

JANUARY 11, 2009

New Technique Lets Researchers Find Cancer-Promoting Gene Fusions

Researchers have created an efficient way to detect genes that have been inappropriately fused together, a type of genetic abnormality that spurs the growth of blood and prostate cancers. The scientists also showed that they could use this technology to identify previously unrecognized gene fusions lurking in tumor cells.

Howard Hughes Medical Institute investigator Arul M. Chinnaiyan and a team of colleagues at the University of Michigan Medical School describe the new technique in an advance online article published in *Nature* on January 11, 2009.

According to current thinking, leukemia, lymphoma, and other blood cancers are caused when chromosomes inappropriately swap pieces of genetic material in a process called translocation. In blood cancers, the reshuffling of broken chromosome segments can lead to a forced marriage between a promoter (a gene control element) and a cell growth gene, creating fusion genes that can spur rapid and uncontrolled cell division. The most well-known fusion event is between two genes known as *Bcr* and *Abl*, which results in a product known as the Philadelphia chromosome. The Philadelphia chromosome triggers the runaway growth of white blood cells characteristic of chronic myelogenous leukemia (CML).

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- Arul M. Chinnaiyan

In contrast to these blood cancers, most solid tumors were thought to be caused by mutations that affect one or more growth-regulating genes in the cell, making it more difficult to design drugs to treat them. In 2005, however, Chinnaiyan and his colleagues showed that fusion genes can also spur the development of a solid tumor: prostate cancer.

“We identified gene fusions in prostate cancer at a very high prevalence - 70 percent or higher,” he says. “That told us that these fusions are likely present in many common solid tumors, but we didn't have a good way to identify them.”

Chinnaiyan and his colleagues have been working on new ways to identify gene fusions in solid tumors, and their *Nature* article describes their success in designing a new approach. The strategy is based on combining two different methods to sequence the messenger RNA inside a cell. Messenger RNA is a copy of the information encoded by that cell's active genes. One sequencing technology produces long sequences that point toward locations where DNA segments may have been inappropriately joined. A second sequencing technology generates shorter but more numerous sequences to confirm and pinpoint the problem. “If you use either of the techniques by themselves, you end up generating too many false positives,” Chinnaiyan says. “But if you combine them, you can home in on the real fusions in the sample.”

Chinnaiyan and his coworkers did a “dry run” of their new technique -- using it to see if they could detect the *Bcr-Abl* fusion gene in leukemia cells. “If it hadn't been discovered by other people, we could have discovered it using this technology.” They also used the technique to identify a common gene fusion and several less common fusions in prostate cancer cells. “It's a proof of concept,” he says. “This is priming us and the research community at large to look for gene fusions in cancer in general.”

The new technique may improve both the early detection and treatment of cancer, Chinnaiyan says. He and his colleagues have identified gene fusions only in cancerous cells, suggesting that fusion genes themselves act as a signpost for the development of cancer.

Already, Chinnaiyan and his colleagues are using gene fusions in new tests for prostate cancer. “We're trying to detect these fusions in the urine of men so we can predict who has prostate cancer and who has the more aggressive forms of prostate cancer,” he says. The current test, which looks for elevated levels of a marker called prostate-specific antigen (PSA), “has a lot of drawbacks, in that only 20 percent of patients who have an elevated PSA actually have prostate cancer. We would like to develop better diagnostics.”

Identifying the fusion responsible for a cancer also can suggest new ways of treating that cancer. For example, if a particular fusion causes a growth-related gene to be overactive, new drugs could shut down the gene or block its products. “Once you have identified a fusion for a particular cancer type, you want to figure out ways to therapeutically target it,” Chinnaiyan says.

Chinnaiyan, who trained as both a physician and a researcher, is the founding director of the Center for Translational Pathology at the University of

Michigan, which has the goal of translating basic research results into real world applications. The center brings together people with different backgrounds to work on research-based treatments for cancer and other diseases. “One type of physician or one type of scientist can't make that happen in isolation,” he says. “We need expertise coming together to translate these findings into the clinic.”