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Using Single-cell Transcriptomics to Study Non-coding RNA in Colorectal Cancer

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Introduction

Colorectal Cancer (CRC) is one of the leading causes of cancer-related mortality worldwide. Despite advancements in treatment, the underlying molecular mechanisms driving CRC progression remain incompletely understood. Recent research has highlighted the crucial role of non-coding RNAs (ncRNAs) in regulating gene expression, cellular differentiation, and tumor progression. With the advent of single-cell transcriptomic technologies, researchers can now decode the complex regulatory functions of ncRNAs at an unprecedented resolution, offering new insights into CRC biology and potential therapeutic targets. Single-cell transcriptomics provides a powerful approach to dissecting the heterogeneity of colorectal tumors at the cellular level. Traditional bulk RNA sequencing methods average gene expression across large populations of cells, potentially masking critical variations in gene regulation. In contrast, single-cell RNA sequencing (scRNA-seq) allows for the profiling of individual cells, uncovering rare cell populations, lineage hierarchies, and dynamic transcriptional changes that drive tumorigenesis. By applying this technology to CRC, researchers can elucidate how ncRNAs contribute to tumor initiation, progression, and resistance to therapy.

Description

Non-coding RNAs, including Micrornas long non-coding RNAs and circular RNAs play fundamental roles in colorectal cancer. miRNAs are short RNA molecules that post-transcriptionally regulate gene expression by targeting messenger RNAs (mRNAs) for degradation or translational repression. Numerous studies have identified dysregulated miRNAs in CRC, with some acting as oncogenes and others as tumor suppressors. Single-cell transcriptomic analysis has allowed for the identification of miRNA expression patterns in distinct tumor cell subpopulations, shedding light on their specific functions in tumor growth and immune evasion. Long non-coding RNAs are another class of ncRNAs implicated in CRC. Unlike miRNAs, lncRNAs are over 200 nucleotides in length and can regulate gene expression through various mechanisms, including chromatin modification, transcriptional regulation, and post-transcriptional control. Some lncRNAs act as Competing Endogenous RNAs by sequestering miRNAs, thereby preventing them from targeting their mRNA counterparts. Single-cell studies have revealed the spatial and temporal expression patterns of lncRNAs within CRC tumors, providing insights into their role in tumor microenvironment interactions, Epithelial-To-Mesenchymal Transition (EMT), and metastatic potential [1].

Circular RNAs represent a unique category of ncRNAs with covalently closed-loop structures that confer stability and resistance to exonuclease degradation. CircRNAs have been shown to function as miRNA sponges, transcriptional regulators, and protein interaction partners. Recent single-cell transcriptomic analyses have identified specific circRNAs enriched in different CRC subtypes, highlighting their potential as biomarkers and therapeutic targets. The ability to resolve circRNA expression at the single-cell level has uncovered novel regulatory networks that contribute to CRC pathogenesis. In addition to characterizing individual ncRNA species, single-cell transcriptomics enables the investigation of their functional interactions within colorectal tumors. By integrating scRNA-seq data with computational modeling and network analysis, researchers can reconstruct ncRNA-mediated gene regulatory networks that drive CRC progression. These approaches have facilitated the identification of ncRNA signatures associated with tumor aggressiveness, drug resistance, and immune evasion, offering potential avenues for precision oncology [2].

The Tumor Microenvironment (TME) plays a critical role in CRC progression, and single-cell transcriptomics has provided new insights into ncRNA-mediated crosstalk between cancer cells and stromal components. Tumor-associated fibroblasts (TAFs), immune cells, and endothelial cells interact with cancer cells through complex signaling pathways regulated by ncRNAs. Single-cell analysis has revealed that specific ncRNAs modulate immune evasion mechanisms, such as PD-L1 expression and T-cell exhaustion, which contribute to immune checkpoint blockade resistance. Understanding these interactions at a single-cell resolution could aid in the development of novel immunotherapeutic strategies targeting ncRNA-mediated pathways. Another promising application of single-cell transcriptomics in CRC research is its role in identifying ncRNA biomarkers for early diagnosis and prognosis. Liquid biopsy approaches leveraging Circulating Tumor Cells (CTCs) and Extracellular Vesicles (EVs) have demonstrated the potential of ncRNAs as minimally invasive biomarkers. Single-cell RNA sequencing of CTCs has uncovered distinct ncRNA expression profiles associated with metastatic dissemination, providing valuable prognostic information. Moreover, the stability of circRNAs in bodily fluids makes them attractive candidates for liquid biopsy-based CRC screening [3].

Despite its numerous advantages, single-cell transcriptomic analysis of ncRNAs in CRC faces several challenges. The low abundance of certain ncRNAs, particularly lncRNAs and circRNAs, can complicate their detection and quantification. Advances in sequencing technologies and computational methods are addressing these limitations by improving sensitivity and accuracy in ncRNA identification. Additionally, integrating single-cell transcriptomic data with other omics approaches, such as single-cell epigenomics and proteomics, will provide a more comprehensive understanding of ncRNA function in CRC. Future research in this field is expected to leverage artificial intelligence and machine learning algorithms to analyze large-scale single-cell transcriptomic datasets. These approaches will enable the identification of novel ncRNA regulatory mechanisms and facilitate the development of targeted therapies. Furthermore, single-cell multi-omics integration will enhance our ability to decipher the interplay between ncRNAs, chromatin modifications, and cellular metabolism in CRC [4,5].

Conclusion

In conclusion, single-cell transcriptomic approaches have revolutionized our understanding of non-coding RNA mechanisms in colorectal cancer. By providing high-resolution insights into the heterogeneity of CRC tumors, scRNA-seq has uncovered novel ncRNA regulatory networks, biomarker candidates, and therapeutic targets. Continued advancements in single-cell technologies will further enhance our ability to translate these findings into clinical applications, ultimately improving CRC diagnosis, treatment, and patient outcomes.

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Conflict of Interest

None.

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