Gene Therapy

6.5

On September 23, 2009, news headlines read "Historic Gene Therapy Trial to Treat Alzheimer's Disease." **Gene therapy** is a brand-new experimental technique in which scientists try to overcome the negative effects of a defective gene by adding a normal gene, or try to repair the defective gene. The cells in which the gene needs to be replaced or repaired are known as **target cells**. In order to insert a normal gene into the genome, a specialized DNA sequence, called a **vector**, must be used to carry the gene into the target cells.

gene therapy the process by which defective genes in a genome are corrected with a normal copy of the gene

target cell one of the cells that contain the faulty gene to be corrected

vector any agent, such as a plasmid or a virus, capable of inserting a piece of foreign DNA into a cell

The Process of Gene Therapy

In Section 6.4 you read that plasmids, a type of vector, are used to carry genes into bacterial cells. Plasmids are useful, but they cannot be used in mammals. The vector of choice for mammals is a virus. Viruses are chosen depending on which type of target cells they need to enter. For example, a cold virus (**Figure 1**) would be a good choice to target lung cells, but not liver cells. The basic process of gene therapy is this:

1. Scientists remove or alter viral DNA so that the viruses cannot harm the cells they enter.
2. Copies of the DNA that include the normal human gene are placed inside each virus and are incorporated into the virus's own DNA.
3. Large numbers of these viruses are used to infect the target cells in an attempt to insert the normal human DNA into the cells' genome.

One limitation of this technique is that there is no way to control where the normal gene is inserted into the target cell's own genome. Recall that most of a genome is non-coding, so usually the inserted gene has no impact on the DNA around it. However, in rare cases the new gene might be inserted into a coding region, and this can disrupt the normal functioning of other important genes.

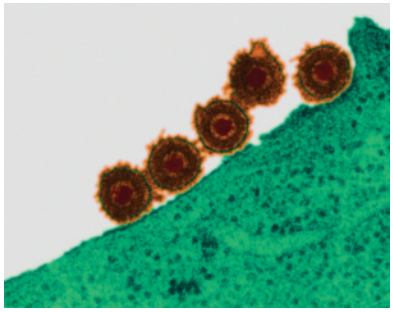

Figure 1 Viruses such as this adenovirus are good vectors for gene therapy. They are able to infect the target cell and transfer their DNA into the target cell. Normally, viruses insert their own DNA and force body cells to make more viruses. However, viruses can be tricked into helping the cells they invade cure themselves by introducing corrective DNA.

Does Gene Therapy Work?

Currently, gene therapy is still in the experimental stages, and no gene therapy product is available for sale. The progress of research has had both minor and major setbacks as well as successes.

Setbacks

In 1999 gene therapy experienced a huge setback when 18-year-old Jesse Gelsinger died. Jesse was being treated for ornithine transcarboxylase deficiency (OTCD). OTCD is a disease of the urinary system in which the body cannot get rid of ammonia. The ammonia builds up and causes liver damage, skin lesions, and developmental delay. Four days after starting the gene therapy treatment, Jesse's organs failed. Doctors believe that Jesse had an unexpected severe immune response to the virus. Recall that a virus delivers the normal gene. Your immune system is programmed to fight viruses. An immune response is expected and planned for, but in Jesse's case, the response was so severe that it led to his death.

In January 2003, gene therapy experienced another setback. A child who had taken part in a French gene therapy experimental trial developed leukemia. The leukemia appeared a few years after the gene therapy had been completed. Another child in the study had the same experience. Both children were being treated for severe combined immunodeficiency (SCID) syndrome, which is also known as "bubble baby" syndrome. Babies who have SCID are born with an underdeveloped immune system and usually die within their first year if exposed to viruses such as chicken pox. They are kept in isolation. In these cases, it seemed that the gene therapy activated another gene that causes leukemia, though scientists have not determined how that happened.

Gene therapy has several obstacles to overcome before it can become an effective treatment. These obstacles include the following:

- The normal gene inserted into the target cell must work for the duration of the target cell's life. Cells are constantly dividing because of mitosis. Therefore, many treatments of gene therapy may be required in order to ensure the normal gene becomes a permanent part of the target cell genome.
- It is not possible to control where a gene is inserted. If it is inserted in the middle of another gene sequence, it may disrupt the function of that gene and may result in more health challenges.
- The body's immune response must be constantly monitored because it is possible that the immune system will attack the foreign virus. Immunosuppressant drugs can be used, but they carry risks of their own.
- The virus may recover its ability to cause disease once it is in the target cell.
- Many disorders are caused by more than one gene. It is difficult to fix all the genes.
- Once the gene is transferred into the target cell, it needs to be regulated so that it is expressed at the required times. For example, a gene that regulates the production of insulin would need to be able to detect a low sugar level in the blood. If sugar levels are low, the gene that directs the production of insulin should not be turned on.
- The vector that is chosen must be able to reach all or most of the target cells specifically.

Successes

There are several examples of successful gene therapy. These include restoring vision in patients with an inherited retinal disease, repairing the gene that causes Duchenne muscular dystrophy, and restoring hearing after hairs in the inner ear are damaged.

INHERITED BLINDNESS

Veterinary vision scientists at the University of Pennsylvania have had success with gene therapy in dogs. The scientists have successfully transferred DNA to photoreceptors in the eyes of dogs to solve sight issues. Photoreceptors are cells in the retina that capture light and change it into an electrical signal that the brain can interpret. These cells were genetically defective in some dogs.

The success of this work is significant, because dogs are excellent model organisms for humans. Recall that model organisms have genomic characteristics similar to those of humans. Therefore, if a procedure works in a model organism, it is more likely to be safe to try in human trials.

In humans, a form of childhood blindness called Leber's congenital amaurosis (LCA) is the first inherited retinal disease for which gene therapy has been tested. Gene therapy has been performed on 12 patients, resulting in almost complete restoration of their vision. **Figure 2** outlines the experimental procedure.

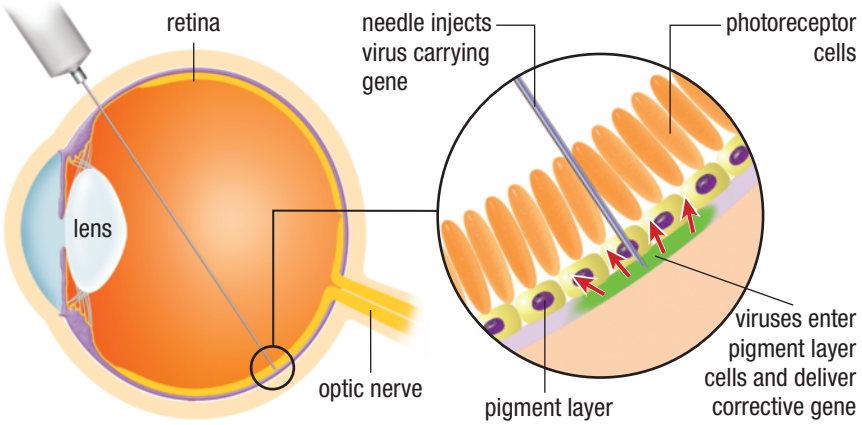

Figure 2 Gene therapy for Leber's congenital amaurosis (LCA). LCA is caused by a genetic defect in pigment layer cells on the retina. These cells are needed to support the photoreceptor cells.

1. An eye syringe is used to inject viruses carrying a normal gene behind the patient's pigment cell layer.
2. The viruses infect the pigment cells and deliver the normal gene.
3. The cells incorporate the normal gene, which restores normal functioning. This results in improved vision.

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) is a severe recessive form of muscular dystrophy. It is sex linked, so it affects mostly males. People who suffer from DMD experience rapid muscle degeneration and have about one-third to one-half the usual life expectancy.

Researchers at Université Laval's Faculty of Medicine have successfully shown that it is possible to repair the gene responsible for DMD. A class of molecules known as meganucleases is able to repair the incorrect base-pair sequence in the faulty dystrophin gene. All the work thus far has been in mice, but it is possible that human trials will begin in two or three years. Considering all the research being done to find a cure for DMD, Muscular Dystrophy Canada believes that gene therapy holds the most hope thus far.

DEAFNESS

Sounds move tiny hairs in the cochlea of the inner ear. The hairs translate sound vibrations into nerve signals that are delivered to the brain. Normally, when hairs are damaged and hearing is lost, the change is permanent.

In 2005, a successful trial was conducted to restore hearing in guinea pigs. The guinea pigs had damaged hairs in their ears. A virus was used to deliver a gene that stimulated the growth of new hairs in the cochlea. Up to 80 % of the guinea pigs' ability to hear was restored! This is considered a hopeful new research direction.

6.5 Summary

- Gene therapy is an experimental technique used to possibly correct the effects of defective genes by inserting a normal gene into the genome or correcting the mistake in the gene sequence.
- There are several drawbacks to gene therapy: placement of the normal gene is random and cannot be controlled, an immune response could be triggered if a virus is used as a vector, and it is difficult to target disorders that result from mutations of multiple genes.
- Gene therapy has shown promise in the treatment of inherited blindness, Duchenne muscular dystrophy, and deafness.

6.5 Questions

1. Outline, using diagrams, the process of gene therapy. K/U C A
2. What characteristics enable viruses to be used as vectors in gene therapy? K/U
3. What are some of the challenges that scientists have to overcome in gene therapy? K/U A
4. Use the Internet and other sources to research a gene therapy success story or a gene therapy setback. Report your findings in two or three paragraphs. T/I C A
5. Make a list of ethical considerations for using gene therapy. Discuss your list with a classmate or group. T/I C A
6. Imagine that you are a member of the medical personnel on a starship colony of humans in the year 2112. Write a personal diary entry describing how gene therapy is used to treat your patients, who are affected by the disorders described in this section. K/U T/I C A

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