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Stem Cells and Transplantation for Retinal Diseases

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Abstract

Stem cells provide a promising tool for treating retinal diseases and injury. Early work focused on embryonic stem cells (ESC). The development of induced pluripotent stem cells (iPSC) alleviates some of the ethical concerns with ESC and the need for immunosuppression. Stem cell-derived retinal pigment epithelial cells (RPE) are comparable to native RPE; and stem cell-derived retinal organoids self-organize into laminated structures that bear some resemblance to the neurosensory retina. Questions remain regarding genetic and epigenetic variability among different stem cell lines, especially iPSC lines. The challenge is in understanding the significance of this variability for transplant and how to control such variability. Transplantation of stem cell-derived RPE and retinal progenitor cells has been tested in both animal models and humans. The cells integrated into the recipient with possible rescue of visual function. These findings encourage researchers to develop refined culture and delivery methods that would increase integration with the host and sustain long-term visual function.

Introduction

Since the beginning of stem cell research, pluripotent cells were seen as a promising tool for tissue regeneration and transplantation. Widely known, stem cells have the ability to differentiate into one or more mature cell types or continue to renew themselves. These properties make stem cells a potential source for sustained supply of tissue for transplantation. There is growing interest in developing stem cell therapies for neurodegenerative diseases, such as Alzheimer and amyotrophic lateral sclerosis (ALS), with the aim of replacing diseased tissue [1,2]. Similarly, research on developing replacement tissues for retinal degeneration has gathered momentum as well.

Sources of Stem Cell-Derived Retinal Cells

In many retinal diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa, there is degeneration of both the retinal pigment epithelium (RPE) and photoreceptors resulting in vision loss. The native retina, being a neural tissue, has little ability to regenerate. Therefore, transplanted tissue needs to replace lost tissue, continue to survive, and integrate functionally into the host retina. Several sources of stem cells have been used for regenerating retinal tissue; the most extensively studied are human embryonic stem cell (hESC) and induced pluripotent stem cell (iPSC). Additionally, researchers have developed and continue to improve different methods of differentiating stem cells into retinal cells.

Embryonic stem cells

Embryonic stem cells (ESC) are pluripotent stem cells derived from blastocysts in early development [3,4]. In stem cell biology, they are considered the gold-standard for comparing pluripotency, and genetic and epigenetic characteristics. The ethical concerns of human ESC have been much debated. Nevertheless, ESC allowed early successful differentiation of retinal cells in culture. hESC-derived RPE demonstrated robust pigmentation, and exhibited similar morphology and gene expression as human fetal RPE [5-8]. These RPE cells also developed appropriate functional characteristics, such as phagocytosis of shed outer segments [9, 10]. Scanning across the literature, there are now various differentiation methods used for generating retinal cells. Some methods involve directed differentiation using small molecules and growth factors, and others allow stem cells to spontaneously differentiate into RPE in specialized media [9,10]. The time taken for retinal cells to differentiate can vary depending on the protocol and the desired cell type. Neuroretinal precursor cells, for example, can appear as early as day 10 in culture, while pigmented cells can take 6-8 weeks to appear [11,12]. Researchers continue to improve

methods to generate retinal cells comparable to native retina in order to study retinal development and to generate tissue for transplantation.

Induced pluripostent stem cells (iPSC)

iPSCs are pluripotent stem cells that are derived from adult cells. Skin fibroblasts and peripheral blood cells are commonly used to generate iPSC. The Yamanaka group were the first to describe this reprogramming by introducing four transcription factors Oct3/4, Sox2, Klf4, and c-Myc, known as the "Yamanaka factors". [13, 14] iPSCs also have been successfully differentiated into retinal cells. iPSC-derived RPE can attain appropriate barrier function including proper distribution of membrane Na-K-ATPase, polarized secretion of VEGF and similar membrane potential as native RPE [15]. Retinal progenitor cells and photoreceptors derived from iPSC also exhibit similar gene expression patterns as those derived from ESC, although there can be variation in the timing of differentiation [16].

iPSC can be a source of unlimited supply of regenerated tissue for studying development and for transplantation. One major foreseeable advantage of iPSC over ESC is the issue of immune histocompatibility. iPSC derived from a patient's adult cells would not cause immune rejection when transplanted into the same person. In practice, not every iPSC line can successfully differentiate into the desired cell type. There is in fact variability among iPSC lines. Some researchers ascribe the cause of variability to differences in reprogramming techniques and lab environment; others propose that iPSC have different epigenetic markers either due to the reprogramming procedure or epigenetic memory of the original adult cell [17-19]. However, there is controversy over how much epigenetic aberrancies contribute to the variability seen among iPSC lines [20].

The ultimate question is how cellular variability affects the safety of iPSC-derived cells for transplantation. There is a need for defining standards not only to evaluate iPSC lines but also the differentiated cells derived from iPSC. Miyagishima et al. [21] proposed a system of authenticating iPSC-derived RPE: in addition to assessing gene expression and morphology, they also assessed cellular calcium flux, membrane electrophysiology and fluid transport in comparison to human fetal RPE [22]. Rigorous testing and characterization is needed to increase the safety and integrity of retinal tissue selected for transplantation.

Retinal Transplantation

Transplantation of stem-cell derived retinal cells in animal models has presented positive results in visual improvement. Human clinical trials demonstrated good long-term safety of transplantation [22,23]. There are several ongoing clinical trials using stem-cell derived retinal cells for retinal diseases. The goals of transplantation are to replenish and rescue degenerating cells, re-establish neural connectivity within the retina, and improve visual acuity.

RPE transplantation

Overall, more translational studies have been done using stem-cell derived RPE than with stem-cell derived neuroretinal cells. Transplantation studies commonly use rodent models of retinal degeneration. A widely used model, for example, is the Royal College of Surgeons (RCS) rat, which has a mutation in MERTK gene and models autosomal recessive retinitis pigmentosa [24]. Transplantation of ESC-derived and iPSC-derived RPE in rodents with retinal degeneration resulted in more photoreceptor survival compared to non-transplanted animals. The photoreceptor layer was thicker at the transplant site compared to control [9,11,25-27].Transplanted RPE also promoted better visual function, measured by electroretinogram or optokinetic testing, compared to control animals [9,11,26]. The exact mechanism of photoreceptor rescue is not entirely elucidated. Given that the transplanted RPE does not always restore the outer blood-retinal barrier, one can postulate that trophic factors secreted by the RPE and the phagocytosis of photoreceptor outer segments may mediate the protective effects on the degenerating photoreceptors.

One major challenge from the studies mentioned above is long-term graft survival and visual improvement. In Carr et al. [10] implanted iPSC-RPE cells were eventually lost in the host retina at 13 weeks after transplant [26]. The mice interestingly retained improved visual function even when transplanted cells were not present. However, it is unknown whether this visual preservation can be sustained for longer. In the Idelson et al. [9] study, for example, the increased electroretinogram signal in transplanted animals eventually diminished at later time points (19 weeks). These results are proof-of-concept for using stem-cell derived retinal tissue to improve vision in retinal diseases. However, they also highlight limitations and challenges that need to be overcome to improve effectiveness of transplantation. The route of transplantation is seen as an area for improvement. In earlier transplant studies, a bolus of cells suspended in solution was injected into the subretinal space. This delivery method limits the ability of the transplanted RPE to re-organize into a functional monolayer; perhaps relatedly, cell survival from bolus injections is low [28]. Active research now focuses on transplanting sheets of RPE grown of various scaffolds to promote increased graft survival in the recipient [29,30].

In 2015, human clinic trial results for hESC-RPE transplantation in two retinal diseases were reported [23]. The trials were phase I/II with primary outcomes of safety and tolerability. The grafted cells were well tolerated without evidence of aberrant growth or serious side effects. When visual acuity was measured at 6 months after transplant, 6 out of the 9 AMD patients showed modest improvement from baseline and 3 out of 8 Stargardt's macular dystrophy patients showed similar improvement. The other patients had stable or decreased visual acuity. The study demonstrated the safety of stem-cell derived

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retinal transplantation in human patients. Other clinical trials are underway to assess different types of stem-cell derived retinal tissue, different methods of delivery, and in different retinal diseases.

Photoreceptor transplantation

Efforts to replace diseased photoreceptors have involved transplantation of retinal progenitor cells (RPC). Understandably, mature neural retina is more challenging to differentiate in culture, given its complex interconnected laminations. However, RPC have been successfully grown from stem cells and transplanted into animal models with the hope that these progenitor cells can continue differentiation into mature retinal cells in the host.

Several groups developed methods of differentiating stem cells into three-dimensional, spherical organoids composed of retinal progenitor cells [31-34]. The organoids (referred to in the literature as optic vesicles) contained cells that expressed developmental markers for photoreceptor, amacrine, horizontal and ganglion cells; with time in culture, the cells within optic vesicles self-organize into crude laminations [32,35]. One group demonstrated electrical excitability in these optic vesicles, indicating functional synaptic connectivity among the cells. The generation of these stem cell-derived optic vesicles offers a method of increasing production efficiency of neural retinal tissue for transplantation. However, the spherical geometry of the organoids makes them unsuitable for implantation, because they fail to flatten and simultaneously interact with the RPE and neurosensory retina. As models of retinal differentiation, they should prove valuable for studying the mechanisms of retinal disease and potential medical therapies.

Transplantation with immature RPC also has had positive results in animal models. Transplanted stem cell-derived retinal precursor cells migrated into and integrated structurally with the host retina, showing synaptic interaction with the host [12,36-38]. Furthermore, better visual function was assessed by optokinetic testing, electroretinogram, and visual cortex activity in transplanted animals compared to control [37,39] Like stem cell-derived RPE, the stem cell-derived neural retinal cells are well tolerated in the recipient. However, there is still little data on long-term survival of these stem cell derived-retinal progenitor cells, and whether vision can also be rescued long-term. These encouraging results highlight the need for more validation studies in preclinical models.

Conclusion

Researchers have successfully differentiated retinal cells from ESC and iPSC. Retinal culture systems, such as the three-dimensional organoids, allow the study of retinal development, mechanisms of disease, and provide tissue for transplantation in retinal diseases. There is continued modification and optimization of these differentiation methods. Both stem cell-derived RPE and retinal progenitor cells have been transplanted in animal models and exhibited graft survival and possible visual improvement. For human patients, early phase trials demonstrated good tolerability of transplantation. More clinical studies are needed to validate the efficiency of retinal transplantation.

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