

Discovery of Epigenetically Silenced Genes by Methylated DNA Immunoprecipitation in Colon Cancer Cells

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CpG island promoter hypermethylation of tumor suppressor genes is a common hallmark of human cancer, and new large-scale epigenomic technologies might be useful in our attempts to define the complete DNA methylome of tumor cells.

Here, we report a functional search for hypermethylated CpG islands using the colorectal cancer cell line HCT-116, in which two major DNA methyltransferases, DNMT1 and DNMT3b, have been genetically disrupted (DKO cells). Using methylated DNA immunoprecipitation methodology in conjunction with promoter microarray analyses, we found that DKO cells experience a significant loss of hypermethylated CpG islands.

Further characterization of these candidate sequences shows CpG island promoter hypermethylation and silencing of genes with potentially important roles in tumorigenesis, such as the Ras guanine nucleotide-releasing factor (RASGRF2), the apoptosis-associated basic helix-loop transcription factor (BHLHB9), and the homeobox gene (HOXD1). Hypermethylation of these genes occurs in premalignant lesions and accumulates during tumorigenesis. Thus, our results show the usefulness of DNMT genetic disruption strategies combined with methylated DNA immunoprecipitation in searching for unknown hypermethylated candidate genes in human cancer that might aid our understanding of the biology of the disease and be of potential translational use.

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