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Short Review

Gene Therapy – Potential, Pros, Cons And Ethics

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Gene therapy offers an incredibly powerful tool for preventing and curing disease and is based on aiding the human body in fighting a disease or the expected onset of a disease The genetic technology involved with gene therapy is not based on altering the human germ line as the misconception goes, a practical truth that many fear misuse of. This type of technology is more similar to medical treatments of the past than most people realize; gene therapy simply takes advantage of the human body's ability to produce its own cure more quickly, safely and effectively than can be done in a lab. Gene therapy lends itself to numerous medical applications.

Basic gene therapy approaches usually involve adding something to a gene through a variety of vectors. Most research and testing has been done with the vector introduction of a sequence that codes for a needed protein, either to counter a deficiency, induce a strong immune response, or destroy tumor cells. Examples of a needed protein introduced to cure a disease include factor IX in hemophilia, and the cystic fibrosis transmembrane conductance regulator (CFTR).(1) Mutations in CFTR cause the lethal genetic disease cystic fibrosis, but gene therapy may be able to cure the disease by introducing the wild-type CFTR into the individual. Once the necessary sequence is incorporated into a vector and introduced into the cells, the necessary protein can be coded for. In this case, the human body is directed into producing the required remedy itself- gene therapy only gives it the plans it needs to produce its own medicine.

Many genetic diseases are polygenic and do not easily lend themselves to such corrective methods ad hence the direct method mentioned above may not be practical always. More effective, and most popular, is another genetic therapy approach that primarily involves altering the immune system. Although some individuals may be genetically predisposed to contracting a certain disease due to an immune deficiency, and therefore may need a boosted immune response the most, most patients could successfully combat their disease with an increased immune response. Customized DNA vaccines could encode for the cancer-specific antigens of the patient. The vaccine would elicit an enhanced immune response to eliminate the unwanted cells.(1) Evidently here, gene therapy simply strengthens the body's own defense response instead of attempting to cure the cancer with methods that could harm the entire system. Even genetically modified T lymphocytes expressing specific receptors designed to enhance their ability to identify and destroy the cancer cells are being developed.

The immune response is not always helpful. Its extreme sensitivity to foreign cells and their antigens may be the first factor that has to be resolved, especially when it is necessary to introduce foreign cells into the body. When a transplant is performed, not only is there a fear that the body's immune system will attack the needed cells, but also that the transplanted T-cells may attack some of the body's vital organs such as the liver, gut and skin. To defeat this disease called "graft-versus-host disease", a

gene therapy technique was developed involving a drug-activated response. Genetically engineered with a self-destruction signal, these "suicide" genes are genetically altered to include a sequence that, when triggered by a drug, will make the cell toxic. Although attempting to sift out all the mature T lymphocytes would make the procedure far safer, practicalities leave it far behind. If a transplanted bone marrow's T-cells begin to attack the host's body, the drug can be administered and the foreign cells will be destroyed before graft-versus-host disease can develop.(2) Taking this procedure, otherwise known as "prodrug activation", a step further could lead us to an entirely new approach to curing diseases such as cancer. By introducing this toxic gene expression into cancer cells, they can be destroyed by administering the corresponding drug. This experiment was successfully conducted in mice, where the prodrug gancyclovir triggered the expression of the herpes virus thymidine kinase. Not only did the cells containing the new sequence die, but even neighboring cancer cells were observed to die due to a bystander effect.

The ability to express an introduced gene at any time and for any duration by simply swallowing a pill makes this type of gene therapy very practical; it would offer an attractive and controlled form of administering therapeutic proteins such as monoclonal antibodies, interferons and even certain growth factors. Adding a coding sequence to a cell is the standard method of conducting gene therapy, and has been most successful, but new approaches take a more complex approach towards curing disease. By actually altering the genetic sequence, instead of simply supplementing it, genetic therapy may be even more powerful in eliminating disease. An approach to defeating such diseases as HIV, hepatitis B, and hepatitis C involves using a ribozyme molecule to cut and destroy certain RNA molecules that correspond to the particular virus.(1) An even more complicated approach involves repairing the gene using chimeric oligonucleotides. Homologous recombination is the natural process that controls the replacement of a defective gene. Gene therapy can harness this natural process and have the body repair its DNA itself. DNA repair is highly precise, and by using DNA oglionucleotides to introduce site-specific changes in the genome, a single incorrect base can be corrected.

Diseases like sickle-cell anemia, that are caused by a single point mutation, are prime candidates for this gene therapy Experimentation on mice have provided promises.(3) Unfortunately, transferring the chimeric oglionucleotide is very inefficient and must be improved on to make the process practical.(4)

As strategies for local expression of the genetically altered cells are developed, even more new possibilities are opened. Arthritis patients could release an anti-inflammatory response from proteins in inflamed joints, and asthma sufferers could similarly reduce the inflamation associated with their ailment. Bio-artificial organs have been proposed, and even tested in some animal trials, that could be transplanted in whole and serve as centers for producing particular proteins.(1)

Even certain aspects of the vector delivery system for the sequences make interesting use of certain diseases. The HIV virus and its ability to infect non-dividing cells could be a boon for medicine. With this ability, HIV could emerge as a very effective viral-vector for delivery into even dormant cells, such as neurons, can be infected without instigating a heavy immune response.(5) In tests with mice, the expression was efficient and stable.(6) A deep concern, of course, accompanies the use of HIV in any form, and its safety would have to be thoroughly confirmed before its use could proceed. Many of the issues associated with gene therapy go far beyond the scientific and medical ones.

A topic, where much of the ethical concern within gene therapy has pooled, is the *in utero* use of gene therapy. Correcting genetic defects in a fetus before birth could allow many children to be born that otherwise would never have survived, and many to live a longer and more enjoyable life than would otherwise be possible. Tests to cure homozygous thalassemia, a hemoglobin disorder that would normally kill the fetus before birth, and a severe immunodeficiency due to a lack of the adenosine deaminase enzyme are some of the first tests planned.(7) However, a new risk is created-the possibility that transplanted genes could end up in the germ line and then be passed on to future generations. Fears like these become even more real when we consider how thin a line exists between reality and ethics of gene therapy.

Can the benefits of such therapy be passed on to the future generations? The current protocols are meant for only somatic cells and hence would be apt to name it "Somatic Gene Therapy". However, if the introduction of a tumor suppressor gene into a germ line cures cancer permanently down the generations forthcoming, it would perhaps be more acceptable than somatic cell protocols.

Conclusion

What should this mean to the scientists and the public today? Should research be stopped in fear of the possible abuses of such abilities? This is the same question science has asked itself many times before, and gene therapy is no different. Genetic technology poses risks along with its rewards, just as any technology has in the past. To stop its development and forfeit the benefits gene therapy could offer would be a far greater mistake than forging ahead could ever be. People must always try to be responsible with their new technology, but gene therapy has the potential to be the future of medicine and its possibilities must be explored. If one could permanently correct a mutation such as those causing Sickle cell anaemia or Cystic Fibrosis (8) in the germ line of an individual, giving the additional benefit of keeping the future generations

away from the risk of inheriting the same mutation, the ethically alert society may consider such molecular therapeutic intervention essential.

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