Stem Cell Therapy and Macular Degeneration

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Abstract
Macular degeneration is the leading cause of vision loss in Americans sixty years and older. Currently, it is an incurable disease. Stem cell therapy is the idea of transplanting stem cells to replace damaged cells in the body. As the demand for transplantable organs far outweighs the supply, stem cells are an encouraging alternative to replace damaged cells. Can stem cell therapy be the first cure for macular degeneration? Many experiments have been done on transplanting stem cells into the eyes of rats with macular degeneration yielding promising results. The first transplantation of retinal pigmented epithelial stem cells into humans to treat macular degeneration was done in 2012. Stem cells were differentiated and inserted into two patients suffering from macular degeneration. Both patients that partook in the study displayed significant visual improvement, and no abnormal growth was observed. In another study, the use of retinal epithelial cells vs. the use of other types of eye cells to treat macular degeneration was studied. Each cell type has the same potential for use in stem cell therapy. Stem cell therapy is a hopeful option for treatment of macular degeneration. Further research is needed before it can be used as a widespread cure.

Introduction
Two important characteristics distinguish stem cells from other cells. Firstly, they are unspecialized cells that have the ability to renew themselves through cell division, and secondly under certain conditions they can be induced to become tissue or organ-specific cells with special functions.

Until recently, scientists have mainly worked with embryonic stem cells and somatic stem cells. Embryonic stem cells are from the blastocyst of the embryo. The blastocyst is composed of an inner cell mass of stem cells that differentiate into different types of cells, giving rise to the entire body of the organism.

Embryonic stem cells are donated for research purposes by eggs that have been fertilized in vitro, and they are not derived from eggs fertilized in a woman's body. The donated stem cells are transferred to a culture dish that contains a nutrient broth called a culture medium where they divide and spread over the surface of the culture dish. When stem cells are grown under specific conditions, they can remain unspecialized. If the stem cells are allowed to clump together to form embryoid bodies, spontaneously they will begin to differentiate. Scientists can modify the stem cells by inserting specific genes or by changing the chemical make-up of the culture. Figure 1 illustrates the process of modifying stem cells to become gene specific stem cells.

Adult stem cells are different from embryonic stem cells because they are found in mature tissues or organs. Adult stem cells are undifferentiated cells that can develop into specific cells of the tissue or organ where it is found. Adult stem cells are found in a specialized region called the stem cell niche. When needed the stem cells will divide and differentiate. This can occur when there is tissue damage or under normal wear and tear conditions—the stem cells will divide in order to replenish the supply of cells. There are various types of adult stem cells that can differentiate into numerous types of cells hematopoietic stem cells (develop into blood cells), mesenchymal stem cells (develop into bone cells, cartilage cells and fat cells), and neural stem cells (develop into cells of the nervous system).

Human induced pluripotent stem cells are an additional type of stem cell. This stem cell is an adult cell that has been genetically reprogrammed to express the characteristics of an embryonic stem cell. The method used to reprogram these cells help researchers learn more about the possibility of reprogramming damaged or diseased cells in the human body.

Human stem cells have many uses in research and clinic. The most important use being cell-based therapy. Cell-based therapy is the potential to direct the differentiation of stem cells in order to transplant them as replacement cells or tissue. Today, tissue and organs are being donated, but the need for transplantable organs and tissue far outweighs the supply. Cell-based therapy can offer a renewable source of replacement cells which can be used to treat different diseases. (Bethesda, 2016).

There are several drawbacks of using transplanted stem cells to treat disease including rejection and long-term side effects are not known. Therefore, a lot of research is still being done before stem cell therapy is used as an established treatment for disease. (Ladock, 2016).

One disease scientists believe stem cell therapy can treat is macular degeneration. Macular degeneration is the most common cause of vision loss affecting more than 10 million Americans.
The retina is the part of the eye that records the images we see and sends them via the optic nerve to the brain. The macula is located in the central area of the retina and is responsible for focusing central vision, seeing fine details, and recognizing faces and color. The anatomy of the human eye is illustrated in figure 2 with the location of the macula shown. Macular degeneration is a disease which causes the deterioration of the cells of the macula. At the present time it is an incurable disease.

Age-related macular degeneration is the most common cause of blindness in people over the age of 60 years old. Age-related macular degeneration gets progressively worse as one ages. It starts with the dysfunction and death of retinal pigment epithelial (RPE) cells. It continues with photoreceptor loss, and insufficiencies in high acuity vision. There are 3 stages of age-related macular degeneration. Early age-related macular degeneration is the first stage where vision loss is not experienced. It can be diagnosed by the presence of small yellow droplets beneath the retina called drusen. The second stage is called intermediate age-related macular degeneration where some vision loss may be experienced. A comprehensive eye exam will look for drusen or pigment change in the retina. The last stage is called late age-related macular degeneration. At this stage vision loss is noticeable. (Buchholz, 2009)

Methods
Literature for this article was obtained primarily using Touro College Online library. Other databases such as PubMed were used. Additionally, Google Scholar was valuable for finding necessary and relevant articles.

Discussion
Only 5.5 millimeters in diameter, the macula is a part of the retina that is responsible for central vision. Researchers have been studying the possibility of using stem cells to treat macular degeneration. The macula is made up of photoreceptor cells called rods and cones. Rods and cones respond to light by sending electrical impulses to the brain through the optic nerve. The brain then interprets these impulses. Behind the rods and cones is a layer of cells called retinal pigmented epithelial cells. (ISSCR, 2015)

Functions of Retinal Pigmented Epithelium
Retinal pigmented epithelial cells have many functions in the eye. Firstly, these cells are responsible for transport in two directions. In one direction they transport glucose and other nutrients from the blood to the rods and cones. In the other direction the transport electrolytes and water from the subretinal area to the choroid. Another function of retinal pigmented epithelial cells is to absorb and filter entering light. The retina is made up of various pigments that are sensitive to different wavelengths of light. Additionally, retinal pigmented epithelial cells are responsible for phagocytosis. (Simó Et. Al. 2010)

The eye is an excellent part of the body for researchers to test stem cell therapy on because the eye is well contained by its many barriers. It is hard for the stem cells to move to other parts of the body. Additionally, researchers can assess the differences between a treated and untreated eye on the same patient. There is equipment available that allows one to see the interior and exterior of a person’s eye.

The focus of scientists has been on using retinal pigmented epithelial cells for stem cell therapy. This is because it is a lot harder to ensure the proper placement of rods and cones in a patient’s eye. Rods and cones connect with nerve fibers, and it is extremely complex to correctly integrate these photoreceptor cells with the nerve fibers. Retinal pigmented epithelial cells do not connect to nerve fibers; therefore they are a better option for stem cell therapy.

It is the goal of scientists to be able to transplant retinal pigmented epithelial cells before the disease has progressed such that the photoreceptor cells have died. In this way, the transplanted retinal pigmented epithelial cells can take on some function of the damaged retinal pigmented epithelial cells and prevent the rod and cone cells from dying, thereby stopping the progression of the disease. (ISSCR, 2015)

Delivery of Stem Cells into the Eye
The following method was used to deliver retinal epithelial cells into rats. The rat was put under anesthesia. A sharp sterilized needle was inserted to make a hole right beneath the limbus, which is the border between the cornea and the sclera.
of the eye. The tip of the syringe was inserted into the hole, injecting the retinal pigmented epithelial cells. The syringe was then taken out slowly, and eye moisturizing drops were given. (Westenskow Et. Al. 2015).

A study of rats with macular degeneration, treated with human embryonic stem cells has shown evidence of rescued photoreceptors and vision loss prevention. Three different levels of pigmented cells were used; light, medium and heavy. Different amounts of cells were used in each group of rats. Visual acuity improved in the groups of rats treated with a dose of between 5,000 – 100,000 retinal pigmented epithelial cells. The cells injected into the rats sustained visual function for at least 60 days. The cells survived in the rats for at least 220 days. All the groups of rats showed deterioration of visual acuity over time. There is no evidence that showed any group having a slower deterioration over time. The deterioration of the visual acuity of the rats in this study may be related to the inadequate use of immunosuppressive drugs to treat the rats. Another hypothesis of why the cells didn’t last is that cell transplantation may need to be repeated several times in order to sustain their therapeutic effect. The study confirmed the long-term safety of retinal pigmented epithelial cells for treatment of macular degeneration in rats. It is a promising step in the research of stem cell therapy to treat specific types of macular degeneration in humans. (Lu Et. Al. 2009).

In one study researchers tested whether human embryonic stem cells can safely be used to treat patients with macular degeneration. Although human embryonic stem cells were first discovered in 1998, this was the first study to report transplanting human embryonic stem cells into human patients. The study tested for signs of hyperproliferation, carcinogenicity, abnormal tissue formation, and rejection. Two patients were selected for the study. One patient had dry age-related macular degeneration and the other had Stargardt’s macular dystrophy (most common pediatric macular degeneration). (Schwartz Et. Al. 2012).

In the experiment human embryonic stem cell culture MA09 (classification of human embryonic stem cells) were used to generate a master cell bank. (Schwartz Et. Al. 2012) Cell line MA09 has contact with the environment before transplanted into the patient and therefore is classified as a xenotransplantation. Xenotransplantation is any procedure that involves the transplantation, infusion, or implantation to humans of nonhuman live cells. (Samdani, 2014) After embryoid bodies were formed and there was multiplication of the cells, retinal pigment epithelial patches were isolated. Embryoid bodies are the first phase of embryonic stem cell differentiation. There are various ways to form embryoid bodies, but it has been a challenge to form embryoid bodies uniform in size. (Xu Et. Al. 2011) The retinal pigmented epithelial cells were tested for pathogens and phagocytosis. They were also tested for RPE and hESC markers.

Human embryonic retinal pigment cells were successfully cultured. The cells showed typical retinal pigmented epithelial cell behavior by losing their pigmented cobblestone morphology during proliferation and re-differentiating into a monolayer of polygonal cuboidal pigmented epithelium.

One hundred and fifty nanoliters of retinal pigmented epithelial cells were injected into the patients’ eyes through a cannula that delivered a dose of 500,000 viable retinal pigmented epithelial cells into the subretinal space. Immunosuppressive drugs; tacrolimus and mycophenolate mofetil were given to each patient a week before the surgery and continued for six weeks after the surgery. Tacrolimus was not given after week six and the mycophenolate mofetil was continued for an additional six weeks. (Schwartz Et. Al. 2012).

There was no hyperproliferation or abnormal growth in either of the patients following surgery as determined by biomicroscopic and ophthalmoscopic clinical examinations. (Schwartz Et. Al. 2012).

Anatomical evidence showed survival of human embryonic stem cells in the patient with Stargardt’s macular dystrophy. The transplanted cells were localized to exactly the correct anatomical location. Increased pigmentation was seen in the retinal pigmented epithelial cells beginning from week one after the surgery up until month three after the surgery.

The patient with age-related macular degeneration did not take the immunosuppressive drugs after the operation; therefore anatomical evidence was difficult to confirm.

Both patients displayed functional visual improvement. The
In this study human embryonic stem cells were safely transplanted into 2 patients. (Schwartz Et.Al. 2012).

A second study compared the effectiveness of using human induced pluripotent cells with using human embryonic stem cells. Both types of stem cells have the ability to differentiate, but it is unclear if they both have the same potential for use in stem cell therapy. The results were determined by finding differentiating ocular cells called retinal pigmented epithelium (RPE).

Transcription factors, protein arrangement, and gene expression were looked at when comparing the two types of stem cells. The study concluded that human induced pluripotent stem cells are a feasible candidate for cellular therapy since they have similar cellular function and possess proper gene expression. (Buchholz Et.Al. 2009).

Where we are now
There are still several difficulties that must be overcome before stem cell therapy is used as a widespread treatment. Many continued years of research are needed.

There are legal and ethical issues with using embryonic stem cells for stem cell therapy; therefore, a lot of effort is being put into generating induced pluripotent stem cells. There is a risk, however, that the induced pluripotent stem cells will turn into cancer cells, and that is a risk not worth taking. Therefore, it has been a challenge for researchers to obtain a readily available bank of stem cells to be used for stem cell therapy.

Can the stem cell therapy be effective if the condition that caused the cells to die in the first place is still present? Most likely, stem cell therapy will need to be combined with additional treatments in order to limit further damage in macular degeneration patients. These additional treatments are still being researched and developed.

An additional difficulty that must be overcome is to find out what exactly is the correct dosage of cells to transplant. There have only been a limited number of clinical procedures done. In order to figure out the correct dosage more clinical studies must be performed.

Scar tissue is present in the damaged eyes of patients with macular degeneration. When new cells are transplanted there is a barrier between the host retina and the grafted cells. This can affect the way the light is transmitted, and the way the patients will see. Treating patients before scar tissue has formed, or discovering ways to get rid of scar tissue is crucial before stem cells can be transplanted. (Barnstable).

Conclusion
There is promising research for use of retinal pigmented epithelial cells to treat macular degeneration. Continued research is needed before stem cell therapy can be used as a widespread treatment for macular degeneration. It is a goal of researchers to treat patients earlier on in the progression of the disease, before complete visual function has been lost.

References


