Oncogenes, Tumor Suppressor Genes, and Cancer

Advances in genetics and molecular biology have improved our knowledge of the inner workings of cells, the basic building blocks of the body. All living things are made of cells. Complex animals such as humans have trillions of cells. Cells work together to form organs, such as the heart, liver, and skin. Human bodies have several organ systems.

As they better understand cells, scientists have also learned a great deal about how and why cancers develop. Here we will review how cells work, how they change to become cancer, and how we may be able to use these changes to better understand, prevent, and treat cancer.

How do cells know what to do?

Each cell has a control center called a nucleus. The nucleus contains the information that tells the cell what to do and when to grow and divide. This information comes in the form of genes, which are contained in chromosomes. In the nucleus of most human cells (except for sperm and egg cells), there are 23 pairs of chromosomes. Chromosomes are passed from parents to their children. One chromosome of each pair is inherited from the mother, and the other comes from the father. This is why children look like their parents, and why they may have a tendency to develop certain diseases that run in their families.

Within each chromosome, there are many hundreds to thousands of genes. Genes and chromosomes are made up of long strands of a substance called DNA (deoxyribonucleic acid). Each gene is made up of a specific DNA sequence that contains the code (the instructions) for that gene's function. Genes tell the cell what to do. Many genes tell the cell to make a certain protein that has a specific job or function in the body. Other genes help regulate how much protein another gene makes. Each human cell has about 25,000 genes.

A cell uses its genes selectively; that is, it can turn on (or activate) the genes it needs at the right moment and turn off other genes that it doesn't need. Turning on some genes and turning off others is how a cell becomes specialized. That is how a cell becomes a muscle cell and not a bone cell, for example. Some genes stay active all the time to make proteins needed for basic cell functions. Others shut down when their job is finished and start again later if needed.

Genes, as the basic units of heredity, serve 2 major roles in cancers: some are part of the development of cancer and others protect the body from cancer.
What are mutations?

Genes are made up of DNA. The arrangement of the DNA building blocks (called bases) determines the gene and its function. Mutations are gene defects. They are abnormal changes in the DNA of a gene. Mutations involve changes in the arrangement of the bases that make up a gene. Even a change in just one base among the thousands of bases that make up a gene can have a major effect.

A mutation can affect the cell in many ways. Some mutations stop a protein from being made at all. Others may change the protein that is made so that it no longer works the way it should or it may not even work at all. Some mutations may cause a gene to be turned on, and make more of the protein than usual. Some mutations don't have a noticeable effect, but others may lead to a disease. For example, a certain mutation in the gene for hemoglobin causes the disease, sickle cell anemia.

Hereditary mutations

Hereditary mutations (also called germline mutations) are gene defects that are passed from a parent to child. Hereditary mutations are present in the egg or sperm that join during fertilization and develop into a fetus. Because the mutation is present at the beginning, it exists in all cells of the body, including reproductive cells (the cells that make sperm in males or the egg cells in females). This means the mutation can be passed from generation to generation.

A hereditary mutation is a major factor in about 5% to 10% of all cancers.

Some people are more likely to develop cancer than others simply because they are born with mutations in their genes. To learn more about this, see our document, Heredity and Cancer.

Acquired mutations

Most cancers are caused by DNA changes that happen during the person's life. These are called acquired, sporadic, or somatic mutations. An acquired mutation can be caused by things in the environment such as exposure to radiation or toxins. But for most acquired mutations, no specific cause can be found.

Unlike the inherited mutations, acquired mutations start in one cell of the body and are found only in the offspring of that cell. They are not in every cell of the body. Because they are not in the reproductive cells, acquired mutations cannot be passed on to the next generation.

It is important to realize that mutations in our cells happen all the time. Usually, the cell detects the change and repairs it. If it can't be repaired, the cell will get a signal telling it to die in a process called apoptosis. But if the cell doesn't die and the mutation is not repaired, it may lead to a person developing cancer. This is more likely if the mutation affects a gene involved with cell division or a gene that normally causes a defective cell to die.

Most scientists today believe that cancer develops in a process that has more than one, and likely several, mutations. We have 2 copies of each gene (one from each chromosome in a pair). So, even when a person inherits a mutation, at least one more mutation is needed to "knock out" the other copy of that gene (so that it doesn't function). This acquired mutation is needed before a person develops a heredity-related cancer. Sometimes acquired mutations in other genes (such as
Gene mutations that can lead to cancer

The 2 main types of genes that play a role in cancer are *oncogenes* and *tumor suppressor genes*. 

**Oncogenes**

Most oncogenes are mutations of certain normal genes called *proto-oncogenes*. Proto-oncogenes are the "good" genes that normally control what kind of cell it is and how often it divides. When a proto-oncogene mutates (changes) into an oncogene, it becomes a "bad" gene that can become permanently turned on or activated when it is not supposed to be. When this happens, the cell grows out of control, which can lead to cancer.

It may be helpful to think of a cell as a car. For it to work properly, there need to be ways to control how fast it goes. A proto-oncogene normally functions in a way that is much like a gas pedal. It helps the cell grow and divide. An oncogene could be compared with a gas pedal that is stuck down, which causes the cell to divide out of control.

As scientists learn more about oncogenes, they may be able to develop drugs that inhibit or stop them. Some drugs that target oncogenes are already being used, and more are on the way. This is discussed in more detail later on in this document.

**Inherited mutations of oncogenes**

A few cancer syndromes are caused by inherited mutations of proto-oncogenes that cause the oncogene to be turned on (activated). For example, multiple endocrine neoplasia type 2 (MEN2) is caused by an inherited mutation in the gene called *RET*. People affected by this syndrome often develop an uncommon thyroid cancer called medullary cancer of the thyroid. They also develop other tumors, including pheochromocytoma and nerve tumors. Inherited mutations in the gene called *KIT* can cause hereditary gastrointestinal stromal tumors (GISTs). And inherited mutations in the gene called *MET* can cause hereditary papillary renal cancer.

**Acquired mutations of oncogenes**

Most cancer-causing mutations involving oncogenes are acquired, not inherited. They generally activate oncogenes by chromosome rearrangements, gene duplication, or mutation. For example, a chromosome rearrangement can lead to formation of the gene called *BCR-ABL*, which leads to chronic myeloid leukemia (CML). Acquired mutations that activate the *KIT* gene cause most cases of gastrointestinal stromal tumor (GIST).

**Tumor suppressor genes**

Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as *apoptosis* or *programmed cell death*). When tumor suppressor genes don't work properly, cells can grow out of control, which can lead to cancer.
Many different tumor suppressor genes have been found, including \textit{TP53 (p53)}, \textit{BRCA1}, \textit{BRCA2}, \textit{APC}, and \textit{RB1}.

A tumor suppressor gene is like the brake pedal on a car. It normally keeps the cell from dividing too quickly, just as a brake keeps a car from going too fast. When something goes wrong with the gene, such as a mutation, cell division can get out of control.

An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the \textit{activation} (turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are \textit{inactivated} (turned off).

\textbf{Inherited mutations of tumor suppressor genes}

Inherited abnormalities of tumor suppressor genes have been found in some family cancer syndromes. They cause certain types of cancer to run in families. For example, a defective \textit{APC} gene causes \textit{familial adenomatous polyposis (FAP)}, a condition in which people develop hundreds or even thousands of colon polyps. Often, at least one of the polyps becomes cancer, leading to colon cancer. There are many examples of inherited tumor suppressor gene mutations, and more are being discovered each year. For more information about inherited mutations and cancer, see our document \textit{Heredity and Cancer}.

\textbf{Acquired mutations of tumor suppressor genes}

Tumor suppressor gene mutations have been found in many cancers. Most of these mutations are acquired, not inherited.

For example, abnormalities of the \textit{TP53} gene (which codes for the p53 protein) have been found in more than half of human cancers. Acquired mutations of this gene appear in a wide range of cancers, including lung, colorectal, and breast cancer. The p53 protein is involved in the pathway to apoptosis. This pathway is turned on when a cell has DNA damage that can't be repaired. If the gene for p53 is not working properly, cells with damaged DNA continue to grow and divide. Over time this can lead to cancer.

Acquired changes in many other tumor suppressor genes also contribute to the development of sporadic (not inherited) cancers.

\textbf{How can oncogenes and tumor suppressor genes be used to help prevent cancer?}

As mentioned before, some gene changes (mutations) can be inherited, which can increase your risk of developing cancer. Some mutations in oncogenes and tumor suppressor genes have been found often enough to be useful in helping decide which people are at higher risk for developing certain types of cancers.

If you have family members with certain cancers known to be caused by genetic mutations, you might find it helpful to know if you also have the mutation. Genetic testing can be used to look for such mutations. But if you are thinking about having genetic testing you need to see a genetic counselor or other genetics professional first. The testing often costs a lot, and a genetic counselor can look at your family's history to see if it is likely to be worthwhile. And the results of genetic
testing are not always clear cut. The genetic counselor can help interpret the results so that you know what they mean to you and your life. The counselor also can help you learn how to deal with the test results. Finding a genetic mutation can have a major impact on a person’s life, as well as the lives of other family members.

If you know that you carry a certain gene mutation, you may be able to take some steps to minimize your risk. For example, women who carry a mutation in one of the BRCA genes have a high risk of getting breast cancer. These women are advised to start screening for breast cancer at a younger age and to consider screening with MRI along with mammography to help find breast cancer early. Some of these women even have surgery to lower their risk of cancer.

People with APC gene mutations have a disease called familial adenomatous polyposis (FAP). They may develop hundreds of colon polyps at a young age. There are so many polyps that it isn’t possible to remove them all, and so these people often need to have their colons removed to prevent colon cancer.

For more information, see our documents, Genetic Testing: What You Need to Know and Heredity and Cancer.

**How can oncogenes and tumor suppressor genes be used to help guide treatment of cancer?**

In some cases, specific gene changes help predict which patients are likely to have a better or worse outlook or which patients are likely to benefit from certain treatments.

For example, HER2/neu is a proto-oncogene present in normal cells. It becomes an oncogene when a cell has too many copies of this gene. When this happens, the cells make too much HER2/neu protein. Many years ago, experts realized that patients with breast cancer with cells that have too much HER2/neu protein had a worse outcome than patients whose cancer cells have normal amounts. Cancers with too much of this protein did not respond as well to certain chemotherapy drugs, so now other drugs are used. Drugs were also designed to specifically attack cells with too much HER2/neu (these are discussed below). Treatment with these drugs have also helped improve outcomes for these patients.

Some tests for certain gene mutations are very sensitive in finding cancer that persists or returns after treatment. For example, the leukemia cells of patients with chronic myeloid leukemia (CML) contain a mutated gene called **BCR-ABL**. Testing for this mutation is used to confirm the diagnosis of CML and then to see if treatment is working. This testing can also be used to see if the leukemia has started coming back after treatment. Instead of having to look for abnormal cells in the bone marrow, a blood test for the abnormal gene can find even small numbers of remaining cancer cells among millions of normal cells. This may signal that new treatment is needed. The **BCR-ABL** gene is also important in the treatment of CML. This is discussed below.

**How can oncogenes and tumor suppressor genes be used to treat cancer?**

The discovery and understanding of oncogenes and tumor suppressor genes has led to the development of new kinds of cancer therapies. The following are some examples of genes that are
cancer treatment targets. Research in this area is progressing rapidly, and new drugs targeting certain genes and proteins are becoming available over time.

**Oncogenes**

In some cases of breast cancer, the cells have too many copies of a gene called HER2/neu and make an excess amount of the HER2/neu protein. This protein promotes the growth of cancer cells. But drugs have been developed that target this protein, slowing cancer cell growth and improving outcomes. These drugs, trastuzumab (Herceptin®) and lapatinib (Tykerb®), only work against cancers that have too much HER2/neu (called HER2-positive). Breast cancers are now routinely tested for the HER2/neu gene and/or protein to identify which patients will benefit from these drugs. Trastuzumab has also been shown to be useful in treating people with stomach cancer that is HER2-positive. Other drugs targeting HER2 are being tested in clinical trials.

In chronic myeloid leukemia (CML), the cancer cells have a gene change called BCR-ABL that makes a type of protein called a tyrosine kinase. Drugs that target the BCR-ABL protein, including imatinib (Gleevec®), dasatinib (Sprycel®), and nilotinib (Tasigna®), are often very effective against CML. They lead to remission of the leukemia in most patients treated in the early stages of their disease. Other drugs to target the BCR-ABL protein are being studied for use if these drugs stop working.

Most gastrointestinal stromal tumors (GISTs) are caused by activation of the oncogene called KIT. Others are caused by activation of PDGFRα, another oncogene. The drug imatinib (Gleevec) targets both of these oncogenes, and is often able to shrink these tumors and help patients live longer. Sunitinib (Sutent®) is also able to target these oncogenes and can be helpful if imatinib no longer works.

**Tumor suppressor genes**

Treating problems in tumor suppressor genes is more difficult. It would mean restoring normal tumor suppressor gene functions, which researchers have not yet figured out how to do effectively. A major stumbling block lies in how to get new DNA into the cancer cells. Another problem is that most cancers have several mutations, so replacing one gene may not be enough to stop the cancer cells from growing and spreading.

Scientists tried to treat some cancers that have mutations in the TP53 gene by inserting normal TP53 genes into viruses and then trying to infect tumor cells with these viruses. This worked well in the lab, but not in human studies.

A newer approach targets the weakness in the cell caused by the abnormal tumor suppressor genes, rather than trying to restore normal gene function. For example, some people inherit a mutation in one of the BRCA genes (BRCA1 or BRCA2). If the second copy of this gene is damaged, the gene no longer works and they may develop a cancer. In cells where a BRCA gene no longer works (like cancer cells), drugs called PARP inhibitors cause DNA damage that can lead to cell death. Cells that have normally functioning BRCA genes can repair this damage. This allows the PARP inhibitor to target the cancer cells while doing little damage to the normal cells.
Future directions

Many researchers are very hopeful about the future of cancer therapies using oncogenes and tumor suppressor genes, and this remains a very active area of research. There are many clinical trials under way today that could lead to better treatments for many types of cancer.

To learn more

More information from your American Cancer Society

We have some related information that may also be helpful to you. These materials may be viewed on our Web site or ordered from our toll-free number, at 1-800-227-2345.

Genetic Testing: What You Need to Know

Heredity and Cancer

National organizations and Web sites*

Along with the American Cancer Society, other sources of information and support include:

HYPERLINK
"/AboutUs/Redirect/index?h=http://medicine.creighton.edu/hcc&n=Hereditary%20Cancer%20Center"
National Cancer Institute
Toll-free number: 1-800-4-CANCER (1-800-422-6237)
Web site: www.cancer.gov

Provides accurate, up-to-date information on a variety of cancer-related topics such as finding support, financial assistance and other resources; coping with cancer; cancer genetics, etc. (click the “Cancer Topics” tab on the home page). Also has an Online Cancer Genetics Services Directory to identify professionals who provide services related to cancer genetics (cancer risk assessment, genetic counseling, genetic susceptibility testing, and others). The direct link is www.cancer.gov/search/geneticsservices.

National Society of Genetic Counselors (NSGC)
Telephone: 1-312-321-6834
Web site: www.nsgc.org

Offers a Consumer Information link with the following:

- Making Sense of Your Genes: a 24-page guide to genetic counseling (may be downloaded and printed)
- Directory of genetic counselors: can be searched by your area
- Five Questions to Ask Before Considering Genetic Testing (can be downloaded and printed)
- Guide on collecting family history: a helpful tool in determining possible genetic risks
- FAQs on genetic testing and genetic counselors

*Inclusion on this list does not imply endorsement by the American Cancer Society.
No matter who you are, we can help. Contact us anytime, day or night, for cancer-related information and support. Call us at 1-800-227-2345 or visit www.cancer.org.

References


Tufts University School of Medicine, Department of Anatomy and Cellular Biology. The somatic mutation theory of cancer: growing problems with the paradigm? Bioessays. 2004; 26:1097–1107.

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