948 DEVELOPING ENGINEERED ANIMAL MODELS TO INVESTIGATE TUMOR-SPECIFIC T CELL RESPONSES AND IMMUNE-RELATED ADVERSE EVENTS AFTER IMMUNOTHERAPY

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Background The rise of immune checkpoint blocking therapies (ICBs) as treatments across multiple cancer types has revealed a previously underappreciated role for the immune response in the natural regulation of cancer development. ICBs potentiate the functions of anti-tumor CD8 T cells, leading to durable tumor regression, yet, ICB treatment (particularly combination ICB) is associated with frequent and poorly-understood immune related adverse events (irAEs), which has limited the broader use of combination ICB. Thus, it is important to better understand how ICBs impact T cell responses in both tumor and non-tumor contexts, and these differ.

Methods A major gap in the field remains the availablity of animal models that faithfully recapitulate the immune-tumor microenvironment associated with different types of human cancers, and models that recapitulate the disease biology of irAEs. Our laboratory previously developed the iNversion INducible Joined neoAntigen (NINJA) model, which allows for tight spatial and temporal regulation of the induction of an known neoantigen. Using NINJA, my lab has now developed autochthonous genetically engineered mouse cancer models for studying anti-tumor T cell responses and models for studying the mechanisms by which ICBs break peripheral T cell tolerance and result in irAEs. We use paired single cell-RNAseq (scRNAseq) and T cell receptor (TCR) seq to validate that our NINJA models faithfully recapitulate the responses of T cells participating in human irAEs and in human cancer. Moreover, because T cells recognize the same antigen across all our models, tumor-specific and disease-causing CD8 and CD4 T cells can be directly compared.

Results In a model of skin-antigen induction, we identified recruitment of CD11c+ CD11b+ CD14+ CD16+ PD-L1+ myeloid cells in response to effector CD8 T cell infiltration, but not disease—unless mice are also treated with anti-PD-1 antibodies—suggesting that skin myeloid cells prevent disease pathology via the PD-1 pathway. Analyses of the CD8 T cells showed a PD-1-blockade induced upregulation of CD103 and Granzyme A, but otherwise minimal transcriptional impact. By contrast, protein-level increases in effector cytokines and degranulation were associated with blockade, as was migration into the epidermis and tissue destruction. Similar clonal CD8 T cell expansion and increased effector gene expression was seen in skin irAE patients.

Conclusions These data highlight that NINJA serves as platform for understanding mechanisms that lead to irAEs in different tissues, which could be used to testing interventions to prevent ICB-induced disease. Ongoing work focuses on elucidating the role of PD-1/PD-L1 in skin-myeloid cell-mediated suppression of skin-specific CD8 T cells.

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