Review

Stem cell-based therapy for myopic maculopathy: a new concept

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Abstract

Myopia has reached epidemic proportions in the world, especially in East Asia. Pathologic myopia is an extreme type of high myopia that can cause irreversible blindness. Myopic maculopathy is one of the characteristics of pathologic myopia. Nowadays, limited treatments can preserve the visual outcome of these patients. We review the current treatment in practice for myopic maculopathy. Furthermore, based on the current stem cell-based therapy used in degenerative ocular diseases, we discuss a new concept of stem cell therapy for myopic maculopathy.

Keywords: Pathologic myopia, myopic maculopathy, stem cell

INTRODUCTION

Myopia is one of the most common ocular disorders in the world, especially in East Asia. High myopia is the condition that eyes have refractive error ≤ -6.00 diopter when ocular accommodation is relaxed[1]. Pathologic myopia is an extreme type of high myopia with characteristic fundus changes including posterior staphyloma and myopic maculopathy equal to or more serious than diffuse choroidal atrophy[2].

The global prevalence of high myopia was 4.0% before 2016[3], and that of pathologic myopia was 0.9%-3.1% before 2014[4]. The prevalence of high myopia presents an increasing trend in recent years. It is estimated that 9.8% of the global population will have high myopia by 2050[3]. An even more astonishing fact is that the prevalence of high myopia in children aged 6-19 years reached 73% in East Asia before 2019[5]. Visual impairment caused by pathologic myopia will also increase correspondingly. Myopic retinopathy is the second leading cause of blindness and low vision in Chinese adults[6,7]. Both genetic and environmental factors contribute to the development of myopia[8,9]. Since the outbreak of COVID-19 in December 2019, students have been confined to the house and attending class online. Students spent more time on near work and less on outdoor activities. Home confinement has resulted in a significant myopic shift in students aged 6-8 years[10,11]. As Bullimore *et al.*[12] stated, even with a one diopter increase in myopia, the prevalence of myopic maculopathy would increase by 67%.

Because many patients with high myopia face the risk of blindness, treatments are urgently required to cease visual loss and preserve the remaining visual function. This manuscript reviews myopic maculopathy with an emphasis on current treatment modalities and conceptualized stem cell-based therapy.

Introduction of myopic maculopathy

Myopic maculopathy, also named myopic macular degeneration and myopic retinopathy, is defined as the condition comprising diffuse or patchy macular atrophy with or without lacquer cracks, choroidal neovascularization (CNV), and Fuchs' spot[1]. Myopic maculopathy is seen in 22.9% of high myopes aged 7-70 years[13]. The severity of myopic maculopathy increases with older age and longer axial length (AL)[13-15]. Myopic maculopathy is not common in young patients. In patients around 20 years, myopic maculopathy is present in 8.3%[16]. In patients younger than 40 years, it is present in 18.7%[13]. In patients aged 40-70 years, the prevalence of myopic maculopathy increases to 58.3%[13].

The meta-analysis for pathologic myopia (META-PM) classification proposed by an international panel of myopia researchers in 2015 is used in pathologic myopia classification[17]. META-PM classification is based on photography [Figure 1]. There are five categories of myopic maculopathy [Table 1]: no myopic retinal degenerative lesion (Category 0) [Figure 1A]; tessellated fundus (Category 1) [Figure 1B]; diffuse chorioretinal atrophy (Category 2) [Figure 1C]; patchy chorioretinal atrophy (Category 3) [Figure 1D]; and macular atrophy (Category 4) [Figure 1E]. The categories indicate progressed chorioretinal atrophy. Additionally, three plus signs for lacquer cracks, myopic CNV, and Fuchs' spot can be applied to any category. The plus signs indicate three statuses of myopic CNV (mCNV). Lacquer cracks are the breaks of RPE [Figure 1F], Bruch's membrane (BM), and choriocapillaris. They provide an entrance of CNV to grow into subretinal space [Figure 1G]. Fuchs' spot is the scar of mCNV with pigmentation[17] [Figure 1H]. The plus signs are lesions that could directly or potentially impair the central visual acuity. Among these three plus signs, only mCNV requires clinical interventions.

This classification system provides ophthalmologists with a simplified and uniform system to categorize myopic maculopathy by severity. The characteristic alternations in each category are presented in Figure 2.

Category 1: tessellated fundus
Tessellated fundus, or tigroid fundus, is the preliminary sign of myopia. It results from thinning of the retina and increasing visibility of the deep choroidal vessels[16]. The factors related to the cause of fundus tessellation include hypoplasia of the retinal pigment epithelium (RPE), reduced filling of the choriocapillaris, and increased pigmentation of the choroidal stroma[18]. Tessellated fundus is not associated with a decline in best-corrected visual acuity (BCVA)[17]. Tessellated fundus can progress to the next

Table 1. META-PM classification for myopic maculopathy[17]

Category	Plus lesion
Category 0: No myopic atrophy	**Lacquer cracks**
Category 1: Tessellated fundus	**Myopic CNV**
Category 2: Diffuse chorioretinal atrophy	**Fuchs' spot**
Category 3: Patchy chorioretinal atrophy	
Category 4: Macular atrophy	

The bold fonts mark stages defined as pathologic myopia. META-PM: Meta-analysis for pathologic myopia; CNV: choroidal neovascularization.
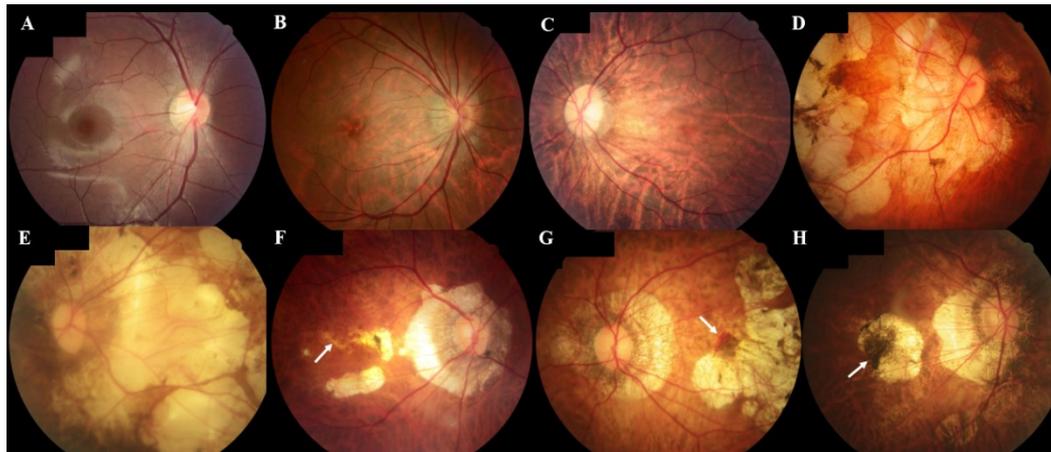
Figure 1. The fundus photography of each category of META-PM classification. (A) Category 0: no myopic retinal degenerative lesion. (B) Category 1: tessellated fundus. Thinning of the retina results in increasing visibility of the deep choroidal vessels. (C) Category 2: diffuse chorioretinal atrophy. An ill-defined yellowish-white lesion can be seen in the posterior pole. (D) Category 3: patchy chorioretinal atrophy. Multiple grayish-white, well-defined atrophy can be seen. The fovea is spared. (E) Category 4: macular atrophy. Atrophy involves the fovea. (F) Lacquer cracks (indicated by white arrow) in the background of patchy chorioretinal atrophy. (G) Active myopic CNV with bleeding (indicated by white arrow) in the background of patchy chorioretinal atrophy. (H) Fuchs' spot (indicated by white arrow) in the background of macular chorioretinal atrophy. META-PM: meta-analysis for pathologic myopia; CNV: choroidal neovascularization.

category in a matter of time. Progression was seen in 19% of tessellated fundus in one ten-year observation[14], and up to 40% high myopic patients with only tessellated fundus or no myopic retinal lesions progressed to myopic maculopathy in follow-ups of more than ten years[15,19].

Category 2: diffuse chorioretinal atrophy
Diffuse choroidal atrophy is the ill-defined yellowish-white lesion in the posterior pole[17]. Diffuse atrophy starts around the optic disc, extends to the macular, and eventually covers the entire posterior pole[20]. Compared with tessellated fundus, patients have thinner choroid and worse visual acuity[21]. A pronounced loss of choriocapillaris, medium, and large-size choroidal vessels can be seen at this stage[2]. The thickness of choroid and sclera decreased due to the elongation of AL, while the thickness of Bruch's membrane stayed the same[22]. Because the outer retina and RPE remain even though the choroid is absent, the visual acuity of patients is relatively preserved[2].

Category 3: patchy chorioretinal atrophy
Patchy chorioretinal atrophy is defined as grayish-white, well-defined atrophy. In this stage, the outer retina layers, RPE, choriocapillaris, and medium- and large-sized choroidal vessels are lost, and the inner retina
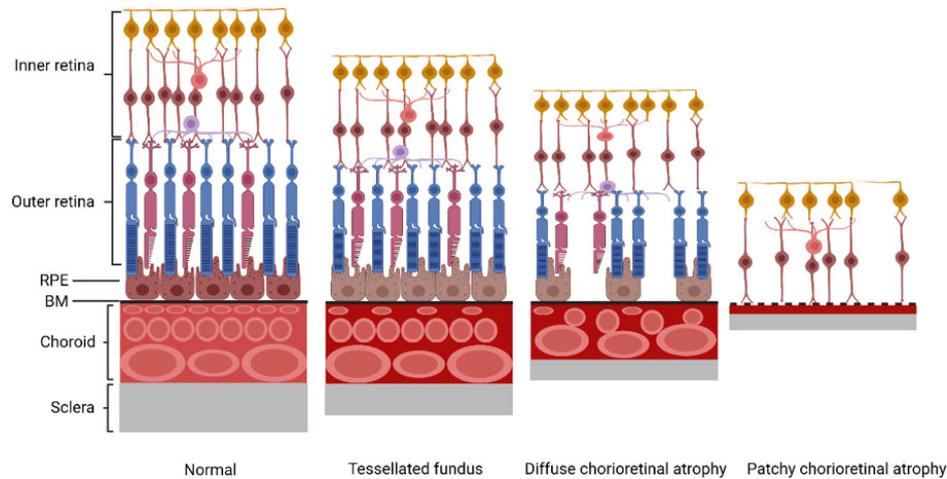
Figure 2. The characteristic alternations of each category based on META-PM classification. The thickness of retina, choroid, and sclera are decreasing along with a higher grade of myopic maculopathy. Tessellated fundus is characterized by hypoplasia of the RPE, reduced filling of the choriocapillaris, and increased pigmentation of the choroidal stroma. Diffuse chorioretinal atrophy is characterized by a marked reduction of all layers of choroidal vessels. In the diffuse chorioretinal atrophy stage, the outer retina and RPE are present even though the choroid is absent. Patchy chorioretinal atrophy is characterized by the absence of the outer retina layers, RPE, and all layers of the choroidal vessels. The inner retina directly touches the sclera. The Bruch's membrane is no longer intact. The structural alternations of macular atrophy are the same as those of patchy chorioretinal atrophy. RPE: retinal pigment epithelium; BM: Bruch's membrane.

directly touches the sclera[23]. It is different from diffuse atrophy because the Bruch's membrane is no longer intact in this stage[24]. Patchy atrophy can develop from lacquer cracks, progress from diffuse chorioretinal atrophy, and can also be seen along the border of the posterior staphyloma[19]. Patchy atrophy usually develops away from the foveal region and expands and merges with each other[19]. Although the central fovea is spared in this stage, deficiency of supply from the choroid still results in visual decrease[19].

Category 4: macular atrophy
Macular atrophy is the final stage of myopic maculopathy, with a well-defined, whitish chorioretinal atrophic lesion at the fovea. In both patchy atrophy and macular atrophy, the Bruch's membrane defect is smaller than the RPE defect in most cases[23,25]. Macular atrophy can be sub-divided into CNV-related macular atrophy (atrophy develops around a regressed CNV) and patchy atrophy-related macular atrophy (one progressed from patchy atrophy). CNV-related macular atrophy almost always develops in CNV patients after a five-year follow-up, and the visual acuity gradually drops, accompanied by enlargement of macular atrophy[26]. CNV-related macular atrophy develops around the scarred CNV and enlarges concentrically[27]. Patchy atrophy-related macular atrophy is more likely a fusion of multiple patchy atrophies[15]. Patients with older age, longer AL, and existing patchy atrophy and lacquer cracks are prone to develop macular atrophy[19]. Patients with a more severe category of myopic maculopathy are more inclined to experience progression. In an 18-year follow-up, progression was also found in 63.7% of patients with diffuse choroidal atrophy, 97.4% of patients with patchy chorioretinal atrophy, and 100% of patients with macular atrophy[15].

Myopic choroidal neovascularization
Introduction of myopic choroidal neovascularization
Myopic CNV (mCNV) is a major cause of irreversible blindness in pathologic myopia, especially in patients < 50 years of age[28]. It causes sudden visual loss on the onset and progressive decline in the natural course[26]. The prevalence of mCNV is reported to be 5.2%-11.3%, and 15% of patients have bilateral CNV[4].

In patients with pre-existing mCNV, the incidence of mCNV will increase in the fellow eye, with a rate of 34.8% in patients with pre-existing mCNV and 6.1% in patients without pre-existing mCNV[29]. Myopic CNV can occur in any degree of myopia[30]. It is estimated that CNV develops in 3.7% and 20% of myopic patients with diffuse chorioretinal atrophy and patchy atrophy, respectively[29]. The final visual outcome is unfavorable even after the application of therapy in most cases[31].

There are three phases of the natural course of mCNV: the active phase, the scar phase, and the atrophic phase[17]. The active phase is determined by the presence of hemorrhage and serous retinal detachment. The scar phase, also called Fuchs' spot, is a dry lesion with a grayish-white scar appearance and sometimes pigmented. When the mCNV progresses into the atrophic phase, the CNV lesion flattens, and chorioretinal atrophy develops around the CNV[32].

Myopic CNV is mostly located at the fovea[33], but it is occasionally located next to the myopic conus[34]. Different from other types of CNV, mCNV is usually small in size and accompanied by little subretinal fluid[35]. Bleeding from mCNV can be absorbed spontaneously in a range of 1-15 months[26,36]. Most of the mCNV remains stable or regressed[36]. Rebleeding occurs in 22% in ten-year follow-up[26].

Risk factors of myopic choroidal neovascularization
The factors associated with the visual outcome of mCNV are the age of onset, follow-up duration, CNV location, and CNV lesion size. Yoshida *et al.*[33] found that patients ≤ 40 years old at the onset of mCNV had a better visual prognosis than those > 40 years old three years after diagnosis. Kojima *et al.*[37] pointed out that the aging RPE cells might lead to less restriction on CNV growth, and then the incompetent RPE cells led to delayed regression of CNV and development of chorioretinal atrophy around the CNV. The visual outcome also depends on follow-up periods. In another study, Yoshida *et al.*[26] investigated the influence of older age. In this study, a group of mCNV patients with a mean age of 46.9 years old were followed up for more than ten years. In the first three years, more than half of them maintained the same visual acuity as the initial value (≥ 20/200). In the tenth year, the visual acuity of 96.3% of patients dropped to < 20/200. Meanwhile, Yoshida *et al.*[26] found chorioretinal atrophy developed in the majority of the eyes after 5-10 years. Therefore, they postulated that the development of CNV-related macular atrophy was responsible for visual loss. On the contrary, patients with younger age and smaller CNV located in the juxtafoveal region had a favorable visual acuity better than 20/40 in a 5-year follow-up[32,38].

Pathogenesis of myopic choroidal neovascularization
The precise pathogenesis of mCNV is still unclear. Mechanical stress, hemodynamic changes, inflammatory factor, and genetic factor have been postulated.

Progressive thinning of the sclera and ectasia of the posterior sclera are the features of pathologic myopia. Similar to the sclera, the choroid becomes thinner during the progression of myopia. The thinning of choroid results from the loss of choriocapillaris and stroma and a reduction in the number of large choroidal vessels[39]. Mechanical stretching of the sclera plays a role in the development of mCNV[40]. In patients with pathologic myopia, the atrophic choroid and sclera make it easy to visualize retrobulbar structures by swept-source optical coherence tomography (SS-OCT) or enhanced depth imaging optical coherence tomography (EDI-OCT). Scleral perforating vessels are linear uniform hyporeflective structures running through the sclera[41]. The choroid circulation receives blood supply from short posterior ciliary arteries (SPCAs). Scleral perforating vessels are originated from SPCAs, which penetrate the sclera in the peripapillary and macular regions[42,43]. The scleral perforating vessels were detected at the site of CNV and lacquer cracks in 70%-80% of mCNV patients[44-46]. The perforating vessels induce weakness of the local

sclera. Meanwhile, the thin choroid in high myopia patients is not competent to buffer the mechanical stress caused by myopia development. In patients with the thin choroid, the force would concentrate in the area of scleral perforating vessels and cause the disruption of RPE and Bruch's membrane. In this way, the mCNV grows through the fissure into the subretinal space and tries to fix the mechanical break[45].

Loss of choroidal vessels causes a choroidal circulatory disturbance, induces hypoxia in the RPE and glial cells, and triggers upregulation of vascular endothelial growth factor (VEGF) expression[47]. VEGF is a family of proteins including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor[48]. VEGF-A is the key regulator for angiogenesis[48]. The receptors of VEGF are VEGFR-1, VEGFR-2, and VEGFR-3. The former two are expressed predominantly on vascular endothelial cells, while VEGFR-3 is expressed on lymphatic endothelial cells[49]. VEGF interacts with VEGFR-1 and VEGFR-2 to initiate an intracellular cascade and induce proliferation and migration of vascular endothelial cells and inhibit apoptosis[50]. In addition to hypoxia-induced expression of VEGF, the mechanical stress posed on RPE induces expression and secretion of VEGF[51].

VEGF, as a common contributor in different types of CNV, can be detected in aqueous humor and vitreous body. The physiologic expression of VEGF levels is lower in the eyes of highly myopic patients than those of non-myopia patients[47]. The VEGF level elevates in myopic patients with CNV compared to those without CNV[47]. When compared with other types of CNV, the VEGF level in the aqueous humor of mCNV patients was lower[52,53]. Several possible explanations for this have been proposed. Firstly, dysfunction of RPE cells causes less expression of VEGF. VEGF, which is expressed by differentiated RPE cells, is essential in the maintenance of choriocapillaris[54,55]. In high myopia, the deteriorated function of RPE cells causes a reduction of VEGF production and corresponding atrophy of choriocapillaris[56]. Secondly, the large vitreous cavity of myopic eyes could dilute VEGF concentration. In highly myopic patients, whether with CNV or not, the VEGF concentration is negatively correlated with AL[47,57]. Researchers have argued that the limited amount of VEGF localized to mCNV is not sufficient to distribute into the anterior chamber. Thirdly, the decrease of VEGF production is due to retinal thinning in myopic eyes. Sawada *et al.*[52] proposed that retinal thinning in myopia patients causes a relative increase in choroidal perfusion. Consequently, retinal hypoxia would be improved, and VEGF production would decrease, correspondingly.

In addition to hypoxia-induced expression of VEGF, the aqueous cytokines indicate that inflammation has a role in the development of mCNV[58]. In the study by Yamamoto *et al.*[58], the levels of interleukin-8 (IL-8) and VEGF were significantly higher in eyes with mCNV. IL-8 is a proangiogenic and inflammatory chemokine that can upregulate VEGF expression in ischemic circumstances[59]. Beyond that, the interleukin-10 (IL-10) and monocyte chemoattractant protein-1 (MCP-1) levels were higher in myopic eyes than in normal eyes in this study. Furthermore, IL-8 and MCP-1 were related to the severity of myopic maculopathy. MCP-1 is a chemokine that regulates monocyte chemotaxis and lymphocyte differentiation in inflammatory diseases[60]. Thus, it is suggested that inflammation is involved in the progression of myopic maculopathy and the etiology of mCNV.

Genetic factors also play a part in the development of mCNV. Leveziel *et al.*[61] compared mCNV cases with high myopia cases and evaluated 15 age-related macular degeneration genetic variants which could also be involved in mCNV development. They found that the rs10033900 single nucleotide polymorphism (SNP) located in *CFI* gene was significantly associated with mCNV in Caucasians. *CFI* encodes complement factor I (CFI), which is a complement regulatory protein in the classical, alternative, and mannose-binding lectin pathways of the complement system[62]. CFI is expressed by hepatocytes, macrophages, lymphocytes, endothelial cells, and fibroblasts[63]. CFI works as a protease to prevent positive amplification of complement

cascade by cleaving C3b and C4b[64]. Leveziel hypothesized that the specific genetic effects related to the inflammatory pathway would increase the risk of mCNV.

In another large case-control study conducted by Miyake *et al.*[65] in Japan, rs10033900 was not found in mCNV patients, but rs12603825 in *PEDF* gene is possibly associated with mCNV patients whose AL is ≥ 29 mm. Pigment epithelium-derived factor (PEDF) is a member of the serine protease inhibitor superfamily[66]. It was first identified as a potent inducer of neuronal differentiation in cultured retinoblastoma cells[67]. In ocular tissue, PEDF is secreted by photoreceptors and RPE cells and released into the interphotoreceptor matrix between RPE and photoreceptors as well as in the inner retina[68,69]. It is also expressed in cornea and ciliary epithelium[70] and can be detected in the vitreous body and aqueous humor. PEDF is a multifunctional protein with antiangiogenic[71], neurotrophic[72], and antioxidant[73] properties in ocular tissue. PEDF exerts its antiangiogenic effect by inducing apoptosis of endothelial cells and interfering with VEGF-induced angiogenesis[74]. In a laser-induced CNV rat model, decreased expression of PEDF was observed at the injury sites, suggesting permission on the formation of CNV[75]. In addition, PEDF protects RPE monolayer and pericytes from oxidant stress[76,77], as well as protects photoreceptors by suppression of apoptotic and inflammatory pathways[78]. According to Costagliola *et al.*[53], after anti-VEGF therapy, the level of VEGF decreases, while the PEDF level increases in the aqueous humor of patients with mCNV. It is known that the development of CNV is an imbalance between angiogenic and antiangiogenic factors. Therefore, the SNP in the *PEDF* gene could be a biological marker associated with mCNV.

The ATN classification

Compared with the META-PM classification, the atrophy-traction-neovascularization (ATN) classification proposed by Ruiz-Medrano *et al.*[79] in 2019 takes tractional and neovascular components into consideration. ATN represents three key factors in myopic maculopathy: atrophy (A), traction (T), and neovascularization (N). The ATN classification is based on both fundus photography and OCT to assess myopic maculopathy. In 2021, Ruiz-Medrano *et al.*[80] updated the ATN system [Table 2]. Based on longer AL and worse BCVA, they defined severe pathologic myopia as eyes graded ≥ A3, ≥ T3, and/or ≥ N2, which indicate a significant myopic macular complication. The atrophic and neovascular classifications in ATN system are the same as META-PM system. Both systems have five classifications on the aspect of atrophy and three statuses of mCNV. The ATN system includes the tractional component, which is closely related to visual acuity[79].

CURRENT INTERVENTIONS TO MYOPIC MACULOPATHY

Currently, no available treatment has been found for myopic maculopathy except for mCNV. Management of mCNV is the same as other types of CNV by laser photocoagulation, verteporfin photodynamic therapy, and anti-VEGF therapy. Approaches have been proposed to retard myopic progression including pharmacologic, surgical, and optical intervention.

Non-surgical interventions

Pharmacologic intervention (e.g., low concentration atropine) and optical intervention (e.g., orthokeratology) are used to slow down myopic progression before the development of myopic maculopathy.

Low concentration atropine

The Atropine in the Treatment of Myopia (ATOM1) study in 2006 suggested that 1% of atropine can slow down the progression of childhood myopia[81]. This study recruited 400 children (6-12 years old) with low to moderate myopia (spherical equivalent of -1.00 to -6.00 D and astigmatism of ≤ -1.5 D). Participants were

Table 2. Updated ATN classification for myopic maculopathy[80]

Atrophy (A)	Traction (T)	Neovascularization (N)
A0: No myopic atrophy	T0: No macular schisis	N0: No myopic CNV
A1: Tessellated fundus	T1: Inner or outer foveoschisis or lamellar macular hole	N1: Macular lacquer cracks
A2: Diffuse chorioretinal atrophy	T2: Inner and outer foveoschisis	**N2a: Active CNV**
A3: Patchy chorioretinal atrophy	**T3: Foveal detachment**	**N2b: Fuchs' spot**
A4: Complete macular atrophy	**T4: Full-thickness macular hole**	
	T5: Macular hole and retinal detachment	

The bold fonts mark stages defined as severe pathologic myopia. ATN: atrophy-traction-neovascularization. CNV: choroidal neovascularization.

randomly assigned to the treatment group (1% atropine) or control group (vehicle eye drops). Only one eye of the participants received treatment. After a two-year follow-up, the progression of spherical equivalent (SE) value was 0.28 ± 0.92 D in the atropine group and 1.20 ± 0.69 D in the control group. The AL remained unchanged in the atropine group, while the AL elongated 0.38 ± 0.38 mm in the control group. Overall, 77% of the atropine group demonstrated a reduction in progression of myopia compared with the control group. ATOM1 demonstrated the efficiency of 1% atropine on myopia control.

The prominent side effect of 1% atropine resulted from mydriasis and cycloplegia. Therefore, lower doses of atropine were used in the ATOM2 study. In the ATOM2 study (phase 1)[82], 0.5%, 0.1%, and 0.01% atropine were used in 400 children (6-12 years old) with myopia of at least -2.00 D and astigmatism of ≤ -1.50 D. Different concentrations of atropine were used in each group bilaterally for two years. The increase in SE value was 0.30 ± 0.60, 0.38 ± 0.60, and 0.49 ± 0.63 D in the 0.5%, 0.1%, and 0.01% atropine groups, respectively. The increase in AL was 0.27 ± 0.25, 0.28 ± 0.28, and 0.41 ± 0.32 mm, respectively, in the groups. A small clinical difference was found among the three treatment arms. The results of ATOM2 suggested that 0.5%, 0.1%, and 0.01% atropine were effective in reducing myopia progression, and higher doses achieved greater effect. Then, the 400 children underwent a one-year washout phase (phase 2)[83]. In this study, different degrees of myopic rebound after cessation of atropine were found in these three groups. The SE value increased 0.87 ± 0.52, 0.68 ± 0.45, and 0.28 ± 0.33 D in the 0.5%, 0.1%, and 0.01% atropine groups, respectively. The Al increased by 0.35 ± 0.20, 0.33 ± 0.18, and 0.19 ± 0.13 mm, respectively, in the groups. The rebound was greater in eyes in the 0.5% and 0.1% groups. During the entire 36 months of phase 1 and 2 ATOM2 studies, the overall increase of SE value was 1.15 ± 0.81 D in the 0.5% atropine group, 1.04 ± 0.83 D in the 0.1% atropine group, and 0.72 ± 0.72 D in the 0.01% group. The results suggest an inverse correlation between doses and myopic increase.

Since the rapid progression of myopia was found in children after cessation of atropine, phase 3 of ATOM2 was conducted[84]. Children in previous studies with a myopic progression of more than 0.5 D were recruited. Overall, 24% of children in the 0.01% group required the phase 3 treatment, while 59% in the 0.1% group and 68% in the 0.5% group needed further treatment. In total, 192 children restarted on 0.01% atropine for 24 months. In the entire five-year follow-up, the overall progression of myopia was slowest in the 0.01% group (SE 1.38 ± 0.98 D; AL 0.75 ± 0.48 mm), followed by the 0.1% (SE 1.83 ± 1.16 D; 0.85 ± 0.53 mm) and 0.5% groups (SE 1.98 ± 1.10 D; 0.87 ± 0.49 mm). Therefore, these studies suggested that 0.01% atropine is an effective treatment in myopic children, especially in those with rapid progression.

Orthokeratology
Orthokeratology (Ortho-K) is a process of reversibly reshaping the cornea by utilizing contact lenses overnight. The efficacy of Ortho-K on myopic control has been proved in clinical trials which recruited

children (6-16 years old) with low to moderate myopia. Compared with the single-vision spectacles group, the axial elongation of the Ortho-K group was reduced by 36%-63% in the ROMIO study (the Retardation of myopia in Orthokeratology)[85], HM-PRO study (the High Myopia-Partial Reduction Ortho-k study)[86], and other clinical trials[87-89]. According to the existing studies, Ortho-K showed benefits to children with low to moderate myopia.

Interventions to myopic CNV

Anti-VEGF therapy

As mentioned above, the angiogenic stimulant VEGF is involved in the pathogenesis of mCNV. Therefore, VEGF is the target to treat choroidal angiogenesis. Nowadays, the widely used anti-VEGF drugs include ranibizumab, aflibercept, and conbercept. These drugs are divided into two groups based on their molecular structure. Ranibizumab is a recombinant, humanized, monoclonal antibody. It is an antigen-binding fragment (Fab) that can neutralize all isoforms of VEGF-A[90]. Aflibercept and conbercept are fusion proteins made of key domains of VEGFR1 and VEGFR2 fused with a portion of human antibody[91]. They act as a decoy receptor for VEGF and prevent VEGF from activating the real VEGFR[92].

Recently, anti-VEGF therapy has become the major treatment and provided good visual acuity benefits[93]. The safety and efficacy of these anti-VEGF agents have been proved in many studies. Similar visual gains and morphological improvements of mCNV patients were achieved by each of these anti-VEGF agents[94-96]. In the REPAIR study published in 2013[97], the efficacy of intravitreal 0.5 mg ranibizumab in mCNV was evaluated. Eyes with mCNV received ranibizumab at baseline and monthly injections as needed. Patients gained 13.8 letters at 12 months on average. The median number of injections was three. In the MYRROR study published in 2015[97], the efficacy of intravitreal aflibercept was evaluated. Patients were divided into the aflibercept and sham groups. Patients in the aflibercept group received one injection of 2 mg aflibercept at baseline and additional injections monthly when mCNV persisted or recurred. Primary efficacy was assessed at Week 24; patients in the aflibercept group gained 12.1 letters, while patients in the sham group lost two letters on average. Then, patients in the sham group received mandatory aflibercept injections for another 24 weeks with the same regimen. By Week 48, patients gained 13.5 and 3.9 letters in the aflibercept and sham/aflibercept groups, respectively. In the aflibercept group, the median number of injections was two during the first eight weeks, and no additional injections were applied during the remaining 40 weeks. In the sham/aflibercept group, the median number of injections was two during Weeks 25-36 and one during Weeks 37-48. Different from exudative age-related macular degeneration or diabetic macular edema, which requires frequent injection[98,99], the management of mCNV required a limited number of injections.

Severe adverse effects have been reported, including subretinal fibrosis[100], retinal detachment[100], and macular hole[101]. The common adverse events are conjunctival hemorrhage, transient increase in intraocular pressure, corneal punctate keratitis, and posterior capsule opacification[96]. Very few systemic complications associated with anti-VEGF therapy have been reported in clinical trials of mCNV patients. Due to favorable visual outcomes and safety profiles, anti-VEGF agents have become the standard treatment for mCNV[102].

Laser photocoagulation and photodynamic therapy

Laser photocoagulation and vPDT had been used to treat mCNV before the availability of anti-VEGF drugs in the past decades[103,104]. Laser photocoagulation is only employed in juxtafoveal CNV. The laser destroys the CNV and causes thermal damage in the outer retina, RPE, and choriocapillaris[105]. Successful laser photocoagulation could improve visual acuity because it prevents the CNV from extending to the fovea[106]. However, the long-term visual outcome is not favorable. Neovascular recurrence is one of the reasons for the deterioration of visual acuity. The incidence of recurrence ranges from 48.2% to 72%[106-108]. Furthermore,

the laser-induced scar enlarged obviously in the first three months, accompanied by decreased visual acuity[109]. Expansion of the laser-induced scar is another cause of visual loss, and it has been regarded as a potential vision-threatening late complication[109].

PDT with verteporfin was a therapeutic modality to treat subfoveal CNV. Patients received an intravenous injection of a photosensitizer named verteporfin and application of a specific wavelength of laser light to the target lesion[110]. Verteporfin can bind to endogenous lipoproteins overexpressed on neovascular endothelial cells. After activation by laser, verteporfin leads to occlusion of the targeted CNV. Compared with laser photocoagulation, PDT induces selective occlusion of the CNV without injuring the surrounding neurosensory retina and RPE[111]. The efficacy and safety of PDT in mCNV have been approved[103,112,113], and the recurrence rate after treatment is around 50%[114,115]. In a meta-analysis, anti-VEGF therapy gained better vision in mCNV patients than photodynamic therapy (PDT) or laser photocoagulation[116]. In the RADIANCE study (Ranibizumab and PDT evaluation in myopic choroidal neovascularization) published in 2014[93], the efficacy and safety were compared between ranibizumab 0.5 mg intravitreal injection and verteporfin photodynamic therapy (vPDT). Patients with mCNV were randomly assigned to ranibizumab treatment guided by visual acuity stabilization criteria (Group 1), ranibizumab treatment guided by disease activity criteria (Group 2), and the vPDT group. Patients in the vPDT group could switch to ranibizumab three months after the initial vPDT. Ranibizumab achieved a rapid improvement in BCVA in Groups 1 and 2 during the first three months and a stable improvement up to the endpoint. The vPDT group improved lower BCVA compared to the ranibizumab group during the first three months. Then, 73% of participants with lower BCVA change in the vPDT group switched to the ranibizumab group. At 12-month follow-up, the mean BCVA improved 13.8 ± 11.42 letters in Group 1, 14.4 ± 10.2 letters in Group 2, and 9.3 letters in the vPDT group. Replicated injections were requested in the ranibizumab group. The median number of ranibizumab injections was four in Group 1 and two in Group 2. In addition to better visual outcomes in the ranibizumab groups, the RADIANCE study also demonstrated that an individualized regimen could achieve optimal visual outcomes.

Due to its advantages in terms of visual outcome and convenient intravitreal injection of drugs, anti-VEGF therapy has become the major treatment of mCNV[102].

Surgical interventions to myopic maculopathy

Posterior scleral reinforcement

Axial elongation contributes to myopic maculopathy. The thin sclera, especially the posterior pole of the globe, facilitates excessive ocular enlargement. Sclera is regarded as a prime target to stop the progression of myopia. Currently, reinforcement of the posterior sclera by different surgical methods is the only available way to managescleral ectasia.

Posterior scleral reinforcement (PSR) was first proposed by Shevelev[117] in 1930, modified by Borley and Snyder[118] in 1958, and then simplified by Thompson[119] in 1978. The surgical process has kept innovating in the following decades. The main procedure of PSR is placing a strip (sclera from donor's eye, fascia lata strip[120] or duramater[121] from cadaver, or biomaterial patch) over the posterior pole to strengthen the posterior sclera and halt axial elongation. In most of the reports on PSR, the results are favorable with stable visual acuity as well as a lower increase in refractive error and AL[121-124]. According to Curtin's grade of posterior staphyloma, the most common staphyloma developed on the nasal side of optic nerve[125]. Therefore, Curtin pointed out that PSR did not protect against staphyloma, which is not located in the macula[126]. In fact, the purpose of PSR is to preserve central visual acuity. Staphyloma located outside macula would not affect the visual outcome of PSR.

Despite mechanically strengthening the posterior sclera, PSR may halt axial elongation by ameliorating hypoxia of sclera. During myopia development, scleral hypoxia plays a pivotal role in sclera remodeling[127]. Choroidal ischemia is a possible cause of myopic maculopathy[128]. A thinner choroid is associated with faster AL growth[129]. Increasing choroidal vascular perfusion can improve oxygenation of the sclera and slow down myopia development in guinea pigs[130]. Zhang *et al.*[131] considered that the allogeneic scleral graft caused a secondary non-specific inflammatory reaction and increased the choroidal blood flow. Whether the improved choroidal circulation after surgery could prevent eye globe elongation still requires further investigation.

Currently, PSR is regarded as an effective way to limit the progression of pathological myopia and reduce the occurrence of myopic maculopathy, especially in patients with fast myopic progression. Studies on the treatment effect of PSR on pathological myopia are listed in Table 3.

Posterior pole buckle
Posterior pole buckle, or macular buckle, is similar to PSR. The main procedure of PSR is to reinforce the ectatic posterior pole, while that of posterior pole buckle is an application of stronger positive forces over the posterior pole to make an iatrogenic dome-shaped macula[132]. Due to scleral protrusion caused by silicone sponge, posterior pole buckle diminishes the high myopia[133]. The diminution degree is correlated with silicone sponge stretching and fixation. Posterior pole buckle is mostly applied in patients with macular membrane, macular schisis, and myopic macular hole with a retinal detachment to release the myopic macular traction[134]. It could be done alone or combined with pars plana vitrectomy[135,136].

The complications of both PSR and posterior pole buckles include lateral rectus weakness, intraocular pressure increase, diplopia, metamorphopsia, and choroidal effusion[134,137]. However, most complications are transient. Both PSR and posterior pole buckles are safe and effective with accurate placement of strip or buckle.

Scleral collagen cross-linking
Cross-linking was first used in keratoconus to increase the stiffness of cornea[138]. Then, in 2004, Wollensak[139] introduced scleral cross-linking for the treatment of high myopia. Cross-linking is the technique to enhance the tensile strength of collagen by the physical way (riboflavin–ultraviolet A[140]) or chemical agents (genipin[141] and glyceraldehyde[142]). Cross-linking strengthens the sclera by forming covalent bonds between collagen molecules[143] and reducing the enzymatic degradation by MMP1[144]. Until now, animal experiments including guinea pig[145], rat[146], and rhesus monkeys[147] have proved the efficiency and safety of scleral cross-linking, but no protocol has been brought to clinical use. Only one study conducted by Xue *et al.*[148] showed the genipin-crosslinked sclera strip used in PSR showed better strength and larger surgical effect size. Further clinical studies are required.

CURRENT STEM CELL-BASED THERAPIES FOR MACULOPATHY
Stem cell-based therapies have been mainly applied in degenerative corneal and retinal diseases. The following summarizes the stem cell-based clinical trials in maculopathy.

The stem cell ophthalmology treatment study
The Stem Cell Ophthalmology Treatment Study (SCOTS) is a series of clinical studies treating incurable optic and retinal diseases with autologous bone marrow-derived stem cells (BMSCs). The completed clinical trials include studies on Usher syndrome[149], dominant optic atrophy[150], Leber's hereditary optic neuropathy[151], relapsing auto-immune optic neuropathy[152], and serpiginous choroidopathy[153]. In these

Table 3. Studies on the treatment effect of PSR on pathological myopia

Authors	Age (year)	Follow-up duration	Control	Baseline AL (mm)	Endpoint AL (mm)	Elongation of AL in PSR group (mm)	Elongation of AL in control group (mm)	P
Xue *et al.*[124]	7.5	10.8-43.2 m	Nonsurgical	26.2 ± 1.33	not mentioned	0.75 ± 0.48	0.94 ± 0.44	0.0001
Li *et al.*[217]	41.03 ± 2.27	5 y	Nonsurgical	29.49 ± 1.21	29.79 ± 1.26	0.30 ± 0.21	1.35 ± 0.56	< 0.01
Peng *et al.*[218]	37.36 ± 16.22	3 y	Spectacles & contact lens	29.42 ± 1.35	29.61 ± 1.61	0.23 ± 0.34	1.01 ± 0.33	0.0423
Dong *et al.*[123]	7.28 ± 3.69	3 y	Spectacles	26.72 ± 1.28	27.00 ± 0.82	0.29 ± 0.33	0.82 ± 0.33	< 0.0001
Shen *et al.*[219]	4.94 ± 0.77	3 y	Contact lens & patching	26.78 ± 1.37	27.38 ± 1.30	0.60	Not mentioned	0.03
Hu *et al.*[220]	8.21 ± 3.86	1 y	Nonsurgical	27.10 ± 1.02	27.23 ± 1.01	0.13 ± 0.17	0.71 ± 1.08	< 0.05
Chen *et al.*[121]	6.50 ± 3.23	4.99 ± 1.3 y	Spectacles	26.55 ± 1.60	Not mentioned	1.27 ± 0.54	2.05 ± 0.91	< 0.001

AL: Axial length; *P*: statistical comparison of AL change between PSR group and control group; PSR: Posterior scleral reinforcement.

studies, patients received subretinal or intra-optic nerve injection alone or a combination of retrobulbar, sub-Tenon's, intravitreal, and intravenous injection. Meaningful visual acuity improvements were confirmed in these studies, and no adverse events were seen. Possible mechanisms in these studies were proposed: BMSCs released exosomes containing microRNA (miRNA) to regulate gene expression in inherited retinal degeneration, transferred mitochondria to rescue ganglion cells in mitochondrial disease, secreted growth factors to promote photoreceptors and neuron survival, and transdifferentiated into neurons or photoreceptors. Although there was a small number of patients enrolled, the favorable visual acuity and visual field improvement make autologous BMSC an option to treat these incurable diseases.

Stem cell-based therapy in macular degeneration

Age-related macular degeneration (AMD) is the most common cause of blindness in patients older than 55 years in developed countries[154]. There were about 196 million patients in 2020, and it was estimated that there will be 288 million in 2040[154]. The exact pathogenesis of AMD is obscure. Factors such as senescence, chronic inflammation, complement pathway, and lipid metabolism are proposed as implicated in the pathogenesis[155-158]. At the cellular level, AMD results from loss or dysfunction of RPE cells and secondary death of photoreceptors. According to the clinical manifestations, AMD is divided into dry (non-exudative or atrophic) and wet (exudative) types. Since the introduction of anti-VEGF treatments in 2004[159], the irreversible visual loss has been slowing down over the past decade[160]. However, the anti-angiogenesis treatment requires long-term repeat applications. Although these two types of AMD are different clinically, they both end up with a complete loss of photoreceptors, RPE, and choriocapillaris. Therefore, replacement therapy is the best way to restore vision.

Stargardt disease, also named Stargardt's macular degeneration (STGD), is one of the most prevalent inherited juvenile macular dystrophies[161]. The early onset of STGD results in a visual loss in the working age population[162]. Three genes have been found responsible for three types of STGD. *ABCA4* (1p22.1), *ELOV4* (6q14.1), and *PROM1* (4p15.32) are implicated in STGD1, STGD3, and STGD4, respectively. STGD1 is an autosomal recessive inherited disease caused by an *ABCA4* gene mutation. This gene encodes the ATP-binding cassette transporters protein (ABCA4) expressed in the outer segment of photoreceptors. ABCA4 transports retinylidene-phosphatidylethanolamine (N-retinylidene-PE) from the inside of disk to the cytoplasmic side of the disk and avoids N-retinylidene-PE reacting with all-trans-retinal and forming di-retinoid-pyridinium-ethanolamine (A2E), which is toxic to photoreceptors and RPE[163]. STGD3 is an autosomal dominant inherited disease caused by a mutation in *ELOVL4*. This gene encodes ELOVL fatty acid elongase 4, which is involved in a catalyzing reaction of the long-chain fatty acids elongation cycle[164]. Mutated *ELOVL4* causes the production of a truncated ELOVL4 protein lacking a motif for endoplasmic reticulum retention. Dysfunction of ELOVL4 protein results in decreased synthesis of long-chain (C28-C36) fatty acids. C28-C36 fatty acids are components of phosphatidylcholines which are distributed in photoreceptor outer segments[165], bind to rhodopsin[166], and regulate activities of photo-transduction proteins[167]. The truncated ELOVL4 protein causes deficiency of C32-C36 acyl phosphatidylcholines, alternation in photo-transduction proteins, and an increase in lipofuscin accumulation[168]. STGD4 is an autosomal dominant inherited disease caused by the mutation in *PROM1* gene[169]. Prominin 1, encoded by *PROM1,* is located at the base of the photoreceptor outer segments and participates in disk membrane formation. Mutated *PROM1* causes overgrown and misoriented outer segment disk membranes, which indicate defective disk morphogenesis[170]. Similar to AMD, complete loss of photoreceptors, RPE, and choriocapillaris is observed at the end stage of STGD.

The key functions of RPE cells are delivering nutrients and disposing waste for photoreceptors and phagocytosis of outer segments of photoreceptors[171]. The purpose of delivering RPE cells to the subretinal space is to rescue the remaining photoreceptors. The subretinal space is an immune-privileged environment suitable for cell-based therapy. Subretinal injection of cell suspension and the delivery of cell patches are new replacement therapy processes[172]. A clinical trial on stem cell transplantation for STGD and dry AMD was first conducted to prove the safety and tolerability of human embryonic stem cell-derived RPE (hESC-derived RPE) in 2012[173]. From then on, the innovation of cell transplantation focuses on sources of cells and approaches of delivery. Because polarized RPE cells array in a monolayer in physical conditions, researchers proposed that loading RPE cells on a bioengineered scaffold is an optimal method for delivery. A synthetic biocompatible membrane for RPE loading made from different materials has been innovated[174, 175], and some tested in clinical studies[176,177]. In 2017, iPSC-RPE cell sheets were first transplanted in one wet AMD patient[178]. Although the visual acuity did not improve, the implanted graft integrated well with the local neuroretina. Thus far, the safety of stem cell-based therapy has been proved, while the efficacy requires further investigation. A recent review comprehensively summarizes the current status of stem cell-based retinal regeneration[179].

CONCEPTUALIZED CELL THERAPY FOR MYOPIC MACULOPATHY

Cell therapy is substitutive therapy by regenerating dysfunctional tissues or cells with curative cells[180]. It is a novel method to treat diseases that were previously regarded as incurable. Here, we review the cells which are theoretically available for cell therapy for pathologic myopia.

Autologous iPSC-RPE

Hypoplasia and loss of RPE are characteristics during the progression of myopic maculopathy. As with other forms of macular degeneration, loss of RPE cells leads to apoptosis of photoreceptors in pathologic

myopia. In patients with high myopic macular hole, the anatomical closure of the macular hole and visual improvements have been the main criteria for a successful surgery. There are reports that failed to improve visual acuity after the closure of macular hole[181]. Ophthalmologists are inclined to attribute the failure to the severity of pathologic myopia or disrupted photoreceptors[182,183]. However, the status of RPE was ignored in the past.

More attention needs to be paid to RPE. Fang *et al.*[184] studied 14 eyes with fovea-centered macular atrophy that developed after successful pars plana vitrectomy (PPV) for myopic traction maculopathy and macular hole retinal detachment. The postoperative visual acuity was even worse than the baseline. These eyes had diffused atrophy or extrafoveal patchy atrophy preoperatively and developed macular atrophy at a median time of 3.5 months after surgery. PPV-related macular atrophy is different from CNV- or patchy atrophy-related macular atrophy as it starts from the fovea. Eyes with macular hole retinal detachment are prone to develop PPV-related macular atrophy. This study emphasized the importance of RPE on the recovery of vision. When reviewing the postoperative outcomes of high myopic macular hole, AL > 30 mm and presence of posterior staphyloma are risk factors for unfavorable visual outcomes[185]. It is rational that a longer AL indicates severe chorioretinal atrophy and loss of RPE.

Therefore, transplantation of RPE cells seems a preferable way to improve the visual outcomes of high myopic patients by replacing atrophic RPE cells with healthy ones. The efficiency and safety of GMP-grade human iPSC-RPE were proved in a pre-clinical study conducted by Zhang *et al.*[172]. Here, the transplanted cells were injected into the subretinal space. However, a cell suspension is not practical to apply in myopic macular hole surgery. Scaffolds for RPE transplantation with excellent cytocompatibility and biocompatibility are required[174]. A cell patch is feasible to place under the macular hole during PPV surgery. The scaffolds act as the Bruch's membrane for functional RPE reconstruction [Figure 3]. Compared with traditional surgery, combination with iPSC-RPE transplantation would reap greater benefits. One concern of RPE cell patch transplantation is the viability of the cell patch when there is a lack of choroidal perfusion from the severely atrophic choroid. Pang *et al.*[186], in 2015, identified that myopic eyes with an extremely thin choroid (≤ 20 μm) could still have BCVA ≥ 20/40. They proposed two explanations: (1) a fovea with extremely thin choroid would receive blood supply from larger patent choroidal vessels located eccentric to the subfoveal area; and (2) an atrophic retina with a thinner layer allows more oxygen to permeate from deep capillary plexus to outer retina. Therefore, we have reasons to believe that transplantation of RPE cell patches to eyes with myopic macular holes is feasible.

Fibroblasts/Myofibroblasts

The sclera, as the wall of eye globe, must have the strength to protect the delicate intraocular structures and some degree of elasticity to buffer fluctuations of intraocular pressure. The sclera is composed of collagens, proteoglycans, non-collagenous glycoproteins, and elastic fibers. In the human sclera, 90% of the components are collagen type I[187]. The collagens form the scaffolds, while proteoglycans and glycoproteins fill the interfibrillar space[188]. Collagen fibrils irregularly arrange and form layers. Fibroblasts intersperse between scleral collagen layers and synthesize sclera extracellular matrix components[189].

The thinning of sclera is a pivotal factor in the progression of myopia. In the histological study of enucleated human eye globes, the scleral volume increases with longer AL in the first two years of life and stays stable in the following years[190]. This finding indicates that scleral thinning due to axial elongation is contributed to the rearrangement of existing sclera tissue rather than synthesizing new sclera. In the posterior sclera of myopic eye, reductions in the number of fibroblasts and the collagen fibril diameter can be found[191]. In addition, unusual fibrils with a star shape on cross section increase in myopic sclera[191]. It is known that an
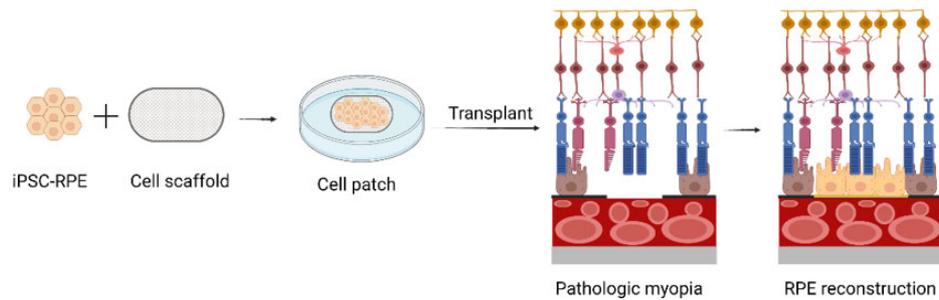
Figure 3. The schematic diagram of iPSC-RPE transplantation in pathologic myopia. Generate a cell patch by culturing iPSC-RPE cells with a cell scaffold. Then, transplant the cell patch into the subretinal space of pathologic myopic eyes. The excellent cytocompatibility and biocompatibility of the scaffold offer RPE cells a suitable circumstance for reconstruction. RPE: retinal pigment epithelium.

increase of matrix metalloproteinase-2 (MMP-2) activity[192], a decrease of turnover rate of proteoglycan[193], and structural changes of collagen fibrils result in a weak and extensible sclera. The changed scleral biomechanics is thought to be responsible for the increasing AL and development of myopia.

Myofibroblasts are a population of scleral cells arising from fibroblasts. The transition is stimulated by mechanical stress, transforming growth factor-β (TGF-β), and cellular fibronectin[194]. Myofibroblasts are highly contractile cells that can express alpha-smooth muscle actin (α-SMA) to respond to scleral mechanical stress and limit expansion of the surrounding matrix[195]. Reduction in the level of TGF-β is a contributor to remodeling of ECM during the development of myopia[196]. TGF-β is important in the regulation of ECM turnover. A reduction of TGF-β would induce a decrease of α-SMA expression and cell-mediated contraction[196]. TGF-β not only induces myofibroblasts to synthesize α-SMA but also promotes the production of collagen type I[194]. Myofibroblasts contract stress fibers, which are attached to the surrounding ECM and cause local contraction of the matrix. Then, the myofibroblasts deposit ECM to stabilize the contraction[197].

Shinohara *et al.*[198] found that transplanting human dermal fibroblasts into sclera is an effective way to reduce axial elongation in form-deprivation myopia rats. The transplanted fibroblasts can synthesize new collagen fibrils with a bundle-like appearance and a stripe-like pattern. The newly synthesized collagen fibrils could reinforce the sclera and slow down the axial elongation of myopic eyes. An immunosuppressant was used in this study due to hetero-transplantation. It is feasible to use autologous iPSC-fibroblasts or autologous iPSC-myofibroblasts as a novel therapy to enhance the posterior sclera. Therefore, fibroblast or myofibroblast transplantation is a promising way to reduce the progression of myopia and prevent myopes from developing myopic maculopathy.

Scleral stem/Progenitor cells
Scleral stem/progenitor cells (SSPCs) have been isolated from murine sclera[199]. SSPCs express stem cell genes *ABCG2, Six2, Pax6*, and *Notch1* and are positive for mesenchymal markers including Sca-1, CD90.2, CD44, CD105, and CD73. In addition, SSPCs can differentiate into adipogenic, chondrogenic, and neurogenic lineages[199]. However, related studies are rare, and investigations characterizing SSPCs are still required.

Mesenchymal stem cells
Mesenchymal stem cells (MSCs) are stromal cells with the abilities of self-renewal and multilineage differentiation. MSCs can be found in various tissue in adults, including bone marrow, adipose tissue, peripheral blood, dental pulp, periosteum, and skeletal muscle[200-204]. In addition, fetal MSCs can be

harvested from fetal tissues and extraembryonic tissues including placenta, amnion, amniotic fluid, and umbilical cord[205-207]. Numerous sources of MSCs have been found, but MSCs derived from bone marrow and adipose tissue are the main sources in current cell therapies. Due to its immunoregulatory capacity and immune privileges, MSCs have been applied in multi-system disease[208].

MSCs work both on innate immune response and adaptive immune response: MSCs induce division arrest anergy of immune cells[209]; prevent maturation of dendritic cells and activation of natural killer cells[210]; inhibit proliferation, differentiation, and chemotaxis of B cells; interfere with antibody production of B cells[211]; and induce T cell unresponsiveness by altering antigen-presenting cell maturation[212]. MSCs can migrate to sites of disease or injury and work as trophic mediators to release a broad range of bioactive molecules including growth factors, cytokines, and chemokines[213].

MSCs exert their therapeutic potential by paracrine effects instead of differentiating into tissue-specific cells[214]. A wide array of proangiogenic cytokines, such as VEGF, basic fibroblast growth factor (bFGF), and placental growth factor (PlGF), can be detected in the conditioned media of MSCs. Injection of the MSC media into murine ischemic limb markedly enhanced the limb's perfusion[215]. Due to decreased choroidal perfusion and hypoxia of sclera in highly myopic patients, the conditioned media of MSCs offers a good option to modify the hypoxic circumstance of sclera. By injection of MSC conditioned media into the sub-Tenon's space or suprachoroidal space, it can exert its angiogenic effect without the risk of tumorigenesis.

In addition to subretinal transplantation of iPSC-RPE, myofibroblasts, sclera stem cells, and MSCs are methods for posterior scleral reinforcement [Figure 4].

What challenges will we meet?
Although we can see the bright prospect of stem cell-based therapy for myopic maculopathy, there are several problems we need to consider.

When is the best therapeutic window?
In myopic patients with patchy or macular atrophy, subretinal transplantation of iPSC-RPE is a good choice to reduce the loss of photoreceptors secondary to RPE loss. However, the best therapeutic window is hard to elucidate. In patients with severe loss of photoreceptors, transplantation of sole RPE is of no help. Another situation is when patchy atrophy develops, sparing the fovea, and the patient maintains good visual acuity. In this case, a surgery with subretinal transplantation of iPSC-RPE poses a great risk to vision.

Difficulties in surgical technique
During the PPV surgery of subretinal transplantation of iPSC-RPE, experienced surgeons are required. Subretinal injections of RPE cell suspension or subretinal placement of RPE cell patch, especially in high myopia patients with thin retina, are elaborate procedures. The surgeons need to prevent transplanted cells from dispersing into the vitreous cavity, or they need to keep the cell patch in a specific position. In addition, specific surgical instruments are required. For example, a 25/41 G dual-bore cannula is used for subretinal bleb creation[216], and a special instrument is required for subretinal cell patch delivery.

CONCLUSION

Until now, the pathogenesis of pathologic myopia is still unclear. The only way to improve the prognosis of patients with pathologic myopia is to prevent the development of myopic maculopathy and restrain it in time. Anti-VEGF agents have partially preserved the vision of patients with mCNV, but the majority of patients with a higher level of myopic maculopathy face a high risk of visual loss. Eliminating blindness is
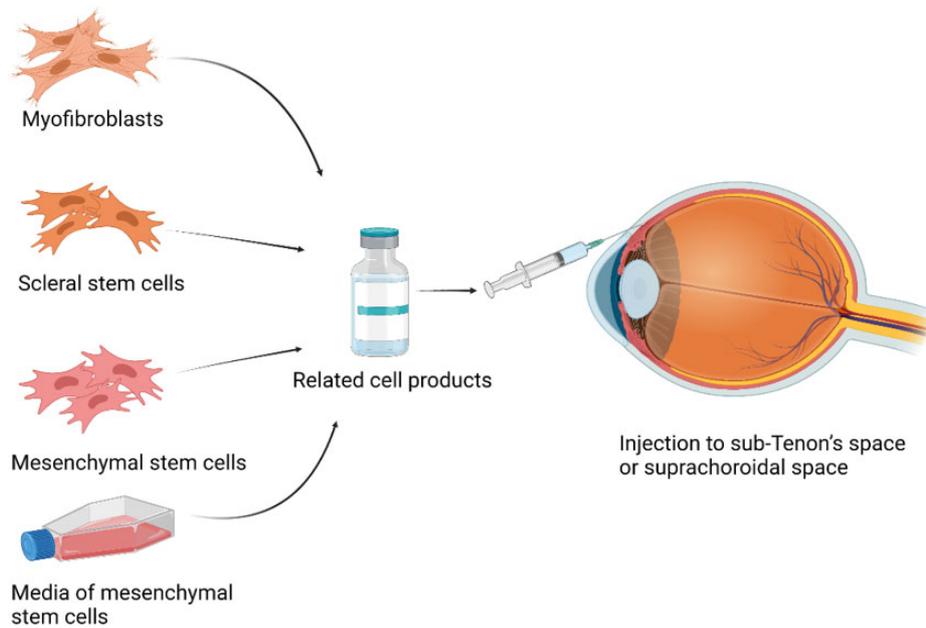
Figure 4. The cells which are theoretically available to cell therapy for reinforcement of sclera in pathologic myopia. Fibroblasts and myofibroblasts are scleral cells maintaining scleral biomechanics. Scleral stem cells might be the native stem cell in sclera. MSCs are stromal cells with the abilities of self-renewal and multilineage differentiation. MSCs exert their therapeutic effect by various paracrine growth factors. The media of MSCs also contains growth factors. Therefore, these cells and media can be made into products and delivered to the posterior sclera and fix the sclera. MSCs: Mesenchymal stem cells.

the common goal of ophthalmologists and scientists. Cell-based therapy has opened a new era of treatment. Stem cell-based therapy has been regarded as the future of medicine and thrown light upon curing incurable diseases. Treatments by stem cell transplantation have made great progress in corneal and retinal degenerative diseases. It is hopeful that the atrophic structures in myopic eyes can be replaced by stem cells and renew the tissue. The preliminary work has shown a promising way in stem cell-based therapy of patients with myopic maculopathy. Therefore, it is possible to achieve the ambitious goal by stem cell-based therapy.

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Review & Editing: Li YP
Conceptualization, Funding acquisition, Supervision: Jin ZB

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
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