

# Genetic and Molecular Basis of Cancer

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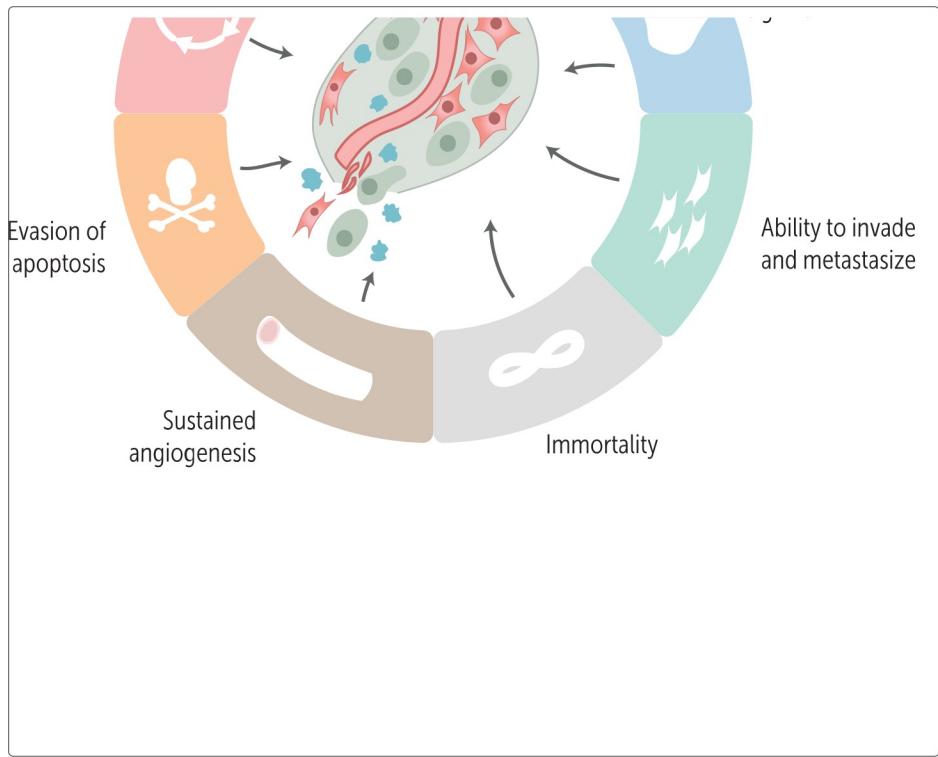
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## [Learning Objectives \(5\)](#)

*After completing this brick, you will be able to:*

- 1 Explain how nonlethal genetic damage is at the center of cancer pathogenesis.
- 2 List and describe the eight hallmarks of cancer cells.
- 3 Explain how cancer cell hallmarks are used in the diagnosis and treatment of cancer.
- 4 Describe the four classes of regulatory genes that are the main targets of cancer-causing mutations.
- 5 Describe the process of clonal expansion, and explain the concept of tumor subclones.



#### QUIZ

Tap image for quiz

Figure 1

## Cancer Cells Grow Like Crazy

Several of these hallmarks have to do with the ability of cancer cells to grow like crazy. Normal cells need growth signals in order to grow, and

when they receive signals to stop growing, they stop. In contrast, cancer cells grow and divide without outside help—and they learn how to find and use energy sources to support an ever-increasing population of tumor cells.

- Cancer cells can grow on their own without any outside signals; this is called **autonomous cell proliferation**.
- Cancer cells can basically just ignore any signals telling them to stop growing, which we call **resistance to growth-suppressing signals**.
- Cancer cells have an **altered metabolism**, too: they use **anaerobic glycolysis** so that they can synthesize everything they need for rapid cell growth.

#### INSTRUCTOR NOTE

Please note - Robbins and Cotran, the traditional textbook of Pathology in its most updated edition (11th, 2025) states that cancer cells use aerobic NOT anaerobic glycolysis - please see below and power point:

"Cancer cells demonstrate a distinctive form of cellular metabolism characterized by high levels of glucose uptake and increased conversion of glucose to lactate (fermentation) via the glycolytic pathway. This phenomenon, called the Warburg effect... also known as aerobic glycolysis.."

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- Cancer cells know how to stimulate the growth of new blood vessels (**angiogenesis**) so that as the tumor gets bigger, the blood supply is

able to keep up.

## Cancer Cells Refuse to Die

Cancer cells also don't die like normal cells do.

- Normal cells can only undergo a certain number of mitoses (usually around 60-70) before they die. But cancer cells are "**immortal**" and can replicate endlessly.
- Normal cells also have a preprogrammed script for a special kind of cell death called apoptosis—and they'll follow that script if they are told to do so. Cancer cells don't follow that script; they are able to **evade apoptosis**.
- Speaking of evasion, cancer cells are also able to **evade the host's immune response**, which typically kills any cell that displays abnormal antigens.

## Cancer Cells Metastasize

One final hallmark of cancer is **metastasis**, which refers to the ability of cancer cells to spread throughout the body. This hallmark more than any other is diagnostic of cancer. Some of these other characteristics are present even in benign tumor cells—but with very few exceptions, benign tumors do not metastasize.

## Cancer Cells Create the Right Conditions for Growth

Acquiring these eight hallmarks is not a simple or quick process. But cancer cells make this task easier by creating two cancer-enabling conditions:

- Genomic instability

- Genomic instability
- Cancer-enabling inflammation

Let's look at genomic instability first. As cancer cells evolve, they acquire gene mutations that enable them to bypass normal processes—such as DNA repair systems—that keep DNA intact and stable. As a result, the DNA of the cancer cell becomes even more susceptible to genetic mutations. This DNA condition is called genomic instability, and it paves the way for the cancer cell to acquire the hallmarks of cancer discussed above.

Another cancer-enabling condition is inflammation. As cancers invade tissues, they attract inflammatory cells such as lymphocytes and macrophages to the region of the tumor. Normally, inflammatory cells are very useful in the fight against foreign invaders. But in this scenario, the tumor manipulates the inflammatory cells into secreting factors that promote cancer cell growth, enhance the cancer cells' ability to resist death, and otherwise enable the cancer cell on its hallmark-acquiring path.

## How Are Hallmarks Used in the Diagnosis and Treatment of Cancer?

We'll now go into more detail on four of those hallmarks of cancer that allow cancer to survive despite all of the checks and balances to prevent it:

- Altered metabolism
- Evasion of apoptosis
- Sustained angiogenesis
- Immortality

These four hallmarks merit a more in-depth discussion because they frequently are used as targets in the diagnosis and treatment of cancer. For example, the altered metabolism of cancer cells is the basis for positron

emission tomography (PET), a diagnostic imaging method that identifies cancer cells by detecting their abnormally high uptake and metabolism of glucose. Another example is traditional chemotherapy, which exploits the replicative immortality of cancer cells by specifically targeting rapidly dividing cells.

## Altered Metabolism

Each cell has metabolic processes that form (anabolic) or break down (catabolic) different molecules. These actions use substrates from the environment to provide energy for the cell. One of the most common sources of energy is glucose.

INSTRUCTOR NOTE

In the presence of oxygen usually glycolysis converts glucose to pyruvate which then enters the TCA cycle and oxidative phosphorylation. Whereas in the absence of oxygen, pyruvate is converted to lactic acid. But in the Warburg effect, the tumor cells can actually do glycolysis and then get pyruvate converted to lactic acid even if they have enough oxygen present. That's why it's called aerobic glycolysis - because the lactic acid fermentation occurs even in the presence of oxygen.

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Glucose can be processed for energy aerobically in the citric acid cycle and the electron transport chain. Or it can be processed anaerobically which

results in the production of lactate. Most cells with mitochondria use aerobic metabolism to generate energy in the presence of oxygen, whereas cells without mitochondria, like red blood cells, use the anaerobic process. Cells with mitochondria also resort to anaerobic glycolysis and produce lactate in the absence of oxygen. Cancer cells behave differently!

INSTRUCTOR NOTE

As per the Robbins text, "Why is it advantageous for a cancer cell to rely on seemingly inefficient glycolysis (2 molecules of ATP per molecule of glucose) instead of oxidative phosphorylation (36 molecules of ATP per molecule of glucose)? The answer: aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are needed for the synthesis of cellular components, whereas mitochondrial oxidative phosphorylation does not."

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Although they have mitochondria, cancer cells preferentially metabolize glucose to lactate, even in the presence of abundant oxygen. We think this allows them to rapidly generate biosynthetic raw materials and energy for proliferation. This unique type of aerobic glycolysis in cancer cells is called the Warburg effect.

The altered metabolism of cancer cells is used to aid in the diagnosis of cancer and detection of metastasis via positron emission tomography (PET) scan. In this scan a radioactive tracer such as 18F-

PET scan. In this scan, a radioactive tracer, such as 18F-fluorodeoxyglucose (18F-FDG), an analog of glucose, is administered. This

is taken up by cells as if it is glucose. Since cancer cells have higher glucose uptake than noncancerous cells, the tracer is significantly absorbed by cancer cells, leading to bright areas visible on the PET scan.

## Evasion of Apoptosis

Apoptosis is programmed cell death, or cell suicide, and it is a normal cellular process. It often occurs when the cell is damaged. For example, when a cell has DNA damage that cannot be fixed, the cell will often induce apoptosis so as not to continue proliferating with this damage, because that could lead to cancer. Think of cancer cells as super cells that have bypassed this well-regulated process.

There are two different pathways to apoptosis: the extrinsic or death receptor-mediated pathway and the intrinsic mitochondrial pathway. Both pathways result in the production of caspases, protease enzymes that breakdown the nuclear and cytoplasmic components of the cell. Cancer cells can downregulate the expression of these caspases or modify their action through phosphorylation. In addition, the molecules in a normal cell that inhibit apoptosis such as the *Bcl-2* family of proteins and the inhibitor of apoptosis proteins (IAPs) are upregulated. This property can be used as a target for antitumor drugs, such as the *Bcl-2* inhibitor venetoclax, a treatment for hematologic malignancies.

How does a cancer cell avoid both the extrinsic and intrinsic pathways of apoptosis?

## Sustained Angiogenesis

As cancer cells proliferate rapidly, avoiding apoptosis and shifting their metabolism to anaerobic pathways, they need to find a way to increase their access to energy, specifically glucose. To accomplish this task, they increase the number of avenues that can provide the nutrients they need. This process is called angiogenesis, or the creation of new blood vessels.

In normal physiology, angiogenesis is regulated. In cancers, this regulation is disrupted. One of the most common angiogenesis signals upregulated by cancer cells is *vascular endothelial growth factor* (VEGF). VEGF is a ligand to VEGF receptor tyrosine kinase. This signaling pathway initiates the production of new blood vessels, which will bring glucose and oxygen to growing cancer cells. In addition, these blood vessels create new avenues through which cancer cells can enter and travel to new parts of the body, a process known as metastasis. Several antitumor drugs take advantage of this upregulation of VEGF; *monoclonal antibodies* against VEGF are used in the treatment of many solid tumors, such as colorectal cancer.

## Immortality

Most cells in the body have an internal limit to the number of times they

MOST cells in the body have an internal limit to the number of times they can replicate. This limit is determined by the length of telomeres, pieces of DNA that are like caps on the end of chromosomes. Each time a cell divides, the telomere shortens. Once the telomere disappears—usually after around 60-70 doublings—the cell can no longer replicate. Cancer cells have mutated to resist this end to their growth.

Cancer cells learn how to generate telomerase, an enzyme that replenishes telomeres after each mitotic division, restoring them to their original length. This action essentially makes the cell able to divide forever. Cancer treatments may be developed to either decrease the function of telomerasess or induce telomere dysfunction to combat this ability.

What does telomerase do to telomeres in cancer cells?

## Which Genes Are the Main Targets of Cancer-Causing Mutations?

Some genes are targeted more often than others by cancer-causing mutations. Can you guess why? If you thought that it might be the genes that induce the actions we described in the previous section, you would be 100% correct! Here, we will look at four classes of genes targeted by cancer-causing mutations and specific examples of each.

### Growth-Promoting Oncogenes

The first class is growth-promoting oncogenes. In normal cells, these genes are referred to as proto-oncogenes and they encode proteins that promote cell growth. However, a single gain-of-function mutation in such a gene can drive a cell toward cancer. This event changes the proto-oncogene to an oncogene, an overactive or overexpressed form of the proto-oncogene. In other words, a gene that originally had one function has gained a new function or increased the action of one of its previous functions. This change results in the cell's propensity toward cancer.

The National Cancer Institute developed a car analogy that we love for understanding how this works. Normally when driving your car, you ease off the gas pedal when you spot something that should slow you down. Imagine hitting a patch of traffic and not slowing down your car at all, instead keeping your foot planted on the gas pedal. A gain-of-function mutation is like having that accelerator pedal stuck on, full speed ahead, regardless of the danger ahead (Figure 2).

## QUIZ

 Tap image for quiz

**Figure 2**

Some examples of proto-oncogenes include Src, RTK, CTK, Myc, and Ras. Src is a nonreceptor tyrosine kinase; RTK is a receptor tyrosine kinase (eg, EGFR,  $\gamma$ EGF—growth factor receptors); and CTK is a cytoplasmic tyrosine kinase (eg, BCR-ABL—the Philadelphia chromosome). In normal cells, these receptors function to initiate signaling cascades through phosphorylation, which promote cell survival and growth. In cancer cells, these receptors are overexpressed or constitutively active, allowing the cell to survive and grow even in the presence of a mutation or a poor environment. Myc is a transcription factor that can be induced at the end of tyrosine kinase or non-tyrosine kinase pathways. As it is an integral stimulator of cell growth and survival, cells have many pathways to upregulate its expression. When it is mutated, the cell continues to grow and survive even with mutations or in a difficult environment.

Ras is unique in comparison with these receptors in that it is a G-coupled protein that resides in the cell membrane. The G stands for GTP. When GTP is not phosphorylated or in the GDP state, the Ras protein is inactive and cannot begin the signaling pathway. When GDP is phosphorylated to GTP, Ras activates its pathway. Aside from cell survival and cell growth,

Ras also initiates transcription, cell cycle progression, cell migration, and endocytosis. When these pathways are overstimulated, these actions can cause cells to become cancerous as they would have the ability to grow, survive, multiply, take in other items from the environment, and move.

## Growth-Inhibiting Tumor Suppressor Genes

Whereas oncogenes result from a gain-of-function mutation, tumor suppressor genes lead to cancer by a loss-of-function mutation. In other words, a gene that is usually expressed in the cell is now no longer being expressed, and the molecule it created is no longer working. Furthermore, unlike proto-oncogenes, which require only a single mutation, tumor suppressor genes require two mutation events to effectively become inactive. This route of mutation is known as the “two-hit hypothesis.” Basically, one allele can have a mutation from an initial event, and you will see no effect in the function of the cell. Then, another mutation event occurs in the other allele, resulting in a total lack of tumor suppressor gene function.

In the case of the car you were driving earlier, imagine if your car had two brakes. One of those brakes stopped working, but you still had the spare. Then, the other broke too. Now, you are moving forward toward your destination because you no longer have brakes to stop you (Figure 3).

**Figure 3**

Two examples of tumor suppressor genes include retinoblastoma (RB) and p53. *RB* and *p53* encode proteins that impede the progression of the cell cycle from the G1 phase (ie, all cellular contents duplicate except the chromosomes) to the S phase (ie, synthesis phase or chromosome duplication phase). The Rb protein (product of the *RB* gene) acts as a growth suppressor, and its inactivation results in inappropriate cell proliferation. *p53* is activated when there are hyperproliferative signals, DNA damage, telomere shortening, or hypoxia and causes cell cycle arrest, senescence, or apoptosis. When inactivated, the cell continues to proliferate even with these issues.

INSTRUCTOR NOTE

There is a significant clinical correlation associated with the tumor suppressor gene *p53*. There are families in which some members inherit one mutated allele. Therefore, based on the "two-hit" hypothesis above, they only need one more hit for cancer to develop. These families usually have members who develop

carcinomas, sarcomas, leukemias, lymphomas, etc., before the age of 50 years. This is known as Li Fraumeni syndrome and is important to keep in mind.

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Oncogenes step on the gas (gain-of-function). Tumor suppressor genes remove the brakes (loss-of-function).

### Genes That Regulate Programmed Cell Death (Apoptosis)

Remember discussing the avoidance of apoptosis by cancer cells? It turns out that there are two anti-apoptotic protein classes: certain members of the Bcl-2 family and the inhibitor of apoptosis proteins (IAPs) are critical for cancer cells to avoid apoptosis.

The Bcl-2 family of proteins has three groups, two pro-apoptotic and one anti-apoptotic. The anti-apoptotic group includes Bcl-2, Bcl-x<sub>L</sub>, and Mcl-1.

Bcl-2 and Bcl-x<sub>L</sub> prevent the release of a cytochrome c, a molecule from mitochondria that triggers the apoptotic process. Mcl-1 protects the cell against hypoxic conditions and other events that induce oxidative stress on the cell. On the other hand, IAPs block caspases. If you recall, caspases are part of the apoptotic pathway. When either the anti-apoptotic Bcl-2 family of proteins or IAPs are overexpressed, a cell can bypass apoptosis even if the conditions would usually promote cell suicide.

How does overexpression of Bcl-2 lead to cancer?

## Genes Involved in DNA Repair

Without successful DNA repair, cells begin to proliferate with mutations. More mutations mean higher chances of developing cancer. The cell has several ways to fix these mutations: DNA mismatch repair, nucleotide excision repair, base excision repair, and double-strand break repair. Double-strand break repair can be completed by homologous recombination repair or nonhomologous end joining.

### Homologous recombination repair or nonhomologous end joining.

Let's take a look at homologous recombination repair more in depth.

In this process, a double-strand break occurs in the DNA due to x-rays, free radicals, or another injury-causing event. After the initial detection of a DNA break, the second step involves several proteins, which form a nucleoprotein filament (ie, a compound that has DNA and protein). The first strand receiving this addition will be known as the leading strand. Then, other proteins help find a homologous portion of the parent DNA to form a template for the lagging strand. The lagging strand elongates with the help of DNA polymerase. Then, the leading strand unites with the lagging strand through DNA polymerase and ligase, resulting in the repair of the double-strand break.

The second step that formed the nucleoprotein filament involves two very well-known proteins: BRCA1 and BRCA2. When these proteins are mutated, homologous recombination repair or nonhomologous end joining (ie, another double-strand break repair mechanism that does not require homologous DNA strands) cannot happen or does not happen as efficiently. This event results in the incomplete repair of DNA and the progression of mutations within the cell, which can result in cancer ([Table 1](#)).

**Table 1 Double-strand DNA repair mechanisms and clinical implications**

	<b>Homologous recombination repair (HRR)</b>	<b>Nonhomologous end joining (NHEJ)</b>
Type of damage repaired	Double-strand breaks	Double-strand breaks
Cause of damage	Gamma rays, x-rays, replication errors, free radicals,	Gamma rays, x-rays, replication errors, free radicals,

	antineoplastic drugs, DS exonucleases	antineoplastic drugs, DS exonucleases
Key proteins/mechanism	BRCA1 and BRCA2, RAD51	BRCA1 and BRCA2, RAD51
Disease connections	Familial breast cancers and ovarian cancer	Severe combined immunodeficiency

## Why Is Cancer So Difficult to Destroy?

Now that we have reviewed the events that can happen to turn a cell cancerous, let's take a look at how cancer becomes more than just one mutated cell. Typically, the mutation that a cancer cell acquires increases the cell's fitness. When a cell's fitness is improved, it has the ability to produce more daughter cells (ie, divide more rapidly) than a normal cell without the mutation. This process of one cell giving rise to many identical daughter cells is called **clonal expansion**.

Sometimes, cancer daughter cell clones develop additional mutations. These additional mutations make these cells even stronger and fitter than the original cancer cells. These cells are known as **subclones**. Subclones are one reason why treating cancer can be so difficult. One treatment may work on the original cancer cell and its clones. However, new subclone tumor cells may arise that are impervious to the original treatment, allowing these cells to continue to grow and metastasize despite treatment. This occurrence is one of the greatest challenges in treating cancer.

quickly?

You explain that cancer cells can shift their metabolism to generate more energy needed to grow, bypass normal conditions that lead to cell death, produce new blood vessels to bring them fuel, and develop the ability to divide forever. All of these factors make cancer cells invincible. "It sounds incredible, and sometimes like a science fiction movie, but it's true. But we can target your treatment to what we know is effective," you say.

## Summary

- Nonlethal genetic damage is at the center of cancer pathogenesis.
- There are eight hallmarks of cancer cells that distinguish them from normal cells: those resulting in increased cell growth (autonomous cell proliferation, resistance to growth-suppressing signals, altered metabolism, angiogenesis), those resulting in decreased cell death (immortality, evasion of apoptosis, evasion of host immune response), and the ability to metastasize.
- Cancer cells acquire these eight hallmarks through the creation of genomic instability and cancer-enabling inflammation.
- Changes in metabolism (the Warburg effect), avoidance of apoptosis, stimulation of angiogenesis, and limitless replication are four critical hallmarks of cancer cells that can be targeted for cancer diagnosis and treatment.
- Growth-promoting proto-oncogenes, growth-inhibiting tumor suppressor genes, genes that regulate programmed cell death (apoptosis), and genes involved in DNA repair are all targets for cancer-related mutation and allow for cancer cells to continuously

grow and proliferate.

- Clonal expansion is the process by which a single cancer cell produces huge numbers of identical cancer cells.
- Tumor subclones with new mutations may emerge over time, and these new subclones may be resistant to the original treatment method; tumor subclones are one of the reasons why cancer is so difficult to treat.

B. *BRCA2*

C. p53

D. Ras

E. *RB*

## Review Questions

Explanation (requires correct answer)

1. Which of the following changes in the cell prevents it from going through the process of cell suicide?

- A. Avoidance of apoptosis
- B. Changes in metabolism
- C. Limitless replication
- D. Stimulation of angiogenesis
- E. Warburg effect

Explanation (requires correct answer)

2. Which of the following is a proto-oncogene?

- A. *BRCA1*

3. Which of the following inhibits caspases, which effectively stops the process of apoptosis?

- A. *BRCA1*
- B. *BRCA2*
- C. IAPs (inhibitors of apoptosis proteins)
- D. p53
- E. *RB*

Explanation (requires correct answer)

4. Which of the following terms describes cancerous cells that have additional mutations and are fitter compared with the original cancer cell?