Multimodal analysis of tissue resident dendritic cells reveals the immunosuppressive role of DCs type 3 in human NSCLC and a mouse lung tumor model

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Abstract:

Conventional dendritic cells (cDCs) play a pivotal role in activating adaptive immune responses against infectious diseases and impact on cancer progression. cDCs include cDC1s and cDC2s, the latter comprising DC2s, which can be further subdivided into DC2As and DC2Bs, and DC3s. DC3s have been implicated in chronic inflammatory conditions such as lupus, psoriasis, and severe COVID-19. Intratumoral cDCs are positively correlated with responsiveness to immune checkpoint blockade (ICB) therapies.

Inflammatory DCs were detected in the ascitic fluid of patients with ovarian or breast tumors. Additionally, DCs expressing CD14 and CD1c — potentially representing the DC3 subtype — identified in the tumor microenvironment (TME) of melanoma patients exhibited immunosuppressive activity. Given this potential intratumoral immunosuppressive role, DC3s may contribute to resistance mechanisms hampering the long-term efficacy of ICB therapies in cancer patients. Non-small cell lung cancer (NSCLC) offers ideal settings to investigate the role of DC3s in tumor progression. Although NSCLC patients initially respond well to ICB therapies, their long-term prognosis remains poor due to the development of resistance.

Leveraging tissue multiplexing techniques, CITE-seq mouse datasets, and publicly available scRNA-seq datasets, we discovered that DC3s expand in early stages of NSCLC patients as well as in preclinical mouse models of NSCLC. The DC3s showed a prominent intratumoral localization and were the main T-cell interacting tissue DCs. Functionally, DC3s displayed enhanced immunosuppressive and reduced antigen-presentation activities compared to DC2Bs. Cross-species alignment analysis using single-cell transcriptomic data of human and mouse lung tumors validated the markers employed to distinguish murine DC3s from DC2Bs and highlighter their functional conservation.

In summary, this work provides compelling evidence of the existence of human and mouse tissue DC3s in lungs and unveils their pro-tumorigenic function. Single-cell analyses, including cross-species alignment, shed new light on the ontogenetic and functional differences between DC2Bs and DC3s, underscoring the heterogeneity of DCs in cancer. These findings bear implications for ICB therapies in cancer, the benefit of which would increase by targeting immunosuppressive DC3s.