Background Myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment are potential therapeutic targets in immune checkpoint cancer therapy, particularly for cancers that are unresponsive to anti-PD-1 therapy. It has previously been demonstrated that trefoil factor family 2 (TFF2), a secreted anti-inflammatory peptide, can partially suppress MDSC expansion and activate tumor immunity through agonism of the CXCR4 receptor.1,2 We investigated whether a novel fusion protein, murine TFF2-murine serum albumin (mTFF2-MSA), has single agent activity and can improve on the therapeutic effects of anti-PD-1 in CT26.wt subcutaneous and CT26-Luciferase (CT26-Luc) orthotopic syngeneic mouse models of advanced colorectal cancer (CRC).

Methods Two syngeneic colon carcinoma mouse models were developed using the CT26.wt and CT26-Luc CRC cell lines grafted subcutaneously and orthotopically, respectively, into BALB/C mice. We generated a recombinant fusion protein, designated mTFF2-MSA, which contains murine TFF2 fused to murine serum albumin (MSA), for the purpose of increasing half-life and reducing the frequency of dosing. Mice subsequently received mTFF2-MSA, anti-PD1 antibody (clone 29F.1A12 for subcutaneous study; clone RMP-1 for orthotopic study) or combination of mTFF2-MSA and anti-PD1. Tumor volume, and survival were measured. At the endpoint, flow cytometry was performed on the blood, bone marrow, tumor, and lymph nodes, to examine treatment-induced effects on cellular immune profiles.

Results In the CT26.wt model, tumor growth was suppressed by mTFF2-MSA, anti-PD1 and by the combination of mTFF2-MSA/anti-PD1 by 16%, 40% and 60%, respectively. Survival in the CT26.wt model on Day 30 treated with vehicle, mTFF2-MSA, anti-PD1 and the combination of mTFF2-MSA and anti-PD1 was 0%, 40%, 60% and 60%, respectively. In the CT26-Luc model, mTFF2-MSA, anti-PD1, and the combination of mTFF2-MSA and anti-PD1 suppressed tumor growth by 42%, 94%, and 94%, respectively. In the CT26-Luc model, neutrophils were significantly reduced in the blood in all treatment groups by flow cytometry. In the bone marrow, a significant reduction in total macrophages, M2 macrophages, and neutrophils was also observed but only in the group treated with anti-PD1/mTFF2-MSA. In the axillary lymph node, there was a significant reduction in TOX+ cells in both CD4+ and CD8+ T-cells in all treatment groups. In the tumor, there was a significant reduction in total macrophages and M2 macrophages in all treatment groups, while NK cells were also increased, but only in the combination anti-PD1/mTFF2-MSA treated group.

Conclusions mTFF2-MSA has single agent activity and is additive to anti-PD1 antibody checkpoint inhibition in treating two syngeneic (subcutaneous and orthotopic) mouse models of advanced colorectal cancer.

REFERENCES

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