# In lung cancer, silencing one crucial gene disrupts normal functioning of genome

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While examining patterns of DNA modification in lung cancer, a team of international researchers has discovered what they say is a surprising new mechanism. They say that "silencing" of a single gene in lung cancer led to a general impairment in genome-wide changes in cells, contributing to cancer development and progression.

In the January 1, 2009, issue of *Cancer Research*, a journal of the American Association for Cancer Research, they also report finding a strong link between modification of the key gene, MTHFR, and tobacco use by lung cancer patients - even if the patient had smoked for a short period of time.

The findings reinforce tobacco's link to lung cancer development, but show that deactivating one specific gene through a process known as hypermethylation causes systemic dysfunction, or hypomethylation, in many genes, said the study's senior investigator, Zdenko Herceg, Ph.D., head of the Epigenetics Group at the International Agency for Research on Cancer (IARC).

"We found that tobacco-mediated hypermethylation of MTHFR, and consequent partial or complete silencing of the gene, may trigger global hypomethylation and deregulation of DNA synthesis, both of which may contribute to cancer development," he said.

This methylation process, which involves chemically modifying normal DNA in order to change its activity, is seen as an increasingly important

factor contributing to so-called "epigenetic inheritance" in cancer development, Herceg said. An epigenetic event is when non-genetic factors cause a gene to change its expression, and this is different from cancer caused by mutated genes that produce errant protein.

"Tobacco smoke contains many carcinogens, most of which are believed to cause genome damage," he said. "While there is evidence that the mutations induced by these tobacco carcinogens do play an important role in cancer development, our study reveals the novel - and surprising - role that silencing of normal genes plays in development of lung cancer."

Cancer is often characterized by an imbalance in methylation, where hypermethylation (inactivation) in specific genes is accompanied by hypomethylation (a decrease in methylation in general) across many genes. But this process has not been well characterized, Herceg said.

In this study, researchers from IARC working with investigators from Russia, Canada, and the United States, quantified methylation patterns in a panel of five cancer-associated genes (CDH1, CDKN2A, GSTP1, MTHFR and RASSF1A) in tumor samples from 209 lung patients and in blood samples from 172 matched "healthy" volunteers.

Noncancerous lung tissue was also examined from 51 of the lung cancer patients.

Their analysis revealed that a high frequency of hypermethylation of MTHFR, RASSF1A and CDKN2A in lung tumors compared to control blood samples, but no significant increase in methylation levels of the other two genes.

Silencing of the RASSF1A and CDKN2A genes makes sense, said Herceg, because these are tumor suppressor genes known to be

inactivated in lung cancer. But the role of MTHFR has been less clear, he said. The enzyme produced by the gene plays a role in processing amino acids into methionine, which the body uses to make proteins and other crucial molecules. Variants of MTHFR, for example, have been linked to increased risk of cardiovascular disease.

"Because the MTHFR gene product plays a role in the maintenance of the cell's pool of methionine, silencing of MTHFR is likely to contribute to global hypomethylation, a phenomenon almost universally observed in human cancer that has been overlooked in favor of gene promoter-associated hypermethylation," Herceg said.

Both global hypomethylation and hypermethylation "coexist in all tumors and can contribute to tumor development and progression through different mechanisms," he said. The researchers say that these two processes likely reinforce each other. Global hypomethylation associated with MTHFR inactivation contributes to development of cancer by destabilizing the chromosome and activating oncogenes.

The researchers also discovered that methylation levels in RASSF1A were influenced by gender - men were much more likely to express this abnormally - and that methylation levels of CDH1, CDKN2A, GSTP1 and RASSF1A were not associated with smoking.

While the findings contribute to the basic understanding of lung cancer development, they may also be useful in designing a "methylation signature" blood or sputum biomarker test to identify individuals who are at risk of developing the disease, the researchers say. "That may prove particularly beneficial in diagnosing patients exposed to passive smoking," Herceg said.

Source: American Association for Cancer Research

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