

Single-cell gene expression profiling of the tumor immune microenvironment (TIME) and its association with immunotherapy response in syngeneic mouse models

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Abstract Content:

The TIME, comprised of the extracellular matrix and a milieu of both immune and non-immune cells, plays a critical role in tumor development, disease progression, and response and resistance to immunotherapy. Much of our understanding of the TIME's immunological features, cellular heterogeneity, and associations with immunotherapy response have come from the use of syngeneic mouse models representing various cancer cell types. To provide further characterization of the TIME in syngeneic mouse lines commonly used for immunogenic drug discovery, Cd45+ single-cell RNA sequencing was performed in 10 syngeneic mouse models representing 7 distinct cancer types (breast mammary carcinoma: 4T1, EMT6, MMTV-PyMT; colon carcinoma: CT26.WT, MC38; glioma: GL261; renal adenocarcinoma: Renca; lung carcinoma: LL2; melanoma: B16F10; and pancreatic adenocarcinoma: Pan02). Further, to unveil cellular subpopulations that correspond to immunotherapy response, anti-PD-(L)1 therapy efficacy studies were performed in the syngeneic models and correlations with the abundances of distinct immune cell populations were explored.

Across all syngeneic tumor lines examined, seven major immune cell populations were identified and subpopulations within T cells, NK cells, innate lymphoid cells, and distinct myeloid cells were characterized. This included a previously unidentified subset of immune cells including Foxp3+ CD8 T cells and Halios-high-Foxp3-/low cells. Efficacy of anti-PD-(L)1 treatment was positively correlated with a unique population of ISGhigh macrophages. Finally, an over-representation of neutrophils and proliferating/C1Q+ macrophage subsets was observed in models exhibiting resistance to anti-PD-(L)1 treatment.

These findings provide further characterization of these syngeneic lines to aid in rational model selection to facilitate translational relevance. This study also provides further insight into how immune cell composition and abundance within tumors may contribute to immune checkpoint blockade resistance.