STEM CELLS - HOPE FOR FUTURE GLAUCOMA THERAPY

Dr. J.C. Das, *MD,* **Ojaswita Singh,** *MBBS, DO,* **Ritu Chaudhury,** *MS*
Shroff Eye Centre, Kailash Colony, New Delhi

A Stem cell is a multipotent cell with the capacity to self renew and to produce daughter cells capable of differentiating into multiple mature cell types. However, progenitor cells, which process the ability to generate a more limited range of adult cell types, may also contribute to tissue repair. Thus stem cells and or progenitor cells offer new hope for treating historically incurable disease, such as glaucoma, via the selective replacement of degenerated cells to restore function.

Objectives

Retinal Ganglion cell replacement

The clinical end point for uncontrolled glaucoma is total visual field loss as a result of progressive RGC death. Despite aggressive treatment, a significant proportion of glaucoma patients experience considerable visual field reduction during their lifetime. In fish and amphibians, retinal regeneration is an automatic process that proceeds via differentiation of ocular stem cells located in the ciliary's marginal zone. In adult mammals, retinal regeneration after injury or in neurodegenerative disease does not occur.

Degenerated retinal neurons can be replaced by a transplantation of suitable precursor cells. It has been demonstrated experimentally that neural precursor cells derived from embryonic stem cells when transplanted into eye, can migrate into the retina and express markers of mature retinal neuron. Transplanted foetal derived hippocampal progenitors also demonstrate the ability to localize to the retinal ganglion cell layer from whence they can extend neuritis into the inner plexiform layer and towards to topic nerve head.

Optic nerve head restoration

Stem cell therapy directed towards repairing the structure and function of the ONH has been proposed as a possible way to slow disease progression. For example, given that fibroblast cells are responsible for maintaining the ONH extracellular matrix, it is conceivable that fibroblast precursor cells could modulate the environment of the glaucomatous ONH to enhance RGC survival.

Trabecular Meshwork Restoration

Restoration of TM function is a potential target for stem cell transplantation. While progenitor cell population isolated from the trabecular meshwork can be expanded in culture, it remains to be established whether such a cell population is capable of improving the conventional outflow pathway in glaucoma patients.

Conjunctival Restoration and Glaucoma Filtering Surgery

One emerging technique to repair leaky blebs is through ocular surface grafting of tissue equivalents. Tissue equivalents can be generated by the isolation and in vitro expansion of conjunctival specimens isolated from the superior fornix, which contains a population of conjunctival progenitor cells.

Sources of stem cells

Embryonic stem cell (ES Cells). These are derived from inner cell mass of the developing blastocyst and are capable of indefinite cell renewal and proliferation in culture. They are also pleuripotent, meaning that they can generate all cell types of the body. In the context of glaucoma, ES cells in vitro have yielded both glial and neuroqal cell types. Differentiation can be accomplished in vitro by mimicking the molecular events that occur during development via exposure of cells to signaling molecules. Thus ES cells have been differentiated mto retinal precursor cells that express markers of retinal development including Pax 16, Lhx 2, Rx/Rax and Six3/6. In addition, ES cell transplants are necessarily allogenic and therefore, carry risk of graft rejection.

Somatic stem cells

Somatic stem cells derived from blood, skin, bone-

marrow and umbilical cord may have neuronal potential. Intraocular implantation of mesenchymal and umbilical cord derived stem cells into a degenerated photoreceptor model has demonstrated an ability to improve retinal structure and function. This would facilitate autologous grafting and would avoid graft rejection and negates the need for immuno suppression.

Neural Stem Cells

These are somatic stem cells that give rise to neurons, astrocytes and oligodendrocytes in the CNS. These are commonly isolated from the sub ventricular zone of the lateral ventricle. In vitro differentiation of NS cells into mature RGCs has yet to be achieved.

Adult Ocular Cells

Like limbal basal stem cells a population of cells in the trabecular meshwork has been isolated and expanded in culture. Genetic analysis suggests these TM cells exhibit an undifferentiated, progenitor phenotype. Proliferative cells capable of generating neural retinal cells have also been cultured form the pigmented ciliary body and the pigmented iris epithelium. The pigmented iris epithelium shares developmental origin with the pigmented ciliary body and the neural retina. This suggests the possibility that these cells, under the correct condition, may possess the potential to generate cells for each tissue type.

Prospects of stem cell therapy in glaucoma

Intravitreal introduction theoretically provides the transplanted cells with direct access to the inner retina. This route may prove to be more appropriate for glaucoma directed therapy, as apposed to outer retinal therapy in retinitis pigmentosa and macular degeneration.

One of the first tasks transplanted cells must accomplish is morphological integration in the host tissue. Integration into the intact rodent retina occurs much more readily in young animals than in adults, although the cells can survive in the posterior segment of adult eyes for weeks. This lack of integration may be partially overcome by injuring the adult retina. It appears that endogenous signals form the injured retina play a key role in determinging the potential for integration of engrafted cells. Transplantation of lineage-restricted cells has shown that grafted cells can differentiate and express some RGC specific markers in vivo. It may not be necessary to create fully differentiated RGCs in vitro for transplantation as it is possible that some of the required signals may remain endogenous to the adult retina, allowing less mature cells to be used. Whether the glaucomatous retina can provide the necessary cures to guide the migration, differentiated, and integration of transplanted cells remains to be established.

Potential Hurdles

Rejection

It is a major complication of allogenic transplantation. Preferentially, autologous transplantation of the recipients own somatic stem cells would be a desirable future therapy.

Reactive Gliosis

Reactive gliosis following neural injury obstructs endogenous neurite regrowth and can impede the migration and integration of engrafted stem cells.

Axonal guidance and myelination

An approach would be to enhance the permissiveness of the host retina and optic nerve to neurite extension. One possible mechanism involves the down regulation of growth inhibitory molecules such as myelin associated protein (MAG) or nogo.

There is difficulty in assessing visual improvement in animal models.

There is continued disease progression.