Liquid biopsy in colorectal cancer beyond targeted analysis of single variants

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Background & objectives

Liquid biopsy for non-invasive disease monitoring of cancer patients is progressing towards routine clinical practice. So far, the main focus is on circulating tumor DNA (ctDNA) analysis, targeting actionable somatic hotspot variants to guide treatment decisions.

Here, we developed a method for the untargeted analysis of ctDNA based on whole-genome sequencing (WGS) providing a promising tool for real-time monitoring of treatment response and the early detection of recurrence.

Methods

We established LIquid biopsy Fragmentation, Epigenetic signature and Copy Number Alteration analysis (LIFE-CNA) using WGS with ~6x coverage in 259 plasma samples collected from healthy individuals and colorectal cancer (CRC) patients.

Results

Using a panel of controls consisting of 55 self-reporting healthy individuals, we established distinct cutoffs for the detection of ctDNA based on global and regional fragmentation patterns,

transcriptionally active chromatin and somatic copy number alterations for the analytical validation of LIFE-CNA. This enabled the accurate prediction of ctDNA in 81% of patients with localized and in 94% of patients with metastatic disease at the time of primary diagnosis. Further, by adding a machine learning classifier to our workflow, whch combines global and regional cfDNA fragmentation, we were able to increase the accurate prediction of ctDNA presence (93% of patients with localized and 94% of patients with metastatic disease at diagnosis). By following individual patients treated with surgery and/or chemotherapy throughout their course of disease, we observed that changes in ctDNA signals reliably predicted response or progression as a result of resistance to treatment up to 5 months prior to clinical manifestation in 77% or 100% of patients, respectively.

Conclusion

We developed and validated a sensitive and cost-effective method for untargeted ctDNA detection at the time of diagnosis or recurrence, as well as for treatment monitoring, expanding the advantages of liquid biopsy. Our approach is applicable to a wide range of cancer patients, and with minor adjustments in the bioinformatics analysis, LIFE-CNA can be easily extended to all tumor entities. The high sensitivity and cost-effectiveness of our approach form the basis for the implementation of LIFE-CNA into clinical practice.