A CXCR4 PARTIAL AGONIST TFF2-MSA SENSITIZED ADVANCED GASTRIC CANCER TO PD-1 BLOCKADE BY SYSTEMATICALLY REDUCING PMN-MDSC ACCUMULATION, IMMUNOSUPPRESSION, AND GENERATION IN BONE MARROW

Jin Qian*, 1Sandra Ryeom, 2Bruce L Daugherty, 1Seth Lederman, 1Timothy C Wang. 1Columbia University Medical Center, New York, NY, USA; 2Tonix Pharmaceuticals, Inc, Chatham, NJ, USA

Background Polymorphonuclear myeloid-derived suppressor cell (PMN-MDSC) is pathologically activated immature neutrophil that exerts immunosuppressive functions. PMN-MDSC is short-lived and constantly replenished through bone marrow (BM) myelopoiesis. Within the BM, histidine decarboxylase (HDC) expressing immature neutrophil constitute a histaminergic niche that enforces hematopoietic stem cell quiescence and inhibits pathological myelopoiesis.1 Trefoil factor family 2 (TFF2), a partial agonist for CXCR4, inhibits CXCL12-dependent chemotaxis.2 Here we engineered a stabilized TFF2 peptide linked to mouse serum albumin (TFF2-MSA), and investigated its effect on PMN-MDSC and combination with PD1 inhibitor in advanced gastric cancer mouse models.

Methods A syngeneic gastric cancer cell line ACKP (Atp4b-Cre; Cdh1-/-; LSL-KrasG12D; Trp53-/-) was grafted subcutaneously into HDC-GFP transgenic mice to trace HDC-GFP+MDSCs. Once tumors reach 200 mm3, mice received TFF2-MSA or/and anti-PD-1 antibody. The CXCR4 antagonist AMD3100 served as comparison to TFF2-MSA. We further established a spontaneous lung metastasis model in which mice bearing ACKP tumors received surgical tumor resection and subsequent TFF2-MSA/anti-PD-1 treatments. In another orthotopic model, ACKP-luciferase cells were implanted to stomach submucosa, and the treatments started after 1 week. At 1 month, flow cytometry and single cell RNA sequencing (scRNA-seq) were performed to study treatment induced immune profile changes.

Results Either TFF2-MSA or anti-PD-1 monotherapy showed little inhibition of subcutaneous ACKP tumor (15% and 25%, N=10, p>0.05), but their combination dramatically suppressed ACKP growth by 78% in a synergistic manner (p<0.0001). In the lung metastasis model, the combination completely abrogated metastasis in 80% mice (N=10, p<0.0001) and prolonged mice survival (p<0.0001), in contrast to minimal effect of either monotherapy (p>0.05). In the orthotopic model, although either monotherapy only slightly delayed tumor growth, their combination successfully eradicated tumor in 80% mice (N=5, p<0.001). Mechanically, TFF2-MSA systematically reduced HDC+ PMN-MDSCs in the TME, spleen and blood, and its combination with anti-PD-1 profoundly increased polyfunctional Tim-3*Lag-3*CD8+ T cells in the TME and TCF1+ T cells in the TDLN. Inside BM, TFF2-MSA decreased PMN-MDSC generation from its precursors (MPP3/CMP/GMP/GP) to a level similar to tumor-free mice, and restored hematopoietic stem cell quiescence via histamine feedback loop. Importantly, flow cytometry, scRNA-seq and functional analysis suggested TFF2-MSA treated PMN-MDSCs display a more mature profile with less immunosuppressive property. In contrast, AMD3100 plus anti-PD-1 failed to decrease tumor growth and TME MDSCs possibly due to destruction of BM hematopoietic homeostasis.

Conclusions TFF2-MSA systematically reduced PMN-MDSC, and its immunosuppression and generation in BM, thereby sensitizing advanced gastric cancer to PD-1 inhibitors.

REFERENCES

Ethics Approval For experiments in mouse models, all procedures for mice were approved by the Institutional Animal Care and Use Committee of Columbia University in accordance with institutional and NIH guidelines (protocol number AAABV0664).

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