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Multi-analyte liquid biomarkers for lung cancer detection and risk assessment

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Lung cancer is the leading cause of cancer deaths. Early detection and surgical resection generate a 5 year survival of 56% compared to only 5% for patients with more advanced (stage III/IV) disease. However, early lung cancer is largely asymptomatic and 80% of patients present with stage advanced disease at diagnosis. Current screening approaches heavily rely on low-dose computed tomography (LDCT), which is often inaccurate, especially in early disease patients, and lead to costly, unnecessary, and invasive follow-up procedures. There is a need for robust early detection strategies. In addition, EGFR mutations activate compensatory resistance mechanisms, leading to highly lethal anti-EGFR resistant lung cancers. The molecular bases of these mechanisms are largely unknown. Understanding and targeting these mechanisms will provide a basis for stratifying and sensitizing patients to therapies.

Liquid biopsies have the potential to noninvasively detect cancers while capturing the broader cancer signaling landscape, which in principle provides a rational for matching patients to appropriate therapies. We isolated plasma extracellular vesicles (EV) from high-risk control and stage IV lung cancer patients and asked whether stage IV EV have unique morphometric characteristics. Importantly, we isolated and sequenced microRNAs (miRNAs) from plasma and EV from the same cohorts and have identified sets of miRNAs that reliably distinguishes stage IV patients from controls. In addition, mutational and copy number alteration analyses of microRNA gene targets using lung cancer genome and outcome data have identified prognostic biomarkers for EGFR mutated lung cancers. We are now evaluating whether targeting these miRNAs or common gene targets re-sensitizes EGFR cancers to EGFR blockade. Thus, our newly identified liquid biomarkers have the potential to improve lung cancer diagnosis and to assist in the effective stratification of patients to anti-EGFR therapies.