A better understanding of HIV-1 latency

Publication in *eBioMedicine*: A fruitful French-Belgian collaboration led by Dr. Carine Van Lint (Université libre de Bruxelles, ULB), with the support of the FNRS (Fonds National Belge de la Recherche Scientifique), the French Agency for Research on AIDS and Viral Hepatitis (ANRS), ViiV Healthcare, and the US National Institutes of Health, contributes to a better understanding of HIV-1 latency: implications for the development of new therapeutic strategies.

The contribution of antiretroviral drugs to the treatment of HIV-1 positive patients has been considerable. However, a major problem remains: despite prolonged and highly effective antiretroviral therapy, cells infected with latent viruses persist in patients and constitute true reservoirs of virus. Indeed, the virus that lies dormant in these cells is invisible to the immune system of the infected individual.

However, virus production can be reactivated in these reservoir cells by numerous cellular stimuli (a simple infection for example). These cells are therefore a permanent source of virus rebound when treatment is stopped. In other words, even when undetectable, the virus is there, ready to be reactivated if the patient stops antiretroviral therapy.

Given the very long life span of some of these reservoirs, it is estimated that their complete eradication would require more than 60 years. Consequently, one of the greatest challenges in current AIDS research is to eliminate the cellular reservoirs. One of the most explored strategies is to administer molecules that reactivate the expression of latent viruses, while maintaining the patient under anti-HIV therapy. The reservoir cells that express the virus could then be recognized as infected and be destroyed by the immune system of the infected individual.

The Service of Molecular Virology of the Faculty of Sciences at the Université Libre de Bruxelles (ULB), headed by Carine Van Lint, FNRS Research Director, has been studying the molecular mechanisms that
regulate HIV-1 gene expression for many years. Such a basic understanding of the molecular mechanisms responsible for HIV-1 latency could allow the design of novel alternative or complementary therapeutic strategies that would force the virus to leave this latent state.

The results published by the ULB researchers this week in the journal *eBioMedicine* mark a new step forward in that direction.

One of the mechanisms of HIV-1 persistence is DNA methylation, a chemical modification of DNA that locks the expression of viral genes in a stable but reversible manner. If DNA methylation of viral genes was known, including in infected individuals, how DNA methylation occurred in HIV-1 genes was not fully understood. In this context, research conducted by Carine Van Lint (ULB), in collaboration with French laboratories, has shown that the cellular protein UHRF1 is involved in the maintenance of HIV-1 latency, notably by recruiting the DNA methylation machinery to the viral genome. Indeed, inhibition of UHRF1 (by molecular or pharmacological manipulation) provokes the reactivation of HIV-1 in the cellular reservoirs, which can then be detected and eliminated by the immune system.

These findings have enabled ULB researchers to propose a new therapeutic strategy to complement current anti-AIDS treatment. Indeed, they have demonstrated that anti-UHRF1 molecules, used in anti-cancer therapies, can "wake up" the silent virus and thus force the latent virus to come out of its reservoirs. In particular, the researchers have demonstrated that the major polyphenolic compound of green tea, Epigallocatechin-3-gallate (EGCG), a known inhibitor of UHRF1, reactivates HIV-1 from latency. EGCG, which can be safely administered to humans, reactivates viral expression in *ex vivo* cultures of reservoir cells isolated from the blood of HIV-positive patients under antiretroviral therapy (having an undetectable plasma viral level for at least one year). These experiments were repeated *ex vivo* in cells isolated from 22 Belgian patients and demonstrate for the first time the reactivating effect of EGCG on HIV-1 reservoirs, in addition to its antiviral properties which limit the spread of the infection. These results are encouraging for the development of innovative anti-HIV therapies based on UHRF1 inhibition.

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