World Journal of Stem Cells

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DOI: 10.4252/wjsc.v7.i1.160

World J Stem Cells 2015 January 26; 7(1): 160-164
ISSN 1948-0210 (online)

Stem cell therapy for retinal diseases

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Telephone: +55-62-35211000
Received: July 29, 2014
Peer-review started: July 29, 2014
First decision: August 14, 2014
Revised: September 26, 2014
Accepted: October 14, 2014
Article in press: December 16, 2014
Published online: January 26, 2015

Abstract

In this review, we discuss about current knowledge about stem cell (SC) therapy in the treatment of retinal degeneration. Both human embryonic stem cell and induced pluripotent stem cell has been growth in culture for a long time, and started to be explored in the treatment of blinding conditions. The Food and Drug Administration, recently, has granted clinical trials using SC retinal therapy to treat complex disorders, as Stargardt's dystrophy, and patients with geographic atrophy, providing good outcomes. This study's intent is to overview the critical regeneration of the subretinal anatomy through retinal pigment epithelium transplantation, with the goal of reestablish important pathways from the retina to the occipital cortex of the brain, as well as the differentiation from pluripotent quiescent SC to adult retina, and its relationship with a primary retinal injury, different techniques of transplantation, management of immune rejection and tumorigenicity, its potential application in improving patients' vision, and, finally, approaching future directions and challenges for the treatment of several conditions.

Key words: Macular degeneration; Human embryonic stem cell; Induced pluripotent stem cell; Retinal pigment epithelium; Stargardt's disease

Core tip: The stem cell (SC) retinal therapy has turned into an potentially useful way of treating blinding disorders, such as, Stargadt's dystrophy, and geographic atrophy. The Food and Drug Administration's approval for clinical trials using SC retinal therapy, and its good results, may appoint to future promising outcomes, providing an anatomical restoration of the retina, and a functional improval of visual function of several patients.

Garcia JM, Mendonça L, Brant R, Abud M, Regatieri C, Diniz B. Stem cell therapy for retinal diseases. *World J Stem Cells* 2015; 7(1): 160-164 Available from: URL: http://www.wjgnet.com/1948-0210/full/v7/i1/160.htm DOI: http://dx.doi.org/10.4252/wjsc.v7.i1.160

INTRODUCTION

The retina is the light sensing, innermost part, in a multilayered structure that relays information to the occipital cortex of the brain *via* the optic nerve. The photoreceptors layer is located in the outer retina, and plays a major part in light perception and the phototransduction[1,2]. The retinal pigment epithelium (RPE) is placed between the adjacent photoreceptors, and the underlying pentalaminar Bruch's membrane[3]. It provides both metabolic and

functional support of photoreceptors, replenishing bleached photopigments that, after a photon is absorbed, initiates the phototransduction, through an active participation from the RPE and the photoreceptors[1,2]. The RPE forms with the photoreceptors a functional unit, and its optimal functioning is critical to sight[1,4]. Loss of the integrity of this unit, promotes apoptosis or degeneration of the photoreceptors[1,2].

Retinal degeneration occurs in several forms, such as age related macular degeneration (AMD), Stargadt's macular dystrophy and retinitis pigmentosa (RP)[2,4,5]. The AMD has a multifactorial pathophysiology, which results in photoreceptors degeneration in the macula. However, the inner retina remains intact, becoming suitable to the possibility of photoreceptors replacement as a potential therapy[2]. Therapeutic options that could substitute affected retinal layers, aim to replace lost or injured retinal components, and reestablish the interaction concerning RPE and photoreceptors[2,5,6]. Autologous full thickness grafts have been used most commonly in humans, but the pursuit for the best method to replace RPE is still ongoing[7].

STEM CELLS AND CELL REPLACEMENT

After recent advances in regenerative medical treatment, the stem cell (SC) therapy started to be actively explored for eventually blinding retinal conditions. SC could be defined as pluripotent, with ability of self renewal, and able of differentiate or just be maintained quiescent, in order of a damage, following injury or stress[8,9]. The introduction of the concept of SC therapy, after bombings in Hiroshima and Nagasaki, discovered that bone marrow (BM) transplanted into irradiated animals produced hematopoiesis. Hematopoietic SC (HSC) were identified in 1961, and their ability to migrate and differentiate into multiple cell types was documented[8-10].

SC transplants may be xenogenic (from another species), allogenic (from another individual) or autograft (from the same individual)[2,4]. The immunological ocular privilege provides, both allogenic and xenogenic intraocular grafts, a long term survival, when compared with similar grafts[11]. The human embryonic (hESC) and the induced pluripotent (iPSC) consist, at this moment, as the major forms of retinal SC therapy[4]. The hESC are derived from blastocysts, left from procedures of "*in vitro*" fertilization. They can remain undifferentiated, or develop into a settled differentiated population. Takahashi and Yamanaka, reprogrammed peripheral normal adult fibroblasts and lymphoblasts, into human iPSC[1,12]. Both hESC and iPSC have similar characteristics and potential for retinal differentiation, with morphological similarities to the RPE, bringing a total new horizon for retinal degenerations, producing RPE in possibly unlimited amounts[1,4,7].

Human iPSC are normal fibroblasts or lymphoblasts, and can be obtained from any adult individual, including the patient itself[1,4]. The first findings about the hESC suggest that there was no sign of abnormal proliferation or growth, such as no immune mediated transplant rejection in the patients. However, the possibility of immune rejection, teratogenicity and ethical restrictions need to be firmly established before bringing hESC into clinical application[5].

The most common techniques of delivering SC are the intravitreal and the subretinal injections. The first approach resulted in a higher survival of SC, according prior reports. The subretinal pathway directs the material to targeted retinal regions with indicated treatment, promoting maturation of hESC RPC to photoreceptors[2]. Unfortunately, lack of integration is a problem when using a suspension as orientation, resulting in unsuccessful outcomes[2,7].

TARGET DISEASES

Loss of highly differentiated photoreceptors and RPE, is a common end point in retinal degenerations[12,13]. First described in medical literature in 1874, AMD still has no permanent solution. The dry form of AMD refers to the condition in which the retina accumulates amorphous deposits, called drusen, with gradual degeneration of the RPE[2,5]. In the wet form, CNV grow progressively, disrupting visual function. It may result in hemorrhagic alterations and fibrosis, affecting the macula[13]. In both types of AMD, loss of photoreceptors has been documented[5]. Current therapeutic options to the wet form include, photodynamic therapy (PDT) and, mainly, antivascular endothelial growth factor (anti VEGF) therapy[5]. The dry form remains an unmet medical need with no available treatment[5,12]. Hereditary retinal degenerations, including RP and Stargadt's macular dystrophy are important blindness related disorders[8,13]. RP is an inherited disorder in which rod photoreceptors degenerate initially, but all photoreceptors frequently become involved as well, leading to total blindness[2]. Stargardt's macular dystrophy was firstly described by Karl Stargadt, in 1905, and is the most common pediatric macular degeneration[12,14]. Patients with this condition usually present with macular atrophy[14].

RPE CELLS REPLACEMENT

The RPE is a hexagonal, monolayer of polarized pigmented cells, densely adherent to one another, as well as to the underlying Bruch's membrane. Among its many functions, it plays a major part in photoreceptor renewal[2,4,12,13]. The AMD is frequently pictured as a local disruption of the RPE photoreceptor unit. Moving photoreceptors to intact underlying regions of the retina had demonstrated good results[14,15]. Transplant rejection was not so manifested in dry form, as in other forms of this disorder[4]. The RPE replacement, prior the development of advanced stages, may signify a crucial alternative, requiring refined surgical methods[5]. The autologous RPE replacement is usually applied from RPE suspension, or autologous full thickness RPE and choroid transplantation. A clinical trial concluded that both had similar results[4,5]. RPE suspensions may product underprivileged orientation and survival, which is an important factor to be considered[2,4,5].

The transplantation of RPE polarized monolayer on a scaffold may provide higher integration and function[4,5]. So far, the parylene membrane has been the only scaffold experienced for subretinal delivery, resulting in a good biocompatibility in RCS rats after implantation[4,12,13]. The RCS rat is a model used in disorders involving the outer retina[11,13]. Genetic studies have demonstrated that Mer is essential for RPE function, and its absence results in inherited abnormal phagocytosis of the photoreceptor outer segment, photoreceptor degeneration and retinal atrophy within 2 mo of birth[1,5,16,17]. Prasad *et al*[17], in 2006, demonstrated the action of Mer, suggesting that the Protein S is a biologically relevant ligand.

The natural formation of hESC into RPE is the most commonly used process to generate this material[18]. Reestablishment of the normal interface had demonstrated good results[14,15]. The hESC initially overgrow in a supplemented hESC medium, until formal contact of its borders. At this point, it is performed the removal of bFGF, and changed until they start to show RPE as a truly small, hexagonal and pigmented morphology[11,13]. In 2004, Haruta demonstrated the generation of RPE derived from hESC, indicating functional recovery and biological function of phagocytosis[1,2,16]. The hESC RPE not only display consistent structure with adult RPE, but also exhibit resemblances, as the ability to phagocytes photoreceptor outer segments. The hESC RPE in animals improved functional performance, after comparing with controls, and significant similarity compared to what is found in adult humans[6,8,9]. The United States FDA recently approved a Ⅰ/Ⅱ clinical trial, currently ongoing with hESC, for the treatment of GA and Stargardt's macular dystrophy[7,19]. Pan *et al*[12], reported the first subretinal replacement of hESC RPE in subjects with Stargardt's and GA[2,5]. A clinical study reported absence of immune rejection 4 mo after transplantation in a group of patients[1,16]. Still, it is hard to find clinical trials showing the results of RPE suspension injection therapy. Ribeiro *et al*[20] conducted a study to determine whether transplantation of a polarized monolayer of hESC RPE, supported on a nondegradable parylene membrane, into the subretinal space of 69 rats, would lead to RPE survival and tumorigenic effects, compared to suspension injection[20]. Polarized monolayers of hESC RPE showed 12 mo survival of 50% and 25% in the hESC RPE suspensions, with no signs of tumoral formation. This survival was confirmed by robust antiTRA185, and antiRPE65 staining[11,20]. Ribeiro *et al*[20] showed that the confocal nearinfrared (NIR) 830 nm imaging modality, capable of visualizing subretinal pathology, was, also capable to identify the "*in vivo*" hESC RPE in the parylene membrane, with subsequent histological confirmation[20].

Possibility of teratomas, management of immune rejection and histocompatibility with the hESC, turns it into a difficult clinical application[11-13]. The iPSC is an interesting alternative to avoid immune rejection, but it is important to point out that iPSC may become imunnogenic after reprogramming[4,6,8,21]. It is predictable that the "autogenous" iPSC RPE transplantation could improve results in patients with retinal degeneration[16]. The iPSC therapy is a possibility for retinal replacement, though remaining problems to be solved, until applying it to daily practice. Thus, both hESC and iPSC, under certain biological conditions, may distinguish into actual RPE[4].

PHOTORRECEPTORS REPLACEMENT

The degeneration of RPE always promotes the induction of photoreceptor damage. But when the loss of photoreceptors is settled, the resulting deficit is permanent. As such, replacing the injured RPE through SC therapy may help to reestablish the integrity of this functional unit[2,11,13]. The generation of photoreceptors has garnered particular interest, probably related with the growing number of patients affected with macular degeneration and inherited disorders in the United States[21]. Several groups have demonstrated successful photoreceptors' transplantations in animals, performing synaptic connections between grafts and host retina, and significant functional improvements[2,22].

Retinal SC (RSC) has been cultured from the peripheral mammalian retina[6]. RSC transplanted subretinally into animal models develop into photoreceptors after integration, with long term survival[2,6]. The hESC may, also develop the RSC[2,8]. In 1998, Reynolds *et al*[1] cultured hESC from human blastocysts. In 2009, with the permission of the FDA, the first hESC clinical trial was approved for spinal cord injury.

The RPC exist in a more advanced ontogenetic stage than hESC, and constitutes the active component of fetal retinal transplants[2,8]. Aftab *et al*[23] showed that human RPC (hRPC), depending of the gestational period, exhibit optimal proliferative dynamics under certain conditions[23]. After the transplantation of human fetal retina, opsin and recoverin could be also developed by the photoreceptors, improving patients' vision transiently[6,8]. The use of hRPC from fetal retina was limit by the low capacity to expand "*in vitro*". Baranov *et al*[24] showed that hRPC expanded in culture conditions submitted to hypoxia, maintaining its multipotency and self renewal characteristics[24,25].

Photoreceptors transplantation requires integration into both outer and inner retina, reforming functional synapses, and acting as an anatomical replacement therapy. This direct contact provides the differentiation of photoreceptors "*in vivo*", which is hard to replicate "*in vitro*". The inner retina of the transplant, including the outer limit membrane, act as a barrier to donor photoreceptors, and its removal may improve the success involving full thickness retinal grafts[2]. In addition, the induced differentiated cells are not similar to photoreceptors in structure and morphology. A recent study successfully molded structures similar to outer segment from hESC[16]. Although the production of phototransduction initiating protein, rhodopsin, it has been difficult to induce electrophysiological responses under light stimuli using the patch clamp technique, indicating a functional defect[2,16]. Researchers treated ESC with Wnt and Nodal antagonists to differentiate SC[2,16]. The inhibition of Notch signaling, also significantly promoted photoreceptor differentiation[16]. In 2006,

Table 1 Clinical trials using stem cell for retinal therapy currently registered on ClinicalTrials.gov

Injury or disorder	Sponsor	Type or source of cells	Delivery	Identification
Stargadt's, AMD (GA)	Advanced cell technology, recruiting	hESC RPE	Subretinal transplantation	NCT01469832
AMD (GA), RP, ischaemic retinopathy	University of Sao Paulo recruiting	BMSC	Intravitreal injection	NCT01518127 NCT01560715 NCT01518842
AMD	Pfizer, ongoing	hESC RPE	Subretinal transplantation	NCT01691261
AMD (GA), RP, RVO, DR	UC Davis recruiting	BMSC	Intravitreal injection	NCT01736059
Stargadt's, Fundus Flavimaculatus, Juvenile Macular Dystrophy	Advanced cell technology, recruiting	hESC RPE	Subretinal transplantation	NCT01469832
Retinal and optic nerve damage	Retinal associates of South Florida, recruiting	BMSC	Retrobulbar, subtenon and intravenous injection	NCT01920867
AMD	Advanced cell technology, recruiting	hESC RPE	Subretinal injection	NCT01344993
AMD	Al-Azhar University, recruiting	BMSC	Intravitreal injection	NCT02016508
RP	Chaitanya Hospital, recruiting	MSC	Not informed	NCT01914913
RP	Mahidol University, recruiting	MSC	Intravitreal injection	NCT01531348
Myopic Macular Degeneration	UC Los Angeles, ongoing	hESC RPE	Subretinal transplantation	NCT02122159
Best disease	Mayo Clinic, recruiting	iPSC RPE	Not informed	NCT02162953
AMD	CHA Bio and Diostech, recruiting	hESC RPE	Subretinal transplantation	NCT01674829
Stargadt's	Advanced cell technology, recruiting	hESC RPE	Subretinal transplantation	NCT01345006
Stargadt's	CHA Bio and Diostech, recruiting	hESC RPE	Subretinal transplantation	NCT01625559

Legends[29]. AMD: Age related macular degeneration; GA: Geographic atrophy; RVO: Retinal vein occlusion; DR: Diabetic retinopathy; SC: Stem cells; hESC RPE: Human embryonic stem cells derived RPE; iPSC: Induced pluripotent stem cells; BMSC: Boné marrow stem cells; RP: Retinitis pigmentosa; MSC: Mesenchymal stem cells.

Lamba *et al*[1] promoted the formation of RPC, and generated photoreceptors from hESC in a culture with supplementation of IGF1, noggin (inhibitor of BMP pathway) and Wnt inhibition[1,10,16]. Reynolds *et al*[1], in 2009, implanted photoreceptor derived from hESC, with the objective of testing hESC to photoreceptor replacement in an animal model. They demonstrated the migration following intraocular injection of hESC derived material, settling into the appropriate layers, and expressing markers, included related to photoreceptors. After transplantation, there is differentiation into functional photoreceptors and restore light responses to the animals[2].

The injection of RPC was promising, but, although it demonstrated robust integration, they did not produce photoreceptor appropriately. Fernandes *et al*[2] demonstrated the subretinal delivery method promote maturation of hESC RPC to photoreceptors. Concluding, alternative approaches and techniques need to be explored to direct RPC transplantation as a therapeutic option, aiming significant survival after transplantation, integration into host retinas and photoreceptor specific differentiation[2]. Scaffold delivery strategy has been shown to enhance the cell survival and differentiation in a variety of retinal degeneration models[24].

RETINAL GANGLION CELL REPLACEMENT

The retinal ganglion cell (RGC) is the primarily part of the retina damaged by glaucoma[26]. In general, the most successful transplantations mentioned before, aiming to repair damaged retinas, restored photoreceptor cells, but not RGC[2]. Nevertheless, RGC production from ESC cultures has been reported[12,13]. Reconstructing the optic nerve through the regeneration of RGC may reestablish sight in glaucoma or traumatic optic nerve injury[2].

NON NEURAL SC REPLACEMENT

The transplantation of nonneural SC, such as BM derived SC (BMSC), UCSC, HSC or MSC has been documented[2,14]. BM transplants still consists in adjunct therapy in cancer patients[8]. The injection of BMSC improves retinal circulation, enhancing survival of outer retina, bringing benefits in retinal degeneration[2]. The BMSC is an important tool in regenerative therapy, directly related to HSC production[6]. HSC is an accepted therapy today. It is a group of multipotent SC, obtained by directly removal[8,9]. BM is supplemented as SC by peripheral blood or cord blood[27]. The HSC therapy performed globally, such as the demand for donors, has progressing annually[28]. Nevertheless, HSC transplantation is still related to significant morbidity and mortality, has a high cost and requires multidisciplinary infrastructure. The identification of small ESC in BM supports the notion that, if transplanted together with HSC, it would be able to participate in regeneration[8,9,27].

CONCLUSION

Several ocular SC clinical trials ongoing have the objective of establish the safety and efficacy of this therapy in humans (Table 1). Additional sources of funding are

therefore imperative to maintain the research programs and integrate these basic and preclinical discoveries and launch early phase clinical trials within the coming years. Although the recent controversy involving changes in strategy planning and funding of the Center of Regenerative Medicine, from the United States NIH, studies of SC therapy for macular degeneration will not be affected.

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P- Reviewer: de Frutos P, Lim JB **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

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