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Commentary

Will LEDGIN molecules be able to play a role in a cure for HIV infection?

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HIV DNA integration is essential for the persistence of HIV infection and, to date, represents an insurmountable obstacle to an HIV cure. By contrast, drugs that block the NS5B polymerase enzyme of HCV for only 12 weeks can frequently cure HCV infection because no integration step is involved in the HCV replication cycle. Although inhibitors of each of HIV reverse transcriptase, protease, and integrase have been successfully used to treat HIV infection, none of these are able to reverse the persistence of integrated DNA copies of the viral genome. Hence, viral loads typically rebound rapidly after treatment interruption due to activation and expression of the viral genome from latently infected cells within the viral reservoir (Chun and Fauci, 2012).

Early initiation of antiretroviral therapy remains the only way to limit the size of the HIV reservoir and, thus far, several interventions, including treatment intensification with the integrase strand transfer inhibitor (INSTI) raltegravir, have failed to achieve diminution of the reservoir. Strategies that have been developed to eradicate HIV include a "Shock and Kill" approach, whereby latently infected cells are activated and then killed by antiretroviral drugs (ARVs), stimulation by Toll-like receptors, and the use of neutralizing or cytotoxic T lymphocyte-specific antibodies (Spivak and Planelles, 2016). Alternative approaches propose to push the virus into latency by using Tat inhibitors that limit HIV post-latency reactivation (Mousseau et al., 2015).

Other HIV inhibitors have been developed that target the interaction between the viral integrase and the cellular transcription factor lens epithelium-derived growth factor (LEDGF) (Christ et al., 2010). The rationale is that LEDGF can increase the efficiency of HIV integration while also being necessary for HIV to integrate preferentially within transcriptionally active genomic regions (Ciuffi et al., 2005). In cells depleted of LEDGF, HIV integration sites were enriched in GC-rich genomic regions and were less frequent in actively transcribed regions than when LEDGF was present (Ciuffi et al., 2005). Of course, integration within transcriptionally active regions has potent implications for the establishment of latency, as the cellular transcriptional state influences both HIV transcription driven by its promoter located in the long terminal region (LTR) and reactivation from latency. Inhibitors that target the interaction between integrase and LEDGF are variously termed non-catalytic integrase inhibitors (NCINIs), allosteric inhibitors (ALLINIs), or LEDGF inhibitors (LEDGINs). The molecular mechanisms by which LEDGINs inhibit HIV replication are not completely understood and some LEDGINs can inhibit HIV post-integration events more efficiently than integrase activity itself.

In this issue of *EBioMedicine*, Vranckx and colleagues show that a LEDGIN termed CX014442 specifically alters HIV-1 genomic integration in a manner that is similar to that associated with LEDGF depletion (Ciuffi et al., 2005; Vranckx et al., 2016). The authors carefully characterized HIV integration sites in the presence of various concentrations of CX014442 and found that this compound caused a dose-dependent shift that now favored GC-rich regions for integration instead of actively transcribed genomic regions (Vranckx et al., 2016). However, the preferential DNA sequences targeted for integration did not change, and Vranckx *et al.* verified that CX014442 did not favor HIV integration within genomic regions that are identified as unsafe integration sites (Vranckx et al., 2016), consistent with the notion that HIV integration does not result in cellular transformation, although HIV integration at sites close to genes involved in cellular survival has been linked to cellular clonal expansion without oncogenesis (Ikeda et al., 2007; Wagner et al., 2014; Maldarelli et al., 2014). The authors further showed that integration events, in the presence of CX014442, were more likely to be localized deeper within the cellular nucleus (Vranckx et al., 2016), consistent with a similar effect of LEDGF knockdown (Marini et al., 2015). The use of the INSTI raltegravir or a catalytically inactive form of integrase had similar effects (Marini et al., 2015).

Most remarkably, using an *in vitro* latency model with a dual-reporter virus, the scientists showed that post-latency reactivation was also inhibited in the presence of CX014442. Accordingly, they argue that LEDGINs may target HIV integration within genomic regions that are less favorable for reactivation than those that are targeted in the presence of a functional integrase–LEDGF interaction. In support of this, the authors also showed that latent infection in LEDGF-depleted cells is less susceptible to reactivation by various latency reversing agents including a combination of the protein kinase C activator prostratin together with SAHA, a histone deacetylase inhibitor. This is important as latency reversing agents are being actively investigated as part of the "Shock and Kill" cure strategy. The authors conclude that LEDGINs may help reduce the portion of the HIV reservoir that is susceptible to

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reactivation *in vivo* and suggest that LEDGINs might have utility early in treatment strategies aimed at reducing the size of the reservoir. One caveat may be that the use of INSTIs or reverse transcriptase inhibitors may actually be more beneficial during early treatment, since the LEDGINs may, in fact, be most active post-integrationally. Further research is needed to better understand the molecular mechanism(s) whereby LEDGINs inhibit HIV replication and to better distinguish between their *anti*-integrase versus post-integration effects. In addition, CX014442 also seemed to be effective at different concentrations in different cell types and this also needs to be further studied as should the reasons for the LEDGIN- and raltegravir-dependent relocalization of integration to sites that are deeper within the nucleus. And, clarification is needed to understand the link between integration sites within specific genomic regions and susceptibility to latency reversal. The use of non-human primate and/or humanized mouse models might also provide much needed insights in regard to the possible role of LEDGINs in HIV eradication.

Disclosure

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