24.3 CLINICAL APPLICATION

Targets of Gene Therapy

Researchers use several methods to introduce therapeutic genes into cells. Healing DNA is linked to the genetic material of viruses from which the known disease-causing genes have been removed; in fatty bubbles called liposomes or complexed with other lipid molecules; "shot" along with metal particles into cells; and as "naked" preparations of DNA alone. The challenge in any nonheritable gene therapy is to target sufficient numbers of affected cells for a long enough time to exert a noticeable effect. Different tissues and organs present different challenges, described here and summarized in figure 24C.

Bone Marrow

Because bone marrow includes the precursors of all mature blood cell types, it provides a route to treat blood disorders and immune deficiencies. Certain stem cells in bone marrow can also travel to other sites, such as muscle, liver, and brain, and either give rise to cells that differentiate there into, respectively, muscle, liver, or neural cells, or fuse with cells. Therefore, many gene therapy targets might be reached via bone marrow.

Skin

Skin cells grow well in the laboratory. A person can donate a patch of skin the size of a letter on this page; after a genetic manipulation, the sample can grow to the size of a bathmat within just three weeks. The skin can then be grafted back onto the person. Skin grafts genetically modified to secrete therapeutic proteins, such as enzymes, clotting factors, or growth hormones, may provide a new drug delivery route.

Muscle

Muscle tissue is a good target for gene therapy for several reasons. It comprises about half of the body's mass, is easily accessible, and is near a blood supply. However, a challenge is to correct enough muscle cells to alleviate symptoms.

Endothelium

Endothelium, which forms capillaries and lines the interiors of other blood vessels, can be altered to secrete a substance directly into the bloodstream. Genetically modified endothelium might secrete insulin to treat diabetes mellitus or a clotting factor to treat hemophilia.

Liver

The liver controls many bodily functions and is a good gene therapy target. A gene therapy that corrects just 5% of the 10 billion cells of the liver could produce an effect. For example, normal liver cells have low-density lipoprotein (LDL) receptors on their surfaces, which bind cholesterol in the bloodstream and bring it into the cell. Liver cells genetically altered to have more LDL receptors can relieve the cholesterol buildup of familial hypercholesterolemia (see fig. 24.7).

Lungs

An aerosol can directly reach respiratory tube lining cells, making it unnecessary to remove cells, alter them, and reimplant them. Lung epithelial cells take up inhaled genes and produce the proteins missing or abnormal in the inherited illness. For example, such gene therapy can provide alpha-1-antitrypsin, an enzyme whose absence causes a form of emphysema.

Nerve Tissue

Gene therapy of neurons is not feasible because these cells do not divide. Altering other cell types, such as neuroglial cells or fibroblasts that secrete nerve growth factor, can circumvent this obstacle. Or, a therapeutic genetic change can be made in neural stem cells. Another route to nerve cell gene therapy is to send in a valuable gene attached to the herpes simplex virus, which remains in nerve cells after infection. Such a herpes gene carrier could alter a neuron's ability to secrete neurotransmitters. ■