Interleukin-33 Promotes Th17 Cell Clonal Expansion in the B16 Tumor Microenvironment

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Cancer immunotherapy has led to vast improvements in long-term survival for patients with cancers like melanoma. However, the low response rate of immune checkpoint blockade (ICB) therapy limits its clinical impact. Thus, the anti-tumor efficacy can be improved by enlisting immune-stimulatory signals. Interleukin-33 (IL33) is a danger signal or “alarmin” highly expressed in normal epithelial cells but downregulated in high-grade tumor cells. Still, whether IL33 drives anti-tumor immune responses is controversial and the underlying cellular mechanisms are not well understood. I hypothesize that IL33 reorganizes the immune cellular network in the tumor microenvironment (TME) through tumor-infiltrating CD4+ T cells. Here, I analyzed deep Single-cell RNA sequencing of 11,022 T cells from genetically engineered mouse models of human melanoma normal tumors (B16) and IL33 secreting tumors (B16-IL33). Dimension reduction and unsupervised clustering enabled me to identify T cell subsets. Furthermore, trajectory analysis coupled with T cell receptor (TCR) sequences delineated their developmental trajectory. Finally, I created genetic signatures and performed survival analysis to determine if subsets were pro- or anti-tumorigenic. I identified 6 subsets of CD4+ T cells: ThNaïve, ThEarly, Th17, Th1, ThExhausted, and ThCytotoxic. Specific subsets like ThNaïve were preferentially enriched in the B16 population. Most notably, clonotype and compositional analysis show tumor-derived IL33 leads to clonal expansion of Th17 cells. Moreover, survival analysis suggests higher levels of Th17 are associated with better clinical outcomes. This study helps further elucidate the role of IL33 in reorganizing infiltrating T cells in the TME and highlights potential paths to improve ICB therapy.

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