High dimensional dissection and therapeutic engineering of the tumor immune microenvironment

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Abstract

Blockade of the PD-1 pathway has not only revolutionized cancer immunotherapy but furthermore, cancer therapy in general. Moving forward, it is critical to understand mechanisms of resistance to anti-PD-1/PD-L1 blockade. One of the best clinical formats to study fundamental mechanisms of resistance is neoadjuvant therapy. Combining coupled single cell RNAseq/TCRseq with a sensitive assay for neoantigen-specific T cells, termed MANAFEST (Mutation-Associated NeoAntigen Functional Expansion of Specific T cells), we have been able to define transcriptional programs of tumor-specific T cells associated with response vs non-response to anti-PD-1 containing treatment regiments. Using this information, we developed a machine learning algorithm to predict tumor-reactive T cells based on expression levels of three genes: CD39, CXCL13 and IL-7R. This signature predicts T cells reactive with mutation-associated neoantigens, tumor-associated cancer-testes antigens and tumor virus associated antigens. Tumor-reactive T cells from anti-PD-1 responders had increased levels of IL-7R and granzyme K, while those from non-responders had higher levels of cytotoxic genes, checkpoints and Tox2. Our single cell analysis also identified distinct subsets of TIL Treg associate with non-response to anti-PD-1, the later being an “ex-Treg” that has acquired a Thelper1 program. These findings identifynspecific molecules as novel therapeutic targeting in combination with PD-1 blockade as well as biomarkers that can guide their application in precision immunotherapy.

Biography

Dr. Pardoll is an Abeloff Professor of Oncology, Medicine, Pathology and Molecular Biology and Genetics at the Johns Hopkins University, School of Medicine. He is the Director of the Bloomberg~Kimmel Institute for Cancer Immunotherapy and Director of the Cancer Immunology Program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Dr. Pardoll has published over 400 papers as well as over 20 book chapters on the subject of T cell immunology and cancer vaccines. Over the past two decades, Dr. Pardoll has studied molecular aspects of dendritic cell biology and immune regulation, particularly related to mechanisms by which cancer cells evade elimination by the immune system. Dr. Pardoll discovered one of the two ligands for the PD-1 inhibitory receptor and leads the Hopkins cancer immunology program that developed PD-1 pathway-targeted antibodies, demonstrating their clinical activity in multiple cancer types.