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Humphrey Center scientists seek insights into the mystery of tumor metastasis

If tumors didn't spread within the body, cancer would be a relatively minor health problem. Consider colon cancer. This disease, which claims the lives of more than 50,000 Americans each year, is readily cured if the tumor is removed before it has spread beyond the colon's inner lining.

Once the cancer starts to penetrate into the colon wall, however, the chances of a cure begin to decline. And after it has gone through the wall—meaning that it can spread to new locations—the chances of a cure diminish significantly.

"The current chemotherapies and radiotherapies for treatment of cancer leave a good deal of room for improvement," says Herbert Z. Kupchik, Ph.D., a scientist at the Hubert H. Humphrey Cancer Research Center and an associate professor of microbiology and pathology at Boston University School of Medicine.

Yet the irony of colon cancer, as with many other types of cancers, is that very few tumor cells have the ability to seed a malignancy in a new location. Typically, only about 1 tumor cell in 100,000 has this capability.

The fact that the ability to metastasize, or spread, is relatively rare raises the intriguing possibility of seeking to target the few cells in a tumor with the trait. Dr. Kupchik and his associates have spent several years working to set the stage for exactly such a strategy.

The first step in colon cancer metastasis is a process called invasion. "An invasive tumor is one that has begun to penetrate the bowel wall," notes Dr. Kupchik.

The process starts when some cells break away from the main tumor mass and begin to squeeze through the bowel wall. These cells lead the invasive front. As the tumor penetrates the wall, eventually more cells will follow.

To isolate cells with a tendency to grow in this way, Dr. Kupchik and his associates needed to mimic the barriers facing a tumor. They chose a tissue called the amnion, a part of the placenta, for the role.

"We obtained cells from a tumor that was already invasive before it was removed," says Dr. Kupchik. "Then, we did a series of experiments to see if we could identify a subset of these cells that could penetrate the amnion."

The reseachers were able to isolate a group of cells that were more invasive by nature than other cells from the same tumor. The key question remained: Could they identify traits that set invasive cells apart from non-invasive cells?

In later experiments, the researchers found that there is a major difference between the two types of cells. The invasive cells were much more strongly drawn toward laminin—a protein found, among other places, in the colon wall's

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Collagen-cancer links may yield ways to pinpoint the nature of specific tumors

Collagen, though but one among the many thousands of types of proteins in our bodies, does have some distinctive traits.

For one thing, it's one of the most common of all our proteins. For another, it's a major component of many of the tissues—tendons, bones, the skin—that determine the way our bodies are put together.

Besides being a key structural protein, collagen also has numerous connections with cancer. For example, it's the main constituent of the coatings that sometimes form around tumors, says Barbara D. Smith, Ph.D., a Hubert H. Humphrey Cancer Research Center scientist and an associate professor of biochemistry at Boston University School of Medicine. "If you have a tumor and your body sees it as foreign," says Dr. Smith, "there are certain cells that can encapsulate it with collagen. These tumors tend to be benign more often than those that aren't so encapsulated."

Collagen is also a key part of the tiny, web-like structure, called a matrix, that exists in the narrow spaces between the cells in our bodies. Cancer cells don't readily attach to matrices, which may be partly why tumors are able to grow so rapidly.

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Tumor metastasis

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outer layer—than the non-invasive cells. "We coated the bottom of a filter with laminin," says Dr. Kupchik, "and the cells that reached it through the filter were the invasive ones."

The discovery, combined with reports from other laboratories linking laminin to invasion-prone tumor cells, raises the prospect of new types of anti-cancer strategies. Dr. Kupchik notes that it's likely so-called laminin receptors in the invasive cells are both stronger and more numerous than those in the non-invasive cells. If so, it may be possible to attack invasive tumor cells by using antibodies—substances that home in on a specific, target molecule—to the receptors.

To be fully successful, however, notes Dr. Kupchik, such a strategy has to take account of the fact that invasive tumor cells are drawn to other colon-wall proteins besides laminin. An anti-laminin approach, he says, "may be part of the answer, but not the whole answer."

Collagen cancer

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Dr. Smith's special interest centers on the fact that some tumor cells don't make normal collagen. Her group has been experimenting with liver cancer cells. Normal collagen molecules consist of three tiny strands wound around each other—a sort of microscopic cable—but not the collagen molecules produced by the cells she's studying. "In these cells, one of the three chains is missing from the molecule," says the scientist.

For certain types of cancer, physicians already use a tumor's interactions with matrices in judging what specific kind of tumor it is—an approach that allows for more carefully targeted treatment strategies. Eventually, says Dr. Smith, it might be possible to use the nature of the abnormal collagen made by a tumor to fine-tune prognostic judgments. Before that can happen, however, there's a need for more understanding of cancer's effects on collagen.

Dr. Smith and her associates have been exploring why the cancerous cells they're working with make collagen that lacks one of the three chains found in the normal version of the protein. Knowing that an altered gene was the most likely explanation, she says, the group "cloned the genes from these cells to see if they were mutated."

Through such experiments, the researchers were able to pinpoint specific segments of DNA that may provide the key to the abnormalities in collagen. These segments, called promoters and enhancers, are part of the gene's regulatory machinery. The researchers have found that certain types of cancer-causing agents can disrupt the normal workings of this machinery. Currently, the group is seeking to confirm their findings through a new series of experiments.

In pursuing their studies of collagen, Dr. Smith and her associates are following a trail originally laid down by the late Sidney Cooperband, M.D., the Humphrey Cancer Center's first director.

Dr. Cooperband's hope, says Dr. Smith, was to find ways to boost the collagen output of cancerous cells. "He felt that if you could increase collagen production," she says, "you'd have a better chance of walling off the tumor and preventing its spread."

That goal has yet to be achieved, says Dr. Smith, and there's no way to predict today whether it will turn out to be achievable. She also says, however, that considering the close links between cancerous growth and collagen production, there's good reason to hope that current studies of how malignancies affect collagen will yield at least some new methods of aiding cancer patients.

CANCER NOTES

CANCER NOTE: About one of every 10 women in the United States will develop breast cancer during her lifetime. Until the disease can be prevented, the best way women can protect themselves is through early detection and prompt treatment. Today, with modern technologies, breast cancer can be detected at very early stages of development, when the chance of cure is highest. The American Cancer Society recommends that women develop a three-part, personal plan of action for early detection of breast cancer. This plan should include a clinical breast examination by a doctor, a mammogram and breast self-examination.

CANCER NOTE: Cancer strikes at any age. It kills more children ages 3 to 14 than any other disease, and occurs more frequently with advancing age. In the 1980s, it was estimated there were over 4.5 million cancer deaths, almost 9 million new cancer cases, and some 12 million people under medical care for cancer. In 1990, about 1,040,000 people will be diagnosed as having cancer.

CANCER NOTE: Many patients with primary bone cancer now are treated successfully by removing and replacing a section of bone rather than by amputating the leg or arm. Drugs and radiation therapy are being used effectively after bone cancer surgery, resulting in dramatic improvement in survival.

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