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Poster Submissions

Poster Title

Regulation of Tumor Suppressor Genes and DNMT1 in Breast and Ovarian Cancer

Authors and their Affiliation

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All authors are affiliated with BUSM Cancer Center, Sibaji Sarkar is also associated with GSI and Department of Medicine, BUSM.

Please describe the extent of your work in this research

My main goal was the determination of the association of HDAC1 and MBDP2 to methylated CpG regions.

Abstract Submission

- GSI-Abstract-2015.docx

Would you like your abstract to be considered for an oral presentation (students and post docs only)?

Yes

Regulation of Tumor Suppressor Genes and DNMT1 in Breast and Ovarian Cancer

Epigenetics regulates gene expression through DNA methylation, histone methylation and acetylation, and is associated with a number of diseases. Several types of cancer have been linked to the dysregulation of oncogenes and tumor suppressor genes. Aberrant silencing of tumor suppressor genes through methylation has been shown to contribute to carcinogenesis. Our laboratory has shown that histone deacetylase inhibitors (HDACi) demethylate and re-express tumor suppressor genes. ARHI is an imprinted pro-apoptotic gene. The maternal allele is silenced by methylation, and the paternal allele is expressed in normal tissues, but is silenced by methylation in breast and ovarian cancer cells, causing loss of heterozygosity (LOH). We hypothesize that re-expression of tumor suppressor genes makes cancer cells susceptible to other drugs. Combination of HDACi and the calpain protease inhibitor calpeptin produced more than additive growth inhibition in breast and ovarian cancer cells. We observed that tumor suppressor genes were demethylated and re-expressed following HDACi treatment. To determine which specific CpG residues were methylated, we sequenced CpG islands in one gene, ARHI. Treatment with HDACi showed differential demethylation in these regions. Demethylation was caused by downregulation of DNMT1. DNMT1 dissociated from HSP90 and HDACi treatment decreased its phosphorylation. We reasoned that some of the demethylated CpG residues regulate the expression of ARHI by the binding of transcription inhibitors, HDAC1 and MBDP2. ChIP analysis revealed that that association of HDAC1 and MBDP2 at the CpG residues decreased after HDACi treatment. These results suggest that HDAC1 and MBDP2 bind to specific methylated regions in the ARHI gene to inhibit transcription. We are further investigating the epigenetic regulation of additional genes in breast and ovarian cancer.