S-adenosylmethionine, a methyl donor, up regulates tissue inhibitor of metalloproteinase-2 in colorectal cancer

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ABSTRACT. DNA methylation is a fundamental epigenetic mechanism in regulating the expression of genes controlling crucial cell functions in cancer development. Gene silencing via CpG island methylation/demethylation in the promoter region is one of the mechanisms by which different genes are inactivated/activated in human cancers. Tissue inhibitor of metalloproteinase-2 (TIMP-2) is known to antagonize matrix metalloproteinase (MMP) activity and to suppress tumor growth, angiogenesis, invasion, and metastasis. TIMP-2 expression has been found to be both upregulated and downregulated in various cancers. The inconsistent TIMP-2 expression and unclear epigenetic regulation lead us to investigate its role in colorectal cancer in the presence of a methylating
Highly invasive human colorectal cells SW-620 were treated with the methyl donor S-adenosylmethionine (SAM) and its effect was evaluated by cell proliferation, cell cycle, invasion and migration assay. The ability of SAM to down regulate a panel of activated prometastatic, angiogenesis and growth- and cell cycle-regulatory genes was evaluated using end-point and real-time PCR. Treatment of SW-620 with SAM diminished cell proliferation and altered cell cycle kinetic G2/M phase cell cycle arrest. An in vitro matrigel invasion assay of SAM-treated cells showed a significant reduction in the invasive potential compared to untreated SW-620 cells. Treatment of SW-620 cells with SAM resulted in activation of TIMP-2 and inhibition of the expression of genes such as MMP (MMP-2, MT1-MMP), urokinase plasminogen activator, and vascular endothelial growth factors. The level of expression of tumor suppressor and apoptotic genes was not significantly higher compared to the untreated control. No changes in the levels of expression of genes (growth and cell cycle regulator), such as TGF-β, Smad2, Smad4, and p21 were observed. Our data support the hypothesis that TIMP-2, along with other prometastatic genes, is hypomethylated and expressed differently in colorectal cancer. Further in-depth analysis is warranted to confirm the promoter region CpG methylation pattern of the TIMP-2 gene.

Key words: Colorectal cancer; Epigenetics; DNA hypomethylation; Gene expression; Metastasis