SOUTHWESTERN NEWS

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UT SOUTHWESTERN RESEARCHERS DISCOVER MECHANISM THAT INACTIVATES TUMOR-SUPPRESSOR GENES IN LUNG CANCER

DALLAS - Aug. 19, 2000 - A team of UT Southwestern Medical Center at Dallas researchers have found the process that turns a key tumor-suppressor gene off in people who have lung cancer. The finding may lead to improved cancer prevention.

The results of their study were published in the August issue of *The Journal of the National Cancer Institute.*

The researchers, led by instructor of pathology Dr. Arvind K. Virmani, discovered how the gene, *retinoic acid receptor* β (*RAR*β), a tumor-suppressor gene, is inactivated in lung cancers and in the bronchial lining of heavy smokers.

Virmani determined that the gene was silenced in a high percentage of lung cancers by a chemical modification process known as methylation -- a process by which methyl groups are added to certain specific deoxyribonucleic acid (DNA) sequences in the genome.

"Methylation is a very interesting process because it is reversible, unlike the other genetic changes present in cancer cells, " said Dr. Adi Gazdar, professor of pathology and holder of the W. Ray Wallace Distinguished Chair in Molecular Oncology Research. "This discovery could have implications for risk assessment and lead to improved cancer prevention and treatment therapies."

The researchers found a high frequency of methylation in the *RAR*β gene. The gene was methylated in 72 percent of small-cell lung cancer and 41 percent of non-small-cell lung cancer tumors and cell lines.

Further study showed that when the gene was methylated, its expression was turned off. "So that confirmed that methylation was shutting off gene expression," Gazdar said.

The researchers determined that the *RAR*β gene silenced in cancer cells could be chemically reactivated. Exposure of the cancer cells to a demethylation agent, 5-aza-2'-

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deoxycytidine, restored gene expression. The investigation of gene expression in eight cell lines revealed complete agreement between aberrant methylation of the promoter and repression of two isoforms of the gene.

"Unlike many of the genetic changes in cancer, methylation is a reversible phenomenon," Gazdar said. "We can (theoretically) administer a demethylating agent to cancer patients, and the genes that are shut off by methylation can be turned on. Our prediction is that this could now stop the cancer cell from being a cancer cell. Early clinical trials testing this hypothesis are currently planned or under way in this country."

Gazdar also said the findings indicate that the methylation status of genes could be a marker for cancer risk assessment. "Silencing of the *RAR*β gene by methylation appears to be important in the development of breast and cervical cancers, as well," he said. "This could be a phenomenon that is present in many different types of tumors.

"The more we study methylation, the more important it seems to be for the development of the cancer process. All cancers that have been studied have some genes silenced by this process. There are about 50 genes known to be silenced by methylation in different cancer types. And we're just beginning to discover all the genes that are turned off in tumors, so that there are many others that remain to be discovered."

The study was sponsored by the National Cancer Institute.

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