Lesson 3 Reading Material: Oncogenes and Tumor Suppressor Genes

Becoming a cancer cell isn't easy

One of the fundamental molecular characteristics of cancer is that it does not develop all at once, but across time, as a long and complex succession of genetic changes. Each change enables precancerous cells to acquire some of the traits that together create the malignant growth of cancer cells.

Genes and Cancer

Two categories of genes play major roles in triggering cancer. In their normal forms, these genes control the **cell cycle**, the sequence of events by which cells enlarge and divide. One category of genes, called **proto-oncogenes**, encourages cell division. The other category, called **tumor suppressor genes**, inhibits it. Together, proto-oncogenes and tumor suppressor genes coordinate the regulated growth that normally ensures that each tissue and organ in the body maintains a size and structure that meets the body's needs.

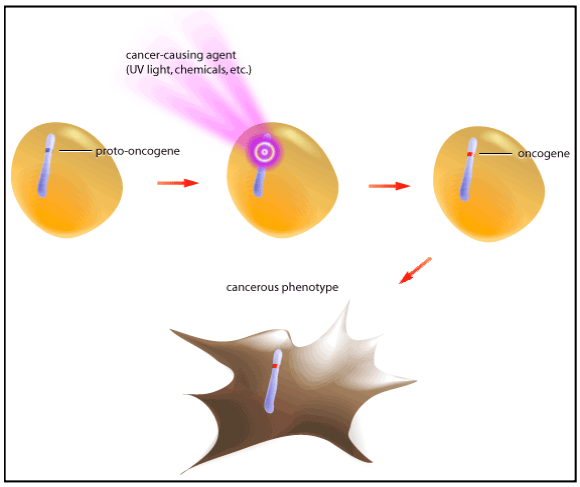
What happens when proto-oncogenes or tumor suppressor genes are mutated?

Mutated proto oncogenes become oncogenes, genes that stimulate excessive division. And mutations in tumor suppressor genes inactivate these genes, eliminating the critical inhibition of cell division that normally prevents excessive growth. Collectively, mutations in these two categories of genes account for much of the uncontrolled cell division that occurs in human cancers.

THE ROLE OF ONCOGENES

What Are Oncogenes?

Oncogenes are normal genes that have been mutated and consequently cause normal cells to grow out of control and become cancer cells. They are mutations of certain normal genes of the cell called *proto-oncogenes*. Proto-oncogenes are the genes that normally control how often a cell divides and the degree to which it differentiates (or specializes). When a proto-oncogene mutates (changes) into an oncogene, it becomes permanently "turned on" or activated when it is not supposed to be. When this occurs, the cell divides too quickly, which can lead to cancer.



Proto-oncogenes can become oncogenes. Proto-oncogenes encode for normal cellular proteins involved in growth signalling pathways. When these genes become mutated as a result of exposure to chemicals, radiation, or other carcinogens, these genes are called oncogenes.

www.bioteach.ubc.ca/CellBiology/Oncogenes/

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 similar to a gas pedal -- it helps the cell grow and divide. An oncogene could be compared to a gas pedal that is stuck down, which causes the cell to divide out of control.

How do proto-oncogenes, or more accurately, the oncogenes they become after mutation, contribute to the development of cancer?

Most proto-oncogenes code for proteins that are involved in molecular pathways that receive and process growth-stimulating signals from other cells in a tissue. Typically, such signaling begins with the production of a growth factor, a protein that stimulates division. These growth factors move through the spaces between cells and attach to specific receptor proteins

located on the surfaces of neighboring cells. When a growth-stimulating factor binds to such a receptor, the receptor conveys a stimulatory signal to proteins in the cytoplasm. These proteins emit stimulatory signals to other proteins in the cell until the division-promoting message reaches the cell's nucleus and activates a set of genes that help move the cell through its growth cycle.

Oncogenes, the mutated forms of these proto-oncogenes, cause the proteins involved in these growth-promoting pathways to be overactive. Thus, the cell proliferates much faster than it would if the mutation had not occurred. Some oncogenes cause cells to overproduce growth factors. These factors stimulate the growth of neighboring cells, but they also may drive excessive division of the cells that just produced them. Other oncogenes produce aberrant receptor proteins that release stimulatory signals into the cytoplasm even when no growth factors are present in the environment. Still other oncogenes disrupt parts of the signal cascade that occurs in a cell's cytoplasm such that the cell's nucleus receives stimulatory messages continuously, even when growth factor receptors are not prompting them.

THE ROLE OF TUMOR SUPPRESSOR GENES.

To become cancerous, cells also must break free from the inhibitory messages that normally counterbalance these growth-stimulating pathways. In normal cells, inhibitory messages flow to a cell's nucleus much like stimulatory messages do. But when this flow is interrupted, the cell can ignore the normally powerful inhibitory messages at its surface. Some of these genes apparently code for proteins that operate as parts of specific inhibitory pathways. When a mutation causes such proteins to be inactivated or absent, these inhibitory pathways no longer function normally. Other tumor suppressor genes appear to block the flow of signals through growth-stimulating pathways; when these genes no longer function properly, such growth-promoting pathways may operate without normal restraint. Mutations in all tumor suppressor genes, however, apparently inactivate critical tumor suppressor proteins, depriving cells of this restraint on cell division.

What Are Tumor Suppressor Genes?

Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, and 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. About 30 tumor suppressor genes have been identified, including *p53, BRCA1, BRCA2, APC, and Rb*. Some of these will be described in more detail later on.

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.

Oncogenes

PDGF	codes for a protein called platelet-derived growth factor (involved in some forms of brain cancer)
Ki-ras	codes for a protein involved in a stimulatory signaling pathway (involved in lung, ovarian, colon, and pancreatic cancer)
MDM2	codes for a protein that is an antagonist of the *p53* tumor suppressor protein (involved in certain connective tissue cancers)

Tumor Suppressor Genes

NF-1	codes for a protein that inhibits a stimulatory protein (involved in myeloid leukemia)
RB	codes for the pRB protein, a key inhibitor of the cell cycle (involved in retinoblastoma and bone, bladder, and breast cancer)
BRCA1	codes for a protein whose function is still unknown (involved in breast and ovarian cancers)

An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the *activation* (turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are *inactivated* (turned off). Another major difference is that while the overwhelming majority of oncogenes develop from mutations in normal genes (proto-oncogenes) during the life of the individual (*acquired* mutations), abnormalities of tumor suppressor genes can be inherited as well as acquired.

Lesson 3 Problem Set: Oncogenes and Tumor Suppressor Genes
Teacher's Answers

Short answer:

1. Explain how a proto-oncogene can be compared to a gas pedal in a car. What would an oncogene be the equivalent to?

2. Explain how mutations in tumor suppressor genes can contribute to cancer.

3. What is an important difference between oncogenes and tumor suppressor genes when it comes to causing cancer?

4. How can a protein be considered an oncogene, when its function is to shut off a tumor suppressor? Give an example of one such oncogene.

5. Knowing what you know about the cell cycle, explain why Rb would be considered a tumor suppressor.

True/False: Determine whether the statements below are true or false. If you choose "false" please correction the part(s) of the statements that are incorrect.

1. A proto-oncogene can cause cancer.

2. Mutation in p53 alone can cause cancer in humans.

3. Mutations in genes will always contribute to cancer.

Vocabulary: Define the following terms.

1. proto-oncogene

2. oncogene

3. tumor suppressor gene

Lesson 3 Problem Set: Oncogenes and Tumor Suppressor Genes
Teacher's Answers

Short answer:

1. Explain how a proto-oncogene can be compared to a gas pedal in a car. What would an oncogene be the equivalent to?

A: A proto-oncogene normally functions in a way that is similar to a gas pedal -- it helps the cell grow and divide. An oncogene could be compared to a gas pedal that is stuck down, which causes the cell to divide out of control.

2. Explain how mutations in tumor suppressor genes can contribute to cancer.

A: Tumor suppressor genes function to regulate growth and can stop cell division during times of repair, or when errors are found in the cell. If a tumor suppressor were mutated and could not function, the cell would continue to divide without control.

3. What is an important difference between oncogenes and tumor suppressor genes when it comes to causing cancer?

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

4. How can a protein be considered an oncogene, when its function is to shut off a tumor suppressor? Give an example of one such oncogene.

A: If an gene functions to inhibit a tumor suppressor, it can be considered an oncogene because it contributes to cancer. Mdm2, an inhibitor of tumor suppressor p53, can be considered an oncogene.

5. Knowing what you know about the cell cycle, explain why Rb would be considered a tumor suppressor.

A: Rb, when hypophosphorylated, is bound to the E2F transcription factor. When Rb becomes hyperphosphorylated, it releases E2F and E2F drives cell cycle progression into S phase. If Rb were to be mutated, E2F would be free to drive cell cycle progression all of the time. Therefore, since it needs to be inactivated to cause cancer, Rb is considered to be a tumor suppressor.

True/False: Determine whether the statements below are true or false. If you choose "false" please correction the part(s) of the statements that are incorrect.

1. A proto-oncogene can cause cancer.

A: False: A proto-oncogene is a normal gene whose function is to grow or signal for cell division, when appropriate. An oncogene could potentially cause cancer because it is signaling the cell to divide all of the time. It is not regulated at all.

2. Mutation in p53 alone can cause cancer in humans.

A: False; it takes many genetic changes to cause cancer, not just one. Cancer is a multi-step process.

3. Mutations in genes will always contribute to cancer.

A: False: Sometimes you can get mutations in genes that are not involved in cell cycle control or cell division and the mutation would have no consequence on the cell.

Vocabulary: Define the following terms.

1. proto-oncogene

A: Proto-oncogenes are the genes that normally control how often a cell divides and the degree to which it differentiates (or specializes).

2. oncogene

A: *Oncogenes* are normal genes that have been mutated and consequently cause normal cells to grow out of control and become cancer cells.

3. tumor suppressor gene

A: **Tumor suppressor genes** are normal genes that slow down cell division, repair DNA mistakes, and tell cells when to die (a process known as *apoptosis* or programmed cell death).