Cancer is a Complex Genetic Disease

Recent laboratory studies have made clear how a normal cell develops into a cancer cell. The information about the mechanisms through which cancer develops shows that cancer is a genetic disease. This DNA, which is the genetic material present in each cell, contains at least 40,000 instructions for the cell. These instructions are coded in the order of ten million building blocks. A genetic disease is one that arises from scrambling of the order or the structure of any one or combinations of these building blocks in the computer program of the cell.

In most cases, cancer tissue starts from a single tumor cell. Changes in hundreds of genes are required before the normal cell takes the irreversible step to cancer growth. Some of the scrambled instructions or genes are overly active, they are called oncogenes, while the other instructions are lost, missing or inactivated and these are called tumor suppressor genes. The discovery of these two types of changes in genes is important since they tell us how cancer starts and they provide a clue as how to develop treatment for cancer which is directed to fixing what is wrong and different about the cancer cell.

Over-expression of oncogenes and loss of function of tumor suppressor genes are usually involved in both malignant conversion of the cells and further growth of tumor cells. However, the growth of the cancer cells themselves due to the growth-promoting effects of overly active oncogenes or due to the loss of the braking function or suppressor function of tumor suppressor genes is not sufficient to establish a clinical cancer disease. A new generation of cancer drugs, like Gleevec, Iressa, Tarciva have been developed to block the cancer causing signals within cancer cells. Antibody molecules, like Herceptin, Retuxin and Ergotrix, block the growth promoting signals that push cancer cells into an unregulated pattern of growth. In contrast to standard chemotherapy, which is quite damaging to the normal tissues of the body as well as the cancer tissue, the drugs like Gleevec and the antibodies like Herceptin, are quite specific for the cancer cells and therefore relatively free of side effects. When the antibodies or the drugs like Gleevec or Iressa are added to chemotherapy, chemotherapy becomes more effective.
Nodules of cancer cells cannot grow beyond one to two millimeters without expanding their blood supply to access every increasing needs for oxygen and nutrients. In order to generate the additional blood supply, the tumor tissue stimulates the elaboration of its own vessel network, through a process called angiogenesis. Since the expanding vasculature of tumor tissue is unique among the tissues of the body, therapy is often targeting to what is unique about the inside surface of the blood vessels in cancer tissue. This is called tumor vascular targeting therapy. If one could cut the blood supply of the tumor it cannot grow beyond one to two millimeters, which means that they cannot grow enough to be diagnosed by the current diagnostic technology and cannot cause a clinical disease. New drugs like Avastin, block the signals that tumor cells release that induce the expansion of the blood supply. When Avastin is added to chemotherapy, the effect of chemotherapy is amplified.

Whenever an antigen either a microbial agent like bacteria or viruses or a foreign protein enters the body, the immune system can recognize those foreign invaders to keep the body healthy. This immune response is very specific and non-toxic for the normal tissues. Though most of the cancer patients has a fairly intact immune system, the cells of the immune system do not usually respond to tumor cells because the immune system cannot differentiate the normal and cancer cells and therefore cannot fight against them. Recently, ways of activating the body's own immune defense against infection to the cancer cell have been developed. This is called immunotherapy or cancer vaccine therapy.

**What is Gene Therapy?**

Gene therapy can be defined as the delivery of genetic elements to the cancer cell or to the cells of the immune response in order to correct the abnormalities in the cancer tissue or to induce an immune response against the cancer cell. The corrective strategies can involve replacing missing or defective genes, suppressing the action of unwanted cancer promoting genes, or programming normal or cancer cells to release into the systemic circulation molecules which suppress the growth of cancer cells or their vasculature.

In order to be successful in the gene therapy of cancer, the therapeutic genes should be introduced into the tumor cells or into the systemic blood stream which feeds all cancer tissue. The vehicles used as the transporters of the genes to the cells are called gene therapy vectors. The vectors used in cancer gene therapy are mainly the viral vectors, non-viral vectors and cells. The viral vectors include retroviruses, adenoviruses, adeno-associated viruses. The gene therapist uses the capability of the virus to enter and reprogram the action of cells for purposes of therapy. These strategies include the replacement of a lost tumor suppressor gene function or the inhibition of an over-expressed oncogene. The therapeutic genetic element is first placed into a viral backbone to produce a complete therapeutic viral vector.
Alternatively, the therapeutic genetic elements can be delivered into the cancer cells through droplets of fat called liposomes or nanoparticles. The genes themselves, in the form of naked DNA or DNA packed into particles can be administered locally or systemically.

A third way of delivering genes to the target tissues is accomplished by using blood cells, supporting cells called mesenchymal, or neuronal stem cells. All of these cells have the capability to home to particular types of target tissue through the bloodstream. In this way, the therapeutic genes can be placed into the brain or other target tissues because of the homing properties of those cells.

**How Could Gene Therapy Be Specific for the Cancer Cells?**

The clinical utility of a treatment is usually dependent on safety and efficacy. In order to maximize the therapeutic index of cancer gene therapy, the expression of therapeutic genes could be restricted to the target tissues. Therefore targeting of gene therapy vectors are the major keys for the success of those treatments. There are three main targeting strategies. The first one is physical targeting by means of some physical instruments as catheters, gene guns, etc. This strategy is usually used for local delivery of gene therapy vectors and is therefore not suitable for most of the cancer patients who may have cancer spread throughout the body. In a second strategy, the viral or non-viral carriers of the genes are modified in such a way that they can only bind to tumor cells but not the normal cells.

Selective targeting of gene therapy vectors to specific cells has a number of advantages. It delivers the genetic elements to the target cancer cells while sparing the normal tissues. This has the potential of the reducing the dose of vectors and thus the toxicity. In recent years, there have been many reports on the targeting strategies of viral and non-viral vectors of gene delivery. The third strategy of targeting is to engineer the vectors so that the therapeutic genes are produced only in the environment of the tumor tissue.

**What are the Targets for Genetic Therapy of Cancer?**

Current gene therapy studies have mainly focused on introducing the genes into the tumor cells to block the action of oncogenes expression, to block the development of tumor vasculature, or to induce the development of an immune response against the cancer tissue.

As mentioned before, the immune system has the key role as a defense mechanism of the body in many diseases. The recent developments in gene therapy have suggested to many cancer therapists that the tumor antigen-specific vaccination strategies have great potential for future use either in the treatment of an established disease or prevention of cancer in people having high risk of developing cancer.
What Are the Drawbacks of Cancer Gene Therapy and Is There a Future for Cancer Gene Therapy?

The most important factors that have limited the success of clinical gene therapy trials in human subjects is the delivery of the vector genetic elements or their products to the target cancer cells and their vasculature. A second problem has been toxicity. Recent advances on improving the delivery and specificity of gene therapy vectors have suggested that in the coming years, these trials may be more successful than in the past. This is especially true of the attempts to use vectors to activate the immune response against the tumor tissue. The continued testing of these strategies in the context of clinical trials may lead to new opportunities for individuals engaged in a personal struggle with cancer to control their disease.

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