Spatial T-cell receptor profiling of cancer tissue in mice and human to dissect tumor and immune co-evolution

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Cancerous tumor growth in itself is evidence for evasion of the immune system. T-cells present unique antigen-specific surface receptors, and are thus a core part of the immune system in recognition and elimination of pathogens, damaged cells, and cancer cells. $CD8^+$ cytotoxic T-cells, as well as the $CD4^+$ helper T-cells play a direct role in elimination and control of cancer cells (Ostroumov et al., 2018). This is accomplished by their display of unique T cell receptors (TCRs), which are constructed through genetic recombination of V(D)J segments, encoding the exceedingly variable complementary determining region (CDR3), defining the specificity and distinctness of TCRs (Liu et al., 2022). TCR repertoire diversity has been shown to be important in cancer prevention and elimination by the immune system (Cader et al., 2020; Schreiber et al., 2019). By spatially profiling the TCR clonotypes presented in cancer tissue as well as deconvolving spatial transcriptomic (ST) data, we are not only able to understand clonotype immune niches, migration of clonotypes, but also visualize tumor immune coevolution as demonstrated in our recent work (Siyu He et al., 2022). To accomplished this, TCRs will be amplified and sequenced from cDNA generated from the Visium protocol in both mice and human cancer tissue (Hudson & Sudmeier, 2022; Sudmeier et al., 2022) with primers adapted from Dash et al., 2011 (mice) as well as Hudson & Sudmeier, 2022 (human), to spatially map the clonotypes present across the tumor tissue using MIXCR (Bolotin et al., 2015; Hudson & Sudmeier, 2022). The Visium ST data will then be deconvolved utilizing Starfysh, as developed in Azizi Lab to model ST and histology data and identify T cell lineages that exhibit plasticity in phenotype through exposure to mini-niches across the tissue (Siyu He et al., 2022). Further exploration of the evolution of clonotypes in cancer tissue, as well as dissection of spatial gene expression to identify T-cell phenotypes such as exhausted $CD8^+$ T-cells, is important to unravel the complex interactions and coevolution in the tumor microenvironment. Novel biology discovered from this spatial TCR technique and Starfysh can potentially provide new insights to further improve immunotherapies. In the future, we would like to simultaneously model paired spatial transcriptomics and TCR data to further investigate the cancer-immune interactions and co-evolution.

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