Exploring the immune-tumor microenvironment using high resolution single-cell spatial transcriptomics

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Cancer immunotherapies manipulate the immune system to repropagate anti-tumor response. Development of such treatments relies on the understanding of the complex spectrum of interactions between immune, tumor and stromal cells infiltrating tumor microenvironment (TME); which are often based on direct cell-cell interactions and local secretion of factors in the TME. Therefore, high resolution spatial mapping of immune cells and adjacent cells is highly valuable resource for deciphering nature of interactions in the TME for the development of novel anti-cancer treatments. Here we harness advancements in MERFISH technology to detect the expression of 350 distinct mRNA transcripts at sub-cellular resolution directly on Ovarian & Colorectal tumor tissue sections. This provides an unprecedented view into the composition and spatial localization of immune-tumor microenvironment. Using the spatial distribution of the transcripts we were able to correlate and cluster the genes and detect those who are co-expressed at similar regions. This clustering separated between distinct cell-lineages such as T-cells (e.g. CD3, CD8), Myeloid (e.g. CD14, CD163), Epithelial (e.g. EPCAM, CLDN4) and other, providing unsupervised means to probe tissue composition. Moreover, cell-segmentation algorithms allow us to obtain single-cell expression data which we use to present preferential spatial-association between CD8 T-cells and activated DC ($p= 3.4e-06$, Z-test) expressing CXCL10, known to chemoattract activated T cells. Furthermore, we also noted that non-activated T-cells are preferentially associated with cancer associated fibroblasts (CAFs) ($p=2.9e-11$, Z-test) unlike more activated T-cell states which were under-associated ($p=0.0008$, Z-test) suggesting that CAFs might play an immune modulatory effect and suppress T-cell activation. Finally, we employ MERFISH to analyze tertiary lymphoid structures (TLS) in tumors and provide an in-depth gaze into the previously described activity of the DNAM-1 axis in these unique regions. These findings highlight the potential of spatial transcriptomics to augment the understanding of the TME and yield impactful findings that could be translated into new therapeutic approaches.