International Agency for Research on Cancer

World Health Organization

PRESS RELEASE
N° 287

22 September 2020

Genes acting as cancer "drivers" across multiple malignancies revealed

Lyon, France, 22 September 2020 – A pan-cancer and multi-omics study led by scientists from the International Agency for Research on Cancer (IARC) has revealed that epigenetic regulator genes, when disrupted through genetic or non-genetic mechanisms, may act as drivers ("epidrivers") in cancer development and have impacts on cancer cell phenotype. These findings were published today in the journal *Genome Research*.[1]

"This study addresses one of the major enigmas of the cancer genome. It explores the significance of the strikingly high rate of mutations (which constitutes a genetic "smoking gun") in epigenetic regulator genes across human cancer types, and supports the notion that epigenetics lies at the very heart of tumorigenesis," says Dr Zdenko Herceg, senior author of the paper and head of the Epigenetics Group at IARC. "It also contributes to the debate sparked by the proposal that epigenetic regulators, when disrupted, constitute the key mechanism fuelling the epigenome alterations that are rampant in virtually all human cancers."

Epigenetic regulator genes are a group of more than 400 coding genes in the human genome, most of which encode enzymes that add ("writers"), modify or revert ("editors"), or recognize ("readers") epigenetic modifications that control a range of critical cellular processes. Based on the observation that many epigenetic regulator genes are frequently disrupted across different malignancies, they are candidates to be drivers of cancer development and progression, potentially acting as oncogenes or tumour suppressor genes.

A comprehensive panel of epigenetic regulator genes (426 genes) was first curated and characterized using literature mining and database screening for functional characteristics, classes, and tumour suppressor or oncogene properties.

The researchers then conducted a pan-cancer and multi-omics analysis integrating (epi)genome, transcriptome, and DNA methylome alterations across 33 cancer types, comprising 10 845 tumour samples (and 730 normal tissues), with sequencing information encompassing a total of 1 500 358 somatic mutations (single nucleotide alterations) and 88 644 447 somatic copy number alterations.

---

[1] Halaburkova A, Cahais V, Novoloaca A, Gomes de Silva Araujo M, Khoueiry R, Ghantous A, Herceg Z (2020). Pan-cancer multi-omics analysis and orthogonal experimental assessment of epigenetic driver genes. *Genome Research*. Published online 22 September 2020. https://doi.org/10.1101/gr.268292.120

Genes acting as cancer “drivers” across multiple malignancies revealed

This analysis revealed that, in addition to mutations, copy number alterations in epigenetic regulator genes were more frequent than previously anticipated and tightly linked to expression aberrations. The scientists further developed and applied a novel bioinformatics approach, integrating the strengths of various driver prediction and multi-omics algorithms, resulting in the identification of functionally important candidate genes with cancer driver potential.

Finally, the driver potential of epigenetic regulator genes was validated in orthogonal state-of-the-art genome-editing in vitro screens (using the CRISPR-Cas9 tool).

This study revealed epidrivers within and across malignancies with shared driver mechanisms, operating across multiple cancer types, that confer the hallmarks of cancer (such as genome instability, evading growth suppressors, enabling replicative immortality, and activating invasion and metastasis).

“This conceptual framework is now used for functional characterization of the mechanistically important molecular driver events that contribute to both cancer phenotypes and their links to environmental exposures,” says Dr Herceg. “The tools developed by IARC should also open up new avenues for different translational approaches, especially considering the growing interest in developing epigenetics-based strategies for early detection, prognosis, and personalized prevention or treatment.”

For more information, please contact

Véronique Terrasse, Communications Group, at +33 (0)6 45 28 49 52 or terrassev@iarc.fr

or IARC Communications, at com@iarc.fr

The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release emailing list, please write to com@iarc.fr.