Abstracts

Immono-Conjugates and Chimeric Molecules

A LISTERIOLYSIN O-CD47 PROTEIN-ANTIBODY CONJUGATE TRIGGERS CGAS-STING ACTIVATION IN SOLID TUMOR MALIGNANCIES

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Background Tumor DNA is a potent activator of the cGAS-STING pathway. 1 CD47 is expressed on various tumor types including breast, prostate, glioblastoma, non-Hodgkin lymphoma, and hepatocellular carcinoma. Interrupting the CD47-SIRP alpha axis by monoclonal antibodies fosters macrophage-mediated phagocytosis of solid and hematopoietic tumor cells. 2 The pore-forming protein listeriolysin O (LLO) polymerizes and activates in the acidic vacuoles of antigen presenting cells. 3 We hypothesize that LLO conjugation to the anti-CD47 mAb (anti-CD47) enhances the release of tumor DNA within macrophages thereby augmenting cGAS-STING activation, antigen presentation, and tumor phagocytosis.

Methods LLO-CD47 is a protein-antibody conjugate that joins anti-CD47 to LLO using a water-soluble SPDP crosslinker and purified by affinity chromatography. The cytotoxicity of LLO-CD47 relative to anti-CD47 was tested in the mouse breast cancer cell line E0771, the human breast cancer cell line MDA-MB-468, the mouse lung cancer cell line LLC, and the human leukemia monocyctic cell line THP-1. C57B6 mouse bone marrow-derived macrophages (BMDM) co-cultured with tumor cell lines were analyzed in the presence of LLO-CD47 and anti-CD47 to determine the efficiency of BMDM tumor cell phagocytosis, STING activation, and antigen presentation.

Results Tumor growth of E0771-bearing wildtype mice was measured following intratumoral injection of anti-CD47 and LLO-CD47.

Conclusions Conjugation of the LLO protein to anti-CD47 enhances macrophage cGAS-STING activation, antigen presentation, and tumor cell phagocytosis. This novel LLO-CD47 protein-antibody conjugate builds on clinical interest in targeting macrophages for the treatment of malignancy and may be studied as a supplemental therapy for patients with tumors resistant or refractory to checkpoint therapy.

Ethics Approval Studies involving animals were submitted to, reviewed, and approved by MD Anderson’s Institutional Animal Care and Use Committee in accordance with all applicable animal welfare regulations; protocol number 00002163-RN00.

REFERENCES