624 TARGETING TYPE I ARGININE METHYLTRANSFERASES PROMOTES T CELL MEDIATED ANTITUMOR IMMUNE RESPONSES

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Background Although immunotherapy produced dramatic clinical responses in a certain population of cancer patients, tumor cells can employ a variety of immunosuppressive measures to limit the immunotherapeutic efficacy. This highlights a great need to develop novel strategies to expand the clinical benefits of immunotherapy to a broader population of cancer patients. PRMTs have been described as vital regulators of immune responsive pathways in several cell types, but the immunoregulatory role of Type I PRMTs in the tumor microenvironment remains poorly understood.

Methods In this study, we analyzed the correlation between Type I PRMT expression levels with the clinical outcome or immune signature. Gene expression changes were evaluated in a panel of immunogenic and non-immunogenic cancer cell lines with Type I PRMT inhibitor treatment. The antitumor and immunological effects of Type I PRMT inhibitor were evaluated in combination with checkpoint blockade in a panel of syngeneic tumor models.

Results Using TCGA dataset analysis, increased mRNA expression levels of several Type I PRMTs were associated with poor clinical response and decreased immune infiltration in melanoma patients. Particularly, tumors with high expression of PRMT1, the major Type I PRMTs, displayed significantly reduced relapse-free survival (HR=1.891, p=0.038), and were associated with lower cytolytic score (logFC=-0.875, p=1.49e-08) and lower lymphocyte infiltration score (logFC=-0.783, p=0.00077). RNA-seq results showed that interferon signaling was significantly altered after Type I PRMT inhibitor treatment in 10 of 15 cell lines analyzed, with most related genes showing increased expression. In addition, VEGFA was downregulated by 25% or more in 7/8 human and 3/5 mouse cancer cell lines, and a moderate decrease in chromatin accessibility at the Vegfa promoter was observed in ATAC-seq data. Furthermore, Type I PRMT inhibitor combined with anti-PD1 treatment significantly extended the survival of tumor-bearing mice and delayed tumor growth in a panel of immunocompetent mouse models. Mechanistically, Type I PRMT inhibitor significantly increased the apoptotic sensitivity of tumor cells to autologous tumor-reactive T cells in vitro and the infiltration of total T cells (CD3+) in 3 of 4 tested tumor models and cytotoxic T cells (CD8+) in two tested tumor models in vivo.

Conclusions Taken together, these data indicated that Type I PRMT inhibition exhibits immunomodulatory properties and synergizes with immune checkpoint blockade to induce durable antitumor responses in a T cell dependent manner. This study provides a rationale to combine Type I PRMT inhibitor with immune checkpoint blockade to maximize clinical benefits in cancer patients.

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