

Small extrachromosomal circular DNAs as biomarkers for potential pan-cancer diagnosis and prognosis

Student: Xuanmei Luo Supervisor: Fei Xiao

Beijing Hospital, Peking University Fifth School of Clinical Medicine,
National Center of Gerontology, National Health Commission, Beijing, China

INTRODUCTION

Small extrachromosomal circular DNA (eccDNA) is a circular DNA molecule that is independent of conventional chromosomes and exists widely in eukaryotes [1]. Recently, small eccDNAs have been reported to be related to microRNA expression and innate immunostimulatory activities[2,3]. However, the formation mechanism and function of small eccDNAs, especially their role in carcinogenesis, need to be further explored. As small circular DNA molecules, small eccDNAs are promising biomarkers in cancer detection because they are structurally more stable than RNA and linear DNA[4,5]. However, it is still unclear whether the small eccDNA profile in cancer plasma can represent that in cancer tissues. Previous studies on small eccDNAs were mostly based on the short-read sequencer[6,7]. Small eccDNAs must be fragmented during sample preparation, thus losing the full-length information that is crucial for functional studies.

MATERIALS AND METHODS

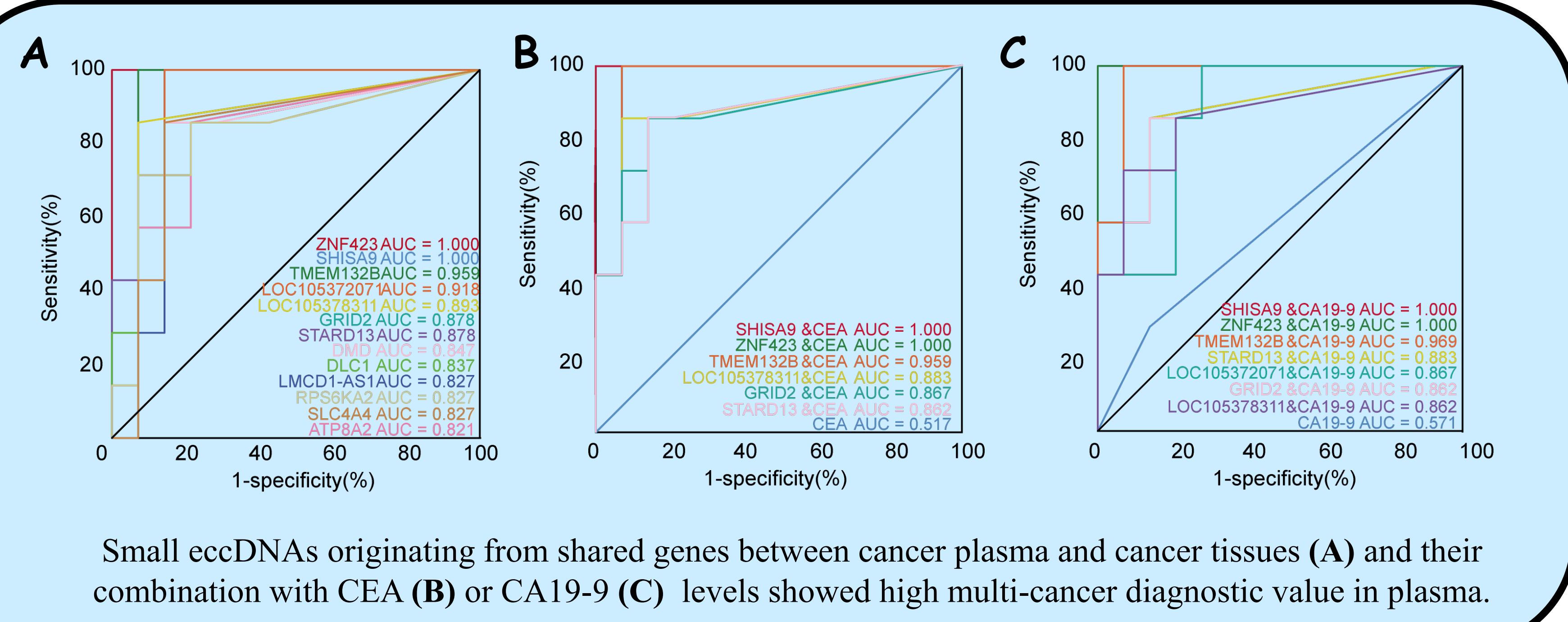
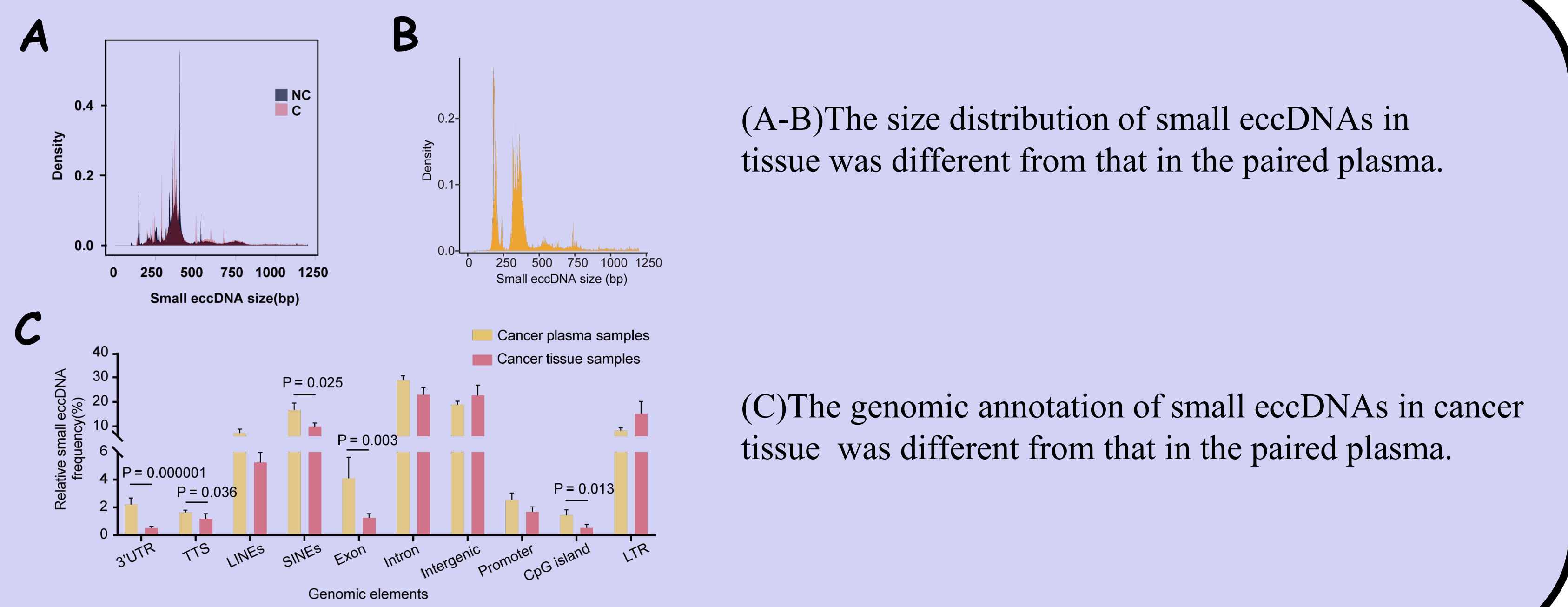
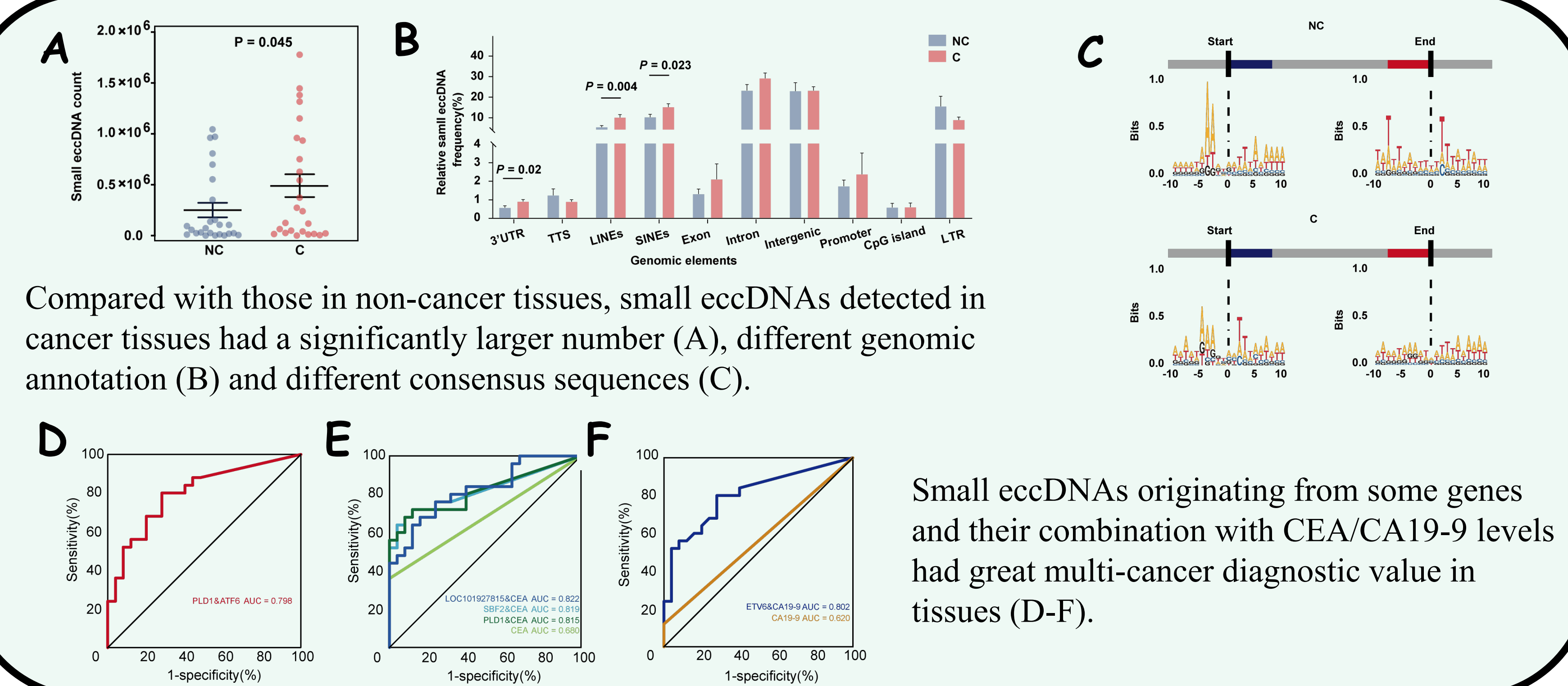
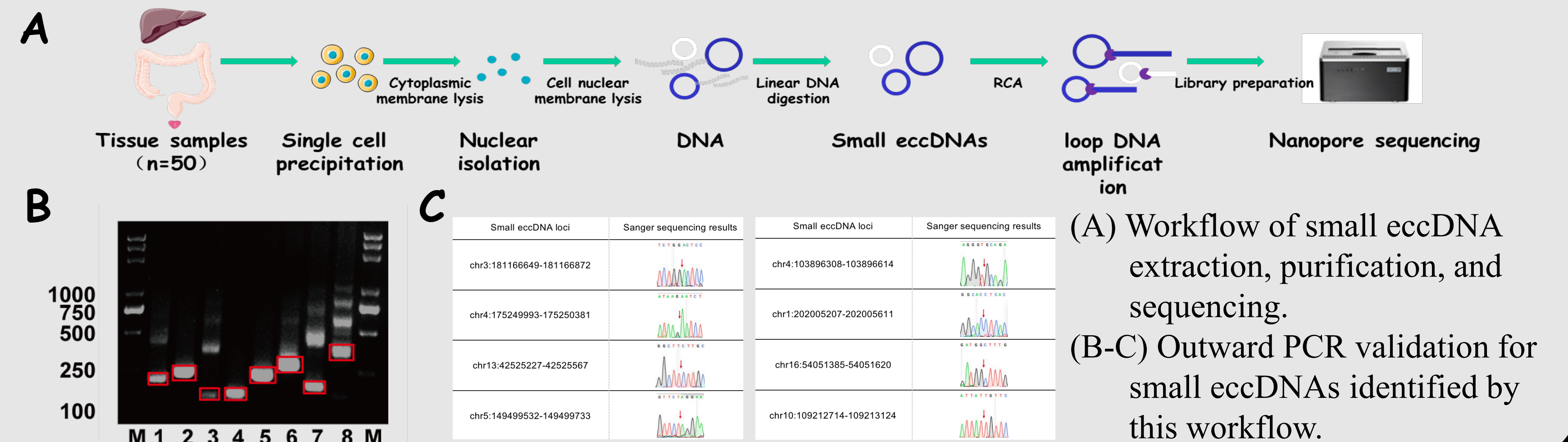
A nanopore sequencing-based rolling circle amplification method was applied to sequence naturally existing full-length small eccDNAs in tissues and paired plasma collected from 25 cancer patients (including prostate cancer, hepatocellular carcinoma, and colorectal cancer), and from an independent validation cohort.

CONCLUSIONS

- The comprehensive characterization profiling of small eccDNAs for cancer patients in our study provides abundant human data for the future study of the mechanism of small eccDNAs in carcinogenesis.
- The small eccDNA data from cancerous and para-cancerous tissues, coupled with those from the remote peripheral blood, can serve as a rich resource for a deeper understanding of the transport and flow of small eccDNAs.
- As independent and stable circular DNA molecules, small eccDNAs in both tissues and plasma can be used as ideal biomarkers for cost-effective multi-cancer diagnosis and monitoring.

RESULTS

A novel sequencing workflow for small eccDNA sequencing was successfully constructed.



REFERENCES

- [1] Wang T, Zhang H, Zhou Y, Shi J. Extrachromosomal circular DNA: a new potential role in cancer progression. *J Transl Med.* 2021;19(1):257.
- [2] Paulsen T, Shibata Y, Kumar P, Dillon L, Dutta A. Small extrachromosomal circular DNAs, microDNA, produce short regulatory RNAs that suppress gene expression independent of canonical promoters. *Nucleic Acids Res.* 2019;47(9):4586-4596.
- [3] Wang Y, Wang M, Djekidel MN, et al. eccDNAs are apoptotic products with high innate immunostimulatory activity. *Nature.* 2021;599(7884):308-314.
- [4] Wu X, Li P, Yimiti M, et al. Identification and Characterization of Extrachromosomal Circular DNA in Plasma of Lung Adenocarcinoma Patients. *Int J Gen Med.* 2022;15:4781-4791.
- [5] Kumar P, Dillon LW, Shibata Y, Jazaeri AA, Jones DR, Dutta A. Normal and Cancerous Tissues Release Extrachromosomal Circular DNA (eccDNA) into the Circulation. *Mol Cancer Res.* 2017;15(9):1197-1205.
- [6] Møller HD. Circle-Seq: Isolation and Sequencing of Chromosome-Derived Circular DNA Elements in Cells. *Methods Mol Biol.* 2020;2119:165-181.
- [7] Kumar P, Kiran S, Saha S, et al. ATAC-seq identifies thousands of extrachromosomal circular DNA in cancer and cell lines. *Sci Adv.* 2020;6(20):eaba2489.