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THE ROLE OF DNA METHYLATION ON GENE EXPRESSION IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Epigenetic modification of the genome has more influence on gene expression than DNA sequence alone. DNA hypermethylation and deacetylation of histone complexes has been shown to down regulate expression of associated genes. These epigenetic modifications may play an important role in the pathogenesis of cancer. Demethylation agents and histone deacetylase inhibitors used to restore gene activity to previous levels could lead to development of novel anti-cancer drugs.

We treated an acute lymphoblastic leukemia cell line with a demethylating agent (5-aza) alone and in combination with a histone deacetylase inhibitor (TSA). We then measured RNA expression using a gene expression microarray. The methylation status of genes with the highest differential expression score after treatment with 5-aza alone and in combination with TSA was recorded to determine if methylation was associated with gene expression. We identified 361 genes that were up-regulated after treatment with a demethylating agent thereby suggesting that the expression of these genes is controlled by methylation. As has been previously reported, we did not observe a one to one correlation between gene methylation and gene re-expression after treatment with a demethylating agent. For example, in 27 key candidate genes only 14 showed methylation before treatment. The location of methylation within these genes was also variable with some being present in the promoter and others within the body of the gene. The variable presence and location of pre-treatment methylation suggests that drugs targeting specific epigenetic DNA modifications act in a more global manner, affecting gene expression via multiple mechanisms.