

Cancer Growth and Metastasis

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Learning Objectives (4)

After completing this brick, you will be able to:

- 1 Explain the concepts of tumor cell doubling and growth fraction.
- 2 Describe how tumor cells invade tissues.
- 3 Explain the mechanisms by which tumor cells evade immune detection.
- 4 Describe the three main pathways by which tumor cells metastasize.

Doubling Time

The doubling time is the amount of time it takes one cell to divide or a group of cells to double in quantity (Figure 1). The doubling time varies from one cancer to another and can vary even between cases of the same type of cancer. The clinical utility of doubling time is to estimate a prognosis based on how fast the tumor doubles in size. This is important because it correlates with the aggressiveness of the tumor. For example, when monitoring a lung nodule, if it was 1 cm in diameter and it grows to 2 cm within 4 years, the doubling time is 4 years. This tumor would not be considered very aggressive. In comparison, if the nodule was 1 cm in diameter and grew to 2 cm within 2 months, the outlook would be very different. This doubling time is 2 months, and the tumor is considerably more aggressive, which would warrant a more aggressive treatment course.

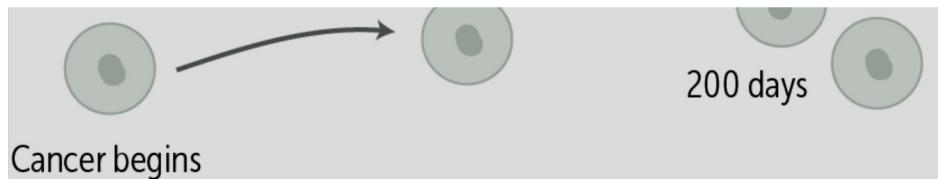


Figure 1

What is the doubling time shown in Figure 1?

Growth Fraction

The growth fraction is the amount of tumor cells that are within the **proliferative phase** of the cell cycle. Most of our cells are in the resting (nonproliferative) phase, which is G0. During periods of growth, cells leave the resting phase (G0) and enter into G1. The cell will proceed through the interphase (G1, S, G2) and M phase (mitosis, cytokinesis) to ultimately divide into two cells (Figure 2).

QUIZ

 Tap image for quiz

Figure 2

When the tumor is still in the early stages of growth, the majority of cells are in the proliferative phase. The interphase requires lots of nutrients, which are supplied by blood flow to the tumor. When a tumor grows too large, it outgrows its blood supply and is no longer able to maintain so many cells in the proliferative phase. As the tumor grows larger, more cells leave the proliferative phase and enter G0. This detail is clinically important because the majority of chemotherapy agents target cells in the proliferative phase of the cell cycle.

Cell Death Rate

There is a natural cycle of old cells dying and being replaced by new ones. This is true in tumors as well. The number of cells that turns over per unit time is known as the cell death rate.

How Do Subclones Increase Malignant Potential?

So how do some tumors decrease their doubling time and evade the immune system? Over time, some tumors acquire a greater malignant potential. This occurs incrementally. With each cell independently mutating, some mutations can prolong tumor cell survival, and others are detrimental to tumor cell survival.

A **subclone** (also known as a tumor cell variant) describes a tumor cell that has acquired additional mutations. Various tumor subclones will have different effects on growth, invasion, metastasis, and resistance to therapies (Figure 3).

Figure 3

Over time, subclones with mutations that portend a survival benefit will accumulate and make up a greater proportion of the tumor. These mutations could inhibit tumor suppressor genes and activate proto-oncogenes. Tumors are initially monoclonal, but by the time they are larger and clinically evident, the cells are heterogenous. Certain subclones undergo immune selection, the highly antigenic subtypes undergo apoptosis, and those that can evade the immune system survive, grow, and invade, leading to metastasis.

What factors determine the rate of tumor growth?

How Do Cancer Cells Invade Tissues?

A cancer is considered to be *in situ* when it does not penetrate through the underlying basement membrane. The basement membrane is a thin layer of connective tissue that separates the epithelium from the underlying tissue. A cancer becomes invasive when it crosses the basement membrane.

Invasive cancers have the ability to metastasize, or spread to other parts of the body. The steps involved in metastasis are invasion, intravasation, extravasation, and growth at distant organ sites ([Figure 4](#)).

Figure 4

To fully understand this process, let's first review the composition of our

To fully understand this process, let's first review the composition of our tissues. Tissues are covered with an outer layer of epithelial cells held together by several proteins. Some proteins that are important in intracellular linkage are E-cadherin and catenins (Figure 5).

Figure 5

Step 1: Invasion

Invasion begins when cancers separate cells by disrupting the function and integrity of E-cadherin or catenins (Figure 6). For example, malignant breast adenocarcinomas cause the downregulation of E-cadherin within breast tissue, making it easier to separate the cells from one another. This

allows malignant cells to easily move from the primary tumor.

Figure 6

The tumor cells from the primary tumor are now mobile and have the task of invading the basement membrane and extracellular matrix. This is done by cleaving, using proteases. The proteases are secreted from the tumor cells themselves or induced by macrophages or fibroblasts within the surrounding tissues. The release of proteases not only degrades the stroma but also promotes tumor cell growth by releasing growth-promoting agents. Tumor cells migrate in an amoeboid-type pattern, using the actin skeleton and signaling between the tumor and stromal cells to ratchet

through the extracellular matrix.

Step 2: Intravasation

Intravasation involves entry into the bloodstream or lymphatics. Many circulating tumor cells will die from shear stress from blood or lymphatic flow or apoptosis due to loss of adhesion. Tumor cells bind to each other or to platelets to survive in the bloodstream. They may activate coagulation factors, resulting in emboli. A tumor cell is significantly larger than most blood cells and for this reason will likely get stuck at the first capillary bed it crosses, getting closer to its final destination.

Step 3: Extravasation

Extravasation is the exit from the bloodstream and into the tissue. Adhesion molecules and anatomic location play a big role. However, some cancers prefer to metastasize to organs that are not nearby. One example of distant metastasis is the predilection of lung cancer to metastasize to the adrenal glands. This may be due to specific adhesion molecules on target endothelium. Tumor cells may express specific ligands (binding molecules) for certain endothelium.

Step 4: Growth at Secondary Site

Growth at a secondary site can only occur if the surrounding tissue of the target organ is favorable. Metastasis will not occur if the stromal environment is not conducive to the tumor's growth, for example, if certain growth factors are not present. A growing tumor requires certain factors to survive.

What are the four steps of tumor cell metastasis?

How Does Cancer Evade the Immune System?

As previously noted, as a tumor grows it develops subclones, each with its own unique features. One such feature is immune evasion. Mechanisms for immune evasion include:

- Antigen masking
- Outgrowth of antigen variants
- Loss of major histocompatibility complex (MHC) molecules
- Lack of co-stimulation
- Immunosuppression
- Apoptosis of cytotoxic T cells

Antigen Masking

Antigen masking is one way that tumor cells hide from the immune

system. Some tumor cells secrete an excess of extracellular matrix material called glycocalyx. This thick coating on cells “masks” the antigens (molecules) on cancer cells, making it more difficult for immune cells to target them for destruction (Figure 7).

Figure 7

Outgrowth of Antigen Variants

If a subclone of tumor cells is highly immunogenic, meaning it can easily present as foreign to host immune cells, the subclone group will be eliminated. In contrast, some tumor subclones can lose the expression of surface antigen or downregulate antigen expression. These tumor cells will not express an antigen that can be recognized by any of our immune cells. Although this has been observed in cancers such as melanoma, the exact mechanism is unknown (Figure 8).

Figure 8

Loss of MHC Molecules

In some cases, tumor cells can change their identity to avoid immune system defenses. Cytotoxic T cells are white blood cells that fight infection and work to kill foreign cells and cancer cells. These T cells identify target cells by looking for MHC class I molecules. MHC is a receptor present on all cells that displays antigens on the cell surface. Some tumor subclones undergo mutations to lose the MHC molecules so they are no longer recognized by cytotoxic T cells (Figure 9).

Figure 9

Lack of Co-Stimulation

In general, a T cell can only be activated after receiving two signals; this ensures that T cells are not destroying host cells (Figure 10). The first signal is from antigen activation presented by MHC class I or MHC class II molecules. The second signal is a co-stimulatory signal from the antigen-presenting cell (APC).

Figure 10

If this co-stimulatory signal is not received, the T cell will undergo apoptosis, programmed cell death (Figure 11). Tumor cells can rid themselves of this co-stimulatory signal, allowing them to evade the immune system and cause destruction of T cells.

Figure 11

Immunosuppression

The immune response is regulated by cytokines, which are small proteins that function as signaling molecules. One of these cytokines is transforming growth factor β (TGF- β), a potent immunosuppressant capable of suppressing the activities of B cells, T cells, dendritic cells, and macrophages. Some tumor cells secrete TGF- β in large quantities, suppressing the immune system (Figure 12).

What potent immunosuppressant do tumor cells use to evade immune system defenses?

Apoptosis of Cytotoxic T Cells

Apoptosis (programmed cell death) is basically a self-destruct button. This process can occur via two different mechanisms: the intrinsic or extrinsic pathway. Tumor cells such as melanoma and hepatocellular carcinoma express a receptor that leads to apoptosis via the extrinsic pathway. They express FasL, which binds to the Fas-receptor on T cells, leading to apoptosis of cytotoxic T cells.

What Are the Different Pathways of Metastasis?

There are three main pathways by which tumor cells can metastasize. Tumors can spread lymphatically (through the lymphatic system), hematogenously (through the circulatory system), or by seeding (directly

Figure 12

onto nearby structures). In many cases, the route of metastasis is determined by the type of cancer.

Carcinomas, epithelial-derived tumors, are associated with lymphatic spread. Sarcomas are of mesenchymal origin and are associated with hematogenous spread. However, this is not a set rule because the reverse can also occur. Although most carcinomas spread lymphatically, four types are known for spreading hematogenously: follicular thyroid carcinoma, choriocarcinoma, renal cell carcinoma, and hepatocellular carcinoma.

Four Carcinomas Route Hematogenously:

- Follicular thyroid carcinoma
- Choriocarcinoma
- Renal cell carcinoma
- Hepatocellular carcinoma

Lymphatic Spread

The reason for a tumor cell to intravasate lymphatically is mostly a mechanical issue. The lymphatic pathway is a low-shear system; it does not have the tight junctions and basement membrane associated with blood vessels, making it easier for a tumor cell to get into a lymphatic

vessel than a blood vessel. An example of a tumor that shows lymphatic spread is breast cancer. Lymph node involvement is based off the path of lymphatic drainage. Breast cancers originating from the upper outer quadrants will first travel to axillary lymph nodes (nodes in the arm pits) because the lymphatic drainage is nearby.

Hematogenous Spread

Hematogenous spread can occur through arteries or veins. Arteries are thicker and harder to penetrate because of their elastin content, so this is a less common route. With venous spread, tumor cells follow the normal venous drainage pattern and become embedded in the first capillary bed they reach. This helps explain why the liver and lung are the most common sites of hematogenous metastasis. All portal blood from the colon, stomach, and pancreas drains into the liver, which is why many liver metastases are from cancers primary to these three organs. Venous blood from the superior and inferior vena cava flows to the lungs. Metastases to the lung are commonly from cancers of the bladder, colon, breast, and prostate.

Seeding

Seeding is another mechanism of cancer spread. We can imagine a process similar to how a gardener sows seeds in an open space of the garden. Cancer seeding occurs in the same fashion, requiring an open space, such as within the peritoneal cavity, pleural cavity, subarachnoid space, or joint cavities. For example, ovarian carcinoma is known for seeding the peritoneal cavity, and glioblastomas use the subarachnoid space to seed within the brain and spinal cord.

By which pathway do carcinomas typically metastasize?

CASE CONNECTION

[BACK TO INTRODUCTION ↑](#)

Thinking back to TF, what are the likely locations and sources of TF's metastases?

Unfortunately, TF has stage IV breast cancer, with involvement of her lymph nodes and lungs. You now know that breast cancer can spread to the axillary lymph nodes directly and to the lungs via the superior vena cava through the process of intravasation and extravasation. You spend a good deal of time with TF, answering her questions and supporting her through the discussion. After discussing things with her family, TF decides to undergo chemotherapy. You call her on the phone the next day to see how she is doing. "Not bad. Today is better than yesterday. I have a wonderful and supportive family," TF says.

Summary

- Doubling time is the amount of time it takes a group of cells to double in size; this varies between different types of cancers.
- The growth fraction corresponds to the number of tumor cells within the proliferative phase, which includes any stage of the cell cycle other than G₀; this indicates that cells are dividing.
- Tumor subclones occur when some of the tumor cells acquire mutations; these mutations can benefit the tumor and lead to immune evasion and eventual metastasis.
- Immune evasion is achieved by antigen masking, outgrowth of antigen variants, loss of MHC molecules, lack of co-stimulation, immunosuppression, and apoptosis of cytotoxic T cells.
- The steps of metastasis are invasion, intravasation, extravasation, and growth at secondary sites.
- Intravasation corresponds to tumor cell invasion through the extracellular matrix, into the bloodstream, and travel to a secondary site.
- In extravasation, tumor cells exit the bloodstream or lymphatics and infiltrate outside of the capillaries.
- Growth of a tumor at a distant site relies on the environment of that tissue; without the proper stromal environment, such as cytokines and growth factors, survival of the tumor cannot occur.
- A tumor can metastasize lymphatically, hematogenously, or by seeding.
- Carcinomas are associated with lymphatic spread.
- Sarcomas are associated with hematogenous spread.
- Seeding occurs within open spaces such as the peritoneal cavity, subarachnoid space, pleural space, and joint cavities.