New fusion gene plays role in some stomach cancers

April 6 2011

A newly discovered hybrid gene appears to play a direct role in some stomach cancers, according to an international team of scientists led by researchers at Duke-NUS Graduate Medical School Singapore.

The hybrid gene is a fusion of two separate genes, and is one of the first described in gastric cancer, which is the most lethal malignancy worldwide after lung cancer. The disease kills an estimated 740,000 people a year, including nearly 11,000 annually in the United States.

The gene discovery may one day give doctors a more effective way to use current therapies, plus help researchers develop new drugs and diagnostic tools for gastric cancer.

"This is an extremely exciting area, as it opens up a potential role for fusion genes in solid cancer diagnostics and treatment, similar to the fundamental role they have played in the blood cancers," said Dr. Patrick Tan, associate professor in the Cancer and Stem Cell Biology Program at the Duke-NUS Graduate Medical School Singapore. Tan was principal investigator of the study published in the April 6, 2011, issue of the journal Science Translational Medicine.

Tan said the research team -- which also included scientists from the National University of Singapore, National Cancer Centre of Singapore, the Genome Institute of Singapore, Yonsei University College of Medicine in Seoul, South Korea, and Howard University -- used a novel genomic approach to isolate the fusion gene.

The technology is called genomic breakpoint analysis (GBA), which has been used to identify fusion genes in leukemia, but has had less success in pinpointing them in complex solid tumors.

By using the technology to home in on abnormal genes in 133 stomach cancer tumors and cell lines, the Singapore-based research group found evidence of a single genetic error that was common to four of the cancer samples.

Finding the error led the scientists to the CD44-SLC1A2 fusion gene, which resulted when two nearby genes blended into one. The SLC1A2 gene is associated with the metabolism of the amino acid glutamate, which can work like a fertilizer encouraging tumor growth and survival, while the CD44 gene serves as a sort of "on" switch.

Melded into one, the CD44-SLC1A2 hybrid appears to fuel stomach tumors. Tan's team estimates the fusion gene may be at work in up to 2 percent of stomach cancers.

"Using high-throughput genomic technologies such as sequencing and GBA, we are now finding that cancers do express many fusion genes," Tan said. "The current feeling is that while most of these are harmless and 'noise' from genomic instability, there can be cases, such as CD44-SLC1A2, where the fusion gene contributes actively to the cancer."

The finding could lead to improved therapies for this subset of stomach cancers. As part of the study, the researchers used a gene silencing approach to reduce the levels of CD44-SLC1A2 in cancer cell lines. They found that this caused a reduction in the glutamate levels of cancer cells, and made the cells more vulnerable to the effects of cisplatin, a common chemotherapy.

"It does suggest that drugs that inhibit SLC1A2 function could be used to sensitize tumors to chemotherapy," Tan said. "Such glutamate uptake inhibitors are available, and we are working very hard to test this possibility."

Provided by Duke University Medical Center