Transcriptional changes induced by epigenetic therapy with hydralazine and magnesium valproate in cervical carcinoma.


Abstract

Aberrant DNA methylation and histone deacetylation participate in cancer development and progression; hence, their reversal by inhibitors of DNA methylation and histone deacetylases is a promising cancer therapy. Experimental data demonstrate that these inhibitors in combination do not only show synergy in antitumor effects but also in whole genome global expression. Ten pairs of pre- and post-treatment cervical tumor samples were analyzed by microarray analysis. Treatment for seven days with hydralazine and valproate (HV) in patients up-regulated 964 genes. The two pathways possessing the highest number of up-regulated genes comprised the ribosome protein and the oxidative phosphorylation pathways, followed by MAPK signaling, tight junction, adherens junction, actin cytoskeleton, cell cycle, focal adhesion, apoptosis, proteasome, Wnt signaling, and antigen processing and presentation pathways. Up-regulated genes by HV, clustered with down-regulated genes in untreated primary cervical carcinomas and were more alike as compared with up-regulated genes from untreated patients in terms of gene ontology. Increased acetylated p53 was also observed. Epigenetic therapy with HV leads to gene reactivation in primary tumors of cervical cancer patients as well as protein acetylation. A number of these reactivated genes have a definitive role as a tumor suppressors. The global expression pattern induced by HV suggests this therapy has an impact on pathways related to energy production which may promote apoptosis.

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