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Editorial

Fibroblast Heterogeneity in Colorectal Cancer: Insights from Integrative Single-Cell Transcriptomics

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See "Identification of Poor Prognosis-Associated Fibroblast Subpopulation Signature Genes Utilizing the Scissor Algorithm to Classify Colorectal Cancer Subtypes and Evaluate the Immune Landscape" by Meng Wang, et al. on page 407, Vol. 20, No. 3, 2026

Colorectal cancer (CRC) remains one of the most common malignancies and a major cause of cancer-related mortality worldwide. Despite substantial advances in screening strategies and therapeutic approaches, tumor progression and metastasis continue to limit long-term survival for many patients. Increasing evidence suggests that tumor behavior is shaped not only by malignant epithelial cells but also by the surrounding tumor microenvironment (TME), which consists of immune cells, stromal fibroblasts, endothelial cells, and extracellular matrix components.[1,2] Understanding the cellular heterogeneity within this microenvironment has therefore become a central focus in contemporary cancer research.

In this issue of *Gut and Liver*, Wang *et al.*[3] present an integrative transcriptomic analysis that combines single-cell RNA sequencing with bulk RNA sequencing data to identify clinically relevant stromal cell populations associated with CRC prognosis. Using the Scissor algorithm, a computational approach that links single-cell profiles to phenotypic information derived from bulk transcriptomic datasets, the authors were able to identify a subset of fibroblasts associated with unfavorable clinical outcomes.[3] This innovative strategy provides a powerful framework for connecting cellular heterogeneity observed in single-cell datasets with clinically meaningful patient phenotypes.

One of the key strengths of the study lies in its integrative analytic approach. Single-cell RNA sequencing has dramatically expanded our understanding of tumor heterogeneity, yet translating these findings into clinically relevant insights remains challenging. By integrating bulk transcriptomic data with single-cell profiles, the Scissor framework enables the identification of cellular subpopulations that are directly linked to patient outcomes. The study by Wang *et al.*[3] therefore represents an important methodological advance in bridging the gap between high-resolution cellular analyses and clinical oncology.

Another notable contribution of the study is the identification of fibroblast populations associated with poor prognosis. Cancer-associated fibroblasts (CAFs) are increasingly recognized as key regulators of tumor progression, contributing to extracellular matrix remodeling, tumor invasion, angiogenesis, and immune modulation.[4] Recent studies have further highlighted the remarkable heterogeneity of CAF populations within tumors, suggesting that specific fibroblast subtypes may play distinct roles in tumor progression and metastasis.[5,6] In this context, the identification of clinically relevant fibroblast subsets provides valuable insights into the stromal components driving disease progression in CRC.

The findings reported by Wang *et al.*[3] also align with a growing body of literature emphasizing the importance of integrating single-cell and bulk transcriptomic analyses to better understand the complexity of the TME. Recent studies have demonstrated that such integrative approaches can reveal heterogeneous immune landscapes and identify cellular populations associated with CRC prognosis.[7] Moreover, transcriptomic signatures related to regulatory T-cell infiltration and epigenetic regulation have been shown to influence tumor progression and patient outcomes.[8,9] These observations further support the concept that TME heterogeneity plays a critical role in determining clinical behavior in CRC.

Importantly, the study also highlights the potential clinical implications of fibroblast-derived transcriptional signatures. Increasing evidence suggests that CAF-related signaling networks contribute to tumor invasion, metastasis, and therapy resistance.[5] Recent mechanistic studies have demonstrated that interactions between CAFs, immune cells, and tumor cells can create a pro-tumorigenic microenvironment that facilitates tumor progression and immune evasion.[10] Consequently, the identification of prognostic CAF-related signatures may have important implications for risk stratification and therapeutic targeting in CRC.

Despite these important contributions, several limitations should be considered. First, the study is primarily based on retrospective transcriptomic datasets and computational analyses. Although these approaches provide valuable insights, prospective validation in independent clinical cohorts will be necessary to confirm the prognostic significance of the identified fibroblast populations. Second, the functional roles of these fibroblast subsets remain largely inferred from transcriptomic signatures. Experimental studies are therefore needed to determine whether these cells directly contribute to tumor progression or simply reflect broader changes within the TME.

In addition, the translational implications of these findings remain to be fully clarified. While transcriptomic signatures can provide important prognostic information, translating these discoveries into clinically applicable biomarkers or therapeutic targets represents a significant challenge. Future studies integrating spatial transcriptomics, functional experiments, and clinical validation will likely be necessary to further elucidate the biological roles of these fibroblast populations.

Nevertheless, the work by Wang *et al.*[3] represents an important step toward a deeper understanding of stromal heterogeneity in CRC. By integrating single-cell and bulk transcriptomic data through a clinically informed computational framework, the study provides valuable insights into the complex interactions within the TME. As multi-omic technologies continue to evolve, such integrative approaches will likely play an increasingly important role in identifying novel prognostic markers and therapeutic targets in CRC.

In conclusion, the growing recognition of TME heterogeneity has transformed our understanding of CRC biology. Studies such as the one presented in this issue of Gut and Liver highlight the critical contribution of stromal cell populations, particularly CAFs, to tumor progression and patient outcomes. Continued exploration of these complex cellular networks may ultimately pave the way for more precise prognostic models and innovative therapeutic strategies in CRC.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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