Sites of HIV Integration Provide Clues to Viral Persistence

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One of the big questions in HIV research has to do with viral persistence. How does the virus remain in infected individuals despite the ability of antiretroviral treatment (ART) to effectively suppress viral replication and reduce the viral load in circulation to below detectable levels? Viral persistence accounts for the rebound in viremia observed when patients stop taking their medication. This rebound can occur even after decades of successful treatment and remains a main hurdle for achieving a cure for HIV infection. One potential explanation for viral persistence is the proliferation of infected cells. A group of researchers from the Seattle Children's Research Institute, University of Washington, and Fred Hutchinson Cancer Research Center recently determined that the site of integration of HIV into an infected cell's genome may promote cell growth and contribute to persistence in the absence of viral replication. Their findings were published in the journal Science.

Upon infection, the HIV genome migrates to the nucleus of the host cell where it integrates into the host cell genome. Previous research on the site of viral integration had primarily focused on how it affected transcriptional activity of the virus. In the current study, Wagner et al. examined the effect of viral integration sites on the fate of the infected cell. By utilizing a method of determining the sites of viral integration and the adjacent viral sequences from individual infected cells, the researchers were able to compare unique sites of integration from three infected individuals over the span of over a decade on ART. The same sites of integration were found in multiple cells within each participant but not across multiple participants, suggesting that these cells had derived from a clonal precursor cell. This conclusion was further supported by the presence of nearly identical HIV proviral sequences at the same site of integration in multiple cells.

Next, the researchers examined if the provirus integrated near genes with known associations to cancer, regulation of cell proliferation, or cell survival. They found that a higher percentage of the genes near HIV integration sites were associated with cancer than the amount of cancer-related genes that exist throughout the genome (12.5% vs. 5.19%, respectively; p < 0.0001). Furthermore, the researchers found that proliferating HIV-infected cells had an even higher percentage of integration sites near cancer-associated genes (17.65%; p = 0.0076). In particular, there were 12 cancer-associated genes that were found with HIV integration that appeared in at least two of the participants.

This study provides new insight into the mechanisms of viral persistence during ART. The long half-life of the infected cells is known to play an important role in HIV persistence, and low-level viral replication may also contribute. The data presented by Wagner et al. provide evidence that HIV-infected cells proliferate and thus contribute to HIV persistence, especially during long-term ART.

Dr. Paul Edlefsen of the Vaccine and Infectious Disease Division was a collaborator on the study and describes the findings as exciting for two reasons. "First, it confirms that one way HIV persists despite ART is by clonal expansion of cells with integrated HIV, and second, it raises the intriguing
possibility that certain sites of integration cause the host cell to clonally expand," he said. Of particular note, he recognizes that this second finding will interest many who are involved in HIV cure research, as it "suggests new avenues of research into treatments that could block the expansion of these cells, which could plausibly enable ART-based eradication of the latent reservoir (and hence a cure)."

Dr. Edlefsen also sees a connection between these findings and cancer research. "I also think that this discovery may lead to improved understanding of how cell proliferation can be dysregulated by specific genomic alterations in certain genes (such as BACH2), which is of value for cancer research (since cancer involves such dysregulation)," he explained.

Whether for research on cancer or HIV persistence, these findings are sure to lead the way for additional projects based on sites of viral integration and their effect on the eventual fate of the infected cell.


Image provided by Tatiana Gill, supported by Dr. Lisa Frenkel.

A close examination of the unique sites of integration led to the findings that integration sites near cancer-associated genes may result in vigorous proliferation, which could contribute to HIV persistence in the absence of viral replication.