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

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Recent studies revealed chemotherapies increase 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 gastric cancer (GC) by reducing tumor myeloid-derived cell (MDSC), which impedes antitumor T cell activity within the TME1.

Granulocytic MDSCs (PMN-MDSCs) are a heterogeneous group of immature myeloid cells that greatly expand in malignancies. They are functionally and transcriptionally distinct from mature neutrophils. PMN-MDSCs are short-lived and constantly replenished by the bone marrow progenitors3.

TFF2 has been shown to inhibit tumor growth by reducing MDSC expansion and proliferation in a colorectal cancer model.

HDC: MDSCs expressed higher levels of CXCR4 and are more immunosuppressive than their HDC counterparts. HDC: MDSCs profusely expand in colorectal cancer and its reduction leads to tumor control6.

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.

• Granulocytic MDSCs (PMN-MDSCs) are a heterogeneous group of immature myeloid cells that greatly expand in malignancies. They are functionally and transcriptionally distinct from mature neutrophils. PMN-MDSCs are short-lived and constantly replenished by the bone marrow progenitors3.

• Trefoil factor family 2 (TFF2) is a partial agonist for CXCR4, able to activate Ca+ signaling but in the presence of SDF-1, TFF2 partially inhibits SDF-1-dependent signaling and chemotaxis18.

• TFF2 has been shown to inhibit tumor growth by reducing MDSC expansion and proliferation in a colorectal cancer model.

• HDC: MDSCs expressed higher levels of CXCR4 and are more immunosuppressive than their HDC counterparts. HDC: MDSCs profusely expand in colorectal cancer and its reduction leads to tumor control6.

References


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 T cell-infiltrated tumor microenvironment.

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