A combination of drug screen and RNA landscape reveals targetable pathways in HIV-1 reactivation

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BACKGROUND

Background. Despite effective antiretroviral therapy, HIV-1-infected cells continue to produce viral antigen and induce chronic immune exhaustion. We propose to identify HIV-1-suppressing agents which can inhibit HIV-1-induced immune activation.

Approaches. We developed a dual-reporter cell line model and screened a library of 1,430 FDA-approved small molecule compounds to identify HIV-1-suppressing agents. Second, we examined the effect of candidate HIV-1-suppressing agents on HIV-1 transcription and HIV-1-driven aberrant transcription at the integration site. Third, we examined cellular transcriptional landscape of cells treated with candidate HIV-1-suppressing agents in three transcriptional analyses to first distinguish pathways that affect cell activation. Fourth, to understand whether candidate HIV-1-suppressing agents can disrupt the proliferation dynamics of HIV-1-infected cells, we examined the frequency of HIV-1-infected cells from HIV-1-infected individuals upon ex vivo T cell activation with and without ex vivo treatment of candidate HIV-1-suppressing agents.

METHOD AND RESULTS

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CONCLUSION

Overall, a combination of drug screening and transcriptome analysis identified the landscape of cellular pathways critical for HIV-1 reactivation and a combination of this landscape identified suppressive HIV-1 transcription and reactivation of HIV-1 suppressive factors. The combination of these pathways with increased selectivity against HIV-1-infected cells provides a new direction to reduce HIV-1 reactivation and a novel HIV-1-suppressing agent filgotinib. Filgotinib suppresses HIV-1 transcription and reducing the proliferation of HIV-1-infected cells.

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