Background: Receptor for hyaluronan (HA) mediated motility (RHAMM) has been shown to work cooperatively with CD44 to mediate tumor progression, but its specific roles in breast cancer are still unclear. In our previous studies, we have shown tumor cell RHAMM deletion significantly inhibits cancer progression in xenograft models and that RHAMM is heterogeneously expressed within human breast tumors. We propose that focal RHAMM upregulation creates an invasive niche and have identified an RHAMM-dependent signature in this niche that is associated with poor prognosis of breast cancer patients. Importantly, we found that Type II Interferon signaling and MHC Class I & Class II Antigen Presentation pathways are co-enriched in the RHAMM high invasive niche. This indicates that RHAMM might be involved in regulating immune responses. Herein we characterize the immune infiltrates associated with the RHAMM high invasive niche using a mass spectrometry-based proteomic imaging technique.

Methods: FFPE tissues from 5 breast cancers were analyzed by multiple ion beam imaging (MIBI). Sections were stained with 20 antibodies simultaneously, including biomarkers to define immune cell phenotypes. Fields of views (FOVs) were selected from RHAMM high regions and RHAMM low regions. Novel machine-learning-based algorithms were applied to segment the images into spatially resolved single-cell data and to classify immune cell populations in RHAMM-high and RHAMM-low regions.

Results: In triple-negative breast cancer (TNBC), the RHAMM-high tumor invasive margin (TI-high) shows a high level of intra-tumoral immune cells compared to the RHAMM-low tumor core (TC-low), wherein immune cells are largely restricted to the peri-tumoral stroma (figure 1). The RHAMM-low invasive margin (TI-low) is fibrotic and only sparsely populated by macrophages. Segmented single-cell data from our novel machine learning-based algorithms show high levels of infiltrating B cells in the TI-high region (figure 2A-B). The invasive margin overall is characterized by higher levels of cytotoxic T-cells, helper T cells, and macrophages vs. the core (figure 2C-F). Notably, the B-cell-rich TI-high region has fewer cytotoxic T cells than the TI-low region.

Conclusions: Our data highlights potentially novel interactions between RHAMM expression/function and B-cell infiltrates in TNBC. Given the dynamic roles of B-cells in cancer immunology, this suggests new possible avenues for immune modulation to inhibit RHAMM-supported breast cancer progression. On-going work is confirming this linkage in additional TNBC and expanding the analysis to other molecular subtypes of breast cancer.

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REFERENCES


Ethics Approval: FFPE tumor tissues (IRB Approval Study# 1409E53504) were collected from archived pathology tissue blocks with de-identified clinical data in compliance with HIPPA regulations and institutional policies. All participants had agreed to the institution’s standard consent for research participation.