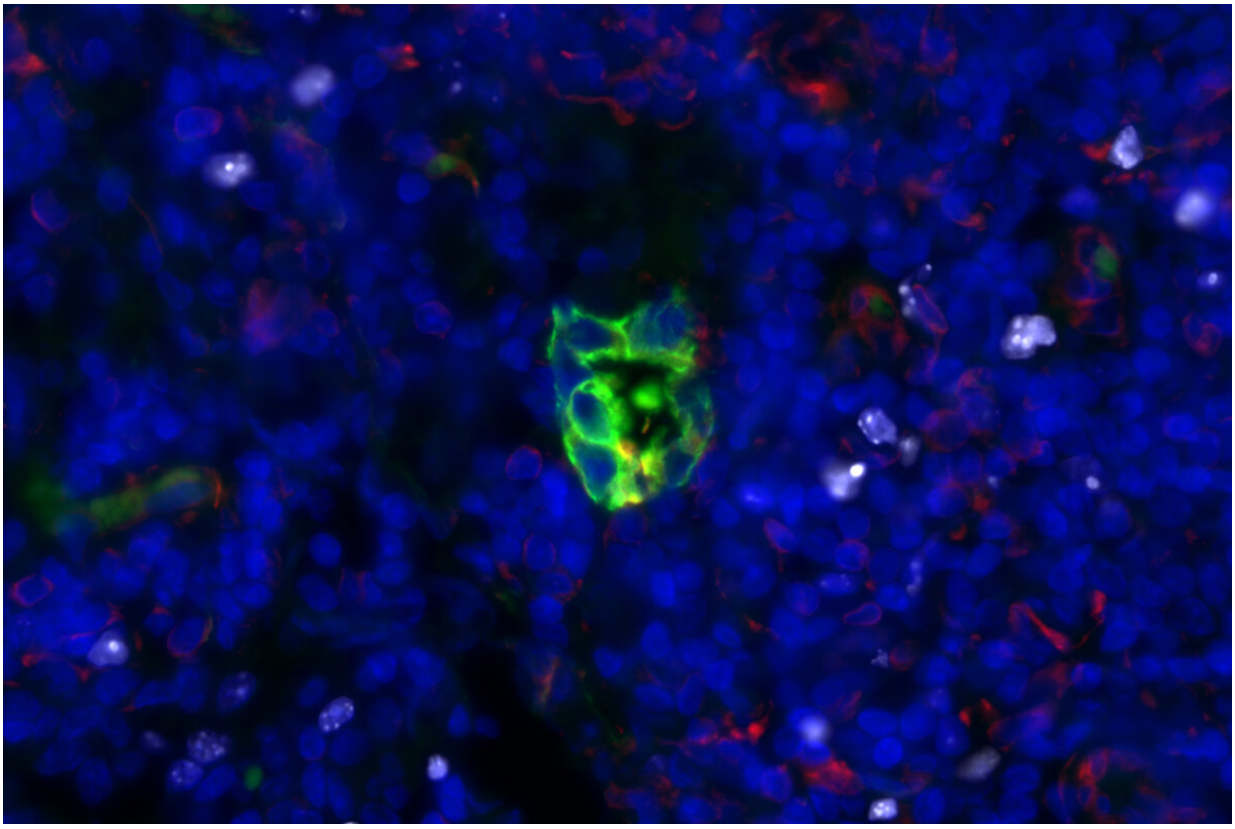
Scientists identify cellular signaling pathway as key player in metastasis

March 29 2023



A quiescent cluster of lung adenocarcinoma tumor cells from a patient's lymph node shows low STING expression. Credit: Massagué Lab, Sloan Kettering Institute.

A team of scientists at the Sloan Kettering Institute have identified the

STING cellular signaling pathway as a key player in keeping dormant cancer cells from progressing into aggressive tumors months, or even years, after they've escaped from a primary tumor.

The findings, which were published in *Nature* on March 29, suggest that drugs to activate STING could help prevent the spread of cancer to new sites throughout the body—a process known as metastasis.

In mouse models of lung cancer, treatment that stimulated the STING pathway helped eliminate lingering cancer cells and prevent them from progressing to aggressive metastases. Known as micrometastases, these cells, which can be found individually and in small clusters, are too small to be detected with standard imaging tests.

"The majority of cancer deaths are caused by metastasis," says Joan Massagué, Ph.D., the study's senior author and Director of the Sloan Kettering Institute—a hub for basic science and translational research within Memorial Sloan Kettering Cancer Center (MSK). "Anything we can do to keep these cells from waking up again or to help the immune system eliminate them could be of great benefit to many people. This research identified a previously unknown role for STING signaling in suppressing the development of aggressive metastasis."

Along with heading a research lab that investigates cancer metastasis, Dr. Massagué also leads the Alan and Sandra Gerry Metastasis and Tumor Ecosystems Center at MSK, which supports efforts across the institution to better understand, prevent, and treat metastasis.

The journey of a metastatic cell

Even when a primary tumor is successfully treated, cells that have broken away from the tumor often linger in the body in a dormant state that allows them to evade detection by the immune system for years at a

time. Then, after the dormant cells have developed new traits to help them survive, they can wake up and start their runaway growth again.

Instead of focusing on late-stage disease, when large, aggressive metastases have already emerged, the researchers focused on earlier stages—after cancer has developed but before it has been able to successfully gain a foothold in new parts of the body, says Jing Hu, Ph.D., a senior research scientist in the Massagué Lab and the first author of the *Nature* study.

"For example, nearly half of patients diagnosed with stage 1 or stage 2 lung adenocarcinoma will develop metastases," she says. "At the time of diagnosis, we believe many of those patients will already have had some cancer cells break away from their primary tumor and travel to other organs, where they will stay in a dormant state until they wake up and generate what we call spontaneous or breakthrough metastases."

Many of these cancer cells that break away from a primary tumor will die during their journey through the bloodstream to far-flung organs. But those that survive learn to adjust to the assaults and stresses of the human body.

"The tumor cells are not in a supportive environment at the beginning," Dr. Hu says. "So they have to adapt and develop their own self-supporting niche until they're ready, eventually, to wake up and start a fast-growing metastasis. The interaction with the person's immune system is very important to this process."

Genetic screen identifies new role for STING

Using mouse models of early-stage metastasis from lung cancer, the research team conducted a genetic screen to look at the activity of genes in the tumor cells that are important for interactions with the host's

immune system.

That's how they identified the STING pathway—an acronym for stimulator of interferon genes—as a suppressor of metastatic outbreaks.

"This made a lot of sense to us because STING signaling is known to be important for triggering an immune response against cells made sick by viruses or by cancer mutations," Dr. Hu adds.

STING activity changes across different stages of metastasis

Importantly, the researchers found that STING expression changes across different stages of metastasis.

In the dormant stage, STING activity is low—and the dormant cells excel at hiding out from immune defenders.

Moving out of the dormant stage and into an awakened, proliferative stage, the metastatic cells start to have increased STING activity. This makes them more vulnerable to attack by the immune system.

But cells that survive this bottleneck to generate larger clusters, called macrometastastes, again show reduced STING levels, which makes them more resistant to the immune system.

"This means that these tumor cells will be recognized differently by the immune system at different stages of metastasis development," Dr. Massagué says. "Using STING activators in conjunction with that window of increased STING activity in the reawakened cancer cells could be an opportunity to help the body's immune defenders destroy them."

Indeed, when scientists artificially increased STING signaling in those aggressive metastatic cells, they attracted more immune defenders like natural killer cells and T cells, which swooped in to kill them off.

And when the scientists activated STING in mice lacking key immune cells, metastasis still developed—pointing to a critical role for STING in recruiting the immune cells to attack the cancer cells.

These tiny micrometastases are much easier to study in mice, however, than in people. So, to verify the applicability of their findings, the scientists compared their observations in the mouse models with small numbers of cancer cells found in the lymph nodes of patients with early-stage lung cancer. What they saw in patients supported what they were discovering in the lab.

The team also identified a new role for the signaling molecule TGF-beta in suppressing STING activity during the dormant stage of metastasis. Dr. Massagué is well known for his pioneering work elucidating TGF-beta signaling and has long studied its importance in cancer. "It's our lab's favorite molecule," Dr. Hu jokes.

Moving toward new treatments for metastasis

Drugs that increase STING activity, known as STING agonists, are already being evaluated in a few clinical trials, Dr. Hu notes. But those trials are for patients with advanced cancers, when aggressive metastases have already emerged. By then, the tumor cells have already reshaped their local environment to better protect themselves from the attacks of the host's immune system.

"At the earlier stages of metastasis, STING agonists may be able to have a better effect," Dr. Hu says. "At that point, the tumor has not yet fully established an immune-evading microenvironment for itself, and STING

signaling within the tumor cells will be higher."

Ultimately, the researchers hope to collaborate with clinicians to develop a clinical trial to target micrometastases' newly discovered vulnerabilities in patients with early-stage disease. One approach would be to leverage STING to kill the cells off before they can start breakthrough metastases. Another possibility could be to try to keep the cells in a dormant state forever.

Meanwhile, the Massagué Lab is continuing to explore STING agonists' ability to destroy lingering metastatic cells, as well as potential opportunities to harness TGF-beta against early-stage metastasis.

"There is a lot more work to be done before these new insights might be applied in the clinic," Dr. Massagué says. "But we are encouraged that these efforts and others are bringing us closer to the day when we can prevent many more cancer deaths from metastasis."

More information: Joan Massagué, STING inhibits the reactivation of dormant metastasis in lung adenocarcinoma, *Nature* (2023). DOI: 10.1038/s41586-023-05880-5.
www.nature.com/articles/s41586-023-05880-5

Provided by Memorial Sloan Kettering Cancer Center