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AntiCancer Inc. Scientists Identify a Key Governing Step in the Metastasis of Cancer

By Gail Dutton

A team of researchers at **AntiCancer, Inc.** (San Diego), working with a novel animal model, says it has identified one of the fundamental clues to the biological basis of tumor cell metastasis. According to Andrew Perry, Ph.D., president of the consumer products group at AntiCancer, the metastasis of tumor cells is controlled by the cells' ability to colonize liver cells.

"If they won't colonize liver cells, they won't colonize other areas of the body," he says.

What is perhaps more interesting, however, is that non-metastatic cells won't colonize the liver when directly seeded on the liver as individual cells or implanted as tissue blocks, a finding which supports long-standing tumor cascade theories advanced by many researchers. The AntiCancer discovery might be valid for other forms of cancer as well, but, "We have only published data on colon cancer," says Dr. Perry. "We believe that this is a definite mechanism for metastasis."

Until now, the grand question has been to determine the mechanism tumor cells use to metastasize, because the same type of tumor would metastasize in some patients but not in others. "We've shown that the colon tumor cells must be able to colonize the liver if they are going to be metastatic," notes Dr. Perry, so if they can't colonize the liver they won't be metastatic. "Tumor cells can't just be released or be invasive or even attach to another organ in order for them to metastasize. A metastatic cell has to be able to colonize the target organ.



AntiCancer, Inc. scientists discovered that the metastasis of tumor cells is controlled by the cells' ability to colonize liver cells. The researchers believe that with further research it may eventually become possible to prevent cells from metastasizing throughout the body.

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New Model

AntiCancer's research group, led by Tsong-Hong Kuo, M.D., and a team of scientists at Keio University in Tokyo, the University of California at San Diego and Massachusetts Institute of Technology, found a new way to answer the century-old question of seed and soil metastasis that was proposed more than one century ago by showing an interesting growth differential phenomenon. Their work used a new and powerful animal model that mimics human cancer growth and metastasis to broadly show that the ability of tumor cells to colonize distant organs gov-

erns the metastatic process.

This recently patented "Meta-Mouse" model is the first model in which animal-implanted human tumors parallel the original tumor's characteristic growth and local invasiveness, its drug sensitivity and its rate of metastases to the target tissues in humans, according to Dr. Perry. MetaMouse can model all major tumor types.

The model is produced by implanting human tumors directly into the corresponding organ, so in lung cancer MetaMouse, for example, the human lung tumor is implanted directly into the animal's lung. Once in place, the tumor grows and metastasizes.



(Left) Junction of normal liver and a tissue block from the M tumor Col-2-JCK. Note extensive invasion and colonization of the liver (H/E; X100). (Right) Junction of normal liver and a tissue block from the non-M tumor Co-4 (H/E; X100).

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sizes according to the clinical course of the patient's cancer. All of the major symptoms, including weight loss, are present.

"They have a good model," notes Lance Liotta, M.D., Ph.D., chief of the section of tumor invasion and metastasis, and chief of the laboratory of pathology at the National Cancer Institute (Bethesda, MD). "It's hard to find cell lines that metastasize in nude mice." The downside, he adds, is that the early stages of the disease aren't modeled, thus leaving a gap in the research.

Colonization

For AntiCancer's colon cancer work, eight human tumor strains were grown in nude mice, removed, minced into 4mm diameter tissue blocks weighing 75 milligrams and transplanted into the colons of other nude mice. The models were created by surgical orthotopic implantation (SOI)—implanting the tumors from humans into corresponding organs in mice as blocks of tissue rather than as dispersed cells. Tissue blocks, as opposed to cell suspensions, explains Dr. Perry, have better architecture and so act more like the original tumor after SOI.

The tumors that were implanted in the colon grew, regardless of whether they were metastatic. Of the eight strains grown, only half metastasized, even at 12 weeks after implantation. Both metastatic and non-metastatic cancers showed similar growth rates and both invaded the vessels of the cecal wall within four to seven weeks of implantation. The primary difference between the two groups, however, is that when the tumors were directly seeded or implanted onto the liver, only the metastatic tumors were able to colonize. Cells from non-metastatic tumors had no detectable growth in the liver after direct seeding or implantation.

Implications

As this research is validated further, it may become possible to prevent metastatic cells from colonizing other organs, according to Robert M. Hoffman, Ph.D., president of the company. General comments within the broad community of cancer researchers are that this research is, indeed worthwhile.

"It's not surprising that metastatic tumor cells colonized the liver, but it is interesting that non-metastatic cells don't grow on the liver when injected," says Dr. Liotta. "The biological basis of the finding could be due to growth factors that also attract tumor cells to the liver. It is conceivable that hepatic growth factor (scatter factor) may be the differential agent controlling behavior of metastatic and non-metastatic cells. That could lead to demonstrations that the Met receptor of the hepatic growth factor (which attracts tumor cells to the liver) determines whether liver colonization takes place and so can lead to the development of an antagonist to block the receptor to the Met cells." That, in turn, has implications for therapy development.

One Oregon-based researcher commented that AntiCancer's studies could lead to a better understanding of the molecular genetics of cancer and might offer an opportunity for molecular manipulation by providing a more clear-cut way to investigate the genetic changes of metastatic tumors.

The company's experiments also open the door to the evaluation and development of new drugs that may prevent tumors from colonizing the liver, thus providing one more weapon in an arsenal to fight cancer. "Ultimately, this research could lead to the development of treatments which could reduce cancer to a chronic disease instead of a life threatening one by eliminating metastasis," pre-

dicts Dr. Perry.

The next step in this research is "to investigate other kinds of tumors," he adds. AntiCancer's team has already developed MetaMouse models of looking at stomach cancer, pancreatic cancer, bladder cancer, lung cancer, ovarian cancer, breast and prostate cancer. These animal-implanted human cancers also show patterns of metastasis that closely mimic those of human patients. As the research expands, investigators plan to identify the mechanism that causes metastasis and to begin to understand it and its implications for research and, ultimately, for patients.

"Currently," says Dr. Perry, "we are considering its value for patients. Can this be used to test individual patient's tumors? If they are determined to be either metastatic or non-metastatic our research may help determine the choice of therapy—surgery or chemotherapy or, possibly, the new antimetastatic drugs now in clinical trials, for example."

However, Dr. Liotta comments that even though this might allow physicians to predict the behavior of a patient's tumor, that ability is unlikely to make much difference in the ultimate outcome if the tumor is metastatic. Additionally, he notes that the FDA is reluctant to approve any new prognosis indicators unless they have a significant effect upon treatment outcome. Therefore, for the moment at least, this research appears to be of greater value in shedding further light on the biological mechanisms underlying cancer development and progression and for the identification of new therapeutic targets and antitumor and antimetastatic drugs than in its use as a prognostic indicator.

Details of AntiCancer's colon-cancer liver metastasis studies appeared in the December 1995 issue of the *Proceedings of the National Academy of Sciences*. ■