Heart toxin reveals new insights into HIV-1 integration in T cell genome

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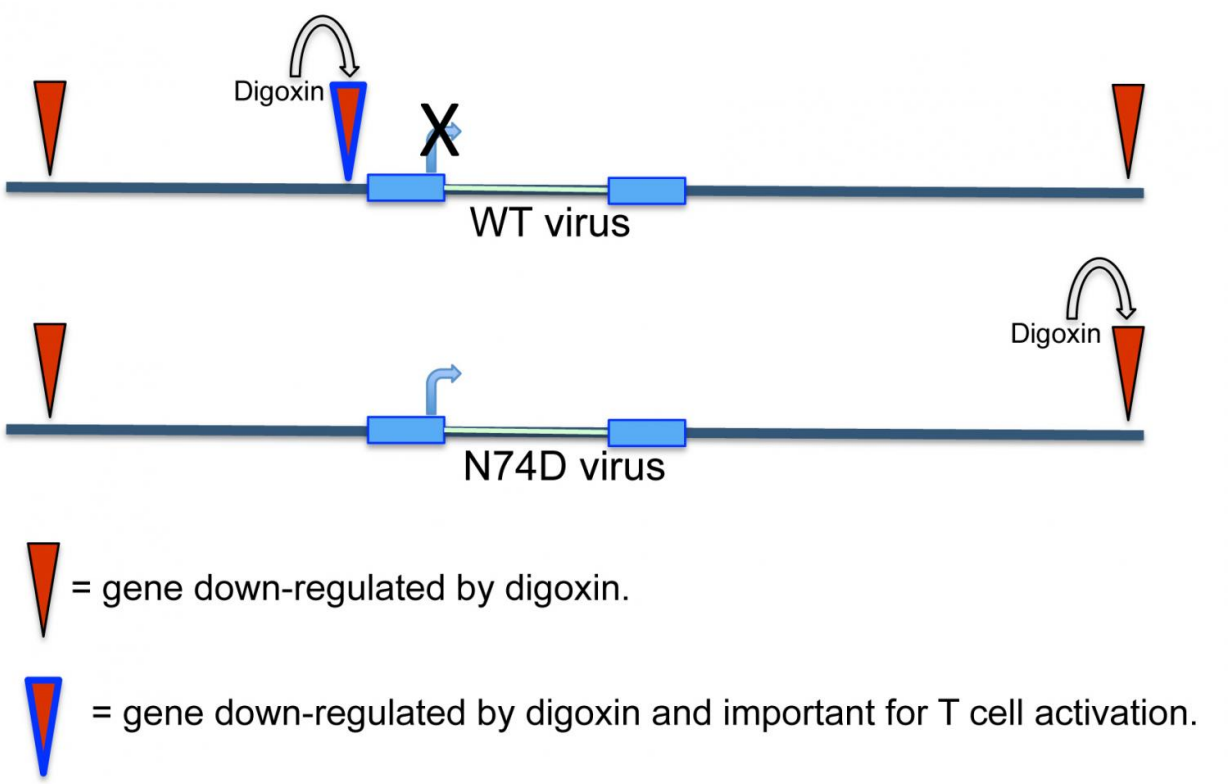

Digoxin exposes link between T cell activation and targeted HIV-1 integration in specific genes. Credit: Zhyvoloup A, et al. (2017)

Human immunodeficiency virus (HIV)-1 may have evolved to integrate its genetic material into certain immune-cell-activating genes in humans, according to new research published in *PLOS Pathogens*.

HIV-1 integrates its own genome into the genome of human immune system cells known as CD4+ T cells, hijacking their cellular machinery to make more copies of itself. Previous research has shown that HIV-1 integrates more frequently into human genes that are transcribed into RNA (the first step in gene expression), but the biological significance of this targeting has been unclear.

In the new study, Alexander Zhyvoloup of University College London, U.K., and colleagues sought to gain more insight into the life cycle of HIV-1 by comparing a normal, "wild type" strain of the virus to a mutated strain. They infected CD4+ T cells with both strains and tested the effects of exposing them to a long list of chemical compounds.

This chemical screen showed that a compound known as digoxin—a plant-derived cardiac toxin often used to treat various heart conditions—inhibited wild type HIV-1 more than the mutated strain. Subsequent RNA sequencing suggested that digoxin inhibits HIV-1 gene expression as well as the activation and metabolism of CD4+ T cells.

Further analysis showed that wild type HIV-1 tends to integrate itself into or near genes affecting CD4+ T cell activation and metabolism more frequently than does the mutant strain. These are the same T cell genes inhibited by digoxin, and since replication of integrated HIV-1 requires transcription of nearby genes, this provides an explanation for why wild type HIV-1 is more susceptible to digoxin: digoxin represses the genes that the virus more frequently targets for integration.

The authors report that their findings represent the first demonstration of a functional link between changes in T cell activation and targeting of specific integration sites by HIV-1. The results may have implications for HIV-1 latency, in which integrated HIV-1 remains dormant in the human genome before being reactivated at a later point.

"HIV-1 infects cells of the immune system called CD4+ T cells," the authors further explain. "These cells can rapidly change they status, from quiescent to activated and vice versa, for the immune system to work well. In this paper, we report that HIV-1 prefers to integrate into o near genes that control such changes in CD4+ T cells so that the virus is better able to remain coupled to the CD4+ T cell status. This has implications for HIV-1 latency and reactivation".

More information: Zhyvoloup A, Melamed A, Anderson I, Planas D, Lee C-H, Kriston-Vizi J, et al. (2017) Digoxin reveals a functional connection between HIV-1 integration preference and T-cell activation. *PLoS Pathog* 13(7): e1006460. doi.org/10.1371/journal.ppat.1006460