Tissue-specific imprinting shapes conventional dendritic cell functionality in tumors and non-malignant tissues

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Abstract:
The tumor microenvironment (TME) is a complex ecosystem comprising diverse cell populations, including immune cells, that play pivotal roles in cancer development and response to therapies. Conventional dendritic cells (cDCs) are crucial antigen-presenting cells influencing adaptive immunity and tumor progression, but their adaptations within the TME remain unclear. Here, by performing an in-depth single-cell analysis, we investigated cDC subsets across human tumors, including both immunologically cold and hot malignancies, and delineating their functional states and tissue-specific plasticity. Our integrated analyses across tumors revealed four cDC phenotypes: cDC1s, cDC2s, CCR7$^+$ DCs, and CD207$^+$ DCs.

CD207$^+$ DCs, enriched in tumor tissues, exhibit a unique transcriptional profile linked to inflammatory responses and type 1 immunity. Strikingly, in immunologically hot cancers, CD207$^+$ DCs are enriched in the early stages of the disease and correlate with improved patient survival. These features were not observed in immunologically cold tumors.

We also investigated the transcriptional alterations in cDC subsets infiltrating hot and cold tumors, showing that cDC2 were the most impacted by the different tumor microenvironments. In detail, in hot tumors, their transcriptomes exhibited upregulation of genes involved in chemokine-mediated immune cell trafficking and antigen presentation, likely promoting immune cell recruitment.

Furthermore, tissue-specific imprinting influences cDC2 plasticity not only within tumors but also in non-malignant tissues, as they were found to have the greatest number of differentially expressed genes (DEGs) among DC subsets when comparing normal tissues, indicating a non-negligible role of tissue imprinting in shaping cDC2 functionality.

Collectively, our findings illuminate cDC adaptations in both tumoral and steady state conditions, particularly highlighting their functional plasticity and role in immune cell recruitment, driven by tissue imprinting and paving the way for tailored immunotherapies. Understanding the interplay between cDC2s and the TME holds promise for enhancing therapeutic strategies and advancing precision oncology, as they could emerge as fire starters for cold tumors.