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MDSC-targeted TFF2-MSA synergizes with PD-1 blockade therapy in advanced gastric cancer models

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Abstract

Recent studies revealed chemotherapy increases anti-PD1 response of gastric cancer (GC) by reducing tumor myeloid-derived cell (MDSC). However, a more potent MDSC-targeted treatment is needed to further improve anti-PD1 efficacy in advanced GC. Trefoil factor family 2 (TFF2), a partial agonist of CXCR4 and a secreted anti- inflammatory peptide, can decrease MDSCs. Here, we developed a novel peptide TFF2-MSA (mTNX-1700) with an extended serum half-life by fusing murine TFF2 to murine serum albumin. Using a syngeneic mouse model of transplanted ACKP (Atp4b-Cre; Cdh1-/-; LSL-KrasG12D; Trp53-/-) GC cells, we investigated whether TFF2-MSA can synergize with anti-PD1 therapy by reducing MDSC accumulation and biogenesis. When the subcutaneously implanted ACKP tumors reached 150-200 mm^3, TFF2-MSA or anti-PD-1 antibody or both was given to tumor-bearing mice. Intriguingly, while either TFF2-MSA or PD-1 antibody showed little benefit as a single agent (TGI 18% and 25% respectively, p>0.05), their combination dramatically suppressed ACKP tumor growth (TGI 78%, p<0.0001) and prolonged mouse median survival (64 days vs. 32.5 days in control) in a synergistic manner. Mechanistically, the combination therapy efficiently reduced intratumoral MDSCs, and profoundly increased tumor-infiltrating CD8$^+$ T cells accompanied by a better effector phenotype. In the bone marrow, biogenesis of MDSC from its progenitors was markedly decreased by TFF2-MSA to the level of tumor-free mice. In an orthotopic model, with implantation of ACKP-luc cells into the stomach submucosa, the TFF2-MSA/PD-1 antibody combo regimen eradicated GC in 80% mice compared to 0% in either monotherapy treatment. Finally, the combination significantly reduced spontaneous lung metastasis in s.c. xenograft resected mice (vs. control, p<0.0001), compared to minimal inhibition with either monotherapy (p>0.05). Overall, our data indicate that targeting MDSCs using TFF2-MSA synergizes with PD-1 blockade therapy in advanced and metastatic syngeneic mouse models of GC.

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Introduction

- Immune suppression within the tumor microenvironment (TME) has been demonstrated as an integral barrier to the efficacy of immune checkpoint blockade therapy. A major tumor- driven mechanism of immune suppression is the generation of myeloid-derived suppressor cells (MDSCs), which impede antitumor T cell activity within the TME[1].
- Granulocytic MDSCs (PMN-MDSCs) are a heterogeneous group of immature myeloid cells that greatly expand in malignancies. They are functionally and transciptionally distinct from mature neutrophils[2]. PMN-MDSCs are short-lived and constantly replenished by the bone marrow progenitors[3].
- Trefoil factor family 2 (TFF2) is a partial agonist for CXCR4, able to activate Ca$^+$ signaling but in the presence of SDF-1, TFF2 partial inhibits SDF-1-dependent signaling and chemotaxis[4].
- TFF2 has been shown to inhibit tumor formation by reducing MDSC expansion and proliferation in a colorectal cancer model[5].
- HDC$^+$ MDSCs expressed higher levels of CXCR4 and are more immunosuppressive than their HDC$^-$ counterparts. HDC$^+$ MDSCs profoundly expand in colorectal cancer and its reduction leads to tumor control[6].

References

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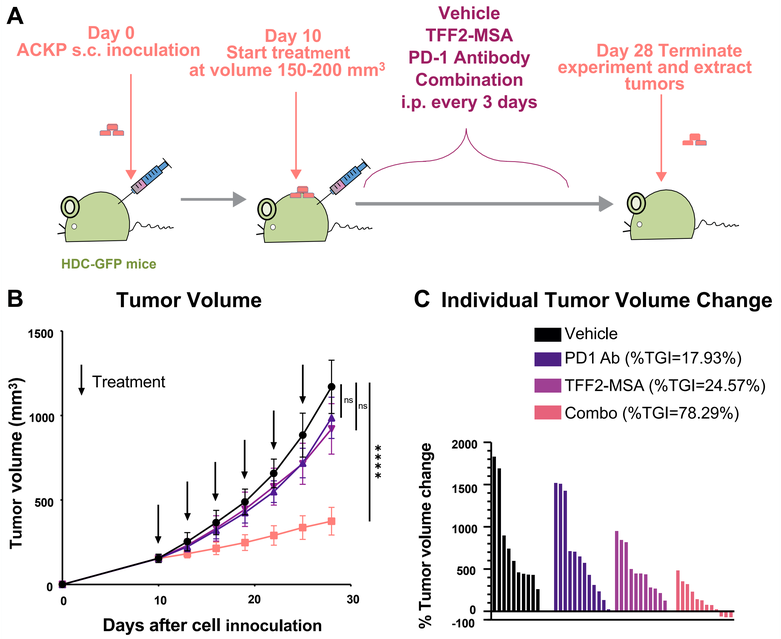
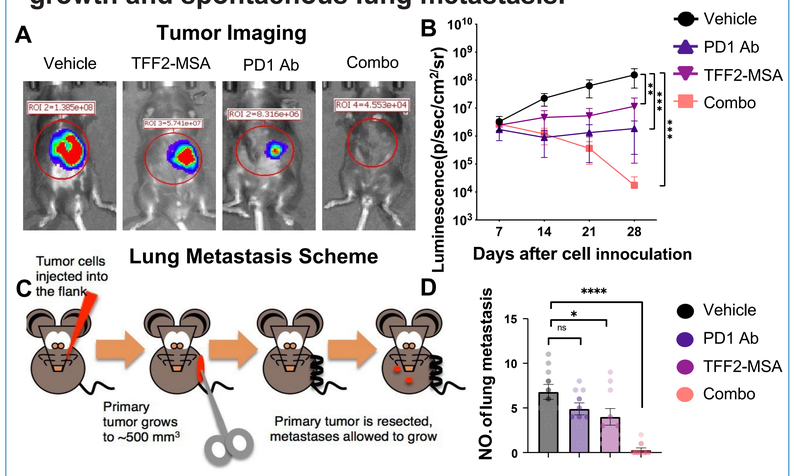
Results

Figure 1. TFF2-MSA showed synergy with anti-PD1 antibody in inhibition of s.c. ACKP xenograft growth.



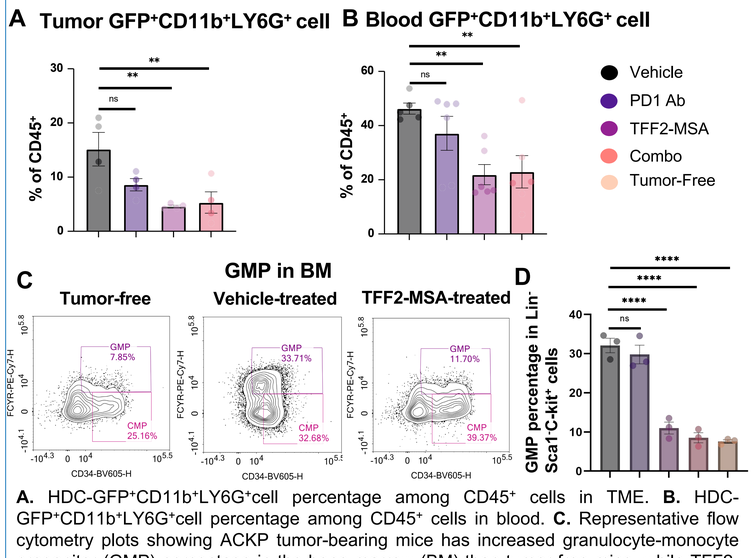
A. Schematic representation of the treatment scheme. **B.** Tumor growth curve of s.c. implanted ACKP tumors in response to anti-PD1 antibody, TFF2-MSA or their combination. **C.** Tumor volume change relative to the initial volume of each tumor. Each bar represents one tumor. Positive or negative value represents volume increase or decrease respectively. **** P < 0.0001.

Figure 2. TFF2-MSA showed synergy with anti-PD1 antibody in inhibition of orthotopic ACKP xenograft growth and spontaenous lung metastasis.



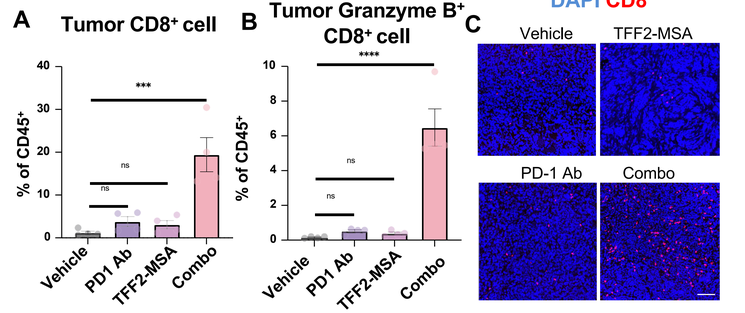
A. Representative bioluminescence images showing orthotopically injected ACKP tumors in response to different treatments. **B.** Bioluminescent intensity curves showing changes of orthotopic tumors. **C.** Schematic representation of the s.c. tumor resection scheme. **D.** Number of lung micrometastasis in mice from different treatment groups. * P < 0.05, **** P < 0.0001.

Figure 3. TFF2-MSA reduced MDSC accumulation in the tumor and biogenesis in the bone marrow



A. HDC-GFP$^+$CD11b$^+$LY6G$^+$cell percentage among CD45$^+$ cells in TME. **B.** HDC-GFP$^+$CD11b$^+$LY6G$^+$cell percentage among CD45$^+$ cells in blood. **C.** Representative flow cytometry plots showing ACKP tumor-bearing mice has increased granulocyte-monocyte progenitor (GMP) percentage in the bone marrow (BM) than tumor-free mice, while TFF2-MSA reduces GMP to a level similar to tumor-free mice. **D.** GMP percentage in Lin$^-$Sca1$^+$C-kit$^+$ cells within the BM. Data are presented as means ± SEM. One-way ANOVA. ** P < 0.01, **** P < 0.0001.

Figure 4. TFF2-MSA/Anti-PD1 Ab combination increased tumor-infiltrating CD8$^+$ T cell associated with a better effector phenotype.



A. CD8$^+$ t cell percentage among CD45$^+$ cells in TME. **B.** Granzyme B$^+$CD8$^+$ t cell percentage among CD45$^+$ cells in TME. **C.** Representative immunofluorescent images showing CD8$^+$ T cell infiltration into the TME. Scale bars: 100μm. Data are presented as means ± SEM. One-way ANOVA. *** P < 0.001, **** P < 0.0001.

Conclusion

TFF2-MSA (mTNX-1700) peptide synergizes with PD1 blockade therapy in advanced and metastatic GC syngeneic mouse models by reducing MDSC biogenesis and promoting a T cell-infiltrated tumor microenvironment.