Study shows ancient viruses fuel modern-day cancers

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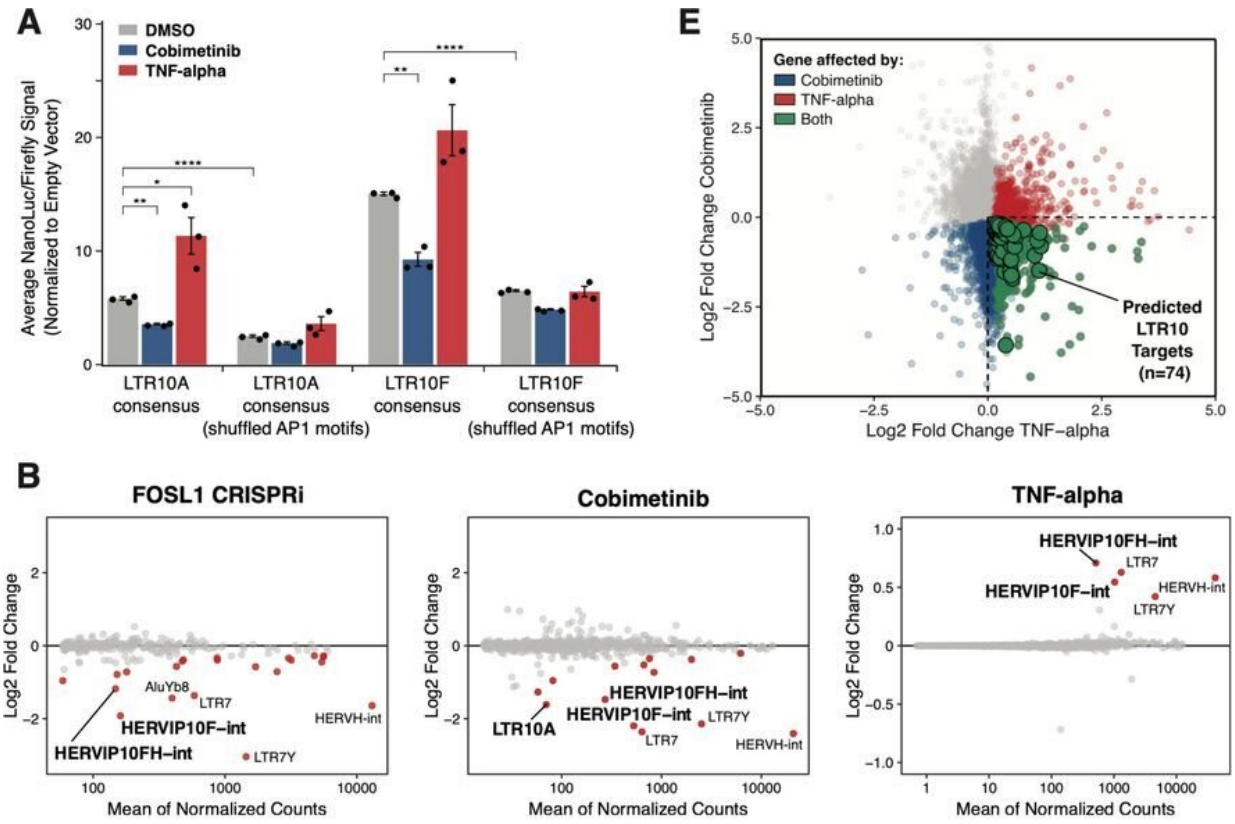

Control of LTR10 activity by AP1/MAPK signaling. Credit: Atma Ivancevic et al

Peek inside the human genome and, among the 20,000 or so genes that serve as building blocks of life, you'll also find flecks of DNA left

behind by viruses that infected primate ancestors tens of millions of years ago.

These ancient hitchhikers, known as endogenous retroviruses, were long considered inert or 'junk' DNA, defanged of any ability to do damage. CU Boulder research published July 17 in the journal *Science Advances* shows that, when reawakened, they can play a critical role in helping cancer survive and thrive.

The study also suggests that silencing certain endogenous retroviruses can make cancer treatments work better.

"Our study shows that diseases today can be significantly influenced by these ancient viral infections that until recently very few researchers were paying attention to," said senior author Edward Chuong, an assistant professor of molecular, cellular and developmental biology at CU's BioFrontiers Institute.

Part human, part virus

Studies show about 8% of the human genome is made up of endogenous retroviruses that slipped into the cells of our evolutionary ancestors, coaxing their hosts to copy and carry their genetic material. Over time, they infiltrated sperm, eggs and embryos, baking their DNA like a fossil record into generations to come—and shaping evolution along the way.

Even though they can no longer produce functional viruses, Chuong's own research has shown that endogenous retroviruses can act as "switches" that turn on nearby genes. Some have contributed to the development of the placenta, a critical milestone in human evolution, as well as our immune response to modern-day viruses like COVID.

"There's been a lot of work showing these endogenous retroviruses can

be domesticated for our benefit, but not a lot showing how they might hurt us," he said.

To explore their role in cancer, Chuong and first author Atma Ivancevic, a research associate in his lab, analyzed genomic data from 21 human cancer types from publicly available datasets.

Study authors Ed Chuong, left and Atma Ivancevic in their office at the BioFrontiers Institute at CU Boulder. Credit: Glenn Asakawa/CU Boulder

They found that a specific lineage of endogenous retrovirus known as

LTR10, which infected some primates about 30 million years ago, showed surprisingly high levels of activity in several types of cancer, including lung and colon cancer. Further analysis of tumors from dozens of colorectal cancer patients revealed that LTR10 was active in about a third of them.

When the team used the CRISPR gene editing tool to snip out or silence sequences where it was present, they discovered that critical genes known to promote cancer development and growth also went dark.

"We saw that when you silence this retrovirus in cancer cells, it turns off nearby gene expression," said Ivancevic.

Experiments in mice yielded similar results: When an LTR10 "switch" was removed from tumor cells, key cancer-promoting genes, including one called XRCC4, switched off too, and treatments to shrink tumors worked better.

"We know that cancer cells express a lot of genes that are not supposed to be on, but no one really knows what is turning them on," said Chuong. "It turns out many of the switches turning them on are derived from these ancient viruses."

Insight into how existing therapies work

Notably, the endogenous retrovirus they studied appears to switch on genes in what is known as the MAP-kinase pathway, a famed cellular pathway that is adversely rewired in many cancers. Existing drugs, known as MAP-kinase inhibitors, likely work, in part, by disabling the endogenous retrovirus switch, the study suggests.

The authors note that just this one family of retrovirus regulates as many as 70 cancer-associated genes in this pathway. Different lineages likely

influence different pathways that promote different cancers.

Chuong suspects that as people age, their genomic defenses break down, enabling ancient viruses to reawaken and contribute to other health problems too.

"The origins of how diseases manifest themselves in the cell have always been a mystery," said Chuong. "Endogenous retroviruses are not the whole story, but they could be a big part of it."

More information: Atma Ivancevic et al, Endogenous retroviruses mediate transcriptional rewiring in response to oncogenic signaling in colorectal cancer, *Science Advances* (2024). DOI: 10.1126/sciadv.ado1218. www.science.org/doi/10.1126/sciadv.ado1218

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