Special Seminar
Department of Medical Microbiology and Immunology
Cancer Immunology Faculty Recruitment

Monday, July 8, 2019 at 2 p.m.
“Resistance Mechanisms and Toxicities to Immune Checkpoint Inhibition”

Publication reference

Abstract
Resistance to checkpoint-blockade treatments is a challenge in the clinic. We found that although treatment with combined anti-CTLA-4 and anti-PD-1 improved control of established tumors, this combination compromised anti-tumor immunity in the low tumor burden (LTB) state in pre-clinical models as well as in melanoma patients. Activated tumor-specific T cells expressed higher amounts of interferon-γ (IFN-γ) receptor and were more susceptible to apoptosis than naive T cells. Combination treatment induced deletion of tumor-specific T cells and altered the T cell repertoire landscape, skewing the distribution of T cells toward lower-frequency clonotypes. Additionally, combination therapy induced higher IFN-γ production in the LTB state than in the high tumor burden (HTB) state on a per-cell basis, reflecting a less exhausted immune status in the LTB state. Thus, elevated IFN-γ secretion in the LTB state contributes to the development of an immune-intrinsic mechanism of resistance to combination checkpoint blockade, highlighting the importance of achieving the optimal magnitude of immune stimulation for successful combination immunotherapy strategies.

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GBSF 1005

Medical Microbiology
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