Tumor content in circulation for monitoring of lung cancer

(循環血液中腫瘤 DNA 含量用於監測肺癌)

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Background

Lung cancer accounted for 11.4% of newly diagnosed cancer cases and 18.0% of cancer-related deaths in 2020, with about 2.2 million new cases and 1.8 million deaths1. Non-small-cell lung cancer (NSCLC) accounts for about 85% of all lung cancer cases, with adenocarcinomas and squamous-cell carcinomas being the major subtypes in NSCLC2. Although new treatments, such as using immune checkpoint inhibitors, have greatly improved patient outcome but is effective in only about 20% of non-selected NSCLC patients3 and the five-year survival rate of all lung cancer patients remains only about 20%1. In contrast, for patients with stage I tumor, the five-year survival rate is about 80%4. These data suggest that detecting lung cancer at an early stage via screening is probably one of the most effective ways to improve survival for lung cancer patients at large.

Low-dose computed tomography (CT) is one way of screening and detecting early-stage lung cancer, with an estimated reduction in the mortality of lung cancer by 24% to 33%5–8. However, in the setting of population-based screening, the exposure to radiation among the large number of subjects in the screening population and the false-positive associated overdiagnosis and overtreatment9 are concerning. Circulating cell-free DNA (ccfDNA), a.k.a. liquid biopsy, shed from solid tumors may provide an opportunity to detect cancer non-invasively and safely. A recent study showed the potential of using liquid biopsy to detect early-stage lung cancer10. However, whether liquid biopsy could be applied to detect pre-clinical lung cancer is largely unknown due to the limited resources on samples collected before diagnosis.

A number of circulating cell-free DNA features, including somatic mutation11,12, nucleosome footprint13, fragmentation profile14, fragment end sequence15, and methylation16–18, have been studied for cancer detection. There are other cancer genome-related features and may be exploited for cancer detection.

Telomeres are located at the terminal ends of linear chromosomes and may affect genome integrity, cell immortalization, and carcinogenesis19. Shortening of telomeres often happens during early stage of cancer development20,21 and is closely related to the number of cell divisions22. At the very end of the telomere is a 3’ overhanging guanine-rich tail or G-tail. In humans, G-tail contains the repeated hexamer 5’-TTAGGG-3’. However, G-tail DNA cannot be detected using the conventional sequencing technologies based on double-strand library preparation, because these methods involve an end-blunting step23,24 that removes single-stranded 3’ overhang, which is the format that G-tail exists in.

In this proposal, we hypothesize that accelerated proliferation of lung cancer genome and accompanying telomere G-tail shortening and releasing into circulation, may increase the abundance of circulating telomere G-tail DNA fragments.

Work done by us

We conducted two prospective cancer screening trials (Clinical trial number: NCT00941538 and NCT02501980)25,26 in 2009 to 2012 in the Xiaolan county, Zhongshan City, Guangdong, China. Briefly, in 2009 to 2012, residents aged 30–69 years were recruited in a cancer screening program. All participants were asked to donate 6 to 8 mL of blood. The blood samples were then separated into plasma and serum, and stored at -20°C. This population has a high incidence rate for nasopharyngeal carcinoma. Therefore, all participants were tested for Epstein-Barr virus antibodies by enzyme-linked immunoassay assays. Participants with positive results were followed up every year with collection of blood sample at each follow-up. The PI is equipped with solid epidemiology theory to design and supervise the clinical and population-based study proposed

here. The PI's lab is well positioned to use advanced NGS technology for the study proposed here. The co-I Prof. Yang is an expert in cancer research and molecular diagnosis.

Aim 1. Compiling lung cancer study cohort, sample processing and molecular assays