878 T CELL IMMUNOTHERAPIES RECRUIT AND ACTIVATE NEUTROPHILS TO ELIMINATE TUMOR ANTIGEN ESCAPE VARIANTS

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Background The immune system eliminates cancers in the early stages of malignant transformation. However, the presence of immune cells exerts selective pressure on tumors, which can result in tumor editing, leading to the development of immune escape variants. A common occurrence in cancers is the loss of antigenic protein expression on tumor cells, which creates antigenic heterogeneity and makes tumors resistant to immunotherapies such as adoptive cell therapies. Consequently, it is necessary to study and engage multiple components of the immune system in immunotherapeutic interventions to effectively eradicate heterogeneous tumors.

Methods This study aimed to assess the efficacy of a combination therapy involving CD4+ T cells recognizing the melanoma antigen Trp1 in conjunction with either OX40 co-stimulation or CTLA-4 blockade (ICB) for eradicating advanced melanomas containing antigen escape variants in preclinical mouse models.

Results The combination therapy successfully eliminated antigen-loss variant clones in a preclinical mouse model of melanoma with heterogeneous Trp1 expression. Mechanistically, tumors from treated mice exhibited significant infiltration of activated neutrophils, which was also observed in cancer patients following ICB therapy. Depletion of neutrophils in our preclinical melanoma model of antigenic heterogeneity abolished the therapeutic efficacy of the combination treatment. Our findings revealed the importance of inducible nitric oxide synthase in neutrophil-mediated elimination of escape variants. Furthermore, neutrophils derived from tumors of treated mice exhibited a distinct transcriptomic and protein surface signature associated with anti-tumorigenic properties. This anti-tumorigenic neutrophil signature was also observed in tumors from melanoma patients treated with ICB that experienced survival benefits.

Conclusions Our findings demonstrate the interplay between T cells, which initiate the anti-tumor immune response, and neutrophils, which contribute to the elimination of tumor antigen loss variants in later stages. These insights underscore the potential of combined therapies in overcoming clonal escape variants in melanoma and provide valuable information on the role of neutrophils in tumor eradication when employing T cell immunotherapies.

Ethics Approval All tissues collected at MSKCC following study protocol approval by the MSKCC Institutional Review Board. Informed consent was obtained for all patients. The study was in strict compliance with all institutional ethical regulations.

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