Stool host transcriptomics enables diagnostic and molecular characterization of colorectal cancer

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Background

The current state of the art for diagnostics of colorectal cancer (CRC) is the use of endoscopy procedures. These are invasive, costly methods that carry risks and involve lengthy preparation. Analyzing the transcriptomic profiles of exfoliated cells in adult stool samples provides a promising non-invasive method for assessing the gut's pathophysiological state. However, the high prevalence of microbial RNA in the adult human colon has limited the detection of host mRNA to only a few dozen genes.

Objective

To evaluate the transcriptomic landscape of human stool in colorectal cancer patients and assess its potential as a non-invasive method to characterize gut function in health and disease.

Methods

In this study, we employ genomic depletion to reduce abundant microbial RNA, combined with a sensitive polyA UMI-based RNA sequencing method, enabling comprehensive gene expression profiling from stool samples. Using this approach, we examined stool samples from 54 colorectal cancer patients and 24 healthy controls, successfully detecting thousands of host genes per sample.

Results

The gene expression patterns in stool mirrored those observed in tumor and healthy tissue, distinguishing disease states with high precision. Furthermore, stool transcriptomic profiles normalized to a healthy expression profile following tumor removal.

Using high resolution spatial transcriptomics of colorectal cancer tissue samples. We found that differentially expressed genes between the tumor epithelial cells and the adjacent healthy epithelial cells exhibited similar trends when comparing stool samples of CRC patients and controls.

Conclusion

Our study indicates that localized intestinal tumors produce sufficient cell shedding to overcome masking of the transcriptional signal of the normally shed colonocytes. This may be due to the excessive division and consequent shedding of tumor cells. Our method provides deep transcriptomic information that can facilitate extraction biological pathway activities, and can thus potentially enable predictions of personalized response to therapies. GET-RIDseq opens up the way for non-invasive molecularly rich interrogation of the cellular state of the human gut. Future studies will apply this to characterize gut development, aging and pathophysiology.