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A new approach to targeting tumors and tracking their spread

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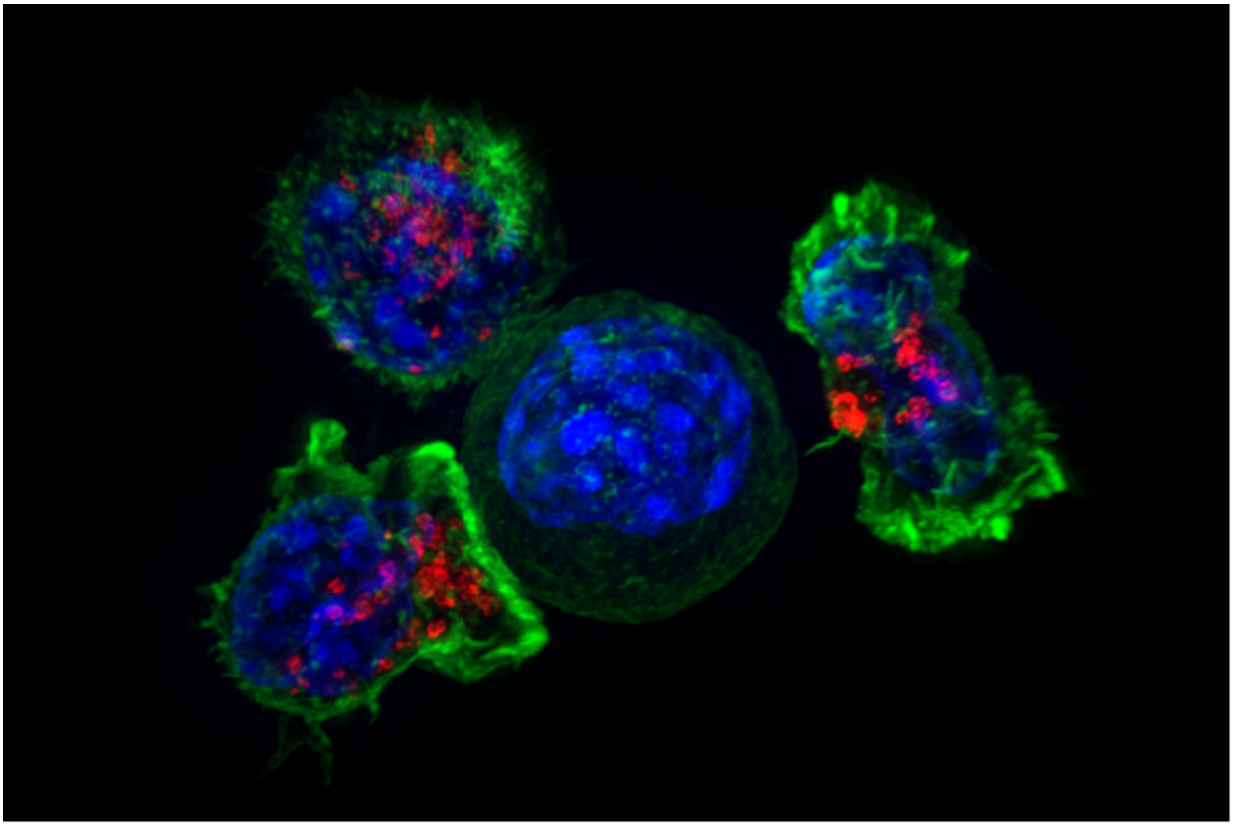

Killer T cells surround a cancer cell. Credit: NIH

The spread of malignant cells from an original tumor to other parts of the body, known as metastasis, is the main cause of cancer deaths worldwide.

Early detection of tumors and metastases could significantly improve cancer survival rates. However, predicting exactly when cancer cells will break away from the original tumor, and where in the body they will form new lesions, is extremely challenging.

There is therefore an urgent need to develop new methods to image, diagnose, and treat tumors, particularly early lesions and metastases.

In a paper published today in the *Proceedings of the National Academy of Sciences*, researchers at the Koch Institute for Integrative Cancer Research at MIT describe a new approach to targeting tumors and metastases.

Previous attempts to focus on the tumor cells themselves have typically proven unsuccessful, as the tendency of cancerous cells to mutate makes them unreliable targets.

Instead, the researchers decided to target structures surrounding the cells known as the extracellular matrix (ECM), according to Richard Hynes, the Daniel K. Ludwig Professor for Cancer Research at MIT. The research team also included lead author Noor Jailkhani, a postdoc in the Hynes Lab at the Koch Institute for Integrative Cancer Research.

The extracellular matrix, a meshwork of proteins surrounding both normal and cancer cells, is an important part of the microenvironment of tumor cells. By providing signals for their growth and survival, the matrix plays a significant role in tumor growth and progression.

When the researchers studied this microenvironment, they found certain proteins that are abundant in regions surrounding tumors and other disease sites, but absent from healthy tissues.

What's more, unlike the tumor cells themselves, these ECM proteins do

not mutate as the cancer progresses, Hynes says. "Targeting the ECM offers a better way to attack metastases than trying to prevent the tumor cells themselves from spreading in the first place, because they have usually already done that by the time the patient comes into the clinic," Hynes says.

The researchers began developing a library of immune reagents designed to specifically target these ECM proteins, based on relatively tiny antibodies, or "nanobodies," derived from alpacas. The idea was that if these nanobodies could be deployed in a cancer patient, they could potentially be imaged to reveal tumor cells' locations, or even deliver payloads of drugs.

The researchers used nanobodies from alpacas because they are smaller than conventional antibodies. Specifically, unlike the antibodies produced by the immune systems of humans and other animals, which consist of two "heavy protein chains" and two "light chains," antibodies from camelids such as alpacas contain just two copies of a single heavy chain.

Nanobodies derived from these heavy-chain-only antibodies comprise a single binding domain much smaller than conventional antibodies, Hynes says.

In this way nanobodies are able to penetrate more deeply into human tissue than conventional antibodies, and can be much more quickly cleared from the circulation following treatment.

To develop the nanobodies, the team first immunized alpacas with either a cocktail of ECM proteins, or ECM-enriched preparations from human patient samples of colorectal or breast cancer metastases.

They then extracted RNA from the alpacas' blood cells, amplified the

coding sequences of the nanobodies, and generated libraries from which they isolated specific anti-ECM nanobodies.

They demonstrated the effectiveness of the technique using a nanobody that targets a protein fragment called EIIIB, which is prevalent in many tumor ECMs.

When they injected nanobodies attached to radioisotopes into mice with cancer, and scanned the mice using noninvasive PET/CT imaging, a standard technique used clinically, they found that the tumors and metastases were clearly visible. In this way the nanobodies could be used to help image both tumors and metastases.

But the same technique could also be used to deliver therapeutic treatments to the tumor or metastasis, Hynes says. "We can couple almost anything we want to the nanobodies, including drugs, toxins or higher energy isotopes," he says. "So, imaging is a proof of concept, and it is very useful, but more important is what it leads to, which is the ability to target tumors with therapeutics."

The ECM also undergoes similar protein changes as a result of other diseases, including cardiovascular, inflammatory, and fibrotic disorders. As a result, the same technique could also be used to treat people with these diseases.

In a recent collaborative paper, also published in *Proceedings of the National Academy of Sciences*, the researchers demonstrated the effectiveness of the technique by using it to develop nanobody-based chimeric antigen receptor (CAR) T cells, designed to target solid tumors.

CAR T cell therapy has already proven successful in treating cancers of the blood, but it has been less effective in treating solid tumors.

By targeting the ECM of tumor cells, nanobody-based CAR T cells became concentrated in the microenvironment of tumors and successfully reduced their growth.

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The researchers are now planning to carry out further work to develop the nanobody technique for treating tumors and metastases.

More information: Noor Jailkhani el al., "Noninvasive imaging of tumor progression, metastasis, and fibrosis using a nanobody targeting the extracellular matrix," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1817442116

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