

Cancers Use “Cellular Bookmarks” to Target Favorite Sites of Metastasis

HHMI RESEARCHERS AND THEIR COLLEAGUES HAVE discovered that nonmalignant bone marrow cells establish “cellular bookmarks” in target organs that guide the spread of cancer cells to their predetermined destinations.

The researchers say their findings could have a major impact on how oncologists assess the likeliness of metastasis to specific organs. Their discovery may also help identify subsets of high-risk cancer patients prone to distant metastases who would likely benefit from a more aggressive therapy to prevent cancer relapse.

Ultimately, understanding how cellular bookmarking works at the molecular level could lead to information that may help thwart metastasis, a major cause of death among cancer patients, says one of the study’s senior authors, Shahin Rafii, an HHMI investigator at Weill Medical College of Cornell University.

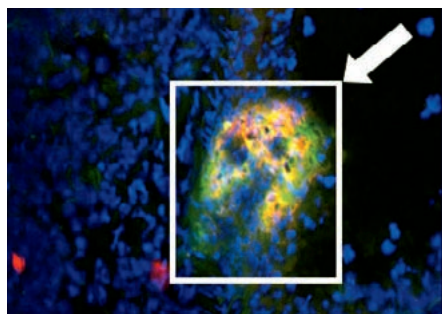
The researchers, led by David Lyden and Rafii, published their findings in the December 8, 2005, issue of the journal *Nature*. Lyden is at Memorial Sloan-Kettering Cancer Center and Weill Medical College.

Rafii and Lyden’s group had established that a specific subset of bone marrow-derived cells (BMDCs)—which are composed of hematopoietic progenitor cells capable of dividing and forming

colonies—are recruited by tumors and aid in the growth of new blood vessels. The generation of new blood vessels occurs through a process called angiogenesis. In previous studies, the researchers had shown that co-recruitment of hematopoietic BMDCs expressing an angiogenic factor receptor, VEGFR1, along with the vascular cells accelerated the assembly of newly formed blood vessels and tumor growth.

“In the current paper, we set forth another novel concept by demonstrating that a nonmalignant cluster of VEGFR1-positive hematopoietic BMDCs were recruited to a premetastatic niche, thereby establishing a permissive docking site prior to the arrival of the circulating tumor cells,” says Rafii. A “premetastatic niche” is a cellular microenvironment that is specialized for the development of metastatic tumor cells.

In experiments with mice that had been implanted with highly metastatic lung cancers or melanoma cells, the scientists discovered that BMDCs arrived at the premetastatic sites before the cancer cells did. They also found that such clusters appeared before metastases developed in mice genetically predisposed to developing tumors—a system that closely mimics how cancers develop. —Dennis Meredith ■



CLUSTERS OF BONE MARROW-DERIVED CELLS (GREEN) AND ANGIOGENIC FACTORS (RED) MAY MARK AREAS FOR METASTASIS

IN BRIEF

BREAST CANCER DRUGS MAY SLOW GROWTH OF LUNG CANCER

A few years ago researchers discovered that, much like breast tumors, some lung tumors also thrive on estrogen. Now a medical student conducting research on an HHMI fellowship and colleagues have managed to stop the growth of human lung cancer cells in mice with a class of breast cancer drugs called aromatase inhibitors.

“It was a natural progression of the work that had already been done linking estrogen and lung cancer,” said **Olga Weinberg**, who delayed her fourth year at Vanderbilt University School of Medicine to work on the project. The findings suggest a new way to treat lung cancer in women—a group whose death rate from the disease is surging.

“More women are dying now from lung cancer than from breast cancer,” said senior author Richard Pietras, Weinberg’s research mentor at the University of California at Los Angeles. “We followed one of the clues as to why this is happening, namely that estrogen drives the growth of certain types of lung cancer in women.”

To see if they could block this growth, the team started with the enzyme aromatase. It was a natural target because it converts testosterone into estradiol, a potent form of estrogen also used in hormone replacement therapy. In addition, drugs that inhibit aromatase have already made it to market as treatments for breast cancer. “The production of estrogen takes several steps, and aromatase is the key to the process,” said Weinberg. “Without aromatase, you don’t get estrogen.”

The studies were reported in the December 15, 2005, issue of the journal *Cancer Research*.

BIOTECHNOLOGY’S NEW CHEMICAL TOOL

Researchers have developed a new technique that allows them to modify specific sequences within a DNA molecule. The approach not only will reveal the impact of biochemical alterations to DNA but also could have far-reaching implications for DNA-based medical diagnosis and nanobiotechnology.

Combining chemistry with biotechnology, **Saulius Klimašauskas**, an HHMI international

research scholar at the Institute of Biotechnology in Vilnius, Lithuania, and chemists at the Institute of Organic Chemistry in Aachen, Germany, harnessed a group of essential enzymes to add various chemical groups to DNA, thereby altering its function.

The enzymes at the heart of the study, known as DNA methyltransferases, are one of the tools cells use to turn genes on and off. In this study, the scientists demonstrated that methyltransferases can be used to transfer sizable chemical groups to large DNA molecules in a sequence-specific manner.

Earlier studies had suggested that transferring chemical groups larger than a methyl group was not feasible. “No one has really thought about possible applications [of this] before because no one thought it was possible,” said Klimašauskas. He predicts that DNA methyltransferases will become a standard laboratory tool like restriction endonucleases.

The work was published in the January 2006 issue of *Nature Chemical Biology*.