

Breast Cancer and Environmental Risk Factors

Tumor Suppressor Genes—Guardians of Our Cells

Tumor suppressor genes play a critical role in regulating when cells are allowed to divide and increase in number. When DNA damage is detected in a cell, some tumor suppressor genes can stop the cell from multiplying until the damage is repaired. Also, specific tumor suppressor genes can stimulate cells with damaged DNA to commit “cell suicide”. When tumor suppressor genes don’t function correctly, the cells with DNA damage continue to divide and can accumulate further DNA damage that can eventually lead to the formation of a cancer cell.

Traffic in the body

Have you ever been caught in a traffic jam because a traffic light was not working? Cars are backed up for miles and there is mass confusion. Traffic lights maintain the right numbers of cars on the road by telling them when to “go” and when to “stop.” All systems that work well must have signals to maintain order. The body works in the same way.

The body’s system is composed of trillions of cells. Even though we stop growing when we become adults, many of our cells continue to grow and divide. Our bodies constantly replace the worn-out cells with new cells to stay healthy. To do this cells must enter a “highway” called the cell cycle. The cell cycle has built-in controls for how fast, and for how long a cell will keep dividing. A cell divides into two identical daughter cells. When enough cells have been made to replace the worn out cells, the cell leaves the cell cycle and stops dividing. The cell depends on signals to decide when to stay in or exit the cell cycle.

Stop and go

Built into the cell’s machinery, are two signals: the “go” signal to stay in the cycle and keep dividing, and the “stop” signal to stop dividing and exit the cell cycle. These “stop” and “go” signals work to maintain the correct balance of healthy, functioning cells in the body.

Operations manual and signals

In each cell, there is an “operations manual” made up of DNA molecules. The information in the manual is contained in “chapters” that are separated into small units called **genes**. Genes are written in a DNA code which must first be

transcribed and translated into another language to make proteins. These proteins then serve as signals in the cell to carry out the work of the genes.

Tumor suppressor genes* code for proteins that serve as the “stop” signals that tell a cell to leave the cell cycle and stop dividing. The genes that code for the “go” signals that tell the cell to stay in the cell cycle and continue to divide are called **proto-oncogenes***. The development of cancer is a complex process that requires the accumulation of damage to the cell’s growth-controlling genes, including damage to tumor suppressor genes and proto-oncogenes. That is why cancer takes so long to develop.

When things go wrong

If the “stop” or “go” signals do not function properly, cells can escape from the tight controls that maintain the correct number of cells in our body. Cells that accumulate DNA damage (called mutations) may lose their ability to respond to or make “stop” signals.

***tumor suppressor genes:** code for “stop” signals

***proto-oncogenes:** code for “go” signals

One of the functions of the tumor suppressor gene **p53** is to prevent cells with damaged DNA from dividing and passing on the DNA damage to daughter cells. The cell can monitor itself for DNA damage during the cell cycle. If DNA damage is detected, the **p53** protein plays an important role in putting a “brake” on the cell cycle. This “brake” is not removed unless the DNA damage is repaired. In a cell with a mutated **p53** gene, the braking system is defective, and the damaged cell goes on in the cell cycle and



divides. A defective **p53** gene deprives the cells of crucial signals that normally put the “brakes” on inappropriate cell division and tumor development.

In cancer cells, mutations to DNA can also convert proto-oncogenes to oncogenes. Oncogenes are like an accelerator pedal on a car. They continuously send “go” signals that tell the cell to stay in the cell cycle and keep on dividing.

Tumor suppressor genes and cell suicide

Our cells have a very efficient repair system for most kinds of DNA damage. However, a small percentage of the time, the damage is not repaired. Another important function of the **p53** protein is to instruct a cell with DNA damage to commit suicide. Cell suicide is a sacrifice that must be made to protect the overall health of the body. Without it, the damaged cells would continue to divide and pass on the defects to daughter cells. More importantly, these damaged cells would continue to accumulate additional mutations that could allow the cell to escape from normal controls, eventually leading to the formation of a tumor.

Cell suicide is also important because it can signal cancer cells to die before they can develop into a life-threatening tumor. You can think of a tumor suppressor gene as an emergency “off” switch. The tumor suppressor gene can prevent a cell with an oncogene from dividing and passing damaged DNA on to other cells. If a tumor suppressor gene is inactivated, or damaged in some way, it can no longer provide this control over abnormal cell division.

Mutations in tumor suppressor genes

How does a cell escape the “stop” signals given by the tumor suppressor gene? One way is to damage the tumor suppressor gene so it can no longer function properly. As mentioned before, tumor suppressor genes are written in a DNA code that must be transcribed and translated to make the protein signal. Mutations to the DNA code can turn off a tumor suppressor gene or disrupt the signal. Here is an illustration of how damage to the DNA code of a tumor suppressor gene can lead to a mutation that makes no sense to the cell.

By changing the DNA code of a tumor suppressor gene, the cell can no longer make a tumor suppressor signal the cell recognizes. By omitting one letter in the DNA code,

the mutated DNA message makes no sense to the cell. In response, the cell may not be able to make the tumor suppressor protein. Other types of mutations can result in the cell producing a defective tumor suppressor protein that can no longer convey the “stop” signal. Since the rest of the cell’s machinery is still intact, the cell can carry on with the other activities needed for survival.

The DNA code is read like the sentence: Stop diyiding now.”

If one letter is removed from the sentence,
it no longer makes sense. Stop diiiding now.”

Similarly, if we cut the sentence off too
early, it does not convey the same message. “Sto.”

Why don’t some forms of cancer therapy work?

The nature of mutated **p53** tumor suppressor genes helps to illustrate why traditional forms of cancer treatment, such as radiation, are not always successful in treating cancer. These treatments rely on damaging the cancerous cells more than the normal cells, so that the cancer cells will commit “cell suicide.”

This would normally work, since the DNA damage would be detected by the cell, and the **p53** proteins would stimulate the cancer cell to commit suicide. However, a cell with a mutated or deleted **p53** gene cannot make the “cell suicide” signal. As a result, the treatment will not work effectively.

Why are some people more at risk for developing cancer?

A cell usually needs to accumulate mutations in both tumor suppressor genes and proto-oncogenes to become a cancer cell. This abnormal cell has a great growth advantage. It is stuck in the cell cycle with no brakes (defective tumor suppressor genes— lacks “stop” signals) and full acceleration (oncogenes send “go” signals). The abnormal cell multiplies out of control, passing on mutations to daughter cells. When the resulting breast tumor reaches a critical size, additional mutations can allow the cancer cells to shed from the breast tumor, travel through the blood or lymph, and invade healthy vital organs such as the liver, lung, or kidney to form “metastatic” tumors. For many types of cancer, this process can take a long time. That is why cancer occurs more often as we get older.

If a mutated tumor suppressor gene is already present in the sperm of the father or egg of the mother, this genetic damage can be passed on to their children. The good news is that each cell has two



copies of the DNA “operations manual.” If a child inherits a mutated tumor suppressor gene from one of their parents, the copy of tumor suppressor gene from the other manual is used. But, if the second copy of the tumor suppressor gene becomes damaged, it can no longer help protect the cell from becoming cancerous. This is called the “2-hit” model because it requires two mutations to inactivate the tumor suppressor gene. Since individuals who inherit a mutated tumor suppressor gene are born with one less working “stop” signal, they are at higher risk of developing cancer at an earlier age. Inherited breast cancer only represents 5 to 10% of all breast cancer cases. One reason is that inheriting a specific mutated tumor suppressor gene is a relatively rare event, and does not always result in developing cancer.

Breast cancer tumor suppressor genes

Scientists have identified several tumor suppressor genes, and some have been associated with increased breast cancer risk. Two tumor suppressor genes that are mutated in a high percentage of early-onset (before the age of 45) inherited breast cancer and ovarian cancer cases are called **BRCA1 (BR**east **C**ancer-1) and **BRCA2**. Scientists are just beginning to discover how these genes function, and how frequently mutations in these genes occur in women with a family history of breast cancer. One recent study found that women of Ashkenazi Jewish descent who had a mutation in **BRCA1** or **BRCA2** had just over a 50% chance of developing breast cancer by age 70. This is a lower figure than predicted by earlier studies. Much more research is needed to determine the breast cancer risk associated with inheriting mutations in these genes.

The **p53** tumor suppressor gene is missing or does not work in more than 60% of all breast cancers. The **p53** gene plays a central role in the cell’s response to DNA damage. We have already mentioned the importance of the **p53** protein in the process of stimulating mutated cells to commit cell suicide, and its role in “braking” the cell cycle to prevent cells with DNA damage from dividing further. In most cases, damage to the **p53** gene is acquired during one’s lifetime, though in rare instances a pattern of early-onset cancers has been traced to inheriting mutated **p53** genes (less than 100 families world-wide with **Li-Fraumeni-Syndrome**).

What are some of the other tumor suppressor genes that may be important in breast cancer?

Researchers are investigating the relationship of the tumor suppressor gene **ATM** (ataxia telangiectasia) and breast cancer risk. The **ATM** gene codes for a protein which is important in

repairing radiation-induced damage to DNA. The retinoblastoma tumor suppressor gene (**RB**), codes for a protein that functions as a “master brake” in the cell cycle. Mutations in this gene have been found in some breast tumors, and a variety of other cancers. A new breast cancer tumor suppressor gene, called **TSG101**, has been recently identified, and studies are underway to study its function.

Conclusions

Tumor suppressor genes function as guardians of our cells by preventing cells with DNA damage from dividing and passing on harmful mutations to daughter cells. Some tumor suppressor proteins function as a braking signal that stops the cell cycle when a cell with DNA damage is detected and needs to be repaired. Other tumor suppressor proteins instruct a cell with damaged DNA to commit cell suicide. Efforts to identify new breast cancer tumor suppressor genes, and to determine how tumor suppressor genes work, will help researchers and clinicians design better ways to detect, treat and someday prevent breast cancer.

Why are more studies needed?

- We do not know how tumor suppressor genes sense DNA damage in a cell.
- We do not know how closely the mutation of a tumor suppressor gene is linked to the development of particular types of cancer.
- We need to know more about the possible role environmental factors may play in causing mutations in tumor suppressor genes.

How can one find out more about tumor suppressor genes?

Three recommended references for further reading are:

- Cooper, G.M. “Tumor Suppressor Genes in Human Neoplasms” Chapter 10, in *Oncogenes*, 2nd ed., Boston, Jones and Bartlett Publishers, pages 145-151, 1995.
- Cox, L.A., and others. “Tumor Suppressor Genes and Their Roles in Breast Cancer” in *Breast Cancer Research and Treatment*, Volume 32, pages 19-38, 1994.
- Weinberg, R. “How Cancer Arises” in *Scientific American*, pages 62-70, September, 1996.




Please note: An extensive bibliography (listing of references) on tumor suppressor genes and breast cancer risk is available on the BCERF web site. (<http://www.cfe.cornell.edu/bcerf/>)

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