Brand New Vision: Embryonic Stem Cells as Regenerative Medicine to Treat AMD

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Introduction

"*Of all the senses, sight must be the most delightful.*"

- Helen Keller

People fully "live" with their eyes because the eyes provide vision for the activities that humans enjoy. There's a wide range to these activities such as handling daily tasks or indulging in entertainment. Vision allows individuals to fully engage in their surroundings because they are able to see what they're doing and what's happening. Therefore losing the ability to see is a concern because "even partial sightedness lowers the ability of the affected individual considerably, preventing him from participating in and enjoying many activities that sighted individuals take for granted" (Belkin, 2006, p. 234). Vision loss causes individuals discomfort because they often must change their lifestyle to cope with having impaired vision.

Age-related macular degeneration (AMD) is a retinal degenerative disease that affects the retinal pigment epithelia (RPE) cells and photoreceptors in the eye, causing cell death and irreversible vision loss. According to Steven Schwartz, Ahmanson Professor of Ophthalmology and chief of the Retina Division at UCLA's Jules Stein Eye Institute, "RPE cells are critical for vision. When those cells go, vision goes" (as cited in Svitil, 2013, para 5). AMD is the leading cause of blindness in the elderly; the organization Prevent Blindness America reports, "[…]approximately 1.65 million Americans over the age of 50 have the disease" (as cited in Kanan et al., 2008, p. 61). There is currently no known treatment for AMD, but recent studies and developments have pointed to a potential method to possibly cure the disease. The California Institute for Regenerative Medicine (CIRM) and many researchers support the endeavor to treat AMD by utilizing human embryonic stem cells (hESC) as regenerative medicine.

Age-Related Macular Degeneration

AMD, a retinal disease, affects roughly 30 to 50 million elderly people worldwide and is the leading cause for blindness in people over the age of 50 (Fields, Hwang, Gong, Cai, & Del Priore, 2013, p. 7). According to Mark Humayun, a professor of ophthalmology and biomedical engineering at the University of Southern California, "more than 450,000 Californians will develop AMD by the year 2020" (as quoted in Romero, 2009, section 2, para. 4). Year after year, this terrifying retinal disease robs the elderly of their vision with no exceptions. According to Clegg et al. (2008), when a person is diagnosed with AMD, he or she will eventually experience vision loss due to the "degeneration of [the] rod and cone photoreceptors" (p. 2) in the macular region of the central retina. The central retina is responsible for providing high acuity in vision, but once the photoreceptors die, this process leads to the programmed cell death, or apoptosis, of RPE cells (p. 2). Once the RPE cells go through apoptosis, the atrophy of the macula begins. From this point on forward, apoptosis is irreversible, and the degeneration can only be slowed down with injections of nutrients and vitamins. Fields et al. (2013) state that AMD primarily exists in two forms: nonexudative (atrophic or dry) AMD and exudative (neovascular or wet) AMD (p. 7). Dry AMD is considered to be the early stage form of AMD and a vast majority of the population are reported to have the early form rather than the more advanced form. Only about 10% of patients with AMD will experience the advanced wet AMD form of the disease (Clegg et al., 2008, p. 2).

Anatomically, AMD affects the outer layers of the retina when the macula deteriorates; the retina is the location where the photoreceptors and RPE cells lie (He, Erol, & Tsang, 2013, p. 107). Unfortunately, the decaying macula triggers the death of the RPE cells and creates an irreversible process. The RPE cells and photoreceptors in the retina cohesively form one

functional unit; thus, the degeneration of one will eventually lead to the degeneration of the other (Clegg et al., 2008, p. 4). The RPE cells play a crucial role in the retina other than providing vision. RPE cells are pigmented cells, and they absorb stray light to increase visual sensitivity while protecting against photo-oxidation. They perform a number of functions to support photoreceptors through light absorption, nutrient transport, and the phagocytosis of damaged photoreceptors in the outer segment (He et al., 2013, p. 108). Additionally, the RPE cells maintain the health of photoreceptors by recycling photopigments and metabolizing vitamin A (Schwartz et al., 2012, p. 1). AMD is not the only retinal disease where the RPE cells are involved. There are other diseases linked to RPE degeneration such as retinitis pigmentosa and Stargadt's disease (Clegg et al., 2008, p. 4). There is hope in the future for curing RPE-linked degenerative diseases if a method to replenish the dying RPE cells were found. Without a doubt, the conjunction of the RPE cells and photoreceptors is significant in discovering a cure for AMD and in restoring vision loss because there is no treatment "…available [to prevent] AMD or [halt] its progression" (Belkin, 2006, p. 234). The best that scientists are able to perform for patients at the moment is to prolong the deterioration of the macula. In order to have a better comprehension of the retinal disease, a greater knowledge of RPE cells and their relation to AMD must be further examined.

Causes and Genetic Studies of AMD

In recent years, many doctors and researchers have examined AMD closely with hopes of obtaining a better understanding of the disease. This includes inquiries such as "what causes RPE cells to deteriorate?" or "why are certain individuals more likely to have AMD?" In recent studies, Clegg et al. (2008) have discovered that AMD is characterized by both environmental and, possibly, genetic factors (p. 2). These factors contribute to the retinal disease, while studies

done in epidemiology have linked AMD to four risk factors: "age, obesity, cigarette smoking, and inheritance" (p. 2). In addition, Zarbin (2012) insists factors for AMD include: "age, white race, and smoking" (p. 125); other studies suggest extreme exposure to light as an environmental factor that can lead to photoreceptor apoptosis and retinal degeneration (Everhart, Stachowiak, Umino & Barlow, 2008, p. 157). These risk factors provide an explanation for why AMD occurs and offer potential methods to prevent it. Although AMD is not considered a "hereditary macular dystrophy," scientists have identified several "susceptibility genes" related to the disease (He et al., 2013, p. 108). Studies done by Clegg et al. (2008) have depicted a better understanding of AMD in genetic studies; they have mentioned that multiple genes are involved (p. 3). Cases have shown that as many as 75% of AMD cases can be explained by "polymorphisms in two genes [while] smaller percentages of AMD, [*sic*] are linked to mutations in ABCA4" (p. 3). Researchers at University of California, Santa Barbara have also identified genes "whose expression levels can identify people with AMD, as well as genes that distinguish clinical AMD subtypes" ("New Study," 2012, para. 2) by tackling this area of focus with a more holistic approach rather than with an emphasis on specific genes one at a time.

With respect to the other risk factors that were introduced, Ho, van Leeuwen, de Jong, Vingerling and Klaver (2013) suggest a modifiable risk factor in the pathogenesis of AMD that has been present repeatedly within individuals with higher body mass index (BMI) (p. 19). BMI is used to measure the amount of body fat present in men and women based on weight and height. It was reported that women were at a higher risk for early AMD when they had a "BMI [greater than or equal to] 28" when compared to "persons…with normal BMI (20-25)" (p. 19). Such findings support evidence that a person who is overweight or obese could be more vulnerable to AMD. Therefore, it is pertinent to maintain a balanced lifestyle through low-fat

diets and physical exercise.

Population-based studies have demonstrated how race and age play a role in determining individuals who suffer from AMD on a large demographic scale. All ethnicities are affected by AMD with age progression since age is the main cause for the disease. Although there are no ethnicities that are an exception to the retinal disease, there are certain races that are more prone to developing late AMD. According to Ho et al. (2013), late AMD was screened highest in Caucasians while the frequency was lower in Asians, Hispanics, and Africans (p. 4). The results from these AMD screenings for these four ethnicities demonstrate that Caucasians were at a higher risk for having the highest late AMD frequency. Ultimately this means that Caucasians are more likely to be a part of the 10% that develops wet AMD, while Asians, Hispanics, and Africans are least likely to have their AMD progress into the advanced stage.

Besides age, smoking is examined to be a well-known environmental factor for causing AMD. Smoking may enhance the progression of AMD since individuals who smoke cause "oxidative insults to the retina, decline of choroidal blood flow, stimulation of choroidal neovascularization, and reduction of serum antioxidants" (Ho et al., 2013, p. 18). Individuals that smoke increase oxidant levels in their bodies, which is a known stimulant for AMD. Increasing an individual's intake of antioxidants can offset the oxidant levels created by smoking and can possibly aid against AMD. Foods that contain high concentrations of antioxidants include blueberries, red kidney beans, pinto beans, cranberries, and other various fruits and legumes (Mathis, 2005, chart).

In other recent studies, reports have indicated that women are usually more susceptible to AMD. Whether this is due to genetic or environmental factors, this discovery is still debatable in the medical field. However, the Blue Mountain Eye Study has recently suggested that women

who have engaged in current or past smoking were at a higher risk for the presence of geographic atrophy (GA); comparatively, men did not meet the same statistics for GA as women did (as cited in Fleckenstein, Schmitz-Valckenberg, Sunness & Holz, 2013, p. 128). GA is the later advanced stage of dry AMD and causes severe vision loss with increasing occurrence and prevalence. Choroidal neovascularization (CNV) is observed to be the common reason for severe vision loss when AMD advances; however, reports indicate approximately 20% of AMD patients who are legally blind have lost central vision due to GA (Fleckenstein et al., 2013, p. 122).

Furthermore, the presence of drusen, abnormal deposits in Bruch's membrane underlying the RPE, is another important feature of AMD. According to Clegg et al. (2008), drusen formation continually occurs before visual symptoms in AMD appear (p. 3). The drusen may be a result from an inflammatory immune reaction against RPE cells, although the immune cells do not clear them (p. 3). The RPE from Bruch's membrane is disrupted by the drusen and this leads to "oxidative and inflammatory responses that […] result in RPE death and central vision loss" (He et al., 2013, p. 108). This is not the case for advanced stages of AMD, because the macula is distinguished by "sub-RPE deposits [and] choroidal neovascularization" (p. 108) instead. Based on research done on AMD pathogenesis, inflammation is a key component in AMD progression (Zarbin & Rosenfeld, 2012, p. 137). Due to the fact that AMD is a largely multifactorial retinal disease, pinpointing specific and distinct causes for the disease proves intricate and problematic. The retinal disease could be a combination of environmental and genetic constituents, or it could stem from unknown origins that scientists have yet to uncover. Since AMD is a gradual disease that "occurs late in life," it is considered extremely "difficult to elucidate the genetic factors [that] correlate with the disease" until an individual has matured in age (Fields et al., 2013, p. 8). Proficiency and knowledge of this disease have grown over the last decade, but there is still a

good deal of progress to be made.

Symptoms and Treatment of AMD

As AMD develops, it begins to show symptoms in patients. Fields et al. (2013) explained, "In early stages of the disease, patients [will] experience minimal vision loss but some symptoms may occur such as blurred vision, visual scotomas, decreased contrast sensitivity, abnormal dark adaptation, and the need for bright light or magnification to decipher images" (p. 8). Impaired vision is always a sign that AMD has struck, and the disease grows worse with time. Patients with dry AMD have reported mild discomfort in their worsened condition with minimal vision loss (Fields et al., 2013, p. 8). These individuals who gradually lose their vision because of AMD may encounter moments of blurry, hazy vision to the point where they cannot distinguish or recognize faces anymore. Daily activities become difficult to oversee and enjoy as patients frequently complain that the "loss of [the ability to read]" (Trauzettel-Klosinski, 2013, p. 287) is a setback.

Currently there is no remedy for AMD, but there are trial treatments in progress that inhibit the progression of the disease; also, ongoing experiments are testing a potential transplant method that will replace dying RPE cells. Some current clinical therapies available include ciliary neurotrophic factor, complement inhibitors, weekly vaccinations with glatiramer acetate, and other chemicals as treatments to hinder the growth of the disease (Fields et al., 2013, p. 8). These treatments sound promising, but there are still no breakthroughs in eliminating AMD. Ho et al. (2013) note that a protective factor for AMD is antioxidants (p. 18). The Age-Related Eye Disease Study (AREDS) has reported, "a combination of [omega-3 fatty acids], zinc, [beta]-carotene, and vitamins C, and E [have] reduced the risk of progression from intermediate to advanced AMD by 25%" (p. 18). This suggests that individuals with low levels of antioxidants

are more likely to have AMD in the future than those with sufficient amounts of antioxidants. Since antioxidants are known to safeguard against AMD, they can be used to stagnate the progression of dry AMD in patients as well (Berson, 2008, p. 24). About 95% of patients who were injected with Lucentis in a trial were able to maintain consistent vision after a follow-up (Pollack, 2010, para. 10). Wet AMD can be drawn out by laser therapy or "…injections of steroids, Macugen [or] Lucentis" (p. 24), but these treatments should not be thought as a cure for AMD. These options only prolong the advancement of the retinal disease to help patients who are readily losing their vision. A possible cure for AMD can be found in stem-cell-based therapeutics with the simple concept of using stem cells as regenerative medicine on the body. Gelman and Tsang (2013) state cell-based therapeutics should be the technology to restore the structure and visual function of the retina for retinal degenerative diseases like AMD (p. 172). If stem cell-based therapies work in restoring lost RPE cells and photoreceptors, then it is probable that AMD can be treated in the future by replacing the lost RPE cells and photoreceptors with new ones derived from stem cells.

Human Embryonic Stem Cells as Regenerative Medicine

The applications of regenerative medicine are extensive, so they can be applied to cell therapy to target cells that go through apoptosis; the therapy will then either regenerate or repair the cells. AMD occurs due to the death of the RPE cells and photoreceptors in the retina, so in theory, hESC properties could hold the key to finding a cure for AMD. Regenerative medicine is viable only with embryonic stem (ES) cells rather than adult stem cells. Adult stem cells are only found in specific organs in the human body, such as bone marrow or the human heart, and will only produce specialized cells for those distinct tissue types (Svitil, 2013, para. 3). The difference between these two stem cell types is striking because ES cells have "the potential to

differentiate into a number of cell types [while being] capable of extended self-renewal" (He et al., 2013, p. 111). Their properties allow stem cells to be the perfect specimen for biotechnology and bioengineering. If the stem cells properly differentiate into new RPE cells, they will be able to replace the dying RPE cells. They are currently being investigated as a prospective source of new RPE cells and photoreceptors, and they are "promising candidates for therapeutic use" (Fields et al., 2013, p. 16). According to Stern, Temple, and De (2006), ES cells are derived from the pre-implanted embryo in its blastocyst stage; this is the earliest stage where a hollow ball of approximately 100 cells (with even smaller clusters of cells inside) exists (p. 261). These inner cell mass (ICM) cells are pluripotent and can efficiently generate RPE cells and other neural tissue in the body (p. 261). The hESC-derived RPE cells are cultured on plates for 6-8 weeks until clusters of the RPE cells begin to appear and proliferate (Klimanskaya, 2008, p. 857). These newly derived cells would be applied as regenerative medicine through surgical methods performed on the eye in hopes of revitalizing the RPE cells and photoreceptors in the retina. Out of the many organs in the human body, Fields et al. (2013) indicate that the eye is "an excellent target organ" (p. 10) for this process since there are exceptional animal models available and there is a clear characterization of the disease. A few examples of animal models that contain differentiable ES cells that can become RPE-like cells are the following: mouse, monkey, and human (Clegg et al., 2008, p. 11). A majority of trials have been completed on mice because they reproduce quickly, are easy to maintain, and share a number of processes with humans. Moreover, the human eye is considered to be optically transparent, so the transplant site on the eye can be monitored with ease through "slit lamp biomicroscopy, indirect ophthalmoscopy, fundus photography, auto fluorescence imaging, [and] fluorescein angiography" (p. 10). AMD is not the only disease that would benefit from cell therapy because "retinis pigmentosa [and]

diabetic retinopathy" (Singec, 2013, p. 14) would profit from the therapy as well. ES-cell-based therapies are beneficial to patients as long as the transplant is successful; this would mean the new RPE cells could replace the old ones without becoming teratomas or cancerous cells. If stem-cell-based therapies are successful, researchers anticipate a day when "stem cell therapy will transform the way doctors treat diseases—by replacing diseased cells with stem cells that have the singular ability to turn into heart cells, eye cells, [or any other cells]" (Lee, 2011, para. 4).

Stem Cell Potential to Treat AMD

The chances that hESC can potentially treat AMD appear favorable. Fields et al. (2013) report that hESC could really be a probable source of photoreceptors and RPE cells; these stem cells are promising candidates for therapeutic use as regenerative medicine (p. 16). Research done on hESC provides evidence that there is a great potential in transplantation methods to cure AMD, but problems such as having a limited reservoir of donor cells exist (p. 15). This is not a problem as long as the ES cells are able to proliferate *in vitro*; different substances *in vitro* produce different results with the ES cells when they are coaxed into RPE cells. Mouse ES cells and human ES cells react differently to certain *vitro*. Stern et al. (2006) explain that mouse ES cells thrive *in vitro* by different stimulations as opposed to human ES cells (p. 261). Both species depend on certain aspects of the gene expression; therefore, researchers should primarily focus on human ES lines (p. 261). The transplantation procedure to treat AMD derives RPE cells from hESC before carefully inserting the transplant into the eye (Fields et al., 2013, p. 16). Scientists have probed this method by utilizing animal models first; mice are used most frequently. According to Schwartz et al. (2012), there is evidence that transplantation of hESC-derived RPE cells can rescue photoreceptors while preventing further loss of vision in mice and rats with

macular degeneration (p. 1). Studies report that the Royal College of Surgeons (RCS) rat, an animal model that experiences retinal dysfunction, had extensive photoreceptor rescue and improvement in vision without pathological effect after a successful subretinal transplantation of hESC-derived RPE cells (p. 1). A recent breakthrough in using ES cells helped blind mice regain their vision. The Discovery News article reported:

> Scientists in Britain used stem cells—early-stage, highly versatile cells—taken from mice embryos, and cultured them in a lab dish so that they differentiated into immature photoreceptors. Around 200,000 of these cells were then injected into the retinas of mice; some cells integrated smoothly with local cells to restore sight. The rodents were put through their paces in a water maze and examined by optometry to confirm that they responded to light ("Stem Cells," 2013, para. 2).

This interesting study is evidence that hESC-derived RPE cells can provide renewed vision for blind mice once the RPE cells are injected and incorporated into the eye. This technique was possible for the animal model; thus, it could be possible for humans as well.

At the moment, there are clinical trials underway to evaluate the potential of stem-cell therapy in humans. According to Fields et al. (2013), Advanced Cell Technology, Inc. initiated a phase-1 clinical trial in humans in 2011 for the treatment of retinal degeneration. This was the first FDA approved trial for using hESC-derived RPE cells (p. 19). The RPE cells originated from a single donor ES cell line, and preliminary reports disclose the safety and tolerability of the cells in patients afflicted with dry AMD (p. 20). After a 4-month follow-up, reports show that the AMD patient had no "clinically detectable sign of successful transplantation [however] there was mild visual improvement in both eyes […] shown by visual acuity and [the] Goldmann visual field test" (p. 20). These results were short-term and preliminary, but they provide

valuable information and evidence for future trials for the treatment of AMD. Schwartz et al. (2012) provide another preliminary report for ES cell trials for macular degeneration using two patients on a very strict criterion: one patient suffered from dry AMD, and the second patient had Stargadt's disease (p. 1). The trial's findings did not identify signs of hyperproliferation, abnormal growth, or transplant rejection while the newly formed RPE cells "had attached and continued to persist [in the study]" (p. 1). Sue Freeman, the 70-year-old test patient who suffered from dry AMD, claimed her vision improved from 21 ETDRS letters to 28; however, Dr. Steven Schwartz said that vision improvement could be a placebo effect (as cited in Pollack, 2012, para. 15). Thomas A. Reh, a professor at the University of Washington who studies retinal regeneration, was not engaged in the study done by Schwartz et al., but agreed that the results were promising even though the two patients required a longer follow-up time before doctors could determine if there really was visual improvement (as cited in Pollack, 2012, para. 20). Safety and feasibility of RPE-cell transplantation have always been a concern, but these factors were proven safe and feasible in 17 patients with advanced AMD (Stern et al., 2006, p. 271).

Besides utilizing human ES cell lines to get hESC for RPE cells, recent studies offer another plausible reservoir of cells for the treatment of AMD and "other disorders" (Fields et al., 2013, p. 20). The suggested reservoir contains induced pluripotent stem (iPS) cells, and the Yamanaka group initially generated them in 2006 "…by reprogramming adult somatic stem cells" (p. 20). The Yamanaka group is not the only group to have tried out iPS technology to generate photoreceptors for transplantation—Tsang et al. (2013) have effectively derived RPE-like cells from human iPS for transplantation (p. 21). In order to use iPS cells to their maximum potential, there needs to be proper protocol to further optimize and standardize the cells. Consistency in generating iPS cells is important because it will "increase efficiency, cell purity,

and safety" (Singec, 2013, p. 14).

Despite demonstrations that prove the security and feasibility of harnessing hESC-derived RPE cells, there is a growing concern about the chances of teratoma formation when differentiating ES cells. Newton (2007) explains that teratomas originate from the Greek words meaning "monstrous tumor" (p. 9), and they consist of large lumps of cells that are either "immature (malignant) [or] mature (benign)" (p. 9). Teratoma formation does not transpire all the time, but it does seem to occur if the transplanted stem cells are not properly controlled or handled. Further examinations discovered that if transplanted stem cells were not properly administered, then the cell would develop and differentiate rapidly to produce a mature teratoma (p. 12). This is a frequent occurrence in ES and iPS cells after being specialized due to their rapid proliferation rate. Chazenbalk, a scientist with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, said that, "Embryonic stem cells and induced pluripotent stem cells […] can exhibit an uncontrolled capacity for differentiation and proliferation, leading to the formation of teratomas" (as quoted in Irwin, 2013, para. 10). Despite this conflict, Fields et al. (2013)believe that so far, the hESC-derived RPE cells can be transplanted into the subretinal area in human eyes "without abnormal proliferation, teratoma formation, graft rejection, or other untoward pathological reaction or safety signal" (p. 20). The reassurance that teratomas can be controlled at this point allows researchers to let out a sigh of relief that there is still a future for hESC to treat AMD.

Conclusion

The future of hESC as regenerative medicine to treat AMD appears encouraging as long as long-term follow-ups with patients show success. Awareness for AMD is extremely crucial in the present day so that people can learn about this disease. Their familiarity with the disease can

help support the use of hESC-derived RPE cells in transplantation to treat AMD. A potential cure for AMD is plausible when researchers have a better grasp of the retinal degenerative disease. This can materialize as long as funding for further research in stem cells as regenerative medicine is endorsed; such actions are significant and involve cohesive collaboration between institutions. Educational institutions that research regenerative medicine for AMD prove to be helpful and offer a whole new spectrum of fresh ideas and devotion. Institutions with strong leadership in stem cell biology, such as UC Santa Barbara's Center for Stem Cell Biology and Engineering, provide "progress toward cures in vision diseases such as macular degeneration" ("Stem Cell," 2012, para. 1) with world-renowned faculty members from the U.S. and Britain. As Bruce Alberts, a prominent American biochemist, states, "the history of science makes it certain that the knowledge derived from research on stem cells will eventually lead to enormous benefits for human health, even if they are unpredictable" (quoted in Carlson, 2007, p. 239). The future of curing AMD with ES cells as regenerative medicine is looking bright—perhaps in a blink of an eye, a breakthrough will be made.

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