MDSCs are a Major Therapeutic Target

Antonio: Myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment are a potential therapeutic target in immune checkpoint cancer therapy, but MDSC-targeted therapies have yet been shown to improve survival. Thelk factor family 2 (TFF2), a secreted anti-inflammatory peptide, can suppress MDSC expansion and activate tumor immunity in part through agonism of the CXCR4 receptor. The aim of this study is to investigate whether a novel TFF2–albumin fusion peptide (TFF2-MSA) can improve survival in anti-PD-1 treated syngeneic colorectal cancer (CRC) mouse models.

Methods: Two syngenic colon carcinoma mouse models were developed using cell lines grafted subcutaneously into mice. MC38 CRC cells were engrafted into C57BL/6 mice while CT26.s CRC cells were implanted 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 dose frequency. Mice subsequently received either mTFF2-MSA or anti-PD-1 antibody (clone 29F.1A12) or both, and tumor volume, and survival were measured. At the endpoint, flow cytometry was performed to examine treatment-induced effects on immune profiles.

Results: In the MC38 model, administration of mTFF2-MSA suppressed tumor growth (TGI 50%), the combination of mTFF2-MSA and anti-PD-1 had an additive effect and increased survival rate of 90% after 50 days, while vehicle and single mTFF2-MSA therapy had little effect, but the combination of anti-PD-1 and mTFF2-MSA showed a profound effect. In the CT26.s model, administration of mTFF2-MSA suppressed tumor growth (TGI 87%), anti-PD-1 alone (TGI 49%) and the combination of mTFF2-MSA and anti-PD-1 (TGI 60%).

Conclusion: Targeting MDSCs using TFF2-MSA fusion protein synergy with PD-1 blockade therapy in advanced and metastatic syngenic mouse models of colorectal cancer. In separate studies, additive effects between mTFF2-MSA and anti-PD-1 antibody were also demonstrated in separate APAP- and Cre-driven CRC xenografts. Tumor microenvironment strategy, combining TFF2-MSA treatment can be applicable to gastric cancer.

References