Epigenetic analysis of stomach cancer finds new disease subtypes

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Researchers at the Duke-NUS Graduate Medical School in Singapore have identified numerous new subtypes of gastric cancer that are triggered by environmental factors.

Reported in the Oct. 17, 2012, issue of the journal *Science Translational Medicine*, the findings are based on the science of epigenetics, a study of gene activity. The insights into the complexities of stomach cancer could lead to better treatment approaches for the second leading cancer killer in the world, behind lung cancer.

"Gastric cancer is a heterogenous disease with individual patients often displaying markedly different responses to the same treatment," said Patrick Tan, M.D., Ph.D at Duke-NUS and lead author of the study. "Improving gastric cancer clinical outcomes will require molecular approaches capable of subdividing patients into biologically similar subgroups, and designing subtype-specific therapies for each group."

Like many cancers, stomach cancer is caused by genetic mutations, but also by external factors that affect the way genes work. These factors, called epigenetic alterations, work by methylation, a chemical process in which specific locations along the DNA, called CpG sites, are modified through the addition of a methyl group. Methylation silences a gene's behavior without actually altering the DNA sequence.

In their study, Tan and colleagues used 240 primary tumors and cell lines to conduct the first full survey of the DNA methylation landscape in

gastric cancer, known as the methylome. Their goal was to identify new molecular subgroups of gastric cancer not caused by primary genetic mutations, particularly those that might be targeted with therapies.

The researchers found that the gastric cancer methylome was widespread, with more than half of the CpG sites analyzed demonstrating altered methylation patterns in cancer. Many of the methylation alterations were associated with significant changes in gene expression, suggesting that the methylation alterations may be functionally important in the development of gastic cancer.

The researchers also identified a subgroup of gastric cancers with extremely high levels of methylation. The CIMP subgroup (CpG Island Methylator Phenotype) had been previously proposed, but its clinical significance remained unclear. The Duke-NUS-led team confirmed the CIMP subgroup, correlating it with younger patients who had a poor prognosis. They also demonstrated in laboratory experiments that these tumors may have increased sensitivity to demethylating drugs.

"Our study does provide clarity in unambiguously demonstrating the presence of this subgroup and its features," Tan said. "What's more, we are encouraged that there may be potential utility in testing the sensitivity of CIMP tumors to more potent DNA demethylating agents and possibly other epigenetic drugs."

The study also discovered long-range regions of epigenetic silencing, some targeting a generalized region and others that targeting a single gene. The finding may help identify novel genes where methylation events play a role in tumor growth.

"Our results strongly demonstrate that gastric cancer is not one disease but a conglomerate of multiple diseases, each with a different underlying biology and hallmark features," Tan said. "If gastric cancer is the result

of multiple interacting factors, including both environmental factors and host genetic factors, we need better ways to diagnosis and treat it.

"These findings move us forward, and additional work will focus on developing simple diagnostic tests to detect gastric cancer at earlier stages, plus drugs and drug targets that might exhibit high potency against different molecular subtypes of disease," Tan said.

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