New view of stomach cancer could hasten better therapies

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Credit: Allison Kudla/Ryo Sakai, Institute for Systems Biology

In a massive effort to catalog the molecular causes of stomach cancer, scientists, including researchers at Dana-Farber Cancer Institute, have identified four subtypes of tumors based on shared mutations and other molecular abnormalities. They say the new classification promises to advance clinical research to develop improved therapies for the third-

leading cancer killer worldwide.

In a report in journal *Nature*, investigators of The Cancer Genome Atlas Research Network said they analyzed 295 samples of gastric (stomach) cancer, looking for ways to sort them into groups with similar key DNA defects and molecular aberrations. It was extremely important, they said, to identify categories that would be useful in guiding therapy for patients.

"We clearly converged on four groups of gastric cancer with distinct features and classes of molecular alterations," said Adam Bass, MD, the corresponding author of the report. He is director for translational research for the Center for Esophageal and Gastric Cancer at Dana-Farber, and an associate member of the Broad Institute of MIT and Harvard.

Grouping the cancers in this way will help researchers enroll patients in clinical trials that test drugs designed to target their particular stomach cancer subtype, said Bass. There is an urgent need for new therapies he said, because "these are aggressive cancers and the five-year survival rate is between 20 and 25 percent."

Gastric adenocarcinomas – the vast majority of stomach cancers – cause more than 700,000 deaths worldwide each year. The American Cancer Society estimates that 22,220 cases will be diagnosed in the United States in 2014, with about 10,990 deaths. Stomach cancer is mainly a disease of elderly people. Infection with the bacterium Helicobacter pylori (H pylori) is a major cause. Other risk factors include diet, smoking, geography and ethnicity, and some inherited cancer syndromes.

Research on the biology of stomach cancer and the development of new therapies has been difficult because of its diversity and the presence of

different pathological forms. "It is a very heterogeneous disease, but most clinical trials have taken a one-size fits all approach and attempted to find a single optimal therapy to apply across gastric cancer," said Bass. "This traditional approach has likely contributed to the slow progress we have made in treatments for this cancer."

The new study is part of The Cancer Genome Atlas (TCGA) project, a federally funded initiative that involves large international groups of researchers and centers that are cataloging genomic characteristics across a spectrum of different forms of cancer with the goal of creating a new foundation of understanding of these cancers, enabling improvements in diagnosis, treatment and prevention.

The gastric cancer research team collected fresh, frozen tissue specimens and blood samples from 295 patients from hospitals around the world who had not been treated with chemotherapy or radiation. The tissue specimens were analyzed with six different molecular analysis technologies. Among them: sequencing the protein-coding DNA in each tumor; detecting mutations or missing or extra copies of gene sequences; determining the methylation status of DNA (chemical changes affecting gene activity); sequencing the messenger RNA and microRNA in the tumors, and assessing expression of key proteins.

When computational methods were applied to the large amount of resulting data, the cancers fell into four subtypes:

- Tumors containing the Epstein-Barr virus (EBV), along with mutations in the PIK3CA gene pathway, extreme DNA hypermethylation, and extra copies of PD-L1 and PD-L2 genes. This group made up about 10 percent of the cancers. Bass said these results suggest that inhibitors of the PI3-K pathway could have great utility in these cancers. Furthermore, he said, the findings of elevated levels of PD-L1 and PD-L2, key regulators

of the immune response, suggest that emerging immunotherapy agents be tested in these patients.

- Tumors in which malfunctioning DNA repair mechanisms cause a high rate of mutations – many of them leading to potential activation of cancer-related signaling proteins that can be targeted with novel precision drugs. About 20 percent of tumors fell into this subtype.
- The largest category of tumors, making up about half of the cancer specimens, was termed "chromosomally unstable." These cancer cells contained a jumble of extra or missing pieces of genes and chromosomes. Bass said these tumors "have a striking number of genomic amplifications [extra copies] of key cancer-promoting genes" for which targeted therapies exist or are in development. This subtype of tumor is frequently found in the junction between the stomach and the esophagus – a type of stomach cancer that has been dramatically increasing in the United States, he said.
- The fourth group of tumors was termed "genomically stable" as they lacked the molecular features of the other three types. These tumors, making up 20 percent of the specimens were largely those of a specific class of gastric cancer called diffuse-type tumors.

"These tumors are especially deadly because of their ability to metastasize rapidly and because we lack effective therapies," said Bass. The team identified a novel set of genomic alterations in a pathway called the RHOA signaling pathway in about 30 percent of these tumors. "This finding result opens up an entirely new line of research to allow us to investigate what underlies this deadly form of gastric cancer and to ultimately develop new therapies," said Bass.

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