

## Lesson IV 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.

## **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.