New horizons for BRD4-modulators in a block-and-lock functional cure of HIV-1 infection

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The persistence of HIV-1 provirus in a transcriptionally silent state in long-lived cells of the immune, known as the latent reservoir, is the main impediment for an HIV-1 cure. Using latency promoting agents (LPAs), the block-and-lock cure strategy aims to establish a cellular reservoir unable to reactivate after treatment discontinuation. However, new drug targets for the development of LPAs are crucial. The epigenetic reader, bromodomain-containing protein 4 (BRD4), plays a role in the establishment/maintenance of latency by regulating HIV-1 transcription. Most BRD4 modulators, such as JQ1, are known to reactivate latency. However, recently, the first BRD4 modulator was reported that epigenetically represses HIV-1 transcription, named ZL0580. To gain insight into the role of BRD4 in the transcriptional regulation of HIV-1 and to validate BRD4 as a block-and-lock cure target, we now investigated the effect of JQ1 and ZL0580 on HIV-1 transcription side-by-side as well as their mechanism of action. In an HIV luciferase reporter assay, JQ1 promoted and ZL0580 hampered HIV-1 transcription, both cell lines and primary lymphocytes. To investigate the mechanism of action, we applied single-cell imaging of both viral DNA and RNA of cells treated with JQ1 or ZL0580, demonstrating that they both work on the transcriptional level. In addition, we corroborated that JQ1 decreases and ZL0580 increases the co-localization of BRD4 with acetylated histones. Finally, we combined LEDGINs with both BRD4 modulators. LEDGINs are well-characterized LPAs, which inhibit the interaction between viral integrase and lens epithelium-derived growth factor (LEDGF/p75). As a result, LEDGINs reduce viral integration and retarget the residual provirus to regions resistant to reactivation. Interestingly, ZL0580 showed an additive effect in combination with LEDGINs in blocking transcription and locking reactivation. These results highlight the potential of latency promoting cocktails to increase the efficiency of block-and-lock therapies.