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Editorial

Kick and Kill Approach: How Far are we from HIV Cure?

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EDITORIAL

The Acquired Immune Deficiency Syndrome (AIDS) is a viral infection caused by HIV-1, which leads to a decrease of the lymphocytes in the human body. Since AZT has proven its effectiveness in inhibiting reverse transcription [1], an important step in the life cycle of the virus, other compounds were synthesized aiming the inhibition of some stage of its cycle, such as fusion inhibitors, integrase and protease inhibitors. It is estimated, at least, thirty approved available drugs to treat HIV infections and the combination between these drugs, acting in different steps in virus life cycle, denominated "combined antiretroviral therapy", shows an efficacy in the control of the infection [2]. HIV-infected individuals who start the treatment with antiretroviral drugs uninterrupted can achieve the viral suppression. Despite that, in 2017, about 36.9 million people worldwide was living with the virus and about 940,000 died by causes related to AIDS [3]. Although the deaths decreased 51% since the advent of the antiretroviral therapy (ART) in 2004 [3], the lack of accessibility and the collateral effects are considered limitations for the treatment to achieve all the HIV-infected individuals in the world. In addition to that, the interruption of the ART leads to resurgence of the infection and its advance to AIDS. The ART is successful in controlling the infection, providing a normal life to HIV-infected patients, however, the virus is not totally eradicated and persists during long periods through mechanisms that lead to latency. The most common cells harboring latent HIV virus DNA are denominated "memory CD4+ T cells", which consists in a small amount of CD4+ T cells infected with viral DNA that was stored in a resting state. This latent reservoir can become a source of new HIV infection and can expand through homeostatic mechanisms [4]. The latency allows the virus to integrate the viral DNA in the host DNA, remaining transcriptionally silent. Some strategies have been studied to eliminate the latent virus, based on its reactivation. One of the strategies, called "kick-and-kill" or "shock-and-kill", implies the use a molecule capable reactivating the latent reservoir (kick-agent), combined with the ART, and another compound responsible for eliminate the re-actived HIV-infected cells (kill-agent). Histone deacetylase (HDAC) inhibitors, bromodomain (BRD) inhibitors and protein kinase C (PKC) agonists are the most studied "kick-agents".

Histone deacetylase (HDAC) enzymes are responsible for the deacetylation of lysine residues in the histone tails, leading to a compact conformation of the chromatin and contributing with HIV-latency through transcriptional repression. The inhibition of these enzymes allows the acetylation by histone acetyltransferase (HATs) enzymes providing a relaxation of the chromatin and contribute to recruitment of transcriptional factors [5]. Some HDAC inhibitors have already been tested in clinical to evaluated the capacity to induce latent HIV-1, as is the case of HDAC inhibitor as vorinostat (VOR), which was tested in and ex vivo demonstrating capacity in reversal the latent reservoir in HIV-infected patients on antiretroviral therapy. In 6 of 7 patients who received VOR doses at 72-hour intervals was observed an increase of rca-HIV RNA levels, however, the study demonstrated that was no depletion of persistent HIV infection in those patients [6]. Panabinostat was used in a clinical trial for 8 weeks demonstrating to be well tolerated and significant increased HIV transcription in patients on antiretroviral therapy. This study also demonstrated no reduction in the number of latently infected cells [7]. Studies involving associations or others HDAC inhibitors, such as valproic acid and romidepsin, are currently being performed and there is not results published up to this moment (www.clinicaltrials.gov).

The protein kinase C (PKC) agonists induces the latent HIV-1 through activation of the transcription factors NF-κB1and AP-1 [5], since the insufficient levels of host transcriptional factors are one of the proposals for HIV latency [4]. There only PKC inhibitor tested in humans was bryostatin-1, in a phase 1 study. The results showed that the drug was safe administered once a day, but the dosage was not sufficient to demonstrate alterations in the PKC activity or on the transcription of latent HIV [8].

Bromodomains are a family of protein domains that can recognize lysine residues, such as those present in histones, and can act on

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remodeling and transcriptional control of chromatin [9]. BRD inhibitors can contribute to the reactivation of latent reservoirs since the bromodomain 4 (BRD4) competes with Tat protein for the transcription factor P-TEFB, blocking the Tat-P-TEFB interaction on the HIV promoter [9].

This strategy is new and different molecules and combinations of doses are being tested to reach more information about the real applicability of the latency reverse agents (LRAs) [10].

The kick-and-kill strategy has been explored through different molecules and approaches, but still requires an intense investigation. The development of new compounds can help achieving results for the best understanding and improvement of this strategy. The combination of different types of LRAs in an attempt to obtain a synergistic effect can also be a good way to explore this, as suggested in a study of the joint action of a PKC agonist and a HDAC inhibitor in inducing latent virus from a HIV-1 patient PBMCs ex vivo [11]. Besides that, the development of a powerful molecule to target the reactivated HIV infected cells, the "kill agent", it is still necessary and an important key factor for this strategy to function. As described in the name itself, "kick-and-kill" strategy needs a combination between effective "kick" and "kill" agents, besides being necessary to maintain the ART during the treatment. The understanding and improvement of this approach is a promising pathway to eliminate HIV from infected people completely reaching the cure.

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