

Scientists identify DNA alterations as among earliest to occur in lung cancer development

September 21 2015



A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Working with tissue, blood and DNA from six people with precancerous and cancerous lung lesions, a team of Johns Hopkins scientists has identified what it believes are among the very earliest "pre-malignant" genetic changes that mark the potential onset of the most common and deadliest form of disease.

In a report on the discovery, published online September 16 in *Nature Communications*, the team says the DNA alterations it uncovered were in pre-malignant lung [lesions](#) known as atypical adenomatous hyperplasia, or AAH, and that the alterations occurred long before the lesions would acquire the ability to invade surrounding tissue and fulfill the definition of adenocarcinoma of the lung.

"We believe we were able to detect, for the first time, DNA circulating in the blood from [precancerous lesions](#) of the lung," says Mariana Brait, Ph.D., an assistant professor of otolaryngology-head and neck surgery at the Johns Hopkins University School of Medicine and a member of the research team. "This work is a big step in advancing our knowledge of [lung cancer](#) because it could give us a chance to find people at risk early."

Their analysis also showed, they say, that different regions of the same lesion had various mutations distinctly associated with good and poor outcomes, and that in patients for whom blood samples were available, circulating DNA evidence of the mutations showed up clearly.

"This study takes detection to a whole new level in terms of size of the lesion," says David Sidransky, M.D., professor of oncology and pathology at the Johns Hopkins University School of Medicine and the director of head and neck cancer research at Johns Hopkins. "I'm not aware that circulating DNA from precancerous lesions this small has ever been identified before."

Sidransky cautions that the findings are preliminary, involved only a few patients and are but a first step in figuring out how DNA testing might be used to detect precancerous changes at their earliest stages. But the knowledge is invaluable, he says, for both understanding the molecular biology of how lung cancer originates and how to use the findings in clinical applications.

According to the American Lung Association, adenocarcinomas are the most frequent subtype of lung cancer and are usually diagnosed after they have spread. The average five-year survival rate for people with adenocarcinoma is 15 percent, even with the most advanced chemotherapy, surgery and other treatments.

The prevailing opinion among lung cancer experts is that adenocarcinomas of the lung develop from microscopic lesions that accumulate multiple genetic alterations over time that then lead to malignancy.

The problem is that many such precancerous lesions regress and disappear after a few years, but some will progress to cancer, says Evgeny Izumchenko, Ph.D., a postdoctoral fellow in Sidransky's laboratory and the lead author of the study.

To help sort out factors that might predict which small lesions progress to lung cancer, the team collected tissue samples from six patients undergoing surgical removal of lung tumors. Then William Westra, M.D., professor of pathology, painstakingly went through the tissue samples millimeter by millimeter to single out tiny precancerous AAH lesions in the lung tissue for study.

The scientists then extracted and sequenced DNA from these AAH lesions, as well as from other adenocarcinomas in situ, minimally invasive adenocarcinomas and fully invasive adenocarcinomas—a

spectrum of lesions that represent the progression from AAH to fully invasive adenocarcinoma.

Using a technique known as targeted next-generation sequencing, which enables rapid sequencing of large stretches of DNA, they next looked for mutations in 125 genes known to play a significant role in cancer development and progression.

By comparing the DNA of the [pre-malignant lesions](#) with DNA isolated from primary invasive cancer within each patient, the sequencing approach showed that in three of the patients, the same mutations were shared between the pre-malignant lesions and the tumor from the same patient. This is the first definitive link ever found between potential pre-malignant lesions and invasive tumors in the same lung, says Izumchenko, and it suggests that those mutations may be the drivers of tumor progression.

The team also found that different AAH lesions from different patients had unique patterns of mutations, indicating that lung cancer can be initiated by disturbances in different molecular pathways. The researchers also discovered, to their surprise, they report, that some of the lesions were "dead ends," harboring mutations in their DNA that most likely were insufficient to progress to full-blown cancer.

When the team further explored different regions within the same lesion, they found genetic differences even within the same lesion. Mutations associated with good and poor prognosis or responses to therapy were seen in different regions of the same tumor, highlighting the limitations of single biopsies commonly used to decide patients' therapies, Sidransky says.

In another experiment using blood plasma and sputum from two patients, the researchers extracted DNA from these fluids and used digital

polymerase chain reaction, an ultrasensitive method for detecting minute amounts of mutated DNA in a sample, to look for the same mutations they had found in each patient's biopsy samples. They detected those mutations in the fluids—even [mutations](#) found in only one specific zone of a lesion. Sidransky says that this finding may indicate that a blood or sputum test could better represent the overall composition of a tumor than a single biopsy sample.

Further studies are planned to confirm the findings in more [lung cancer patients](#). "We have a glimpse into the future in which we can detect premalignant lesions in the lung before they become tumors," says Izumchenko. "But it is only the beginning of a long road we must travel to figure out how to interpret these discoveries to use them optimally in the clinic."

More information: Targeted sequencing reveals clonal genetic changes in the progression of early lung neoplasms and paired circulating DNA, *Nature Communications* 6, Article number: 8258 [DOI: 10.1038/ncomms9258](#)

Provided by Johns Hopkins University School of Medicine

Citation: Scientists identify DNA alterations as among earliest to occur in lung cancer development (2015, September 21) retrieved 25 April 2024 from <https://medicalxpress.com/news/2015-09-scientists-dna-earliest-lung-cancer.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.