Spatial transcriptomic evidence for an inflammatory, pro tumorigenic microenvironment in normal human dense breast tissue

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Ana Karina de Oliveira (ak4yj@virginia.edu), "Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA, United Sta, **Patcharin Pramoonjago**, Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA, United Stat, **Christopher A. Moskaluk**, Department of Pathology, University of Virginia School of Medicine, Charlottesville, VA, United Stat, **Jay W. Fox**, "Department of Microbiology, Immunology and Cancer Biology, University of Virginia School of Medicine

Breast cancer affects over 2,000,000 women worldwide, with more than 680,000 deaths per year. Increased breast density is one of the risk factors for breast cancer. It has been suggested that high breast density accounts for 15% of the breast cancers diagnosed. How these changes may play a role in increased risk for tumorigenesis are not well described. This study examined the spatial transcriptomes of specific regions in normal breast tissue containing dense regions, including the interface of dense and non-dense regions, using the GeoMx Digital Spatial Profiling system (DSP), multi-label immunofluorescence. This cute-edge technology was used to distinguish tissue morphology in FFPE samples from two healthy patients where we selected 24 regions of interest (ROIs). Using barcoded DNA oligos attached in situ hybridization probes (for RNA) via UV-photocleavable linkers, we screened over 1800 genes from Cancer Transcriptome Atla. Our results indicated an elevated expression of CD68 and CD33, markers for macrophages and myeloid-derived suppressor cells (MDSCs) in dense breast regions as compared to the non-dense areas. Identifying markers for myeloid lineage cells was followed by an increased expression of the genes EOMES, TIGIT and RORA, which are engaged in the immunosuppressive phenotype. This could be hypothesized to support a pro-tumorigenesis microenvironment preventing T cells from recognizing newly arisen tumor cells. In addition, we also observed a significant expression of cytokines (IL12A and IL26) and chemokines (CCL19 and CXCL10) in the dense breast, which are involved in the regulation of inflammatory response and chemotaxis of monocytes and T-lymphocytes cells. Both CCL19 and IL26 have been demonstrated to play a role in cell proliferation. Thus, these initial studies suggest that the dense breast microenvironment is potentially a pro-tumorigenic environment that, with sufficient factors, gives rise to tumorigenesis. These data also suggest potential nodes of therapeutic intervention that may lower such risk.