Set of genetic markers in lung cancer identified

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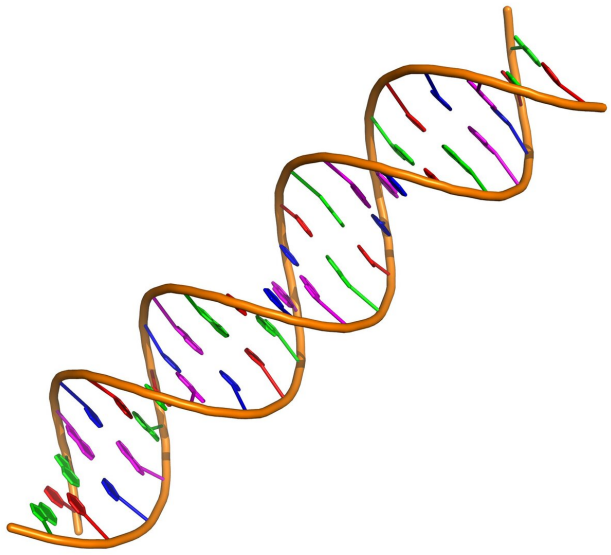

A double stranded DNA fragment. Credit: Vcpmartin/Wikimedia/ CC BY-SA 4.0

Investigators at Wake Forest School of Medicine, part of Wake Forest Baptist Health, have identified a set of new genetic markers that could potentially lead to new personalized treatments for lung cancer.

The study appears online in *Cancer Research*, a journal of the American Association for Cancer Research.

This study was built on a previous discovery by the precision oncology team at Wake Forest Baptist's Comprehensive Cancer Center, directed by Wei Zhang, Ph.D., professor of cancer biology at Wake Forest School of Medicine and a co-corresponding author of this study. Using DNA sequencing technologies, Zhang's team found that tumors with mutated KMT2 genes, a family of proteins, exhibit a feature of genetic instability with numerous mutations in the genome.

"These findings suggest that KMT2 genes may be required for the repair of DNA damages caused by carcinogen exposure such as excess tobacco smoking. We speculate that tumor cells containing mutations in KMT2 genes are unable to repair these DNA damages, causing accumulation of mutations in the genome," said Peiqing Sun, Ph.D., co-corresponding author of the study and professor of cancer biology at Wake Forest School of Medicine.

In the current study, the researchers found that KMT2C, a member of the KMT2 family of proteins, is indeed capable of regulating DNA damage responses and DNA damage repair. It directly binds to DNA damage sites, where it mediates methylation of histones, proteins responsible for wrapping DNA into compact chromosomes. This histone modification process relaxes the chromosome structure in the vicinity of the damaged DNA, which in turn, makes room for other key proteins needed for repairing damaged DNAs.

These findings reveal a novel mechanism for the repair of damaged DNA, Sun said.

This study also provides a basis for potential new personalized treatments for lung cancer. Researchers found that mutations in KMT2C and KMT2D (other members of the KMT2 family) make non-small cell lung cancer more sensitive to Poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors are already approved for treating prostate, pancreatic, ovarian and breast cancer patients whose tumors have mutations in BRCA1 and BRCA2 genes, which are also known to be essential for the repair of DNA damages.

BRCA1 and BRCA2 mutations occur at relatively low frequencies in lung cancer. Researchers in this study suggest that mutations of KMT2C and KMT2D may play a similar role as BRCA1 and

BRCA2 mutations as an indicator for improved response to PARP inhibitors.

"In our study, we demonstrated a novel role of KMT2C in DNA damage responses and identified KMT2C and KMT2D mutations as the much-needed biomarkers that could guide PARP inhibitor therapies for non-small cell lung cancer," Sun said.

He added that further clinical studies are planned to test the efficacy of PARP inhibitors in lung cancer patients.

More information: Antao Chang et al. Recruitment of KMT2C/MLL3 to DNA damage sites mediates DNA damage responses and regulates PARP inhibitor sensitivity in cancer. *Cancer Res* April 14 2021 DOI: 10.1158/0008-5472.CAN-21-0688

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