

Methylation Profiling of Lung Cancer: A Decade of Progress

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Commentary on:

Shinichi Toyooka, Kiyomi O. Toyooka, Riichiroh Maruyama, Arvind K. Virmani, Luc Girard, Kuniharu Miyajima, Kenichi Harada, Yutaka Ariyoshi, Takashi Takahashi, Kenji Sugio, Elisabeth Brambilla, Michel Gilcrease, John D. Minna, and Adi F. Gazdar. **DNA methylation profiles of lung tumors.** *Mol Cancer Ther* 2001;1:61–7.

The term epigenetics refers to heritable changes in gene expression that occur without changes in the DNA sequence. Epigenetic regulation includes DNA methylation and covalent histone modifications. Although both mechanisms play crucial roles in carcinogenesis, methylation is more widely studied because it is less complex and easier to document. In human malignancies, whereas global DNA hypomethylation occurs, selective DNA hypermethylation occurs in the promoter regions of crucial tumor suppressor genes to downregulate their functions. Ten years ago, in the first volume of *Molecular Cancer Therapeutics*, we published a methylation profile of lung cancers, comparing and contrasting the various types, including non-small cell adenocarcinomas and squamous cell carcinomas, and the neuroendocrine tumors small-cell lung cancers and bronchial carcinoids. By present standards, our methodology, using a nonquantitative assay for only 6 genes, may seem relatively crude and

limited. Nevertheless, we demonstrated, for the first time, important differences in the profiles of these major forms of lung cancer.

In the decade following the publication of this article, our knowledge of epigenetics, both of its basic biology and its role in carcinogenesis of specific tumor types, has greatly increased (1). We know now that individual tumors may have epigenetic changes in literally hundreds of genes and many histone marks. Improvements in methodology now permit analysis of whole genome methylation, both hypo- and hypermethylation. A single microarray chip analysis of 450,000 sites permits a detailed methylation profile including CpG and CNG sites, CpG islands/shores/shelves/open sea, noncoding RNA (microRNAs and long noncoding RNAs) and sites surrounding the transcription start sites for coding genes. Such an analysis also allows examination of the corresponding gene bodies and 3'-untranslated regions, in addition to intergenic regions (2).

DNA methylation can now be detected in clinically accessible samples, including sputum and plasma, as well as in surrogate organs that are easily accessible. Thus, in addition to diagnostic tests, our knowledge of epigenetic changes has led to novel therapeutic applications, including reactivation of epigenetically silenced genes through the use of DNA methyltransferase inhibitors agents and histone deacetylation inhibitors.

In the time since our article was published, the field of lung cancer genetics and epigenetics has undergone explosive growth. However, the concept that different forms of lung cancer have different pathogenetic mechanisms and that these differences can be exploited for improved clinical management has been verified.

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