ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

Section Editor: Clifford A. Hudis, MD

Breast Cancer In Focus

Tumor Self-Seeding in Breast Cancer

Larry Norton, MD
Deputy Physician-in-Chief, Breast Cancer Programs
Medical Director, Evelyn H. Lauder Breast Center
Norna S. Sarofim Chair in Clinical Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

H&O Can you explain the concept of tumor self-seeding and the mechanism of the process?

LN My colleague Dr. Joan Massagué has been studying metastasis using both mouse and human cancers in animal systems. He discovered that the same genes that cause metastasis to the lung cause faster growth in the primary site, the mammary fat pad. The obvious reason could have been that the mitotic rates were increased, but it turns out that this is not the case. The faster growing (and metastatic) tumors had the same fraction of dividing cells as the slower growing, nonmetastatic tumors. Furthermore, the genes involved in metastasis plus faster growth are not ones that are primarily associated with increased cell division or decreased programmed cell death (apoptosis). So looking over these data we needed to determine a mechanism whereby metastasis and growth are linked, but that linkage is independent of the mitosis-apoptosis axis. What we came up with was the idea that mobile cancer cells, in addition to localizing in and colonizing metastatic sites, could also return to the primary site from where they originated. How this solves the enigma can be explained by a simple mathematical formula: if there are 10 things growing at rate X each, they are growing 10 times faster than 1 thing growing at rate X. Yet, if you measure the rates, they are X in both cases. Weeds, for example, seem to grow quickly to dominate a garden. But this is not because each weed plant grows quickly; it is because there are so many of them: they seed new weed plants very efficiently. An oak tree, in contrast, seems to grow relatively slowly when it is small because it is just one plant. Were a cancer like a weed bed, with cells breaking free of the main mass and—by direct extension and/or by circulating and then returning—starting many "new" masses in the main location, this would explain the association of metastasis and growth. The normal organ, in contrast, is mathematically more like the oak tree.

Dr. Massagué and I published this concept as a hypothesis in 2006. Following 3 years of meticulous laboratory work, Dr. Mi-Young Kim from Dr. Massagué's laboratory was the first author of a paper offering definitive proof—using diverse laboratory models and several kinds of cancers—of the validity of the idea. That paper and ongoing work concerns the biologic basis for the phenomenon.

H&O How does self-seeding enhance the growth of tumors?

LN One can think of these seeds as tumor-initiating cells or cancer stem cells, although those terms have different meanings in different contexts. They also might be the cells others have labelled as having undergone epithelial-mesenchymal transformation, which is, in fact, all about cell mobility. We have shown that when the seed cells return to the tumor they attract leukocytes that secrete growth-promoting chemicals and also white blood cells

that differentiate into endothelial cells (ie, blood vessels). These phenomena—growth-enhancing and angiogenic leukocyte recruitment—promote the growth not only of the seed cells but also of other cancer cells in their vicinity.

H&O What is the significance of tumor self-seeding in regard to breast cancer?

LN Self-seeding could explain a number of mysteries in clinical breast cancer medicine. For example, we resect a cancer to clear margins (no demonstrable cancer), yet if we do not irradiate the breast, the cancer could not only grow back there, but there is a greater chance that the patient could develop metastatic disease. The concept here is that seed cells that are in the circulation, or recruited from distant metastatic sites, are returning to self-seed the breast and, hence, if left untreated, metastasize to other distant sites. Therapeutic irradiating interrupts that process. Self-seeding also could explain why the cardinal characteristics of cancer—anaplasia, hyperplasia, angiogenesis, and mass development—are always linked: they are all manifestations of growth-by-seeding, like a weed bed. In the 19th century, before mastectomies became common, and in many parts of the contemporary world where breast cancers are sometimes ignored, huge tumors could develop without patients showing distant metastases. In these cases, it is possible that the cancers are metastatic, but all the seeds are coming back to the primary site rather than to distant sites. These are just a few examples.

H&O What is the current focus of research looking at self-seeding?

LN Most of the drugs that we use to treat breast cancer are very effective at disrupting the mitosis of the cancer cell. Much research in that regard needs to be done. We are now also starting to look for drugs that interfere with the ability of cancer cells to self-seed. We have identified abnormal molecules in the cancer cell that are important in the self-seeding process, and we are seeking to develop interventions that can disturb the function of those molecules.

H&O What is some ongoing research in genes as targets?

LN There is one very important gene family that may be a therapeutic target center on CXCL1, which is critical for attracting leukocytes to the tumor. There is also interest in the matrix metalloproteinase (MMP) inhibitors since MMPs seem to play a major role in the metastatic constellation. The molecules that we found to be most important in attracting seeds back to the tumor mass are the inflammatory tumor-derived cytokines interleukin (IL)6 and IL8. There are also the chemicals that are released in inflammation, which might just possibly explain the association between inflammation and cancer: more IL6/8 equals more seeds, which equals more tumor-infiltrating leukocytes, which equals more growth stimulation. One of the key observations is that knocking down just 1 molecular axis has some effect in inhibiting tumor growth, but knocking down 2 or especially 3 pathways is dramatically more effective. This means that combinations of targeted therapeutics would probably be essential to get optimal clinical results.

H&O What are the future avenues of research in this area?

LN In addition to the development of anti-seeding drugs, we are looking at the possibility of making the tumor a poisoned sponge. As I described above, irradiation might already be doing that to some extent: allowing seeds to return to the breast, where—because of the irradiation—they cannot colonize, and also cannot travel anywhere else to cause trouble. We are looking at other ways to attract and kill circulating seeds, including immunologic approaches that seem—on the basis of animal experiments—to be quite promising.

One of the things about this research direction that is most appealing and encouraging is that it absolutely depends upon experts in many areas—biology, genetics, biochemistry, and clinical oncology—to work together effectively. The productivity of the team is more than the sum of the isolated capacities of its individual members. The potential impact of metastasis research on clinical medicine is so profound that I am delighted to be part of this effort, working so closely with accomplished and creative investigators.

Suggested Readings

Kim MY, Oskarsson T, Acharyya S, et al. Tumor self-seeding by circulating cancer cells. *Cell*. 2009;139:1315-1326.

Norton L, Massagué J. Is cancer a disease of self-seeding? *Nat Med*. 2006;12:875-878.