Genes that kill malignant skin cancer cells

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Is it possible that our own genes hold the key to finding new ways to fight cancer? Researchers at London's Brunel University think so. In February, they announced the discovery of two new genes that dramatically halt the growth of malignant melanoma, a type of skin cancer. It is hoped that by unlocking the secrets of how these genes work, scientists will be able to develop new ways to treat this deadly disease.

These Tumour Suppressor Genes (TSGs) are important in controlling the growth of cells. Cancer is a disease that causes cells to multiply uncontrollably. Scientists have known for some time about the ability of TSGs to stop healthy cells from becoming cancerous. For example, one such TSG--P16--is known to inhibit melanoma.

In laboratory tests at Brunel, scientists transferred groups of healthy genes directly into melanoma cancer cells, and discovered another two TSGs that dramatically stop the malignant growth of the cells. The discovery paves the way to isolate and clone (copy) the genes so that scientists can find out more about the way they work and exactly how they stop the disease.

One of the researchers, Professor Newbold, commented: "This is an exciting discovery. We now know that by placing these genes into the cancer cell they stop malignant melanoma in its tracks. This is really just the beginning, because at this stage we have no idea how the new genes work. By finding out more about their function it may eventually lead to new ways of treating malignant melanoma."

The urgency of the research can be seen from the figures relating to melanoma. In the United Kingdom, 1,500 people die each year. In the United States 32,000 cases are diagnosed annually and the incidence is increasing by 4.3 percent a year: one of the fastest rates of increase for any cancer. According to the American Academy of Dermatology, one person dies from malignant melanoma every hour and, by the year 2000, an American's lifetime risk of developing melanoma will be one in 75.

The disease is now the most commonly occurring cancer in women between the ages of 25 and 29, and is second only to breast cancer in women aged 30 to 34. Skin cancer rates in Australia are the highest in the world with a lifetime risk of one in 50 for melanoma. The disease is the most common cause of cancer deaths in people aged 25 to 40.

Melanoma is a cancer of the melanin-forming cells; tumours usually occur in the skin but are also found in the eye and the mucous membranes. The spread of the cancer to other parts of the body, especially to the lymph nodes and liver, is common and often rapid.

There is considerable evidence that skin cancers are mainly caused by exposure to ultraviolet radiation from sunlight, particularly high exposure to sunlight during childhood. The depletion in the ozone layer has had a significant impact on the increased occurrence of skin cancers. For example, Australia suffered an average 2 percent ozone loss over the period 1980-88, and an estimated annual average ultraviolet B increase of 3 to 11 percent over the same period. For every 1 percent increase in UV radiation, a corresponding 2,500 new cases of skin cancers are expected each year.

At present surgery is the most common treatment for melanoma. Other treatments include chemotherapy, immunotherapy, radiation therapy or a combination of the three. Chemotherapy and radiation therapy are very damaging both to the cancer cells and also to the patient's healthy cells, and can actually lead to further malignancies.

Immunotherapy, also known as biological therapy, is designed to help the immune system to fight off the malignant cancer cells. Interferon and Interleukin are common forms of immunotherapy used for melanoma. Interferon, a substance naturally produced in the body, works to boost the body's immune reaction to cancer

cells and may even inhibit the growth of these cells. Interleukin stimulates the growth of white cells, the body's main defence mechanism.

Gene therapy may offer a radical new approach in the treatment of melanoma and other cancers. Over the past decade, considerable advances have been made in understanding and manipulating genes. Genes are the biological units of heredity that determine a person's traits such as hair and eye colour, or more complex characteristics such as the oxygen-carrying ability of the blood. It is estimated that a human being has 100,000 genes. A flaw in almost any one of them can result in a disease.

One of the first diseases to be treated with gene therapy was adenosine deaminase (ADA). This rare genetic disease occurs when children are born with a deficiency of an enzyme called adenosine deaminase, which is essential to the functioning of the immune system. As a result, ADA-deficient children are prone to repeated and serious infections. Even the most minor of viral illnesses can be life threatening. The ADA gene therapy trial began in September 1990. Two children were treated and the results have been promising. Since then trials using gene therapy have been tested on other genetic disorders such as cystic fibrosis and familial hypercholesterolemia (high serum cholesterol), cancers such as melanoma, neuroblastoma and brain tumours, and AIDS.

Scientists researching the treatment of cancer with gene therapy have three basic approaches. One way is to genetically alter a person's immune cells that are already naturally targeted to kill cancer cells. By arming immune cells with cancer-fighting genes, it is hoped they could more forcefully attack the cancer. Clinical trials along these lines are in progress for the treatment of melanoma.

Another method is to take cancer cells from the body and alter them genetically so that they elicit a strong immune response. These cells can then be returned to the body to act as a type of cancer vaccine. Various clinical trials using this approach are under way.

The third approach is to inject a tumour with a gene that renders the tumour cells vulnerable to an antibiotic or other drug. Such trials are in progress for the treatment of brain tumours.

There are, however, major problems yet to be overcome before gene therapy can become a common way of treating diseases. Scientists have to learn how to isolate and deliver curative genes. They have to develop vectors (carriers) that can be injected directly into the patient. These vectors have to be able to home in on cancer cells and successfully integrate the desired gene into the DNA of these cells.

The vectors currently being tested include adenoviruses and retroviruses. Scientists select a virus that normally infects cells of the desired type. The gene chosen for transfer is snipped out of the DNA using so-called "restriction enzymes" that cut DNA at specific locations. This gene and a marker (or selector) gene are inserted together into the virus vector with the help of other enzymes. The altered virus infects the target cells, integrating the new genes with the existing DNA. By making use of the properties of the marker gene, such as sensitivity to a particular antibiotic, it is possible to select out those cells that have successfully integrated the new genes.

Two other advances are needed: methods for delivering genes consistently to a precise location in the patient's genetic material, and the ability to ensure that the body can regulate the transplanted genes.

Genetic research has developed at an astonishing pace over the last 40 years or so. In the early 1950s, James Watson and Francis Crick explained the structure of DNA. By the 1960s scientists had cracked the genetic code. In the 1970s, the discovery of "restriction enzymes" enabled researchers to isolate specific genes from DNA and then develop gene- splicing technology. During the 1980s, gene transfer systems using retroviruses and lymphocytes were first developed.

At this stage, gene therapies are considered experimental. The research at Brunel University is still in the realm of the laboratory test tube, but it opens up the possibility of developing treatments which target cancer cells directly without damaging healthy cells, and are thus far less toxic to the patient's body than chemotherapy and radiotherapy. Such a breakthrough would represent a major advance.