Single-cell analysis reveals distinct differentiation trajectories and immunoregulatory roles of DC3 subsets in NSCLC

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Abstract:

Conventional dendritic cells (cDCs) are central to activating adaptive immune responses and include cDC1s and cDC2s, with cDC2s further classified into DC2s and DC3s. DC3s have been implicated in chronic diseases such as lupus, psoriasis, and severe COVID-19.
Moreover, advanced-stage NSCLC human samples revealed an enrichment of DC3s with a potential immunosuppressive phenotype, alongside a reduction in DC2 and cDC1 subsets.

Our study focused on leveraging computational pipelines tailored for the intricate nature of dendritic cell subpopulations. To deepen our understanding of their roles, we produced a CITE-seq dataset of dendritic cells from healthy and tumoral mouse lung tissues. Using this dataset, I performed a specifically customized single-cell workflow, encompassing cell clustering, differential gene expression analysis, gene set enrichment analysis, and pseudotime trajectory inference.

Significant effort was dedicated to benchmarking and refining various trajectory analysis methods to identify the most reliable approach that ensured robust identification of DC subsets and highlighted their transcriptional dynamics.
This computational framework provided key insights into the distinct differentiation trajectories of DC3s compared to other cDC2s. It also shed light on their potential immunosuppressive role and distinct behaviors arising from diverse cellular ontogenesis.

These analyses lay the groundwork for advanced spatial localization studies in NSCLC mouse samples. Such analyses aim to elucidate the immune regulatory role of DC3s in advanced NSCLC and highlight the potential impact of DC3- and CD4+ T cell-enriched microenvironments on the efficacy of immune checkpoint blockade (ICB) therapy.