ID: 03352

Topic: INMUNOTHERAPY

Spatial single-cell analysis of systemic breast cancer metastasis reveals immune mediators of multi-organ colonization

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Metastasis frequently affects not only one, but several organs in stage IV breast cancer patients. The most common sites of distant metastasis in breast cancer are brain, lung, liver, and bone, and multi-organ metastasis is associated with dismal disease outcome. Although many efforts have been made to decipher mechanisms of metastatic growth in individual secondary sites, less is known about common mechanisms enabling systemic cancer cell colonization of multiple organs. Various cell types within distant organs engage in homo- and heterotypic molecular interactions, forming metastatic ecosystems that dictate colonization. Deconvoluting this cellular and molecular complexity at a systems level and elucidating common mechanisms that promote cancer cell growth in different organs is essential to develop novel strategies to control advanced disease.

To dissect cellular and molecular complexities of systemic metastasis, we combined an immunocompetent mouse model of multi-organ metastasis with single-cell RNA sequencing (scRNA-seq). We employed GFP/luciferase-labeled cancer cells secreting a niche-labeling mCherry tag that were inoculated systemically via intracardiac injection, which resulted in metastatic seeding in multiple organs. Following colonization, we used flow cytometry to separate cancer cells, metastatic niche, and distant stroma populations from brain, lung, liver and bone, and subjected them to scRNA-seq.

Spatially compartmentalized analysis revealed similarities in metastatic ecosystems across different sites, along with organ-specific differences. Metastatic niches across all organs were prominently enriched in myeloid cells, particularly tissue-resident as well as bone marrow-derived macrophages with immunosuppressive activity. Interestingly, we also observed accumulation of myeloid-derived suppressor cell (MDSC)-like neutrophils in metastasized organs, and exclusion of T cells from metastatic niches. To identify common pro-metastatic molecular interactions between cancer cells and metastasis-associated macrophages (MAMs) across organs, we computed cell-to-cell communication. This revealed that the ligand-receptor interaction between cancer cell derived macrophage migration inhibitory factor (MIF) and CD74 expressed on MAMs occurs in brain, lung, liver, and bone metastases. This analysis also predicted interaction between cancer cell-derived Pleiotrophin (PTN) and its cognate receptor Nucleolin (NCL) in cancer cells and in MAMs across metastatic sites. Importantly, we demonstrate that both MIF and PTN promote multi-organ metastatic colonization in breast cancer.

Our work provides an unprecedented spatially resolved scRNA-seq dataset encompassing metastasis to multiple organs within the same host. By analyzing this dataset, we identified MIF and PTN as mediators of systemic metastasis in breast cancer. This data suggests that pharmacological targeting the MIF-CD74 and the PTN-NCL axes may represent a promising therapeutic strategy for patients with advanced breast cancer.