

Chemotherapy Resistance: The Fault in Our Cells

[MUSIC PLAYING]

JOHN F. KENNEDY: We choose to go to the moon. We choose to go to the moon in this decade and do the other things, not because they are easy, but because they are hard.

RACHEL LEESON: In 1961, President Kennedy set the goal of sending a man to the moon. By the end of the decade, he had achieved that goal.

RICHARD NIXON: More people each year die of cancer in the United States than all the Americans that lost their lives in World War II.

RACHEL LEESON: In 1971, President Nixon set a goal of eradicating cancer by the end of the decade. How hard could that be compared to sending a man to the moon? As it turned out, curing cancer is extremely hard. And decades later, we still haven't achieved Nixon's goal. To see why that's true, let's think about how doctors treat cancer today.

Hi, I'm Rachel. And I'm a researcher here at MIT's Koch Institute for Integrative Cancer Research. Today, we're going to tell you a little bit about one of the challenges we face in curing cancer and what research we're doing to overcome it.

SIMONA DALIN: I'm Simona. I'm a graduate student at MIT. And I do research here at the Koch Institute. A cancerous growth, or a tumor, is really just a bunch of cells that is growing so fast that it interferes with the normal function of the body. To treat the patient, doctors try to remove the cancerous cells with surgery, or kill the cells using radiation or chemotherapy.

Surgery can be really invasive and sometimes ineffective, because doctors can't see all the cancer cells to remove them. Radiation therapy is often not an option if the cancer is deep inside the body. For instance, cancer of the large intestine-- chemotherapy is often the best treatment.

But different cancer types respond differently to each drug, which makes it tricky for doctors to decide which drugs are best for a particular patient. And on top of that, some cancer cells aren't always killed by certain drugs. We call this unfortunate phenomenon chemotherapy resistance.

EMMA SEDIVY: Hi, I'm Emma. I'm also a graduate student at MIT and a researcher at the Koch Institute. Scientists at the Koch Institute want to learn more about how different cancer cells react to chemotherapy, so that doctors can use existing therapies more effectively to treat patients.

One of the ways that we do that is by studying the different cells that make up tumors. We've learned that cancer cells often carry mutations in important genes. You may have heard about mutations before when people talk about why things like smoking and sunburns are bad for you.

Do you know what mutations are? How could mutations be problematic for the cells in your body? Take a minute to talk about this amongst yourselves.

RACHEL LEESON: Hi, welcome back. What did you guys discover you knew about mutations? You may know that the genes in our DNA contain the instructions to make proteins, the machines and building blocks of our cells. If the DNA letters coding for our protein get changed to other letters, the cell will no longer have the right instructions to make that protein.

We call these changes mutations. A mutated protein might not function well or gain new harmful functions. In order to become malignant, or harmful, cancer cells must find ways to escape the natural checks that our

bodies put on their growth and division. And mutations in the genes that provide these checks allow them to grow more and divide more quickly.

SIMONA DALIN: There are lots of possible mutations that could cause a cell to grow out of control and become cancerous. Some proteins help cells grow and divide more. We call the genes that carry the instructions for making these proteins 'oncogenes'.

If you think of cell division and growth as a car driving, then oncogenes are the gas pedal which makes the car forwards. There's other proteins which slow cell growth and division. We call these tumor-suppressor genes. In the car analogy, tumor-suppressor genes are like the brake pedal, which makes the car slow down. In a properly driven car, the brake pedal and the gas pedal are used together to avoid getting into car accidents.

Likewise, in healthy cells, oncogenes and tumor-suppressors balance each other out to make sure that cells only grow and divide our bodies need them to do so. But in unhealthy cells, something else entirely can happen.

EMMA SEDIVY: An out-of-control driver might use the gas too much or the brakes too little. Similarly, in cancer cells, mutations disrupt the careful balance of oncogenes and tumor-suppressors. Many cancer cells make too many oncogenic proteins, too few tumor-suppressor proteins, or versions of these proteins that can no longer carry out their proper functions, because the DNA that codes for these proteins has been permanently changed by mutations.

Before you start your activity, we'd like you think about how similar or different cancer cells might be to each other. What do you think of the following possibilities? One, all cancer cells have the same mutations. Two, different types of cancers have different mutations, but all the cells of a certain cancer type will have the same mutations.

For example, all lung-cancer cells are homogeneous or identical. But lung-cancer cells are different from liver-cancer cells. Three, different tumors-- even tumors that come from the same tissue-- might have different mutations. But within each tumor, all the cells will have the same mutations.

And four, within one tumor, there might be several different populations of cells, each with different combinations of mutations. Take a minute to discuss these options. And then, take a vote.

RACHEL LEESON: Hey, everyone. Welcome back. Which option was the most popular in your class? Well, to find out that answer, we've got to think about how cells divide. And we move to the perfect place to do that, the tissue-culture room, where we culture cells like these and watch how they divide and grow.

Cell division is a complicated process that requires different parts of the cell to coordinate and work together to create two new daughter cells from a single parent cell. One of the most important stages in this process is DNA replication. Every piece of DNA in the cell must be duplicated so that both daughter cells have a copy. And both daughter cells need to get one copy of every chromosome.

Any mistakes that might have happened during DNA replication need to be fixed before the cell divides, or else the daughter cells will get DNA with mistakes, or mutations, as we discussed earlier. If this happens, all the descendants of that daughter cell will also inherit that mutation. Because of this, option three does make a lot of sense.

SIMONA DALIN: However, it turns out that tumors are made up of different populations of cells, each carrying different combinations of mutations. When healthy cells divide, they constantly check back to make sure that they've done everything right, including copying all of their DNA perfectly.

Unfortunately, mutations still happen. Our cells are constantly exposed to things that put us at risk of mutating our DNA, including the UV rays in sunlight and the toxic chemicals in cigarette smoke. A healthy cell might turn into a precancerous cell by acquiring certain mutations that allow them to start dividing faster. And when cells divide faster, they get worse at making sure that there are no mistakes in their DNA and that they have the right number of chromosomes.

This means that they acquire more mutations as they go along, each one making them more malignant. If this goes on for a long time, the precancerous cells become a tumor. When one of the tumor cells gets a new mutation, it gives rise to a new population within the tumor. Therefore, option four is correct, as you can see in this diagram.

As you can imagine, the complexity and heterogeneity, or diversity, of different populations within tumors can make it very difficult to treat cancer. There are lots of different chemotherapy drugs in clinics today. And each one works best on certain types of cancer and on cells with specific sets of mutations within that cancer. This means that different cancer cells might be more or less sensitive to a certain type of chemotherapy.

EMMA SEDIVY: Today, we're going to model what happens when you treat a heterogeneous tumor, one with different types of cells inside of it, with one type of chemotherapy. On the table in front of you, you should have a paper bag, which represents the tumor that you're going to treat with chemotherapy.

If you look inside the paper bag, you'll see that it's full of beads of different colors. Each of the beads represents a cancer cell. And the color of the bead represents the combination of mutations that's found in that cancer cell. And you have five populations of different cancer cells with different mutations in your tumor.

You should also have some cups in front of you on your table, which will represent the cell division that happens as your tumor grows and divides. And each of the cells in your tumor has a different growth rate. So each of the types of cells has a different number of cells in your cup, which represents the rate at which it divides in one period of division. You'll know what one period of division is, because your teacher or one of your classmates will have a timer also.

Now, all of this will become clear to you in one second when we tell you what the three people in the group that you're in will be doing. One person will be growth. That's me. One person will be chemotherapy. That's Rachel. And one person will be chemotherapy resistance. That's Simona. If your job is to make the tumor grow, like me, what you're going to do is add one of these cups of dividing cells into the tumor every time the timer goes off or your teacher tells you to do that.

RACHEL LEESON: If, on the other hand, you're lucky enough to have the job of chemotherapy-- the best job-- what you'll do is you'll reach into the bag. And you'll pull out cells one at a time and drop them into your dead-pile. Try to keep them on the dead-pile and off the floor.

Now, the speed at which you can do this varies, and that's fine. But it's really important that you pull out just one bead at a time so that your results are fair and equivalent everybody else's. And now, I need to pull out just a few more beads. All right, we're good. Let's move on to chemotherapy resistance.

SIMONA DALIN: So if your job is chemotherapy resistance, your job is to save the resistant cells from chemotherapy. For our group, the resistant cell colors are green and blue. What you do is, as chemotherapy kills cells, they'll put them in the dead-pile. For sensitive cells, you'll leave them in the dead-pile, because sensitive cells are killed by chemotherapy.

But every time that you see three resistant cells-- so here, we have three green cells-- you'll take two of them and save them by putting them back into the live tumor bag. This means that every sensitive cell that's treated by chemotherapy will die. But only one out of three resistant cells will die when it's treated by the chemotherapy.

RACHEL LEESON: Hello again. I hope you guys enjoyed your tumor growth experiment.

SIMONA DALIN: Before you look at the rest of the cells in your tumor, take a few minutes to think over the following questions with your group. One, do you think your tumor is bigger or smaller than before? Two, do you think the proportions of beads of each color changed? Three, what proportions of beads of each color do you expect?

EMMA SEDIVY: When you're done making predictions, let's have a look at the data. Take a look inside your tumor. Sort all of the cells by type. And then, record the number of each type in the table that your teacher has for the whole class.

RACHEL LEESON: Hey there. You have all your data in a table now. But sometimes, looking at a table can make it really hard to tell which tumors grew the most.

SIMONA DALIN: As scientists, we often have this problem with large data sets. We handle it by making visual representations that let us see differences more easily.

EMMA SEDIVY: Make a bar chart of your data, so you can more easily see which populations grew the most. Then, answer these questions. One, do you think the resistant cells helped the tumor grow? Two, do you think the tumor with no resistance grew slower or faster? Three, were there are other factors that could have affected tumor size and growth?

RACHEL LEESON: Hi, and welcome back. You probably have some bar charts and tables now that represent your data. Maybe your observations matched up with what you expected and, maybe they didn't. The populations could have grown and changed a little differently than you expected. And that's OK. Science works like that.

SIMONA DALIN: Even in a perfect experiment, random variability can result in different outcomes. So how do know that the differences in your numbers represent real differences in your cell populations? This is why scientists usually repeat an experiment several times. At the end, we use statistical analysis to compare the different experimental conditions. We usually report the mean of all the repeated experiments with a standard deviation of that mean to tell us how much variation was present in those experiments.

EMMA SEDIVY: If we want to determine the probability that the differences in our conditions is due to random chance, we can compute a test statistic, like the student's t-test. If the differences in our data are less than 5% likely to occur by random chance, we say that the differences in the data are significant.

Calculate the following, then answer the questions below. A, the mean number of cells of each type within a repeated group. B, the mean number of cells of each type across different groups. C, the mean number of all resistant cells versus all non-resistant cells.

Now discuss. One, do you think the resistant cells help the tumor grow? Why you think that happened? Two, did the tumor with no resistance grow slower or faster? Why you think that happened? Three, were there any significant differences between the growth of resistant cell populations and non-resistance cell populations?

Four, how did the original growth rate of the cells affect the final tumor composition? Five, what other factors could have affected tumor size and growth? And six, how did your group's tumor compare to other tumors?

RACHEL LEESON: Scientists at the Koch Institute have recently done the experimental version of the activity you just did today. They took cancer cells from a few different types of cancers-- sometimes the same type of cancers but different patients-- and they used the same treatment on all of them. And they found out that cancer cells don't respond the same to the same treatment. As you can see, the types of cells

within a cancer, and even within an individual tumor, can affect whether or not the chemotherapy is going to work. In fact, they can determine how effective the chemotherapy treatment is going to be.

EMMA SEDIVY: This is very challenging. Because it's hard to look inside of a tumor. But scientists and engineers at the Koch are working together on ways to detect the different types of cancer cells, using only a blood sample from the patient.

SIMONA DALIN: Looking for and learning about cancer cells in a tumor can help us design more effective cancer therapies.

RACHEL LEESON: Cancer is really complex. But the more we learn about individual tumors and, thus, individual cancers, the more we can tailor our treatments to that patient. And the more effective our treatments will be.

EMMA SEDIVY: I wanted to become a scientist, because I like learning how things work on a very detailed molecular level. So I like thinking about how things inside of a cell work. And I just love that I get to come to work every day and learn new things. It's very exciting and it keeps me on my toes.

SIMONA DALIN: I like being a scientist because I get to discover new things about a topic that interests me. I also enjoy knowing that my research on tumor heterogeneity might one day help people who are dealing with cancer.

RACHEL LEESON: I became a scientist because I'm really interested in looking at how everything your body interacts with every other thing. And the really cool thing about researching cancer is that you get to look at that on all kinds of different levels, everything from how your cells interact to how the molecules in your body interact with different cells to how your immune system interacts with cancers, or even, on a much larger level, looking at the skin as an organ or the liver or the stomach-- anyways, I just think it's really cool. And I hope that, if you share my passion and curiosity, you start finding out answers for yourself.

Hi, thanks for checking out our video and our activity on tumor heterogeneity. We're really excited that you're considering using it for a class, and we really hope you do. We think it's awesome. This activity simulates resistance of cancer cells to chemotherapy through acquired mutations. As cancer cells mutate, they gain or lose mutations, which can affect how they react to chemotherapy.

Why do we care about this? Well, chemotherapy can have some major side effects. And we want to make sure it's going to work before we administer it. There's also a secondary consideration, which is chemotherapy has what's called a "lifetime limit." Unlike NyQuil, which you can take every time you have a cold, no matter how many colds you get in a lifetime, you can only give so much chemotherapy in a person's lifetime before it is unsafe to give them any more, regardless of what disease you're trying to treat.

This means that, whenever we use chemotherapy, we want to make sure that it's the best choice of drugs that we can give to that patient to make sure that we're able to treat not only that cancer but any further problems that may arise in the patient's future. Thus, knowing what kind of mutations cancer cells have and how they affect chemotherapy treatment is actually really important. As we learn more about tumors, tumor heterogeneity, and various mutations within cells and a patient's cancers, we can learn more about why chemo doesn't work on certain patients and can make better cancer treatment decisions.

SIMONA DALIN: During this activity, students will mimic a tumor being treated with chemotherapy. In our simulation, cells are represented by beads. Each population of cancer cells is a different color and has a different set of mutations. In our simple example, every tumor starts with five equal populations of cancer cells. Students simulate chemotherapy by simply removing cancer cells from the tumor.

But there's a catch. Some of the cell populations are resistant to chemotherapy. And instead of dying and being removed permanently from the tumor, they are "rescued" and added back to the tumor. After the

activity, the students will chart the tumor's composition. So for example, how many beads of each color are still there in the tumor? And before the activity, they'll make predictions about which populations will grow the fastest. After, they'll discuss how the resistance affected the tumor and how the results compared to what they expected.

If your class has not been introduced to statistical analysis before, they can work on creating a bar chart that visually represents the data. If your students are already comfortable with graphing techniques, you can generate the bar chart for them and, instead, ask them to focus on using statistical tests to determine whether their results represent real differences between cell populations. If you want your class to work on statistics, you should have a relatively large class or enough time to repeat the simulation three times.

EMMA SEDIVY: Be prepared for some questions on difficult subjects. But students will generally ask you about facts and not about personal experiences. They may ask you about tumors and about available treatments. But make sure to tell them that you're not a doctor and that we're not doctors either.

Sometimes, they'll ask about what causes cancer or how they can reduce their risk for cancer. And fortunately, there are many excellent resources online that they can refer to if they're interested about learning more about either cancer research or the treatments available for cancer. This activity is not meant to be a comprehensive introduction to the field of cancer research or to the state-of-the-art cancer treatment in clinics. So we've posted a PowerPoint. And there will also be references at the end of the activity that your students can use to learn more if they are interested.

RACHEL LEESON: The activities that we discuss here help students develop an appropriate context for exploring the complex issues of cancer research and treatment. They allow you, the teacher, to make connections between basic cellular processes they are studying in the standard curriculum-- like cell division, DNA mutations, and current research in the laboratory-- and ongoing clinical challenges.

The Koch Institute for Integrative Cancer Research at MIT, where we work, is a basic, non-clinical, cancer research center designated by the National Cancer Institute. Non-clinical, if you're interested, just means that we don't do any work with patients. All of our work is in the lab. Our research includes biologists, chemists, and engineers from a variety of disciplines all working together to develop new insights into cancer processes, as well as new tools and technologies to better treat, diagnose, and prevent the diseases of cancer.

This work builds on the legacy of MIT's Center for Cancer Research, founded in 1974 in direct response to President Nixon's challenge. The lesson draws on our desire to make a difference in how cancer is understood and treated, and to inspire the next generation of researchers who will likely be the ones to overcome many of the challenges we are exploring / uncovering today.

Cancer was originally thought of as one disease, caused by maybe a virus or a bacteria or a single mutation that people inherited. But the more we study it, the more we've come to realize that it's actually many, many, many diseases. Experiments like the one in this video help illustrate the complexity of the disease and the associated difficulties in treating them.

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