New test traces DNA origins to monitor transplant rejection and reveal hidden cancers

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A new technique that can trace which tissues and organs the DNA in our blood comes from has been reported today in the open-access *eLife*

journal.

The method, called GETMap, could be used in prenatal screening, to monitor organ transplant rejection, or test for cancers that are concealed in the body.

"Analysis of circulating free DNA has been shown to be useful for screening for early asymptomatic cancers," explains first author Wanxia Gai, Postdoctoral Fellow at the Chinese University of Hong Kong, Hong Kong SAR, China. "As cancer-associated DNA changes are present in a wide range of cancer types, detection of such changes can be used as a universal test for concealed cancers. However, in patients with a positive test result, you still need to follow up with tests to find the tumor's location, for example, with a whole-body positron emission tomography, or PET, scan."

To address this, the team developed a test that looks for genetic differences, as well as epigenetic changes to DNA (changes which do not affect DNA sequences) known as methylation. The DNA in our cells has a unique methylation 'fingerprint'. Comparing the methylation fingerprints of different genetic types of DNA molecules circulating in the blood, for example molecules from a fetus, transplanted organ or tumor, with that of different tissues identifies where the DNA has come from.

The team first tested their approach in pregnant women, where they knew that blood DNA would include DNA from the mother, fetus, or both. As expected, GETMap found that DNA carrying fetus-specific genetic markers carried methylation signatures exclusively from the placenta. On the other hand, DNA molecules carrying mother-specific genetic markers carried methylation signatures from white blood cells. DNA molecules carrying genetic markers shared by both the mother and fetus were derived from both tissues.

Next, they tested the approach in blood donated by patients following a lung transplant. Detecting unusually high concentrations of DNA from a transplanted organ in blood can be a sign of organ rejection. But immediately after a transplant, there is often an unexplained surge in donor-derived DNA in the transplant recipient's blood. This makes it challenging to detect whether the organ is being rejected if only genetic markers are used. By using a combination of genetic and epigenetic markers, the team identified the origins of this surge in donor DNA.

At 72 hours after transplantation, only 17% of the circulating DNA was from the lung, compared with 78% from blood cells. This surprisingly high contribution from the blood cells was likely due to the release of DNA from blood cells in the blood vessels of the transplanted lung. With time, the amount of circulating DNA from the lung increased, and the amount from blood cells decreased. There also seemed to be more donor lung DNA in the blood of patients whose new lungs were rejected, compared to those who had a successful transplant.

The team also tested whether GETMap could detect the origin of tumor-derived DNA in the blood. In two patients with liver cancer, they found that 90% and 87% of the plasma DNA carrying mutations had come from the liver. To test this, they needed to know the exact tumor mutations they were looking for, and tumor tissue is not always available if its location is unknown. The team therefore tried to use methylation fingerprints to identify cancer mutations directly from blood DNA rather than tumor tissue. Although fewer mutations were found, the liver was still correctly identified as the source of the tumor-derived molecules. This suggests GETMap could help to reveal the tissue and location of concealed cancers in people who have tumor markers in their blood.

Finally, they challenged the GETMap test in a woman who developed lymphoma during pregnancy. In this instance, they were able to

distinguish between the fetal-specific genes which were derived from the placenta, and the tumor-specific genes which originated solely from a family of white blood cells that were related to the cell type of the lymphoma.

"We have demonstrated the powerful synergy between genetic and epigenetic approaches for identifying the origin of circulating DNA in the blood, and shown its potential applications in cancer screening, prenatal testing and organ transplant monitoring," says co-senior author Dennis Lo, Director of the Li Ka Shing Institute of Health Sciences, and the Li Ka Shing Professor of Medicine at the Chinese University of Hong Kong.

"Our test could bring us closer to the vision of a blood test for a universal cancer marker, by allowing more targeted follow-up tests in specific organs," concludes co-senior author Allen Chan, Professor of Chemical Pathology at the Chinese University of Hong Kong. "This could make cancer diagnosis earlier and more accurate, and reduce the use of whole-body scans and the associated exposure to radiation."

More information: Wanxia Gai et al, Genetic-epigenetic tissue mapping for plasma DNA: applications in prenatal testing, transplantation and oncology, *eLife* (2021). DOI: 10.7554/eLife.64356

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