How Do Dormant Cancer Cells Become Metastases?

Some cancer cells spread, enter a dormant state and later awaken to form tumors. New research explores this process and how it can be prevented.

April 21, 2025 By National Cancer Institute

By Edward Winstead

Why do some cancers come back many years after treatments had eliminated all signs of the disease? The answer may involve rogue cancer cells that spread to other parts of the body early in the disease and then enter a sleeping, or dormant, state, according to a growing body of research.

These dormant cancer cells can survive in the body undetected for months, years, or even decades, the research suggests. At some point, however, the cells may awaken and begin the process of forming metastatic tumors.

What causes disseminated cancer cells to enter, and then to leave, a dormant state is not known.

But recent studies of tumor dormancy have yielded clues that scientists believe could one day help them find ways to prevent metastases, which account for most cancer deaths.

“Patients don’t want a new treatment for a metastasis that only gives them a minimal reprieve—they want us to prevent a recurrence from ever happening,” said Patricia S. Steeg, Ph.D., who until recently studied breast cancer metastasis at NCI’s Center for Cancer Research.

Understanding tumor dormancy is part of research on preventing metastases, Dr. Steeg continued. “But no one has a good handle on how dormancy occurs and how it is broken to produce a metastatic tumor.”

That is starting to change, she added. Two recent studies in mice, for example, identified immune cells that may keep dormant cancer cells from awakening and forming metastatic tumors.

In one study, dormant breast cancer cells that had migrated to the lungs were kept in check by immune cells that reside there, researchers at the Albert Einstein College of Medicine reported.

In the other study, immune cells called natural killer cells helped to control dormant breast cancer cells in the bone marrow, scientists at the University of Michigan Rogel Cancer Center found.

These results—and earlier studies linking natural killer cells to dormancy—illustrate the progress researchers have been making toward a better understanding of the biology of cancer dormancy, Dr. Steeg said.

“We have always wondered what dormancy is,” she continued. “Is it a balance between the growth and death of tumor cells? Or is it controlled by the normal tissue in the tumor cell environment? The two recent studies provide examples of the latter.”

Evidence for the existence of dormant cancer cells

Scientists have found clinical evidence to support the existence of dormant cancer cells in many common cancers, including breast, prostate, lung, colon, and kidney cancers, as well as melanoma and cancers of the blood, such as leukemia and multiple myeloma.

Some of this evidence has come from rare instances of people developing cancer after receiving an organ transplant from a donor who had had cancer in the past but was thought to be in remission at the time of the donation. For example, four individuals developed breast cancer after receiving an organ from a donor who had a history of the disease but was considered cancer-free at the time of donation. Genetic tests confirmed that the tumors in the recipients matched the donor’s cancer.

In that case, researchers believe the donor’s immune system might have kept dormant tumor cells in check, preventing a recurrence. The dormant tumor cells began to divide within 16 months to 6 years after being transplanted into the organ recipients, whose immune systems had been suppressed to prevent them from attacking the transplanted organs.

Exploring the characteristics of dormant cancer cells

An English pathologist named Geoffrey Hadfield proposed in 1954 that late cancer recurrences after treatment may be caused by cancer cells that had remained dormant. But only recently have researchers have begun to describe the characteristics of disseminated tumor cells.

“Disseminated cancer cells are a special subset of cancer cells,” said Joan Massagué, Ph.D., chief scientific officer of Memorial Sloan Kettering Cancer Center, who studies cancer dormancy. “They have the features of what we call primitive progenitor cells, a family of cells that can generate healthy tissue and repair damaged tissue.”

But rather than producing healthy tissue, dormant cancer cells have the potential to regenerate tumors, often at a distance from a primary tumor, Dr. Massagué continued.

“The term ‘metastasis’ was coined to describe this phenomenon,” he added.

Because dormant cancer cells grow slowly or not at all, cancer treatments that target actively

dividing cells, such as chemotherapy, are unlikely to work against these cells.

Dormant cancer cells also have the ability to evade detection by the immune system. Dormancy may therefore be a kind of protective state, researchers say.

“Tumor cells have developed mechanisms that allow the dormant cells to hide from immune cells, a phenomenon sometimes known as cloaking,” said Li Yang, PhD, of NCI’s Center for Cancer Research, who studies dormancy. “This means the dormant tumor cells cannot be recognized and then be destroyed.”

More research is needed to better understand how some dormant cancer cells break through immune surveillance and start the process of forming metastatic tumors, Dr. Yang added.

Probing interactions between cancer cells and the microenvironment

Toward that end, researchers have been investigating the role of the tumor cell environment in controlling dormancy and reactivation.

This work has pushed scientists to develop mouse models that have functional immune systems. Earlier mouse models lacked immune systems so that scientists could implant human tumors into the mice without triggering an attack by immune cells. But these models could not shed light on the immune system’s role in dormancy.

Researchers’ use of these new models has paid dividends in the form of important new insights. Some recent studies, for example, have suggested that dormancy may be controlled in part by communication between dormant tumor cells and components of the tumor microenvironment, such as stromal cells and components of the extracellular matrix.

“The maintenance of dormancy and subsequent reactivation [of dormant cancer cells] is a kind of tango between the cells and cues from the microenvironment,” said Benjamin Izar, MD, PhD, of Columbia University, who studies tumor dormancy.

“We are just beginning to learn the steps of this dance,” Dr. Izar continued. He and his colleagues recently identified an RNA molecule that helps awaken dormant tumor cells and enables them to avoid detection by the immune system.

“Our study provides an example of how the reactivation of dormant cells and escape from the immune surveillance can be regulated by the same process,” Dr. Izar said.

Mechanisms for maintaining dormancy

There are likely to be many biological mechanisms for maintaining dormancy, and these may vary depending on the type of tumor cell and the cell’s location in the body, noted Brunilde Gril, PhD, of NCI’s Division of Cancer Biology.

In the Albert Einstein College of Medicine study, for example, alveolar macrophages—immune cells that protect the lungs—appeared to keep disseminated cancer cells from early-stage breast tumors in a dormant state for periods that were equivalent to more than a decade in people.

These macrophages, the researchers found, produce a protein called TGF-β2 that binds to receptor proteins on the surface of breast cancer cells. This binding triggers the transmission of signals that force the breast cancer cells to remain dormant.

“When we eliminated the macrophages, we eliminated the signals that kept the breast cancer cells dormant,” said the study’s lead investigator, Julio Aguirre-Ghiso, PhD, director of the Cancer Dormancy Institute at the Montefiore Einstein Comprehensive Cancer Center in New York. “The result was a metastatic awakening.”

Although the macrophages controlled disseminated cancer cells from early-stage tumors, they could control disseminated cells from some advanced breast tumors but not from others. This finding underscores the biological complexity inherent in the regulation of tumor dormancy, Dr. Aguirre-Ghiso noted.

“But to move the field forward,” he added, “we have to embrace complexity.”

The University of Michigan study focused on natural killer cells, a type of immune cell that can attack both tumor cells and virus-infected cells.

In several mouse models, natural killer cells kept breast cancer cells that had spread to the bone marrow in a prolonged dormant state. The cells remained inactive for half the lives of the mice, which is the equivalent of 20 years in people.

“When the dormant cells did begin to grow, they were recognized by the natural killer cells and killed,” said the lead investigator, Max Wicha, MD, of the University of Michigan Rogel Cancer Center.

His team identified two proteins in the dormant breast cancer cells, called BACH1 and SOX2, that helped to prevent the cells from being harmed by the natural killer cells.

“Both the maintenance of dormancy and the timing of when cells come out of dormancy probably relate to changes in how the dormant cells interact with the immune system,” Dr. Wicha said.

The new findings add to evidence of the immune system’s important role in regulating cancer cell dormancy, according to Frank Cackowski, MD, PhD, of the Karmanos Cancer Institute and Wayne State University.

In the mouse models, Dr. Cackowski said, the dormant tumor cells produced proteins to fend off attacks by natural killer cells. “Rather than just running and hiding from the immune system, some dormant cells might fight back,” he said.

Dr. Yang echoed this idea. “It seems possible that disseminated tumor cells may take steps on their own to prevent the immune system from attacking them,” she said.

Strategies for addressing the threat posed by dormant tumor cells

Two main strategies have been proposed for addressing the threat posed by dormant tumor cells.

One approach would identify and kill dormant cancer cells, perhaps by making the cells sensitive to attack by immune cells. Another approach would keep disseminated cancer cells in a dormant state, ensuring that they could never cause harm.

“The ultimate aim of our research would be to remove the risk of late metastases by getting rid of dormant cancer cells,” Dr. Wicha said. “But another option would be to leave the dormant cancer cells and just prevent them from ever awakening.”

Dr. Aguirre-Ghiso has also been exploring ways to intervene early to prevent a metastatic recurrence.

His team recently identified an experimental drug that targets a signaling pathway that dormant cancer cells need to stay alive during their hibernation. The drug, called HC-5404, prevented dormant cancer cells in mice from causing metastases.

The treatment was subsequently tested in patients with advanced cancers, and the Food and Drug Administration has granted HC-5404 Fast Track designation, which can speed up the review of new therapies.

“The hope is that you could prevent doctors and patients from having to deal with advanced disease,” Dr. Aguirre-Ghiso said. “But to do that you need to understand the mechanisms that control dormancy.”

Testing drugs that target the STING pathway

One such mechanism is the STING signaling pathway, which helps the immune system respond to threats such as virus-infected cells. Drugs that boost the activity of the STING pathway are being evaluated in clinical trials as treatments for people with advanced cancer.

Researchers have also been testing these drugs, called STING agonists, on dormant cells in mice.

Dr. Massagué’s team found that STING signaling helps suppress the progression of dormant mouse cancer cells to aggressive metastatic tumors. In the study, mice that received a STING agonist had fewer metastatic tumors than those that did not receive the drug. “It took much longer for the metastases to develop,” Dr. Massagué said.

Building on this work, Dr. Wicha’s team showed that a STING agonist called MSA-2 made dormant

mouse cancer cells vulnerable to attack by natural killer cells.

Both groups would eventually like to test the approach in clinical trials.

Dr. Steeg called the research on the STING pathway encouraging. “The first steps toward making a dormancy maintenance therapy have been taken,” she said.

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