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Research Progress Review of Stem Cell Therapy in Dry Age-Related Macular Degeneration (AMD)

Ziping Geng

Medical School of Ophthalmology and Optometry of Shandong University of TCM, Jinan, China
1071003577@qq.com

Abstract. Dry age-related macular degeneration (AMD) is a major cause of blindness in the elderly, characterized by progressive degeneration of the retinal pigment epithelium (RPE) and irreversible loss of photoreceptors. Current clinical treatments can only delay disease progression, lacking curative effects. Stem cell therapy has emerged as a promising strategy for dry AMD, with embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) as the main research objects. Stem cells exert therapeutic effects through RPE cell replacement, paracrine action, immune regulation, and retinal neuroprotection. Preclinical studies and early clinical trials have verified the safety and preliminary efficacy of stem cell transplantation, but challenges such as tumorigenicity, immune rejection, and cell survival remain. This review systematically summarizes the research progress, mechanisms, clinical advances, challenges, and future directions of stem cell therapy for dry AMD, aiming to provide a reference for its clinical transformation.

Keywords: dry age-related macular degeneration, stem cell therapy, retinal pigment epithelium, immune regulation, clinical trial

1. Introduction

1.1. Overview of age-related macular degeneration (AMD)

Age-related macular degeneration (AMD) is a chronic degenerative retinal disease. Its main pathophysiological features consist of degenerative lesions in the outer retina, retinal pigment epithelium (RPE), Bruch's membrane and choriocapillaris, and it has currently become the leading cause of blindness among the elderly. AMD is clinically divided into two main subtypes, dry AMD and wet AMD. This paper mainly discusses the research progress of stem cell therapy applied to dry AMD. Dry AMD accounts for more than 85% of all AMD cases. It features insidious pathological progression: the disease initiates with the accumulation of extracellular deposits (drusen) between the RPE and Bruch's membrane, gradually advances to geographic atrophy, and eventually causes irreversible loss of RPE and photoreceptors, resulting in severe impairment of central vision. The pathogenesis of dry AMD involves the interaction of multiple cellular and molecular pathways, which may be associated with damage to retinal pigment epithelial cells, lipid abnormalities of Bruch's membrane, oxidative stress-induced RPE injury and drusen biogenesis, chronic inflammation and dysregulation of the complement system, among other factors [1].

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1.2. Current treatments and challenges for dry AMD

At present, there is no curative treatment capable of reversing the disease course of dry AMD. Nutritional supplements remain the widely recommended clinical interventions, yet such therapies yield limited therapeutic effects. They can only slow down the progression of early-stage disease to a certain extent and fail to repair advanced geographic atrophy. Recently, the U.S. Food and Drug Administration (FDA) has approved Pegcetacoplan (a C3 inhibitor), which inhibits complement activation and alleviates inflammation, and Avacincaptad pegol (a C5 inhibitor), which reduces the formation of membrane attack complexes. However, these two drugs can only slow the expansion rate of geographic atrophy by approximately 25–27%, require repeated intravitreal injections, and may raise the risk of choroidal neovascularization [2]. Besides, other therapeutic approaches for dry AMD including integrin inhibitors and neuroprotective agents have not been established as standard treatments and still require experimental investigation [3]. In general, existing therapeutic interventions have limited efficacy and cannot meet clinical demands. Novel therapies targeting the core mechanisms of the disease to slow or halt disease progression are urgently needed.

1.3. Potential value of stem cell therapy

Stem cell therapy has a broad range of applications in regenerative medicine, centering on four core fields: regenerative and transplantation medicine, disease modeling, drug screening and discovery, as well as research on human developmental biology. Stem cell therapy holds great potential for the treatment of dry AMD by restoring the function of cells, tissues and even organs lost due to injury, disease or aging. Differentiating stem cells such as embryonic stem cells and induced pluripotent stem cells into RPE cells to replace damaged cells, or adopting mesenchymal stem cells to repair impaired retina via paracrine effects and immunomodulatory functions that improve the microenvironment, offer neuroprotection and combat inflammation, is a strategy with long-term safety and carries profound significance for the management of dry AMD [4].

2. Types of stem cells and their applications in dry AMD

2.1. Embryonic stem cells (ESCs)

ESCs are derived from the inner cell mass of blastocysts. Cells derived from human embryonic stem cells (hESCs) possess the capacity for unlimited proliferation and differentiation into functional RPE cells. They can integrate into the subretinal space and differentiate into RPE cells in a directed manner, express markers including RPE65 and CRALBP, and secrete trophic factors in place of damaged RPE cells to restore partial visual function in patients [5]. At present, numerous experimental data and clinical trial outcomes have verified the safety and preliminary efficacy of this approach. In clinical trials NCT01344993 (for dry AMD) and NCT01345006 (for Stargardt disease), transplantation of hESC-RPE showed favourable safety profiles. Vision remained stable or improved in some participants, with no reported tumour formation or immune rejection [6]. Nevertheless, their derivation from the inner cell mass of blastocysts gives rise to certain ethical controversies, and ESCs have been gradually replaced by iPSCs.

2.2. Induced pluripotent stem cells (iPSCs)

iPSCs refer to a type of stem cells acquired by reprogramming terminally differentiated somatic cells (such as skin and blood cells) isolated from dry AMD patients via the introduction of specific

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transcription factors. Patient-specific iPSCs can be applied for autologous transplantation, which effectively avoids immune rejection and ethical concerns and holds potential for personalised therapy [7]. Studies have demonstrated that iPSCs can be directionally differentiated into RPE cells and photoreceptor precursor cells, forming monolayer structures with typical polarity and functions, and further developing into three-dimensional RPE-like organoids. These organoids exhibit features analogous to native RPE: apical microvilli, tight junctions, the ability to phagocytose photoreceptor outer segments, and collagen IV-positive basement membrane-like structures mimicking Bruch's membrane, which is of great importance for ameliorating retinal conditions in patients with dry AMD [1].

Clinical trials investigating iPSC therapy for dry AMD have been conducted and yielded certain achievements in China, the United States, Japan, India and other countries. The research team led by Takahashi in Japan completed the world's first transplantation of autologous iPSC-RPE sheets, and the treatment was proven safe and effective four years after the operation. Meanwhile, iPSCs can be produced on a large scale and utilised for disease modelling and drug screening. They assist researchers in elucidating pathogenesis and studying disease progression, and support high-efficiency screening of therapeutic drugs for dry AMD in individual patients, further facilitating the implementation of personalised treatment for dry AMD [8, 9]. Admittedly, iPSCs still carry risks of immune rejection. Specifically, when integrating viruses are adopted for iPSC reprogramming, persistent expression of exogenous genes and mutation risks caused by random insertion of viral vectors may be recognised and eliminated by immune cells in the recipient's body, resulting in graft failure. For this reason, non-integrating methods have attracted growing attention. These techniques deliver reprogramming factors into cells without integrating vector genes into the host genome, which can markedly reduce the risk of immune rejection and represent the preferred technology for iPSC generation at present [9].

2.3. Mesenchymal stem cells (MSCs)

MSCs are a class of adult stem cells with self-renewal capacity and multipotent differentiation potential. They are widely found in adipose tissue, umbilical cord, bone marrow and other tissues, capable of differentiating into adipocytes, osteocytes, chondrocytes and other cell types, and possess functions including immune regulation, anti-inflammation and promotion of tissue repair. In the treatment of dry AMD, MSCs can be induced to differentiate into RPE-like cells in vitro. They exert neuroprotective, anti-inflammatory and antioxidant effects by secreting paracrine factors, exosomes, anti-inflammatory factors and other substances through paracrine action, so as to protect RPE cells and photoreceptors and improve the retinal microenvironment [10]. Clinical trials (NCT01088541, NCT01560715) indicate that MSC transplantation can improve visual acuity in the short term with limited long-term efficacy. Additionally, MSCs feature low immunogenicity (absence of HLA-II expression), easy isolation and expansion, low tumorigenic risk and no ethical concerns, making them an excellent candidate for the treatment of dry AMD [11, 12].

2.4. Other types of stem cells

Apart from the three major types of stem cells mentioned above, retinal progenitor cells (RPCs), neural progenitor cells, retinal pigment epithelial stem cells and other stem cells also hold important research value for the treatment of dry AMD. Derived from fetal or adult retina, RPCs can differentiate into photoreceptors and RPE cells, integrate into host tissue after transplantation and restore visual function. RPCs have immune-privileged properties that eliminate the need for long-

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term immunosuppression, which facilitates the survival of transplanted cells in recipients. Neural progenitor cells originate from the central nervous system; they secrete neurotrophic factors and phagocytose photoreceptor outer segments to support the survival of retinal cells [13]. Retinal pigment epithelial stem cells are isolated from the RPE layer of adult human eyes. These cells are naturally committed to the RPE lineage, non-tumorigenic, and can be transplanted at the early progenitor stage. They have demonstrated favourable safety profiles and marked visual improvement in clinical trials, rendering them a stem cell type with significant research value and clinical transformation potential for cell therapy of dry AMD [14].

3. Mechanisms of action of stem cell therapy

3.1. RPE cell replacement

RPE cells are essential cells for maintaining the normal physiological activities of photoreceptors, whose functions include phagocytosis of photoreceptor outer segment discs, transport of nutrients, maintenance of the outer blood-retinal barrier and regeneration of the visual cycle [11]. The core pathological features of dry AMD consist of progressive atrophy and dysfunction of RPE cells, which ultimately cause degeneration and death of the overlying photoreceptors. Accordingly, replacing dysfunctional RPE cells via stem cell transplantation stands as one of the most direct strategies for treating dry AMD. Both hESCs and iPSCs can be induced in vitro to differentiate into polarized RPE cells with capacities of phagocytosis, ion transport and growth factor secretion. After transplantation, these cells can integrate with the host retina and form a functional monolayer, support the survival of photoreceptors so as to halt or slow photoreceptor degeneration, and partially restore visual function [6].

3.2. Paracrine effects

The pathological microenvironment of dry AMD is characterized by oxidative stress, chronic inflammation and apoptosis. In stem cell therapy, paracrine effects mean transplanted stem cells act on surrounding host cells and the microenvironment by secreting a series of bioactive factors, so as to counteract these pathological processes, promote tissue repair, preserve neuronal survival and inhibit further damage. Transplanted stem cells (especially MSCs) can secrete multiple neurotrophic factors including brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF) and others. These factors directly act on dying RPE cells and photoreceptors, activate their intracellular anti-apoptotic signaling pathways, help them resist injuries such as oxidative stress, thus delaying or preventing cell death and stabilizing retinal structures [15]. The paracrine effects of stem cells can also markedly regulate local immune responses. MSCs suppress immune reactions and inflammation by releasing immunomodulatory proteins such as Th2-associated cytokines. These cytokines reduce continuous inflammatory assaults on RPE cells and photoreceptors, break the vicious cycle of "inflammation-cell death-more inflammation", and build a more stable environment for retinal tissues [12, 13].

3.3. Immunomodulation and inflammation suppression

Stem cells, especially mesenchymal stem cells and RPE cells derived from induced pluripotent stem cells (iPSC-RPE), possess potent immunomodulatory and anti-inflammatory capacities, which are

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regarded as core mechanisms for the treatment of dry AMD. Stem cell therapy regulates inflammatory alterations in dry AMD through multiple pathways.

Stem cell therapy modulates the complement system and inhibits its excessive activation. In dry AMD, aging and oxidative stress trigger chronic activation of the alternative complement pathway, leading to the deposition of C3a, C5a, complement factor B and membrane attack complexes within drusen. These complement components induce RPE cells to release inflammatory cytokines and cause sublytic cellular injury, driving chronic low-grade inflammation, and ultimately resulting in RPE cell death, photoreceptor degeneration and the formation of geographic atrophy. Such pathological change constitutes a central pathological link of dry AMD [15, 16]. MSCs exert paracrine secretion of soluble regulatory factors including complement factor H, or upregulate the expression of CD46 and CD59 on themselves and adjacent RPE cells. These actions suppress the formation of C3 convertase and block the assembly of C5b-9 complexes, alleviating complement-mediated damage to the RPE and choroid [17]. Stem cell therapy inhibits inflammasome activation. The activation of the NLRP3 inflammasome acts as a critical bridge connecting oxidative stress and inflammation, and stem cells can effectively interfere with this process. Stem cells reduce the production of reactive oxygen species and oxidized phospholipids such as oxidized phospholipids via antioxidative effects, eliminating the initial signals that activate NLRP3 and restraining inflammasome activation. Factors secreted by MSCs including prostaglandin E2 and tumor necrosis factor-α-induced protein 6 inhibit the assembly of the NLRP3 inflammasome and the activation of caspase-1 to mitigate inflammation. Meanwhile, stem cells regulate the balance of mature inflammatory cytokines including IL-1β and IL-18 generated after inflammasome activation. Stem cells lower the level of IL-1β and may modulate the activity of IL-18, helping restore the balance between pro-inflammatory and anti-inflammatory signals and relieve tissue damage caused by the imbalance of IL-1β and IL-18 [12, 17].

Stem cell therapy regulates immune cells to improve the retinal microenvironment. Lesional areas of dry AMD are infiltrated by immune cells such as macrophages and mast cells, which trigger retinal damage. Pro-inflammatory M1-type macrophages accumulate in the subretinal space in the early stage of AMD and promote retinal inflammation. Cytokines secreted by MSCs such as IL-10 and IL-13 facilitate the polarization of macrophages from pro-inflammatory M1 phenotype to anti-inflammatory and reparative M2 phenotype. M2 macrophages contribute to the clearance of cellular debris including photoreceptor outer segments, secrete anti-inflammatory factors and accelerate tissue repair. In addition, mast cell granules increase in the choroid of patients with dry AMD. MSCs stabilize mast cells through cell-to-cell contact or secretion of stem cell factor, preventing the release of harmful substances such as histamine and proteases so as to protect Bruch's membrane and choroidal blood vessels [17].

Stem cell therapy indirectly suppresses inflammation through antioxidation. Oxidative stress is a major promoter of inflammation, and the antioxidative property of stem cells is vital for inflammation control. Conditioned medium or exosomes derived from stem cells can activate the Nrf2 signaling pathway in RPE cells and upregulate the expression of antioxidant enzymes including HO-1 and NQO1, reducing reactive oxygen species at the source. This prevents complement activation and inflammasome initiation induced by reactive oxygen species and strengthens endogenous antioxidant defense [17].

3.4. Vascular protection and retinal neuroprotection

In dry AMD, the apoptosis of RPE cells leads to atrophy of the underlying choriocapillaris, which further aggravates ischemia and death of photoreceptors. Under physiological conditions, RPE cells

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secrete vascular endothelial growth factor toward the choroid from their basal side to maintain the survival and normal function of choriocapillaris. Meanwhile, RPE cells secrete pigment epithelium-derived factor, a powerful anti-angiogenic and neurotrophic factor, toward photoreceptors from their apical side. The balance between the secretion of vascular endothelial growth factor and pigment epithelium-derived factor is essential for the health of the retinal-choroidal interface. In dry AMD, dysfunction or death of RPE cells causes insufficient secretion of vascular endothelial growth factor and subsequent atrophy of the choriocapillaris [16]. Transplanted healthy iPSC- or ESC-derived RPE cells can re-establish this critical secretory balance. These cells secrete physiological levels of vascular endothelial growth factor from the basal side to support and rescue degenerating choriocapillaris and halt further atrophy. Simultaneously, pigment epithelium-derived factor secreted from the apical side inhibits pathological angiogenesis and exerts neurotrophic effects. Transplanted healthy iPSC/ESC-RPE cells also secrete various neurotrophic factors including glial cell line-derived neurotrophic factor, ciliary neurotrophic factor and brain-derived neurotrophic factor. These factors directly promote photoreceptor survival and inhibit their apoptosis, serving as potent endogenous neuroprotective agents. Furthermore, the transplanted intact monolayer of RPE cells, especially sheet grafts supported by scaffolds, reconstructs the outer blood-retinal barrier formed jointly by the RPE layer and underlying Bruch's membrane. This reconstruction restores ionic and fluid balance, enables strict regulation of material exchange between the choroid and neural retina, and provides a stable microenvironment for photoreceptors and choroidal blood vessels [8].

4. Advances in Clinical research of stem cell therapy

4.1. Preclinical research

Preclinical research on animal models acts as a vital bridge translating stem cell therapy from laboratory settings to clinical practice. An ideal animal model should mimic the key pathological features of dry AMD, particularly the loss and dysfunction of RPE cells, and be applied to assess the safety, integration capacity and functional repair efficacy of transplanted cells. In their 2019 research on iPSC-RPE patch therapy, Sharma et al. carried out systematic experiments across multiple complementary animal models. They verified that iPSC-derived RPE patches seeded on degradable PLGA scaffolds markedly improved the integration rate of cells onto the host Bruch's membrane compared with conventional cell suspension therapy, and formed mature monolayers with apical-basal polarity. This finding provides critical preclinical evidence for the clinical application of iPSC-RPE patches [4].

4.1.1. Selection and application of animal models for dry AMD

Sharma et al. adopted three distinct animal models: an immunodeficient rat (Cri:NIH-Foxn1rnu) model for safety and integration assessment, a Royal College of Surgeons (RCS) rat model for retinal degeneration associated with RPE dysfunction, and a large animal model of laser-induced RPE injury in pigs to simulate AMD lesions.

The immunodeficient rat model for safety and integration assessment lacks functional T cells, which effectively prevents xenogeneic immune rejection after human cell transplantation. It thus enables exclusive evaluation of the in vivo survival, integration and biosafety of human iPSC-RPE patches. This model is mainly used to observe the long-term fate of transplanted patches in the subretinal space, verify their successful integration into the host Bruch's membrane, and monitor adverse events such as tumour formation.

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In the RCS rat model of RPE dysfunction-related retinal degeneration, a mutation in the Mertk gene impairs the ability of RPE cells to phagocytose photoreceptor outer segments, triggering progressive photoreceptor degeneration. This model serves as an ideal tool for evaluating cell replacement therapies, especially those targeting photoreceptor layer repair, and was used in this study to assess the efficacy of iPSC-RPE patches and cell suspensions in rescuing photoreceptors and restoring visual function.

The large animal model of laser-induced RPE injury in pigs simulates regional RPE loss lesions in dry AMD. A 532 nm micropulse laser is applied to selectively ablate RPE cells in the visual streak of porcine eyes, causing focal RPE atrophy and photoreceptor damage. Testing human clinical equivalent doses of iPSC-RPE patches in porcine eyes, which are closer to human eyes in anatomical structure and size, yields indispensable data for first-in-human trials and lays a solid foundation for subsequent clinical studies.

4.1.2. Efficacy evaluation of stem cell transplantation in animal models

Assessments in immunodeficient rats revealed that iPSC-RPE patches successfully integrated into the rat Bruch's membrane and formed continuous polarized monolayers. No teratomas or tumour formation were detected in eyes receiving patch transplantation, demonstrating superior integration properties and favourable safety profiles of RPE patches. Moreover, evaluations in RCS rats confirmed that iPSC-RPE cell transplantation exerted prominent photoreceptor-rescuing effects. Optokinetic nystagmus (OKN) tests showed that the therapeutic efficiency of patch treatment was far higher than that of cell suspension treatment. Further assessments in the laser-injured porcine model validated the surgical feasibility and functional integration of patch therapy, with appropriate experimental adjustments made to meet clinical requirements. Using custom surgical instruments, researchers successfully delivered 4×2 mm iPSC-RPE patches of human clinical equivalent dose to laser-injured sites. Ten weeks after transplantation, the patches integrated firmly onto the porcine Bruch's membrane. The photoreceptor layers above the grafted regions retained intact structures, and human RPE cells effectively rescued porcine cone photoreceptors. Multifocal electroretinogram recordings demonstrated significant recovery of electrophysiological signals in grafted areas within 10 weeks [18].

Apart from the above research, numerous preclinical studies on dry AMD therapy have achieved remarkable progress. Qu et al. performed systematic preclinical evaluation of rat embryonic stem cell-derived retinal progenitor cells (rESC-RPCs) using the RCS rat model [19]. Macečková Brymová et al. confirmed the potential of hiPSC-RPE cells loaded on PDLLA scaffolds to survive in the retina, maintain RPE cell characteristics and interact with photoreceptors via subretinal transplantation into healthy miniature pigs [20, 21].

4.2. Clinical trials

Remarkable progress has been achieved in the clinical translation of stem cell therapy for dry AMD. Multiple types of stem cells including ESCs, iPSCs, RPCs and MSCs have entered clinical trials of various phases, with their safety and potential therapeutic effects preliminarily validated.

ESC-derived and iPSC-derived RPE cells, which aim to replace damaged cells, rely on the strong differentiation capacity of the two kinds of stem cells to repair and regenerate the RPE layer via differentiation into functional RPE cells. A number of clinical trials of ESC-RPE transplantation have provided pivotal evidence for its safety. For instance, a phase I/II study led by Schwartz's team (NCT01345006) performed subretinal transplantation of hESC-RPE cells in patients with dry AMD

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and Stargardt disease. No cell-related tumour formation or severe immune rejection was reported during the 22-month follow-up period, and visual acuity remained stable or improved in some patients, verifying the feasibility of this therapy [22]. Similarly, a Korean study conducted by Song's team (NCT01625593) also confirmed the favourable safety profile of hESC-RPE in Asian populations. Four patients (2 with AMD and 2 with Stargardt disease) were enrolled in this research. No transplantation-related tumours, abnormal proliferation or serious safety issues were detected within the one-year follow-up. Visual acuity improved by 9 to 19 ETDRS letters in three patients and remained stable in one patient [23].

Among clinical trials of iPSC-RPE transplantation, the first autologous iPSC-RPE sheet transplantation carried out by Takahashi's team in Japan (UMIN000011929) marked a milestone toward personalized therapy. This case successfully proved that autologous transplantation could avoid immune rejection. Nevertheless, gene mutations were later detected in donor cells of the research, prompting the team to construct an allogeneic iPSC bank with HLA matching. This shift highlights severe challenges faced by iPSC therapy regarding genomic stability and tumorigenic risk, which constitute major bottlenecks for its clinical translation [22, 24].

In addition to the above two stem cell types, a first-in-human, open-label, dose-escalating phase 1/2a clinical trial (NCT04627428) evaluated the safety and preliminary efficacy of RPE cells derived from adult retinal pigment epithelial stem cells for dry AMD treatment in recent years. Six patients were enrolled in the low-dose group (50,000 cells) and divided into a poor baseline vision subgroup and a good baseline vision subgroup, all receiving subretinal injection and 6-month immunosuppressive therapy. The 12-month follow-up results showed that the mean best-corrected visual acuity of the poor vision subgroup increased by 21.67 ETDRS letters, while that of untreated fellow eyes decreased by 1.33 letters; the mean visual acuity of the good vision subgroup rose by 3.0 letters at 6 months, with a decrease of 1.0 letter in untreated eyes. In terms of safety, no tumour formation, severe inflammation, product-related serious adverse events or significant immune rejection was observed. This study proves that low-dose RPESC-RPE transplantation is safe and well-tolerated in patients with dry AMD, and yields clinically meaningful visual improvement especially in patients with poor baseline vision, laying a foundation for subsequent dose-escalation studies [14].

RPC and MSC transplantation targeting neurotrophy and microenvironment regulation differs from the ESC/iPSC approach. This strategy exerts neuroprotective, anti-inflammatory and immunomodulatory functions mainly through the paracrine effects of RPCs and MSCs so as to delay or stabilize disease progression, and multiple clinical trials have verified the feasibility of this pathway. For example, a phase I/IIa trial for retinitis pigmentosa conducted by JCyte (NCT02320812) explored the safety of neurotrophic effects via intravitreal injection of fetal-derived RPCs, providing references for the application of similar strategies in dry AMD treatment [25]. A clinical trial conducted in the United States (NCT01560715) demonstrated the safety and feasibility of intravitreal injection of autologous bone marrow-derived MSCs, with short-term visual function improvement observed in part of the patients [26]. Notably, the therapeutic effect of MSCs tends to stabilize the illness and slow degeneration rather than greatly improve vision, making them a desirable option for early intervention of dry AMD. Their mechanism of action does not depend on long-term engraftment and differentiation into RPE cells, thereby evading the tumorigenic risk of the ESC/iPSC pathway. However, sustaining their long-term efficacy remains a key focus for optimization in future research.

Overall, clinical trials of stem cell therapy for dry AMD are still in the early stage, yet preliminary data have confirmed the safety of hESC-RPE transplantation and its potential to

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improve vision to a certain degree. iPSC therapy shows unique advantages in addressing personalized treatment and immune rejection, whereas its genetic stability requires further improvement. Adult stem cells occupy an important position in neurotrophic and immunomodulatory therapeutic strategies owing to their favourable safety and easy accessibility. Large-scale, rigorously designed phase II/III clinical trials combined with functional imaging and objective visual function assessment will be essential to clarify the efficacy of various stem cell therapies in the future.

5. Challenges and future perspectives of stem cell therapy

5.1. Technical challenges

Despite the promising prospects of stem cell therapy, it still encounters a host of severe technical challenges during clinical translation, which exert profound impacts on therapeutic outcomes.

5.1.1. Efficiency and regulation of in vitro culture and differentiation

Large-scale acquisition of target cells with high purity and mature functions in vitro serves as the primary prerequisite for clinical application. Studies have revealed that apart from RPE cells, other stem cell types, especially iPSCs, generally show low and unstable efficiency when differentiating into specific retinal cells such as photoreceptors. Compared with ESCs, iPSCs exhibit greater variability in differentiation potential. Differentiation efficiency differs dramatically among distinct cell lines and even different clones derived from the same cell line. Only a small subset of MSCs, such as MUSE cells, possess high transdifferentiation capacity, resulting in final products that are heterogeneous cell populations with impaired functions. All these issues pose substantial obstacles to the production of standardized cell products [24, 27].

5.1.2. In vivo survival, integration and functional reconstruction of transplanted cells

The long-term survival of transplanted cells in the host retina is a key factor determining the therapeutic effect on dry AMD. Transplanted cells are exposed to the harsh microenvironment of the host retina characterized by oxidative stress and inflammation, leading to massive cell death within a short period. In addition, reliable non-invasive approaches to evaluate cell survival and functional integration are still lacking [28]. Currently, there are two major transplantation modalities: RPE cell suspension and RPE monolayer combined with permanent or degradable scaffolds. Conventional injection of cell suspensions frequently causes cell reflux and death at the injection site, and the suspended cells tend to disperse with inconsistent survival rates. By contrast, scaffold-based grafts demand sophisticated surgical manipulation and carry the risk of tissue detachment. Furthermore, integration with the neural retina, particularly photoreceptors and retinal ganglion cells, remains a tough problem. Transplanted cells need to migrate to the correct locations and form functional synaptic connections with the host retina so as to integrate into the existing visual pathways [29]. Multiple studies have indicated that the visual improvement achieved by stem cell therapy may decline over time, suggesting that transplanted cells may fail to survive long-term or gradually lose secretory functions [24]. To address the above problems, novel strategies can be adopted in the future, including robotic systems for automated adherent culture and artificial intelligence-based image analysis for cell status and function assessment. These methods can reduce manual

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intervention and subjective deviations, and improve the consistency and stability of the whole process [30].

5.1.3. Standardization of cell sources and manufacturing

RPCs feature favourable safety but limited proliferative ability in vitro. Primary culture cannot generate sufficient cells to treat a large number of patients. Although relevant research has increased the passage number of RPCs to 16 under hypoxic culture conditions, further breakthroughs are still required to achieve large-scale production. Meanwhile, the production of clinical-grade cells is costly and suffers from obvious batch-to-batch variation. Standardized quality control indicators for metabolic functions are not yet established, and there is no consensus on the optimal option between cell suspension, cell sheets and biological scaffolds across different clinical trials [31]. To meet the quality criteria for clinical-grade cell products, it is necessary to develop xeno-free and feeder-free culture systems and adopt standard procedures complying with good manufacturing practice. These requirements greatly raise the difficulty and cost of process development [24].

5.2. Safety concerns

While stem cell therapy holds great potential, safety remains the most critical consideration in its clinical translation. Major risks mainly include tumorigenicity, immune rejection and complications associated with transplantation surgery.

5.2.1. Risk of tumor formation

Tumorigenicity is the most prominent safety concern for stem cell therapy, especially therapies based on pluripotent stem cells. If incompletely differentiated pluripotent stem cells remain in the differentiated products of ESCs or iPSCs, these residual cells may develop teratomas after transplantation in vivo [32]. Although literature has proven that MSCs carry an extremely low tumorigenic risk, the reprogramming process of iPSCs may lead to genomic instability in derived hESC-RPE and iPSC-RPE cells, such as amplification of chromosomes 1q, 12p and 17q, which constitutes potential carcinogenic hazards. Additionally, iPSC-RPE cells may retain an immature phenotype and tend to form contractile aggregates, hindering cell integration [33]. Even fully differentiated cells may experience uncontrolled proliferation after being transplanted into a new in vivo microenvironment. Studies have indicated that under certain pathological conditions, bone marrow-derived MSCs may accidentally promote pathological angiogenesis by secreting factors such as IGF-1. Moreover, the immunomodulatory functions of MSCs are highly dependent on local cytokine environments. Chronic low-grade inflammation in dry AMD, including microglia activation and complement dysregulation, may alter the polarization of MSCs. If the inflammatory microenvironment shifts toward a pro-inflammatory state, MSCs may lose their inhibitory effects and even facilitate Th17 cell differentiation, which exacerbates inflammation. Therefore, long-term monitoring of the behaviour of transplanted cells is strictly required [34].

5.2.2. Immune rejection

The retina is an immune-privileged site, and cells such as MSCs possess low immunogenicity. Nevertheless, diseases or surgical trauma may break this immune privilege, so the risk of immune rejection still exists. Allogeneic ESCs, iPSCs and MSCs express low levels of HLA-I molecules despite the absence of HLA-II expression on MSCs, making them recognizable and vulnerable to

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attacks by the host immune system. Research has demonstrated that epigenetically modified iPSC-derived cells can still trigger T cell or NK cell-mediated immune rejection, and short-term immunosuppression is necessary after allogeneic transplantation. Autologous cells such as patient-specific iPSCs and autologous MSCs can avoid rejection, but they come with high costs and complex manufacturing procedures. Furthermore, transplantation may damage the blood-retinal barrier, exposing autoantigens to the immune system and inadvertently activating autoimmune responses to aggravate local inflammation [29].

5.3. Ethical and regulatory issues

Stem cell therapy brings unprecedented hope for the treatment of dry age-related macular degeneration. However, every step from laboratory research to clinical application is accompanied by intense ethical controversies and complicated regulatory challenges. These issues concern not only the safety and efficacy of the technology, but also philosophical discussions on the origin of life, the boundary of commercialization of human tissues, and equity in global scientific research.

5.3.1. Fundamental ethical controversies over stem cell sources

Stem cell sources lie at the core of ethical debates. Human embryonic stem cell-derived RPE cells are generally isolated from the inner cell mass of blastocysts at 5 to 6 days post-fertilization. The acquisition process inevitably causes irreversible damage to embryos, which directly challenges the definition of the moral status of human embryos. Opponents argue that destroying embryos for research purposes is equivalent to terminating potential human life, an uncrossable ethical red line [31]. Relevant supportive policies mostly adopt a moderate stance of "respect without personification". For instance, the *Warnock Report* in the United Kingdom states that embryos deserve special respect and can only be used for essential and irreplaceable research [35]. In the context of dry AMD treatment, it is essential to rigorously demonstrate the necessity and irreplaceability of hESC-based RPE therapy for this blinding disease. Induced pluripotent stem cells bypass the ethical disputes over embryo destruction yet raise new ethical concerns. First, the rights of somatic cell donors must be fully protected. Their genetic information may be extensively analyzed and shared along with the application of cell lines, so informed consent must cover such future uses. Second, gene-editing technologies such as CRISPR can correct disease-related mutations in patient-derived iPSCs to enhance therapeutic effects. However, this practice blurs the line between medical treatment and human enhancement, and arouses long-term ethical concerns over germline editing and the creation of "designer babies".

5.3.2. Donor rights: a neglected ethical aspect

Current policies on stem cell research systematically neglect the rights of gamete and embryo donors, particularly female donors. Firstly, oocyte collection for research is an invasive procedure accompanied by hormonal burden and medical risks. In many cases, oocytes are not purely donated, but obtained through financial compensation or "egg sharing", where donors receive free or discounted IVF treatment in exchange for oocytes. Under circumstances of economic and social inequality, such practices are highly likely to exploit vulnerable women. Secondly, the establishment of hESC and iPSC cell lines for AMD research cannot completely eliminate the demand for oocytes. Nevertheless, existing ethical standardization practices for stem cell banks mainly focus on the completeness of informed consent, while ignoring the fairness of collection procedures, rationality

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of compensation and long-term wellbeing of donors. This creates an "ethical divide" between stem cell ethics and broader reproductive ethics [35].

5.3.3. Diversified international regulatory landscape and challenges

Globally, the establishment and operation of stem cell banks are governed by vastly different national laws and regulations, which directly affect the accessibility of stem cell resources, quality control and international research collaboration. In terms of supervision, all countries classify stem cell products as advanced therapy medicinal products, which are subject to rigorous preclinical and clinical trial reviews similar to conventional drugs. Meanwhile, the "hospital exemption" clauses adopted in some regions allow individualized cell therapy within designated medical institutions. While such clauses facilitate early exploration, the lack of scientific basis and standardized supervision may lead to regulatory arbitrage, unpredictable treatment outcomes and increased safety risks. Governance models of stem cell banks also vary greatly across nations, hindering resource accessibility, raising research costs and reducing the efficiency of international cooperation. In addition, stem cell technologies are covered by a large number of patents, creating conflicts between intellectual property rights and commercialization. Stem cell banks are originally designed to promote resource sharing. However, once a certain cell line becomes the foundation of commercial therapies, patent holders tend to restrict its widespread distribution to prevent competitors from developing biosimilars or obtaining unfavourable research data. The conflict between the spirit of scientific sharing and commercial monopolization is particularly prominent in countries with mandatory cell banking policies [31, 35].

5.4. Future development directions

Despite encouraging safety outcomes in early clinical trials, stem cell therapy still faces universal challenges including tumorigenic risks, immune rejection, inconsistent cell source standardization and sustained therapeutic efficacy. Future research shall confirm treatment effects through large-sample and long-term follow-up randomized controlled trials. Integrated application of emerging technologies such as gene editing, biomaterials, tissue engineering and cell therapy will also be actively explored to mature this revolutionary treatment.

5.4.1. In-depth integration with gene editing technologies

The advancement of gene editing technologies, especially CRISPR/Cas9, has provided new tools to address the core obstacles of stem cell therapy regarding safety and efficacy, and further expanded its therapeutic potential. For instance, MSCs can be genetically modified to overexpress neurotrophic factors such as NT-4 and PEDF, or chemokine receptors including CXCR4 [36]. To mitigate the potential tumorigenicity of iPSCs and ESCs, inducible suicide gene systems such as LVCAGs can be introduced to precisely eliminate residual undifferentiated cells and malignantly transformed cells in vivo, so as to establish safety-enhanced stem cell lines. For hereditary dry AMD driven by specific gene mutations, a combined strategy of iPSC technology and gene editing can be adopted. Pathogenic genes are repaired in patient-derived somatic cells in vitro, which are then differentiated into functional RPE cells for transplantation, realizing dual effects of gene correction and cell replacement [37]. To reduce immune rejection after cell transplantation, researchers may generate low-immunogenicity iPSCs by knocking out MHC I/II genes and overexpressing CD47. Similarly, knocking out HLA molecules via gene editing can produce low-immunogenicity hESC-

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RPE cells. These approaches help reduce reliance on immunosuppressants, improve cell survival rate and maintain a favorable retinal microenvironment [29, 31].

5.4.2. Combination of stem cells with biomaterials and tissue engineering

Simple injection of cell suspensions is hindered by low cell survival rate and poor functional integration in the treatment of dry AMD. Combining stem cells with biomaterials and tissue engineering has become a core strategy to improve therapeutic outcomes. Adherent culture systems are commonly used for small-batch parallel production to maintain cell phenotypes, while conventional monolayer culture vessels are inadequate for high-throughput and decentralized large-scale production across multiple medical centers [30]. Future studies will focus on developing degradable biomimetic scaffolds that replicate the structure and functions of native Bruch's membrane. Such scaffolds offer physical support and a suitable microenvironment for transplanted stem cells and their differentiated RPE cells, facilitating cell adhesion, survival, polarization and functional integration. Meanwhile, efforts will be made to combine cell sheet engineering with minimally invasive surgical instruments to alleviate surgical trauma [31, 38]. For example, hydrogels loaded with stem cell exosomes or growth factors can be delivered into the subretinal space via minimally invasive surgery to achieve long-term local treatment. The hydrogel also provides physical protection during injection and elevates cell survival rate [37]. This cell-material combined strategy shifts the therapeutic goal from simple cell replacement to functional tissue reconstruction, enabling more effective repair of damaged retinal pigment epithelium.

5.4.3. Expansion from cell therapy to cell-free derivative therapy

To resolve the drawbacks of live cell transplantation such as tumorigenesis, immune rejection and difficulties in storage and transportation, cell-free therapy based on stem cell derivatives has emerged as a promising branch in regenerative medicine. Studies have verified that stem cell-derived exosomes and conditioned media contain abundant bioactive molecules including miRNAs, growth factors and cytokines. They can mimic the paracrine effects of stem cells and exert anti-inflammatory, anti-apoptotic and neuroprotective activities [34, 38]. For dry AMD characterized by chronic neurodegeneration, these derivatives can be administered via intravitreal injection to regulate the retinal microenvironment, protect photoreceptors and RPE cells, and slow disease progression. Featuring low immunogenicity and high controllability, cell-free therapy possesses broad prospects for clinical translation [37]. Additionally, the concept of efferocytosis offers a novel perspective for dry AMD treatment. When infused stem cells are engulfed by host macrophages, the macrophages are induced to secrete anti-inflammatory factors such as IL-10 and IDO, thereby achieving systematic immune regulation. This mechanism shares high similarities with the immune tolerance of maternal bodies to fetal cells during pregnancy [39]. In future clinical research, apoptotic stem cells or engineered microparticles simulating apoptotic cell signals can be developed as cell-free therapeutic regimens for dry AMD, to completely avoid the risks of tumorigenesis and immune rejection associated with live cell transplantation [39].

5.4.4. Coordinated development of standardization, industrialization and personalized therapy

Successful clinical translation of stem cell therapy relies on strict quality control and well-defined regulatory frameworks. Traditional manual assessment of cell confluency and morphology is subject to individual discrepancies among operators. Hence, real-time and non-invasive quality evaluation

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methods are urgently needed [30]. It is essential to further optimize the GMP-compliant systems for stem cell preparation, purification and quality control, so as to guarantee the stability, purity and safety of cellular products. With deeper understanding of AMD pathogenesis, treatment strategies will become more personalized. On one hand, the reactivity of peripheral blood or local ocular immune cells to stem cell products can be explored as potential biomarkers for therapeutic effect prediction. On the other hand, since dominant pathological mechanisms vary across disease stages, individualized regimens can be formulated accordingly: immune regulation and antioxidation are prioritized for early-stage dry AMD, while RPE cell replacement is required for advanced cases [37, 39]. Personalized and precision medicine will drive the transformation of stem cell therapy from universal treatment to tailored therapy. Clinical practices of autologous iPSC-RPE transplantation have proven that patient-derived cells can avoid immune rejection and sustain long-term therapeutic effects. Establishing high-quality iPSC banks and HLA-matched allogeneic cell banks will balance the cost and accessibility of personalized therapy. Moreover, determining the optimal transplantation timing, cell types and administration routes based on biomarkers including patient genotypes, disease stages and inflammatory status will be critical to improving curative effects [28, 36].

5.4.5. Transformation from cryopreserved and thawed cells to metabolically active cells

Discrepancies between preclinical findings and clinical trial results are partially attributed to differences in cell viability. Most current clinical trials adopt cryopreserved cells for direct infusion after thawing. These cells present markers of cellular damage, suppressed biological functions and shortened in vivo survival time. In contrast, phase III trials with favorable outcomes use fully activated cells after post-thaw cultivation, which conform to the optimal cell state observed in preclinical studies. For dry AMD treatment, standardized protocols for cell thawing and activation should be established. Regardless of MSCs, ESCs or iPSC-derived RPE cells, short-term cultivation and activation before infusion are recommended. Optimization of cell pretreatment and industrial technologies, such as cytokine intervention and hypoxic preconditioning, can enhance the immunomodulatory and neurotrophic functions of MSCs and restore their optimal metabolic activity [34]. In terms of local administration such as subretinal and intravitreal injection, fresh cellular products can be adopted whenever possible. New cryoprotectants and thawing techniques should also be developed to minimize cryoinjury and preserve cell viability to the maximum extent [39].

5.4.6. Improvement of regulatory frameworks to enhance equity and accessibility

Multiple measures should be taken to promote the ethical development of stem cell therapy in the future. First, accelerating the application of iPSCs to replace ESCs can fundamentally resolve ethical controversies over embryo destruction, and gene editing can be combined to further improve safety. Second, a robust global regulatory system must be established to crack down on unlicensed stem cell clinics and protect patients from fraud and health hazards. Third, greater efforts should be made to safeguard the rights of gamete and embryo donors, especially female donors. Attention shall be paid to the fairness of cell collection procedures, rational compensation and long-term wellbeing of donors. Fourth, medical insurance policies and cost control measures need to be implemented to improve treatment accessibility and equity, and prevent the widening gap in medical resources. Furthermore, prudent management and international consensus are required to address ethical challenges brought by germline gene editing, alongside rigorous informed consent regulations. Only when ethical governance and technological innovation advance in tandem can stem cell therapy achieve safe, equitable and sustainable clinical application [36].

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6. Conclusion

Stem cell therapy has opened up brand-new possibilities for the treatment of AMD. Transplantation of RPE cells differentiated from hESCs and iPSCs has demonstrated the capacity to replace damaged RPE cells and sustain photoreceptor survival in preclinical models and early-stage clinical trials. Case studies on autologous iPSC-RPE transplantation have verified the feasibility of personalized cell therapy. Although its therapeutic effect mainly lies in stabilizing the disease, this approach eliminates immune rejection and lays a practical foundation for precision medicine. MSCs exert anti-inflammatory, anti-apoptotic and immunomodulatory effects via paracrine factors and exosomes, and present neuroprotective effects in relevant retinal disease models, holding promise for the early intervention of dry AMD in the future.

Nevertheless, stem cell therapy still faces multiple challenges. In terms of safety, vigilance must be maintained against the tumorigenic risk of transplanted cells, especially those derived from ESCs and iPSCs, as well as immune rejection. Relevant ethical codes and regulations also need further improvement. Technically, a series of issues remain unresolved, including the control of cell differentiation purity, long-term survival and functional integration of cells after transplantation, and the standardization of cell sources, manufacturing procedures and supporting systems. These factors collectively restrict the further popularization and application of stem cell therapy for dry AMD.

Looking ahead, research on stem cell therapy for dry AMD needs to advance in the following directions. First, combine gene editing technology to enhance the neurotrophic and homing abilities of stem cells, or repair patient-specific disease-causing mutations. Second, adopt biomaterials and tissue engineering techniques such as degradable scaffolds and hydrogels to improve the survival and integration efficiency of transplanted cells. Third, promote personalized treatment strategies and realize precise intervention based on patients' genotypes, disease stages and biomarkers. Fourth, explore combined cell therapy or integrated cell-drug regimens to synergistically slow disease progression. Fifth, transform the application mode from using thawed cryopreserved cells to metabolically active cells, so as to fully restore cellular metabolic function and viability. Sixth, optimize the regulatory framework for stem cell therapy to improve the equity and accessibility of treatment, and protect the interests of both donors and patients. Meanwhile, establishing standardized systems for cell preparation and quality control, and conducting long-term safety follow-up studies are essential steps to translate stem cell therapy from laboratory research into clinical practice, which deserve greater attention [36].

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