Regenerative Therapy 26 (2024) 382–386

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

The application of retinal organoids in ophthalmic regenerative medicine: A mini-review

Xinmei Lan [1], Huixia Jiang [1], Qian Wang, Qin Shiqi, Yu Xiong*

Ophthalmic Center, The Second Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi Province, 330006, China

ARTICLE INFO

Article history:
Received 28 May 2024
Received in revised form
16 June 2024
Accepted 20 June 2024

Keywords:
Retinal organoids
3D culture
Cell transplantation
Biomaterials
Regenerative medicine
Glaucoma
Retinal degenerative diseases

ABSTRACT

Retinal organoids are three-dimensional (3D) microscopic tissues that are induced and differentiated from stem cells or progenitor cells in vitro and have a highly similar structure to the retina. With the optimization and development of 3D retinal culture system and the improvement of induced differentiation technology, retinal organoids have broad application prospects in retinal development, regenerative medicine, biomaterial evaluation, disease mechanism investigation, and drug screening. In this review we summarize recent development of retinal organoids and their applications in ophthalmic regenerative medicine. In particular, we highlight the promise and challenges in the use of retinal organoids in disease modeling and drug discovery.

Contents

1. Introduction

Due to the non-renewability of ganglion cells and photoreceptor cells, glaucoma and retinal degenerative diseases are both irreversible blinding eye diseases, seriously affecting the life and visual health of the patients. Currently, there are no effective cure and prevention methods for glaucoma and retinal degenerative diseases. With recent progress on stem cell biology, cell regeneration therapy has provided the possibility for the treatment of blinding eye diseases [1].

Retinal organoids are a 3D cell complex formed by inducing the differentiation of stem cells or progenitor cells using 3D culture technology in vitro, which is structurally and functionally similar to

* Corresponding author.
E-mail address: sherry_0118@163.com (Y. Xiong).
Peer review under responsibility of the Japanese Society for Regenerative Medicine.
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.reth.2024.06.013

the retina (Fig. 1) [2]. Retinal organoids mimic the retina and contain most types of retinal cells, such as posterior retinal pigment epithelium (RPE). The outer limiting membrane (OLM) is formed by the Müller cell end-feet and photoreceptors. The photoreceptor nuclei constitute a layer called the outer nuclear layer (ONL), while their axons meet with bipolar and horizontal cells in the outer plexiform layer (OPL). The inner nuclear layer (INL) contains the nuclei of bipolar and horizontal cells and Müller glia, while the inner plexiform layer contains the synapse of bipolar cell and retinal ganglion cell (RGC). Therefore, subcellular structures specific to the retina can be observed in retinal organoids [2].

Compared with traditional two-dimensional cell culture system, three-dimensional retinal organoids better simulate the interactions between the microenvironment in each layer *in vivo*, and provide a new treatment approach for retinal regeneration diseases [3,4]. In this review, we summarize recent development of retinal organoids and discuss their advantages and deficiencies, and highlight their potential applications in ophthalmic regenerative medicine.

2. Sources and culture of retinal organoids

At present, the main sources of retinal organoids are embryonic stem cells (ESCs), adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs) [5]. Compared with ESCs, iPSCs are not affected by ethical and immune rejection, and have a lower risk of tumor formation, making them widely used [6]. Currently, traditional 2D monolayer cell culture platforms are used in most studies on iPSC disease models. Compared with traditional 2D culture, 3D culture can better simulate complex cell microenvironment, and is convenient for investigating the retinal circuit and the connections between neurons.

While 3D culture system has been optimized to mimic retinal tissue, the maturation of photoreceptor cells in retinal organoids takes about 6 months, and how to shorten culture cycle and increase production is currently an urgent problem to be solved. It

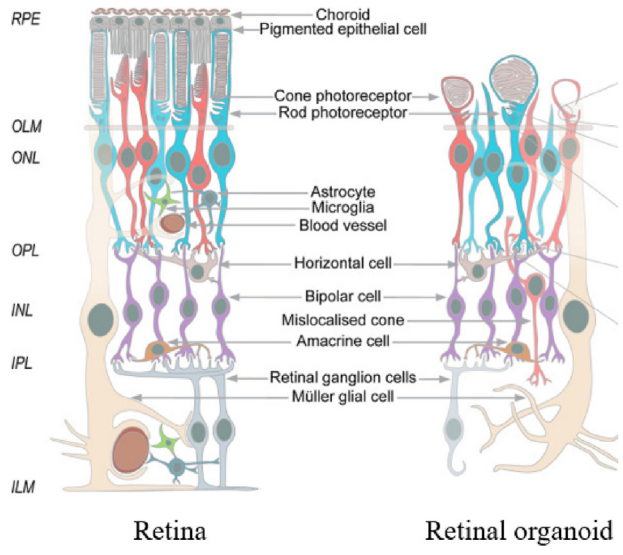

Fig. 1. Comparison of the origination of retinal organoids and the retina. Retinal organoids mimic the retina and contain most types of retinal cells, such as posterior retinal pigment epithelium (RPE). The outer limiting membrane (OLM) is formed by the Müller cell end-feet and photoreceptors. The photoreceptor nuclei constitute a layer called the outer nuclear layer (ONL), while their axons meet with bipolar and horizontal cells in the outer plexiform layer (OPL). The inner nuclear layer (INL) contains the nuclei of bipolar and horizontal cells and Müller glia, while the inner plexiform layer contains the synapse of bipolar cell and retinal ganglion cell (RGC).

was reported that adding retinal pigment epithelium and decellularized extracellular matrix to the culture medium could significantly increase the production of rod-shaped photoreceptors, and promote photoreceptor cell maturation and synapse formation [7]. Moreover, adding retinoic acid at a specific stage of cell differentiation promotes the generation of rod and cone photoreceptors in the formation of retinal organoids [7].

A commonly used neural induction method involves dual SMAD inhibition (dSMADi). In this method, both BMP and TGF-β signaling are inhibited through small molecule inhibitors to achieve the differentiation of the neuroectodermal organoid lineage. The use of bioreactors could help increase the production of photoreceptors compared to traditional suspension culture dishes, which may be related to the reduction of apoptotic cells and the increase of cell proliferation in bioreactor culture [8]. By promoting oxidation and promoting nutrient absorption, culture conditions can be improved, and these characteristics can in turn regulate cell survival and proliferation. A rotating wall vessel (RWV) bioreactor has been developed to culture retinal organoids from mouse pluripotent stem cells [9]. The proliferation of organoids cultured with RWV was accelerated, and neuronal differentiation was enhanced. These results indicate that the bioreactor can accelerate and improve the growth and differentiation of retinal organoids [10].

The scaffolds have been applied in tissue engineering. Scaffolds include both natural and synthetic scaffolds, and provide physical support carriers for cell transportation, integration, and delivery of cell matrix [11]. Natural polymers such as polysaccharides, proteins, and polyesters maintain various characteristics of natural tissues and membranes, such as inherent biological activity, and are widely used as cell delivery scaffolds. However, the small variability of mechanical properties, relatively poor environmental stability, potential immune reactions, and risk of infection are currently the main obstacles to the use of natural scaffold materials. Synthetic polymer scaffolds based on polyesters, polylactic acid (PLA) and polyglycolic acid (PGA) have a wide range of applications, but the disadvantage is that they have less cell adhesion. By changing the physical and chemical surface properties of the top layer of the scaffold, such as modifying hydrophilic/hydrophobic properties, surface topology, pH level, and surface adhesion properties, cell adhesion to the scaffold can be enhanced [11]. Moreover, the modification of scaffolds with stem cells provide a novel approach for regenerative medicine [12,13]. Recently, bioprinting technology is applied to create 3D tissue structures. The retina contains 9 cell layers, each of which performs specific tasks. Most of the functions of natural RPE are related to the 3D structure of the retina. Masaeli et al. successfully designed a portion of the complex 3D structure of the retina using 3D inkjet bioprinting technology [14]. After printing, RPE cells were well positioned within the 9-layer structure without altering their biological function. After four bioprints, RPE was able to perform specific retinal functions [14].

Many organ-like models lack matrix components, especially the vascular system. Fortunately, the angiogenic capacity of mesenchymal stem cells could be utilized for potential therapeutic application [15]. Organ chip technology combines microfluidic technology, biomaterials, and cell culture technology, which can simulate the microstructure and function of human organs at a micro scale, and has recently attracted much attention. Achberger et al. established in vitro 3D model of the human retina by combining hiPSC-ROs with hiPSC derived RPE on a retinal chip (RoC). This method can enhance the formation and preservation of inner and outer segments, enabling direct interaction between retinal pigment epithelium and photoreceptors, and achieving precise and controllable vascular perfusion [16]. The same group further demonstrate the potential of iPSC-based Organ-on-chip models as the next generation of screening platforms for gene

therapy [17]. Moreover, an in vitro rabies virus-based monosynaptic retrograde tracing assay was recently developed to identify de novo synaptic connections among early retinal cell types following RO dissociation [18].

3. Application of retinal organoids in ophthalmic regenerative medicine

Retinal ganglion cells (RGCs) are central nervous system projection neurons with complex patterns, and play a crucial role in visual information transmission between the eyes and the brain. At present, one of the main technical limitations of simulating glaucoma with retinal organoids is that RGC needs to establish a long-distance connection with the visual center of the brain [19]. Fligor et al. showed that the long-distance growth of RGCs axons was regulated by external factors, including substrate composition and signal transduction through growth factors. Among many substrates, laminin and matrix gel are most conducive to increasing the neurite length. In addition, in the presence of Netrin-1 and BDNF growth factor, RGCs from retinal organoids can extend significantly more axons [20]. In addition, bioengineering methods may overcome current limitations. Chen et al. showed that the polybenzyl glutamate (PBG) biocompatible scaffold could promote the growth of neural stem cells and RGC progenitor cells [21].

Electrospinning is a technology to manufacture nanofiber scaffolds. Kador et al. demonstrated that polylactic acid electrospun scaffolds can reconstruct the directionality of retinal nerve fibers, and fixing gradient Netrin-1 protein onto the electrospun scaffold can increase the RGC of the axon guiding scaffold center from 31% to 52% [22]. Currently, animal experiments support the transplantation of RGCs. Oswald et al. transplanted RGCs derived from mouse iPSCs/ESCs into the retinas of healthy and glaucoma mice. The transplanted RGCs were able to polarize and form axonal processes within the host retina. The donor cells survived for up to 12 months [23]. Chao et al. injected donor cells into the retina of squirrel monkeys. Despite immune suppression, the donor cells survived for three months after transplantation, and many axonal projections were observed throughout the process. Some donor cells integrated into the host's inner retina, demonstrating the feasibility of replacing hESC derived retinal cells in non-human primate eyes [24]. Before being used in clinical practice, there are still many key obstacles that need to be overcome, such as the injection of ganglion cells from the vitreous body into the eye, with an integration efficiency of only 1–7% [25]. How to control the growth of axons in the correct direction of the optic nerve bundle is also a problem that needs to be solved.

With the development of 3D retinal culture technology, retinal organoids can generate photoreceptor cells and tissues required for transplantation in vitro, providing hope for treating irreversible ophthalmic diseases such as retinitis pigmentosa (RP). Mandai et al. transplanted the iPSC retina into the eyes of late-stage RP mice, producing mature ONL, and nearly half of the transplanted mice responded to light [26]. Lin et al. transplanted human retinal organoid cells into rats with RPE dysfunction, and the transplanted photoreceptors could function [27]. These experiments indicate that stem cell organoid transplantation may be an effective method to treat RP diseases, but rodents are nocturnal animals with a higher proportion of rod photoreceptors and a lack of cone photoreceptors [28]. This is not consistent with the characteristics of the human retina, but obtaining samples from the human retina is difficult.

It is proposed to use iPSCs produced by patients' fibroblasts for transplantation to avoid rejection risks and ethical issues, but derived iPSCs still carry pathogenic mutations, and new gene editing techniques may solve this problem. Bassuk et al. applied short palindrome repeat sequences (CRISPR) to correct pathogenic mutations in RP. They generated specific iPSCs from a patient with X-linked retinitis pigmentosa (XLRP) and corrected point mutations in the ORF15 region of the RPGR gene by transfecting CRISPR gRNA/Cas9 with donor homologous templates. Therefore, CRISPR technology can accurately edit pathogenic mutations and generate gene corrected hiPSCs, which can ultimately be applied to autologous transplantation for the treatment of RP. This is the first successful gene correction report related to RP, providing ideas for personalized transplantation of various retinal diseases [29].

In addition, photoreceptor replacement therapy provides great hope for the treatment of age-related macular degeneration (AMD). Mandai's team successfully transplanted RPE cells derived from autologous iPSCs into the retina of patients with AMD for the first time [30]. One year after surgery, the patient's best corrected visual acuity did not improve or deteriorate, and the graft remained intact. Ribeiro's team transplanted purified hPSC derived cone cells into mice with advanced retinal degeneration. The transplanted donor cells matured in the body and formed synaptic connections with the recipient cells, producing new photoreceptor cells [31]. These studies demonstrate the feasibility of transplanting retinal organoids for the treatment of ophthalmic degenerative diseases.

4. Conclusion and prospects

Compared to traditional cell culture and animal models, retinal organoids have unparalleled advantages [32,33]. In this review we provide a brief overview of the sources, cultivation methods, and applications of retinal organoids in treating retinal degenerative diseases such as glaucoma, AMD, and RP. Retinal organoids have a wide range of applications (Fig. 2). First, they can be used for disease modeling. Due to the inability of animal models to accurately reflect all the characteristics of human diseases, experimental results may be inaccurate. The application of 3D organoid technology can model complex ophthalmic diseases [34,35]. Second, potential pathogenetic mechanisms of ophthalmic diseases can be studied based on omics analysis including but not limited to genomics, transcriptomics, proteomics and metabolomics [36]. Third, drug testing and safety evaluation can be conducted. The effects of drugs on different patients may vary, and specific effects can be tested on the patient's retinal organoids to find the best individual treatment [37]. In addition, retinal organoids can be analyzed and tested for drug side effects and pharmacodynamics [38].

In recent years, research on retinal organoids has made rapid progress, bringing new hope for the treatment of blind eye diseases. However, there are still many issues that need to be addressed in order to achieve sustainable, repeatable, and safe treatment of retinal diseases on a large scale. (1) The technical bottleneck of cultivation. Despite significant progress in the field of retinal organoids technology in recent years, it is still difficult to produce retinal organoids in vitro with identical biochemical and physiological characteristics as mature retinas *in vivo*. Integrating smooth muscle cells, vascular systems, and immune cells in culture can help establish a better in vitro model. (2) Ethical issues regarding stem cell sources; (3) How to avoid rejection reactions although recent studies have shown promise [39,40]; (4) How to improve the homogeneity of differentiation between different cell lines and batches in preparation for mass production; (5) How to reduce various complications caused by subretinal transplantation; (6) The maturation of photoreceptor cells in retinal organoids takes about 6 months, with a long time cycle. How to improve the differentiation ratio of photoreceptor cells in retinal organoids and promote the maturation of photoreceptor cells, while shortening the cultivation time. (7) How to integrate other stem cells and stem cell-derived secretome in the design of retinal organoids [41].

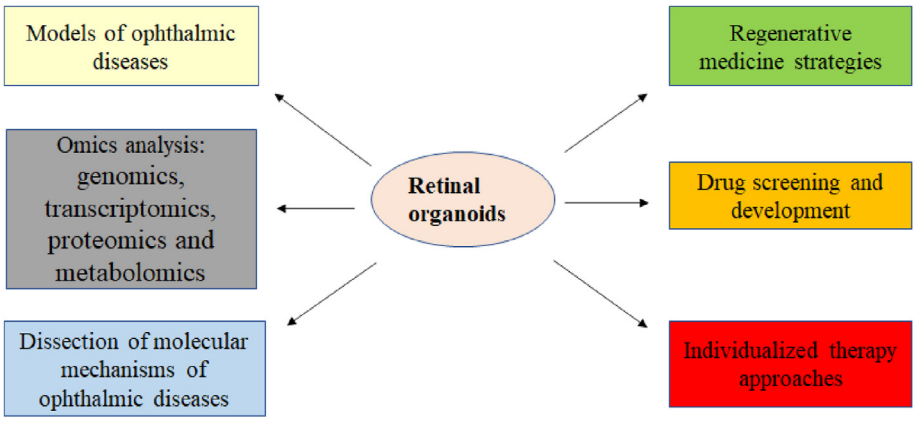

Fig. 2. The application of retinal organoids in ophthalmic medicine. Retinal organoids can be applied in both basic and translational ophthalmic medicine.

5. Conclusion

In summary, retinal organoids have very broad applications. However, there is still a long way to go to fully utilize retinal organoids in the clinical practice, and the universality and efficiency of their induced differentiation, the heterogeneity of organoid induced differentiation, and the differences between them and embryonic retinal development are urgent issues to be solved in the field [42,43]. We should further optimize numerous differentiation protocols and co-culture systems of retinal organoids and promote clinical application of retinal organoids.

Authors contributions

XL, HJ, QW and SQ collected and analyzed the references, YX designed the study and wrote the manuscript. All authors reviewed and agreed on the final manuscript version.

Ethics approval and consent to participate

Not Applicable.

Funding

This study was supported by the grants from National Natural Science Regional Foundation of China (81960179), Major Discipline Academic and Technical Leaders Training Program-Young Talent Project of Jiangxi Province of China (20204BCJL23055), Natural Science Fund for Distinguished Young Scholars of Jiangxi Province of China (20192ACB21028), Chinese Medicine Project of Jiangxi Provincial Health Commission (No. 2018B003), and Postgraduate Innovation Project of Jiangxi Province (YC2022-S200, YC2023–S182).

Consent for publication

Not Applicable.

Data availability statement

Not Applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not Applicable.

References

[1] Pan D, Zhang X, Jin K, Jin ZB. CRX haploinsufficiency compromises photoreceptor precursor translocation and differentiation in human retinal organoids. Stem Cell Res Ther 2023;14(1):346.
[2] Afanasyeva TAV, Corral-Serrano JC, Garanto A, Roepman R, Cheetham ME, Collin RWJ. A look into retinal organoids: methods, analytical techniques, and applications. Cell Mol Life Sci 2021;78(19–20):6505–32.
[3] Zhao H, Yan F. Retinal organoids: a next-generation platform for high-throughput drug discovery. Stem Cell Rev Rep 2024;20(2):495–508.
[4] Liang Y, Sun X, Duan C, Tang S, Chen J. Application of patient-derived induced pluripotent stem cells and organoids in inherited retinal diseases. Stem Cell Res Ther 2023;14(1):340.
[5] Sharma K, Krohne TU, Busskamp V. The rise of retinal organoids for vision research. Int J Mol Sci 2020;21(22):8484.
[6] Chehelgerdi M, Behdarvand Dehkordi F, Chehelgerdi M, Kabiri H, Salehian-Dehkordi H, Abdolvand M, et al. Exploring the promising potential of induced pluripotent stem cells in cancer research and therapy. Mol Cancer 2023;22(1):189.
[7] Manafi N, Shokri F, Achberger K, Hirayama M, Mohammadi MH, Noorizadeh F, et al. Organoids and organ chips in ophthalmology. Ocul Surf 2021;19:1–15.
[8] Ovando-Roche P, West EL, Branch MJ, Sampson RD, Fernando M, Munro P, et al. Use of bioreactors for culturing human retinal organoids improves photoreceptor yields. Stem Cell Res Ther 2018;9(1):156.
[9] DiStefano T, Chen HY, Panebianco C, Kaya KD, Brooks MJ, Gieser L, et al. Accelerated and improved differentiation of retinal organoids from pluripotent stem cells in rotating-wall vessel bioreactors. Stem Cell Rep 2018;10(1):300–13.
[10] Xue Y, Seiler MJ, Tang WC, Wang JY, Delgado J, McLelland BT, et al. Retinal organoids on-a-chip: a micro-millifluidic bioreactor for long-term organoid maintenance. Lab Chip 2021;21(17):3361–77.
[11] Lim KT, Patil TV, Patel DK, Dutta SD, Ganguly K, Randhawa A. Mesenchymal stem cells, the secretome and biomaterials: regenerative medicine application. Biocell 2022;46(10):2201–8.
[12] Chen Q, Zhao X, Ma W. Game-changing insights on vertebral skeletal stem cells in bone metastasis and therapeutic horizons. Oncology Research 2024;32(1):95–8.
[13] Petrella F, Cassina EM, Libretti L, Pirondini E, Raveglia F, Tuoro A. Stem cell technology for antitumor drug loading and delivery in oncology. Oncology Research 2024;32(3):433–7.
[14] Masaeli E, Forster V, Picaud S, Karamali F, Nasr-Esfahani MH, Marquette C. Tissue engineering of retina through high resolution 3-dimensional inkjet bioprinting. Biofabrication 2020;12(2):025006.
[15] Nguyen VTT, Pham KD, Cao HTQ, Pham PV. Mesenchymal stem cells and the angiogenic regulatory network with potential incorporation and modification for therapeutic development. Biocell 2024;48(2):173–89.
[16] Achberger K, Probst C, Haderspeck J, Bolz S, Rogal J, Chuchuy J, et al. Merging organoid and organ-on-a-chip technology to generate complex multi-layer tissue models in a human retina-on-a-chip platform. Elife 2019;8:e46188.
[17] Achberger K, Cipriano M, Düchs MJ, Schön C, Michelfelder S, Stierstorfer B, et al. Human stem cell-based retina on chip as new translational model for validation of AAV retinal gene therapy vectors. Stem Cell Rep 2021;16(9):2242–56.
[18] Ludwig AL, Mayerl SJ, Gao Y, Banghart M, Bacig C, Fernandez Zepeda MA, et al. Re-formation of synaptic connectivity in dissociated human stem cell-derived retinal organoid cultures. Proc Natl Acad Sci U S A 2023;120(2):e2213418120.

[19] Watari K, Yamasaki S, Tu HY, Shikamura M, Kamei T, Adachi H, et al. Self-organization, quality control, and preclinical studies of human iPSC-derived retinal sheets for tissue-transplantation therapy. Commun Biol 2023;6(1):164.
[20] Fligor CM, Langer KB, Sridhar A, Ren Y, Shields PK, Edler MC, et al. Three-Dimensional retinal organoids facilitate the investigation of retinal ganglion cell development, organization and neurite outgrowth from human pluripotent stem cells. Sci Rep 2018;8(1):14520.
[21] Chen TC, She PY, Chen DF, Lu JH, Yang CH, Huang DS, et al. Polybenzyl glutamate biocompatible scaffold promotes the efficiency of retinal differentiation toward retinal ganglion cell lineage from human-induced pluripotent stem cells. Int J Mol Sci 2019;20(1):178.
[22] Kador KE, Alsehli HS, Zindell AN, Lau LW, Andreopoulos FM, Watson BD, et al. Retinal ganglion cell polarization using immobilized guidance cues on a tissue-engineered scaffold. Acta Biomater 2014;10(12):4939–46.
[23] Oswald J, Kegeles E, Minelli T, Volchkov P, Baranov P. Transplantation of miPSC/mESC-derived retinal ganglion cells into healthy and glaucomatous retinas. Mol Ther Methods Clin Dev 2021;21:180–98.
[24] Chao JR, Lamba DA, Klesert TR, Torre A, Hoshino A, Taylor RJ, et al. Transplantation of human embryonic stem cell-derived retinal cells into the subretinal space of a non-human primate. Transl Vis Sci Technol 2017;6(3):4.
[25] Hertz J, Qu B, Hu Y, Patel RD, Valenzuela DA, Goldberg JL. Survival and integration of developing and progenitor-derived retinal ganglion cells following transplantation. Cell Transplant 2014;23(7):855–72.
[26] Mandai M, Fujii M, Hashiguchi T, Sunagawa GA, Ito SI, Sun J, et al. iPSC-Derived retina transplants improve vision in rd1 end-stage retinal-degeneration mice. Stem Cell Rep 2017;8(1):69–83.
[27] Lin B, McLelland BT, Aramant RB, Thomas BB, Nistor G, Keirstead HS, et al. Retina organoid transplants develop photoreceptors and improve visual function in RCS rats with RPE dysfunction. Invest Ophthalmol Vis Sci 2020;61(11):34.
[28] Kostic C, Arsenijevic Y. Animal modelling for inherited central vision loss. J Pathol 2016;238(2):300–10.
[29] Bassuk AG, Zheng A, Li Y, Tsang SH, Mahajan VB. Precision medicine: genetic repair of retinitis pigmentosa in patient-derived stem cells. Sci Rep 2016;6:19969.
[30] Mandai M, Watanabe A, Kurimoto Y, Hirami Y, Morinaga C, Daimon T, et al. Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med 2017;376(11):1038–46.
[31] Ribeiro J, Procyk CA, West EL, O'Hara-Wright M, Martins MF, Khorasani MM, et al. Restoration of visual function in advanced disease after transplantation of purified human pluripotent stem cell-derived cone photoreceptors. Cell Rep 2021;35(3):109022.
[32] Ma C, Jin K, Jin ZB. Generation of human patient iPSC-derived retinal organoids to model retinitis pigmentosa. J Vis Exp 2022;184. https://doi.org/10.3791/64045.
[33] McDonald A, Wijnholds J. Retinal ciliopathies and potential gene therapies: a focus on human iPSC-derived organoid models. Int J Mol Sci 2024;25(5):2887.
[34] Lei Q, Xiang K, Cheng L, Xiang M. Human retinal organoids with an OPA1 mutation are defective in retinal ganglion cell differentiation and function. Stem Cell Rep 2024;19(1):68–83.
[35] Becker S, L'Ecuyer Z, Jones BW, Zouache MA, McDonnell FS, Vinberg F. Modeling complex age-related eye disease. Prog Retin Eye Res 2024;100:101247.
[36] Kurzawa-Akanbi M, Tzoumas N, Corral-Serrano JC, Guarascio R, Steel DH, Cheetham ME, et al. Pluripotent stem cell-derived models of retinal disease: elucidating pathogenesis, evaluating novel treatments, and estimating toxicity. Prog Retin Eye Res 2024;100:101248.
[37] Zhao H, Yan F. Retinal organoids: a next-generation platform for high-throughput drug discovery. Stem Cell Rev Rep 2024;20(2):495–508.
[38] Fathi M, Ross CT, Hosseinzadeh Z. Functional 3-Dimensional Retinal Organoids: technological progress and existing challenges. Front Neurosci 2021;15:668857.
[39] Yamasaki S, Sugita S, Horiuchi M, Masuda T, Fujii S, Makabe K, et al. Low immunogenicity and immunosuppressive properties of human ESC- and iPSC-derived retinas. Stem Cell Rep 2021;16(4):851–67.
[40] Hirami Y, Mandai M, Sugita S, Maeda A, Maeda T, Yamamoto M, et al. Safety and stable survival of stem-cell-derived retinal organoid for 2 years in patients with retinitis pigmentosa. Cell Stem Cell 2023;30(12):1585–1596.e6.
[41] Harrell C-R, Volarevic A, Pavlovic D, Djonov V, Volarevic V. Mesenchymal stem cell-derived exosomes as new remedy for the treatment of inflammatory eye diseases. Biocell 2022;46(10):2195–200.
[42] Santa Cruz-Pavlovich FJ, Bolaños-Chang AJ, Del Rio-Murillo XI, Aranda-Preciado GA, Razura-Ruiz EM, Santos A, et al. Beyond vision: an overview of regenerative medicine and its current applications in ophthalmological care. Cells 2024;13(2):179.
[43] Chakrabarty K, Nayak D, Debnath J, Das D, Shetty R, Ghosh A. Retinal organoids in disease modeling and drug discovery: opportunities and challenges. Surv Ophthalmol 2024;69(2):179–89.