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Identification of cancer-restraining fibroblasts in colorectal cancer

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Abstract

Cancer-associated fibroblasts (CAFs) can promote cancer progression through extracellular matrix remodeling, reciprocal signaling with cancer cells, and regulation of the immune response. However, recent studies have found that specific subset of CAFs exhibit cancer-restraining roles. Understanding these fibroblast populations is critical for advancing cancer research and developing CAF-targeted therapies. To assess whether cancer-restraining fibroblasts exist in patients with colorectal cancer (CRC), we integrated multiple large-scale publicly available single-cell RNA sequencing (scRNA-seq) datasets and spatial transcriptomic datasets from human colorectal tissues, spanning diverse phenotypes. We identified a distinct fibroblast subpopulation uniquely expressing a proprietary gene (undisclosed for intellectual property protection). Survival analysis indicated that CRC patients with high expression of this marker had significantly longer overall survival. In the integrated scRNA-seq analysis, gene ontology (GO) enrichment revealed that this fibroblast population – designated as proto-CAF - is associated with apoptosis and alpha-beta T-cell activation. Pseudotime trajectory analysis further suggested that these cells represent a transitional fibroblast state between normal fibroblast and CAFs. Spatial transcriptomics analysis revealed that proto-CAFs were highly enriched in normal tissue samples but were also observed to a lesser extent within tumor tissues. Additionally, cell-cell interaction analysis showed active CXCL14-CXCR4 signaling between proto-CAFs and immune cells across both scRNA-seq and spatial transcriptomics data. Overall, our findings suggest that proto-CAFs may represent potential therapeutic targets for restraining tumor progression and enhancing anti-tumor immunity in CRC.

Keywords: Cancer-restraining fibroblasts, scRNA-seq, Colorectal cancer, Tumor microenvironment