

MYELOID DIVERSITY IN HORMONE RECEPTOR POSITIVE BREAST CANCER REVEALS MYELOID AND LYMPHOID SIGNALING PATHWAYS THAT CORRELATE WITH T CELL INHIBITION

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Background Targeting the body's own immune system to fight cancer has focused on activating T cells through immune checkpoint blockade (ICB). Because ICB agents work by reinvigorating pre-existing T cells, it is less likely that these agents will be effective in tumors with low levels of T cell infiltrate. Hormone receptor positive (HR+) breast cancer (BC) is characterized by low T cells. Consistent with this, studies to date have shown that ICB has minimal clinical activity in HR+ BC. The tumor microenvironment (TME), devoid of nutrients and oxygen, recruits tumor associated macrophages (TAMs) that promote angiogenesis, metastasis and tumor growth and inhibit anti-tumor T cell responses. Removal or conversion of TAMs to an anti-tumor phenotype enhances chemo- and immuno-therapy and establishes TAMs as targets for anti-cancer therapy. We have revealed that TAMs are prevalent in HR+ BC however the relationship between TAMs and T cell infiltration has not yet been extensively studied in this context. This study aims to uncover the diversity of myeloid cells in HR+ breast cancer and determine their relationship with lymphoid cells.

Methods We conducted a comprehensive transcriptomic and phenotypic analysis of myeloid cells from 20 primary, treatment-naïve HR+ breast tumors using single cell RNA sequencing (scRNA-seq). We identified key signaling pathways involved within the myeloid and lymphoid populations using Louvain clustering algorithm and single sample gene set enrichment analysis (ssGSEA) to identify key signaling pathways involved within the myeloid and lymphoid populations. We focused on pathway and phenotype analysis and investigated the relationship between myeloid and lymphocyte populations.

Results Clustering of the scRNA-seq data revealed 33 distinct populations that were identified as tumor, myofibroblasts, endothelial, lymphoid, or myeloid cells. Re-clustering of myeloid (10,637 cells) and lymphoid (17,688 cells) clusters revealed 18 distinct clusters of both myeloid and lymphoid cells that were present in most tumors. C1Q+ macrophages with antigen presentation and IFN γ signaling pathways were associated with proliferating T cells, CXCL13+ T cells and CD8+ T cells whereas SPP1+CD36+ lipid-associated TAMs were associated with FoxP3+ T cells as well as B cells.

Conclusions Our findings reveal a diverse myeloid landscape in HR+ breast cancer that is associated with differences in T phenotype and activity. The highlighted myeloid subsets and signaling pathways might serve as therapeutic targets. Ongoing investigation includes validation of these results and exploring potential strategies to modulate myeloid cell function, aiming to enhance the efficacy of immunotherapies in HR+ breast cancer.

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