

Human Cancer Cells, Normal Adult Cells, Somatic Stem Cells and Embryonic Stem Cells Have Distinct DNA Methylation Signatures

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A new method for determining the methylation state of 1536 CpG sites simultaneously uses bisulfite treatment to convert cytosine into uracil, leaving methylcytosine unchanged, followed by “genotyping” using the GoldenGate® assay to distinguish uracil from methylcytosine. We designed probes for 1536 CpG sites from 371 genes chosen for their importance in biological processes related to cell growth, differentiation, apoptosis and oncogenic transformation, as well as imprinted genes and genes previously reported to be differentially methylated. The assay requires 200 ng of bisulfite-converted DNA and reports the quantitative degree of methylation at each CpG site.

We determined the methylation status of a large number of cancer cell lines, adult tissues, lymphoblastoid cell lines, somatic stem cells and embryonic stem cells. Human embryonic stem (hES) cells are unique among human cell lines in their ability to self-renew and to differentiate into multiple cell types. Remarkably, unsupervised clustering based on the methylation status of all 1536 sites cleanly separated ES cells, other normal cells, and cancer cell lines into three distinct groups. By analyzing which CpG sites contributed most to differences among cells types, we identified 49 methylation sites from 45 genes that classified all four cell types into separate groups. Despite their origins from 14 independent isolates in laboratories around the world, the 34 hES cell samples analyzed had nearly identical methylation patterns at these 49 sites.

We also used the same assay set to compare 23 lung adenocarcinoma and 23 normal lung samples. We identified 55 CpG loci that provide good discrimination between the cancer and normal lung tissue samples. DNA methylation profiling provides a powerful method for discovering biomarkers that characterize cancer cells and other cell types.