The epithelium-stroma interface serves as a barrier to immune cell infiltration across tumor immune phenotypes in epithelial cancers

Background: Tumor immune phenotypes - immune-infiltrated, immune-desert, and immune-excluded - are associated with patient response to immune checkpoint inhibitor therapy. Understanding the distribution of lymphocyte density at the cancer epithelium-stroma boundary can further our understanding of immune phenotypes and provide insights into how barriers to lymphocyte entry into the cancer epithelium may impact therapeutic response to immunotherapy.

Methods: Human tumor samples (n=102) from 5 tumor indicatives (colorectal, ovarian, non-small cell lung, triple negative breast, and pancreatic cancer) were classified as infiltrated, desert, or excluded by pathologist assessment. H&E-stained whole-slide images were further analyzed using AI-powered tissue microenvironment (TME) models developed by PathAI (Boston, MA; commercially available as PathExplore™) for tissue segmentation and cell type classification. Computationally-extracted features for each image included lymphocyte density in cancer epithelium, cancer stroma, and within varying distances (0–60 μm and 60–120 μm) from the epithelium-stroma interface (ESI) (figure 1). Lymphocyte densities in different ESI distance bands, and their gradient of change across the ESI from the outer stroma to the inner epithelium were calculated and compared within and between tumor types and by immune phenotype.

Results: Lymphocyte densities dropped by an average of 5-fold from the stroma side to the epithelium side of the ESI in all tumor types tested (table 1, figure 2). While the observed gradient across the ESI was greatest in excluded tumors (3.7–28.1 fold change compared to baseline), it was also observed in infiltrated (3.9–6.8 fold change) and desert tumors (2.7–22.3 fold change) (table 1). The difference between excluded and infiltrated tumors was greatest in colorectal cancer, where the gradient fold-change compared to baseline was over four times greater in excluded than infiltrated tumors (28.1 vs 6.8). The most pronounced decrease in lymphocyte density occurred within 60 μm of the ESI (figure 2), suggesting that barriers to lymphocyte infiltration occurs at the ESI and in the immediately adjacent stroma.

Conclusions: This analysis of H&E-based spatial features revealed that barriers to lymphocyte infiltration exist at the transition between cancer epithelium and stroma in tumors of all immune phenotypes. While the gradient in lymphocyte density from stroma to cancer epithelium was much lower in tumors classified as infiltrated than excluded, the presence of this gradient even in non-excluded tumors suggests that therapeutics which seek to address barriers to lymphocyte infiltration may benefit patients with all tumor immune phenotypes.