's unique metabolic and signaling pathways.[25]

MMP - 2 Pathway

Studies utilizing family - based and twin models have established the heritability of myopia. Currently, over 30 regions across the human genome, encompassing nearly all chromosomes, have been identified to harbor susceptibility or causative variants associated with myopia. Genome - wide association studies have further screened 284 candidate myopia genes.[26]

MMPs are zinc - dependent metalloendopeptidases capable of cleaving or degrading a diverse array of ECM components and other extracellular proteins. Among them, MMP - 2, a gelatinase initially discovered in cardiomyocytes, participates in multiple biological processes, including inflammation and immune responses, and plays a crucial role in cell migration, chemotaxis, and mitosis. Notably, MMP - 2 is present not only in the cytoplasm but also in the nucleus. Its transcription is influenced by DNA methylation and histone acetylation, and post - transcriptional regulation is mediated by microRNA (miRNA) mechanisms.[27] However, in a study of form - deprivation myopia in guinea pigs, no significant changes in the methylation level of MMP - 2 were observed.[28] Protein kinase C has been shown to significantly modulate the phosphorylation process of MMP - 2, although this aspect has not been extensively explored for myopia control. In form - deprivation (FD) - induced myopic mice, an elevated MMP - 2 content was detected in the sclera, accompanied by decreased collagen content, which led to enhanced ECM degradation.[29]

Research on scleral remodeling - related pathways aims to identify strategies for antagonizing or inhibiting these pathways to retard myopia progression and mitigate associated complications. Beyond its role in reducing aqueous humor production and lowering intraocular pressure, the α - receptor agonist brimonidine has been found to downregulate MMP - 2 expression. This pharmacological action affects the scleral structure and helps control myopia progression.[30] She et al demonstrated that amphiregulin (AREG) is involved in scleral remodeling during form - deprivation myopia via the ERK1/2 - MMP - 2 pathway.[31] By administering an AREG antibody, the activation of MMP - 2 by related signaling pathways can be blocked, thereby reducing scleral remodeling. However, brimonidine is associated with neurological side effects, such as drowsiness and fatigue, which are particularly prevalent in pediatric patients.[32]

TGF -β Pathway

TGF-β, a pivotal regulator of fibrosis, is categorized as a potent fibrosis-inducing factor. Secreted as inactive precursors, TGF-β proteins are subsequently transported to the ECM.[33] Previous studies have demonstrated that TGF-β facilitates fibroblast repair and promotes the transdifferentiation of cardiomyocytes into myofibroblasts.[34] In the context of scleral biology, a reduction in TGF-β levels has been associated with decreased myofibroblast density, while diminished expression of TGF-β subtypes leads to a decrease in scleral collagen content, thereby contributing significantly to scleral remodeling.[35]

Notably, different TGF-β subtypes exhibit distinct effects on ECM remodeling. Studies in tree shrews have investigated the impact of individual TGF-β subtypes on myopia development, highlighting their differential roles in myopia progression. Zhang et al reported that compared with the control group, levels of TGF-β1, COL-1, and α-smooth muscle actin (α-SMA) were significantly decreased in a lens-induced myopia model, suggesting the occurrence of scleral remodeling.[36]

The biological functions of TGF-β are primarily mediated through the activation of the TAK1/NF-κB signaling pathway.[37] Specifically, TGF-β1 modulates scleral remodeling by regulating MMP-2 activity. During the early stages of endoplasmic reticulum (ER) stress, TGF-β1 expression and COL1A1 synthesis are upregulated via the activation of the inositol-requiring enzyme 1 (IRE1), protein kinase R-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) signaling pathways.[38] This process initiates the unfolded protein response (UPR), ultimately enhancing scleral strength.[39] Conversely, elevated TGF-β2 expression may contribute to scleral thinning by inhibiting collagen synthesis or promoting its degradation, thereby exacerbating axial myopia progression.[40] These findings suggest that pharmacological interventions targeting ER stress pathways may represent a promising strategy for controlling myopia progression.

cAMP Pathway

Cyclic adenosine monophosphate (cAMP), a well - characterized second messenger, plays a crucial role in signal transduction. It activates protein kinase A and cAMP response element binding proteins. cAMP is synthesized from ATP through the catalytic action of adenylate cyclase (AC), and its degradation is mediated by phosphodiesterase.[41]

AC has been shown to inhibit collagen synthesis and impede the transformation of fibroblasts into myofibroblasts. Conversely, the inhibition of cAMP hydrolase phosphodiesterase 4B (PDE4B) expression results in a reduction of scleral collagen fiber expression.[42] The regulation of cAMP - related processes operates within a dynamic equilibrium. A moderate increase in cAMP levels can facilitate normal refractive development, whereas excessive activation exacerbates pathological remodeling. In the context of cardiovascular disease research, cAMP has been demonstrated to modulate the TGF - β pathway.[43]

Future investigations focusing on the sclera should aim to further elucidate the differential expression patterns of cAMP across various myopia models. Additionally, exploring precise intervention strategies targeting the cAMP pathway, such as local drug delivery systems or gene - editing techniques, is essential. These approaches seek to balance the pro - fibrotic and anti - fibrotic effects of cAMP, thereby offering novel perspectives for the prevention and management of myopia.

Wnt Signaling Pathway

The Wnt signaling pathway exerts a multifaceted influence on myopic scleral alterations, primarily through three distinct yet interrelated mechanisms: retinal signal transduction, modulation of scleral fibroblast biological behavior, and ECM remodeling.[44] Upon exposure to myopia-inducing visual stimuli, such as form deprivation or prolonged near work, retinal ganglion cells and retinal pigment epithelial cells (RPE) release an array of signaling molecules, including dopamine and TGF-β1. These molecules activate the Wnt signaling cascade in the sclera via intercellular communication, driving the proliferation, migration, and transdifferentiation of scleral fibroblasts into myofibroblasts. Consequentially, these cellular transformations lead to significant changes in the composition of the scleral ECM, most notably a reduction in COL-1 synthesis.[45]

Furthermore, research has revealed that the expression level of DKK-1, a potent inhibitor of the Wnt/β-catenin pathway, is markedly decreased in the blood of myopic patients.[46] Supplementation with DKK-1 has shown promise in decelerating axial eye growth and impeding myopia progression. Animal studies have firmly established a strong correlation between excessive activation of the Wnt signaling pathway and myopia development. In a form-deprivation-induced myopia mouse model, for instance, activation of the Wnt pathway was evidenced by an upregulation of β-catenin levels. Oral administration of Wnt pathway inhibitors led to a significant increase in TGF-β1 expression in the cell supernatant of the myopic group compared to untreated myopic controls.[47] Leveraging the well-characterized interaction between TGF-β1 and MMP-2, this intervention effectively mitigated myopia progression. Collectively, these findings provide compelling evidence for the pivotal role of the Wnt signaling pathway in the pathogenesis of myopia, thereby offering a robust theoretical foundation for the development of Wnt pathway-targeted prevention and treatment strategies.

Inflammatory Factor Pathways

Currently, accumulating evidence suggests a correlation among axial length elongation, scleral thinning in high myopia, and inflammatory factors.[48] Interleukin-6 (IL-6), a well - characterized cytokine, plays a central role in the inflammatory cascade and is involved in inflammation and immune regulation across diverse tissues.[49] IL-6 has been extensively studied in the context of diabetic retinopathy, age - related macular degeneration, and other aqueous humor - associated cytokines.[50]

Yu et al reported that elevated concentrations of IL-6 and IL-1β in aqueous humor were significantly correlated with myopic axial length.[51] Subsequent studies with larger sample sizes also demonstrated overexpression of IL-6 in the aqueous humor of high myopia patients. While increased levels of inflammatory factors in the aqueous humor have been detected, their definitive relationship with axial length requires further investigation. Chen et al demonstrated that inhibiting inflammatory factors such as IL-6, IL-8, and TNF-α using specific reagents effectively controlled myopia progression, highlighting the role of inflammation in myopia development.[52]

Scleral macrophages, which differentiate from monocytes, have been shown to upregulate MMP-2 expression in the sclera.[53] By interacting with fibroblasts, these macrophages contribute to ECM remodeling. In form - deprivation myopia (FDM) - induced mouse models, M2 macrophage polarization was observed, and inhibition of this polarization effectively suppressed myopia progression.[54] Research on scleral fibroblasts has revealed that IL-6 expression is upregulated under hypoxic conditions. This upregulation affects the proliferation and differentiation of human scleral fibroblasts through the TGF-β1/ Smad2/ MMP-2 signaling pathway, leading to scleral remodeling.[55] These findings indicate that hypoxia can trigger inflammatory responses. Moreover, studies in other disease models have shown that hypoxia acts as a pathogenic factor in certain inflammatory diseases, while an inflammatory state can reciprocally induce hypoxia.[56] Illustrates the interrelationship of the above pathways (Figure 1).

Sclera-Targeted Strategies for Myopia Prevention and Control

Scleral staphyloma is a characteristic manifestation of pathological myopia, although it can also be observed in non-high myopia cases. Patients with scleral staphyloma have an elevated risk of choroidal retinal atrophy. The advent of wide - area optical coherence tomography (OCT) has enabled more timely detection and diagnosis of scleral staphyloma. The presence of scleral staphyloma is associated with significant thinning of scleral collagen, as well as elongation and attenuation of scleral tissue.[57]

Posterior scleral reinforcement (PSR), a treatment modality aimed at controlling the progression of pathological myopia, was first introduced in 1930. In 1961, Curtin proposed the X - shaped buckle method, which was further refined into the Snyder - Thompson single - band reinforcement method in 1972. Over time, continuous advancements have been made in both reinforcement materials and surgical techniques. PSR has become the most widely used surgical approach for the treatment of pathological myopia.[58,59]

Posterior scleral contraction (PSC) represents a modified surgical procedure.[60–62] This technique employs a widened reinforcement material. The length of the pressure band is approximately 1.5 times the axial length, while the bandwidth in the macular area is around 0.4 times the axial length, with careful avoidance of the vortex veins. The bandwidth on the rectus muscle side is approximately 2–3 mm, and the material is sutured adjacent to the superior and inferior rectus muscles. The reinforcement materials have evolved from allogeneic sclera to allogeneic dura mater. A study by Jinlei Ma et al demonstrated that genipin - cross - linked allogeneic dura mater exhibits higher density compared to allogeneic sclera. Following enzymatic degradation, it shows enhanced elasticity, superior control of axial growth, excellent histocompatibility, and no reported adverse effects.[63] The effectiveness of these surgical interventions in improving fundus diseases associated with pathological myopia has been substantiated.

Currently, scleral collagen cross - linking has only been performed in animal experiments, and further research is required to evaluate its safety and efficacy.[64]

Conclusion

The structural alterations of the sclera during axial elongation have been well-documented. These scleral changes, characterized by the thinning of COL-1 fibers and remodeling of the ECM, lead to irreversible ocular modifications and significant visual impairment, thereby substantially impacting the quality of life and health of modern populations. The pathogenesis of myopia involves the dysregulation of multiple signaling pathways. Among these, the scleral hypoxia-associated HIF-1α and HIF-2α pathways play a pivotal role in myopia development. Hypoxic conditions activate glycolysis, increasing lactic acid production and promoting scleral ECM remodeling. The molecular mechanism of the HIF-1α/miR-150-5p/LAMA4/p38 MAPK axis has been experimentally validated, while HIF-2α contributes to myopia progression by upregulating MMP-2.Upon activation by hypoxia-inducible factors (HIFs), the VEGF pathway indirectly influences scleral structure by promoting angiogenesis, altering metabolic processes, and disrupting ECM homeostasis. In the MMP-2 pathway, elevated MMP-2 levels exacerbate ECM degradation. Although α-receptor agonist brimonidine and amphiregulin (AREG) antibodies can modulate MMP-2 activity to control myopia progression, their potential side effects require further investigation.In the TGF-β pathway, different subtypes exert opposing effects on scleral remodeling and participate in myopia development via endoplasmic reticulum stress or regulation of MMP-2 activity. The cAMP

pathway maintains a dynamic equilibrium in regulating scleral collagen synthesis and cellular transformation, yet precise intervention strategies targeting this pathway remain to be explored.

Collectively, these findings on signaling pathways provide a robust theoretical foundation for the development of targeted myopia therapies. Notably, Zhang et al demonstrated that octahedral palladium (Pd) nanocrystals can mitigate oxidative stress in scleral fibroblasts, thereby retarding myopia progression.[65] Additionally, various drug intervention strategies can modulate scleral metabolism by targeting distinct signaling pathways, offering promising avenues for future myopia management.

Currently, prevalent myopia control methods include spectacle correction, orthokeratology (Ortho - K) lenses, and atropine eye drops. Orthokeratology lenses primarily reshape the anterior corneal surface without altering the overall corneal curvature. Night - time wear of Ortho - K lenses can result in central corneal epithelial thinning or thickening, increased astigmatism, higher - order aberrations, and refractive changes. In clinical investigations, 0.01% atropine often demonstrates limited efficacy in halting myopia progression, whereas 0.05% atropine exhibits a more favorable control effect.[66] Corneal refractive surgeries correct ametropia by modifying the corneal anterior surface; however, they carry a risk of rare but severe complications, such as corneal ectasia.[67] Studies on defocus glasses have indicated that optical effects regulate normal ocular growth in healthy eyes.[68] Nevertheless, this optical regulation has minimal impact on scleral remodeling processes in patients with pathological myopia.

Despite the steadily increasing annual incidence of myopia, implementing evidence - based strategies to safeguard adolescent ocular health and mitigate the impact of myopia - related complications can effectively reduce the burden on public health.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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