

The Genetic Approach to Cancer

Why is the second leading cause of death still such a mystery to modern science? Cancer, a disease that has been plaguing both those who suffer from it and those who are attempting to cure it, continues to remain partially an enigma, evading comprehension. No one quite knows why any one person contracts cancer. There is no one single cause in any person. It is always a combination of factors or a sequence of factors that are said to cause the disease. However, almost everyone is at risk somehow, and one in two men and one in three women in their lifetime will develop it. The technology of medicine needs to catch up to the complexity of this disease if it is ever to be cured. Granted, there has been progress, but not enough to help the 553,400 people expected to die from cancer this year in the United States. That works out to 1,500 people per day. This disease of epidemic proportions has got to be stopped. And the solution just might lie in the study of genetics. For about a decade, geneticists have been working to create a method of treating cancer by treating the source of the cancer: the very cells themselves, at the most basic level, the gene. The goal of this paper is to explore all the ways in which the practice of genetics can help in the fight against cancer, after a brief overview of the disease itself.

Cancer is a disease of the cells. It happens when normal cell processes go awry. Normally, in the life of the cell, the cell fulfills its function in the body, divides, and dies. However, sometimes cells divide more often than usual. Since the body is not accustomed to having these extra cells, they just accumulate, until they form a massive growth, or a tumor. Having a tumor, though, does not mean that a person has cancer. Two types of tumors can be found in the body: benign tumors and malignant tumors. Benign tumors are not cancer. They are cured simply and easily by removing them. They do not grow back. Therein lies the problem with cancer: cancer grows back. A malignant tumor, unlike a benign tumor, is a cancerous one. It occurs when the normal process of cell division becomes deregulated, resulting in an inordinate amount of cell divisions in the affected area. The problem with this is not only the excessive dividing, but the fact that the cells split, but do not die as they should. For this reason, they

just continue to proliferate until they begin to cause other problems, interfere with the functioning of their own or adjacent organs. In the worst of cases, cells even break off and travel through either the blood stream or the lymphatic system, finally planting themselves somewhere else in the body. A patient could end up with lung cancer in his stomach, for example. This spreading of the disease is called metastasis. While the exact causes of this disease are again not yet known, they have been narrowed down to a range of internal factors, including hormones, immune conditions and inherited gene mutations, and external factors, such as contact with chemicals, radiation, and viruses.

With the varied factors leading to cancer, part of this horrible disease can actually be prevented. There are many types of cancer over which humans have a reasonable amount of control, as the causes are in some cases external. Some of these can be avoided by simple changes in behavior. Two such types are immediately clear: cancers from tobacco and from alcohol. The American Cancer Society estimated 172,000 cancer deaths from tobacco and 19,000 from the overuse of alcohol in 2001 in the United States alone. In fact, one-third of the ACS's projected fatalities could have been prevented by lifestyle changes. By simply putting on sunscreen, or protecting themselves somehow from harmful UV rays, one million cancers expected in 2001 could have been avoided. Some types of cancers that cannot be prevented by behavior changes can be stopped instead by vaccines. Certain viral infections are known to cause cancer, but for most there exist already vaccinations to protect the general public from contracting them. Hepatitis B virus (HBV) and the human papillomavirus (HPV), both known to cause cancer, each have a vaccine available. And as for HIV, or human immunodeficiency virus, while it has no cure, there are still steps of precaution that one can take to protect oneself.

The cancers that are neither behavioral, nor viral in origin, are generally due to a genetic defect. While other types of cancers are caused by damage to genes in their lifetime, these inherited mutations at the genetic level account for 5 - 10% of cancer cases that cannot be cured by simple vaccination. For this type of the disease, the unpreventable, we are left to search for a cure, and the search is making headway in the field of genetics.

Currently, people have the option of undergoing five different methods of treatment to fight their cancer. They are: surgery, radiation therapy, chemotherapy, hormone therapy, and biological or immunotherapy. Surgery is the simplest, and generally the first of the treatments. The affected area, including the tumor and a sufficient margin, are removed from the body. One hopes that this procedure will cure the cancer, but in many cases the cancer has spread elsewhere before being removed. For this reason, surgery is usually paired with another type of treatment to target cancer cells remaining in the body. With radiation and chemotherapy, X-rays or chemicals are introduced into the body, directed against the cancer cells. The problem with these therapies is that it is not only the cancer cells that are affected. Many other of the body's living, reproducing cells come under attack as well. It is for this reason that cancer patients lose their hair. Unfortunately hair cells, since they are always being produced, look the same to the chemicals as cancer cells. Hormone therapy and immunotherapy treat those whose cancer is biological in origin, stemming from one of the internal factors named above. These therapies can cure some cases of cancer, or at least prolong the lives of those who have developed cancer. The five year survival rate for the three most common types of cancer, breast, colon/rectum, and prostate, is 81%. However, the survival rates are not this high for all cancers, so scientists are searching for more effective, more individually-tailored treatments with fewer side effects as well.

Gene therapy is a treatment that theoretically is tailored to each patient's specific genome, as it is created from the patient's original tumor cells. It has a few basic principles that are currently being applied to develop four main types of gene therapy. Gene therapy can be applied in one of two basic ways: *ex vivo* and *in vivo*. With *ex vivo* treatment, cells are taken from the patient and cultured in the lab. The new gene is inserted into these cells, which are then injected *in vitro* back into the patient. As for *in vivo* treatment, the transfer of genes occurs in the patient's body. This means that there has to be a way for the genes to arrive at the desired location, and this is where vectors come in. A vector is an agent, generally a virus, used to introduce the chosen gene into the target group of cells to change the expression of those cells. The most commonly used vectors are adenovirus and the herpes virus. These viruses copy their DNA into the DNA of the cells they affect, which results in a transfer of DNA into the

cell. Harnessing this power, scientist can insert into the virus DNA the genetic information that they wish to transfer into the target cell. Then all they have to do is administer it. One major setback with this method is that scientists do not as of yet have control over where the virus inserts the DNA into the cell. It could theoretically be inserted anywhere. This haphazard transfer could result in a bad combination of DNA, which could possibly create another cancer site. This has happened before in patients. So, what scientists are searching for now is a way to have more control over the specificity of how the DNA is delivered to the target.

Using these two basic principles of genetic transfer, four main methods of gene therapy are currently being developed: replacement therapy, knockout therapy, suicide therapy, and immunomodulatory therapy. The goal of replacement therapy is generally the substitution of a faulty tumor suppressor gene with a functioning one. The therapy aims to promote cell death, also called apoptosis, of the proliferating tumor cells. The shortcoming of this treatment, however, is that a large number of the target genes for therapy could not only maintain, but cause malignancy as well. In other words, the treatment could spark the disease all over again. Another problem with this method is a practical one. It is not feasible to transduce, or transfer, enough healthy cells into the body to cure the disease. If only it were possible to induce proliferation of transduced healthy cells while at the same time causing the apoptosis of the cancer cells. But if scientists knew how to control the division of cells in order to propagate the healthy cells, then they would know how to stop the division of cancer cells in the first place. So unfortunately this solution is not an option, and the lack of sufficient healthy cells to run a bodily organ remains a road block for the method of replacement therapy.

Knockout therapy works instead on the products of oncogenes. An oncogene is a gene that has the ability to turn a normal cell into a cancer cell. Instead of targeting the most basic level, the gene itself, as replacement therapy does, knockout therapy focuses on the next level after the gene, the proteins produced by the gene. It attempts to altogether prevent the production of these proteins that affect the change of normal cells to cancer cells. Scientists have created the following method: a mutant oncogene is transduced that acts on the mRNA of the oncogene. The mutant oncogene's antisense mRNA, for

which it was chosen, attaches itself to the original oncogene's mRNA preventing it from fulfilling its purpose. Now, replacement therapy and knockout therapy both slow the growth of tumors, but neither one is able to stop them completely. Multiple replacements would be needed to do that, if it were even to be possible. Despite their inability to cure completely, these treatments do work better than scientists had expected, due to what has been called the "bystander effect." For some thus far unknown reason, more cells die than are expected when cells are transduced. In this case, more of the neighboring cancer cells die after a transduction, which helps to slow the growth of the tumor. For the moment, this phenomenon works in geneticists' favor, but it needs to be studied in more depth to uncover the reasoning behind it.

After replacement and knockout therapies, there is what is called suicide therapy. For this method, a gene is transduced which converts a "pro-drug," which is non-toxic, into a toxic substance, which kills the cells around it. The problem with this treatment is the low rate of specificity inherent in the design. With the bystander effect and its low specificity, this treatment does induce apoptosis; however, these factors could just as easily work against the treatment if they turn on healthy cells and not cancer cells. Too little is known now to be confident in predicting which cells will take the brunt of the suicide treatment.

Finally, there is the immunomodulatory treatment. This treatment has two approaches. The first approach is taking tumor cells that have been irradiated to render them inactive, then transducing them with a cytokine gene and reinjecting them into the patient. This cytokine gene then acts as a stimulant to the immune system, sparking a response against tumor-specific antigens. To look at it another way, this method basically vaccinates the patient against his own cancer! The second approach is to alter the "presentation" of tumor cell antigens so as to render them more recognizable by the immune system. This alteration can be affected with surface-modifying, "co-stimulatory" molecules. In summary, the immunomodulatory method is a means of helping the immune system to conquer the cancer on its own.

Apart from the specific limitations of each of the individual methods, there are other stumbling blocks in the development of genetic methods of treating cancer. A problem with gene therapy itself is that in implanting genes for expression that dominates cancer gene expression, patients can have a

problem with overexpression of the new gene. The specific side effects of this phenomenon depend on the case and the gene being over expressed. Perhaps even more pertinent than the present physical risks of the treatments are the current limitations placed by moral disputes over the subject. There are moral risks inherent in studying gene therapy. Many people do not like scientists studying a subject that if not used for the health benefit of cancer patients, could be used for abhorrent ends such as cloning a master race, or even just creating one by choosing the characteristics of every child born into the world. These are the extremes to which some people's minds wander at the mention of genetics. In order for these treatments ever to be perfected, or at least improved so that their benefits outweigh their side effects, more research needs to be done. And for more research to be done, research that will actually lead to progress, scientists need to have the freedom to experiment on the stem cell.

Gene therapy has the potential to change the way people view cancer. If it is successful, the mystery of the disease would be gone, and people could begin to be confident about what is going on in their own bodies. Psychology has a lot to do with people's ability to heal. The mere loss of uncertainty can make a huge difference in a patient's recovery. By discovering a treatment for cancer, scientists would have discovered indeed how the disease works. The mask would be gone. In order for this to happen, however, the legal restrictions on genetic studies need to be lifted. People are worried for the future, but this anxiety is inhibiting progress that might help these very people in the future. The legal system will catch up to the genetic progress in a few years' time. The legal restrictions and guidelines necessary to make such studies safe are already in place in other countries. So why is the United States holding back its scientists? The problem is education. The public does not know enough about genetics studies not to be afraid of them. It is up to the scientists to inform the public, but ultimately it is up to the people. They need to chose between a state of safety, but surrounded by fear, or a state of progress, which while a journey into the unknown, has the possibility to create a world of benefits and save a world of people. You make the choice.

Works Consulted

<http://www.cancer.gov/cancerinfo/prevention-genetics-causes/genetics>

www.cancer.gov/cancerinfo/wyntk/overview

www.genome.gov/glossary.cfm

<http://cancercontrol.cancer.gov/ocs/prevalence/>

http://seer.cancer.gov/csv/1973_1999/overview/overview25.pdf

<http://www.cancer.org/downloads/STT/F&F2001.pdf>

<http://intouchlive.com/home/frames.htm?http://intouchlive.com/cancergenetics/therapy.htm&3>

<http://intouchlive.com/home/frames.htm?http://intouchlive.com/cancergenetics/index.htm&3>

http://cis.nci.nih.gov/fact/7_18.htm