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Pancreas cancer liquid biopsy flows from blood-borne packets of tumor genes

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Pancreatic cancer tumors spill their molecular secrets into the blood stream, shedding their complete DNA and RNA wrapped inside protective lipid particles that make them ripe for analysis with a liquid biopsy, researchers at The University of Texas MD Anderson Cancer Center report online at the *Annals of Oncology*.

The team conducted whole genome, whole exome and gene expression analysis of tumors in three patients using DNA and RNA found inside exosomes circulating in their blood or other liquid biospecimens.

"Analysis of exosomal DNA and RNA allows us to do everything you can do off a direct biopsy of tumor tissue," said senior author Anirban Maitra, M.B.B.S., professor of Pathology and director of MD Anderson's Sheikh Ahmed Bin Zayed Al Nahyan Center for Pancreatic Cancer Research.

The research was conducted under MD Anderson's Moon Shots Program to accelerate development of clinical and prevention advances from scientific knowledge. Maitra is co-leader of the Pancreatic Cancer Moon Shot, one of 12 in the program.

The proof of principle study opens the door to validation studies in multiple tumor types of a liquid biopsy that could be used to determine prognosis, guide targeted therapy and monitor treatment.

Meeting pancreatic biopsy challenge

Maitra and colleagues detected a variety of cancer-derived biomarkers, including genetic mutations, insertions, deletions, copy number profiles and gene fusions that can act as neoantigens - new targets for the immune system. Potentially treatable mutations, including BRCA2 and NOTCH1, were identified.

"A comprehensive liquid biopsy would meet one of the major challenges of characterizing pancreatic cancer and other cancers deep in the body," Maitra said. "These tumors are hard to access, even using needle or core biopsies, so getting enough tissue to enable a full next-generation sequencing is difficult."

Other liquid biopsies under development rely mainly on cell-free DNA found circulating in the blood. Unprotected DNA in the blood is chopped up by enzymes, so cell-free DNA allows some genomic analysis, Maitra said, but not whole genome or whole exome sequencing.

Cell-free RNA is even more easily destroyed in the blood. Exosomes are membrane balls that protect the DNA and the RNA cargo inside from destruction, preserving high-quality samples.

Analyzing gene expression

"Full RNA sequencing is important because genome sequencing tells you what genes are altered, while analysis of RNA tells you what abnormal genes are actually being expressed," he said. "Shed exosomes allow us to do matched DNA and RNA simultaneously in liquid biopsies at a resolution that is not amenable with cell-free approaches."

Common clinical practice now calls for only a pretreatment biopsy in

deeply located tumors at presentation. Conducting biopsies during treatment would more closely monitor therapy success or failure and help researchers better understand how the cancer genome evolves in response to treatment.

"Tumors continuously evolve during therapy. New changes, new pathways, new mutations show up," Maitra said. Payers don't usually cover multiple biopsies. "Now you can bypass the need for tissue and get the full genome, exome and transcriptome from a vial of blood," Maitra said.

Exosomes may actually paint a more complete picture of a tumor's genomic diversity because all genetic mutations present in primary and metastatic tumors would flow into a liquid biopsy via the exosomes, the researchers noted. Sampling part of a tumor might only capture mutations in that area and not reflect its overall genomic diversity.

Exosomes were isolated from blood samples in two patients and also from pleural fluid in a patient who had lung metastases. Whole genome sequencing covered up to 91 percent of the human genome while exome sequencing of only the protein-coding genes covered 95 to 99 percent.

Validation in larger sample, more cancers

Co-author Ignacio Wistuba, M.D., chair of Translational Molecular Pathology, is working with Maitra and other investigators at MD Anderson to develop an assay to capture exosomes and validate the approach across other "visceral" (deeply located) cancers.

Maitra and Wistuba plan to work with other cancer moon shots initially, with the ultimate goal of developing a clinical-quality liquid biopsy for use institutionwide.

"We'll validate in a larger population cohort and correlate our findings with patient outcomes," Wistuba said. "There's no clinical application yet, we're early in development, but it's very exciting."

Provided by University of Texas M. D. Anderson Cancer Center