HOST MYELOID RESPONSE TO TUMOR AND IMMUNOTHERAPY IS ASSOCIATED WITH HETEROGENEITY IN OUTCOMES TO ANTI-PDL1

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Background Immune checkpoint inhibitors (ICI) improve patient survival in some cancer types but yield limited success in breast cancer. Phase-III clinical trials in triple-negative breast cancer (TNBC) patients, who harbor extensive tumor-infiltrating lymphocytes, demonstrate increased progression-free survival (IMpassion130) and pathologic complete response (KEYNOTE-522). Consequently, combinations of ICI and chemotherapy have been FDA-approved for metastatic TNBC patients. However, the therapeutic benefit of ICI alone and the most efficacious chemotherapy combinations are poorly characterized. We sought to model ICI response in vivo to elucidate the mechanisms of immunotherapy efficacy in breast cancer and ascertain the therapeutic benefits of different chemotherapeutic combinations with ICI.

Methods Using an immunocompetent EMT6 orthotopic mammary tumor model, we investigated the efficacy of single-agent immunotherapy and in combination with standard-of-care chemotherapy (paclitaxel [PAC] or doxorubicin [DOX]). We used single-cell RNA sequencing and bulk RNA and T-cell receptor (TCR) sequencing to assess the cellular landscape of the primary tumor in response to combinatorial therapeutic strategies and identify systemic genetic alterations and T-cell expansion, respectively.

Results Single-agent anti-PD-L1 robustly suppressed primary tumor growth ($p = 0.0046$) and extended survival ($p < 0.0001$) beyond the isotype control. Chemotherapy demonstrated moderate therapeutic efficacy without potentiating the benefit of single-agent anti-PD-L1. Interestingly, despite using a genetically identical murine tumor model/host, anti-PD-L1 induced heterogeneous responses, from complete response to intrinsic resistance. Longitudinal analysis of peripheral blood from heterogeneously responding mice uncovered myeloid cell recruitment signatures corresponding to transient responses ultimately converting to resistance. We identified specific clonal T cell expansion present only in responders. Single-cell transcriptomic profiling of the tumor microenvironment revealed increased T cells and natural killer cells and reduced regulatory T cells in the combination groups versus chemotherapy alone, although this did not translate into improved benefit. Gene-set enrichment analysis on infiltrating T cells identified a robust signature of cytotoxic T cell activation characterized by a significant enrichment in inflammatory pathways in both single-agent anti-PD-L1 and in combination with chemotherapy.

Conclusions We identify a heterogeneously ICI-responsive in vivo model that emulates TNBC patient response to combinatorial ICI approaches. We describe single-agent ICI efficacy in upregulating cytotoxic immune cell infiltration and expansion within the primary tumor that diminishes tumor growth and enhances survival. Moreover, this study describes differential responses in a genetically similar host, which reflects heterogeneous patient response to ICI. Further characterization may identify systemic biomarkers and tumor antigen-specific T cell clones to accurately predict immunotherapy response in patients and uncover mechanisms for sensitizing refractory tumors to ICI