Nature Reviews Microbiology | AOP, published online 26 October 2009; doi:10.1038/nrmicro2263

HIV

No place to hide

BANANASTOCK

> it is possible to reactivate latent pools of HIV-1 without triggering toxic global T cell activation

Although highly active antiretroviral therapy (HAART) can reduce viral load below detectable levels, it cannot cure HIV-1 infection, owing to the presence of a reservoir of latent integrated HIV-1 proviruses in resting $CD4^+$ T cells. Coupling the reactivation of this viral reservoir with HAART could provide a way to purge infection completely. However, early efforts to reactivate latent HIV-1 proved to be toxic, probably as a result of nonspecific T cell activation. Yang *et al.* now describe the development of a primary cell model of HIV-1 latency that can be used to screen for compounds that are able to reactivate latent HIV-1 in the absence of global T cell activation.

Existing models for studying HIV-1 latency use transformed T cell lines, which differ from resting $CD4^+$ T cell populations owing to their proliferative nature and altered signalling pathways. To generate a model system that more closely resembles resting $CD4^+$ T cells, the authors transduced primary human $CD4^+$ T cells with B cell lymphoma 2 (BCL-2), a downstream effector of interleukin-7 signalling that is known to be important for maintaining the survival of resting $CD4^+$ T cells. Eighty percent of the cells were lost during the first 3 weeks but, in comparison with cells that had not been transduced with BCL-2, the remaining viable cells exhibited greatly improved survival and showed many of the features that are typical of resting $CD4^+$ T cells. To monitor the activation of latent HIV-1, the authors infected these viable cells with an attenuated HIV-1 strain expressing green fluorescent protein (GFP) but lacking viral factors that exhibit cytopathic effects. After 4 weeks in culture, 20–30% of the HIV-1-infected cells had stopped expressing GFP, suggesting that in these cells HIV-1 had become latent. In this population, GFP expression could be detected in 1–3% of cells following T cell activation, providing a readily detectable level of reactivation of latent virus.

The authors used this system to screen two libraries for compounds that could reactivate latent HIV-1. One compound, 5-hydroxynapthalene-1,4-dione (5HN), was identified in both libraries and was able to reactivate latent HIV-1 without inducing global T cell activation. A natural quinone that is found in the black walnut tree, 5HN can be reduced to a semiquinone radical by enzymes such as NADPH oxidoreductase, leading to the production of reactive oxygen species (ROS). ROS indirectly activate the nuclear factor-κB (NF-κB) signalling pathway, which is known to play a part in reactivation of latent HIV-1. Accordingly, the authors found that treatment of latent HIV-1-infected cells with 5HN led to increased NF-κB expression and stimulated expression of HIV-1 genes. Antioxidants could block the stimulatory effects of 5HN, suggesting that activation of NF-κB through the production of ROS is likely to be the mechanism by which 5HN can reactivate latent HIV-1.

These data suggest that it is possible to reactivate latent pools of HIV-1 without triggering toxic global T cell activation. Coupled with HAART, such an approach may help overcome the latent HIV-1 reservoir.

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ORIGINAL RESEARCH PAPER Yang, H. C. *et al.* Small-molecule screening using a human primary cell model of HIV latency identifies compounds that reverse latency without cellular activation. *J. Clin. Invest.* **119**, 3473–3486 (2009)
FURTHER READING Coiras, M. *et al.* Understanding HIV-1 latency provides clues for the eradication of long-term reservoirs. *Nature Rev. Microbiol.* **7**, 798–812 (2009)