ANTI-VEGF TREATMENT AMPLIFIES IMMUNE CHECKPOINT INHIBITOR INDUCED IMMUNE RESPONSES BY TARGETING B AND REGULATORY T CELLS

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Background We have previously reported early and unexpected results of an open label phase II trial treating patients with histologically confirmed hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) treated with anti-CTLA4 + anti-VEGF + anti-PD-L1. We described exceptional clinical responses in 6 out of 7 patients accompanied with moderate to severe immune-related adverse events in the majority of patients. Preliminary correlative studies using paired PBMC and serum samples demonstrated a proinflammatory cytokine profile, reinvigoration of precursor exhausted CD8+ T cells, and expansion of the Treg and non-classical monocyte subsets. Herein, we aimed to further translate these findings to better understand the mechanisms behind the striking clinical efficacy and treatment-related toxicity.

Methods We utilized the subcutaneous (s.c.) and intrahepatic CCA SB1, as well as the plasmid-induced YAP-AKT CCA mouse models, previously described by our group, to study treatment efficacy, explore changes in the tumor immune microenvironment (TME), and investigate the mechanistic interplay potentiated by the treatment combination.

Results In three murine CCA models, the anti-VEGF/anti-CTLA4/anti-PD-L1 combination therapy induced significantly better tumor growth control over the anti-CTLA4/anti-PD-L1 double therapy or vehicle-treated groups (figure 1A). Cytokine analysis of mouse tumor lysates revealed that additional VEGF-A blockade led to an IFN signature characterized by higher levels of CXCL9, CXCL10, IFN-g and IFN-a in mice. Tumor immune profiling revealed an increase of infiltrating B cells, driven by higher levels of monocyte-derived B cell activating factor (BAFF) in the TME. Activated B cells adopted a Be-1 phenotype characterized by enhanced IL-12 production. Furthermore, there was an increase in the frequency of Tregs in the TME of triple-treated mice. These tumor-infiltrating Tregs were rewired towards a ‘fragile’ Th1-like phenotype characterized by higher expression levels of IFN-g and T-bet (figure 1B). Congruently, the suppressive function of triple-treated tumor-infiltrating Tregs was impaired. IL-12 blockade abrogated the therapeutic effects of the triple-therapy in mice and reversed the fragile Treg phenotype previously observed (figure 1C). B cell depletion and BAFF blockade similarly reversed the therapeutic efficacy of the triple therapy in mice.

Conclusions We identify a novel mechanism describing how additional VEGF blockade could induce critical changes in the immune contexture of HCC and CCA, sensitizing tumors to anti-CTLA4 + anti-PD-L1 therapy. Specifically, we found that the triple combination potentiated an IFN signature leading to BAFF production by the myeloid compartment. BAFF acted on B cells, resulting in enhanced IL-12 production, reinvigorating Tregs towards a less suppressive, proinflammatory ‘fragile’ phenotype.

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REFERENCES
