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 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

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