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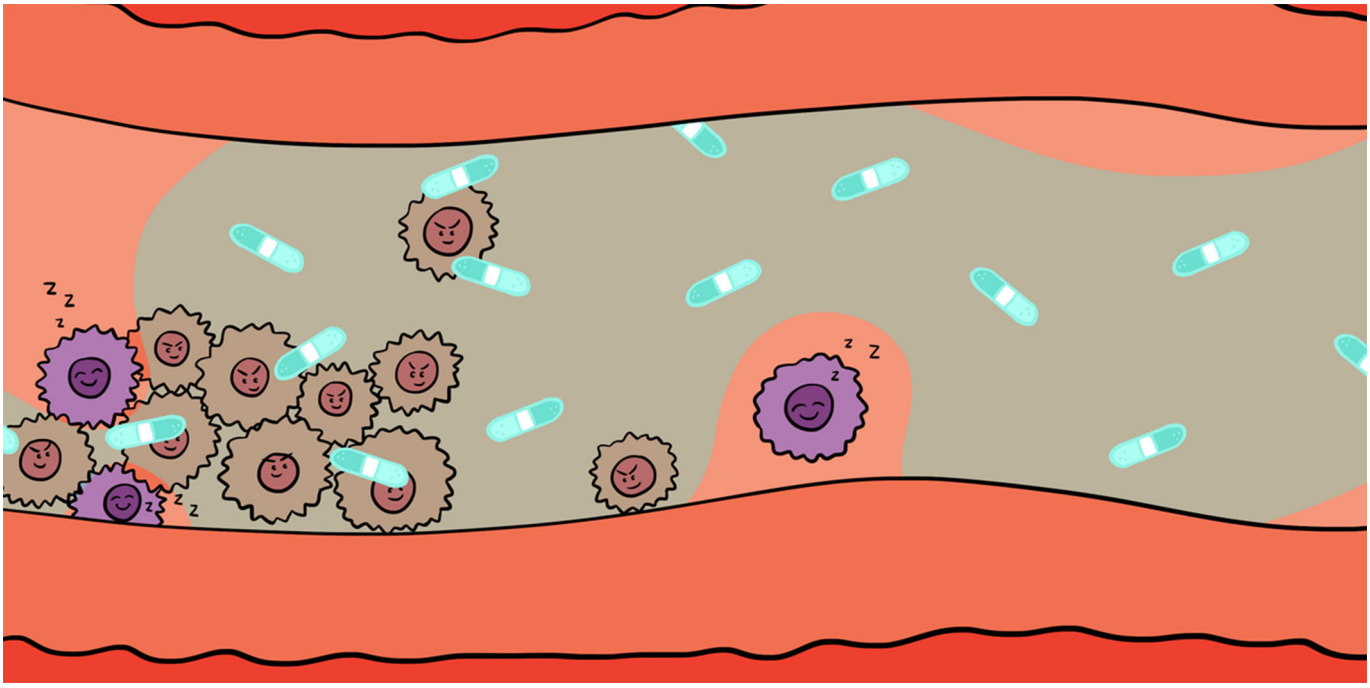

CANCER PERSISTERS: HOW PLAYING DEAD HELPS CANCER CELLS SURVIVE TREATMENT

Prashant Karki and Mehmet A. Orman *

Department of Chemical and Biomolecular Engineering, University of Houston, Houston, TX, United States

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NAYAN
AGE: 13

STEFANIA
AGE: 16

Cells may occasionally have errors in their DNA, called mutations, which may lead to various diseases. Cancer cells are mutated cells that have lost their ability to control their growth. These cells divide rapidly and can spread to other parts of the body. Scientists take advantage of this trait of cancer cells to try to design various therapies to kill only cells that are dividing very quickly. But what would happen if cancer cells grew slowly or just stopped growing? Well, recent evidence shows that such cancer cells do exist. These cells, also referred to as cancer persisters, are generally non-growing cells that cannot be easily eliminated by traditional cancer therapies. In this article, we will describe what cancer persisters are and why we should make a significant effort to study them.

CANCER: A DIFFICULT PROBLEM

Cancer is one of the leading causes of death, and many scientists have been working very hard to find new ways to cure cancer. It is estimated that, in 2020, there will be ~1.8 million new cases of cancer and around

600,000 cancer deaths in the United States alone [1]. In 2015, about 80.2 billion U.S. dollars were spent on medical expenses related to cancer [1]. Still, there has not been a single known cure for cancer. So, what is cancer and why is it so difficult to treat?

Cancer is a group of diseases that can be observed in various organs/tissues of our bodies. Cells in cancer tissues divide at unusually high rates and these cells can spread to other parts of the body through the blood and lymph systems, in a process called **metastasis**. These abnormally growing tissues are also called tumors. Every moment, millions of cells are dividing and dying in our bodies. However, the rates of cell death and division are usually under the tight control of certain proteins. Cancer is usually caused by **mutations**, which are mistakes in DNA. Environmental factors, such as the chemicals in tobacco or ultraviolet rays from the sun, can contribute to these mutations. DNA carries information on how to make all of a cell's proteins; thus, mutations in DNA can result in abnormal proteins. If the proteins that regulate cell growth undergo mutations, then their incorrect versions may result in abnormal cell growth and can lead to cancer.

METASTASIS

Spread of cancer from the place of origin to different parts of the body.

MUTATION

A process that causes a change in the DNA sequence.

There are more than 200 different cancer types, and each type is caused by a different mutation. Also, because cancer cells divide so quickly, they are prone to even more mutations. So, designing a single cure for all types of cancer is difficult. Most of the common therapies for cancer targets fast-growing/dividing cells, because rapid cell division is one of the major traits of cancer cells.

WHAT ARE CANCER PERSISTER CELLS?

But what if some of the cancer cells stop growing or stay **dormant**, which means in a sleep-like state? Recent studies have shown that a small subpopulation of cancer cells basically stops growing in the presence of anti-cancer drugs [2, 3]. These non-growing cells are also called cancer **persisters**. Since they are not growing, the anti-cancer medicines do not attack these cells. However, once the patient is no longer taking the drugs, the dormant persisters wake up and resume growing again (Figures 1, 2). This has made complete eradication of cancer extremely difficult to achieve.

DORMANT

Inactive cell state.

PERSISTERS

Non-growing cells that temporarily survive the drug treatment.

How do some cancer cells become persisters? Lack of nutrients and oxygen can make some cancer cells dormant. Anti-cancer medicines can also trigger dormancy in some cells. This brings up another question: if dormancy can help cancer cells survive treatments, why do only some of the cells become dormant? Would not it be beneficial for all cancer cells to be persisters? Well, one of the reasons for only some cells become persisters is that cancer cells are highly diverse. Basically, cancer cells have different observable traits, similar to the way that each person has their own personality. This means that each individual

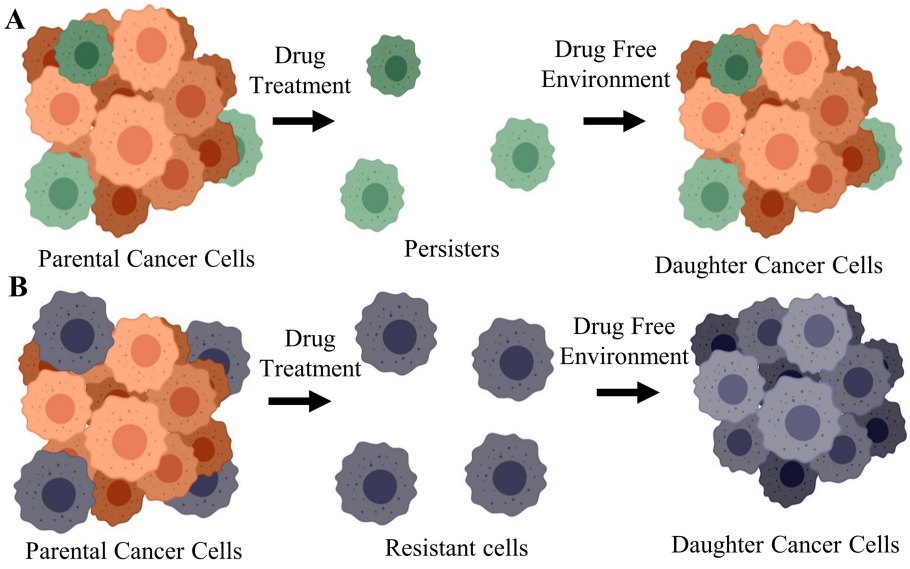

Figure 1

Figure 1

Persister vs. Resistant Mutants. This figure shows the difference between persister (green) and drug-resistant (gray) cells. Normal cancer cells (orange) do not survive high doses of anti-cancer drugs. **(A)** Persisters survive the treatment and resume growth when the drug is removed. The daughter cells generated by persisters are similar to the original cell population and they are sensitive to the drug. **(B)** Resistant cells can survive drug treatment as well, but their daughter cells are also resistant to the drug, because resistance is transmissible via cell division, but the trait that makes cells persistent is not (created with Biorender.com).

cancer cell may be slightly different from the rest of the cancer cell population. So, some cells may have certain proteins that allow them to enter the dormant state, while others do not. Unfortunately, there are still many unanswered questions about cancer persisters, and we still need to do a lot of research to understand these cells.

HOW DO PERSISTER CELLS SURVIVE DRUG TREATMENTS?

Before discussing how persister cells survive drug treatments, we need to first understand the differences between resistant cancer cells and persister cells. Remember how we talked about the DNA mutations that can cause cancer by disturbing cell growth? Resistant cancer cells are tumor cells with additional mutations that allow them to survive a drug treatment and continue to grow, even in the presence of the drug. These cells, upon cell division, can generate new cells, called **daughter cells**, that are resistant to the drug as well. Persisters, on the other hand, do not grow or grow only very slowly during drug treatment. Once persisters start dividing, they generate daughter cells that are sensitive to the anti-cancer drug. This is to say that, unlike resistance, the survival mechanism of persisters is not transmittable via cell division (Figure 1).

DAUGHTER CELLS

Cells that are formed after a cell undergoes cell division.

So, we know that persister cells survive drug treatment because they are temporarily dormant. However, there might be other mechanisms at play that help these persister cells to survive drug treatment. What could these mechanisms be? One possibility is that persisters might push the drugs back out of the cell at a higher rate than non-persisters do. Or, persisters might more efficiently repair the damage caused by

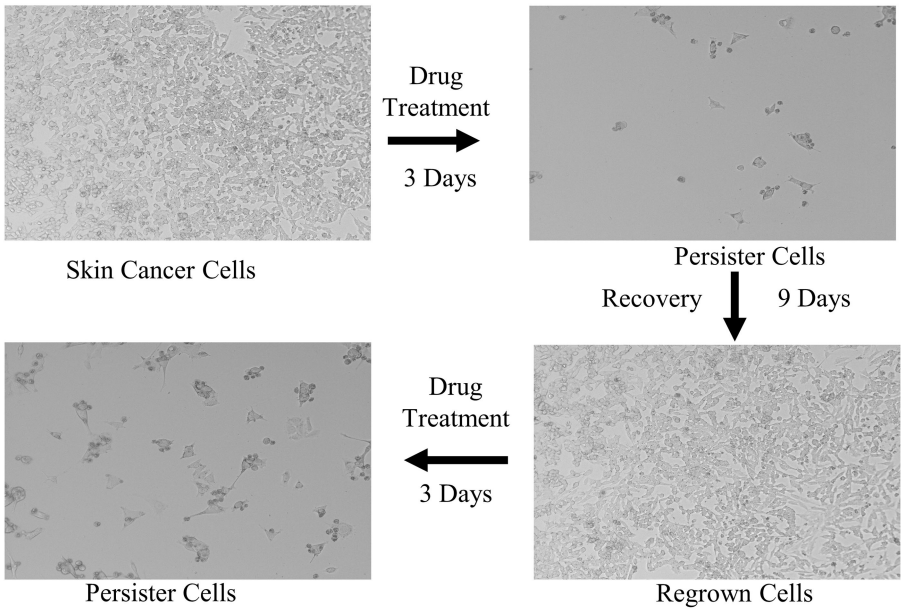

Figure 2

Isolation of cancer persisters. Melanoma (skin cancer) cells were treated with a very high concentration of a drug called gemcitabine for 3 days. After 3 days, the persister cells that survived were collected and regrown in a drug-free environment. The regrown cells were then treated again to test their sensitivity to the drug. You can see that persister cells were able to regrow and form daughter cells after the removal of the drug. As expected, the daughter cells largely became sensitive to the drug when treated again.

ENZYMES

Proteins that help speed up and regulate reactions in the body.

drugs. Recently, studies have shown that persister cells might contain special **enzymes** that non-persisters do not have [2, 3]. These enzymes help persisters survive various stresses in their environments, including drugs. These findings are a significant step toward understanding how persister cells work. Many more studies are still needed before we will have a clear understanding of persisters. However, to conduct these studies we need to overcome some barriers, one of which is to be able to separate the persister cells from "normal" cancer cells.

HOW DO WE STUDY PERSISTER CELLS?

The first step to study persister cells is to isolate them from normal cancer cells. How do we achieve that? Well, we can treat the cancer cells with a drug for a long time. This treatment should kill the normal cells but not persisters. After the treatment, we remove the drug and then regrow the persister cells in a fresh environment without the drug. Persister cells eventually wake up and multiply to form daughter cells. Then, we can treat the daughter cells with the drug and test whether they are sensitive to the treatment (Figure 2). If the daughter cells are sensitive to the drug, then we can conclude that the cells we isolated initially were persisters, and not resistant mutants. This step of verification is important because remember, unlike the resistant mutants, the daughter cells of persisters are drug sensitive. Isolation of persisters by this method is very common. After isolating persisters, we can do a lot of interesting studies: we can study the way they function, including their metabolism; we can monitor how and when they wake up; and we can also use them to try to find new, more effective anti-cancer drugs.

WHY DO WE NEED TO STUDY PERSISTERS?

So, why are we interested in learning about persisters? One of the main reasons for studying persisters is to reduce the rate of reoccurrence of cancer. There are many cases in which cancer patients undergo expensive and painful treatments. Sometimes the doctors conclude that the treatment was successful; however, occasionally the cancer can return after some time has passed. Persisters are believed to be one of the main reasons for cancer reoccurrence. Persisters have been shown to exist in various cancer types, which include, but are not limited to, breast, lung, and skin cancer. These are some of the most common types of cancer, and they all have high risks of reoccurrence.

The cancer therapy that is available now has advanced from what it was a couple of decades ago. This is thanks to all scientists and research groups that are committed to studying this topic. Unfortunately, with every new breakthrough we find about cancer, we also come across new complications associated with it. The existence of persisters is without a doubt one of the major setbacks in cancer therapy. We need more researchers who can study persister cells to answer the many questions associated with them. Without a clear understanding of all the properties of persister cells, a complete treatment/eradication of cancer will remain a far-fetched dream.

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CONFLICT OF INTEREST: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

YOUNG REVIEWERS

NAYAN, AGE: 13

My name is Nayan and I really like to play soccer. For fun, I fly remote control airplanes and drones. For exercise, I like to run and ride my bike. Science is fun.

STEFANIA, AGE: 16

My name is Stefania. I am 16 years old and I love music, especially when I am sad. I enjoy spending my free time with my close friends and my family. My qualities are that I am very sociable and I like helping whenever I have the occasion.

AUTHORS

PRASHANT KARKI

I am a graduate student at the University of Houston and am currently pursuing my Ph.D. in Chemical and Biomolecular Engineering. My research project focuses on understanding the mechanism associated with cancer persisters. I am very interested in learning about cancer and different challenges involved with establishing new therapeutic approaches that could give us an advantage against it.

MEHMET A. ORMAN

Dr. Orman has obtained his Ph.D. in 2011 from Rutgers University and completed his post-doctoral studies at Princeton University and Memorial Sloan Kettering Cancer Center. He is currently an assistant professor at the Chemical and Biomolecular Engineering Department at the University of Houston. Dr. Orman's research group focuses on persister cells that are observed in both bacterial and cancer cell populations. *morman@central.uh.edu