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Stem Cells Therapy for Retinal Degeneration

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Abstract: Stem cell therapy is widely considered as a therapeutic approach for retinal degeneration. Retinal injury results in permanent visual disturbance or blindness. Repair of such damage by stem cells is one of the most feasible types of central nervous system repair. In this review, we consider how stem cells might be optimized for use as donor cells. We discuss the benefits of stem cells for transplantation in retinal degenerative disease. A wide range of stem cells from different sources is being investigated for the treatment of retinal degeneration. This study reviews the recent and old achievements about stem cells for retinal repair.

Key words: Retina, stem cells, transplantation, differentiation

INTRODUCTION

Every year many people suffer from visual degradation or even blindness caused by retinal damage. Many eye disease, such as age related macular degeneration (AMD) (Hogg and Chakravarthy, 2006) diabetic retinopathy (DR) (Meyer-Rusenberg *et al*., 2007) and glaucoma (Harwerth and Quigley, 2006), can produce pathological changes in photoreceptors or inner retinal neurons (Xin and Bloomfield, 2000) and progressive cell death (Bi *et al*., 2009). There is currently no effective treatment for degenerative disease except in the case of AMD (Bi *et al*., 2009). Retina, as part of the Central Nervous System (CNS), is made up of neurons which degenerate progressively throughout life. Like in other CNS, retinal neuron in the mammalian has little ability to regeneration and repair (Cepko *et al*., 1996). In recent decades; it has become apparent that mammalian visual pathway has considerable plasticity (Comyn *et al*., 2010). In rodents, adult retinal cells can regenerate along a peripheral nerve graft to form functional synapses in the tectum (Vidal-Sanz *et al*., 1987; Whiteley *et al*., 1998) and during late development, ganglion cells can regenerate and migrate through the optic chiasma (MacLaren and Taylor, 1997). The photoreceptor layer of outer retina may be one of the CNS region. Several groups have demonstrated successful transplantation of photoreceptors into the degenerating mouse retina and results show there are several synaptic connections between transplanted cells and host retina (Bartsch *et al*., 2008; Kwan *et al*., 1999; MacLaren *et al*., 2006). Several studies have shown the possibility of non retinal stem cells such as embryonic stem cells (Bamin *et al*., 2006) hippocampal stem cells (Safari *et al*., 2009) brain-derived precursor cells (Wojciechowski *et al*., 2004) hematopoietic stem cells (Otani *et al*., 2004; Tomita *et al*., 2006).

Eye-derived stem cells: In general two sources of stem cells with differentiation potential have been identified in the mammalian retinal system. These SCs are able to differentiate into retinal specific cells. One is the adult retinal Pigmented Ciliary Margin (PCM) located between the iris and the retina (Perron and Harris, 2000). In addition, Muller glia have shown a remarkable capability to differentiate into a number of retinal cell types.

Ciliary body stem cells: The Ciliary Body (CB) contains two layers: the inner layer including non-pigmented epithelium and the outer layer consisting of pigmented epithelium (Fischer and Reh, 2000). The non -pigmented cells of ciliary body in chickens are able to differentiate into different types of retinal neurons in the presence of some growth factors such as Epithelial Growth Factor (EGF) and Fibroblast Growth Factor (FGF) (Fischer and Reh, 2003). Some cells that isolate from CB have been characteristic of neural stem cells and have the capacity of generate retinal neurons (Ahmad *et al*., 2000). Immunocytochemistery studies revealed that Crx and Otx2 gene transfers could regulate the expression of photoreceptor phenotypes in the ciliary body (Akagi *et al*., 2004). Study of Moes show, adult human ciliary body cells could express nestin and Sox-2 markers of stem cells (Moe *et al*., 2009). The cells of CB express protein that are also present in fetal retinal progenitor cells (RPCs), including CHX10, PAX6 (Fischer and Reh, 2000).

In summery the ciliary body cells of human retina are a potential source of retina specific cells that have properties of neural stem cells (Abdouh and Bernier, 2006).

Iris pigmented epithelial cells: The iris is located between the anterior and posterior chamber. It contains no cells for generating neurons. However iris pigmented epithelial cells (IPS) is a possible source for the treatment of neurodegenerative disease (Arnhold *et al*., 2004). Iris derived cells express some neuronal antigens (Haruta *et al*., 2001) and so express rod photoreceptor antigens such as Crx gene and Otx2 homeobox gene (Akagi *et al*., 2004). Ipe is composed of inner and outer layers. Inner layer express nestin but there is a different pattern in nestin expression between inner and outer layers. These deferent cells displayed the ability to differentiate into multiple neuronal cell types (Asami *et al*., 2007). Ipe cells of chicken under certain condition such as culture in the presence of FGF-2 or EGH lost their melanin and forming neurosphere-like cells. These cells express Pax 6 and vimentin but was not found Glial Fibrillary Acidic Protein (GFAP). This finding revealed that the ipe cells could only differentiate into retinal progenitor cells under specific conditions. When ipe cells cultured onto collagen coated dish in the presence of FGF2 these cells express neuronal markers such as rhodopsin, iodopsin, PKC (bipolar cell) and HPC1 (amacrine cell). This findings show that the ipe cells have a potential source for neuronal cells (Sun *et al*., 2006).

Retinal stem cells: Mouse RSCs isolated from the neuroretina and Retinal Progenitor Cells (RPC) from E17 and Post Natal Day 1(PN1) (Klassen *et al*., 2004). Human fetal RPCs (6th-13th week of gestation) have been isolated from the neural retina. These cells show high proliferation in presence of growth factor (EGF) or FGF2 and expressed NES (Kelley *et al*., 1995). The genes of Chx10 and Mift control the RPC population *in vivo*. Deletion of one of these genes leads to lower number of RPC. This loss of RPC caused higher number of RSC, indicating a response of mammalian RSC population to signals from RPC (Coles *et al*., 2006). RPC play a significant role in retinogenesis proceeds (Marquardt, 2003). RPC s that isolated from rat retina can differentiate into photoreceptor cells which expressing opsin (Chacko *et al*., 2000). Recently, RPC transplanted into the vitreous body could migrate into different layer of the retina (Chacko *et al*., 2003). RPCs could be found in the Ciliary Marginal Zone (CMZ), which is located at the retina extremities in lower vertebrate such as fish, frog, amphibians and even chickens (Fischer and Reh, 2000; Kubota *et al*., 2002; Perron *et al*., 1998). The CMZ is not found in higher species such as the mouse. This phenomenon indicates a progressive reduction in the size and number of cells that can proliferate of CMZ in higher vertebrate (Kubota *et al*., 2002). RPCs were found in human retina from postnatal to 70 years of age. These cells were transplanted into the eyes of mice where they displayed the potential to survive, migrate, integrate and differentiate into retinal cells (Coles *et al*., 2004). Therefore, human RPCs may be an important future source for retinal regeneration therapy.

Embryonic stem cells: Embryonic stem cells (ESCs), isolated from the inner cell mass of the blastocyst, contains a significant potential to differentiate into retinal neurons (Lamba *et al*., 2009; Meyer *et al*., 2006; Osakada *et al*., 2009). Mouse ESCs have advantages for research such as easy to culture and readily differentiate into the cells found in the retina. One of the studies that used mouse ESCs to treat retinal injury promoted the formation of retinal neurons for transplantation (Meyer *et al*., 2006). Transplanted cells demonstrated the ability to restore degenerated retina and enhance the survival rate of host photoreceptor cells. Mouse ESCs were induced by bFGF and Retinoic Acid (RA) to promote recovery in retina (Zhao *et al*., 2002; Safari *et al*., 2008, 2009). Studies show ESC could differentiate into neural retina, RPE, (Hirano *et al*., 2003) and RGS (Aoki *et al*., 2008). Recently, studies have shown that ESCs in rodent and primate in presence of defined factors such as FGF, sonic hedgehog, taurine and RA can differentiate into retinal specific cells (Osakada *et al*., 2008; Ikeda *et al*., 2005). Differentiation of ESCs into retinal cells will facilitate the development of transplantation therapies for retinal repair (Osakada *et al*., 2009). The transplanted human ESC- derived photoreceptors could express markers appropriate for rod and cone photoreceptor differentiation and display the morphology similar to that of the host photoreceptors (Lamba *et al*., 2009). When ESCs co-cultured with retina in the presence of noggin, Dickkopf (dkk1) and IGF1, human ESC-derived progenitor cells could differentiate and integrate into the mouse retina (Lamba *et al*., 2006).

Bone marrow stem cells: It has been reported that Bone Marrow Stem Cells (BMSCs) differentiate into neural cells (Woodbury *et al*., 2000). BMSCs are attractive for transplantation, because they are easily harvested from

bone marrow. Human and rat BMSCs can differentiate into photoreceptor like cells (Chiou *et al*., 2005). Adult BMSCs in the presence of EGF, activinA, taurine could differentiate into photoreceptor like cells that express specific markers such as rhodopsin, opsin and recoverin (Kicic *et al*., 2003). When human BMSCs were co-cultured with human RPE cells they differentiate into retinal cells and cells with photoreceptor characteristic (Chiou *et al*., 2005). Tomita have shown when BMSCs injected in the vitreous space of injured eye, two weeks after transplantation, these cells had been incorporated and differentiated into cells that express markers of retinal neural cells such as calbindin, rhodopsin and vimentin (Tomita *et al*., 2002). Recently, autologous human BMSCs were transplanted into the eyes of 43-year-old patient whose visual acuity was at light perception (Jonas *et al*., 2008).

Neural stem cells: Neural stem cells (NSCs) isolated from different part of CNS. NSCs differentiate into glial and neuronal lineage. An important alternative to embryonic NSCs is adult NSCs which could potentially be obtained from patients or cadavers and be transplanted into injured eyes (Yang *et al*., 2006; Nobakht *et al*., 2010). When adult NSCs injected into the retina m these cells at first migrate into the inner retina and extend processes presented throughout the Inner Nuclear Layer (INL), then migrate into the Ganglion Cell Layer (GCL) and then emerge at the optic nerve. During these process, these cells display morphologies of retinal specific cells such as bipolar (Guo *et al*., 2003). Other study shows that NSCs could be transplanted into the retina and then differentiated into cells of the neuronal lineage. These cells express Microtubule-Associated Protein (MAP2) and MAP5 rather than HPC-1, calbindin and rhodopsin, suggesting that NSCs cannot differentiate into mature retinal neurons (Nishida *et al*., 2000).

Propagation of retinal stem cells: The large number of cells is necessity for well control transplantation. Studies have shown that some of the growth factors such as EGF, FGF-2 and TGFA are important for self renewal of RSCs. These growth factors promote proliferation of RSCs and the survival of photoreceptors (Anchant *et al*., 1991; Lillien and Cepko, 1992). Current culture mostly uses EGF or FGF2 (Angénieux *et al*., 2006; Merhi-Soussi *et al*., 2006) Culture of RSCs in the presence of EGF enables expansion through more than 60 passages (Klassen *et al*., 2004). Cells of neonatal RSCs express the radial glial marker RC2 and the pax6 and Ascll genes, which are expressed in the other area of the CNS (Conti *et al*., 2005). These cells are able to proliferate to at least passage 34. These cells remain in an undifferentiated state, even after several passages and express progenitor markers NES, BMII, Asc II and pax 6 (Angénieux *et al*., 2006). These cells have a capacity to generate neurons after extensive passaging (Merhi-Soussi *et al*., 2006). Human RSCs have been successfully cultured as spheres to at least passage 13. Recent studies have shown that the addition of 20% porcine aqueous humor to culture medium containing EGF enhances the proliferation of rat RSCs and spheres are also larger when aqueous humor is supplemented (Yang *et al*., 2006). The addition of ascorbic acid may help to propagate human RSCs that show limited expansion and undifferentiated state of RSCs (Bi *et al*., 2009).

Differentiation of retinal stem cells: Mammalian retina including several neural cells which are derived from one population of stem cells (Turner *et al*., 1990). RSCs differentiate into six neuronal cell types and glial type (Cepko *et al*., 1996). Retinal Ganglionic Cells (RGCs) in culture medium differentiate in to cones, amacrine, rods and bipolar cells. *In vitro*, RSCs at different condition have different cell fate, suggesting that the determination of cell fate is regulated by both cell intrinsic and extrinsic factors (Watanabe and Raff, 1990; Belliveau and Cepko, 1999). Results show that mouse RSCs have a potential to differentiate toward glial or neural cells (Angénieux *et al*., 2006). An extensive analysis of neonatal RSCs isolated from radial glial colony has demonstrated their potential to differentiate into photoreceptor cells (Merhi-Soussi *et al*., 2006).

Differentiation to photoreceptors Invitro is density dependent (Safari *et al*., 2009; Altshuler and Cepko, 1992) suggesting that extrinsic factors control cell fate. Induction of retinal neurons, including photoreceptors, is mostly performed by administration of retinoic acid and other retinoids (Safari *et al*., 2009). Retinoic acid regulates the expression of Nrl(neural retina leucine zipper), a basic motif-leucine zipper (bZIP) transcription factor, which activates the expression of rod specific genes (Khanna *et al*., 2006). Addition of retinoic acid and 9-cis retinoic acid to hippocampal progenitor cells and retina stem cells culture of neonatal rats because a dose dependent specific increase in the number of photoreceptors (Safari and Ghahari, 2009). Culture of RSCs in FGF2 and B27 supplement induces neuronal commitment toward a photoreceptor, amacrine, or muller cell fate. Culture of RSCs onto laminin-coated and incubation with B27 without FGF-2, produce a large number of glial cells and few neurons, so showing that the FGF-2 is necessary to generate numerous neurons (Merhi-Soussi *et al*., 2006). Administration of all Trans RA to human fetal RSCs leads to a higher cell number an increase of four fold in recoverin positive cells (Kelley *et al*., 1995). Upon differentiation, human fetal

RSCs express neuronal markers such as beta tubulin, NSE and glial marker GFAP indicating their potential to develop into neurons and glial Invitro (Yang *et al*., 2002). Growth factors such as FGF-2 and taurine enhance the formation and proliferation of rod photoreceptors. However, the effect of taurine is cell density dependent, indicating that taurine dose not act alone in promoting rod photoreceptor formation (Hicks and Courtois, 1992; Altshuler *et al*., 1993). In dissociated chicken retina, the addition of ciliary neurotrophic factor (CNTF) increase the number of rod photoreceptors. Combination of CNTF and Leukemia Inhibiting Factor (LIF) strongly decrease rod photoreceptor differentiation (Schulz-Key *et al*., 2002) and change their phenotype toward the bipolar cell and glia (Roger *et al*., 2006). CNTF and LIF up regulate *pleiotrophin*, the over expression of which prevents photoreceptor differentiation and induces bipolar cell formation (Roger *et al*., 2006). CNTF and LIF regulate the expression of endothelial and brain nitric oxide synthase genes, therefore regulate cell death of rod precursor cells (Elliott *et al*., 2006; Safari and Ghahari, 2009).

Transplantation of stem cells: The aim of cell transplantation is differentiation of the transplanted cells in the right place. Fetal retinal sheet transplant making it an attractive candidate for treatment of degenerated retinas (Sagdullaev *et al*., 2003). In retinas undergoing degeneration, cell transplantation is better method (Canola *et al*., 2007). In comparison with adult stem cells such as bone marrow or mesenchymal retinal stem cells has been reported to give a better result (Tomita *et al*., 2006). Transplantation of fresh retinal cells from newborn mouse has shown that large number of cells migrate and engraft into the photoreceptor layer. These cells have rod and cone morphology and con express markers of rhodopsin. The best results are obtained with cells at PN3-5 (MacLaren *et al*., 2006). Study have shown that transplantation of RSCs dissociate cells from E17 rat retina into the sub retinal space lead the organization of a sheet composed of several layers of cells at the transplantation area. The large of these cells express photoreceptor markers (Qiu *et al*., 2005). Rat muller glia transplanted into the sub retinal space exhibit the expression of photoreceptor-specific opsin marker (RET-P1) (Kubota *et al*., 2006). The use of a biodegradable polymer such as the combination of poly lactic-co-glycocylic acid and poly L-lactic acid shows an improvement and the success rate of transplantation (Lavik *et al*., 2005). Recent finding s revealed that sub retinal transplantation of isolated retinal cells between embryonic day 16.5 (E16.5) and post natal day 11 (P11) can achieve several requirements to replace photoreceptors such as successful integration, correct orientation, adequate morphology, expression of factors, synapse formation (MacLaren *et al*., 2006).

For clinical applications the determination of the specific therapeutic windows for transplantation would be advantageous, as it might provide a better result for treatment of patients with retinal degeneration.

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