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Preview

Early diagnosis of cancer using circulating microbial DNA

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The study by Chen et al. has advanced research by developing predictive models based on circulating microbial DNA, offering potential for early cancer detection and personalized treatment. However, further validation and simplification of techniques are needed for widespread clinical application.

Microbes, including bacteria, fungi, and viruses, play important roles in cancer development, treatment responses, and prognosis. It is well established that microbial dysbiosis in the gastrointestinal (GI) tract correlates with the development and treatment outcome of not only GI cancers but also other cancers that do not have direct contact with the GI tract. The correlations between microbes and cancer are intriguing and have attracted many researchers to dissect the underlying mechanisms.

Some viruses (such as Epstein-Barr virus, human papillomavirus, and hepatitis B virus) are known biological carcinogens for various cancers, but the detection of bacterial DNA in "sterile" tumor tissues has redefined the concept of intra-tumour microbiome.[1] It has been hypothesized that gut microbiota and metabolites may regulate the metabolism and immunity in the tumor microenvironment. However, the validation of their impact in diverse cancer progression and treatment context is needed.[2]

More recently, the detection of circulating microbial DNA (cmDNA) has opened a new era of cancer diagnostic approach and cancer-microbiome-immunity research.[3,4] Some studies have suggested that microbes leaked into the circulation due to the increased permeability of the oral and intestinal epithelial barriers.[5] Limited data are available for the comparison between cmDNA and intra-tumour DNA, let alone the immunomodulatory effect of the cmDNA in cancer. However, there is increasing evidence that cmDNA provides opportunities for improving the diagnosis and prognosis of cancer.

A recent study by Chen et al. delves into previously unexplored territory by employing whole genome sequencing on cell-free DNA present in the plasma samples obtained from both lung cancer patients and healthy controls.[6] By using an average sequencing depth of 5 times human genomes, Chen et al. was able to capture microbial reads in 0.012% of the total genomes in healthy controls and 0.009% of the total genomes in lung cancer patients.[6] These filtered reads revealed a diminished alpha-diversity in lung cancer subjects compared to controls, alongside shifts in microbial taxa.[6] Notably, the study pinpoints a significant elevation in the cmDNA levels of *Acinetobacter*, a microbe notably enriched in lung cancer cases.[6]

In their study, Chen et al. advanced the field by developing a diagnostic model that exhibited high sensitivity and specificity, with values of 87.7% and 79.4%, respectively.[6] The model's effectiveness was further confirmed by an area under the ROC curve (AUC) of 93.2% in independent datasets.[6] Interestingly, the AUC of Chen et al.'s model is comparable to the AUC of a model developed by Poore et al., despite the latter being based on a smaller sample size.[3,6] Poore et al.'s model incorporated cmDNA from fewer than 100 subjects, encompassing both lung cancer patients and healthy individuals.[3] Chen et al.'s study, however, utilized a sample size four times larger, thereby validating the findings of Poore et al.'s research.[3,6] This validation was further strengthened by the fact that the model's performance remained unaffected even when the sequencing depth was reduced from 5 to 1 times the human genome,[6] attesting to its robustness and stability. Moreover, the microbial signatures identified in the model were confirmed to be neither environmental nor human-genome contaminants.[6] This was evidenced by their absence in the negative controls and their non-alignment with the human genome, as determined by two bioinformatic filtering steps.[6] This validation could potentially put to rest the ongoing debate about the accuracy of the identified microbial signature in blood samples.[7] The results underscore the potential of such microbial signatures as reliable diagnostic markers, paving the way for future research in this area.

The model developed by Chen et al. is also able to identify early pathological features of lung cancer with sensitivity rates exceeding 86% for stage I tumors and tumors smaller than 1 cm.[6] Moreover, they developed a cmDNA biomarker panel tailored to predict lung cancer recurrence post-surgery with a AUC of 80.9% in the test set.[6] However, this panel was generated from a small sample size. Thus, additional validation cohorts are required to verify these biomarkers.

Despite the excellent performance of Chen et al.'s model in early lung cancer detection, which was based on a heterogeneous mixture of lung cancer types,[6] Zhou et al. took a different approach by

re-analyzing the cmDNA data from Poore et al. with a focus on developing a prognostic model for non-small cell lung cancer (NSCLC).[8] They constructed a circulating microbial abundance prognostic scoring (MAPS) system, comprising 14 circulating microbes, which emerged as an independent prognostic indicator for overall survival in NSCLC.[8] Incorporating circulating MAPS into a nomogram alongside clinical factors such as age, subtype, gender, and stage significantly improved the prognostic performance for NSCLC.[8] Additionally, Zhou et al. investigated the interplay between circulating MAPS and the tumor immune microenvironment.[8] Notably, they observed that the MAPS-low group exhibited enrichment of plasma B cells within the tumor and activation of humoral immune response, while the MAPS-high group showed enrichment of $CD4^+$ Th2 cells within tumor and pathways associated with proliferation.[8] However, Chen et al. did not investigate this association. Hence, there is a need for future large-scale human studies to validate Zhou et al.'s findings. Lastly, the drug sensitivity analysis conducted by Zhou et al. hinted at the potential for circulating MAPS to predict chemotherapy efficacy, although its predictive power for immunotherapy efficacy is limited.[8]

Exploring the application of cmDNA signatures in additional cancer types beyond the studied cancers such as lung cancer, breast cancer, and melanoma, particularly in non-GI cancers, is imperative. However, many current techniques necessitate sophisticated next-generation sequencing and complex bioinformatic analysis, resulting in delays in diagnosis and prognosis as well as high costs. Therefore, future efforts should focus on developing simpler and more cost-effective quantitative PCR-based methods utilizing identified microbial signatures for pan-cancer diagnosis and prognosis. These methods, including the implementation of gold-standard microbiology practices and aseptic technique, should be designed to be readily deployable in pathology laboratories, offering a streamlined approach for pan-cancer blood-based diagnostic and prognostic testing.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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