SPATIAL CHARACTERIZATION OF PRO-INFLAMMATORY PATHWAYS IN THE PATHOGENESIS OF IBD-ASSOCIATED COLORECTAL CANCER

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Abstract

Background While immunotherapy has transformed the management of metastatic and recurrent solid tumors, survival rates for patients with advanced colorectal cancer (CRC) remain very poor, with treatment still limited to MSI-H and dMMR-expressing tumors in a chemotherapy refractory setting. Ideally, additional insight is needed to investigate the potential role of immunotherapy at all stages of CRC progression, regardless of microsatellite or MMR gene status. To that end, data from a large number of experimental studies have previously demonstrated that chronic inflammation is highly correlated with the occurrence and development of CRC, indeed inflammatory bowel disease (IBD), including, ulcerative colitis (UC) and Crohn’s disease (CD) has been proven to be an independent risk factor for CRC. To address the relationship of IBD and CRC pathogenesis, the use of multiplex approaches can be applied to discover common cell types, populations, inflammatory pathways and spatial distribution of infiltrating immune cells that may help in ultimately predicting clinical response. We will therefore perform a comprehensive tissue analysis using the Cancer Transcriptome Atlas (CTA) on the NanoString GeoMx® Digital Spatial Profiler (DSP). The CTA panel is designed to profile the global immune response and all aspects of tumor microenvironment biology, including the various inflammatory cells that participate in the establishment of the chronic inflammatory intestinal microenvironment required for the onset of colorectal cancer.

Methods For DSP analysis, a total of 20 FFPE samples including 5 CRC patients, 5 UC patients, 5 CD patients, and 5 matched normal samples have been spatially profiled for up to 1,800 genes. Selection of regions of interest (ROI) is guided by both H&E staining and fluorescent markers (CD45, PanCK, Syto13), and profiling of tumor and TME regions is achieved through segmenting by PanCK+/PanCK- followed by collection of indexed oligonucleotides and sequenced on NextSeq 550 Illumina instrument. For all samples, crypt and villus regions are selected for a detailed spatial analysis.

Results Prolonged inflammatory signaling in IBD dramatically increases the risk of CRC, our comprehensive data highlight the genes and pathways potentially involved in the progression of IBD to CRC by utilizing large-scale spatial gene profiling by DSP CTA.

Conclusions It is our hope that this will provide not only a better understanding of the underlying mechanisms of IBD and colon cancer but also the opportunity for the development of novel targets of prevention and therapy for IBD-associated CRC.

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