Mechanisms of Metastasis: Theories Focus on Microenvironment, Host Factors, Genes

By Rabiya S. Tuma

In 1889, Stephen Paget, an English surgeon, hypothesized that as plant seeds need congenial soil to grow, cancer cells can proliferate only when they reside in a hospitable organ. Although few cancer researchers would have contested the idea that surrounding tissue influences tumor growth in recent decades, they have just recently begun to tackle the mechanisms by which context drives metastasis.

“Cancer research, in the 30 years from 1970 to 2000, focused almost exclusively on cell-autonomous phenomena—what’s happening inside the cancer cell,” said Robert Weinberg, Ph.D., a founding member of the Whitehead Institute for Biomedical Research and professor of biology at the Massachusetts Institute of Technology in Cambridge. “And now we begin to understand that those are only part of the equation.

“That is a major paradigm shift, not only for the field of metastasis research, but for cancer research,” he said.

Evidence for the new interest in metastasis research can be found in many arenas. A recent meeting in Vancouver, British Columbia, cosponsored by the Metastasis Research Society and the American Association for Cancer Research, was the largest meeting on the subject ever held in North America.

Tumor-Host Signaling

One area of intense interest is the host and tumor microenvironment. Weinberg’s group, for example, recently published evidence that, in mice, a tumor growing in one site can influence the growth rate of a tumor at a distant site. To investigate the systemic influence that one tumor can have on another, the researchers worked with two different human breast cancer cell lines. One of the cell lines, which they referred to as an instigator line, results in rapidly growing xenograft tumors when injected under the skin of mice. The other, which they referred to as a responder line, results in slow-growing, or indolent, xenograft tumors.

However, when the researchers injected responder cells into one flank of an animal and instigator cells into the opposite flank, the responder cells grew rapidly and accumulated bone marrow–derived stromal cells, as did the instigator tumors. Further experiments demonstrated that the instigator cells secreted human osteopontin, which activated the bone marrow and caused the release of stromal precursor cells into the bloodstream. Once these bone marrow–derived cells were in the blood, the responder tumors could grab them and incorporate them into the tumor stroma. Instigator cells that could not produce osteopontin did not stimulate responder cell growth.

If researchers can extrapolate these findings to the situation of a primary tumor and a distant metastatic lesion, then the work will have two far-reaching findings, Weinberg said. “It seems, from these experiments, that at least some primary tumors can cause growth of metastases by influencing the behavior of bone marrow,” he said. “And we need to begin to think of metastasis as a systemic disease long before a metastatic tumor becomes visible.”

Previous data from other groups suggest that Weinberg’s group may be onto something. Scientists already knew that circulating osteopontin is elevated in patients with metastatic disease and that many tumor cell types secrete the hormone. Weinberg’s work suggests what the physiological effect of the hormone might be. Corroborating the MIT data, other groups have also...
reported evidence that bone marrow–derived stromal cells are incorporated into growing tumors and that their presence increases the invasiveness of the tumor.

Dan Welch, Ph.D., who chaired the August meeting in Vancouver, cautions that the Weinberg results, though exciting, are still early. The findings need to be tested in more cancer cell lines and cell types to learn whether osteopontin is a commonly used signal, or even whether the instigator–responder phenomenon can be extrapolated at all beyond the cell lines tested, said Welch, a professor of pathology at the University of Alabama in Birmingham.

**Host Factors**

One of the big shifts in metastasis research, experts agree, is a growing understanding that host factors, including germline genetics, can influence the likelihood that metastatic disease arises in the presence of a primary tumor. Using a combination of mouse models and human epidemiology studies, Kent Hunter, Ph.D., head of the metastasis susceptibility section and senior investigator at the National Cancer Institute, and colleagues have shown that genetic polymorphisms affect whether an animal—and perhaps patients—will develop a metastasis.

Transgenic mice of the FVB/NJ strain that express the polyoma T oncogene (PyMT) readily develop metastatic mammary tumors. However, when Hunter’s team crossed these animals to other inbred strains, the frequency of metastatic lesions in the offspring varied substantially. Because the primary oncogene remained the same in the offspring, the researchers hypothesized that something in the animals’ genetic background influenced the rate of metastasis formation. The team has since identified 8 polymorphic genes that contribute to the likelihood that metastatic disease will develop. These include Sipa1 polymorphisms, which have been associated with metastatic disease and survival in breast cancer patients (J Natl Cancer Inst 2008;100:768–9).

Thus, although the field has devoted much of its work in the last several decades to looking inside tumor cells, Hunter is convinced that those cell-autonomous traits are only part of the picture.

“We are seeing the same change in opinion in the field of metastasis that we saw with the tumor cell studies about 10 years ago... It is the microenvironment, the organism that the tumor cells are in, the basal state of that organism, the stresses it undergoes—all those things are relevant to metastasis.”

Hunter acknowledged that not everyone in the metastasis field would take such a broad view of the situation, but he thinks that the field is expanding its horizons. “The field is definitely changing,” he said. “It is happening in a lot of ways simply because the technology is available to do it. Just like tumor biology has changed because we can do genomewide association studies, we are now turning around and applying the genome projects to metastasis.” New high-throughput approaches are “forcing us to reevaluate how we are studying metastasis.”

**Metastasis Suppressor Genes**

Not all the newsworthy discoveries are coming from outside the tumor cell, however. Welch and others have identified more than 20 genes in tumor cells that can suppress metastasis. Some of these genes are expressed at a reduced level in metastatic tumors in mouse models and in samples from aggressive human disease. If the investigators experimentally increase the expression of one of these genes to its normal level in cancer cells, the rate of metastases decreases after injection into animals, though the cells still form primary tumors.

The metastasis suppressor genes categorized so far do not neatly fall into one molecular category but rather span a variety of cellular functions, including cell adhesion, regulation of transcription and molecular signaling, chromatin remodeling, and cytoskeletal regulation. One theme that does appear to run through the list, according to Welch, is that the gene products are well positioned to amplify molecular signals.

In his own recent work, Welch has identified several microRNAs that are regulated by the metastasis suppressor gene BRMS1, which is a chromatin remodeling gene. BRMS1 increases microRNAs that suppress metastasis and decreases those that promote disease spread.

Exactly how the microRNAs affect the likelihood of metastasis is still unclear. When BRMS1 expression is restored to wild-type levels in breast cancer cells, the cells can enter the bloodstream and even invade a distant tissue, but once there, they sit dormant. “Our working hypothesis is that somehow they are interfering with signals the cells are receiving from the stroma,” he said, a hypothesis consistent with the idea that tumor cells can stimulate the release of bone marrow–derived stromal cells.

Other approaches to metastasis research abound. Preventing brain metastasis by using small-molecule tyrosine kinase inhibitors is one emerging area of investigation, for example. (J Natl Cancer Inst 2008;100:1054–7). Other researchers are pursuing a theory that centers on
epithelial-to-mesenchymal transition, the process by which tumor epithelial cells transform into cells similar to embryonic mesenchymal cells, the highly mobile cells that give rise to bone, muscle, and other tissues in the developing embryo (J Natl Cancer Inst 2008;100:232–9). And some investigators are intrigued by the cell fusion theory of metastasis, which holds that macrophages fuse with cancer cells to trigger metastasis (J Natl Cancer Inst 2008;100:1279–81).

**Technology Advances**

Welch echoes Hunter’s point that part of the reason that the field is moving forward is advancing technology. “Metastasis involves multiple steps, and the studies up to this point have focused largely on reductionist science,” he said. “One of the major issues is that when you isolate the metastatic cells from the cells that they interact with, they don’t behave the same. It is not exactly rocket science to think that way, but we haven’t had the tools to think that way.”

To get a better idea of what is happening, scientists are developing systems that allow them to reconstitute the tumor cell environment. For example, although researchers and clinicians know that breast cancer cells have a preference for forming metastases in bone, teasing apart that interaction has been difficult. Now molecular biologists and materials scientists at Pennsylvania State University in University Park are using a newly developed bone culture system to explore the interactions between the cancer cells and bone. They reported earlier this fall in *Clinical and Experimental Metastasis* that breast cancer cells not only increase bone resorption, as previously known, but also disrupts bone formation. That observation, they suggest, may be why bisphosphonates slow metastatic tumor growth in breast cancer patients but do not promote bone healing.

The field has made progress, Welch said—just not as much as some other areas. Acknowledging that truth is important for patients, physicians, and future researchers. “We have to inspire people to get into the field no matter how tough it is, and we need to motivate people from other fields to come at it with different eyes,” he said. “I think there was a sense leaving the meeting in Vancouver that we have turned a corner.”

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