538 LONGITUDINAL TRANSCRIPTOMIC LOCAL AND PERIPHERAL CHANGES ARE ASSOCIATED WITH IMMUNOTHERAPY RESISTANCE IN MURINE MODEL OF TRIPLE NEGATIVE BREAST CANCER

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Background Immune activating checkpoint inhibitors (ICI) improve patient survival in many cancer types with limited success in breast cancer. Phase-III clinical trials in triple-negative breast cancer (TNBC) patients report increased pathologic complete response. Despite FDA approval of ICI combinations with standard-of-care chemotherapy, many patients treated are resistant to ICI, and the underlying mechanisms of resistance and their diversity are poorly understood.

Objective Identifying reliable pre-clinical models to evaluate therapeutic resistance, heterogeneity in response, synergistic therapeutic efficacy, and predictive biomarkers for response to ICI.

Methods Using an immunocompetent murine tumor model of TNBC (EMT6), we investigated the efficacy of anti-PD-L1. To identify local and systemic transcriptomic alterations as well as clonal T-cell expansion, fine-needle aspirations of the primary tumor microenvironment and peripheral blood from mice with differential responses were longitudinally assessed by single-cell (or bulk) RNA sequencing and T-cell receptor (TCR) sequencing.

Results Systemic PD-L1 blockade significantly reduced mammary EMT6 tumor growth and promoted dendritic and CD8 T cell infiltration. Similar to clinical findings, favorable response was independent of PD-L1 expression. Combinations of standard-of-care chemotherapy (paclitaxel or doxorubicin) demonstrated modest therapeutic efficacy without potentiating anti-PD-L1 monotherapy benefit. Interestingly, anti-PD-L1 induced heterogeneous responses, recapitulating clinical patient outcomes, denoted by complete response and both acquired and intrinsic resistance. Mice transplanted with previously anti-PD-L1-treated (resistant) tumors retained heterogeneous responses, indicating that host-intrinsic, rather than tumor-intrinsic factors, dictate response to ICI. Despite using a genetically identical murine tumor model/host, transcriptomic analysis of the primary tumor landscape showed upregulated cytotoxic T cell response and activation signatures, specifically inflammatory interferon signaling (both at baseline and post anti-PD-L1 administration) that corresponded to favorable response to ICI. Longitudinal analysis of the peripheral blood uncovered clonal T cell expansion present only in responder mice. Further transcriptomic analysis revealed modest changes among mice at baseline, particularly myeloid cell recruitment signatures, that progressively deviated by response type (resistant-vs-responder mice). Blocking myeloid cell recruitment using navaraxin (CXCR1/2 inhibitor), anti-LY-6G or anti-CSF1R enhanced response to ICI, further suppressing tumor growth and enhancing survival.

Conclusions We describe a heterogeneously ICI-responsive mammary murine model, which reflects heterogeneous patient response to ICI. Longitudinal host-specific signatures, specifically myeloid and T cells, correlating with differential response to ICI may serve as rationale for tracking ICI response in peripheral blood from breast cancer patients. Ongoing efforts to phenotypically characterize clinical specimens from patients treated with CXCR1/2 inhibitors will elucidate mechanisms responsible for response to ICI and uncover strategies for sensitizing refractory tumors to ICI.

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