Solving mystery of rare cancers directly caused by HIV

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John Mellors, M.D. Credit: UPMC

For nearly a decade, scientists have known that HIV integrates itself into genes in cells that have the potential to cause cancer. And when this happens in animals with other retroviruses, those animals often develop

cancer. But, perplexingly and fortunately, that isn't regularly happening in people living with HIV.

A team led by University of Pittsburgh School of Medicine and National Cancer Institute (NCI) scientists announce today in *Science Advances* that they've discovered why doctors aren't seeing high rates of T cell lymphomas—or cancers of the immune system—in patients living with HIV.

"We seem to have explained some of the mystery of why HIV is rarely the direct cause of cancer," said co-lead author John Mellors, M.D., who holds the Endowed Chair for Global Elimination of HIV and AIDS at Pitt. "Our investigation showed that it requires a very unusual series of events involving changes in both HIV and additional mutations in human genes for someone with HIV to develop lymphoma. Clinicians should always screen their patients for cancer as part of routine health care, but people with HIV do not need to fear that they will inevitably develop lymphomas."

When HIV enters the body, it seeks out T cells and inserts its genetic sequence—called the "provirus"—into the cell's DNA. This effectively hijacks the T cells, which normally patrol the body in search of foreign pathogens, instead instructing them to produce more HIV.

Previous research by the NCI and Pitt teams discovered that the provirus can insert itself into the T cells' genetic code in a place that prompts these infected cells to grow into large, noncancerous clones of themselves and, in some instances, these clones can carry complete, infectious proviruses. Such clones are called "repliclones" because they carry a replication-competent provirus. It isn't necessarily the goal of the virus to induce the growth of repliclones; it's just the result of where the provirus happened to insert itself in the T cell's genetic code.

These prior discoveries gave rise to a paradox: If HIV can integrate into T cell oncogenes (genes involved in normal cell division that, when mutated, result in cancerous cell growth), then shouldn't it also cause lymphoma?

To answer this question, the team obtained samples from 13 HIV patients with lymphoma and picked out three that had high levels of HIV proviruses, indicating that the virus might be implicated in the cancer formation.

They then examined those samples to learn where the provirus had inserted into the T cell DNA. This painstaking analysis revealed that when the HIV provirus inserts into a gene called *STAT3* or *STAT3* and another gene called *LCK*, it can prompt cells with those proviruses to activate cell proliferation. With additional nonviral mutations in other human genes, this can result in T cell lymphomas.

"This is a complicated, multistep process that requires rare events—insertion into *STAT3* or *STAT3* and *LCK* genes in just the right spot—to even begin," said Mellors, who also is chief of the Division of Infectious Diseases at UPMC. "As a physician, I am reassured that these events are rare. Although we need to be aware of the potential for HIV to cause lymphomas, it's such a rare occurrence that there is no need for heightened anxiety, yet."

Because people with HIV are living longer due to advances in medication and care, there are more years in which mutations could accumulate in host genes. When that is coupled with the effects of proviruses already inserted in oncogenes, the frequency of lymphoma could increase over time, Mellors noted. So far, this has not been observed. Nevertheless, the research team stressed the importance of additional studies to assess the role that HIV medications may play in preventing T cell lymphomas, coupled with continued surveillance for T

cell lymphomas in people with HIV.

More information: John W. Mellors et al, Insertional activation of STAT3 and LCK by HIV-1 proviruses in T cell lymphomas, *Science Advances* (2021). DOI: 10.1126/sciadv.abi8795. www.science.org/doi/10.1126/sciadv.abi8795

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