323 IMMUNOGENIC SYNGENEIC MODEL MC38-OVA FOR THE PRECLINICAL EVALUATION OF IMMUNE EVASION AND CHECKPOINT BLOCKADE

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Background The development of immuno-oncology (I/O) therapeutics has revolutionized the cancer treatment landscape. Despite this achievement, the mechanism behind limited responses is poorly understood. Tumor immune evasion has been reported to arise through the loss of tumor necrosis factor (TNF) signaling, interferon-γ (IFN-γ) signaling, and antigen presentation pathways, which are crucial to CD8+ T cell-mediated killing. Syngeneic mouse models have been widely used as they have an intact immune system, are easily accessible, and have a vast array of historical data for comparison. However, limited syngeneic models respond to immune checkpoint inhibitors, possibly due to low intrinsic immunogenicity. The expression of ovalbumin (OVA) has previously shown to sufficiently alter the susceptibility of syngeneic tumors to host T cell-mediated responses. In this study, the newly developed OVA-expressing MC38 syngeneic line was characterized for tumor immunity, checkpoint blockade response and response durability.

Methods Murine colon cancer MC38 cells were transduced by lentiviral vector with chicken OVA coding cDNA. A single clone was selected, and OVA expression was confirmed by western blot. The MC38-OVA cells were subcutaneously implanted into immunocompetent mice to evaluate the tumorigenicity and in vivo response to anti-PD-1 antibody treatment. Blood was collected 2 days post final dose of anti-PD-1 treatment for phenotypic analysis by FACS. Spleen and tumor draining lymph nodes were collected at termination for FACS analysis of IFN-γ+ T cells and OVA specific CD8+ T cells. Adoptive transfer was evaluated by challenge studies in both MC38-OVA and MC38 tumor-bearing mice with T cells derived from MC38-OVA mice, anti-PD-1 cured mice and OT-I mice. In vitro killing assays were performed to evaluate the function of adoptive CD3+ T cells transfer.

Results OVA-expressing MC38 presented complete regression under anti-PD-1 treatment in vivo. T cell expansion was observed after anti-PD-1 treatment in peripheral blood with increased IFN-γ+ T cells in both tumor-draining lymph nodes and spleen. Additionally, anti-PD-1 cured mice generated robust tumor specific memory T cell, which successfully inhibited MC38-OVA and MC38 tumor growth following adoptive transfer. CD3+ T cells from MC38-OVA-bearing mice and OT-I mice showed anti-tumor immunity in vivo. In vitro killing assay demonstrated increased immunity.

Conclusions Syngeneic mouse tumor models are preferred preclinical models for I/O research, despite limited intrinsic immunogenicity. OVA expression in syngeneic tumors largely increased T cell-mediated immunity to enhance antigen-specific T cell responses during tumorigenesis, providing novel immunogenic models for preclinical immunotherapy evaluation.

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