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REVIEW

Importance of the stem cell microenvironment for ophthalmological cell-based therapy

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Abstract

Cell therapy is a promising treatment for diseases that are caused by cell degeneration or death. The cells for clinical transplantation are usually obtained by culturing healthy allogeneic or exogenous tissue *in vitro*. However, for diseases of the eye, obtaining the adequate number of cells for clinical transplantation is difficult due to the small size of tissue donors and the frequent needs of long-term amplification of cells *in vitro*, which results in low cell viability after transplantation. In addition, the transplanted cells often develop fibrosis or degrade and have very low survival. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPS) are also promising candidates for cell therapy. Unfortunately, the differentiation of ESCs can bring immune rejection, tumorigenicity and undesired differentiated cells, limiting its clinical application. Although iPS cells can avoid the risk of immune rejection caused by ES cell differentiation post-transplantation, the low conversion rate, the risk of tumor formation and the potentially unpredictable biological changes that could occur through genetic manipulation hinder its clinical application. Thus, the desired clinical effect of cell therapy is impaired by these factors. Recent research findings recognize that the reason for low survival of the implanted cells not only depends on the seeded cells, but also on the cell microenvironment, which determines the cell survival, proliferation and even reverse differentiation. When used for cell therapy, the transplanted cells need a specific three-dimensional structure to anchor and specific extra cellular matrix components in addition to relevant cytokine signaling to transfer the required information to support their growth. These structures present in the matrix in which the stem cells reside are known as the stem cell microenvironment. The microenvironment interaction with the stem cells provides the necessary homeostasis for cell maintenance and growth. A large number of studies suggest that to explore how to reconstruct the stem cell microenvironment and strengthen its combination with the transplanted cells are key steps to successful cell therapy. In this review, we will describe the interactions of the stem cell microenvironment with the stem cells, discuss the importance of the stem cell microenvironment for cell-based therapy in ocular diseases, and introduce the progress of stem cell-based

therapy for ocular diseases.

Key words: Microenvironment; Niche; Stem cell; Cell-based therapy; Ocular diseases; Ophthalmology

Core tip: Cell therapy is a promising treatment for the diseases caused by cell degeneration or death. However, the transplanted cells often develop fibrosis or are absorbed and cannot survive long. It is not simply because of seed cells, but also due to the cell microenvironment. How to reconstruct the stem cell microenvironment and strengthen its combination with the transplanted cells is the key to successful cell therapy. We will discuss the importance of the stem cell microenvironment for cell-based therapy in ocular diseases and introduce the progress of cell therapy for ocular diseases.

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INTRODUCTION

Limbal stem cell deficiency, corneal endothelial decompensation, corneal grafts endothelial decompensation, retinitis pigmentosa, age-related macular degeneration, Stargardt disease and other hereditary retinal diseases are all caused by cell degeneration or death. There is no effective clinical treatment currently available. Unlike traditional medicine or surgical therapy, cell therapy is a promising treatment and can treat the abnormal cells most directly and efficiently.

The road to cell therapy has been a long and tortuous process. In the early days, most of the efforts to obtain sufficient therapeutic seed cells were based on establishing cell lines or improving tissue culture methods with the expectation that they will provide therapeutic effects after the cell transplantation. The former long-term passaged cell lines were mainly obtained by transgenic or nuclear atypia. Because of biosecurity risks and allograft immune rejection, cells obtained by this method are mainly used for basic research[1]. The cells for clinical transplantation are usually obtained by culturing healthy allogeneic or exogenous tissue *in vitro*. It is hard to get large tissue from the eye to obtain a sufficient amount of cells and the culture often needs to go through long-term amplification *in vitro*, resulting in low cell viability after transplantation. Cells often develop fibrosis or are absorbed and cannot survive long. Thus, the desired clinical effect of the cell therapy cannot be accessed and so it was shelved for a while.

Considerable progress has been made in the induction and differentiation of embryonic stem cells (ESCs) since the last century and it brought new vitality to cell therapy. However, the differentiation of ESCs can bring immune rejection, tumorigenicity and differentiation of uncertainty, which limits its clinical application. Although induced pluripotent stem cells (iPS) can avoid the risk of immune rejection caused by ESC differentiation post-transplantation, the low conversion rate and the risk of tumor formation still exists and the potentially unpredictable biological danger achieved through genetic manipulation hinders its clinical application. Thus, cell therapy returns to the transplantation of the cultured autologous cells, especially the enriched stem cells and the methods and the results have been greatly improved.

With the development of research, it is increasingly recognized that the reason the implanted cells cannot survive long-term in cell therapy is not simply because of seed cells, but also because of the cell microenvironment which determines cell survival, proliferation and even reverse differentiation. The birth of Dolly the sheep is the best example. In a good embryo environment, mature breast cells can be re-developed into a new individual sheep. From a biological point of view, whether it is a cell or an organism, it must exist in its surroundings with exchange material, energy and information. In terms of cell therapy, the transplanted cells need a specific three-dimensional structure to anchor and specific extra cellular matrix (ECM) components and cytokine biological information transfer to support their growth. These structures are present in the matrix in which the stem cells located and are called the stem cell microenvironment. The microenvironment interacts with the stem cells and they are interdependent, mutually promote and complement each other, working together to maintain the stem cell homeostasis[2-5]. A large number of studies suggest that exploring how to strengthen the organic combination of the transplanted cells and the stem cell niche and reconstructing the stem cell microenvironment is the key to successful cell therapy.

In this review, we will recount the interactions of the stem cell microenvironment with the stem cells, discuss the importance of the stem cell microenvironment for cell-based therapy in ocular diseases, and introduce the progress of stem cell treatment for ocular diseases.

THE ROLE OF THE STEM CELL MICROENVIRONMENT

Obtaining autologous cells for cell therapy aided by the stem cell microenvironment

In the process of inducing embryonic stem cells and iPS cell differentiation, it was discovered that the adult cells can induce embryonic stem cells to differentiate

and the embryonic stem cells can promote somatic cell proliferation, repair the defects of co-cultured cells, or even reverse the differentiation state of somatic cells[6-9] by improving the microenvironment *via* secreting a variety of factors and cell interactions, *etc.*

We began to work on the induction and differentiation of embryonic stem cells and epidermal stem cells[10-12] in 1997 and found that when the adult cells were treated with supernatant from cultured embryonic stem cells or co-cultured with the embryonic stem cells, the aging process of adult cells can be slowed down or even reversed into progenitor cells and their self-renewal and proliferation capacity can be increased significantly[13-18], whereas the adult cells can also induce embryonic stem cells to differentiate. We found a phenomenon that the corneal epithelial cells maintain long-term proliferative capacity and tissue-specific cell phenotype by factors secreted from murine ESCs. Rabbit corneal epithelial cells, cat corneal endothelial cells, rabbit skin epithelial cells and rabbit conjunctiva epithelial cells grew very well in culture medium with addition of ESC conditioned medium. These corneal epithelial cells were serially subcultured for more than 20 passages and maintained high cell purity, cobblestone-like morphology, enhanced colony forming efficiency, normal diploid and capacity to regenerate a functional stratified corneal epithelial equivalent. The rabbit corneal epithelial cells cultured in the embryonic stem cell microenvironment can be continuously passaged over 55 generations in 22 wk, gradually restoring its precursor characteristics, such as: decreased corneal epithelial cell specific differentiation markers K3/K12 expression, increased corneal epithelial precursor cell markers *P63* and *ABCG2* expression, but the expression of *Oct-4* was not detected, indicating that the embryonic stem cell microenvironment treated cells obtained a strong proliferative capacity without the potential tumorigenicity and uncertain differentiation[13-18]. Zhang *et al*[13] also found that the proliferation and maturation of the dendrite cells co-cultured with the bone marrow mesenchymal cells were able to be significantly promoted, with the enhanced precursor cell marker expression and reduced expression of differentiation markers, so that the mature dendritic cells were reversed to the original progenitor cell stage. Pearton *et al*[9] reported that mouse embryonic skin can induce the terminal rabbit central corneal epithelial cells to reverse to the limbal stem cells by gradually losing specific marker K12 and K3. These results strongly suggest that the stem cell microenvironment can significantly regulate adult cell proliferation. It has the potential to become a more effective and safe method to access autologous seed cells with high proliferative activity which are close to pluripotent stem cells or transient amplifying cells without uncertain differentiation direction or tumorigenicity and render them more suitable for clinical use.

Repair of the stem cell microenvironment is the basis for long-term efficient cell-based therapy

Stem cell microenvironment is the general term of the three-dimensional structure and a variety of signaling molecules (growth factors and their receptors, hormones and signaling molecules) present in the stroma where the stem cells reside and it can regulate the fate (proliferation/differentiation) of the stem cells. Because of its specific three-dimensional structure, it is vividly called niches (niche), which consists of three components: the extracellular matrix (ECM), niche cells (supporting cells, stem cells) and soluble factors derived from the niche cells (Figure 1). The proliferation and differentiation of stem cells are pre-programmed by themselves and are also affected by the microenvironment where they are residing. The stem cell microenvironment can anchor stem cells *in vivo* and regulate the self-renewal and production of their progeny cells through cell-cell, cell-ECM and cytokine-cell interactions. The different macromolecules or properties of the cells and ECM interact with each other in a complex and dynamic network[19,20]. Nowadays, there is increasing evidence showing that the ECM is not only the supportive scaffold but also plays a fundamental role in cell biology. It plays important roles in the development of the cells and can regulate their behavior[21] by the production, degradation of its components and the remodeling of the structure[22,23] and the direct and indirect signaling properties[21]. The polarity, division and migration of the cells can be influenced by the physical properties of the ECM, such as rigidity, porosity, topography and insolubility[24]. Cytokines play an important role in exchanging information from cell-cell and cell-ECM. The changes of the extracellular matrix components also affect the differentiation of the stem cells and the induced differentiation *in vitro* is accomplished by mimicking the cell microenvironment. So, it is difficult to obtain a long lasting therapeutic effect in cell-based therapy without the support of a good stem cell microenvironment, even when excellent cells are transplanted.

The importance of stem cell microenvironment in tissue engineering has also been verified. How to rebuild the stem cell microenvironment becomes the biggest challenge currently for constructing tissue engineered tissues and organs. In the past, because the scaffolds for tissue engineering of organs and tissues had no such sophisticated stem cell microenvironment, the desired therapeutic effect could not be achieved and the structure and function could not be completely recovered after transplantation. In 2009, we introduced phospholipase A2, which can specifically hydrolyze the phospholipids of the corneal stroma cell membrane, can destroy the cell structure and be used to prepare acellular porcine corneal stroma acellular porcine corneal stroma

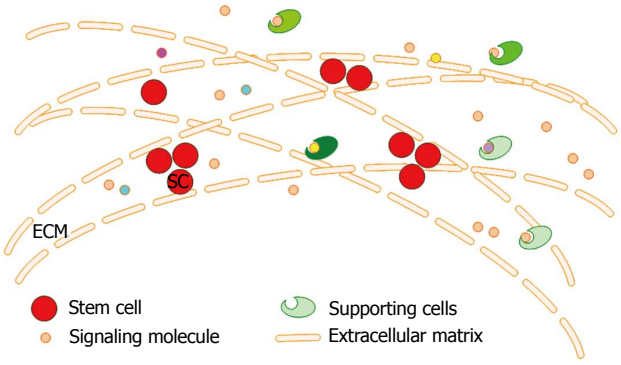

Figure 1 Schematic overview of the stem cell microenvironment components. ECM: Extra cellular matrix; SC: Stem cell .

(APCS) for biological tissue engineering cornea[25]. The natural corneal collagen structure and 80% of the extracellular matrix components can be retained by this means. This APCS not only has good biocompatibility and biomechanical strength, but also keeps the limbal stem cells microenvironment necessary for their long-term proliferation. The grafts of APCS maintained good biomechanical strength and high transparency post-transplantation in animal experiments and it can help to rebuild the limbal stem cell microenvironment[26-30]. Nakayama *et al*[31], Ott *et al*[32], Petersen *et al*[33], Uygun *et al*[34] and Conrad *et al*[35] have also reported the use of acellular matrix as a scaffold in tissue engineering in kidneys, lungs, heart, trachea and bladder. As Song *et al*[36] stated, using an acellular matrix scaffold with natural extracellular matrix to build tissue engineering products can mediate organ development, reparation and regeneration which cannot be accessed by synthetic materials. There are further experiments that proved that the acellular materials with extracellular matrix play an important role in the regulation of stem cells[37]. These studies showed that a decellularized tissue with the natural ECM scaffold can induce the stem cells to differentiate into cell types present in certain tissue[31] and thus the decellularized organ has already been used in tissue engineering and cell therapy[31,36].

The microenvironment has a great effect on the fate of stem cells. In recombination experiments, hair follicle stem cells were induced to differentiate into corneal epithelial cells when they were cultured in a limbus-specific-like niche[38]. These cells grow into stratified epithelium and express the cornea-specific markers K12 and Pax6 while the epidermal specific K10 obviously down-regulated[38]. While in other studies the rabbit epithelial cells from the central cornea differentiated into epidermal keratinocytes when recombined with mouse embryonic dermis, it lost corneal-specific marker K3/K12 together with the down-regulation of Pax6 and expressed keratinocyte marker K5/K14[9]. All of these changes showed that the microenvironment has an important regulation role in the fate of the stem cells.

Stem cells can sustain and repair the structure and the function of the niche

On the other hand, evidence *in vivo* showed the relevance of the ECM and the stem cell behavior in that the altered properties or the aged niches' ability of maintaining stem cells' stemness can be reduced[39] and it further affected stem cell proliferation and updated, which created a vicious cycle. Scientists from Harvard University attempted to study the relationship between human aging and microenvironmental changes between stem cells via the stem cell microenvironment (niche) and they found that altering the aged microenvironment with the young microenvironment can improve the ability of the proliferation and renewal of the stem cells. The study also found that adding "insulin-like growth factor-1" (IGF-1) can also improve the state of the aging stem cell microenvironment.

Cell receptors can directly mediate the interactions between the stem cells and the ECM where they are located. It was also found that integrins, a large family of heterodimeric transmembrane receptors, are important receptors for the ECM-stem cell interactions and can regulate cell survival, migration, proliferation and differentiation by connecting the ECM to the intracellular cytoskeleton[40] as well as the adhesion, anchorage and homing of the stem cells. Different kinds of integrins bind to different ECM components or different cell surface adhesion molecules and receptors[41-43]. Integrins can regulate the self-renewal and proliferation of the stem cells by directly activating focal adhesion kinase (FAK) and the phosphoinositide 3-kinase (PI3K) signaling pathway[40,44,45]. The $\alpha 6\beta 1$ integrin can bind to the ECM protein laminin and help the spermatogonial stem cells home in to the testicular niche[46] and NSCs (neural stem cells) adhere to the vascular niche[47]. The $\alpha 9$ integrin is essential for the proliferation of the HSC[48] and NSC microenvironment[49] *via* binding protein tenascin-C in the ECM. The $\alpha 4$, $\alpha 6$, $\alpha 9$ and $\beta 1$ integrin chains are also important to the HSCs in their homing in to the bone marrow niche[50-53]. HSC homing and proliferation are also regulated by $\alpha v\beta 3$ integrin[54-56]. Furthermore, $\beta 1$ integrins can control the balance between symmetric and asymmetric divisions in skin and brain, as well as the differentiation and self-renewal of the stem cells[57-60] by regulating the activity of the Notch pathway and EGF receptor[61,62]. They are also important for the proliferation of intestinal stem cells (ISCs) *via* the Hedgehog signaling pathway[63]. Signaling pathways of the growth factors and cytokines, such as IL-3 and TGF-β[43,64-67], can also be regulated by integrins and these signaling pathways can regulate the expression of integrins conversely[46]. Therefore, the receptors

have specific activities in a certain kind of stem cell microenvironment.

Some ECM components can regulate their availability by setting a biochemical gradient and binding growth factors[21]. On the one hand, the ECM can also make the growth factors insoluble, unavailable or not bioactive and serve as the reservoir for them, like proteoglycans, collagens, fibronectin and vitronectin, which bind VEGFs, FGFs, HGFs, TGF-β and BMPs. On the other hand, ECM proteins and proteoglycans can be induced to be soluble and remodeled to release and distribute growth factors under the action of enzymes, such as metalloproteinase[21]. The function NSC can be favored by the ECM components in its niche by promoting growth factor activity *via* capturing FGF-2 from it[68,69]. Similarly, in the procedure of the regulation of muscle satellite cells, all kinds of growth factors bind to the cell surface or the basal lamina proteoglycan and then they can be activated in a certain signaling pathway[70].

The biophysical properties of the ECM can determine the behavior of stem cells. The balance of the internal forces generated by cell cytoskeleton tension and the external forces from the compression of the neighboring cells and the stiffness of the surrounding ECM maintains the shape of the cells and makes them stay in their anatomical localization[71], which can regulate the cell behavior finally[72-74]. Recently, the YAP/TAZ transcriptional factors were found to have key biological effects on the ECM elasticity, cell geometry and cytoskeletal modulation[71,74,75] among the mechanotransduction pathways (Wnt/β-catenin, PI3K/Akt, TGF-β, Ras/MAPK, and RhoA/ROCK pathways). In fact, ECM organization and composition can regulate tissue stiffness and then have an influence on the stem cell behavior[72,76]. The human mesenchymal stem cells can express organ-specific transcription factors and differentiate into myoblasts, neurons and osteoblasts[77] when they are cultured on ECMs with similar stiffness of the muscle, brain or bone respectively. Culture on hydrogel with the same elastic modulus as the bone marrow can increase the self-renewal ability and maintain multipotency of the hMSCs (human mesenchymal stem cells) compared to those cultured on stiffer substrates[78]. NSCs cultured on hydrogel with similar stiffness to the brain tissue gain the neuronal differentiation potential, while the stiffer gels make them differentiate into glial cells[79]. That the stiffness gradients of the hippocampus regulate NSC behavior *in vivo* confirmed that ECM and its biomechanical properties play important roles in the fate of the stem cell[80]. This opens new insights in to the role of ECM mechanical properties in the stem cell microenvironment.

Stem cells in ocular tissues: Several studies showed the conjunctiva epithelial stem cell niche located in the fornix by growth potential assays, label-retention analyses and keratin expression detection[81-84]. They have bipotential to differentiate into both epithelial cells and goblet cells[85].

Corneal epithelial stem cells resident at the basal limbal epithelium and called limbal stem cells were first applied to clinical use in ophthalmology. Tung-Tien Sun's group did immunostaining with monoclonal antibodies against the corneal-specific K3[86] and showed the negative expression of K3/K12 in the limbal basal layer, which gave rise to a number of experiments that verified that the corneal stem cells were located in the limbus[86-88]. These label-retaining limbal cells[89] have a higher proliferative potential[90] and colony-forming ability[91] compared with central ones.

People made efforts to find specific molecules markers of the limbal stem cells. p63[92], vimentin[93-95], α-enolase[96,97], α9β1 integrin[98], tenascin-C and EMILIN1[99], ABCG2[100-103] and ABCB5[104] are all highly expressed in the basal layer of limbal epithelium but none of them are the specific markers of the limbal stem cells as expected. This is because the early differentiating cells[105,106] still have the stem cell markers and show intermediate profiles between stem and differentiated cells until the stem cell markers are down-regulated with the expression of the differentiated phenotype[107]. Thus, we can only enrich the stem cells while separating them with these molecules markers[108].

Since it is complex and difficult to characterize the corneal stem cells, people try to identify them by analyzing their niches and the regulatory functions of the niche.

The limbus is a specific region which is characterized by the palisades of Vogt with the papillae-like projections and the vascular net in the peripheral cornea[109]. It enables the epithelial cells to interact with ECM and chemical signals diffused from the vascular network[110]. Some studies showed that the limbus has a specific anatomic structure such as the niche, the LEC (limbal epithelial crypt) or LC (limbal crypt), which consists of a cord or finger of cells that are located between the palisades of the limbal stroma and extends radically to the conjunctiva stroma[92,93]. The high expression of K14[111], ABCG2[112] and p63[92,93] in cells at the LEC[112]/LC[113] suggest that they are the microenvironment of the limbal stem cells but the LEC/LC structure has not been found in other species besides humans and pigs[94].

This tissue with unique cellular properties can synthesize different kinds of ECM substrates. Several studies on the ECM components of the cornea were performed regarding the aspect of the biochemical and immunological characteristics. Corneal stroma comprises collagen type Ⅰ-Ⅵ[114-117], glycosaminoglycans (chondroitin, heparin, dermatan) and keratan sulfates[118-122], fibronectin and laminin[105,123] and hyaluronic acid[124] and the limbal epithelial cells are more likely to adhere to a rougher surface than those in the central cornea[125]. To further study the interaction between corneal stem cells and their

microenvironment and the different functions between the central cornea and the limbus, the corneal basement membrane components were analyzed by several studies. These studies found that the conjunctiva, limbal and central corneal epithelia have a heterogeneous composition of the basal membrane (BM)[126]. Some studies reported that there was no collagen Ⅳ in the central cornea BM[127], while others had the controversial results that collagen Ⅳ presented both in the limbal and the central corneal BM[126]. Later, people found that collagen IV α1 (Ⅳ) and α2 (Ⅳ) chains show more intense staining at the corneal limbus and the α3 (Ⅳ) chain shows an abrupt decrease at the limbus[128,129], while collagen types Ⅳ (α3-α4 chains) and XII are only expressed in the central cornea[128]. Then, other components of the limbal BM were studied further. Laminin α2-α5, β1-β3, γ1-γ3, nidogen-1, -2, SPARC/BM-40, as well as agrin are preferentially expressed in the limbal BM[128], which colocalized with the ABCG2/p63/K19-positive and K3/Cx43/desmoglein/integrin-a2-negative stem cells and early progenitor cell clusters[128,129]. The BM components, such as type XVI collagen, fibulin-2, tenascin-C/R, vitronectin, bamacan, chondroitin sulfate and versican, are colocalized with the putative vimentin-positive late progenitor cells[128-130] at the limbus. On the contrary, type Ⅴ collagen, fibrillin-1 and 2, and thrombospondin-1 were almost only found in the corneal BM[128]; others, such as type Ⅳ collagen α5 and α6 chains, collagen types Ⅶ, XV, XVII and XVIII, laminin-111, laminin-332, laminin chains α3, β3 and γ2, fibronectin, matrilin-2 and 4, and perlecan, were expressed throughout the epithelial layer on the ocular surface[129,130]. All these studies showed that the BM at the limbus has a specific ECM composition which is different from that in the peripheral or central cornea. This suggested that the EMC at the LEC/LC created a microenvironment that regulates stem cells and their progeny by supporting stemness while inhibiting the differentiation and preserving the proliferative abilities in limbal cells.

The stem cells of the corneal endothelium and the trabecular meshwork are believed to be located at the transition zone between the peripheral corneal endothelium and the anterior non-filtering portion of the trabecular meshwork[131]. Corneal stroma stem cells are located in the limbal stroma, play roles in visualization and have corresponded to the limbal niche cells[132].

At the early stage, the stem cells of the lens were assumed to be the label-retaining cells which are located at the anterior central region of the lens[133]. Yamamoto *et al*[134] concluded that the germinative zone of the lens epithelium contains transient amplifying cells with the positive expression of proliferation markers, such as A1, B1, C and D1 cyclins and PCNA (proliferating cell nuclear antigen), and can be labeled by BrdU (5-bromo-2'-deoxyuridine). On the other hand, other studies showed that they were probably located in the region anterior to the germinative zone. However, Remington *et al*[135] assumed that lens stem cells resided in the ciliary body because the lens is non-vascular, its epithelium does not have the morphology of other stem cells and no type of tumors are derived from the lens. Thus, the existence of the lens stem cells remains controversial and needs to be elucidated.

Previously, it was believed that there were no stem cells in the mammalian retina since it cannot regenerate[136] but von Leithner *et al*[137] found retinal precursors in the peripheral retinal pigment epithelium later. However, the cells from the pigmented ciliary margin were later found to have the ability to form spherical colonies and produce various types of differentiated retinal cell[138]. These results gave the evidence that retinal stem cells are located in the pigmented ciliary margin epithelium.

CELL-BASED THERAPY IN OCULAR DISEASES

Progress in the research of stem cell therapy for corneal diseases

Limbal stem cell deficiency can be caused by a myriad of insults that present with the following pathological states: damaged corneal barrier function, persistent corneal epithelium defects or recurrent corneal erosions, chronic inflammation associated with corneal stromal scarring, visualization, conjunctivalization and eventually blindness. Some researchers speculate that this occurs due to gradual deterioration of the limbal stromal niches[139]. Thus, limbal epithelial stem cell transplantation and the reestablishment of the limbal stem cell microenvironment are necessary for ocular surface reconstruction in these diseases[139].

Autologous or allogenic limbal transplantation has achieved good clinical efficiency in the treatment of limbal stem cell deficiency. However, in successful cases post limbal transplantation, there is a doubt as to whether there is a causal relationship between the survival of the donor limbal stem cells and the clinical effect. Shimazaki *et al*[140] detected the presence of donor-derived epithelial cells in 60% of cases (10 eyes/9 cases) post human limbal transplantation with fluorescence in situ hybridization assay, with 77.8% by RFLP analysis. At the same time, the authors stated that there was no difference in the postoperative clinical outcomes whether the presence of survived donor-derived cells was detected. Thus, more studies should be carried out to confirm the clinical significance of the survival of donor cells. Furthermore, it was reported that donor-derived cells were undetected in cases with objective clinical improvement after three to five years post limbal transplantation, even with DNA fingerprinting analysis[141]. This suggested that the survival of

donor-derived cells is not essential for improvements of the clinical symptoms. These results indicated that limbal transplantation might simply serve as the corneal stroma transplantation. Presumably, limbal transplantation improves the residual stoma stem cell microenvironment, making residual stem cells in the patient regenerate on the ocular surface and allowing for improvement of the ocular surface[142]. Therefore, some scholars believe that the essence of limbal transplantation may be the restoration of the limbal stroma resulting in increased stability of the limbal stem cell "niche"[143]. So, limbal epithelial stem cell deficiency treatment lies in the application of various methods to restore the normal limbus matrix.

Although traditional corneal transplantation, limbal transplantation, has already achieved good results in ocular surface reconstruction for corneal diseases, there still several problems that have hindered clinical application, such as the shortage of donors, the immune rejection post-transplantation and other issues. Therefore, the construction of tissue engineering cornea *in vitro* with appropriate biomaterials and synthetic materials is the hope for solving these questions. How to get a sufficient amount of high activity seed cells for tissue engineering has been the challenge for tissue engineering product construction and cell therapy. The microenvironment plays an important role in the survival and development of cells and tissues. The microenvironment or simulated microenvironment can effectively induce ES and iPS differentiation in a certain direction and the embryonic microenvironment also has the effect of reverse differentiation of the adult cells. We have considered two aspects in our studies: (1) cellular microenvironment: embryonic stem cell microenvironment culture systems can make the differentiated corneal epithelial cells, conjunctiva epithelial cells[15] and even human corneal endothelial cells[17] obtain a strong proliferation ability and can be passaged long-term with de-differentiation cell marker expression, normal cell morphology and karyotype, but no tumorigenicity. Our preliminary findings showed that the ES microenvironment may inhibit the apoptosis of the cells by activating telomerase *via* integrin the b1-FAK-PI3K/Akt, telomerase-p21-mitochondrial axis and FAK/Wnt signaling pathway[18,144]; and (2) stromal microenvironment: the APCS limbal produced by lipase (not existing protease digestion)[25,30] can retain the normal extracellular matrix, collagen lamellar micro ultrastructure. It can repair and maintain the stemness and proliferation ability of the limbal stem cells after it is transplanted to the limbal stem cell deficiency rabbit model. In short, the microenvironment can be used to obtain sufficiently pure seed cells with strong proliferation capability but no immunogenicity. The microenvironment plays an important role in cell therapy and is the basis for the long-term efficacy of the treatment. Establishment of seed cells using the microenvironment will make cell therapy return to autologous cell transplantation. Maintaining the specific three-dimensional structure and the extracellular matrix to promote the proliferation and long-term survival of the transplanted cells[145] has great meaning. Professor Ott *et al*[32] stated that acellular matrix has a natural extracellular matrix which can mediate and guide organ development and mediate repair and regeneration. The key steps for the best clinical efficacy of cell transplantation are the long-term survival of the seed cells and the reconstruction of the stem cell niche.

Progress in the research of stem cell therapy for the retinal and optic nerve diseases

Retinal stem cells and optic nerve repair: Retinal diseases such as age-related macular degeneration, Leber congenital amaurosis and cone rod dystrophy are caused by lesions of retinal neuronal cells, which have an irreversible pathological process of degeneration and damage of the retinal neuronal cells, causing serious visual impairment or even blindness which currently cannot be effectively treated. Since the stem cells have self-renewal and multi-differentiation potential abilities, using stem cells as donor cells for retinal diseases treatment has become a hot topic.

In 2000, Wirtschafter *et al*[83] found that groups of self-renewing cells in the ciliary epithelium of the adult mice can form neurospheres when they were cultured *in vitro*. They can be induced to differentiate into specific types of neuronal cells in the retina, such as the rod cells, bipolar cells and glial cells, indicating that retinal stem cells exist in adult mammalian eyes. Ballios *et al*[146] found that retinal stem cells (retinal stem cell, RSC) also exist in the ciliary margin zone in people of different ages. These cells have proliferative capacity *in vitro* and can be induced to differentiate into different retinal neurons. Some of these stem cells can migrate and integrate into the host retina and can even differentiate into photoreceptor cells. These studies suggested that RSCs from different sources of animals or humans can survive and migrate to the host retina layers after transplantation. Although the implanted RSCs can migrate into the retina and differentiate into a variety of retinal cells, most transplanted RSCs remain in the subretinal space or the vitreous body, while less can be integrated and induced to differentiation, so the efficiency is not ideal.

Meyer *et al*[147] transplanted GFP-labeled ESCs into mouse vitreous after induced differentiation and found that the transplanted cells can migrate into the entire retina layers and differentiate into retinal neurons cells with the expression of markers such as NeuN, calretinin and cPKC-a. In 2010, Parameswaran *et al*[148], using a similar method as embryonic stem cell differentiation, completed the differentiation of mouse iPS cells into retinal ganglion cells, which not only highly express the retinal ganglion cells

regulation gene *Ath5*, *Wtl*, *Brn3b*, *Rpfl* and *lrx2*, but also can specifically project upwards to the superior colliculus with the synapse structure formation which has a sensitive tetrodotoxin voltage-dependent sodium current. This fully proved that iPS cells can differentiate into retinal ganglion cells. In glaucoma and traumatic optic neuropathy, the regeneration of retinal ganglion cells may be the only way to restore vision. The finding that iPS cells can differentiate into retinal ganglion cells provides a new method for the treatment of such diseases.

Arnhold *et al*[149] found that the cones cannot survive without healthy rod cells. Therefore, it is difficult to achieve the aim of the treatment by simply transplanting the induced iPS cells into the retina of patients with retinitis pigmentosa because the rod cells will eventually die.

Stem cell treatment for retinitis pigmentosa: Retinal pigment epithelium (RPE) is a single layer of epithelium with polarity and a rich pigment that is located between the neural retina and choriocapillaris layer. It can support the metabolism and activities of the retinal photoreceptor cells and phagocytose the outer segment photoreceptors. Recent studies show that the retinal pigment epithelium also has self-renewing stem cells that can be induced to form other cell types under suitable conditions.

RPE degeneration diseases caused by age-related macular degeneration (AMD), hereditary retinal degeneration, macular dystrophy and Stargardt disease result in the death of photoreceptors and neural retina and eventually cause blindness. There is currently no effective treatment for retinitis pigmentosa. The transplantation of the induced differentiated stem cells to establish the retinal pigment epithelium membrane *in vivo* has been studied extensively but it is still far from functional reconstruction. Thus, looking for new ways to stimulate the repair of RPE is an important research direction for the future. With the rise of regenerative medicine research, stem cell transplantation as a regenerative therapy becomes a hotspot for research. In the past decade, scholars induced bone marrow mesenchymal stem cells, iPS cells and embryonic stem cells to differentiate into retinal pigment epithelial cells but the process of differentiation into RPE cells is not clear and only a small fraction of cells can be differentiated into RPE cells. So, the research of finding the desired factors to directly induce cell differentiation is still very popular.

In 2010, Geron biopharmaceutical company (Geron, United States) sponsored the world's first clinical trial on using hESC to repair damaged nerves. Currently, the United States Food and Drug Administration has approved the ACT company (Advanced Stem Cell Technologies) to carry out two Phase II clinical trials on using embryonic stem cells to treat macular degeneration in the United States, dry AMD and juvenile macular dystrophy (Stargardt disease). This time, they induced hESCs to differentiate into retinal epithelial cells with purity over 99%. Approximately 50000 retinal pigment epithelial cells were isolated and injected into the retina of two patients. Four months later, the researchers found that RPE had been completely replaced by the injected retinal epithelial cells. They measured the visual acuity of the two female patients and the data confirmed that the injected cells survived and largely improved their vision. Early data suggest that hESC therapy is not only safe but also efficient. The research paper was published in the world's oldest and most respected peer-reviewed medical journal, "The Lancet"[150]. These results from ACT have brought new optimistic hope for stem cell research. This same study found that it is crucial that the transplanted cells can attach to the Bruch's membrane and integrate into the host RPE layer and survive to have a successful therapeutic effect[149].

CONCLUSION

In summary, recent studies show that real cell therapy is not a simple supplement of cells. The interaction, interdependence, mutual promotion and supplementation between the transplanted cells and the microenvironment are more important. The microenvironment of the recipient can regulate the transplanted cell behavior and decide their fate. The transplanted cells cannot survive long-term without the support from the microenvironment of the recipient. The survived transplanted cells can not only completely replace the recipient's cells, but also supplement the sufficient quantity and function of the recipient's cells. More importantly, they are involved in the cellular microenvironment reconstruction so the stem cells obtain a stronger self-renewal capacity and proliferation ability. Therefore, in order to improve clinical cell therapy, we should pay more attention to the characteristics and components of each stem cell microenvironment and put efforts into understanding the regulation mechanisms of the stem cell microenvironment[151].

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