

Fused Genes May Help Explain the Origins of Prostate Cancer

Although gene fusions are well known to drive the development of blood cancers, such as leukemias and lymphomas, only rarely have they been detected in the common solid cancers, such as breast, prostate, colon, and lung cancer. Now researchers have uncovered the first evidence that such fusions play a widespread role in prostate cancer.

The finding comes from Arul Chinnaiyan of the University of Michigan Medical School in Ann Arbor and his colleagues. On page 644, they report that perhaps as many as 80% of prostate tumors carry fusions of a segment of a gene called *TMPRSS2* with either of two genes encoding related proteins, *ERG* and *ETV1*, involved in gene regulation.

Because the two proteins are components of a major cell growth control pathway, the finding may help explain the origins of prostate cancer and provide a new target for therapeutic drugs. "If it holds up, it's the most common somatic [genetic] change in prostate cancer—and it's a fascinating one," says William Isaacs, a prostate cancer expert at Johns Hopkins University School of Medicine in Baltimore, Maryland. "It will invigorate the field in terms of looking for these kinds of fusions in other common cancers."

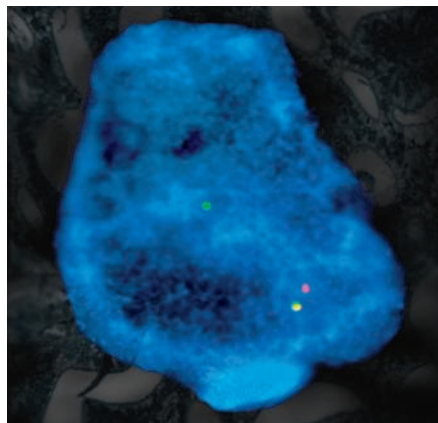
Although cancer researchers suspected that gene fusions might be lurking in solid cancers, the abnormalities eluded detection partly because the tumors display so many chromosomal abnormalities that it's hard to sort out which are significant. To get around this, Chinnaiyan and his colleagues took a bioinformatics approach to look for "outlier" genes: those that show very high expression in a set of cancers. They first surveyed the Oncomine database, a set of gene-expression data from DNA microarray experiments that was compiled by the Michigan team. "We found that we were picking up known gene rearrangements," Chinnaiyan says. "That told us we were on the right track."

Among the top 10 outlier genes identified were *ERG* and *ETV1*—both overexpressed in prostate cancers. *ERG* was already known to be involved in oncogenic fusions, especially in Ewing sarcoma, a relatively rare bone cancer. And earlier this year, a team led by Gyorgy Petrovics and Shiv Srivastava of the Uniformed Services University in Rockville, Maryland, reported that the gene is overexpressed in prostate cancer. Now, the Chinnaiyan team's work provides a possible explanation for why *ERG* is overactive.

The researchers found that in prostate cancers, each gene was frequently fused to the beginning segments of *TMPRSS2*, which

encodes a protein-cutting enzyme that is turned on by the male hormone androgen. The gene fusions occurred both in cultured lines of prostate cells and also in about 80% of the 29 primary prostate cancers examined. They were present, however, only in those cells with high expression of *ERG* or *ETV1*, an indication that the fusions might underlie the excess activity of the genes. The overactivity may be due to the fact that the fused *TMPRSS2* sequences carry so-called androgen response elements needed for androgen stimulation.

Indeed, androgen treatment greatly enhances *ERG* production in cell lines carrying the fused gene. The finding is intriguing



Getting together. In this prostate cancer cell, the *ETV1* gene (red) and the *TMPRSS2* gene (green) are joined (yellow) on one chromosome.

because many prostate cancers are androgen-dependent early on and thus can be treated with drugs that block action of the hormone. Ultimately, though, this dependence is lost and the cancers grow again. The fused *ERG* and *ETV1* genes would be one place to look for the changes leading to that outcome, Isaacs says.

Whether identifying these gene fusions will lead to better therapies for prostate cancer remains to be seen. There is precedent, as the leukemia drug Gleevec blocks the product of a fused kinase gene. But *ERG* and *ETV1*, which are transcription factors that regulate gene expression, present tougher targets.

Also unknown is whether similar gene fusions, also called translocations, occur in other common solid cancers. Janet Rowley of the University of Chicago, who pioneered the early translocation work, is eager to find out. "This approach cries out for application to all large [gene] expression databases as a remarkable tool for discovery of critical genes and, potentially, new common translocations," she says.

—JEAN MARX

ITER Head Named

The first director-general of the \$11 billion International Thermonuclear Experimental Reactor (ITER) is likely to be Kaname Ikeda. A University of Tokyo engineering graduate, Ikeda worked his way up through the ranks at the former Science and Technology Agency before entering Japan's diplomatic corps; he is currently ambassador to Croatia. Barring objections from other ITER partners, Ikeda's appointment will likely be formally announced at an ITER meeting in Vienna in December. European negotiators agreed after an 18-month standoff over the reactor's site to support Japan's director-general nominee; Japan in turn agreed to back the European Union's candidate site of Cadarache, France, where construction could begin by 2007.

—DENNIS NORMILE

Prize for Cheap Sequencing

The first team to demonstrate a genome sequencing method costing \$1000 could win a prize under consideration by the X Prize Foundation in Santa Monica, California. Announced last week at a Hilton Head, South Carolina, meeting and expected to be in the millions of dollars, the award would supplant a \$500,000 pledge by the J. Craig Venter Science Foundation in 2003. The X Prize Foundation, which has previously funded space-flight prizes, will decide next week about the new prize's future. The rules will likely demand that a contestant completely sequence 100 human genomes by the end of the decade—or sooner.

—ELIZABETH PENNISI

Stem Cell Law Decelerated

Frustrated activists are looking toward next year for a Senate vote to relax restrictions on stem cell research. In July, Senate Majority Leader Bill Frist (R-TN) promised a prompt vote on S. 471, a measure passed by the House in May that would allow federally funded researchers to work with human embryonic stem cell lines now restricted by the White House. Lobbyists say the measure can easily pass the Senate, but hurricanes and Supreme Court nominees have blown stem cells off the calendar. Co-sponsor Arlen Specter (R-PA) said last week that Frist has now committed to bringing it to the floor before next Easter. The House bill passed 238–194 in May; President George W. Bush has threatened a veto.

—CONSTANCE HOLDEN