Modification of the epigenome in human cancer cells by expression of a DNA demethylase from plants

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Patterns of DNA methylation, an important epigenetic modification involved in gene silencing and development, are disrupted in cancer cells. Understanding the functional significance of aberrant methylation in tumors remains challenging, due in part to the lack of suitable tools to actively modify methylation patterns. DNA demethylation caused by mammalian DNA methyltransferase inhibitors is transient and replication-dependent, whereas that induced by TET enzymes involves oxidized 5-meC derivatives that perform poorly understood regulatory functions. Unlike animals, plants possess enzymes that directly excise unoxidized 5-meC from DNA, allowing restoration of unmethylated C through Base Excision Repair. Here we show that expression of *Arabidopsis* 5-meC DNA glycosylase DEMETER (DME) in colon cancer cells demethylates and reactivates hypermethylated silenced loci. Interestingly, DME expression causes genome-wide changes that include both DNA methylation losses and gains, and partially restores the methylation pattern observed in normal tissue. Furthermore, such methylome reprogramming is accompanied by altered cell-cycle responses and increased sensibility to anti-tumor drugs, decreased ability to form colonospheres, and tumor growth impairment *in vivo*. Our study shows that it is possible to reprogram a human cancer DNA methylome by expression of a plant DNA demethylase.

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