Host DNase TREX1 hides HIV from DNA sensors

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Human immunodeficiency virus type 1 (HIV-1) seems to avoid detection by nucleic acid sensors. This is probably due to the host exonuclease TREX1, which degrades HIV DNA generated during HIV-1 infection.

Type I interferon is a crucial component of antiviral defense. Most cells have intrinsic sensors of nucleic acids that detect viral infections and subsequently trigger interferon responses to combat such infections. Strikingly, infection of T cells and macrophages with human immunodeficiency virus type 1 (HIV-1) does not induce antiviral interferon responses. How HIV-1 avoids triggering the viral sensors is an open question. In this issue, Yan *et al.* show that the host exonuclease TREX1 hides HIV-1 from DNA sensors[1].

Mutations in the human gene encoding TREX1 cause autoimmune diseases that are in part similar to systemic lupus erythematosus[2,3]. TREX1 deficiency leads to the accumulation of cytosolic DNA from endogenous retroelements, which are mobile DNAs that are relics of retroviruses trapped in the genome and require reverse transcription for their movement throughout the genome. The accumulation of such DNA leads to interferon responses that cause autoimmunity in TREX-deficient mice[4,5]. Such data link enhanced interferon responses resulting from TREX1 dysfunction to the initiation of autoimmunity[4] and therefore suggest that TREX1 protects against autoimmunity by suppressing interferon responses. Yan *et al.* now show that TREX1 degrades HIV DNA generated during HIV-1 infection and thereby prevents triggering of intrinsic DNA sensors[1]. HIV-1 infection in the absence of TREX1 leads to the accumulation of HIV-1 DNA, which triggers DNA sensors that induce antiviral interferon responses. Thus, by protecting against autoimmunity, TREX1 facilitates HIV-1 infection by degrading HIV-1 DNA so HIV-1 is not detected.

The detection of viral DNA or RNA is linked to the induction of interferon that initiates the transcription of the so-called interferon-stimulated genes. Many of these genes encode antiviral proteins that interfere with various steps of virus replication. Thus, interferon responses are paramount for effective combating of viral infection. Cells express two complementary systems, Toll-like receptors (TLRs) and cytosolic nucleic acid sensors, that detect DNA or RNA to trigger antiviral interferon responses. TLRs are transmembrane proteins, and the TLRs that recognize nucleic acids (TLR3, TLR7, TLR8 and TLR9) are located in endosomes of antigen-presenting cells and recognize nucleic acids derived from internalized viruses or infected apoptotic cells. TLR7 and TLR8 detect genomic HIV-1 single-stranded RNA (ssRNA)[6], and infection of dendritic cells with HIV-1 triggers TLR8 by endocytosis of HIV-1 particles[7]. Whereas the endosomal TLRs detect nucleic acids after internalization, specialized cytosolic nucleic acid sensors detect cytosolic RNA or DNA derived from infection not only with viruses but also with fungi or intracellular bacteria. The nucleic acid sensors are able to detect viral infection in the cell and are therefore crucial in activating antiviral defense mechanisms that limit replication in the cell and the spreading of infection. Although several RNA and DNA sensors have been identified, no cytoplasmic sensor has been identified that detects HIV-1 RNA or DNA. Data from Yan *et al.* now suggest that no such sensor has been identified because HIV-1 DNA is degraded under normal circumstances[1]. Only in the absence of the exonuclease TREX1 is HIV-1 DNA detected by one or many DNA sensors[1]. Better understanding of the intrinsic mechanisms that lead to HIV-1 degradation and identification of the DNA sensor involved might lead to better strategies for limiting or even preventing HIV-1 infection of the host.

HIV-1 contains two copies of its ssRNA genome that are introduced into the cell after infection. The viral ssRNA is converted into double-stranded DNA (dsDNA) by the HIV-1 enzyme reverse transcriptase through a multistep process (**Fig. 1**). After reverse transcription, the HIV-1 dsDNA is integrated into the host genome, and transcription of the integrated HIV-1 provirus leads to viral replication, budding and dissemination. The high error rate of reverse transcriptase causes the generation of nonproductive dsDNA and short single-stranded DNA (ssDNA) oligonucleotides that, together with the HIV-1 ssRNA, can potentially trigger cell-intrinsic DNA or RNA sensors. However, Yan *et al.* show that infection of mouse fibroblasts, human T cells or macrophages with HIV-1 does not lead to interferon responses[1]. Moreover, HIV-1 DNA generated during reverse transcription is largely degraded by the exonuclease TREX1. Ablation of TREX1 results in DNA accumulation and the induction of interferon responses that inhibit HIV-1 infection at multiple levels, including replication and spreading. The interferon responses in TREX1-deficient cells after HIV-1 infection are inhibited by inhibitors of reverse transcriptase but not by inhibitors of integrase, which suggests that nonintegrated DNA is recognized by a DNA sensor. Notably, HIV-1 infection in the presence of TREX1 does lead to some DNA accumulation but does not lead to any interferon response. The authors suggest that there might be a DNA threshold that must be exceeded before the DNA sensor is triggered. Further studies will be needed to investigate the nature of the undigested DNA, as this DNA might be protected from degradation by other proteins or it might be a specific form of DNA. TREX1 seems to have specificity for DNA derived from both endogenous retroelements and HIV-1.

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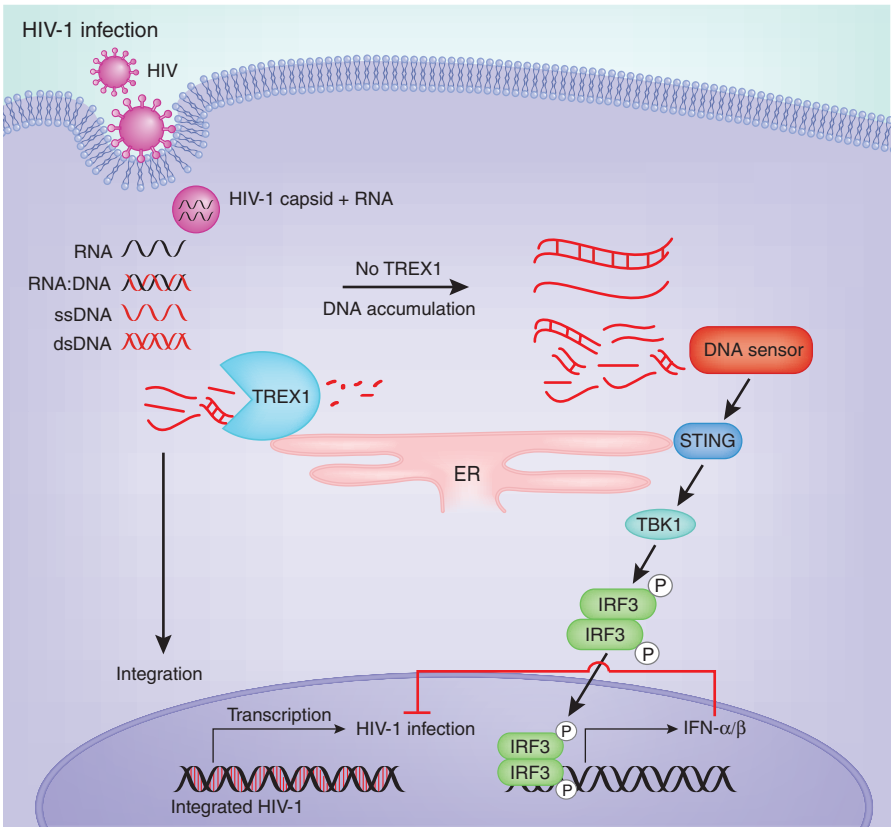

Figure 1 TREX1 helps HIV-1 escape an innate DNA-recognition pathway. After infection of the cell with HIV-1, HIV-1 ssRNA is converted into dsDNA by reverse transcriptase. Partly because of this error-prone enzyme, ssDNA and dsDNA oligonucleotides are generated that are potential targets of cytosolic DNA sensors. However, the cellular DNase TREX1 degrades HIV-1 ssDNA, which prevents recognition by a DNA sensor. HIV-1 dsDNA integrates into the host genome, and this leads to infection of the cell. Silencing of TREX1 by RNA-mediated interference leads to DNA accumulation, and this triggers an unknown DNA sensor. Triggering of this sensor by HIV-1 DNA activates STING, activating TBK1, which phosphorylates IRF3. Phosphorylated IRF3 dimerizes and translocates into the nucleus, where it interacts with the promoters of interferon genes, inducing an interferon response (IFN-α/β) that interferes with HIV-1 infection at various levels.

The question of why such DNA is degraded by TREX1 remains. TREX1 might have an affinity for ssDNA generated during reverse transcription, or it might recognize specific elements in the DNA that HIV-1 and retroelements have in common. TREX1 might also hide other retroviruses so they are not detected.

Various DNA sensors with distinct specificities survey the cytoplasm but seem to have a common denominator in the endoplasmic reticulum–resident protein STING (stimulator of interferon genes). STING acts upstream of the kinase TBK1, which phosphorylates the transcription factor IRF3, leading to dimerization and nuclear translocation of IRF3 (ref. 8). IRF3 binds to the promoters of interferon genes and thereby induces transcription of type I interferons[8,9] (**Fig. 1**). HIV-1-induced interferon responses in TREX1-deficient cells require STING, TBK1 and IRF3 (ref. 1), which indicates that a DNA sensor is involved, although other innate receptors might also use this pathway.

The authors use RNA-mediated interference in TREX1-deficient cells to exclude the possibility of a role for known DNA sensors such as TLR9, AIM2 and LRRFIP1, as well as RIG-I, which detects RNA transcribed from cytosolic DNA[1,10]. It is unclear whether one unknown DNA sensor or multiple known DNA sensors that act redundantly are involved. Cell-type and species differences in the use of DNA sensors might also complicate the identification of the DNA sensors involved. Such identification will be crucial for understanding how HIV-1 is recognized and to further delineate the pathway triggered by HIV-1 to induce interferon responses.

The recognition of infection and induction of interferon-mediated antiviral responses is a very powerful and ancient defense mechanism that is intrinsic to most cells and is paramount to a successful antiviral counterattack. The identification of the negative regulators of these systems and how they are involved in HIV-1 infection is important and might lead to new ways to help infected cells to combat the virus and prevent spreading. Silencing of TREX1 in T cells and macrophages decreases but does not completely abrogate HIV-1 infection[1]. This might be due to the experimental setup, such as viral concentration or incomplete silencing, or perhaps HIV-1 has other mechanisms that prevent the induction of interferon-mediated antiviral or innate immune responses. The finding that ssRNA from HIV-1 does not induce interferon responses suggests that HIV-1 indeed does have other mechanisms that either prevent activation of cytosolic RNA sensors or suppress interferon responses. No inhibitors of TREX1 are known, and such inhibitors must be developed to test these hypotheses in humans. The fact that human polymorphisms that abrogate TREX1 function are known will facilitate such studies. It will be interesting to determine whether patients with mutant TREX1 have cells that are less susceptible to HIV-1 infection or have a more favorable disease course. It is clear that tampering with these regulatory mechanisms is not without danger, as shown by the linkage of *TREX1* mutations with several autoimmune diseases[2–4]. Nevertheless, transient inhibition of these regulatory systems might not affect self-recognition and thus represents a powerful new way to combat HIV-1 infection. Inhibition of TREX1 might initiate antiviral programs in macrophages and T cells infected with HIV-1, and this would theoretically prevent HIV-1 replication and spreading in the infected host. Further studies are needed to investigate whether TREX1 is also involved in suppressing interferon responses in dendritic cells, which are involved in HIV-1 transmission as well as the induction of antiviral adaptive immune responses.

The identification of TREX1 as a crucial component in HIV-1 infection for the suppression of interferon responses, as well as the identification of the unknown sensors for HIV-1 DNA, will be the basis for further exciting research that will hopefully lead to new strategies for combating HIV-1 infection.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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