A tale of two species: Unveiling the involvement of type 3 dendritic cells with immune checkpoint blockade poor outcome

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Abstract:
ICB therapies represent the preferred choice for lung cancer treatment. However, only a minority of patients benefit from these immunotherapies. Conventional dendritic cells (cDCs) play a pivotal role in activating adaptive immune responses. They include cDC1s and cDC2s, with cDC2 represented by two major populations: DC2s and DC3s. DC3s have significant implications in chronic conditions such as lupus, psoriasis, and severe COVID-19.

We investigated the potential role of DC3s in lung cancer by analyzing publicly available scRNAseq datasets of non-small cell lung cancer (NSCLC). We observed an enrichment of DC3s with a potential immunosuppressive phenotype in advanced stages. This was accompanied by a reduction in the frequency of DC2 and cDC1 subsets. By conducting cross-species scRNAseq analysis of human and mouse lung cells, we identified tissue murine DC3s and established a flow cytometry-based method for cDC1s, DC2s, and DC3s distinction. We confirmed DC3 enrichment in an ICB-resistant adenocarcinoma mouse model, mirroring findings in advanced human lung adenocarcinoma.

Using a multiplexing analysis, we spatially mapped immune components in mouse adenocarcinomas. This revealed that DC2s were located outside the tumor, while DC3s were positioned inside the tumor near CD4+ T cells, including Tregs. Similar proximity between cDC2s and CD4+ T cells was confirmed in human tumors. DC3s constituted the primary subpopulation among cDC2s in NSCLC. Furthermore, an analysis of whole-slide sections demonstrated remarkable heterogeneity in T cell and DC distribution within the same tumor. Some regions were enriched in DC3s and CD4+ T cells, while others in CD8+ T cells but lacked DC2s.

Our investigation is still ongoing to obtain functional insights through CITE-seq and single-cell spatial transcriptomic analyses on adenocarcinoma samples. Given that ICB therapy relies on reactivating CD8+ T cells, confirming that DC3-and CD4+ T cell infiltration is preferred in advanced stages could provide valuable insights into ICB treatment outcomes.