Antiviral Research 97 (2013) 180–182

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Commentary

Nucleotide embargo by SAMHD1: A strategy to block retroviral infection

Eduardo Pauls, Ester Ballana, José A. Esté *

IrsiCaixa, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain

ARTICLE INFO

Article history:
Received 6 November 2012
Revised 5 December 2012
Accepted 10 December 2012
Available online 21 December 2012

Keywords:
HIV-1
Restriction factor
Vpx
SAMHD1
Immune response
Antiviral target

ABSTRACT

SAMHD1 (sterile alpha motif and histidine/aspartic acid (HD) domain-containing protein 1) has been identified as a novel HIV-1 restriction factor in myeloid cells and resting CD4+ T lymphocytes. SAMHD1 restriction is antagonized by the lentiviral protein Vpx. Here, we comment on the latest knowledge of SAMHD1 biology, focusing on how it regulates the pool of intracellular nucleotides to control HIV replication. We discuss how HIV restriction by SAMHD1 and viral counter-restriction mechanisms may suggest new strategies for therapeutic intervention.

1. SAMHD1, a HIV-1 restriction factor

With a myriad of genome-wide association studies and whole-genome RNA interference-based screenings already published, it has become apparent that an incredibly high number of cellular factors modulate human immunodeficiency virus (HIV) infection (Blankson, 2010; Bushman et al., 2009). Moreover, recent work has highlighted the complex network of protein–protein interaction leading to effective virus replication (Jager et al., 2011). However, only a few of them have been unequivocally identified as genuine restriction factors, that is, cellular proteins that actively inhibit retrovirus replication, protecting cells from infection (Goff, 2004). APOBEC3G, tetherin and TRIM-5α are some of the most notable restriction factors targeting primate lentiviruses that, in turn, have met their viral counterparts in the HIV-1 proteins viral inhibitory factor (Vif) and viral protein u (Vpu) (Adamson and Freed, 2010; Greene et al., 2008; Kirchhoff, 2010). Recently, the sterile alpha motif (SAM) and histidine/aspartic acid (HD) domain-containing protein 1 (SAMHD1) has also been identified as a specific HIV-1 restriction factor. Like other restriction factors, SAMHD1 has found its nemesis in the HIV-2-encoded lentiviral gene product x (Vpx).

When in 1991 Vpx was reported to be strictly required for the infection of macrophages by simian immunodeficiency virus of rhesus macaques (SIVmac) (Yu et al., 1991), the molecular mechanism behind this observation was still 20 years away from being resolved. Vpx is an accessory protein encoded in the genome of HIV-2 and its ancestor virus in sooty mangabeys (SIVsmn). In contrast, HIV-1 and its ancestral chimpanzee virus (SIVchz) do not encode Vpx. Studies focused on the construction of gene therapy vectors identified Vpx as an adjuvant for the transduction of dendritic cells with HIV-1-based vectors (Mangeot et al., 2002). Crucially, in 2007 it was clearly demonstrated that Vpx-mediated suppression of HIV-1 restriction was dependent on the proteasomal degradation system (Goujon et al., 2007). Vpx was later found to interact with the enzymatic complex E3 ligase $CRL4^{DCAF1}$, leading to its ubiquitylation and degradation by the proteasomal machinery (Sharova et al., 2008; Srivastava et al., 2008). Other HIV accessory proteins, Vif or Vpu, have a similar ability to interact with different E3 ligase complexes, inducing degradation of restriction factors (APOBEC3 proteins and tetherin, respectively). Thus, it was just a matter of time to find the main target for the Vpx-mediated degradation.

Two independent groups recently identified SAMHD1 as the restriction factor targeted by Vpx in cells of myeloid lineage (monocytes, macrophages, and dendritic cells) (Hrecka et al., 2011; Laguette et al., 2011). When Vpx, which is directly loaded into SIVsmn or HIV-2 viral particles, is delivered into the cytoplasm, SAMHD1 becomes ubiquitinated and is degraded by the cell proteasome, relieving retroviral restriction. SAMHD1 has been identified as a deoxynucleoside triphosphate (dNTP) triphosphohydrolase enzyme (Goldstone et al., 2011), i.e., it hydrolyzes dNTPs to deoxynucleosides and inorganic triphosphate, controlling the size of the intracellular dNTP pool.

* Corresponding author. Address: IrsiCaixa, Hospital Germans Trias i Pujol, Ctra. Canyet s/n, 08916 Badalona, Spain. Fax: +34 934653968.
E-mail address: jaeste@irsicaixa.es (J.A. Esté).

0166-3542/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.antiviral.2012.12.009

Once delivered into the cytoplasm, single-stranded HIV RNA is reverse transcribed to DNA, a step that is dependent on the cytoplasmic availability of dNTPs. SAMHD1 has been found to control dNTP levels in myeloid cells below the Michaelis constant (km) of the HIV-1 reverse transcriptase (RT), preventing proviral DNA formation and HIV-1 replication (Lahouassa et al., 2012). Delivery of Vpx degrades SAMHD1, increasing dNTP concentrations, allowing higher infection efficacy. In fact, early observations had already suggested that dNTP availability for the HIV-1 RT was a restriction step in viral replication, as exogenous addition of dNTPs led to increased HIV replication (Gao et al., 1993).

Like any good story, the identification of this restriction factor has an interesting subplot. The *SAMHD1* gene was found to be mutated in people suffering from the Aicardi-Goutières syndrome, a rare autoimmune disease characterized by an interferon-stimulated gene expression signature that resembles a congenital viral infection (Fazzi et al., 2012). This observation initially suggested that SAMHD1 might play a role in interferon production. Given its capacity to degrade dNTPs, one may speculate that SAMHD1 prevents the accumulation of nucleotides, or promotes the synthesis of abortive DNA forms that would trigger innate immune sensors, leading to undesired interferon production and chronic inflammation. Strikingly, an endonuclease TREX1, which has also been shown to be mutated in some Aicardi-Goutières syndrome patients, had been previously identified as a regulatory factor of the HIV-induced production of interferon (Yan et al., 2010). Other mutations in *ADAR1* (Rice et al., 2012) or *RNAase H2A*, *B,* and *C* have been identified in these patients. Not surprisingly, the ADAR1 protein, a RNA-specific adenosine deaminase, has been identified as a factor affecting HIV replication, although the exact mechanism remains unclear (Biswas et al., 2012; Phuphuakrat et al., 2008). Thus, there seems to be a tight link between the innate immune mechanisms leading to Aicardi-Goutières syndrome and HIV-1 infection. It is tempting to speculate that a better understanding of this rare disease may shed light on some of the interactions between HIV and the innate immune system.

HIV-1 does not express Vpx, but it encodes the accessory viral protein Vpr, which is also present in HIV-2. However, Vpr from HIV-1 cannot degrade SAMHD1. Because HIV-1 Vpr also has the capacity to interact with the $CRL4^{DCAF1}$ complex, it was initially thought that HIV-1 Vpr might have evolved to lose its capacity to degrade SAMHD1. Instead, it seems that Vpr from the HIV-1 lentiviral lineage never acquired this function, indicating that HIV-1's direct ancestors never possessed the ability to degrade SAMHD1 (Lim et al., 2012). Conversely, early Vpx/Vpr HIV-2 ancestors developed and retained the ability to degrade SAMHD1. It is puzzling that a pathogen as successful as HIV-1 never acquired a function that would allow increased replication in dendritic cells and monocytes. Because HIV-1 primarily targets CD4+ T lymphocytes, it has been hypothesized that limiting viral replication capacity in myeloid cells may confer an evolutionary advantage by avoiding recognition by the innate immune system (Ayinde et al., 2012). However, recent findings indicating that SAMHD1 also restricts HIV-1 replication in CD4+ T lymphocytes (Baldauf et al., 2012) clearly challenge this hypothesis.

2. SAMHD1 restricts HIV-1 in CD4+ T cells

It is generally accepted that activated, but not resting CD4+ T lymphocytes, are preferentially infected by HIV-1, but the molecular basis for this restriction was not known. It has now been suggested that SAMHD1 dNTP-mediated restriction also exists in resting lymphocytes, based on evidence similar to that obtained in myeloid cells: a genetically modified HIV-1 clone carrying Vpx was shown to infect resting lymphocytes; downregulation of SAMHD1 through RNA interference allowed virus replication in resting cells; and resting lymphocytes obtained from a patient with Aicardi-Goutières syndrome, encoding a mutation in SAMHD1, could be infected with HIV-1 (Baldauf et al., 2012; Descours et al., 2012). Notably, Vpx-induced degradation of SAMHD1 in activated lymphocytes did not increase virus replication, suggesting that SAMHD1 depletion of the dNTP pool was absent in activated lymphocytes (Descours et al., 2012). Indeed, as previously indicated (Gao et al., 1993), nucleotide levels were higher in activated than in resting lymphocytes. The observation that SAMHD1 expression is not altered in HIV-resistant resting T cells, as compared to HIV-susceptible activated cells (Baldauf et al., 2012) suggests that unidentified regulatory mechanisms may activate/deactivate SAMHD1 function in T cells. It is also important to note that restriction at a posttranscriptional step may exist in resting lymphocytes, as HIV-1 Gag protein production may not be found even when SAMHD1 is degraded.

3. Prospects for drug development

The role of SAMHD1 in virus replication suggests new opportunities for drug discovery and development. Inhibition of HIV RT activity is a successful antiviral approach, judged by the use of nucleosides and non-nucleoside analogues in antiretroviral therapy (Cihlar and Ray, 2010; de Bethune, 2010). Limiting the cytoplasmic nucleotide pool available for reverse transcription has the potential to achieve a similar effect, and SAMHD1 offers the molecular target for this strategy. However, understanding the control mechanisms of SAMHD1 function will be a prerequisite. The activity of SAMHD1 may be regulated by a posttranslational modification, binding to a regulatory protein complex or its cellular compartmentalization.

In addition to SAMHD1, a complex regulatory network controls the intracellular dNTP pool, so that cellular uptake or endogenous synthesis may also provide interesting antiviral targets. The dimeric enzyme ribonucleotide reductase is probably the major source of dNTPs in mammalian cells. Increased expression of ribonucleotide reductase has been associated with an increase of dNTPs induced by *Leishmania* infection, favoring HIV-1 replication (Mock et al., 2012). Decreasing the dNTP reservoir through treatment with FDA-approved anti-cancer drugs that inhibit dNTP synthetic pathways, targeting ribonucleotide reductases with hydroxyurea (hydroxicarbamide) or gemcitabine, has been shown to inhibit retroviral infection (Clouser et al., 2010; Gao et al., 1993; Kootstra et al., 2000; Lori et al., 1994; Meyerhans et al., 1994). Two other ribonucleotide reductase inhibitors, didox (3,4-dihydroxybenzohydroxamic acid) and trimidox (3,4,5-trihydroxybenzamidoxime) have shown antiviral efficacy in an animal model of retroviral infection (Mayhew et al., 2002, 2005). It remains to be seen if decreasing the dNTP pool would be a valid approach for long-term anti-HIV therapy.

The rate of SAMHD1degradation by Vpx is mechanistically tied with HIV-2 DNA synthesis. Accelerated reverse transcription is induced by the tight interplay between SAMHD1 degradation and dNTP pool increase, which greatly improves the overall success rate of proviral DNA synthesis (Kim et al., 2012). An alternative antiviral strategy may arise from the use of HIV-1 RT inhibitors and the generation of drug-resistant RT mutants with a reduced capacity to bind dNTPs and, therefore, more susceptible to the effect of SAMHD1. The HIV-1 RT mutation Met184Ala (M184A), which confers resistance to lamivudine (3TC, Epivir™), induces a significant increase in the km of mutant RTs for dNTPs as compared to wild type enzymes (Pandey et al., 1996).

It has been proposed that a greater infection of myeloid cells may shift the balance of antigen presentation and interferon response, favoring adaptive responses and HIV control (Manel and

Littman, 2011). Deactivation of SAMHD1 may decrease cell death associated with uncontrolled immune activation that may be triggered by retroviral replication intermediates or abortive HIV infection in both dendritic cells, macrophages and CD4+ T lymphocytes (Doitsh et al., 2010; Manel and Littman, 2011). Small molecule inhibitors of SAMHD1 could play a relevant role in controlling T cell depletion, a hallmark of HIV-1 infection and AIDS. Understanding the mechanism of regulation of SAMHD1 and its role in innate immunity is crucial to assessing its potential as a therapeutic target.

Acknowledgements

Work in our laboratory is supported by the Spanish *Ministerio de Economia y Competitividad* (MEC, projects BFU2009-06958, BFU2012-31569), FIPSE 360783-09 and *Gala contra la SIDA*. EP and EB are research fellows from MEC. The authors declare no competing interests.

References

Adamson, C.S., Freed, E.O., 2010. Novel approaches to inhibiting HIV-1 replication. Antiviral Res. 85, 119–141.

Ayinde, D., Casartelli, N., Schwartz, O., 2012. Restricting HIV the SAMHD1 way: through nucleotide starvation. Nat. Rev. Microbiol. 10, 675–680.

Baldauf, H.M., Pan, X., Erikson, E., Schmidt, S., Daddacha, W., Burggraf, M., Schenkova, K., Ambiel, I., Wabnitz, G., Gramberg, T., Panitz, S., Flory, E., Landau, N.R., Sertel, S., Rutsch, F., Lasitschka, F., Kim, B., Konig, R., Fackler, O.T., Keppler, O.T., 2012. SAMHD1 restricts HIV-1 infection in resting CD4(+) T cells. Nat. Med. 18, 1682–1689.

Biswas, N., Wang, T., Ding, M., Tumne, A., Chen, Y., Wang, Q., Gupta, P., 2012. ADAR1 is a novel multi targeted anti-HIV-1 cellular protein. Virology 422, 265–277.

Blankson, J.N., 2010. Effector mechanisms in HIV-1 infected elite controllers: highly active immune responses? Antiviral Res. 85, 295–302.

Bushman, F.D., Malani, N., Fernandes, J., D'Orso, I., Cagney, G., Diamond, T.L., Zhou, H., Hazuda, D.J., Espeseth, A.S., Konig, R., Bandyopadhyay, S., Ideker, T., Goff, S.P., Krogan, N.J., Frankel, A.D., Young, J.A., Chanda, S.K., 2009. Host cell factors in HIV replication: meta-analysis of genome-wide studies. PLoS Pathog. 5, e1000437.

Cihlar, T., Ray, A.S., 2010. Nucleoside and nucleotide HIV reverse transcriptase inhibitors: 25 years after zidovudine. Antiviral Res. 85, 39–58.

Clouser, C.L., Patterson, S.E., Mansky, L.M., 2010. Exploiting drug repositioning for discovery of a novel HIV combination therapy. J. Virol. 84, 9301–9309.

de Bethune, M.P., 2010. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), their discovery, development, and use in the treatment of HIV-1 infection: a review of the last 20 years (1989–2009). Antiviral Res. 85, 75–90.

Descours, B., Cribier, A., Chable-Bessia, C., Ayinde, D., Rice, G., Crow, Y., Yatim, A., Schawartz, O., Laguette, N., Benkirane, M., 2012. SAMHD1 restricts HIV-1 reverse transcription in quiescent CD4+ T-cells. Retrovirology 9, 87.

Doitsh, G., Cavrois, M., Lassen, K.G., Zepeda, O., Yang, Z., Santiago, M.L., Hebbeler, A.M., Greene, W.C., 2010. Abortive HIV infection mediates CD4 T cell depletion and inflammation in human lymphoid tissue. Cell 143, 789–801.

Fazzi, E., Cattalini, M., Orcesi, S., Tincani, A., Andreoli, L., Balottin, U., De Simone, M., Fredi, M., Facchetti, F., Galli, J., Giliani, S., Izzotti, A., Meini, A., Olivieri, I., Plebani, A., 2012. Aicardi-Goutieres syndrome, a rare neurological disease in children: A new autoimmune disorder? Autoimmun. Rev. doi.org/10.1016/j.autrev.2012.08.012.

Gao, W.Y., Cara, A., Gallo, R.C., Lori, F., 1993. Low levels of deoxynucleotides in peripheral blood lymphocytes: a strategy to inhibit human immunodeficiency virus type 1 replication. Proc. Natl. Acad. Sci. USA 90, 8925–8928.

Goff, S.P., 2004. Retrovirus restriction factors. Mol. Cell 16, 849–859.

Goldstone, D.C., Ennis-Adeniran, V., Hedden, J.J., Groom, H.C., Rice, G.I., Christodoulou, E., Walker, P.A., Kelly, G., Haire, L.F., Yap, M.W., de Carvalho, L.P., Stoye, J.P., Crow, Y.J., Taylor, I.A., Webb, M., 2011. HIV-1 restriction factor SAMHD1 is a deoxynucleoside triphosphate triphosphohydrolase. Nature 480, 379–382.

Goujon, C., Riviere, L., Jarrosson-Wuilleme, L., Bernaud, J., Rigal, D., Darlix, J.L., Cimarelli, A., 2007. SIVSM/HIV-2 Vpx proteins promote retroviral escape from a proteasome-dependent restriction pathway present in human dendritic cells. Retrovirology 4, 2.

Greene, W.C., Debyser, Z., Ikeda, Y., Freed, E.O., Stephens, E., Yonemoto, W., Buckheit, R.W., Este, J.A., Cihlar, T., 2008. Novel targets for HIV therapy. Antiviral Res. 80, 251–265.

Hrecka, K., Hao, C., Gierszewska, M., Swanson, S.K., Kesik-Brodacka, M., Srivastava, S., Florens, L., Washburn, M.P., Skowronski, J., 2011. Vpx relieves inhibition of HIV-1 infection of macrophages mediated by the SAMHD1 protein. Nature 474, 658–661.

Jager, S., Cimermancic, P., Gulbahce, N., Johnson, J.R., McGovern, K.E., Clarke, S.C., Shales, M., Mercenne, G., Pache, L., Li, K., Hernandez, H., Jang, G.M., Roth, S.L., Akiva, E., Marlett, J., Stephens, M., D'Orso, I., Fernandes, J., Fahey, M., Mahon, C., O'Donoghue, A.J., Todorovic, A., Morris, J.H., Maltby, D.A., Alber, T., Cagney, G., Bushman, F.D., Young, J.A., Chanda, S.K., Sundquist, W.I., Kortemme, T., Hernandez, R.D., Craik, C.S., Burlingame, A., Sali, A., Frankel, A.D., Krogan, N.J., 2011. Global landscape of HIV-human protein complexes. Nature 481, 365–370.

Kim, B., Nguyen, L.A., Daddacha, W., Hollenbaugh, J.A., 2012. Tight interplay among SAMHD1 protein level, cellular dNTP levels, and HIV-1 proviral DNA synthesis kinetics in human primary monocyte-derived macrophages. J. Biol. Chem. 287, 21570–21574.

Kirchhoff, F., 2010. Immune evasion and counteraction of restriction factors by HIV-1 and other primate lentiviruses. Cell Host Microbe 8, 55–67.

Kootstra, N.A., Zwart, B.M., Schuitemaker, H., 2000. Diminished human immunodeficiency virus type 1 reverse transcription and nuclear transport in primary macrophages arrested in early G(1) phase of the cell cycle. J. Virol. 74, 1712–1717.

Laguette, N., Sobhian, B., Casartelli, N., Ringeard, M., Chable-Bessia, C., Segeral, E., Yatim, A., Emiliani, S., Schwartz, O., Benkirane, M., 2011. SAMHD1 is the dendritic- and myeloid-cell-specific HIV-1 restriction factor counteracted by Vpx. Nature 474, 654–657.

Lahouassa, H., Daddacha, W., Hofmann, H., Ayinde, D., Logue, E.C., Dragin, L., Bloch, N., Maudet, C., Bertrand, M., Gramberg, T., Pancino, G., Priet, S., Canard, B., Laguette, N., Benkirane, M., Transy, C., Landau, N.R., Kim, B., Margottin-Goguet, F., 2012. SAMHD1 restricts the replication of human immunodeficiency virus type 1 by depleting the intracellular pool of deoxynucleoside triphosphates. Nat. Immunol. 13, 223–228.

Lim, E.S., Fregoso, O.I., McCoy, C.O., Matsen, F.A., Malik, H.S., Emerman, M., 2012. The ability of primate lentiviruses to degrade the monocyte restriction factor SAMHD1 preceded the birth of the viral accessory protein Vpx. Cell Host Microbe 11, 194–204.

Lori, F., Malykh, A., Cara, A., Sun, D., Weinstein, J.N., Lisziewicz, J., Gallo, R.C., 1994. Hydroxyurea as an inhibitor of human immunodeficiency virus-type 1 replication. Science 266, 801–805.

Manel, N., Littman, D.R., 2011. Hiding in plain sight: how HIV evades innate immune responses. Cell 147, 271–274.

Mangeot, P.E., Duperrier, K., Negre, D., Boson, B., Rigal, D., Cosset, F.L., Darlix, J.L., 2002. High levels of transduction of human dendritic cells with optimized SIV vectors. Mol. Ther. 5, 283–290.

Mayhew, C.N., Mampuru, L.J., Chendil, D., Ahmed, M.M., Phillips, J.D., Greenberg, R.N., Elford, H.L., Gallicchio, V.S., 2002. Suppression of retrovirus-induced immunodeficiency disease (murine AIDS) by trimidox and didox: novel ribonucleotide reductase inhibitors with less bone marrow toxicity than hydroxyurea. Antiviral Res. 56, 167–181.

Mayhew, C.N., Sumpter, R., Inayat, M., Cibull, M., Phillips, J.D., Elford, H.L., Gallicchio, V.S., 2005. Combination of inhibitors of lymphocyte activation (hydroxyurea, trimidox, and didox) and reverse transcriptase (didanosine) suppresses development of murine retrovirus-induced lymphoproliferative disease. Antiviral Res. 65, 13–22.

Meyerhans, A., Vartanian, J.P., Hultgren, C., Plikat, U., Karlsson, A., Wang, L., Eriksson, S., Wain-Hobson, S., 1994. Restriction and enhancement of human immunodeficiency virus type 1 replication by modulation of intracellular deoxynucleoside triphosphate pools. J. Virol. 68, 535–540.

Mock, D.J., Hollenbaugh, J.A., Daddacha, W., Overstreet, M.G., Lazarski, C.A., Fowell, D.J., Kim, B., 2012. Leishmania induces survival, proliferation and elevated cellular dNTP levels in human monocytes promoting acceleration of HIV co-infection. PLoS Pathog. 8, e1002635.

Pandey, V.N., Kaushik, N., Rege, N., Sarafianos, S.G., Yadav, P.N., Modak, M.J., 1996. Role of methionine 184 of human immunodeficiency virus type-1 reverse transcriptase in the polymerase function and fidelity of DNA synthesis. Biochemistry 35, 2168–2179.

Phuphuakrat, A., Kraiwong, R., Boonarkart, C., Lauhakirti, D., Lee, T.H., Auewarakul, P., 2008. Double-stranded RNA adenosine deaminases enhance expression of human immunodeficiency virus type 1 proteins. J. Virol. 82, 10864–10872.

Rice, G.I., Kasher, P.R., Forte, G.M., Mannion, N.M., Greenwood, S.M., Szynkiewicz, M., Dickerson, J.E., Bhaskar, S.S., Zampini, M., Briggs, T.A., Jenkinson, E.M., Bacino, C.A., Battini, R., Bertini, E., Brogan, P.A., Brueton, L.A., Carpanelli, M., De Laet, C., de Lonlay, P., Del Toro, M., Desguerre, I., Fazzi, E., Garcia-Cazorla, A., Heiberg, A., Kawaguchi, M., Kumar, R., Lin, J.P., Lourenco, C.M., Male, A.M., Marques Jr., W., Mignot, C., Olivieri, I., Orcesi, S., Prabhakar, P., Rasmussen, M., Robinson, R.A., Rozenberg, F., Schmidt, J.L., Steindl, K., Tan, T.Y., van der Merwe, W.G., Vanderver, A., Vassallo, G., Wakeling, E.L., Wassmer, E., Whittaker, E., Livingston, J.H., Lebon, P., Suzuki, T., McLaughlin, P.J., Keegan, L.P., O'Connell, M.A., Lovell, S.C., Crow, Y.J., 2012. Mutations in ADAR1 cause Aicardi-Goutieres syndrome associated with a type I interferon signature. Nat. Genet. 44, 1243–1248.

Sharova, N., Wu, Y., Zhu, X., Stranska, R., Kaushik, R., Sharkey, M., Stevenson, M., 2008. Primate lentiviral Vpx commandeers DDB1 to counteract a macrophage restriction. PLoS Pathog. 4, e1000057.

Srivastava, S., Swanson, S.K., Manel, N., Florens, L., Washburn, M.P., Skowronski, J., 2008. Lentiviral Vpx accessory factor targets VprBP/DCAF1 substrate adaptor for cullin 4 E3 ubiquitin ligase to enable macrophage infection. PLoS Pathog. 4, e1000059.

Yan, N., Regalado-Magdos, A.D., Stiggelbout, B., Lee-Kirsch, M.A., Lieberman, J., 2010. The cytosolic exonuclease TREX1 inhibits the innate immune response to human immunodeficiency virus type 1. Nat. Immunol. 11, 1005–1013.

Yu, X.F., Yu, Q.C., Essex, M., Lee, T.H., 1991. The vpx gene of simian immunodeficiency virus facilitates efficient viral replication in fresh lymphocytes and macrophage. J. Virol. 65, 5088–5091.