New Clue to Prostate Cancer Spread

Discovery of a gene that appears to suppress prostate cancer metastasis may aid both the understanding and the treatment of this dangerous cancer

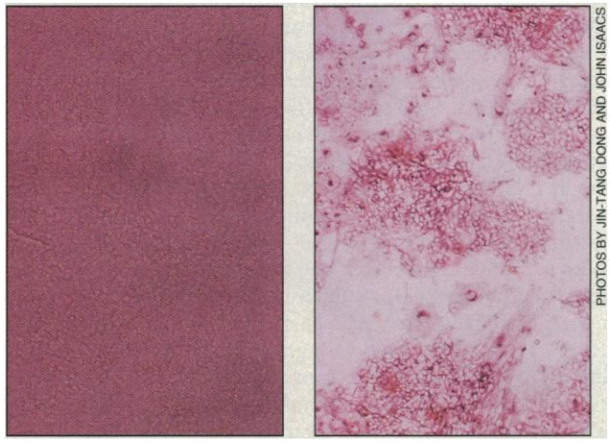
Breast cancer gets massive publicity these days, thanks partly to the political muscle of the women's health movement. But prostate cancer, which gets far less attention, may be just as big a public health problem. The American Cancer Society estimates that 244,000 men will be diagnosed with prostate cancer in 1995, compared to 182,000 women with breast cancer. And while many of the small, localized prostate cancers detected today appear not to be life-threatening, those that spread to other sites in the body are almost invariably fatal: Such metastatic prostate cancers are expected to cause more than 40,000 deaths this year, only 6000 fewer than the number of expected breast cancer deaths. Now cancer researchers may be getting a handle on the gene changes that make some prostate cancers so dangerous, information that may help physicians make better decisions about how to treat men with early forms of the disease.

On page 884, a team led by Carl Barrett of the National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, North Carolina, and John Isaacs of Johns Hopkins University School of Medicine report their identification of a gene that suppresses the ability of prostate cancer cells to metastasize in animals. Their results suggest that decreased activity of this gene, which encodes a member of a family of membrane proteins previously identified by other researchers on lymphocytes and other cells, may be one of the factors that makes some prostate cancers lethal by allowing them to seed new tumors.

Researchers who study this process of metastasis are intrigued by the discovery because it may help them understand the molecular changes that bring about this most dangerous phase of cancer development. "I think it is potentially very important," says Patricia Steeg, whose team at the National Cancer Institute discovered a gene called *nm23* that may suppress metastasis by melanoma, breast, and other cancers. "Clearly prostate cancer patients succumb to metastatic disease, and we need to know how the metastatic cascade in prostate cancer is regulated." Such information may eventually help, she notes, in the design of new drugs or even gene therapies that block metastasis.

But whether or not these therapeutic possibilities pan out, the new metastasis-suppressing gene, which the researchers have named *kang ai 1* (*KAI1*) from the Chinese for anti-cancer, may have a more immediate clinical application: helping physicians decide which men with apparently localized tumors need surgery and other aggressive treatments to try to prevent the growth of life-threatening metastatic tumors.

The difficulty of determining the best course of treatment for these individuals has long plagued clinicians, says Isaacs, a prostate cancer expert. In fact, it was one of the things that motivated his group to try and locate the genes that bring about prostate cancer metastasis. "My lab is very pragmatic," he says. "The genes are interesting, but we want to use them for something." He hopes, for example, that it might ultimately be possible to pick out the dangerous prostate tumors by looking for those with decreased expression of the *KAI1* gene and other cell changes indicative of metastasis.



PHOTOS BY JIN-TANG DONG AND JOHN ISAACS

A shade of difference. Prostate cancer cells that express the KAI1 protein *(shown by red stain)* are much less metastatic than control cells that lack the protein *(left)*.

Although the Isaacs team's search began in rat cells, Isaacs says he decided to take a different tack after talking with cancer gene researcher Barrett at a meeting. Barrett pointed out that even if they found rat genes that suppress prostate cancer metastasis, it might be difficult to find the equivalent human genes because the rat genome hasn't been mapped well enough to know which parts correspond to which elements of the human genome. He suggested that Isaacs should instead use a technique being applied in Barrett's lab that allows single human chromosomes to be transferred into cells. That method, argued Barrett, should make it possible to identify any human chromosome carrying metastasis-suppressor genes .

In 1990, Tomohiko Ichikawa, then a postdoc in the Isaacs lab, went to NIEHS to learn the technique, a trip that paid off when he found that human chromosome 11 seemed to fit the bill. When he introduced the chromosome into highly metastatic rat prostate cancer cells and then injected the cells into nude mice, he found that they produced far fewer lung metastases, even though they were just as efficient as controls at forming tumors at the injection sites. The team subsequently narrowed down the location of the gene needed for this metastasis suppression to region p11.2-13 of chromosome 11.

Now Jin-Tang Dong, a postdoc in the Barrett lab, has cloned the gene itself, and several lines of evidence indicate that he found the right one. For example, gene transfer experiments showed that *KAI1* was just as effective at reducing the metastatic properties of the rat prostate cancer cells as the intact chromosome 11. Whereas prostate cancer cells given only a control DNA and injected into nude mice produced 58 metastases per animal, cells carrying the transferred *KAI1* gene produced a mere six or seven. And even these may have been able to grow because they managed to inactivate the gene, as the researchers could not detect *KAI1* expression in most of the 28 metastatic tumors. There is preliminary evidence that *KAI1* inactivation may also contribute to metastasis of human prostate cancer cells because its expression is lower in cell lines derived from metastatic human tumors than in normal prostate tissue. "What has been presented already is a substantial body of evidence" that *KAI1* is a true metastasis suppressor, Steeg says.

Exactly how it might interfere with the spread of prostate cancers is unclear. But there are clues. One clue comes from the *KAI1* DNA sequence, which reveals that the gene's protein is identical to a protein previously found by other researchers on certain immune cells. This protein belongs to the

"transmembrane 4" (TM4) family, which is so called because all its members—now numbering about 15—have structures suggesting that they weave through the outer cell membrane four times. Because the TM4 family is only a few years old, researchers are just beginning to learn what its members do. "There is no definitive biological understanding of what any of this extensive family of proteins is doing," says cell biologist Martin Hemler of Harvard Medical School, whose own work recently intersected with the TM4 family.

But circumstantial evidence suggests that the TM4 group might be involved in maintaining normal cell adhesion and growth control. That's intriguing, because metastasis requires that cells must first break away from the primary tumor, travel through the bloodstream, and then invade distant organs, where they grow into new tumors. Alterations in TM4 genes might therefore help a tumor cell achieve one or more steps in the metastatic process. Indeed, researchers have evidence suggesting that at least two other proteins in this family have metastasis suppression capabilities in other tumors, including breast and lung cancer and the dangerous skin cancer melanoma.

Consistent with what is known about the other family members, Barrett, Isaacs, and their colleagues have found in a lab assay that prostate cancer cells lacking the *KAI1* protein migrate better than cells with ample amounts of the protein, indicating that the deficient cells are more invasive, a change that may contribute to their increased metastatic ability. "The gene affects the invasive ability of cells," says Isaacs. "It's a relevant phenotype."

But *KAI1*'s ability to stop metastasis may be limited to prostate cancers. Robert Kerbel, a metastasis researcher at Sunnybrook Health Science Center in Toronto, points to the Barrett-Isaacs group's finding that chromosome 11 had no effect on metastasis by rat mammary carcinoma cells. And if the gene's action is specific, that would be intriguing from a biological point of view, Kerbel says, because "there are few, if any, precedents for a tumor-specific suppressor gene." It might mean that cancers take different routes to the metastatic state and that there are other specific metastasis suppressors in the genome. Kerbel adds, however, that more work will be needed to determine whether *KAI1*'s effects are limited to prostate cancer. Barrett and Isaacs agree, and Barrett says the group's plans include experiments in which *KAI1* will be introduced into other kinds of cancer cells to see what effect it has on them.

As that fundamental research proceeds, they are also pushing ahead on the "pragmatic" front that Isaacs says his lab values. They are making antibodies to the *KAI1* protein, which will be employed to measure how much of that protein is in prostate cancers removed from patients. The team can then determine whether patients with decreased levels do worse than those with higher levels, as their theory predicts.

Experience with other cancers suggests, however, that accurate detection of dangerous tumors may require more than one such marker, and there are several other candidates for prostate cancer—including one from another member of the Isaacs family. William Isaacs, John's brother, who is also at Johns Hopkins, and Jack Schalken of Catholic University in Nijmegen, the Netherlands, have evidence indicating that loss of a cell adhesion molecule called cadherin E also correlates with prostate cancer metastasis. In addition, John Isaacs, Barrett, and their colleagues have found that human chromosomes 8, 10, 16, and 17 suppress metastasis by the rat prostatic cancer cells. The team is now trying to identify the genes responsible.

If *KAI1* or these other genes do prove to be markers for metastatic tumors, it "would be a fundamental advance," says pathologist Gary Miller of the University of Colorado Health Sciences Center in Denver, as it would help solve a problem that plagues physicians who care for prostate cancer patients. Better diagnostic techniques—including screening for a protein called prostate surface antigen, whose blood concentration goes up in men with prostate cancer—are identifying increasing numbers of men who have very small islands of tumor cells in their prostate glands. There may be as many as 10 million such men over the age of 50 in the United States alone. But many of those small cancers are likely to be harmless. Autopsy studies have shown, for example, that 50% of men between the ages of 70 and 80 who died of other causes had localized prostate tumors without ever having experienced symptoms.

From these and other findings, urologist Peter Scardino of Baylor College of Medicine in Houston has estimated that 80% of men with small tumors don't need any therapy, while half of the remaining 20% need only surgery to remove their tumors. The remaining 10%, however, will already have microscopic metastases at the time of diagnosis and might benefit from hormonal or other adjuvant therapies. The problem is that with current technology it's not possible to sort out those three groups in the clinic.

Miller is intrigued by the idea that the *KAI1* work could help solve that clinical dilemma. But he cautions that the problem of identifying prostate cancers with metastatic potential may not be solved easily, for host characteristics, such as age, immune status, or nutrition, may also influence whether a metastatic tumor takes root. Kerbel also expresses caution. "Nevertheless," he says, "it seems to be some kind of new suppressor gene, and that makes it very interesting."

–Jean Marx

ASTRONOMY

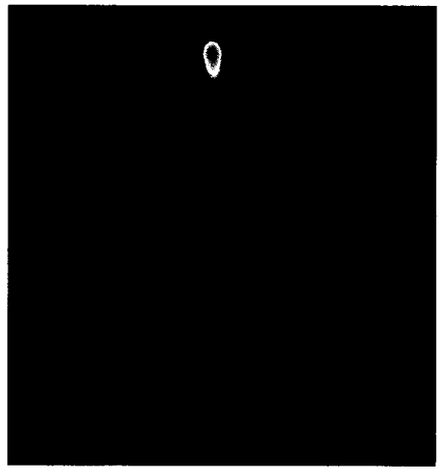
Battle Is Joined Over Gamma Bursts

In 1920, no one knew how the stars shine. No one knew for sure how big our galaxy is, or whether other galaxies existed. These puzzles created deep divisions in the astronomy community, dramatized in April of that year when eminent astronomers Harlow Shapley and Heber Curtis squared off at the National Museum of Natural History to debate some of the most pressing of them.

And while the mysteries that perplex astronomers have changed over the years, the debating tradition has not. In a 75th anniversary celebration* of the Shapley-Curtis debate—held on 22 April in the same auditorium as the 1920 affair—Princeton University's Bohdan Paczyński and Donald Lamb of the University of Chicago took up arms over one of today's knottiest puzzles: How far away are the titanic explosions that about once a day send a burst of gamma rays toward Earth?

Before an audience of 350 astronomers and laypeople, Paczyński and Lamb laid out two radically different answers to that question, answers that entail very different conceptions of what the sources might be. Lamb spoke for the minority of astronomers who think there is strong new evidence that the bursts are coming from our own corner of the

*75th Anniversary Debate: The Distance Scale to Gamma Ray Bursts, 22 April 1995, sponsored by NASA, the Smithsonian Institution, and George Mason University. Principal organizers: Robert Nemiroff and Jerry Bonnell, NASA-Goddard Space Flight Center.



D. FRAIL, N. KASSIM, AND K. WEILER

Blast off. A pulsar (a radio-emitting neutron star) shoots from the wreckage of the supernova explosion in which it was born.