Mitotic defects induced by MAT2A inhibitors guide translational drug combination strategies with AG-270 and taxanes

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Background: The MAT2A gene is a candidate in chromosome 9p21, both of which are deleted in sporadic colorectal cancers (CRC), and is deleted in some tumors with KRAS mutations. The DNA MTAP (Methylthioadenosine phosphorylase) gene on chromosome 9p21, both of which are deleted in sporadic colorectal cancers (CRC), and is deleted in some tumors with KRAS mutations.

Methods: To evaluate the growth inhibitory activity of AG-270 in both MTAP-null and MTAP-wt cells, we performed MTT assays and Western blots for phosphorylated Aurora B and H3K18Me3. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to Western blotting protocols. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to Western blotting protocols.

Results: AG-270 treatment led to substantial dysregulation of splicing, including an increased number of transcripts containing DIs, in MTAP-wt and MTAP-null models and a substantial number of transcripts fail to export into the cytosol and thus are not translated. Inhibition of PRMT5 activity altered splicing and gene expression, leading to impaired cell growth and increased cell death.

Discussion: This work was funded by Avery Pharmaceuticals, Inc. and the National Cancer Institute. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to Western blotting protocols. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to Western blotting protocols.


Disclosure: This work was funded by Avery Pharmaceuticals, Inc. and the National Cancer Institute. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to Western blotting protocols. A knockdown of MAT2A expression in HCT116 MTAP-null cells using siRNA was performed. Western blots were performed according to Western blotting protocols.

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