MedicalXpress

Scientists develop method to determine order of mutations that lead to cancer

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Zeroing in on the early cell mutations that enable a cancer to grow is one of the best ways to find a personalized therapy to stop it. Scientists were able to use a statistical approach for the first time to map out the order in which these abnormalities form to analyze the pattern of DNA changes in advanced skin and ovarian tumors.

The study's findings, which are published in the July edition of Cancer *Discovery*, are the result of a collaboration of scientists at the Oregon Health & Science University Knight Cancer Institute; the Lawrence Berkeley National Laboratory, the University of California, San Francisco; and the Samsung Advanced Institute of Technology.

The researchers focused on assessing mutations involving TP53, a gene that normally prevents cells from becoming cancerous. By examining how additional copies of the mutant gene accumulated, they found that changes in TP53 occurred earlier in the disease's progression than previously believed.

Cancers are the result of multiple mutations, but the ones that happen first set the stage for additional abnormalities.

"We anticipate that this information will enhance our ability to detect cancer early when it is more likely to respond well to treatment," said Joe Gray, Ph.D., associate director for translational research for the OHSU Knight Cancer Institute.

Early mutations are also important because they are found in every cell of the cancer. "By understanding what happens early in a tumor's growth, you can develop therapies that will target all cancer cells," said Paul Spellman, Ph.D., of the Lawrence Berkeley National Laboratory and one of the lead scientists on the study. Spellman will join the OHSU Knight Cancer Institute in July.

Getting information about the order in which aberrations occur previously was difficult because it required the ability to analyze tumors as they developed. But, many cancers aren't detected until they've progressed beyond the initial growth phase. The researchers got around this problem by developing a novel statistical strategy. They integrated measurements of mutations with measurements of structural variations in a genome, which result in the cell having abnormal numbers of copies of one or more sections of DNA. "Now we have an ordering tool that should be broadly useful," Gray said.

So far, the researchers have investigated only a few types of cancer. Going forward, the analysis could be applied to all cancers. One near-term goal, Gray said, is to identify early mutations for which there are therapies already available.

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