THE POTENTIAL USES OF EMBRYONIC STEM CELLS IN GENE THERAPY

By
STEPHEN AUGER

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Abstract
Following the lectures that I attended at Medisix, I searched the internet in order to gain a wider understanding of embryonic stem cells’ function and find out what current research was being conducted in this field. After a few weeks of considering the capabilities and properties of embryonic stem cells, I thought of a possible application for them in future medicine, as a vector for or for general use in gene therapy. As far as I could tell from searching the internet, no current or previous research had been conducted with this subject and so I decided use this as my research topic. I considered the applications, advantages and disadvantages of using embryonic stem cells for gene therapy and have come to the conclusion that they could be a very effective help in future medical gene therapy.

Introduction
Stem cells are unspecialized cells, with the capability of ‘differentiating’ into more than one type of cell and so develop as more than one form of tissue. They are able to replicate indefinitely and if they don’t specialise or differentiate in doing so, then they’re called a stem cell line. The stem cells may be totipotent (such as embryonic stem cells, able to develop into all the different types of cells of an organism), pluripotent (such as embryonic stem cell lines, able to develop into most types of tissue) or multipotent (being able to develop into a limited number of tissue types). The multipotent stem cells have already differentiated slightly and so are less capable of developing into any tissue type, for this reason, they’re less useful than the other two forms for medical research. They are the only type of stem cell present in an adult human body. For example, stem cells in the brain form neurones and glial cells, but researchers are unable to form cells from other organs in the body from stem cells found at the brain.

The pluripotent stem cells have the widest potential to developing into any cell type and so these are used most by researchers. Embryonic stem cells are extracted just five to six days after the first cell of an embryo begins dividing. Removing the forty or so cells that exist at this time, cause the embryo to stop developing and so the existence of the embryo is brought to an end. This stops the development of a human being, which is the source of much controversy. However, once the embryonic stem cells are extracted, they are just like any other form of human tissue and lose their ability to develop into a human being. Once extracted, the stem cells are kept alive and replicate/proliferate indefinitely. In the future, researchers hope to be able to introduce stem cells at this stage to the right conditions to allow them to develop into specific tissue types and so grow ‘spare’ tissues or maybe one day even ‘spare’ organs for transplant.

Gene Therapy is an application of genetic engineering, used to replace defective genes with effective ones. The defective gene may result from an incorrect base sequence in a DNA molecule or an inability of a certain gene to express the characteristics it codes for. Gene Therapy uses vectors, such as adenoviruses, retroviruses or liposomes to insert a normal gene into a cell in the place of a defective one. These vectors have their limitations, which currently limit the success of present-day gene therapy. Gene delivery is ineffective and brings about an immune response from the body; also any gene therapy is short lived, as the current vectors can only alter the outermost cells of tissues/organs, which soon die and are replaced. Gene Therapy has the potential to cure many genetic diseases such as Cystic Fibrosis, a cure for which would be an exciting and influential breakthrough in modern-day medicine.

Discussion
Clearly gene therapy has great potential as a possible future cure for currently incurable diseases. However, its methods are currently highly limited in practice. For gene therapy to be an absolute success, problems with gene delivery and expression have to be overcome. This is where I believe embryonic stem cells could possibly be of help.

Embryonic stem cells could be manipulated into ideal vectors for the delivery of these genes. In delivering a gene, many difficulties have to be overcome; delivery needs to be to the correct organ and has to be able to cross the relevant cell membrane in order to enter the nuclei of defective cells and express itself; lysosomal degradation is also a problem. The primary problem with current vectors, however, is the immune response they induce in the patient’s body. Vectors derived from embryonic stem cells would bring about no/little immune response and so make gene delivery less problematic and more comfortable for the patient. The ability of embryonic stem cells to differentiate into any cell type means a vector could be designed to avoid all current problems with gene therapy. Genes delivered by a vector which is accepted by the body are likely to be readily accepted by the cells of the defective organ/tissue and so gene expression could potentially be more successful. A vector could be designed to carry much more genetic information than current delivery systems which can only carry up to 30kb of genetic information at this moment in time, giving the potential for treatment of more extensive genetic disorders. Lysosomal degradation would also no longer be a problem. So such vectors could aid the progression of gene therapy to great effect.

However, this method of gene delivery still has its limitations. The problems associated with ensuring the gene is delivered to the correct organ in the human body would still be present. With treatment of conditions such as cystic fibrosis, it is easy to access the problem areas with an inhaler (for accessing the lungs) or pills (to treat the problems in the digestive system). If the genetic defect were in the brain, though, then it would be much more difficult to deliver some sort of gene treatment to this area alone. Also the very nature of embryonic stem cells means that there is the possibility of uncontrolled proliferation of the stem cells, which could result in a cancer forming. The treatment has the potential to perhaps be fatal. Also the problems that come with gene expression would remain unsolved. The gene needs to be expressed in the correct tissues, at correct levels and at correct times in a way that the cell can regulate. This would require some sort of manipulation of the gene itself and not just the vector.

The problem of possible uncontrolled proliferation could in theory be prevented by only using the embryonic stem cells to encase a current vector used in gene therapy. This would ensure immune response was still prevented, whilst removing/severely limiting the possibility of a cancer forming. However, gene expression may only be relatively short lived with this method of delivery, as the gene delivered may not be able to be fully integrated into the genome of the patient. Both of the potential uses of embryonic stem cells in gene therapy I have suggested are still limited in that even if gene expression is successful, once the cells treated die and are replaced by new cells (as happens naturally in the body), these new cells would not contain the effective DNA. For this to be possible, all the cells in the body would have to be treated, which would be near impossible and highly expensive even if it were possible or the early embryonic cells would have to be treated. However, this is
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both illegal and highly unlikely to have no side effects; any current gene therapy is only permitted on mature somatic cells.

Nevertheless, I still believe the combination of gene therapy treatment and use of embryonic stem cells has great potential to cure many diseases. Instead of using the embryonic stem cells to aid gene therapy, embryonic stem cells could undergo gene therapy and be transplanted into the body, once fully differentiated, to replace defective tissues. This would require much more advanced science and could not be carried out for a number of years, due to its complexity. However, it could be the key to future genetic treatment. If whole tissues or even organs could be cultured, genetically modified and transplanted into the human body in the place of genetically or even non-genetically defective ones, then any medical problem could in theory be curable in the future. However, it may be centuries until the relevant science and understanding of the human body have progressed to make this a safe possibility. Also, the potential problem of uncontrolled cell proliferation may still affect the feasibility of this form of treatment. This level of scientific research and experimentation would also require vast amounts of funding, which could probably be better spent elsewhere.

**Conclusion**

Clearly, embryonic stem cells could theoretically provide great breakthroughs in gene therapy in the future. Their ability to be inserted into the human body without inducing an immune response could be extremely useful. Vectors composed of embryonic stem cells would be extremely stable and so perhaps have a longer lasting effect on the defective genes being treated, providing more effective, less discomforting treatment. Their potential to hold vast amounts of genetic material could also cause great advances in gene therapy. Embryonic stem cells do provide many prospective dangers though. The possibility of uncontrolled proliferation could bring about fatal side-effects and the lack of current knowledge on the subject means development will be slow and probably extremely expensive.

However, I believe embryonic stem cells treated with gene therapy before being transplanted into the body could be a realistic way forward in embryonic stem cell research. Such experimentation could be tested outside the human body before trial inside the body, making it much less harmful and potentially life threatening. Nevertheless, there are still many limitations and potential problems with this form of medical treatment. Before genetically modified embryonic stem cells can be used as a common, widespread treatment, a vast number of practise trials will need to be conducted. This would be extremely expensive and could still threaten lives whilst we are still uncertain about what the consequences of such treatment are. Trials for gene therapy at the Necker Hospital in Paris, led to three of the eleven test subjects developing leukaemia, which is potentially fatal. To date there is no evidence that cells generated from embryonic stem cells can be safely transplanted back into adult animals to restore the function of damaged or diseased adult tissues. Also even if the treatment seemed successful at first, the long term consequences could still not possibly be known, due the complexity of the human genome and immune system. Therefore, even though the use of embryonic stem cells in this way could potentially be extremely influential in future medicine, I believe that experimentation in this field is reasonably unlikely, as any progress will be limited and extremely expensive. A
naïve faith in the scientific theory behind the use of embryonic stem cells in gene therapy could waste vast amounts of money which could be better spent elsewhere and cause serious illness, maybe even death in the subjects tested.

References


