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Extrachromosomal DNA is common in human cancer and drives poor patient outcomes

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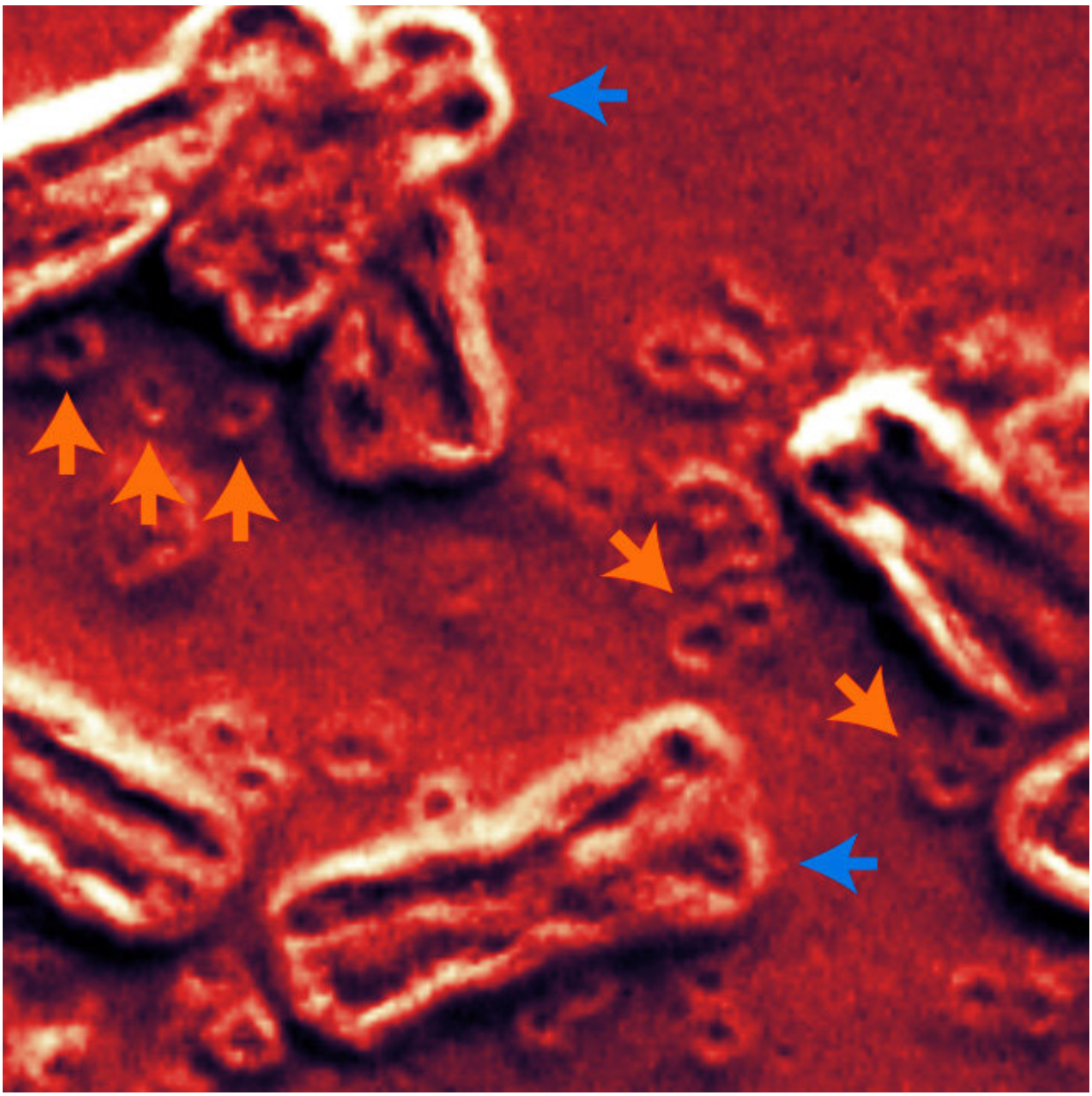

In this scanning electron micrograph of inside the nucleus of a cancer cell, chromosomes are indicated by blue arrows and circular extra-chromosomal DNA are indicated by orange arrows. Credit: Paul Mischel, UC San Diego.

The multiplication of genes located in extrachromosomal DNA that have the potential to cause cancer drives poor patient outcomes across many cancer types, according to a *Nature Genetics* study published Aug. 17, 2020 by a team of researchers including Professors Vineet Bafna and Dr.Paul Mischel of the University of California San Diego and Professor Roel Verhaak of Jackson Laboratories.

This is the first time that a study has shown that the multiplication of these extrachromosomalDNA (ecDNA) genes—a phenomenon called ecDNA oncogene amplification— is present in a broad range of cancer tumor types. The researchers found that ecDNA is a common event in human cancer, occuring at minimum in 14% of human tumors, with far, far higher frequencies in the most malignant forms of cancer, including glioblastoma, sarcoma, esophageal, ovarian, lung, bladder, head and neck, gastric, and many others. The findings demonstrate that ecDNA plays a critical role in cancer.

"We also find that patients whose cancers have ecDNA have significantly shorter survival than all other cancer patients, whose tumors are driven by other molecular lesions, even when grouped by tumor type," said Dr. Mischel, one of the study's authors and a distinguished professor at the UC San Diego School of Medicine and a member of the Ludwig Institute for Cancer Research.

The shorter overall survival raises the possibility that cancer patients

whose tumors are driven by ecDNA may not be as responsive to current therapies and may be in need of new forms of treatment. The researchers' hope is that these findings will be applied to the development of powerful anti-cancer therapies for individuals with ecDNA-driven cancers.

"This study provides a new window into the molecular epidemiology of ecDNA in cancer, providing a unique opportunity to study patients longitudinally to better understand how and why they respond poorly to treatment," Dr. Mischel said.

The researchers observed that ecDNA amplification occurs in many types of cancers, but not in normal tissue or in whole blood, and that the most common recurrent oncogene amplifications frequently arise on ecDNA. Notably, ecDNA-based circular markers of amplification were found in 25 of 29 cancer types analyzed, and at high frequency in many cancers that are considered to be among the most aggressive histological types, such as glioblastoma, sarcoma, and esophageal carcinoma.

"It seems that cancers have pulled an ancient evolutionary trick. Oncogenes and surrounding regulatory regions untether themselves from their chromosomal constraints, driving high oncogene copy number, accelerating tumor evolution, contributing to therapeutic resistance, and endowing tumors with the ability to rapidly change their genomes in response to rapidly changing environments, thereby accelerating tumor evolution and contributing to therapeutic resistance," Dr. Mischel said.

To get to this finding, the research team used intensive computational analysis of whole-genome sequencing data from more than 3,200 tumor samples in The Cancer Genome Atlas (TCGA) and the Pan-Cancer Analysis of Whole Genomes (PCAWG), totaling over 400 terabytes of raw sequencing data, to observe the impact of ecDNA amplification on patient outcomes.

"We developed a powerful computational approach called Amplicon Architect, which identifies ecDNA based on three key features-circularity, high copy number, and "reuse of breakpoints," said paper coauthor Bafna,a professor in the UC San Diego Department of Computer Science and Engineering.

Dr. Mischel and Bafna are cofounders of Boundless Bio, a company developing innovative new therapies directed to extrachromosomal DNA (ecDNA) in aggressive cancers.

"These results point to the urgent need for therapies that can target ecDNA and interfere with their ability to drive aggressive cancer growth, resistance, and recurrence," said Jason Christiansen, chief technology officer of Boundless Bio.

What is ecDNA?

Extrachromosomal DNA, or ecDNA, are distinct circular units of DNA containing functional genes that are located outside cells' chromosomes and can make many copies of themselves. ecDNA rapidly replicate within cancer cells, causing high numbers of oncogene copies, a trait that can be passed to daughter cells in asymmetric ways during cell division. Cancer cells have the ability to upregulate or downregulate oncogenes located on ecDNA to ensure survival under selective pressures, including chemotherapy, targeted therapy, immunotherapy, or radiation, making ecDNA one of cancer cells' primary mechanisms of recurrence and treatment resistance. ecDNA are rarely seen in healthy cells but are found in many solid tumor cancers. They are a key driver of the most aggressive and difficult-to-treat cancers, specifically those characterized by high copy number amplification of oncogenes.

More information: Kim, H., Nguyen, N., Turner, K. et al. Extrachromosomal DNA is associated with oncogene amplification and

poor outcome across multiple cancers. *Nat Genet* (2020). doi.org/10.1038/s41588-020-0678-2