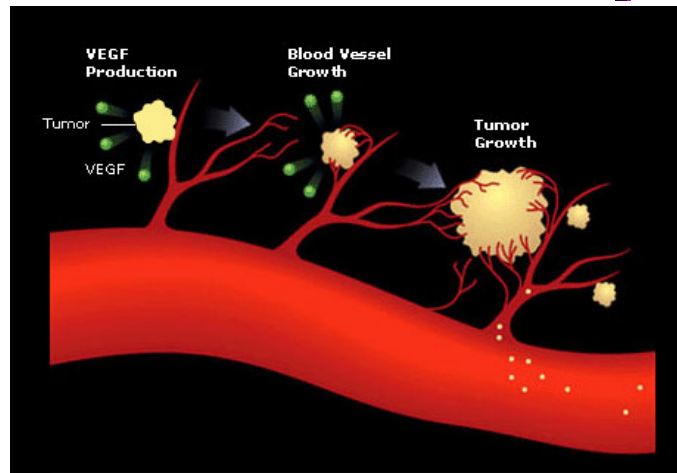


Lesson 4 Reading Material: Angiogenesis and Metastasis

TUMOR CELLS NEED NUTRIENTS

Cancer cells divide geometrically, meaning one cancer cell makes two. Then, two cancer cells become four. Then, four cancer cells become eight and so on and so forth. Imagine cancer cells that have divided geometrically and have resulted in a tumor. The cancer cells on the outside of the tumor will be in contact with nutrients and oxygen, but the cells on the inside will begin to starve. If a tumor does not receive nutrients, it cannot grow bigger than 1mm. How do the cancer cells on the inside get their nutrients? They initiate a process called **angiogenesis**.



Angio- : blood vessels

Genesis -: suffix that refers to the beginning, development, or production of something

Therefore, angiogenesis means the production of new blood vessels. These blood vessels arise by branching off of blood vessels that already exist.

Tumor cells, after being starved of nutrients and oxygen, can secrete molecules such as vascular endothelial growth factor (VEGF). Blood vessels are made up endothelial cells. Imagine endothelial cells all lined up and making a circular tube for blood, nutrients, and oxygen to flow through. Therefore vascular endothelial growth factor would mean:

Vascular: Of, characterized by, or containing vessels that carry or circulate fluids, such as blood, lymph, or sap, through the body of an animal or plant.

Endothelial: Endothelial cells are cells that make up blood vessels.

Growth Factor: a molecule that enhances or enriches growth.

VEGF, therefore, enhances the growth of endothelial cells that make up blood vessels or vasculature. When tumor cells secrete VEGF, it signals nearby endothelial cells in existing blood vessels to start proliferating and make new branches of blood vessels. These new branches will grow towards the tumor and eventually infiltrate to the inner most parts of the tumor allowing the inner cells to receive nutrients and oxygen. This aids in the tumor growth and allows the tumor to grow to enormous sizes.

For an animation of angiogenesis visit:

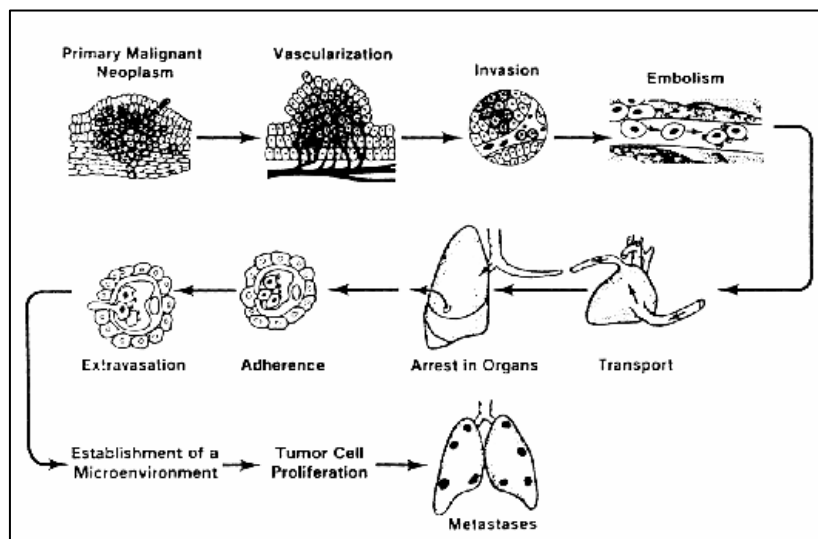
http://www.hhmi.org/biointeractive/animations/angiogenesis/angio_splash.htm

METASTASIS:

Once the tumor has been infiltrated with blood vessels, the tumor cells have a way of invading the blood vessel network of the host organism and a tumor cell can travel through the blood and eventually exit out into another organ. For example, a breast cancer cell that has recruited new blood vessels, can enter the blood vessels and travel to a distant site such as the lung, and exit there and begin growing another tumor in the lung. This process is called metastasis.

Metastasis: The migration of cancer cells from the original tumor site through the blood and lymph vessels to produce cancers in other tissues.

Metastasis also is the term used for a secondary cancer growing at a distant site.



For a cancer cell to metastasize, there are a series of steps it must go through. Each step is rate-limiting, meaning until each step is completed, the cell is limited and will not continue. Failure to complete any of the steps prevents the tumor from producing metastasis. There are several steps in metastasis:

Angiogenesis: The recruitment of new blood vessels

Detachment: The individual tumor cell must detach from the whole tumor. There is a decrease in cell adhesion molecules allow the tumor cell to separate from its neighbor. The tumor secretes factors helpful in motility, so the cell can maneuver its way around. There are proteases (enzymes that degrade proteins) that can cut through the extracellular matrix by degrading proteins within it. This allows the cell to move forward.

Intravasation: The tumor cell will invade into the host blood network or lymphatic system. Enzymes called metalloproteinases produced by the tumor can destroy the basement membrane and connective tissue.

Evasion of host defense: Now that the tumor cell is inside the blood vessel, it must survive and avoid any natural defenses. Less than 1 out of 10,000 tumor cells that leave the primary site survive in circulation. Sometimes it is not just a single tumor cell that is traveling through. There can be an aggregate of tumor cells traveling together. This is called an embolus. The chance a tumor cell will survive in circulation increases if it forms aggregates or clusters of cells.

Arrest at a distant site: Tumor cells will come to a halt at a particular spot in circulation. This can be due to the embolus getting stuck, or host cells encompassing the individual tumor cell and eventually attaching to a particular site.

Attachment: The tumor cell/embolus must attach to the wall of the blood vessel or lymphatic vessel. This requires the interaction of adhesion molecules expressed by endothelial cells.

Extravasation: The tumor cell, once attached to the inside wall of the blood vessel must then exit by invasion into the extracellular matrix of a different organ/site. This involves proteases, proteinases and the digestion of the basement membrane and extracellular matrix.

Establish New Growth: The tumor cell or embolus has now invaded into the extracellular matrix of a new site and it must establish growth again. The process can repeat itself by the new tumor growth recruiting more blood vessels.

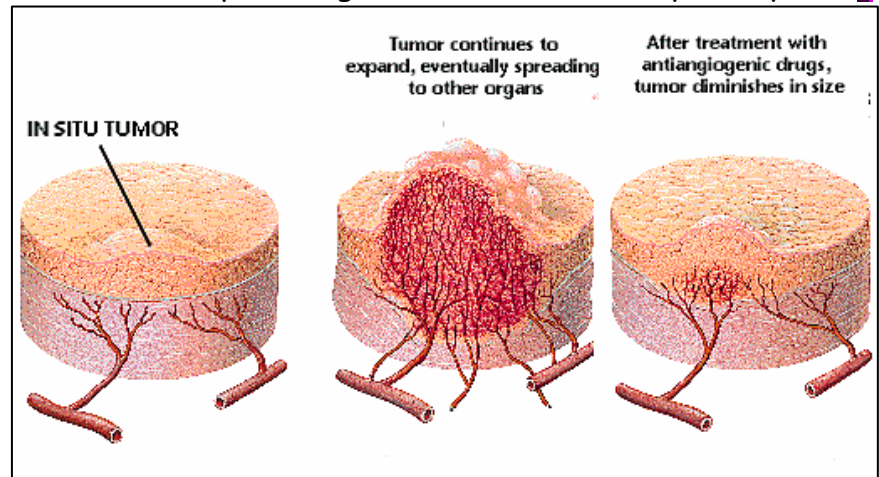
CATCH IT BEFORE IT GETS AWAY!

Early detection of cancer is very important, because catching the tumor before it has had a chance to metastasize is crucial. Once the tumor has invaded the blood and lymph system, it is very hard to determine where tumors will pop up. Imagine if a tumor has already metastasized, but the new site that the tumor is growing in is undetectable. The doctor will surgically remove the primary tumor, but the secondary tumor could be growing and they wouldn't even know it. Years later, the secondary tumor will start to cause problems in the patient.

STARVE IT

A lot of work has been done on trying to use our knowledge on angiogenesis to our benefit. A very smart doctor at Harvard University, by the name of Dr. Judah Folkman, was the first person to come up with the idea that if we starve a tumor of nutrients, it would remain 2mm and a manageable size that can be removed by surgery. This was in 1970, and thus began the hunt for angiogenesis inhibitors. In theory, if you can cut off the blood supply to the tumor, it would not receive nutrients and oxygen and won't be able to grow, invade, or metastasize.

Some angiogenesis inhibitors are in clinical trials and being used in combination with other chemotherapeutic agents. Sometimes the primary tumor can be surgically removed and then the patient can be kept on low doses of angiogenesis inhibitors for their lives in order to prevent recurrence of tumors.



References:

<http://www.moffitt.usf.edu/pubs/ccj/v2n5/art13img2.gif>

<http://www.gene.com/gene/research/focusareas/oncology/angiogenesis.jsp>

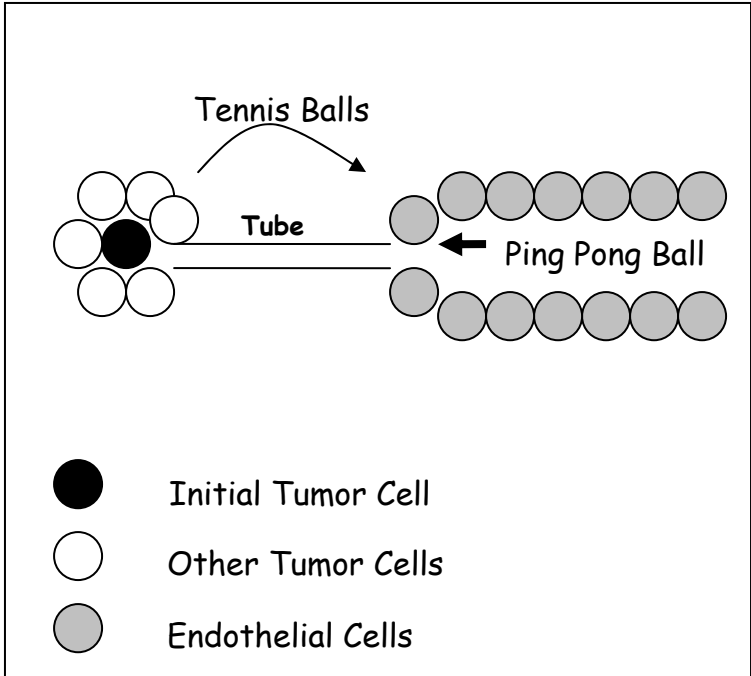
Lesson 4 Activity: "Angiogenesis and Metastasis" Teacher Handout

You will need:

Two different kinds of balls (tennis balls, ping pong balls, etc)
Long Tube (cardboard tube inside wrapping paper works well)

The objective of this activity is to have the students acting as tumor cells and endothelial cells, and the tennis balls and ping pong balls acting as pro-angiogenic factors and nutrients, respectively.

1. Pick one student to act as the initial tumor cell. Have the student stand up in the front of class and tell them that the student represents a tumor cell. A single tumor cell or a small tumor can easily get nutrients and oxygen from its host. (Toss the tennis balls at the student and tell them the tennis balls represent nutrients and oxygen). The tumor will then start to divide and grow.
2. To represent the tumor growing, bring more students up and have them surround the initial student. Now throw them the tennis balls and demonstrate that when a tumor gets very large, it is hard for the inside of a tumor (the initial student) to get nutrients and oxygen. Only the tumor cells on the periphery of the tumor (students on the outside) are able to easily get nutrients. The lack of nutrients in the inside of the tumor cell cause's the cells to release pro-angiogenic factors (tennis balls) to attract endothelial cells.
3. The tumor cells (students) should throw tennis balls to the students that are acting as the endothelial cells. This causes the endothelial cells to divide and form a new network (a new blood vessel that can infiltrate the tumor.) Have the endothelial cells line up like a blood vessel (2 lines of students). At the end of the 2 lines, the "blood vessel" would get thinner and become the long cardboard tube. This tube can infiltrate or invade the tumor reaching the student who was the initial tumor cell. Walk a ping pong ball in between the two lines of students (represents nutrients going through the blood vessel) and then once you reach the long cardboard tube, roll the ping pong ball through the tube and will hit the innermost (initial) tumor cell.



Lesson 4 Problem Set: Angiogenesis and Metastasis

Short Answer:

1. Why is angiogenesis important for tumor growth?
2. Besides nutrients, what else do blood vessels allow the tumor to do?
3. List the steps of metastasis:
4. Why is early detection so important in cancer in terms of metastasis.
5. What kind of cells are blood vessels made up of?

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

1. Tumor cells metastasize only by traveling through the host's blood circulation.
2. There are several steps in metastasis. A tumor cell must complete each step before moving on to the next one.
3. Once angiogenesis is established, it is almost certain that tumor cells will metastasize because it is very easy for tumor cells to survive in circulation.
4. The strategy behind angiogenesis inhibitors is to feed the tumor with poison through the new blood network that the tumor has established.

Vocabulary: Define the following terms:

1. Metastasis:

2. Intravasation:

3. Extravasation:

4. Angiogenesis:

5. VEGF

Lesson 4 Problem Set: Angiogenesis and Metastasis Teacher's Answers

Short Answer:

1. Why is angiogenesis important for tumor growth?

A: A tumor that has grown to a certain size needs nutrients and oxygen, otherwise it won't grow any further. The recruitment of new blood vessels that infiltrate the tumor (angiogenesis), allow the innermost part of the tumor to receive nutrients and oxygen and therefore, continue to grow.

2. Besides nutrients, what else do blood vessels allow the tumor to do?

B: Tumor cells can detach from the primary tumor and use the blood supply to travel the host's circulation in order to take up residence elsewhere in the body (metastasis).

3. List the steps of metastasis:

A: Angiogenesis
 Detachment from primary tumor
 Intravasation
 Evasion of host defense
 Arrest at a distant site
 Attachment
 Extravasation
 Establishment of new growth

4. Why is early detection so important in cancer in terms of metastasis.

A: The goal of early detection is to catch the tumor while it remains local. Once it has had a chance to enter circulation, you might be able to remove the primary tumor, however, you could have metastases and growth of new tumors elsewhere.

5. What kind of cells are blood vessels made up of?

A: Endothelial cells

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

1. Tumor cells metastasize only by traveling through the host's blood circulation.

A: False; tumor cells can also invade the lymph system and travel through lymphatic vessels

2. There are several steps in metastasis. A tumor cell must complete each step before moving on to the next one.

A: True

3. Once angiogenesis is established, it is almost certain that tumor cells will metastasize because it is very easy for tumor cells to survive in circulation.

A: False; it is very difficult for tumor cells to survive in circulation. In fact, only 1 out of 10,000 cells that enter circulation will survive.

4. The strategy behind angiogenesis inhibitors is to feed the tumor with poison through the new blood network that the tumor has established.

A: False; the idea behind angiogenesis is to cut off the tumor's blood supply so that you can "starve" the tumor of nutrients and oxygen, keeping it dormant and manageable.

Vocabulary: Define the following terms:

1. Metastasis:

A: The migration of cancer cells from the original tumor site through the blood and lymph vessels to produce cancers in other tissues. Metastasis also is the term used for a secondary cancer growing at a distant site.

2. Intravasation:

A: The process by which tumor cells invade and enter into the blood circulation or lymphatic system.

3. Extravasation:

A: The process by which tumor cells exit out of the blood vessel.

4. Angiogenesis:

A: the formation of new blood vessels from pre-existing ones

5. VEGF

A: Vascular Endothelial Growth Factor; a molecule that is secreted by tumor cells and stimulates the growth of endothelial cells and the production of new blood vessels