Retinal repair with induced pluripotent stem cells

SHOMOUKH AL-SHAMEKH, and JEFFREY L. GOLDBERG

SAN DIEGO, CALIF; MIAMI, FLA; AND RIYADH, SAUDI ARABIA

Retinal degeneration such as age-related macular degeneration and other inherited forms, such as Stargardt's disease and retinitis pigmentosa, and optic neuropathies including glaucoma and ischemic optic neuropathy are major causes of vision loss and blindness worldwide. Damage to retinal pigment epithelial cells and photoreceptors in the former, and to retinal ganglion cell axons in the optic nerve and their cell bodies in the retina in the latter diseases lead to the eventual death of these retinal cells, and in humans there is no endogenous replacement or repair. Cell replacement therapies provide 1 avenue to restore function in these diseases, particularly in the case of retinal repair, although there are considerable issues to overcome, including the differentiation and integration of the transplanted cells. What stem cell sources could be used for such therapies? One promising source is induced pluripotent stem cells (iPSCs), which could be drawn from an individual patient needing therapy, or generated and banked from select donors. We review developing research in the use of iPSCs for retinal cell replacement therapy. (Translational Research 2014;163:377–386)

Abbreviations: AMD = age-related macular degeneration; BEST1 = bestrophin 1; bFGF = basic fibroblast growth factor; ECM = extracellular matrix; FACS = fluorescent-activated cell sorting; FGF = fibroblast growth factor; hESC = human embryonic stem cell; hiPSC = human induced pluripotent stem cell; IGF-1 = insulin growth factor 1; iPSC = induced pluripotent stem cell; IRBP = interphotoreceptor retinol binding protein; RA = retinoic acid; RGC = retinal ganglion cell; RP = retinitis pigmentosa; RPC = retinal progenitor cell; RPE = retinal pigment epithelium; SHH = sonic hedgehog

The retina is an outgrowth of the central nervous system and, because of its direct accessibility for visualization and drug delivery, it provides an optimal opportunity to examine stem cell biology and therapeutics. The light-sensitive retina lies in the back of eye, is approximately 30–40 mm in diameter and 0.5 mm thick in humans, and accommodates 5 broad classes of neurons: photoreceptors, horizontal cells, bipolar cells, amacrine cells, and retinal ganglion cells (RGCs). The cell bodies of these neurons are elegantly arranged in 3 layers: the outer nuclear layer, which contains cell bodies of both photoreceptors, rods and cones; the inner nuclear layer, which contains the cell bodies of the bipolar, horizontal, and amacrine cells as well as the Muller glia; and the ganglion cell layer, which contains the cell bodies of RGCs and displaced amacrine cells. Synapses lie between each cell layer in the outer and inner plexiform layers. Light stimulates the photoreceptors, which then synapse to the other interneurons, which activate the RGCs. RGC axons combine to form the optic nerve, which then carries all the visual information to the brain. In the center of the retina lies the macula, with the fovea positioned in the center. The fovea contains the highest density of cone photoreceptors in the retina and is responsible for our central, high-acuity vision.[1]

Just behind the retina lies the retinal pigment epithelium (RPE) The RPE is composed of a monolayer of

From Shiley Eye Center, University of California, San Diego, Calif; Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Fla; Department of Ophthalmology, King Abdulaziz University Hospital, King Saud University, Riyadh, Saudi Arabia.

Submitted for publication August 26, 2013; revision submitted November 3, 2013; accepted for publication November 4, 2013.

Reprint requests: Jeffrey L. Goldberg, Shiley Eye Center, 9415 Campus Point Dr. #0946, University of California, La Jolla, CA 92093; e-mail: jlgoldberg@ucsd.edu.

1931-5244/$ - see front matter

http://dx.doi.org/10.1016/j.trsl.2013.11.002

pigmented cells and serves many important roles in the retina. The tight junctions of the RPE cells contribute to the blood-retina barrier, and RPE cells are responsible for transporting nutrients from the blood to the photoreceptors, and waste products in the opposite direction.[1] RPE cells also phagocytose the outer segments of the photoreceptors, and they harbor essential enzymes responsible for regenerating visual pigments needed by the photoreceptors to convert photons of light into chemical signals.[2] Loss of RPE is associated with hereditary or age-related retinal degeneration, such as age-related macular degeneration (AMD), Stargardt's disease, or retinitis pigmentosa (RP). More than 40 million people have from AMD worldwide and it is a leading cause of blindness in people older than 60 years. The death of RPE cells is associated with loss of photoreceptors in the macula and eventual loss of vision. The cellular atrophy that accompanies AMD is normally irreversible and, unfortunately, other than delaying the disease process by supplements, medications, or surgery, there are no treatments to recover lost cells or to prevent completely ongoing damage to the remaining cells. Therefore, cell replacement therapy and regenerative medicine creates a new window of hope for treatment of retinal degenerative conditions through a number of potential avenues, by replacing lost cells, by supplying neuroprotective molecules to at-risk cells, and by improving disease models in the laboratory to help us understand more completely the pattern and cause of these diseases.[3-6]

SOURCES OF CELLS FOR RETINAL REPAIR

Primary retinal cells and retinal progenitor cells. It has long been attractive, even before the current era focused on stem cells, to consider the transplant of fully differentiated photoreceptors and RPE cells, whether from a patient's fellow eye or from human donors. In preclinical models, animal data suggest that newly differentiated rod photoreceptors may integrate better after cell transplant than retinal progenitor cells (RPCs).[7] In the outer retina, similar data suggest that primary RGCs integrate better and receive more retinal synapses than RPC-derived RGCs.[8] Early work in human trials demonstrated that transplanted neural tissue can survive in human patients without immunosuppression and without apparent inflammation or rejection, and suggested the possibility of vision improvement after implanting retina with RPE.[9-11]

During normal retinal development, RPCs clearly have the capacity to differentiate into all the cells of the retina,[12] but currently it is difficult, experimentally and politically, to garner enough RPCs from human embryos to pursue this approach. Although many groups continue to focus much of their attention on human RPCs, Muller glia, and RPE progenitors,[13-17] large cell-banked supplies of lines from these sources have not be demonstrated and could prove more difficult to generate. Thus, between limited cell or tissue supply, and the excitement about the prospects for stem cell-derived products, primary retinal cells have not been pursued much further.

Human embryonic stem cells. Human embryonic stem cells (hESCs) are undifferentiated cells derived from the inner cell mass of the blastocyst. They are characterized by the ability to proliferate indefinitely without differentiating, and by the capacity to differentiate into all cell lineages. The discovery of hESCs in 1998 was a breakthrough in the field of regenerative medicine.[18] Since then, there has been a leap in progress in generating retinal cells from hESCs, including differentiating and purifying hESC-derived RPCs, photoreceptors, RPE, and RGC-like cells.[19-28] Furthermore, hESC-derived RPE and photoreceptor cells integrate successfully into the retina, express specific retinal markers, and enhance visual function in preclinical animal models.[29-37] Last, trials have begun in human retinal degeneration (Stargardt's disease and AMD) with hESC-derived RPE, raising the exciting possibility of translating these therapies into human use.[38]

Induced pluripotent stem cells. In 2006, it was first reported how to reprogram adult somatic mouse cells and, in 2007, human cells to a hESC-like state by introducing 4 factors, (OCT3/4, KLF4, SOX2, C-MYC) into somatic cells.[39,40] During subsequent years, this approach has been refined both through altering the vectors used (eg, with other viruses, messenger RNA, or even pharmacologic agents[41-47]) as well as through the specific genes used. For example, OCT4, SOX2, NANOG, and a different gene LIN28 are as effective at cellular reprogramming.[48]

There are many promises of induced pluripotent stem cells (iPSCs)—that they may allow for personalized treatment with a patient's own cells, that they should be safe from the ethical and immunologic concerns related to hESCs, and that they will allow cells and tissues from patients with specific diseases to be recapitulated and studied in a laboratory dish. Some of these promises are already demonstrating fruition throughout the body, but what about progress toward diseases in the eye? Recently, the Japanese Ministry of Health, Labor and Welfare has approved the world's first clinical trials involving iPSCs to try to restore vision in patients with AMD by transplanting iPSC-derived RPE cells[49]. In this review, we focus on advances in generating RPE cells, photoreceptors, and RGCs, and discuss the implications of bringing them to human trials.