THE CELL BIOLOGY (PART 3)

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CANCER

CANCER AND THE CELL CYCLE

HOW CANCER DEVELOPS

CELL CYCLE REGULATORS AND CANCER

ONCOGENES

TUMOR SUPPRESSORS

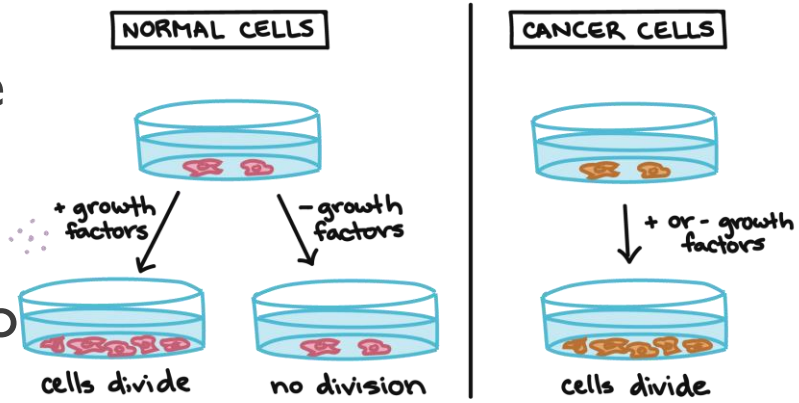
CANCER AND THE CELL CYCLE

- Cancer is basically a disease of uncontrolled cell division. Its development and progression are usually linked to a series of changes in the activity of cell cycle regulators. For example, inhibitors of the cell cycle keep cells from dividing when conditions aren't right, so too little activity of these inhibitors can promote cancer.

- Similarly, positive regulators of cell division can lead to cancer if they are too active. In most cases, these changes in activity are due to mutations in the genes that encode cell cycle regulator proteins.

WHAT'S WRONG WITH CANCER CELLS?

- Cancer cells behave differently than normal cells in the body. Many of these differences are related to cell division behavior.
- For example, cancer cells can multiply in culture (outside of the body in a dish) without any growth factors, or growth-stimulating protein signals, being added. This is different from normal cells, which need growth factors to grow in culture.
- Cancer cells may make their own growth factors, have growth factor pathways that are stuck in the "on" position, or, in the context of the body, even trick neighboring cells into producing growth factors to sustain them



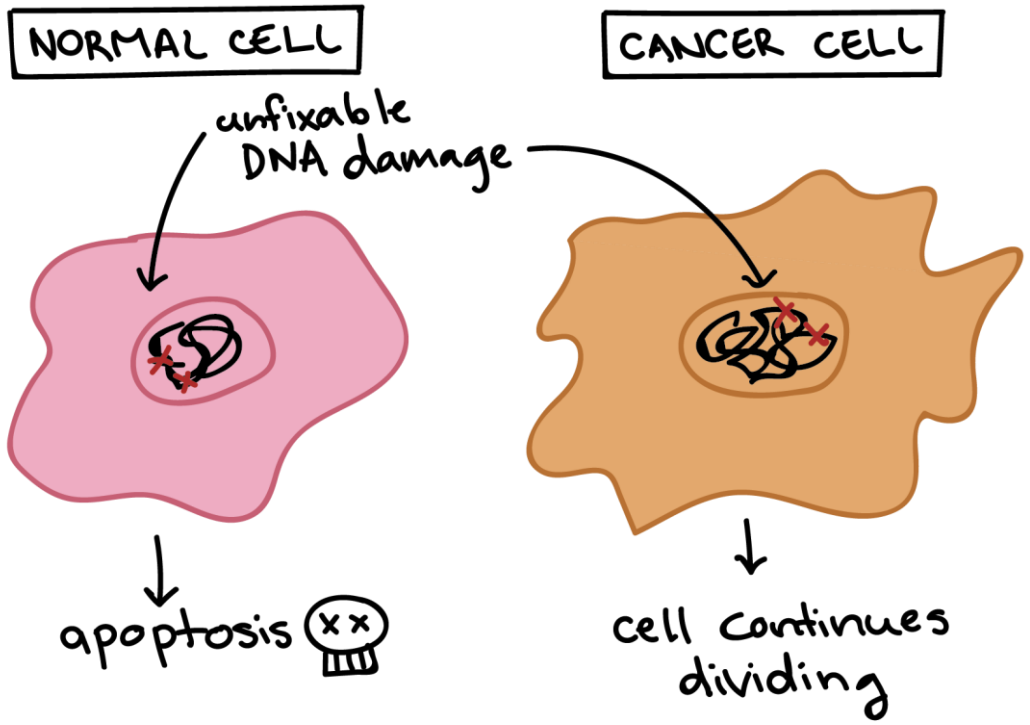
WHAT'S WRONG WITH CANCER CELLS?

- Cancer cells also ignore signals that should cause them to stop dividing. For instance, when normal cells grown in a dish are crowded by neighbors on all sides, they will no longer divide. Cancer cells, in contrast, keep dividing and pile on top of each other in lumpy layers.
- The environment in a dish is different from the environment in the human body, but scientists think that the loss of **contact inhibition** in plate-grown cancer cells reflects the loss of a mechanism that normally maintains tissue balance in the body.
- Another hallmark of cancer cells is their "replicative immortality," a fancy term for the fact that they can divide many more times than a normal cell of the body. In general, human cells can go through only about 40-60 rounds of division before they lose the capacity to divide, "grow old," and eventually die.

WHAT'S WRONG WITH CANCER CELLS?

- Cancer cells can divide many more times than this, largely because they express an enzyme called telomerase, which reverses the wearing down of chromosome ends that normally happens during each cell division.
- Cancer cells are also different from normal cells in other ways that aren't directly cell cycle-related. These differences help them grow, divide, and form tumors. For instance, cancer cells gain the ability to migrate to other parts of the body, a process called **metastasis**, and to promote growth of new blood vessels, a process called **angiogenesis** (which gives tumor cells a source of oxygen and nutrients). Cancer cells also fail to undergo programmed cell death, or **apoptosis**, under conditions when normal cells would (e.g., due to DNA damage). In addition, emerging research shows that cancer cells may undergo metabolic changes that support increased cell growth and division

WHAT'S WRONG WITH CANCER CELLS?



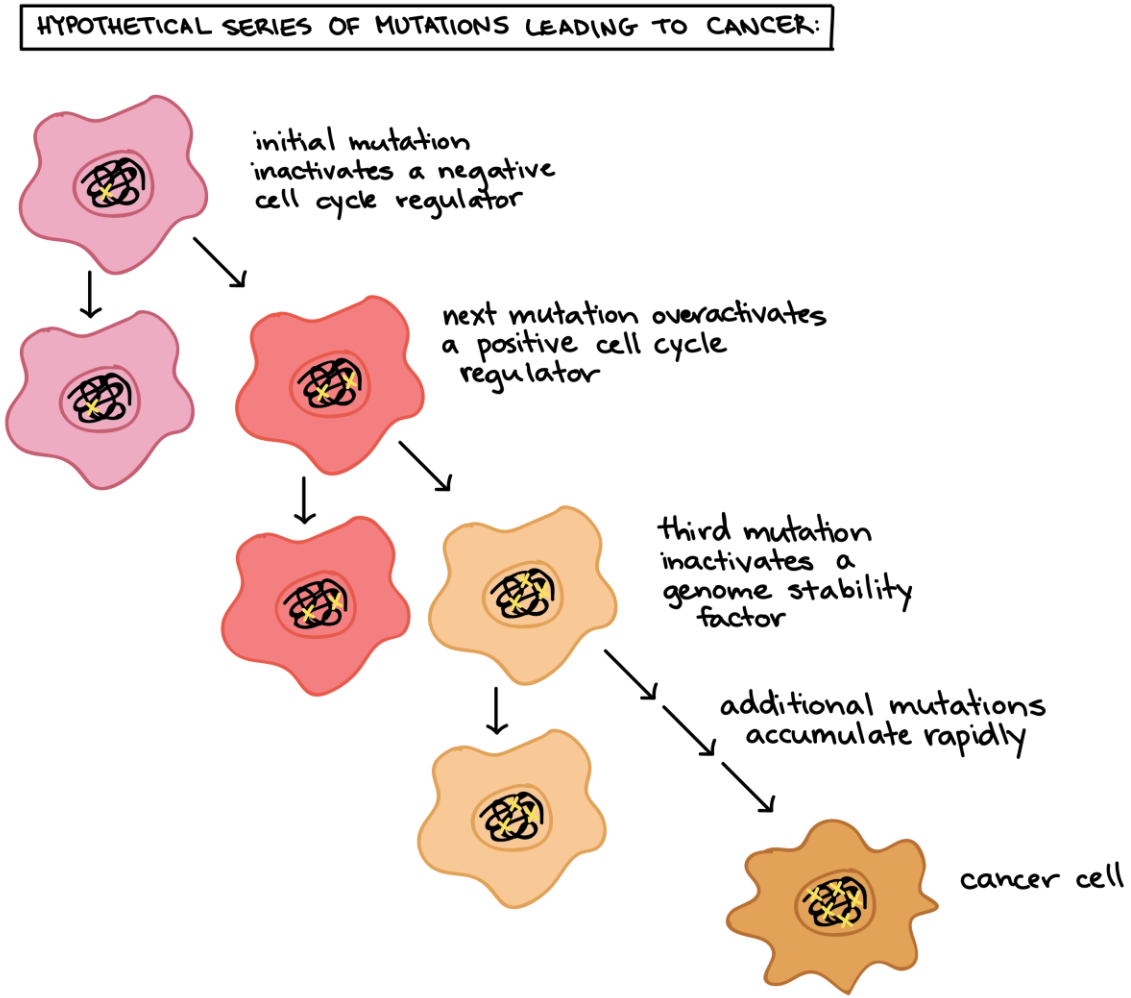
HOW CANCER DEVELOPS

- Cells have many different mechanisms to restrict cell division, repair DNA damage, and prevent the development of cancer. Because of this, it's thought that cancer develops in a multi-step process, in which multiple mechanisms must fail before a critical mass is reached and cells become cancerous. Specifically, most cancers arise as cells acquire a series of **mutations** (changes in DNA) that make them divide more quickly, escape internal and external controls on division, and avoid programmed cell death

HOW CANCER DEVELOPS

- How might this process work? In a hypothetical example, a cell might first lose activity of a cell cycle inhibitor, an event that would make the cell's descendants divide a little more rapidly. It's unlikely that they would be cancerous, but they might form a **benign tumor**, a mass of cells that divide too much but don't have the potential to invade other tissues (metastasize).
- Over time, a mutation might take place in one of the descendant cells, causing increased activity of a positive cell cycle regulator. The mutation might not cause cancer by itself either, but the offspring of this cell would divide even faster, creating a larger pool of cells in which a third mutation could take place. Eventually, one cell might gain enough mutations to take on the characteristics of a cancer cell and give rise to a **malignant tumor**, a group of cells that divide excessively and can invade other tissues

HOW CANCER DEVELOPS



HOW CANCER DEVELOPS

- As a tumor progresses, its cells typically acquire more and more mutations. Advanced-stage cancers may have major changes in their genomes, including large-scale mutations such as the loss or duplication of entire chromosomes. How do these changes arise? At least in some cases, they seem to be due to inactivating mutations in the very genes that keep the genome stable (that is, genes that prevent mutations from occurring or being passed on).
- These genes encode proteins that sense and repair DNA damage, intercept DNA-binding chemicals, maintain the telomere caps on the ends of chromosomes, and play other key maintenance roles. If one of these genes is mutated and nonfunctional, other mutations can accumulate rapidly. So, if a cell has a nonfunctional genome stability factor, its descendants may reach the critical mass of mutations needed for cancer much faster than normal cells.

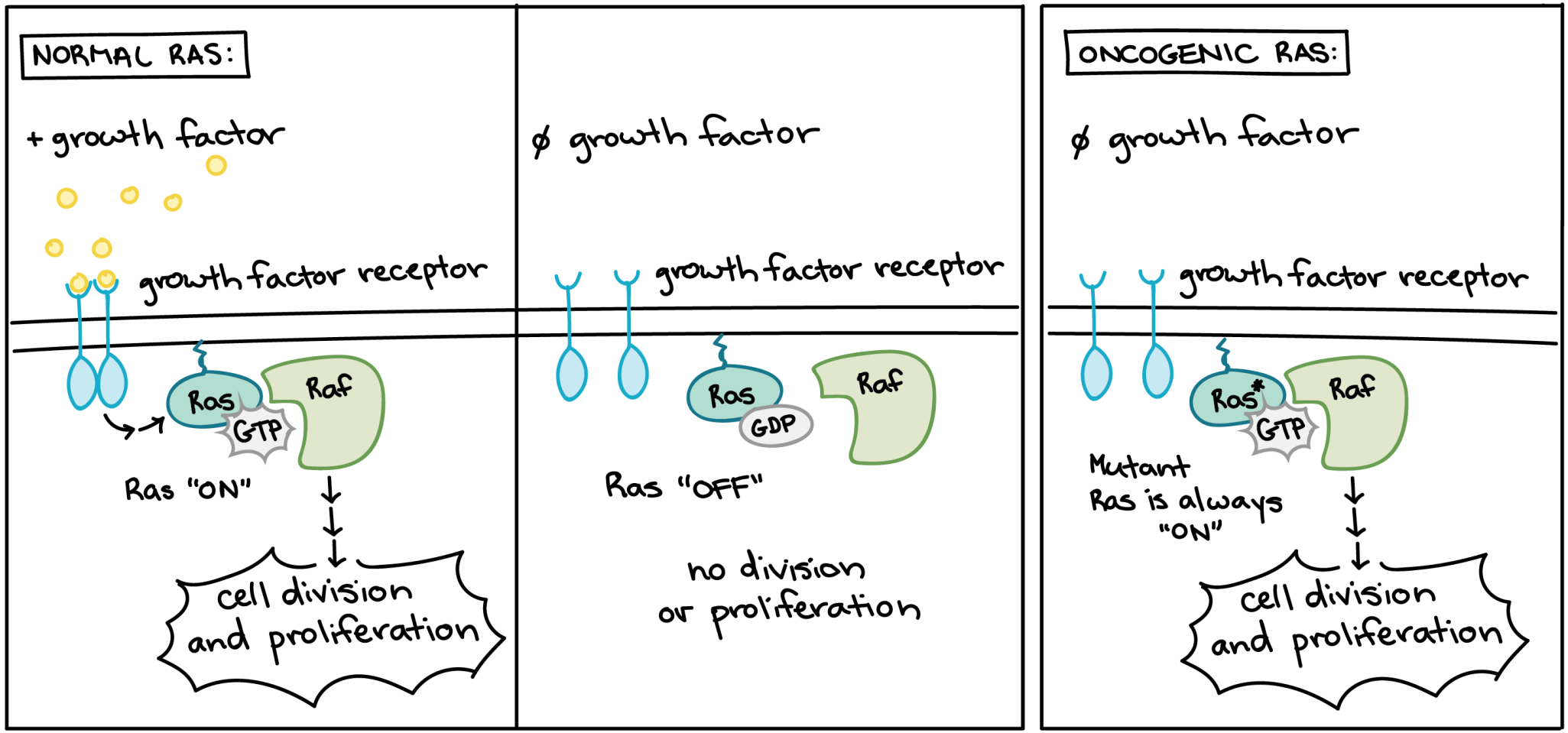
CELL CYCLE REGULATORS AND CANCER

- Different types of cancer involve different types of mutations, and, each individual tumor has a unique set of genetic alterations. In general, however, mutations of two types of cell cycle regulators may promote the development of cancer: **positive regulators** may be overactivated (become oncogenic), while **negative regulators**, also called tumor suppressors, may be inactivated.

ONCOGENES

- Positive cell cycle regulators may be overactive in cancer. For instance, a growth factor receptor may send signals even when growth factors are not there, or a cyclin may be expressed at abnormally high levels. The overactive (cancer-promoting) forms of these genes are called **oncogenes**, while the normal, not-yet-mutated forms are called **proto-oncogenes**. This naming system reflects that a normal proto-oncogene can turn into an oncogene if it mutates in a way that increases its activity.
- Mutations that turn proto-oncogenes into oncogenes can take different forms. Some change the amino acid sequence of the protein, altering its shape and trapping it in an "always on" state. Others involve **amplification**, in which a cell gains extra copies of a gene and thus starts making too much protein. In still other cases, an error in DNA repair may attach a proto-oncogene to part of a different gene, producing a "combo" protein with unregulated activity

ONCOGENES


NORMAL RAS:
+ growth factor
growth factor receptor
Ras
GTP
Raf
Ras "ON"
cell division and proliferation
ø growth factor
growth factor receptor
Ras
GDP
Raf
Ras "OFF"
no division or proliferation
ONCOGENIC RAS:
ø growth factor
growth factor receptor
Ras*
GTP
Raf
Mutant Ras is always "ON"
cell division and proliferation

ONCOGENES

- Many of the proteins that transmit growth factor signals are encoded by proto-oncogenes. Normally, these proteins drive cell cycle progression only when growth factors are available. If one of the proteins becomes overactive due to mutation, however, it may transmit signals even when no growth factor is around. In the diagram above, the growth factor receptor, the Ras protein, and the signaling enzyme Raf are all encoded by proto-oncogenes.
- Overactive forms of these proteins are often found in cancer cells. For instance, oncogenic Ras mutations are found in about 90% of pancreatic cancers. Ras is a G protein, meaning that it switches back and forth between an inactive form (bound to the small molecule GDP) and an active form (bound to the similar molecule GTP). Cancer-causing mutations often change Ras's structure so that it can no longer switch to its inactive form, or can do so only very slowly, leaving the protein stuck in the "on" state.

TUMOR SUPPRESSORS

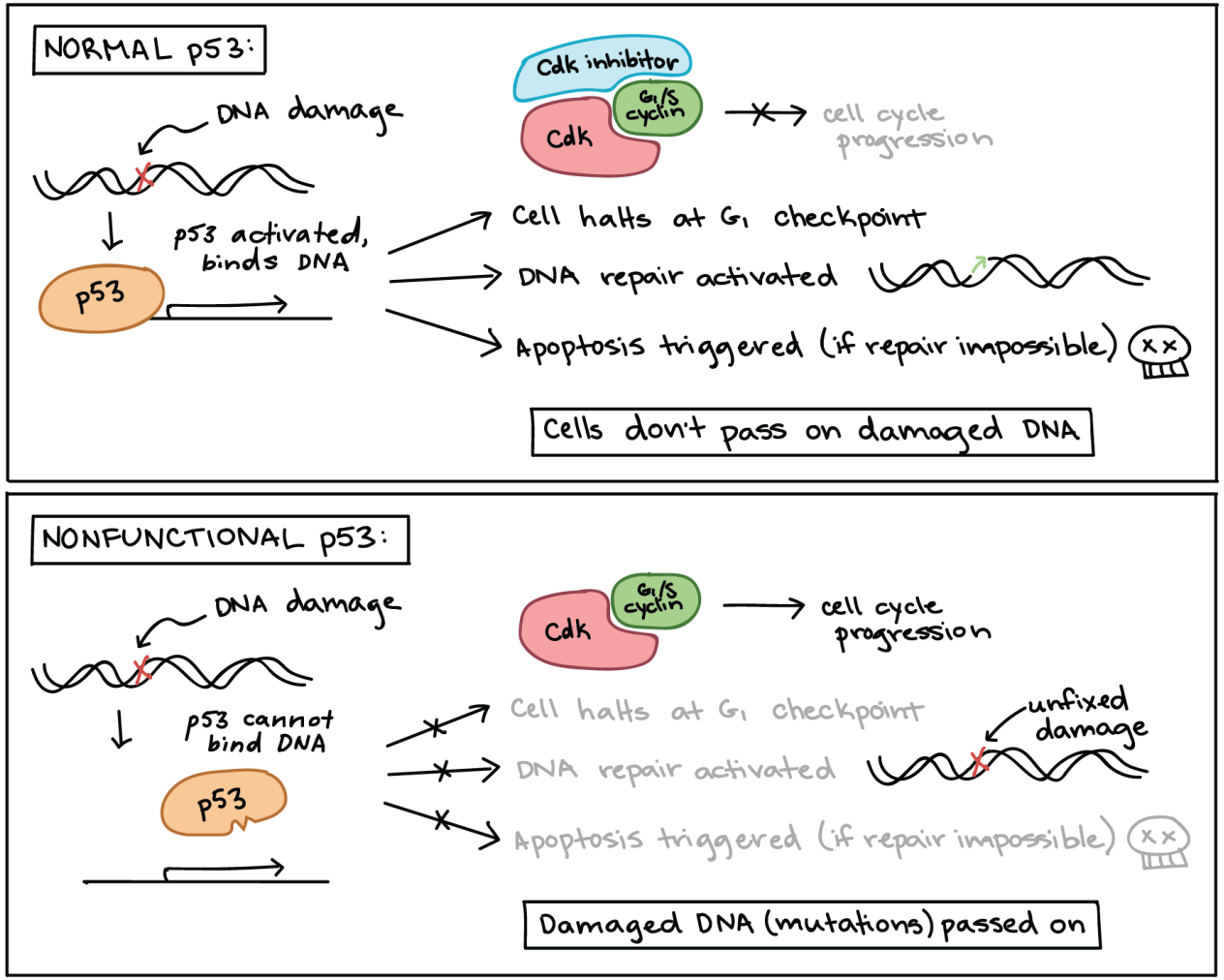
- Negative regulators of the cell cycle may be less active (or even nonfunctional) in cancer cells. For instance, a protein that halts cell cycle progression in response to DNA damage may no longer sense damage or trigger a response. Genes that normally block cell cycle progression are known as **tumor suppressors**. Tumor suppressors prevent the formation of cancerous tumors when they are working correctly, and tumors may form when they mutate so they no longer work.

- One of the most important tumor suppressors is **tumor protein p53**, which plays a key role in the cellular response to DNA damage. p53 acts primarily at the G1 checkpoint (controlling the G1 to S transition), where it blocks cell cycle progression in response to damaged DNA and other unfavorable conditions.

TUMOR SUPPRESSORS

- When a cell's DNA is damaged, a sensor protein activates p53, which halts the cell cycle at the G1 checkpoint by triggering production of a cell-cycle inhibitor. This pause buys time for DNA repair, which also depends on p53, whose second job is to activate DNA repair enzymes. If the damage is fixed, p53 will release the cell, allowing it to continue through the cell cycle. If the damage is not fixable, p53 will play its third and final role: triggering apoptosis (programmed cell death) so that damaged DNA is not passed on.

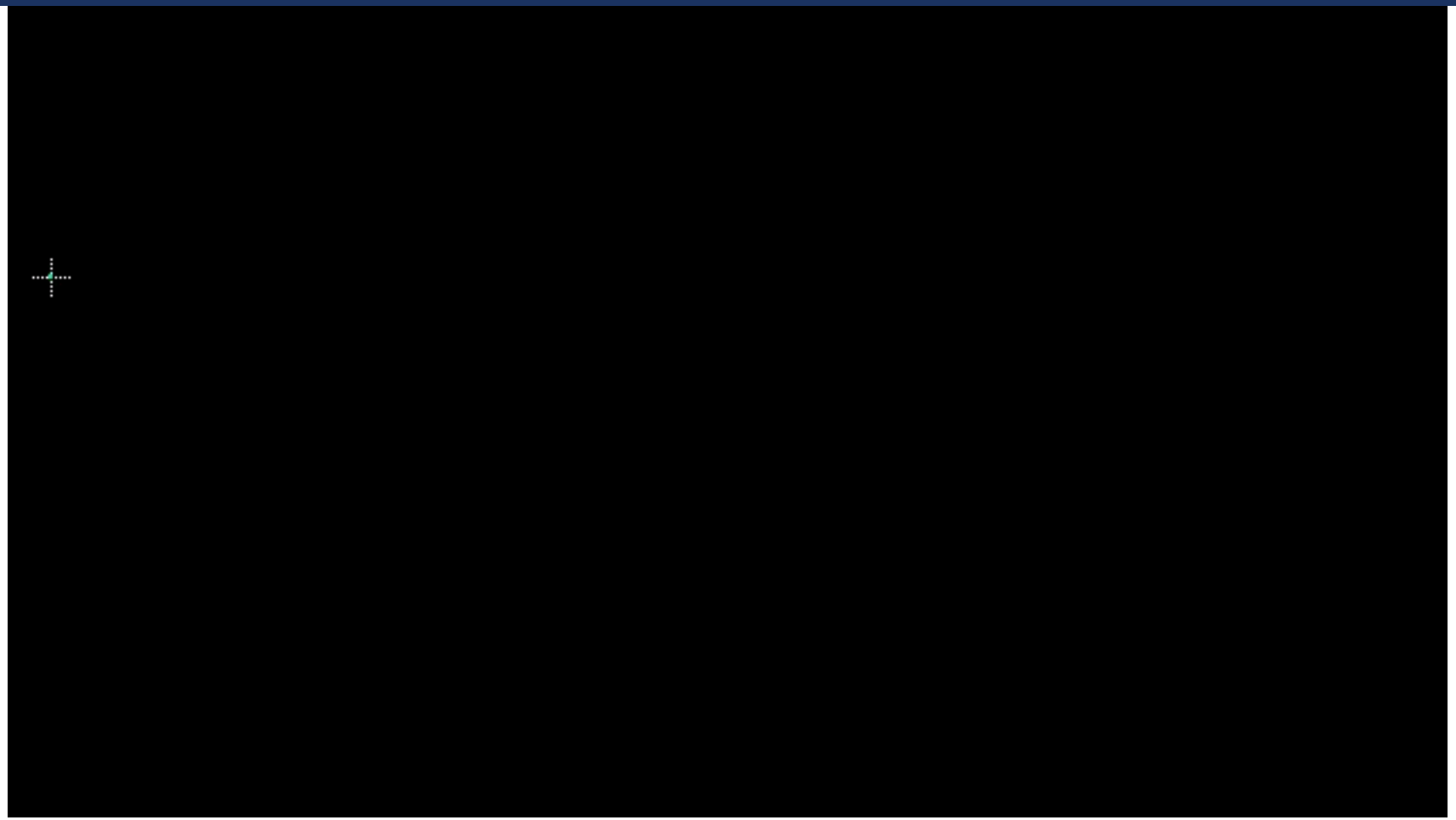
TUMOR SUPPRESSORS



TUMOR SUPPRESSORS

- In cancer cells, p53 is often missing, nonfunctional, or less active than normal. For example, many cancerous tumors have a mutant form of p53 that can no longer bind DNA. Since p53 acts by binding to target genes and activating their transcription, the non-binding mutant protein is unable to do its job.
- When p53 is defective, a cell with damaged DNA may proceed with cell division. The daughter cells of such a division are likely to inherit mutations due to the unrepaired DNA of the mother cell. Over generations, cells with faulty p53 tend to accumulate mutations, some of which may turn proto-oncogenes to oncogenes or inactivate other tumor suppressors.
- p53 is the gene most commonly mutated in human cancers, and cancer cells without p53 mutations likely inactivate p53 through other mechanisms (e.g., increased activity of the proteins that cause p53 to be recycled)

CANER



APOPTOSIS

APOPTOSIS VS. NECROSIS

NECROSIS (THE MESSY WAY)

APOPTOSIS (THE TIDY WAY)

WHY DO CELLS UNDERGO APOPTOSIS?

APOPTOSIS

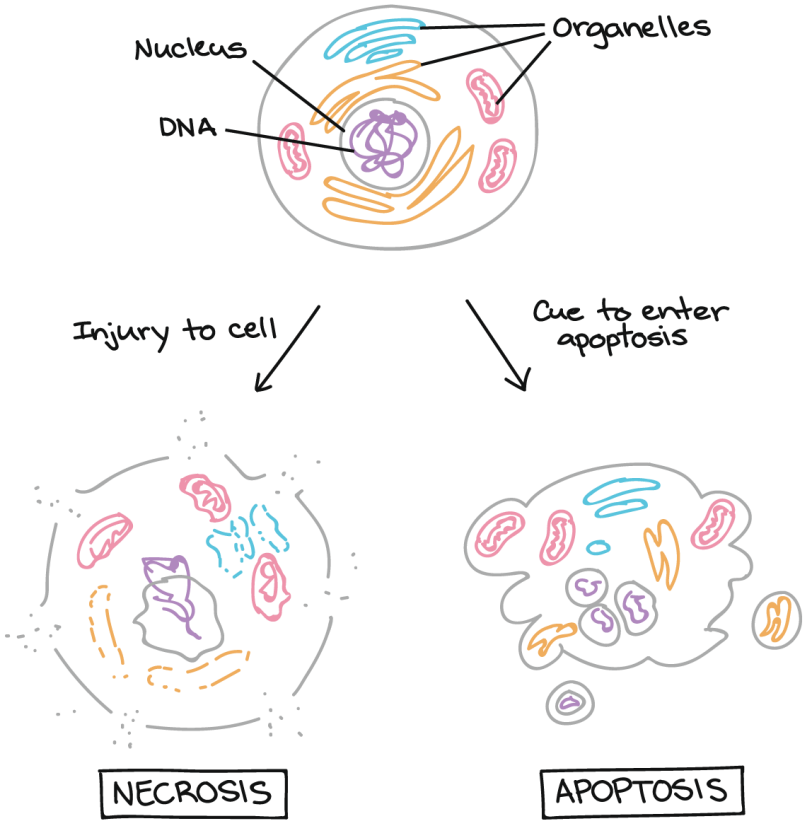
- You may think of it as a bad thing for cells in your body to die. In many cases, that's true: it's not good for cells to die because of an injury (for example, from a scrape or a harmful chemical). However, it's also important that some cells of our bodies *do* die – not randomly, but in a carefully controlled way.
- For example, have you ever wondered how your fingers formed? It turns out that the cells between your developing fingers were instructed to die long ago, while you were still an embryo. If they hadn't done so, you would have webbed hands, or perhaps just paddles of tissue with no fingers at all.
- The cells between your embryonic fingers died in a process called **apoptosis**, a common form of programmed cell death. In **programmed cell death**, cells undergo "cellular suicide" when they receive certain cues. Apoptosis involves the death of a cell, but it benefits the organism as a whole (for instance, by letting fingers develop or eliminating potential cancer cells

APOPTOSIS VS. NECROSIS

- Broadly speaking, there are two ways that cells die in a multicellular organism such as yourself:
- They are killed by things that harm them (such as toxic chemicals or physical injury), a process called **necrosis**.
- They are triggered to undergo programmed cell death. The best-understood form of programmed cell death is **apoptosis**.
- Necrosis and apoptosis occur under different circumstances and involve different steps. Simply put, necrosis is messy and causes an immune response of inflammation, while apoptosis is tidy and splits the cell into little parcels that can be taken up and recycled by other cells.

NECROSIS (THE MESSY WAY)

- When cells are damaged by harmful factors (such as injury or toxic chemicals), they usually "spill their guts" as they die. Because the damaged cell's plasma membrane can no longer control the passage of ions and water, the cell swells up, and its contents leak out through holes in the plasma membrane. This often causes inflammation in the tissue surrounding the dead cell



APOPTOSIS (THE TIDY WAY)

- Cells that undergo apoptosis go through a different and much more orderly process. They **shrink** and develop bubble-like protrusions (technical name: "**blebs**") on their surface. The DNA in the nucleus gets chopped up into small pieces, and some organelles of the cell, such as the endoplasmic reticulum, break down into fragments. In the end, the entire cell splits up into **small chunks**, each neatly enclosed in a package of membrane.
- What happens to the chunks? They release signals that **attract** debris-eating (phagocytic) immune cells, such as **macrophages**. Also, the fragments of the dying cell display a lipid molecule called **phosphatidylserine** on their surface. Phosphatidylserine is usually hidden on the inside of the membrane, and when it is on the outside, it lets the **phagocytes** bind and "**eat**" the cell fragments

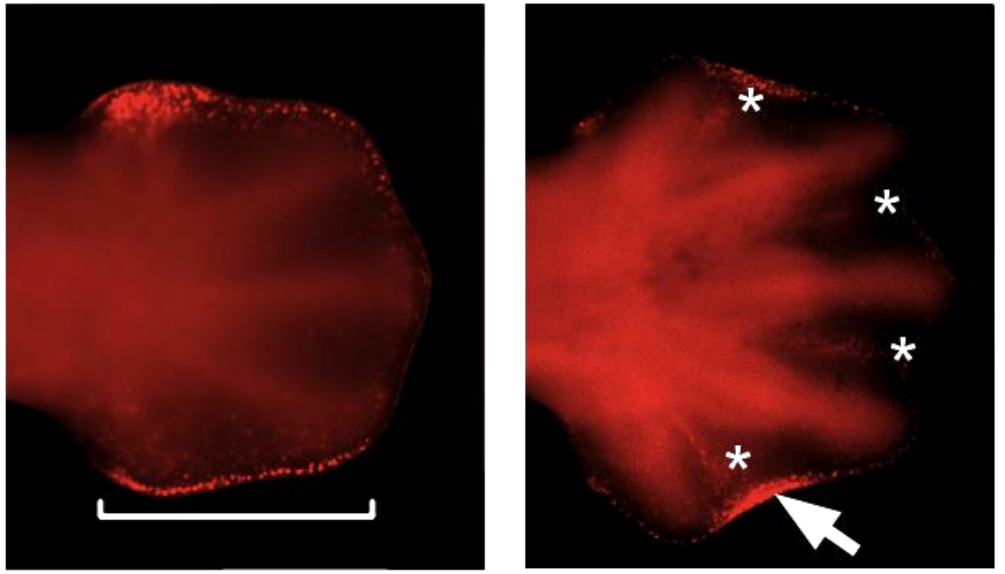
WHY DO CELLS UNDERGO APOPTOSIS?

- Many cells in the human body have the built-in ability to undergo apoptosis (in the same way that they have the built-in ability to copy their DNA or break down fuels). Basically, apoptosis is a general and convenient way to **remove** cells that should no longer be part of the organism.
- Some cells need to be "**deleted**" during development – for instance, to whittle an intricate structure like a hand out of a larger block of **tissue**.
- Some cells are **abnormal** and could hurt the rest of the organism if they survive, such as cells with **viral infections** or **DNA damage**.
- Cells in an adult organism may be eliminated to **maintain balance** – to make way for **new cells** or remove cells needed only for **temporary tasks**

APOPTOSIS IS PART OF DEVELOPMENT

- In many organisms, programmed cell death is a normal part of development. In some cases, apoptosis during development occurs in a very predictable way: in the worm *C. elegans*, cells will die by apoptosis as the worm develops from a single cell to an adult (and we know exactly which ones they are)!
- Apoptosis also plays a key role in human development. For instance, as we saw in the introduction, your hand started out as a paddle-like block of tissue when you were an embryo. The block was "carved" into fingers by apoptosis of the cells in between the developing fingers

Red dots show cells undergoing apoptosis

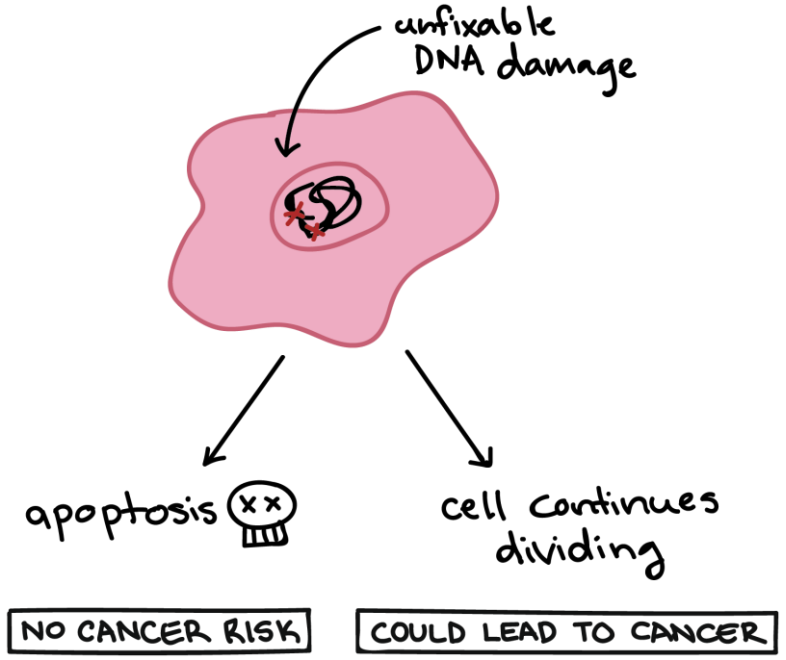


Developing mouse paw, embryonic day 12.5

Developing mouse paw, embryonic day 13.5

APOPTOSIS CAN ELIMINATE INFECTED OR CANCEROUS CELLS

- In some cases, a cell can pose a threat to the rest of the body if it survives. For instance, this may be the case for cells with DNA damage, pre-cancerous cells, and cells infected by viruses. If these cells undergo apoptosis, the threat to the rest of the organism (such as cancer or spread of a viral infection) is removed.
- When a cell's DNA is damaged, it will typically detect the damage and try to repair it. If the damage is beyond repair, the cell will normally send itself into apoptosis, ensuring that it will not pass on its damaged DNA. When cells have DNA damage but fail to undergo apoptosis, they may be on the road to cancer



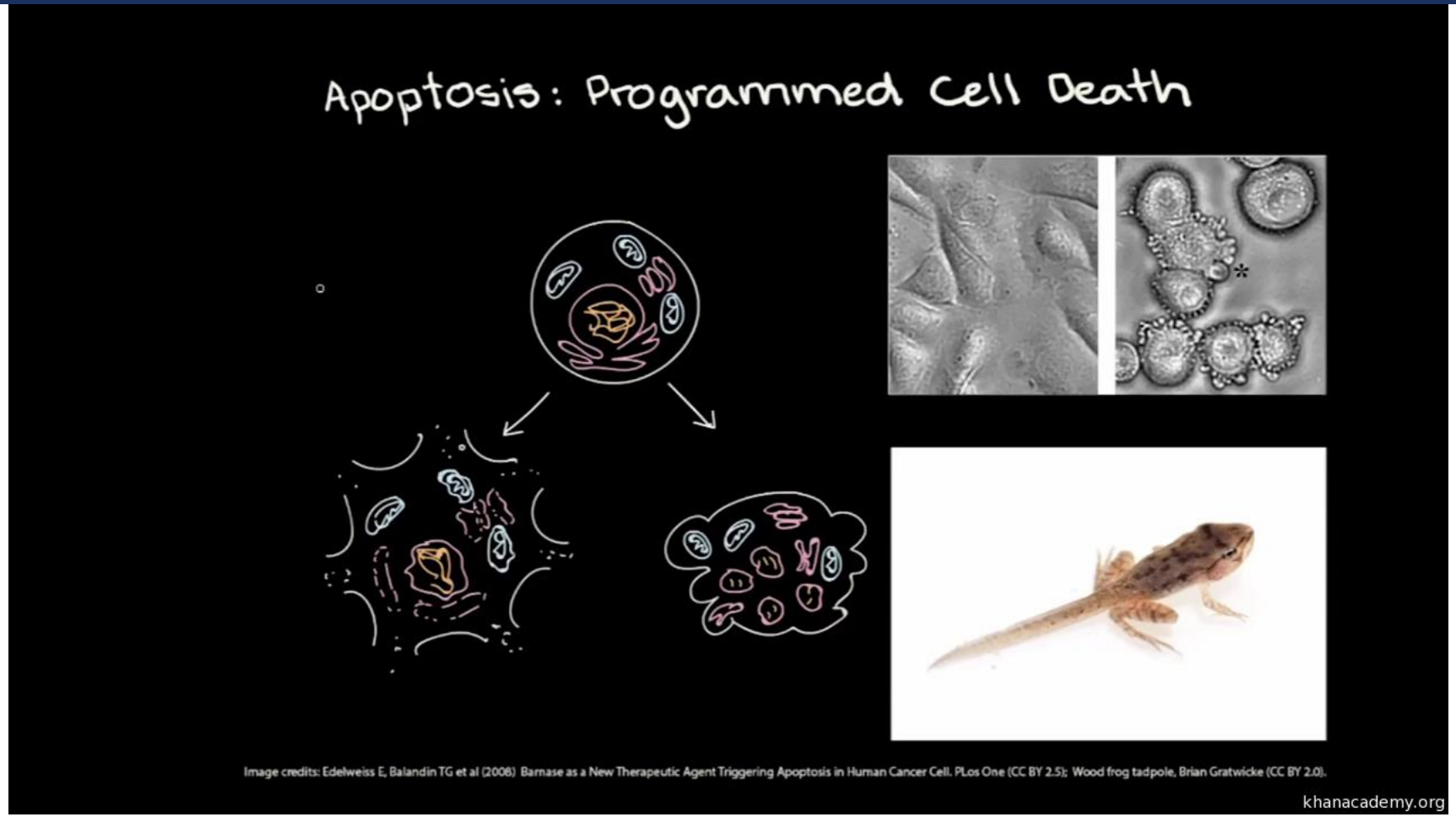
APOPTOSIS IS KEY TO IMMUNE FUNCTION

- Apoptosis also plays an essential role in the **development** and **maintenance** of a healthy **immune system**. When B and T cells (immune cells that bind specific molecules) are first produced, they're tested to see if they react against any of the body's own "**self**" components. Cells that do are eliminated right away by **apoptosis**. If this process fails, self-reactive cells may be released into the body, where they can attack tissues and cause **autoimmune conditions**.
- Apoptosis also plays an important role in allowing the immune system to **turn off its response to a pathogen**. When a pathogen is **detected**, the immune cells that recognize the pathogen divide extensively, undergoing a **huge increase in numbers** with the purpose of destroying the pathogen. Once the pathogen is **cleared** from the body, the large numbers of pathogen-specific immune cells are no longer needed and must be **removed by apoptosis** to maintain homeostasis (balance) in the immune system

SUMMARY

- Apoptosis is a form of **programmed cell death**, or "cellular suicide." It is different from necrosis, in which cells die due to injury. Apoptosis is not the only form of programmed cell death, but it is the form we understand best.
- Apoptosis is an orderly process in which the cell's contents **break down** and are packaged into small packets of membrane for "**garbage collection**" by immune cells. It contrasts with **necrosis** (death by injury), in which the dying cell's contents **spill out** and cause **inflammation**.
- Apoptosis removes cells during **development**. It also eliminates **pre-cancerous** and **virus-infected** cells, although "successful" cancer cells manage to escape apoptosis so they can continue dividing. Apoptosis maintains the **balance** of cells in the human body and is particularly important in the **immune system**

APOPTOSIS


Apoptosis: Programmed Cell Death
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