COULD MACULAR DEGENERATION BE CURED
BY THE USE OF EMBRYONIC STEM CELLS?

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RESEARCH PAPER
BASED ON
PATHOLOGY LECTURES
AT MEDLINK 2011
ABSTRACT

With the science of medicine constantly evolving, new technology and ideas about how we treat diseases are developing too. Stem cells are of particular interest to scientists; due to their unspecialised nature, they can be induced into specialisation and therefore provide living material for medical conditions that involve damage to tissues or organs. Macular degeneration leads to loss of central vision, and is the leading cause of visual impairment in the UK. This research paper will explore the use of embryonic stem cells to treat macular degeneration, and how successful the procedure has been in various cases. We will assess the major benefits of embryonic stem cells for this condition as well as addressing the ethical issues that surround their use.

INTRODUCTION

Stem cells can be described as the most basic ‘building blocks’ of the human body. Like most cells, they have the ability to self-replicate; however, they also have the ability to develop into a number of different specialised cells, and under the right conditions, it is also possible for scientists to induce this process of specialisation. For example, if stem cells are provided with the right growth factors, it may be possible for them to develop into the kind of cells that are damaged by Alzheimer’s disease. Thus, medical researchers are aiming to develop new techniques in which stem cells can be used to repair and regenerate tissue and organs that have suffered from damage. If this research proves successful, therapies and treatments for common diseases such as Alzheimer’s, heart disease and diabetes could be developed. It could also mean the end of many of the rudimentary mechanical devices that are used to treat a lot of diseases – for example, artificial arteries and titanium joints could be replaced by living, interacting matter that is completely natural. Stem cells can, in theory, continue to multiply and divide indefinitely (when this state occurs, a stem cell line has been established); if stem cells could be used to treat diseases inside the body this would be an enormous benefit – the cells could continue to replenish themselves without the need for replacement or aided renewal.

Embryonic stem cells are one of the three types of stem cells found in the body (the other two types being adult/somatic and foetal, found in cord blood). Embryonic stem cells are derived from blastocysts, embryos that are around 4-6 days old. At this stage, the blastocyst consists of around 100 cells. Embryonic stem cells are always taken from fertilised eggs donated for IVF treatment. Around 5 days after fertilisation, the cells start to differentiate, meaning that they start to become specialized (take on a particular type, structure and function). Scientists separate the outer mass (which eventually develops into the placenta) from the inner mass (which contains the stem cells). These inner cells can then be developed into stem cell lines.

Although there are many difficulties that scientists will have to face in order to make stem cell treatment common practice, the benefits to the medical world would be incomprehensible. The benefits are already being seen in areas such as cardiology. An article posted on the 14th February 2012 through www.medicalnewstoday.com presented evidence from a small clinical trial that had been documented in the Lancet Journal. Scientists helped patients that had suffered from heart attacks to re-
grow healthy tissue to replace the scar tissue left by the heart attack, using a combination of the patients’ own heart stem cells.

However, as well as being used to treat heart damage, interesting developments into the use of stem cells has revealed that they can be used to treat eye disease - specifically macular degeneration.

Macular degeneration is a condition of the eye that causes loss of central vision – you lose the ability to see what is directly in front of you so are left unable to read, write or drive (in more severe cases). The macula is the area responsible for central vision. This can become damaged with age, or be caused by genetic factors. Figure 1 shows the position of the macula in the eye, and figure 2 shows what vision might be like for a person with macular degeneration. A form of the condition usually known as age-related macular degeneration, (AMD), occurs in those over 50. Around 30% of people over 75 show signs of AMD, with around 7% being in the more advanced stages of the disease. Stargadt’s macular dystrophy, another form of macular degeneration, is the most common form of paediatric macular degeneration. So, what developments have been made into treating macular degeneration with embryonic stem cells, and what have the results shown?

DISCUSSION

Recent clinical trials have shown the safety of the use of human embryonic stem cells (hESCs) to treat conditions of the eye. In ‘the Scientist’, an article published on January 24th 2012 and written by Hannah Waters explains clinical trials published in the Lancet that had been carried out by stem cell research company Advanced Cell Technology (ACT). The studies, taking place in the US, are looking into stem cell treatment of Stargadt’s macular dystrophy and dry AMD. Chief Scientific Officer Robert Lanza had an aim to remove the damaged retinal pigment epithelium (RPE) layer damaged in both diseases and replace with a layer of stem cells to halt the progress of both diseases. The damage of RPE cells can lead to the loss of photoreceptor cells – this loss characterizes diseases such as AMD and Stargadt’s macular dystrophy. The team induced hESCs into early-stage bone and nervous tissue, and then caused the cells to differentiate into the RPE cells. Four months after these cells had been injected under the retina of a 70 year old woman with dry AMD and a middle aged woman with Stargadt’s, tests were performed to measure results. Tests showed that there had, in fact, been physical replacement of the retinal cells, and that there was a sizeable improvement in the eyesight of both patients. So what developments can be made in the future regarding the use of embryonic stem cells to treat diseases of the eye such as macular degeneration?
The purpose of this clinical trial was to assess the tolerability of the RPE cells that were inserted into the eyes of the patients. A small number of cells were inserted (50,000) in order to minimise the risk of damage should the patient not accept them. Cells were also only inserted into one of the patient’s eyes. Now the safety of the procedure has been assessed, scientists should be working on testing the efficacy using visionary assessments. This clinical trial has so far only treated 2 patients and there have not as of yet been any quantitative results regarding the efficacy of the procedure. Now that the procedure has been classified as safe, the real question is whether or not the benefits of the process outweigh any risks from the treatment.

The macula is a densely packed region of cells in the back of the eye; 50,000 cells are not enough to, in effect, ‘replace lost sight’. It is also likely that many of the cells injected into the eye will not attach to what is known as ‘Bruch’s membrane’ (RPE cells transport waste from photoreceptors across this membrane to the choroid). The build-up of ‘drusen’, white or yellow deposits made of lipid and calcium, are a tell-tale sign of what is known as dry AMD. These deposits occur because it is not possible for metabolic waste to be passed across Bruch’s membrane, and these deposits can damage the RPE layer. The next step is to ensure that clinical trials are done to test how many cells can be inserted into the eye of a patient with macular degeneration, and how many will attach to the membrane successfully. It is therefore a possibility that a large population of cells could be inserted into the macula of both eyes; inserting a large population of cells increases the likelihood of many managing to attach and function in the way that ‘natural’ RPE cells would.

A possibility of ensuring that the cells attach and can replicate to rebuild the RPE layer is to insert lightly pigmented RPE cells into the affected area. Evidence from the clinical trial showed that there were a minimal number of floating lightly pigmented cells after 3 days of culture and that the number of lightly pigmented cells had increased rapidly, whereas the cells that were heavily pigmented had a high number of floating cells with a significantly lower number of replicated cells – in fact, there were over 10% less heavily pigmented cells than light – after the same culture time. Figure 3 shows the difference in cell attachment 21 hours after injection – picture A shows the lighter lot and picture B shows the darker lot. You will notice that many of the cells in picture B are still rounded and unattached, whereas the cells in picture A have attached more successfully.

In the past, the replacement of the RPE layer with somatic stem cells engrafted into the subretinal space has brought about no improvement to central vision. However, the use of hESCs has seemingly been successful in improving central vision, albeit very modestly (as of yet the full benefits of the most recent clinical trial have not been observed – in the long term there may be no improvement of central vision,
and the improvements observed a short time after the transplantation may simply have been a placebo effect). The reason for this difference is that embryonic stem cells are not limited to developing into one type of mature cell, and also have the ability to divide and replicate indefinitely (as opposed to somatic stem cells which are usually restricted to developing into a cell specific to the organ in which it is found and cannot divide and replicate like an embryonic stem cell can). However, although human embryonic stem cells could potentially provide a large number of youthful and unspecialized cells, their use causes a great deal of controversy worldwide (due to ethical views that shall be discussed later). Thus, the pressure is on for scientists to either be able to cause excessive proliferation of hESCs (in order to create an abundance of cells that can be used in many procedures) or to harvest somatic stem cells and create a process by which their division and replication can occur at a faster rate and their limitation to developing into one type of cell can be ‘switched off’. An ideal situation would be the establishment of an embryonic stem cell line that could continue to divide and replenish itself indefinitely on a large scale.

The main argument opposing the use of hESCs arises from the belief that, since life begins at the moment of conception, the destruction of embryos is the destruction of human life. This is particularly relevant for faith-based opponents to embryonic stem cell research, as well as some secular ethicists. However, one only has to spend but a short time in a stroke unit, spinal unit or children’s oncology ward to witness the need for a fresh approach in the treatment of these conditions which continue to elude healthcare professionals in their search for a cure.

Some would argue that the potential curative effect stem cell therapy appears to promise justifies the research into embryonic stem cell therapy in the worldwide search for treatments and cures for an array of debilitating diseases.

On the other hand, central to the argument lies the question ‘when does human life begin?’ Those who share the belief that human life is sacred from the moment of conception would argue that the use of hESCs is unethical, with the inevitable destruction and disposal of embryos being synonymous with ‘murder’ and, subsequently, many would see such an act as harming this most innocent and vulnerable form of human life; which, whilst ‘participating’ in the process, is incapable of consent, informed or otherwise. Moreover, many religious believers share the belief that a human being’s existence is ordained by God and therefore, any intervention in the process of life-between conception and death-interrupts God’s plan for each individual.

Furthermore, a study by the British Fertility Society revealed that 1 in 4 couples have experienced a period of infertility (lasting at least one year) at some point in their reproductive lives. Such findings lead some to deem the use of hESCs in medical research unethical and insensitive, as healthy embryos are repeatedly destroyed, whilst some couples are unable to conceive in the first instance. This lack of respect, evidenced by the destruction of a potentially viable human life, could be deeply distressing for those desperate to create an embryo of their own and who feel anguish and heartache at the thought of being incapable of starting a family.

Proponents of hESCs, including the British Humanist Association, might argue that it could be deemed more acceptable to sanction the life of an embryo, which before
the 14 day stage has no brain, no self awareness or capacity to feel pain, in the hope of improving and prolonging the life of a human being with a brain, with self awareness and who is enduring the pain and suffering of a debilitating and often degenerative disorder such as AMD or Parkinson’s Disease, to name but two such conditions. Moreover, tests are often carried out on animals in the early stages of drug testing, followed by clinical trials on those participating in human research. Even these drugs, considered ‘safe’ and ‘effective’, may cause unwelcome and undesirable side effects; however the pursuit of stem cell research aspires to isolate a therapy which is not dependent on drugs which require such trials. Ethically, it could be argued that tests on embryonic stem cells cause less distress than in alternative animal or human testing.

The rapid advances being made in the field of stem cell research have led some observers to become increasingly apprehensive about future research projects and to question where next the science might evolve. Although the aim of current research is to discover whether stem cells are safe and effective when used to treat certain medical conditions, professionals and the public alike harbour concerns for the future, recognising the potential for such treatment methods to be exploited into the controversial realms of cloning, synthetic biology and even the ‘creation of human life’ with the selection of features deemed more aesthetically pleasing or culturally acceptable.

Ultimately, questions concerning stem cell research will only be answered in the fullness of time when further research has been carried out and the long term benefits or risks become more apparent and are subjected to rigorous evaluation. Until then, medical professionals have the task of quantifying risks and benefits before validating the process of Embryonic Stem Cell Therapy, satisfying the relative needs of patients whilst at the same time working within the boundaries of ethically acceptable practise and procedure.

Stem Cell Therapy has been hailed as the great panacea of the 21st century. These are exciting times in the field of medicine and there have been promising results from stem cells assisting in the repair of heart muscle damaged as a result of a heart attack and there is hope of a successful stem cell treatment for restoring the production of insulin in patients suffering type 1 diabetes but illness and disease might be considered nature’s way of population control in a world struggling to feed its seven billion inhabitants. There are ethical concerns about the ability to prolong life in the face of limited resources.

Aside from the use of stem cells to treat macular degeneration, what other options are available? Ophthalmologists treat with caution talks of a miracle cure for fear of compromising the already limited sight enjoyed by a patient who initially presents with the symptoms of early onset AMD. Invasive treatments usually carry an unacceptable level of risk, leaving surgeons with the difficult task of quantifying risk against potential benefit.

Unfortunately, most of the current treatments available for patients with macular degeneration aim to slow down or prevent further vision loss as opposed to
attempting to improve vision in those with the condition. Treatments such as Thermal Photocoagulation; where an Argon or Krypton laser shines a beam upon the affected area of the retina, in the hope of burning the abnormal blood vessels beneath the macula to induce the formation of scar tissue which acts to prevent leakage from these blood vessels; and macugen treatment; whereby a drug named macugen is injected into the eye via an intravitreous injection; the aim being to impede VEGF (Vascular endothelial growth factor; a protein found in the eye that causes the growth of abnormal blood vessels) and thus prevent the formation (and leakage) of any new blood vessels; are both effective in slowing the gradual degeneration of vision but are incapable of improving vision, or curing the condition.

However, research has led to the discovery of Ranizumab as a treatment for Macular Degeneration. Present in Lucentis, this antibody is thought to target VEGF-A in the hope of not only preventing the deterioration of vision caused by the leakage of blood vessels but aiding the improvement of already poor vision.

In the development of macular degeneration, blood vessels in the back of the eye begin to grow abnormally and often leak or bleed into this area, resulting in a rapid and significant reduction in central vision. Vascular endothelial growth factor A (VEGF-A) has been identified as the substance responsible for causing the blood vessels’ abnormal growth and leakage. Ranibizumab is a monoclonal antibody that has been designed to specifically recognise and bind to Vascular Endothelial Growth Factor A. By binding to VEGF-A, Ranibizumab blocks the action of this substance, and aids in suppressing the growth and subsequent leakage of blood vessels in the macula. The medicine has been associated with a twofold advantage; it can help improve damaged vision, or prevent it from getting worse.

In an investigation carried out by Philip J. Rosenfeld, M.D., Ph.D et al into the efficacy of Ranibizumab, published in the New England Journal of Medicine (October 2006), it was reported that the therapeutic use of Ranibizumab resulted in clinically and statistically significant benefits with respect to visual acuity, with a very low rate of ocular adverse effects.

Dr. Rosenfeld conducted a randomized study over two years, involving 716 patients gathered from a diverse area; 96 separate sites in the USA. Two thirds of the 716 patients were given a dose of either 0.3mg or 0.5mg of Lucentis (containing Ranibizumab) with the remaining third administered with a ‘sham injection’ or placebo. Each patient’s visual acuity was examined and recorded at the start of the trial, and compared with the findings at 12 and 24 monthly intervals. It was noticeable at the outset that the participants in the trial had lost the ability to recognise the baseline characters on the sight chart.

The results showed that between 12 and 24 months, approximately one quarter of patients treated with 0.3 mg and one third of patients treated with 0.5 mg of Lucentis had gained 15 or more letters in visual acuity, compared to a mere 5% or less of those administered with the ‘sham injection’.

Results further highlighted the apparent efficacy of Ranibizumab when, at 12 months, mean increases in visual acuity were 6.5 letters in the 0.3mg group and 7.2
letters in the 0.5-mg group, as compared with a decrease of 10.4 letters in the ‘sham injection’ group, as evidenced on the graph below.

CONCLUSION

The use of hESCs to treat diseases such as macular degeneration is still a fresh and developing area of medicine – much more research needs to be carried out concerning stem cells before any kind of treatment method can begin. By no means can it be said that a ‘cure’ has been found for macular degeneration through the use of human embryonic stem cells. Further developments need to be made in order to make this procedure accessible and efficient; just some of the possible developments have been detailed above. For example, it may be possible for a large number of cells to be inserted into the eyes in order to maximise the chances of cells attaching to Bruch’s membrane and integrating into the remaining ‘natural’ RPE layer. It may be possible also to induce cells to develop lightly pigmented as opposed to heavily pigmented, as it seems that the cells that attached and integrated better in the two patients treated were those that were lightly pigmented. A further development with a particularly large benefit would be the establishment of a stem cell line on a large scale, which would not only be an advantage to those with macular degeneration, but also to other sufferers of diseases that could later be treated using human embryonic stem cells.

These developments will present with major problems in the future. Of course, there is much controversy surrounding the use of hESCs, and the constant war waged on their use by so-called ‘medical ethicists’ presents a large problem for scientists trying to develop them. There would have to be further trials involving human embryonic stem cells, and many would argue that such waste of human life and human potential is categorically wrong. Although the use of stem cells to treat diseases would be a revolutionary achievement, this does not mean to say that their use is right. There are also difficulties involved with establishing a stem cell line. Setting up
the line itself is often unsuccessful after many attempts. Another problem with the use of hESCs that continually divide is the risk of a tumour occurring; if an undifferentiated cell is injected into the eye (somehow managing to sneak through quality control) there is the potential that it could turn cancerous and cause the formation of a teratoma – a type of cancer made of cysts that contains one or more of the three types of cells found in an embryo.

In response to the reservations that medical ethicists have surrounding the use of embryonic stem cells, Barak Obama stated: ‘As the US invests in science and innovation and pursues advances in biomedical research and healthcare, it is imperative that we do so in a responsible manner.’ This is a reminder to all that although we are in the process of making incredible developments into the use of stem cells, we should not forget that the sanctity and value of human life should always be acknowledged.

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Key facts on infertility, IVF and NHS provision