Antibody targeting soluble NKG2D ligand sMIC remarkably enhances CTLA4 blockade therapy for metastatic prostate cancer in pre-clinical models

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Background: Shedding of soluble NKG2D ligand sMIC is prevalent among almost all solid-tumor originated malignancies. Tumor-derived sMIC has been shown to interfere with optimal CD8 T cell function by downregulating NKG2D expression. This concept was supported by the clinical observation that cancer patients developed anti-sMIC autoantibody responded more favorably to checkpoint CTLA4 blockade. However, how elevated serum sMIC in cancer patients interferes with the efficacy of CTLA4 blockade and whether sMIC-neutralizing antibody can enhance the responsiveness to anti-CTLA4 therapy remains unknown. Due to the limitation that rodents do not express orthologue of human MIC and the discrepancy in behavior of human and mouse NKG2D natural ligands, these questions had not been interrogated in an *in vivo* model.

Methods: Using a "humanized" MIC-transgenic spontaneous prostate cancer mouse model which recapitulates the NKG2D-mediated onco-immune dynamics of human cancer patients, we addressed the impact of tumor-derived sMIC on the efficacy of anti-CTLA4 therapy. We also addressed the combinatory therapeutic effect of a sMIC-neutralizing antibody B10G5 and anti-CTLA4 antibody. We also recapitulated the observation in TRAMP/MIC mice with transplantable tumor models.

Results: 1) TRAMP/MIC mice with elevated serum sMIC ($sMIC^{hi}$) responded poorly to anti-CTLA4 therapy with significantly shortened survival due to worsening diseases; 2) co-administration of a sMIC-neutralizing antibody with anti-CTLA4 antibody alleviated the unfavorable responses in $sMIC^{hi}$ animals and generated cooperative CD8 T cell anti-tumor responses and therapeutic effect.

Conclusion: These findings endorse a new therapeutic modality to improve the clinic response to anti-CTLA4 therapy. Our findings also suggest the need for pre-screening cancer patients for serum sMIC to eliminate the potential unfavorable effect of CTLA4 blockade therapy to worsen diseases.

Conflict of Interest: Jennifer Wu is the inventor the sMIC-neutralizing antibody B10G5 and is also founder of CanCure LLC who is developing B10G5 into commercialization.

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