Investigation of the Effect of 5-Aza-2'-Deoxycytidine on p15INK4, p16INK4, p18INK4, and p19INK4 Genes Expression, Cell Growth Inhibition, and Apoptosis Induction in Hepatocellular Carcinoma PLC/PRF/5 Cell Line

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Abstract

Cyclin-dependent kinases (CDKs) are the key regulators of cell-cycle transitions and characterized by needing a separate subunit, a cyclin, which provides domains essential for enzymatic activity. The activities of cyclin-CDK complexes are controlled by a group of molecules that inhibit CDK activity and CDK inhibitors (CKIs). Cancer often exhibits an aberrant CpG methylation of promoter regions of tumor suppressor genes such as CKIs. Treatment with the DNA demethylating agents, such as 5-aza-2'-deoxycytidine (5-Aza-CdR), can restore and upregulate CKIs. Previously, we reported the effect of 5-Aza-CdR and genistein on DNA methyltransferase (DNMTs) in hepatocellular carcinoma (HCC). The aim of the present study was to evaluate the effect of 5-Aza-CdR on p15INK4, p16INK4, p18INK4, and p19INK4 genes expression, cell growth inhibition, and apoptosis induction in HCC PLC/PRF/5 cell line.

Materials and methods: The effect of 5-Aza-CdR on the cell growth of PLC/PRF/5 cells, genes expression, and apoptosis induction were assessed by 3-[4, 5-dimethyl-2-thiazolyl]-2, 5-diphenyl-2H-tetrazolium bromide assay, real-time quantitative reverse transcription-polymerase chain reaction analysis, and flow cytometry, respectively.

Results: 5-Aza-CdR (0, 1, 5, 10, 25, and 50 μM) inhibited PLC/PRF/5 cell growth at different periods significantly. This compound induced apoptosis and reactivated p15INK4, p16INK4, p18INK4, and p19INK4 genes expression at a concentration of 5 μM significantly.

Conclusion: 5-Aza-CdR can inhibit cell viability and induce apoptosis by epigenetic reactivation of p15INK4, p16INK4, p18INK4, and p19INK4 genes in HCC PLC/PRF/5.

Keywords: 5-aza-2′-deoxycytidine; cyclin-dependent kinase inhibitor; hepatocellular carcinoma.