Lung inflammation contributes to metastasis

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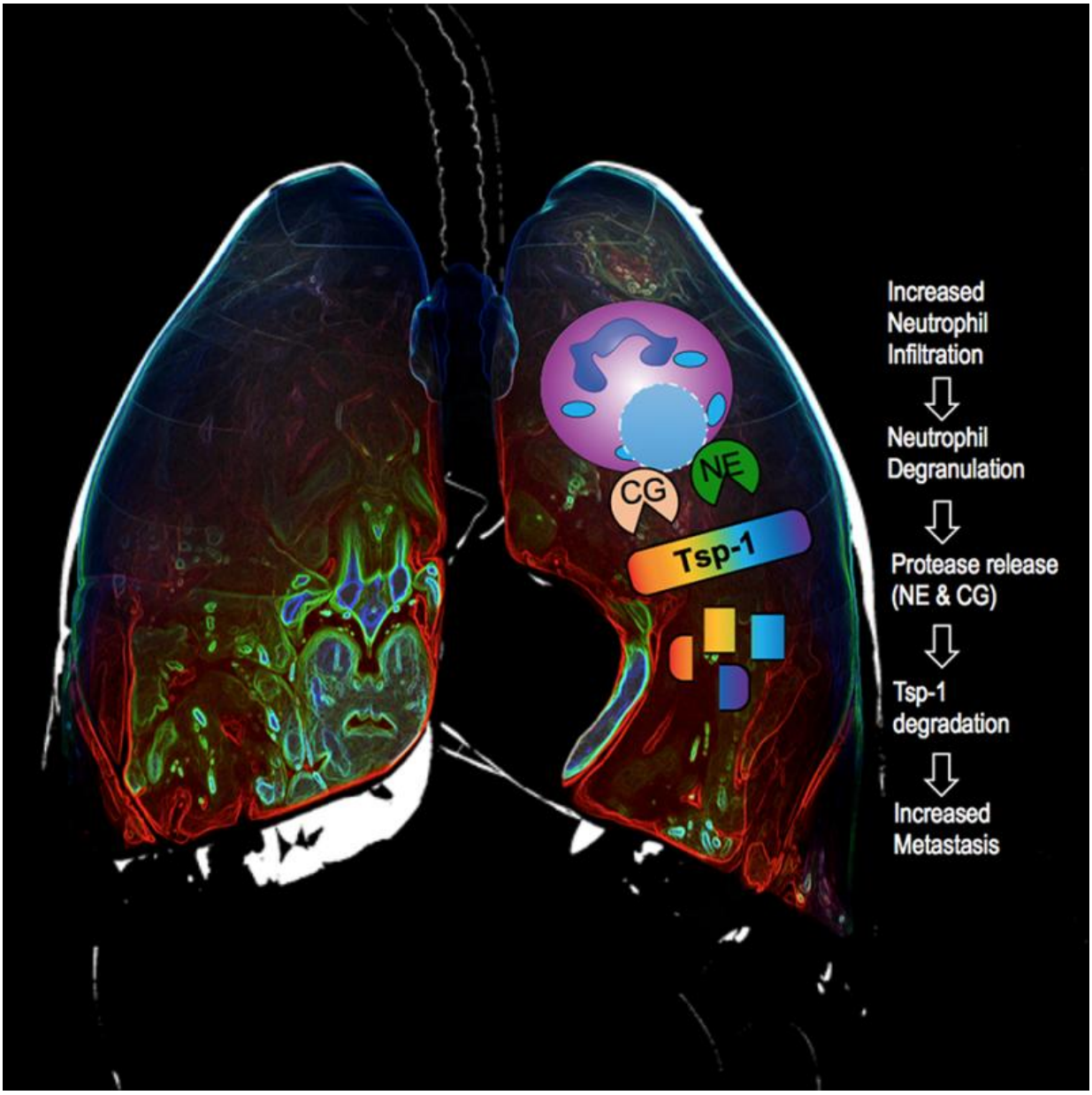

Inflamed lungs increases the risk that cancer will spread to the organ. White

blood cells called neutrophils are recruited to inflamed lungs, where they release the enzymes Cathepsin G (CG) and Neutrophil Elastase (NE). These enzymes target and destroy the protein Thrombospondin 1 (Tsp-1), which protects lung tissue from metastasis. Credit: Mittal lab

Pre-existing inflammation in the lungs may increase the risk that cancers beginning elsewhere will spread to that organ, according to new research from Weill Cornell Medicine.

Physicians have long noted an association between lung inflammation – seen in smokers or in people with lung diseases such as asthma, COPD and emphysema, and pneumonia – and the development of lung tumors. But it's been unclear whether inflammation also increases the risk of pulmonary metastasis from other tumors.

In their study, published this week in the *Proceedings of the National Academy of Sciences*, the investigators reveal a mechanism by which this occurs, shedding light on how pre-existing lung inflammation creates an environment ripe for cancer spread to the organ. The findings may provide doctors new insights into how to treat and possibly prevent metastases.

"Identifying the molecular mechanisms by which pre-existing inflammation in the lungs enhances metastasis has huge clinical implications," said senior author Dr. Vivek Mittal, director of the Neuberger Berman Foundation Lung Cancer Laboratory and an associate professor of cell and developmental biology in cardiothoracic surgery and of cell and developmental biology at Weill Cornell Medicine. "Our research suggests that therapies could be designed to target this pathway to mitigate metastasis to the lung, particularly in cancer patients who exhibit lung inflammation due to exposure to cigarette smoke, bacterial

infections and other environmental pollutants."

Metastasis occurs when cells break away from a tumor and travel through the bloodstream or lymph vessels to other parts of the body. The lungs are a common site of metastasis from other cancers, including those of the bladder, breast, colon, kidney, prostate and brain. Lung metastases are hard to cure; in general, the five-year survival rate for patients with lung metastasis is near 30 to 40 percent.

"Metastasis is the major cause of death for people with cancer, so finding better ways to target metastatic tumors is critical," said Mittal, who is also a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine.

For their study, the researchers first induced inflammation in the lungs of mice by administering a bacterial toxin through the rodents' noses. They then injected the mice with melanoma cells, which grew into skin tumors and spread to the lungs.

"We found increased metastases in inflamed lungs compared to non-inflamed controls," Mittal said, "proving that inflammation plays a role in the spread of the cancer."

When they analyzed the inflamed lung tissue, the researchers found increased numbers of white blood cells called neutrophils, which release two enzymes into the lungs. These enzymes, neutrophil elastase (NE) and Cathepsin G (CG), target and destroy a protein known as Tsp-1, which protects lung tissue from tumors.

"Since Tsp-1 protects against metastasis, this creates an environment favorable to the spread of cancer," Mittal said.

The investigators say their findings could lead to new treatment

strategies that focus on changing the environment inside the lungs that allows metastatic cancer cells to grow. A synthetic form of Tsp-1 that is resistant to the action of NE and CG, but contains characteristic cancer-suppressive properties could protect the lungs from metastatic cells,. Mittal said.

Another option is a drug called Sivelestat, which is a known inhibitor of NE and used to treat patients with acute lung injury. Importantly, the investigators found that it also inhibits CG, making it an ideal therapeutic choice. Both of these strategies would allow Tsp-1 to function normally and target cancer cells that travel to the lungs, preventing metastasis.

"The preclinical data obtained from these studies will generate unique translational opportunities, and may lead to the design of future clinical trials for cancer patients who exhibit pulmonary inflammation," said first author Dr. Tina El Rayes, a Weill Cornell Medicine postdoctoral associate.

Mittal believes intervention against inflammation-driven cancer spread can lead to the development of an anti-metastatic therapy. He is leading a preclinical study that investigates whether dual inhibition of NE and CG can effectively prevent breast cancer from metastasizing to inflamed lungs.

Mittal's research also points to the need to understand whether inflammation in other organs might contribute to the spread of cancers as well.

"It should be applicable to any tumor with metastatic potential," he said. "It's really a hopeful finding for cancer treatment."

More information: Tina El Rayes et al. Lung inflammation promotes

metastasis through neutrophil protease-mediated degradation of Tsp-1, *Proceedings of the National Academy of Sciences* (2015). DOI: 10.1073/pnas.1507294112