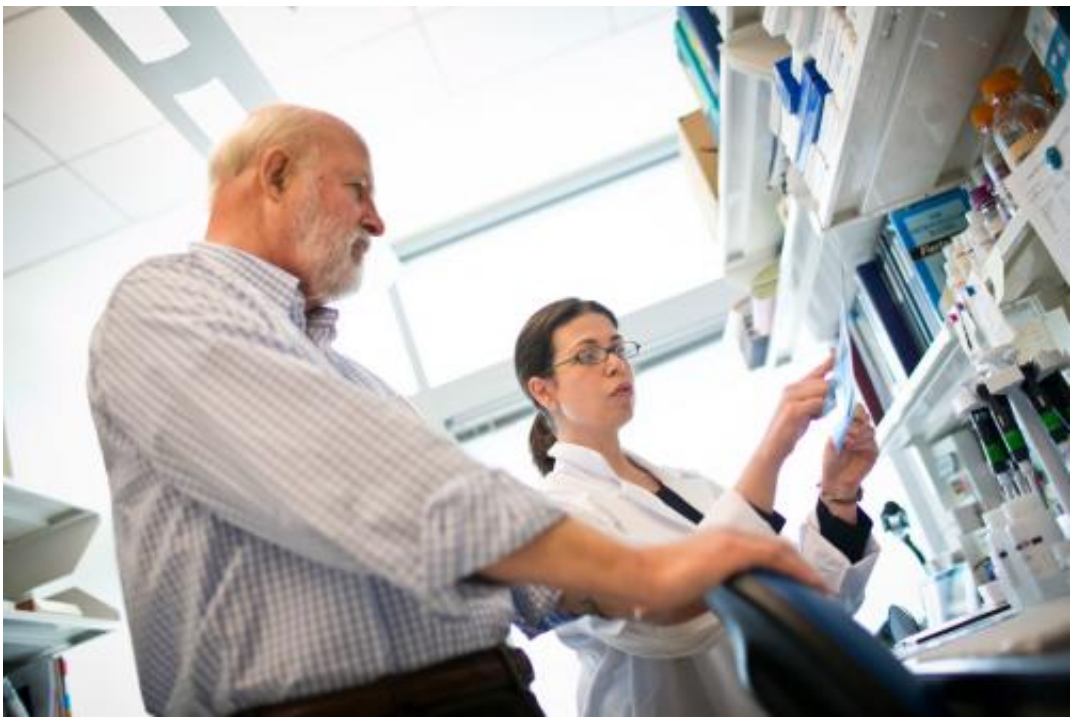
# Biologists identify extracellular proteins that help aggressive tumors spread through the body

March 11 2014, by Anne Trafton



Professor Richard Hynes and Koch Institute postdoc Alexandra Naba in their lab. Credit: Dominick Reuter

About 90 percent of cancer deaths are caused by tumors that have spread from their original locations. This process, known as metastasis, requires cancer cells to break loose from their neighbors and from the supportive scaffold that gives tissues their structure.

MIT cancer biologists have now discovered that certain proteins in this structure, known as the extracellular matrix, help cancer cells make their escape. The researchers identified dozens of proteins that surround highly metastatic tumors, but not less aggressive tumors, and found that four of those proteins are critical to metastasis.

The findings could lead to new tests that predict which tumors are most likely to metastasize, and may also help to identify new therapeutic targets for metastatic tumors, which are extremely difficult to treat.

"The problem is, all the current drugs are targeted to primary tumors. Once a metastasis appears, in many cases, there's nothing you can do about it," says Richard Hynes, leader of the research team and a member of MIT's Koch Institute for Integrative Cancer Research. "In principle, one could imagine interfering with some of these extracellular proteins and blocking metastasis in a patient. We're a long way from that, but it's not inconceivable."

Koch Institute postdoc Alexandra Naba is the lead author of the study, which appears in the March 11 online edition of the journal *eLife*. Other authors are Steven Carr, director of the Proteomics Platform at the Broad Institute; Karl Clauser, a research scientist at the Broad Institute; and John Lamar, a research scientist at the Koch Institute.

## Decoding the matrix

The extracellular matrix is made mostly of collagens, proteins that provide structural support for living tissues. But the matrix also includes hundreds of other proteins that guide cells' behavior and help them communicate with each other.

Scientists believe that cancer cells alter the composition of the matrix to stimulate their own growth and survival. Patients whose tumors have a

greater abundance of extracellular matrix proteins have a poorer prognosis, but until now, scientists did not know why.

"The matrix has really been understudied, because it's not easy," says Hynes, the Daniel K. Ludwig Professor for Cancer Research in MIT's Department of Biology. "This study couldn't have been done five to 10 years ago. It's dependent on modern technology—having the genome sequences, having mass spectrometry machines that are really good, and collaborators who know how to use them."

Researchers in Hynes' lab previously developed a method for identifying extracellular matrix proteins by enriching them from tumors and then breaking them into shorter fragments. Analyzing these fragments with mass spectrometry reveals the extracellular matrix composition.

In this study, the researchers focused on about 1,000 proteins, including about 300 that have been identified in genomic studies as components of the matrix. The remaining proteins include enzymes that modify or degrade the matrix and growth factors that bind to it.

To compare the extracellular matrix proteins found in different tumor types, the researchers implanted metastatic and nonmetastatic human breast cancer cells into mice. They identified 118 extracellular matrix proteins that were found in both types of tumors. However, there were also several dozen proteins that were abundant in either metastatic or nonmetastatic tumors, but not both.

## Manipulating the environment

It appears that metastatic tumors, as well as the supportive cells that surround them, secrete certain proteins into the extracellular matrix to make it easier for them to escape and survive at a distant site, the researchers say. Many of the proteins overexpressed in the more

aggressive tumors are activated by the same cellular signaling pathways, including one controlled by a growth factor called TGF beta, which controls cell proliferation and is often elevated in cancer cells.

Other matrix-associated proteins were controlled by pathways stimulated by low concentrations of oxygen—a condition known to make cancer cells more aggressive.

In further experiments, the researchers analyzed five of the proteins that are elevated in highly aggressive tumors and found that four of them are necessary for metastasis to occur. When the genes for those proteins were knocked down, one at a time, tumors failed to spread.

"This elegant study sheds new light into the extracellular matrix proteins involved in various steps of the metastatic cascade," says Rakesh Jain, a professor of radiation oncology at Harvard Medical School and Massachusetts General Hospital. "Our knowledge about the abundance of [extracellular matrix] proteins in tumors has been limited. This study utilizes the power of proteomics to identify extracellular matrix proteins critical in metastasis."

Many of the proteins identified interact with cancer cells by binding to proteins called integrins that are found on cell surfaces, so it may be possible to create drugs that prevent metastasis by interfering with that binding. "We need to understand how the proteins communicate with the cells, identify the cellular receptors, and then hopefully we can block the interaction," Naba says.

The researchers also compared their results with human tumor samples and found that when the proteins they had identified in mice were overexpressed in human tumors, the patients had lower survival rates. It would be impractical to do this kind of large-scale protein screen in patients, but it could be possible to test samples for certain proteins using

antibodies, say the researchers, who are now developing such antibodies.

"That could become part of a kit that doctors would use to distinguish a patient who has a tumor that's going to metastasize, so they would follow the patient differently from a patient with a tumor they know won't metastasize," Naba says.

The researchers are now seeking extracellular matrix proteins that are overexpressed in other metastatic cancers, including colon and pancreatic cancers. They are also studying whether extracellular matrix proteins in tissues to which escaped tumor cells often metastasize—such as the bone, liver, and lungs—make them more receptive to invading cancer cells. If such proteins could be identified, they could also be good drug targets.

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