Researchers Tackle Metastasis, Cancer’s Last Frontier

By Vicki Brower

New research, including a phase II clinical trial in advanced melanoma, is adding to growing evidence that slowing metastasis may be more important than the traditional goal of reducing tumor volume.

“Looking at tumor volume to extend life is looking in the wrong direction,” said David Cheresh, Ph.D., professor of pathology and cancer biology at the University of California in San Diego and inventor of the drug etaracizumab (Abegrin), which extended the life of stage IV melanoma patients. “Instead, we need to attack the metastatic cascade.”

Metastasis has long been known as cancer’s true killer, but it hasn’t been well understood. Now that researchers are teasing apart the steps in the metastatic cascade, they are trying to arrest the process by taking a range of new vascular biology approaches, including targeting a tumor’s blood vessels, its communications system, and its lymph system. Other research is looking at the tumor’s microenvironment, certain transcription factors, chemokines, and signaling pathways.

Patients don’t usually die from their primary tumor; 90% of patients with solid tumors die from metastases, said Joan Massagué, Ph.D., chairman of cancer biology and genetics at New York’s Memorial Sloan-Kettering Cancer Center. Until recently, much basic research and drug development has focused on genetic mutations and conditions responsible for originally transforming healthy cells into malignant ones in primary tumors. However, few meaningful gains have been made in extending the lifespan of cancer patients over the past few decades because of the deadly effect of metastasis, Massagué said.
“Metastasis is the last frontier of cancer research,” said Massachusetts Institute of Technology’s Robert Weinberg, Ph.D., professor of biology and cancer research. Relatively little is understood about why and how cancer cells leave home, travel to distant sites in the body, and establish new colonies, Weinberg said.

“Metastasis is so complex it hasn’t been well studied—perhaps because of its complexity—and not much progress had been made,” said Marsha Moses, Ph.D., associate professor of surgery at Harvard University Medical School in Boston. “We are now gaining a better understanding of the metastatic cascade as live imaging, microarrays, and animal models have improved.”

The metastatic cascade is a series of events orchestrated by signals from both a tumor and its microenvironment. These signals guide cells on their escape from the primary tumor, into the bloodstream and lymph system, and through the body to distant organs where they may anchor and thrive. The prevailing wisdom has held that metastasis was a late-stage phenomenon, but a surprising finding in 2002 by the Whitehead Institute’s Eric Lander, Ph.D., and Todd Golub, M.D., challenged that notion. Using microarray technology, the Cambridge, Mass., team discovered that some primary tumors resemble metastatic tumors in their gene expression signature.

“These results suggest that the metastatic potential of human tumors is encoded in the bulk of a primary tumor, thus challenging the notion that metastases arise from rare cells within a primary tumor that have the ability to metastasize,” the author wrote in Nature Genetics.

**Targeting Tumor Vessels**

Cheresh is one of a group of researchers who are taking a vascular biology approach to metastasis. Their focus on the role of new blood vessels in metastasis rests on Judah Folkman’s 1971 observation that tumors can grow larger than 1–2 mm and metastasize.

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This knowledge helped change the research focus from the traditional mutated cancer cell—notoriously hard to treat without creating resistance—to the tumor microenvironment and its more genetically stable elements, including endothelial cells that are recruited to form tumor blood vessels, adhesion molecules, chemokines, and growth factors expressed by tumor and microenvironment cells. Tumor blood vessels are also a good target because they are genetically stable and give tumor cells an escape hatch by which cells can leave the primary tumor, enter the bloodstream, and establish themselves in distant sites.

Vascular biology researchers are looking for new ways to detect and arrest early metastasis by focusing on modifying the surrounding cells rather than the tumor cells themselves. Newly designed drugs focus on the biology of tumor blood vessels. Etaracizumab, for instance, targets a protein expressed on newly formed tumor blood vessels and on certain other cells, and it has been found to reduce bone metastases and angiogenesis and slow tumor growth. The researchers are also using different doses of older drugs like paclitaxel, which is known to have antiangiogenic effects, to improve survival rates by suppressing or reducing metastasis or keeping metastases dormant. If they can stop the vascular system’s growth, it may be possible to extend life without ridding the body of the primary tumor, Folkman said.

Vascular biology researchers are also exploiting the major difference between normal and tumor blood vessels: Tumor vessels are leaky partly because of the increase in vascular endothelial growth factor (VEGF) in tumors and surrounding cells. By reducing VEGF expression with drugs such as bevacizumab, researchers have shown that antiangiogenic therapies can not only cut off blood supply to tumors but also normalize the tumor vasculature, prevent tumor cells from escaping, improve the delivery and efficacy of therapeutics, and extend life without shrinking a primary tumor.

“Antiangiogenic therapy makes it harder for cancer cells to enter blood or lymphatic vessels because it transforms leaky vessels into normal ones. Normal blood vessels also facilitate drug delivery through the tumor,” said Rakesh Jain, Ph.D., professor of tumor biology at Harvard Medical School. Several tyrosine kinase inhibitors, which also affect the VEGF family, are now in phase II trials.

**Lymph System Delivery**

Another set of researchers is targeting lymph system metastasis, a particular problem in breast and head and neck cancer. A major goal in treating cancers that often metastasize to the lymph system is preventing cells from entering that system in the first place, Jain said. In a recent issue of Cancer Cell, he showed that it might be possible to stop lymph metastasis. Jain observed lymph system metastasis in live mice for the first time by using microscopy, which showed that VEGF-C increases metastasis by ferrying cancer cells to lymph nodes without affecting the cells’ survival.

“Giving mice with tumors VEGF-C, we could see cancer cells moving into lymph nodes and sit there without growing. When we blocked it with a monoclonal antibody, we blocked the movement of malignant cells into the lymphatic system,” Jain said. But giving the antibody when lymph nodes were already seeded with metastases had no effect.

“Interfering with the VEGF-C signaling pathway may be a good therapeutic strategy in those cancer types to try to prevent lymph metastasis,” Jain said. He sees potential in using a VEGF-C blockade to prevent lymph metastasis in patients with...
residual cells postsurgery, inoperable tumors, and risk of local failure after initial treatment.

Other recent work capitalizes on the differences found between normal lymph and blood vessels and those found in cancer. Erkki Ruoslahti, Ph.D., a researcher at the Burnham Institute in La Jolla, Calif., developed tumor-homing peptides that are cell specific: They penetrate the tumor endothelial cells that make up tumor blood vessels but not normal tissues. These peptides can be used for diagnosis and for drug delivery to blood and lymph vessels.

Ruoslahti also discovered “vascular ZIP codes” in lymph system tissues—endothelial cells that direct lymphocytes to certain lymph tissues. This finding helps explain why cancer cells migrate to certain organs and not others.

“The holy grail in metastasis is to understand why some cancer cells metastasize to certain organs, like lung and bone, and not elsewhere,” noted Moses, whose own group has discovered five new angiogenesis inhibitors, three of which are in clinical development, and a urine test for cancer on the basis of enzymes that detect angiogenesis.

### The Signaling System

Focusing on signaling between cancer cells and the environment may also be a good way to slow or stop metastasis. Cancer cells display a unique long-distance communication capability that sets the stage for metastasis, David Lyden, M.D., Ph.D., and Shahin Rafii, M.D., of Weill Cornell University in New York City recently discovered. In a report published in *Nature*, they showed that tumors signal nonmalignant VEGF receptor 1+ (VEGFR1+) cells in the bone marrow, which then travel to and prepare distant sites for new blood vessel growth. These “pre-metastatic niches” are the sites where metastases later form. In animal experiments, interfering with VEGFR1+ cell mobilization decreased later tumor metastasis, and there is hope that interfering with such signals in humans could reduce metastasis. It also may be possible to use these cells’ presence in a diagnostic test that indicates a cancer’s metastatic potential, they noted.

Bruce Zetter, Ph.D., professor of cancer biology at Children’s Hospital of Boston and Harvard Medical School, is examining which tumor cells will migrate. He has identified many markers that may pinpoint which prostate tumors will metastasize. One molecule in particular, thymosin B-15, stimulates prostate cancer cell migration and metastasis and therefore can be used to predict spread or recurrence. Zetter is also refining a set of markers that indicate that a tumor has made the metastatic switch—the point at which a tumor develops the ability to spread—although validation will require a long-term prospective study with many participants, he said.

While predicting which tumors will metastasize could help guide treatment and ultimately reduce mortality, detecting a tumor while it is still microscopic and has not made the metastatic switch would be even better, Folkman said. Recently, he discovered that platelets, which stick to tumors, also selectively capture other angiogenic-related factors, including VEGF. Mouse experiments have shown that it is possible to measure the platelet angiogenic proteome in plasma to detect human cancers when they are still dormant and less than 1 mm, he said. Using a panel based on several of these proteins is more precise than using one biomarker to detect a wide range of tumor types and sizes.

Folkman hopes to begin testing a platelet-related panel in colon cancer patients in a clinical trial. “Half of those operated on in colon cancer are cured, while half will have recurrences; the problem is we don’t know who is in each group.” By tracking these patients long-term after surgery, Folkman hopes to be able to eventually predict who will have a recurrence and to treat them with angiogenesis inhibitors long before disease or metastasis is visible.

© Oxford University Press 2007. DOI: 10.1093/jnci/djk047

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### Other Approaches To Tackling Metastases

**Who:** Robert Langer, Ph.D., Massachusetts of Technology and the Whitehead Institute  
**Looking at:** transcription factors involved in embryonic development and wound healing that are reactivated when cells change from stationary to mobile and capable of metastasizing—known as the epithelial–mesenchymal transition (EMT).  
**Findings so far:** TWIST, FOXC2, Goosecoid, and Slug transcription factors can program most, if not all, of the transition.

**Who:** Joan Massagué, Ph.D., Memorial Sloan-Kettering Cancer Center  
**Looking at:** TGF-β signaling pathway, which is important in embryogenesis, tissue maintenance, and metastasis.  
**Findings so far:** His team has identified a genomic fingerprint that predicts breast cancer spread to bone and another that predicts spread to the lung.

**Who:** Sam Hwang, M.D., Ph.D., National Cancer Institute  
**Looking at:** chemokines and receptors that facilitate metastasis, including causing tumor cells to adhere to the endothelium and exit from blood vessels.  
**Findings so far:** Pretreatment with CXCR4-blocker before chemotherapy leaves receptors vulnerable to destruction.