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Tumor intrinsic and extrinsic origins of circulating genomic and proteomic biomarkers for early detection of lung cancer

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Background

Cell-free DNA (cfDNA) and circulating protein biomarkers are beginning to be used for non-invasive lung cancer detection but their biological origins remain incompletely understood. Tumor-derived molecules released from malignant cells have traditionally been considered the primary signal, whereas host-derived molecules originating from non-malignant tissues have largely been regarded as background. Growing evidence demonstrates that tumor–host interactions may influence tumorigenesis and progression. However, the degree to which tumor- and host-derived changes contribute to circulating proteomic and cfDNA fragmentation signals, as well as their complementarity for early cancer detection, has not yet been explored.

Methods

We evaluated sources of signal in genome-wide cfDNA fragmentomes for 718 individuals with or without lung cancer, and in circulating proteins for a subset of patients, including individuals from the prospective LUCAS diagnostic lung cancer study at Copenhagen University Hospital. Separately, we analyzed blood samples from 400 individuals enrolled in the prospective MICA study of patients suspected of having malignancy and presenting to Copenhagen University Hospital. Circulating proteins were quantified from serum using multiplexed targeted immunoassays. cfDNA was isolated from plasma and analyzed using low-coverage whole-genome sequencing.

Results

Analyses of tissue- and cell-type-specific genomic, transcriptomic, epigenomic and chromatin alterations identified both tumor-intrinsic and extrinsic host responses as origins of cfDNA fragmentation profiles and protein biomarkers in cancer patients. Tumor-extrinsic signals were particularly informative for detecting early-stage disease, where tumor-derived cfDNA and protein biomarkers had limited signal. An integrated cfDNA fragmentomic-proteomic machine learning classifier enhanced detection of lung cancer (AUC=0.91, 95% CI=0.86–0.96) and was validated in the independent prospective MICA cohort.

Conclusions

Together, these findings establish a framework for interpreting the biological origins of circulating biomarkers and for rational design of multi-analyte approaches for lung cancer detection.

Clinical trial identification

The LUCAS study was approved by the Danish Regional Ethics Committee (H-2-2011-147) and the Danish Data Protection Agency (j.nr. 2012-58-0004; HEH 750.24.56 and HGH-2018-017; I-Suite nr. 6215 and PRIVACY P-2024-15458). The MICA study was approved by the Regional Ethics Committee (H-7-2014-011) and the Danish Data Protection Agency (HEH-2014-105 and PRIVACY P-2020-578). All participants were informed and signed an informed consent declaration before participation.

Legal entity responsible for the study

The authors.

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Disclosure

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