Genetic differences distinguish stomach cancers, treatment response

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Stomach cancer is actually two distinct disease variations based on its genetic makeup, and each responds differently to chemotherapy, according to an international team of scientists led by researchers at Duke-National University of Singapore Graduate Medical School.

The finding, published in the Aug. 1, 2011, edition of the journal *Gastroenterology*, is the first large-scale genomic analysis of gastric cancer to confirm the two discrete tumor types.

The researchers also found that a certain regimen of chemotherapy is more effective on one tumor type, while a different drug works best on the other, setting the groundwork for a more effective approach to treating gastric cancer patients.

"Our study is the first to show that a proposed molecular classification of gastric cancer can identify genomic subtypes that respond differently to therapies, which is crucial in efforts to customize treatments for patients," said Patrick Tan, M.D., PhD, senior author of the study and associate professor in the Cancer and Stem Cell Biology Program at the Duke-NUS Graduate Medical School.

An estimated 21,000 people in the United States will be diagnosed with stomach cancer this year, and 10,570 will die of the disease, according to the National Cancer Institute. Worldwide, only lung cancer is more lethal.

Patients have long had markedly different responses to treatments, suggesting that their tumors may have underlying differences.

Hinting at those differences, a microscopic pathology test developed in the 1960s broadly described how well the tumor cells clumped together, typing them as either "intestinal" or "diffuse." Known as the Lauren classification, after the doctor who first described the distinctions, the analysis fell short as a reliable prognostic tool.

"Most gastric cancer patients today are still being treated with a common one-size-fits-all regimen," said Tan, who also serves as group leader at the Genome Institute of Singapore and a senior investigator at the Cancer Sciences Institute of Singapore.

"One reason for this is that the Lauren classification requires significant gastric cancer experience and there is considerable variation in classifying gastric cancers, even among qualified pathologists," Tan said.

But the genetic findings by the Singapore-based researchers add greater specificity to the microscopic classifications and, for the first time, provide some guidance for doctors to prescribe effective treatments.

The team first analyzed 37 gastric cancer cell lines, which were pure cancer cells free of blood, tissue and other adulterations that could skew results.

Gene expression profiles yielded highly distinct patterns that indicated the two subtypes. In 64 percent of cases, the genetic subtypes validated the Lauren classifications – either intestinal or diffuse. In the other 36 percent of cases, the genomic process distinguished the subtypes where the pathology test could not.

Findings were confirmed using tumor samples from 521 cancer patients.

"It was quite reassuring to us that the genomic subtypes were associated with Lauren's system," Tan said. "There is a general assumption in the field that intestinal and diffuse gastric cancers (as classified by Lauren) represent two very different versions of gastric cancer, and now genomic data confirms this by demonstrating that the two genomic subtypes have very different molecular patterns."

Establishing the highly accurate definition of tumor subtypes enabled the researchers to observe the different responses to chemotherapy. The intestinal-type tumors showed significantly better response to the chemotherapies 5-fluorouracil and oxaliplatin, and were more resistant to cisplatin than the diffuse tumors.

"The exact mechanistic reasons for this difference are currently unclear, and this is an area that we are actively working on," Tan said, adding that the researchers are working to find subtype-specific molecular vulnerabilities to drugs.

The researchers have launched a prospective clinical trial, called the 3G study, where gastric cancer tumors will be genomically profiled, and treatments will be allocated on the basis of the tumor type.

Provided by Duke University Medical Center