Utility of Retinal Organoids

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The eye is one of the most important sensory organs in humans, providing us with a valuable remote sense, vision. A wealth of information enters the visual system through the eyes, creating complex images with shapes, colors, and textures. Despite the progress of modern medicine in the last decades, millions of people diagnosed with retinal dystrophies (RDs), such as retinitis pigmentosa (RP), or age-related diseases, such as age-related macular degeneration (AMD), are suffering from severe visual impairment or even legal blindness. On one hand, the reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) and the progress of three-dimensional (3D) retinal organoids (ROs) technology provide a great opportunity to study, understand, and even treat retinal diseases. On the other hand, research advances in the field of electronic retinal prosthesis using inorganic photovoltaic polymers and the emergence of organic semiconductors represent an encouraging therapeutical strategy to restore vision to patients at the late onset of the disease.

retinal dystrophy retinal organoids

1. Cell Replacement and Gene Therapies

One of the potential uses of human PSC-derived retinas is as a tissue source for retinal cell replacement therapy for blindness conditions, such RP, AMD, and glaucoma [1][2][3]. The key concern of cell replacement is to transplant and functionally integrate cells capable of developing into mature photoreceptors (PRs), to restore the defective retinal tissue. Currently, two techniques of PR restoration are being pursued: transplantation of dissociated cells and transplantation of “sheets” of embryonic retinal tissue. Each of those techniques showed potential in animal models and even in a human clinical trial for retinal sheets [4][5]. Despite this intricacy, the PSC-derived retina experiments showed that PSC-derived differentiating tissues have a remarkable capacity to organize and self-pattern [4][6]. Nonetheless, taking into account the diseased retina environment may be essential for successful transplantation because the cytoarchitectural remodeling of inner retinal neurons, namely gliosis, and neural retinal thinning at late stages may impair transplanted cells or the tissue’s ability to restore the precise neural circuitry that underpins the visual signals exiting the retina [6][7]. As a result, optimal functional restoration may need pre- or post-transplantation retinal remodeling.

ROs are a very new and quickly developing technology. They can be used to investigate gene therapy for a variety of retinopathies, such as by examining gene delivery in a human system. Therapies based on adeno-associated virus (AAV) vectors are gaining momentum as a potential treatment for retinal diseases. One major reason is the accessibility of the eye, which makes it suitable for intravitreal or subretinal injection surgery. AAVs can infect human cells, allowing long-term expression of the transgene after a single dose. Delivery of AAV by intravitreal

injections is a safe method, but it often leads to low transduction efficiencies of PRs. A novel injection system using peripapillary intravitreal injection promises to be a safe and efficient alternative to standard intravitreal injections [8]. This, together with recent positive results on retinal-transduction efficiency of newly designed second-generation AAVs, combined with the accessibility of human retinal tissue through ROs to test their efficiency, holds hope for the future of AAV-based retinal therapies when combined with intravitreal delivery.

Another type of therapeutic strategies are RNA-based therapies, such as antisense oligonucleotides (AONs), which are becoming popular in treating inherited RDs [9][10]. AONs are relatively small nucleic acid molecules that target the pre-mRNA or mRNA to modify the splicing process, alter translation, or degrade a transcript. Combining organoid applications with other technologies increases their considerable potential in clinical and translational research. CRISPR-Cas9 genome-editing technology, for example, may be employed virtually to modify PSC lines in order to generate ROs with any desired genetic modification [11][12]. As a genome-editable system, ROs are perfectly suitable to take advantage of the increasingly sophisticated toolbox being developed by optogeneticists, synthetic biologists, and even sonogeneticists to engineer new circuits and functions with remote switches in order to sensibly control cellular behavior [13][14][15].

2. Retinal Organoids as Human In Vitro Models

ROs open up a slew of new research opportunities, filling a gap left by inconsistencies between animal models and human disorders. The organoid cell population and the molecular profile appear to be similar to those of the human retina [16]. Recently, ROs have been employed to replicate inherited RDs [17][18], although organoids appear to be best suited to represent severe phenotypes with early disease onset. As previously reviewed by Zhang et al., 24 studies have so far modelled several aspects of retinal diseases using 3D ROs either derived from patients or from genetically manipulated PSCs. These diseases include retinitis pigmentosa, Leber's congenital amaurosis, glaucoma, macular telangiectasia type 2, microphtalmia, retinoblastoma, Stargardt disease, and X-linked juvenile retinoschisis [19].

Other situations in which human PSC-derived retinas can be applied include screening for drugs that are active in a patient-specific genetic background. The PSC-derived retinas can be applied to the design of "clinical trials in a dish" by facilitating the sampling of a diverse population in drug-screening assays. In vitro ROs can be employed as testbeds to assess the pharmacological effects of moxifloxacin (a retinotoxic drug at higher dosages), resulting in effective reproduction of in vivo-like retinal cell damage, including the loss of PRs and amacrine cells [20]. Finally, ROs can be applied not only to the screening of compounds and small molecules, but also to the testing of gene therapy strategies and certain drug delivery approaches, including the use of nanoparticles.

3. Retinal Organoids as In Vitro Models for Retinal Prostheses

Despite the advancement in both research fields, ROs and retinal prostheses were always studied independently and in parallel. Surprisingly, we were unable to find any publication that directly intersected both fields. As mentioned earlier in this review, ROs can now represent key features of the native human retina and are currently used as disease models to decipher specific disease mechanisms to treat or reverse retinal degeneration [17][19]. In addition, few studies employed electrode arrays to show that hiPSCs-derived ROs are light-responsive [21][20], proving the applicability of ROs as in vitro models. However, to test the efficiency of an inorganic or organic retinal prosthesis and to quantify stimulated retinal activity, most of the recent studies have based their investigations on animal models of RDs or animal in vitro explants. The retina in these models largely differ from the human retina and do not fully represent or recapitulate the human eye (patho)physiology [22][23]. Therefore, it is now of the utmost importance to use the potential of ROs, not only to investigate retinal disease mechanisms or gene- and cell-replacement therapies, but also as human in vitro models for retinal prosthesis optimization. The human organoid models can mimic the complex physiology of the retina in a more simplified setting, and therefore offer a more selective stimulation of retinal cell population. In addition, the identification and quantification of the photostimulated retinal activity of organic semiconductors in different configurations can be evaluated on the retinal tissue of human organoids derived from RD patients, instead of using ex vivo retina from animal models.

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