
REVIEWS

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HIV Restriction Factors and Their Ambiguous Role during Infection

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Currently, more than 37 million individuals worldwide are infected with the human immunodeficiency virus (HIV). Antiretroviral therapy may control the viral infection but is incapable of eradicating it. It is important to understand how cells respond to HIV-1 infection and what cellular factors are involved in this process to develop novel classes of antiviral drugs. This review summarizes the current understanding of the HIV restriction mechanism. We discuss the ambiguous role of HIV restriction factors in viral infection and counteraction mediated by HIV-1 accessory proteins.

Keywords: HIV, restriction factors, ISGs, HIV accessory proteins

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The human immunodeficiency virus (HIV) is a member of the family Retroviridae, genus Lentivirus, with a long incubation period. HIV includes the following species: HIV-1, the most widespread and pathogenic, and HIV-2, differing from HIV-1 in structure and pathogenic effect. There are four groups of HIV-1: M (Major), N (Non-M, Non-O), O (Outlier), and P (Putative). It is currently believed that HIV-1 group M originated from the chimpanzee immunodeficiency virus (SIV) at the beginning of the XX century shown in [1]. More than 70 million people are infected with HIV-1 group M; for 30 million people, this disease has already led to fatal outcomes. HIV-1 from other groups (N, O, P) also originated from SIV (chimpanzee in group N and gorilla in groups O and P) but occurs in humans much less frequently. HIV-1 group O was found in approximately 100 thousand people in Cameroon and in neighboring countries in [2]; group N and P viruses have been found only in a few individuals in [3–5].

After decoding the nucleotide sequence of HIV-1, it became clear that its genome was much more complex compared to those of many animal retroviruses. The latter genomes include the *gag*, *pol*, and *env* genes encoding only structural proteins (e.g., the murine leukemia virus (MuLV) genome). Open reading frames uncharacteristic of other members of the family have been found in the 3'-region of the HIV-1 genome. Here, regulatory proteins Tat and Rev and accessory proteins Vif, Vpr, Vpu, and Nef are encoded (in HIV-2, they also include Vpx). Tat and Rev are necessary for HIV-1 replication in host cells: they acti-

vate transcription of genes from proviral DNA and provide viral RNA transport from nucleus to cytoplasm. Accessory proteins are needed for replication only in some types of cells, though they are commonly believed to counteract the cellular mechanisms of antiviral protection. It took years to find out the targets of HIV accessory proteins: restriction factors (Fig. 1). Although there is a considerable body of literature on restriction factors (e.g., reviews in [6–8]), its amount continuously increases, while the role of some of these factors is not quite clear or revised and, therefore, new data have to be periodically generalized.

The best-known restriction factors with established mechanisms of action are IFITM1–3 in [9], APOBEC3 in [10–12], TRIM5 α in [13–15], Mx2 in [16–18], Schlaffen11 in [19], SAMHD1 in [20–22], and BST-2 (also known as Tetherin) in [23, 24].

Below we will thoroughly consider the cellular proteins involved in HIV restriction, in the order they influence different stages of the HIV replication cycle: from early to late.

IFITM

The penetration of HIV-1 into a cell causes activation of pattern-recognizing receptors (PRR), including Toll-like receptor 7 (TLR7), and the production of the type I interferons (IFN) in [25]. Numerous genes of restriction factors of different viruses have been found in recent years, their expression being dependent on type I IFN production. Some of them (MxB, BST-2, APOBEC3) were thoroughly studied in the

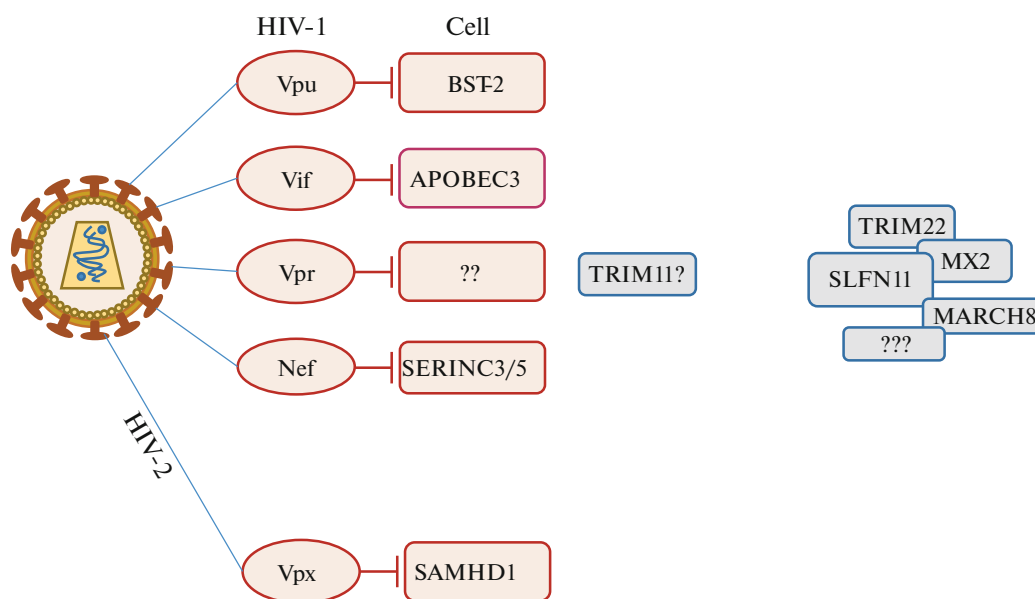


Fig. 1. The counteraction of accessory viral proteins to cellular restriction factors.

context of specific viral infections, in particular, retroviral infection. Among such IFN-stimulated genes (ISGs), the interferon-induced transmembrane gene family (IFITM) with broad-spectrum antiviral activity was identified.

The IFITM protein family was described 30 years ago, with the simultaneously revealed induction of their expression via type I and II IFN in [26]. The antiviral function of IFITM1, IFITM2 and IFITM3 proteins was found in 2009, as a result of screening small interfering RNA (siRNA) in [9]. These proteins performed the function of restriction factors at the early stages of cell infection with influenza A virus, subtype H1N1, as well as flaviviruses: the Dengue and West Nile fever viruses in [9]. The antiviral effect of IFITM proteins against HIV-1 was shown in 2011: the IFITM1, IFITM2, and IFITM3 knockdown resulted in enhanced infection in [27].

IFITM1 is localized on the cell plasma membrane, while IFITM2 and IFITM3 are localized in late endosomes and lysosomes in [28, 29]. The proteins contain two transmembrane domains and an extremely conservative intracellular domain, which interestingly mirrors the structure of another restriction factor, BST-2, acting at the stage of particle release from infected cells in [24] (see below). The principle of restriction of virus penetration into a cell by IFITM proteins is associated with two aspects: the regulation of cell membrane cholesterol content and the inhibition of virus–cell fusion in [30–32]. In addition, IFITM proteins can be incorporated into viral particles, which leads to a decrease in their infectivity in [33]. Cell membrane fusion is impaired in this virions. In human SupT1 T cells with a Tet-On-regulated expression of different IFITM, all three proteins

inhibit the infection with cell-free HIV-1 in [27]. However, IFITM3 demonstrates low efficiency in HIV-1 restriction during cell-to-cell transmission in [33].

The study of IFITM-mediated HIV-1 restriction depending on viral tropism (the virus uses CCR5 or CXCR4 as coreceptors to penetrate into a cell) has shown that the X4-tropic virus effectively undergoes restriction via the IFITM2 and IFITM3 proteins in endosomes and lysosomes, whereas the R5-tropic virus undergoes restriction via IFITM1 expressed on the cell plasma membrane in [34]. This selectivity is determined when the HIV-1 virion penetrates into a cell by fusing with the endosomal membrane, while CXCR4 is used as a coreceptor, and with the plasma membrane for CCR5-tropic viruses in [34].

The IFITM-mediated restriction goes on until integration of the provirus into the cell genome and, therefore, HIV-1 with IFITM restriction can be controlled in one of the following ways: modification of the site for particle penetration into a cell or the presence of proteins counteracting the restriction factor in virions. The accumulation of mutations in the Env protein in due course allows the virus to avoid restriction in [35].

Thus, IFITM proteins are integral to the process of viral and cell membrane fusion at the stage of virion incorporation into a host cell, as well as during cell-to-cell transmission. This process involves the envelope protein of HIV-1; however, its exact mechanism is still unclear.

TRIM

The proteins of the TRIM family, E3-ligases, participate in cell cycle regulation, autophagy, and innate

immune responses. TRIM proteins are involved in the NF- κ B and type I IFN signaling pathways and indirectly influence HIV infection. However, several proteins of this family directly inhibit viral infection at different stages of virus replication, inter alia, providing proteasomal degradation of viral proteins in [36–41].

The TRIM family was characterized, for the first time as early as in 2001, as a group of proteins with a conservative three-component (TRIPartite Motif) N-terminal domain RBCC (Really Interesting New Gene (RING) E3 ligase domain, B boxes and Coiled-Coil domains) in [42]. The RBCC domain provides the E3-ligase function of the protein, as well as oligomerization, which is necessary for its functional activity in [43, 44].

The C-terminal domain, on the contrary, is variable and responsible for the interaction between TRIM and partner proteins. TRIM proteins are divided into 11 subfamilies by type of C-terminal domain. The PRY/SPRY (SP1a and the RYanodine Receptor) motif occurs at the C-terminus of more than 30 TRIM proteins and is associated with the antiviral activity of TRIM5, TRIM22, TRIM11, and TRIM15 proteins of the respective subfamilies in [40, 45, 46].

The TRIM5 α protein of the TRIM family is considered the key molecule providing resistance of Old World monkeys (African green monkeys, rhesus macaque, etc.) to the HIV-1 infection in [13]; in New World monkeys (e.g., night monkeys), this function is performed via TRIM5 fused with cyclophilin A (TRIMCyp) in [14, 47].

Several models describing the mechanism of HIV-1 restriction via the TRIM5 α protein have been proposed; each is based on interaction between the SPRY domain and the viral capsid, which leads to the impairment of virus disassembly (early “uncoating”). However, the exact mechanism of TRIM5 α interference in unpacking of the virion has not yet been elucidated. For binding with the capsid, TRIM5 α forms antiparallel dimers and trimers due to coiled-coil domains. TRIM5 α forms a hexagonal lattice surrounding the capsid in [48–51]. Interestingly, the formation of hexagonal lattice is also true for TRIM-Cyp, suggesting the existence of a common mechanism of HIV restriction via different TRIM proteins in [52].

One more consequence of the formation of hexagonal structures via TRIM5 α molecule on the viral capsid is the triggering of the antiviral response of the cell in [53] (Fig. 2). Dimerization of the RING domains of TRIM5 α on the capsid surface results in enhanced E3-ligase activity of TRIM5 α and activated synthesis of polyubiquitin chains linked to the side chain of Lys63. These ubiquitin chains activate the TAK1 kinase complex through autophosphorylation which, in turn, leads to the translocation of transcription factors AP-1 and NF- κ B to the nucleus, followed by the expression of type-I IFN in [51].

One more successful antiviral strategy is implemented via TRIM proteins from addressing viral components to proteasomal degradation. However, it is still an open question whether TRIM5 α performs this function with respect to HIV-1 capsid. At the moment, no ubiquitination sites have been found at the HIV-1 capsid protein in [54], but the ability of TRIM5 α to promote self-ubiquitination is known, followed by degradation in the proteasome where it probably carries viral components in [55] (Fig. 2). In addition, virus nucleocapsid components, including integrase, undergo effective proteasomal degradation (not without the involvement of TRIM5 α) in [56].

Interestingly, the human homologue of TRIM5 α has no marked antiviral activity. However, the only amino acid substitution in PRY-SPRY domains of the human TRIM5 α is able to appreciably rehabilitate it as a HIV-1 restriction factor in [57]. Another protein of the family, TRIM22, being a human paralog of TRIM5 α , participates in the inhibition of HIV-1 replication via type I IFN in [58, 59]. In addition, TRIM22, irrespective of the inherent ligase function, inhibits the Tat- and NF- κ B-independent transcription of viral genes from the LTR-promoter of HIV-1 through direct interaction with the Sp1 factor in [60, 61]. These observations are especially noteworthy for clinicians: the possibility of controlling viral genome transcription in the latent period is under discussion in [62].

It is yet unclear how exactly HIV-1 encounters TRIM-mediated restriction. The level of TRIM11 expression in the cell is regulated via accessory viral protein Vpr at low intracellular concentrations in [63]; however, this regulatory mechanism is still far from being understood.

SAMHD1

The role of SAMHD1 (sterile alpha motif and histidine-aspartate domain containing protein 1) in HIV restriction was independently determined via two research teams in 2011. The protein was identified using mass spectrometry as a partner of accessory protein Vpx of the HIV-2 virus (in HIV-1, there is no Vpx) in [20, 64]. SAMHD1 is expressed at a high level in myeloid cells and resident CD4⁺ T cells and is a deoxynucleoside triphosphatase responsible for the regulation of dNTP pool and inhibition of HIV reverse transcription in [20, 22, 64, 65].

The histidine/aspartate (HD) catalytic domain of SAMHD1 protein hydrolyzes dNTP with the formation of deoxyribonucleoside and triphosphate, thereby removing structural blocks for the synthesis of viral cDNA in [22]. The enzyme activity is determined through tetramerization and allosterically controlled by the GTP and all four dNTPs in [66–70].

SAMHD1 also has a metal-dependent 3'→5' exonuclease activity against single-stranded DNA and RNA, suggesting the existence of one more HIV

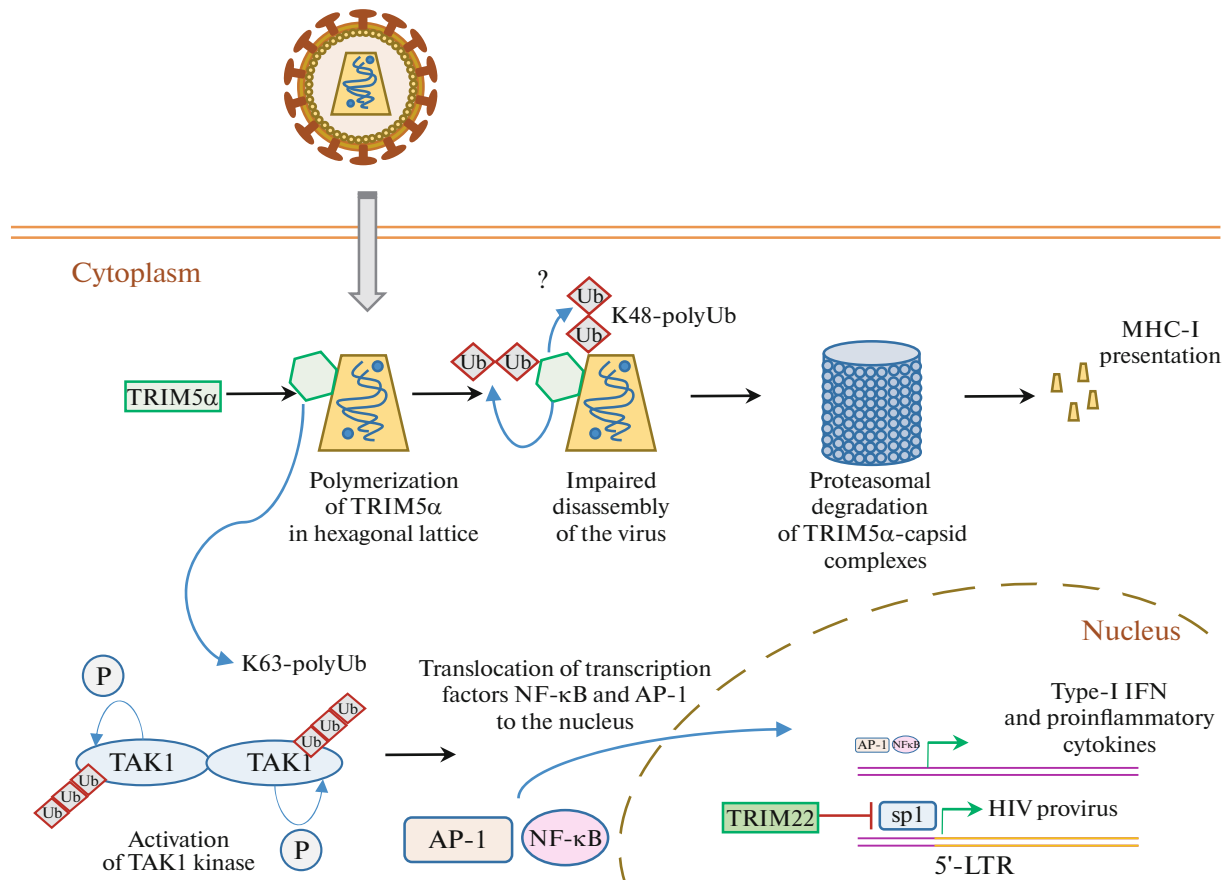


Fig. 2. The role of TRIM proteins in HIV replication. Ub, ubiquitin; K48-, K63-polyUb, ubiquitin chains linked via Lys48 and Lys63, respectively; P, phosphorylation.

restriction mechanism peculiar to this enzyme: viral RNA binding and degradation in [71]. dNTP triphosphate hydrolase and 3'→5' exonuclease activities of SAMHD1 are performed via the HD domain. In the SAMHD1 point mutants with D137N or Q548A substitutions, Ryoo et al. in [72] have demonstrated the ability of SAMHD1 to inhibit HIV-1 infection without dNTP triphosphate hydrolase activity and by maintaining 3'→5' exonuclease activity. However, the inhibitory effect of SAMHD1 was not observed in the reverse situation. Thereby, the authors concluded that it is the 3'→5' exonuclease activity of SAMHD1 that majorly contributes to HIV-1 restriction in [72]. Although these results were not confirmed later in [73, 74], Ryoo et al. explained this with the differences in experimental setup in [75]. The significance of the 3'→5' exonuclease activity of SAMHD1 for HIV restriction is an open question to date.

The accessory HIV-2 protein Vpx binds to the SAMHD1 C-terminus and adapter molecule DCAF1 and initiates the formation of E3-ubiquitin ligase complex, followed by proteasomal degradation of SAMHD1 in [20, 64, 76, 77]. The mechanism of this HIV-1 resistance to SAMHD1 restriction has not yet

been completely studied. Vpr has carried the same motif as Vpx, which is necessary for binding with the DCAF1 adapter and arresting the cell cycle in the G2 phase in [77]. In addition, Kyei et al. in [78] have recently shown that HIV-1 can use cell cycle regulator cyclin L2 to neutralize SAMHD1 in macrophages. The importance of SAMHD1 in HIV-1 restriction has been shown via macrophages isolated from patients with the Aicardi–Goutieres syndrome caused by mutations in SAMHD1. The macrophages of such patients are characterized by much higher sensitivity to HIV-1 infection compared to the macrophages of healthy people in [21].

APOBEC3 (CEM15)

APOBEC3 (apolipoprotein B editing complex 3) is a family of cytidine deaminases comprising seven proteins in primates: APOBEC3A (A3A), A3C, A3H with one catalytic domain and A3B, A3D, A3F, A3G with two domains in [79, 80]. APOBEC3 proteins, especially A3G, are characterized by the high level of expression in many types of cells including CD4⁺ T cells, dendritic cells, and macrophages in [81]. In

addition, the expression of APOBEC3 is stimulated via type I IFN in [81]. A3G was originally given precedence over other proteins of the family, but later it became clear that A3H, A3F, A3D and A3B were also active against HIV, while the viral protein Vif counteracted each in [82].

The antiviral role of APOBEC3 proteins is evident once they have entered viral particles, i.e., only in the next cycle of virus replication in [83, 84]. Restriction occurs via deaminase-induced C→U transformation in the (–)-strand of HIV DNA. Uracil is recognized by polymerase as thymine, which leads to the G→A mutation in the synthesis of DNA (+)-strand in [83]. Hypermutation during the reverse transcription of viral RNA into DNA has two important consequences: first, aberrant sequences are recognized via the cells and eliminated; second, the mutated DNA of the provirus is integrated in the cell genome, however, due to the great number of premature stop codons (formed, e.g., after TGG→TAG substitution) and other mutations, infectious viral particles are not produced in [10, 83]. APOBEC3-dependent mutagenesis occurs at a higher frequency at the 3'-end of viral sequence. In contrast to viral DNA (–)-strand synthesized from a single site (primary binding site) in the 5'-LTR region, the synthesis of DNA (+)-strand is initiated from two polypurine tracts: the central (cPPT) and that at the 3'-end (3'-PPT). The presence of two sites for initiation of the synthesis of DNA (+)-strand and simultaneous RNA cleavage creates the prerequisites for the nonequilibrium and longer single-stranded state of DNA (–)-strand (which is a substrate for APOBEC3) in the 3'-region of the HIV genome in [85, 86].

The proteins of the APOBEC3 family inhibit lentiviral infection via the alternative mechanism not associated with deaminase activity. A3-deaminases impair reverse transcription by preventing (–)-strand synthesis and tRNA binding with the viral mRNA in [10, 87]. However, this hypothesis was not confirmed in some works in [88, 89] as they showed that APOBEC3 proteins were incapable of HIV restriction without deaminase catalytic domain.

HIV uses accessory protein Vif, which induces degradation of deaminases prior to their incorporation into viral particles, as a tool for counteracting APOBEC3-mediated restriction. Vif binds to APOBEC3 molecule in the infected cell, followed by the involvement of the E3-ubiquitin ligase complex comprising elongin B, elongin C, and RBX1, with the subsequent degradation of APOBEC3 in [84, 90, 91]. However, Vif cannot completely eliminate APOBEC3 in virus-producing cells, as has been demonstrated by the presence of numerous mutations in proviruses of the cells of patients with acute and chronic HIV infection, as well as during the vertical transmission of HIV to newborn infants in [82, 92]. Probably, the induction by type I IFN shifts the APOBEC3–Vif balance towards restriction factors, so

they have time to enter viral particles before binding with Vif.

The virus seems to gain additional benefits in partial containment of APOBEC3-mediated restriction. It may happen that A3 deaminases do not completely suppress virus replication but provide a high level of mutagenesis and, therefore, a higher risk of appearance of escape-mutants resistant to antiretroviral drugs. The low efficiency of antiretroviral therapy in some patients is already associated with defective Vif in [93]. Thus, APOBEC3 can be considered an example of a restriction factor the virus turns to its own advantage.

MxB

MxA and MxB (Mx1 and Mx2 in mice) are proteins of the GTPase family; the expression of both proteins is induced by type-I IFN. MxA is known to have a broad-spectrum antiviral activity against DNA- and RNA-containing viruses but not retroviruses in [94, 95]. Recently, three independent research teams have shown that MxB is involved in HIV-1 restriction: without affecting the reverse transcription of viral RNA, it destabilizes the preintegration complex and thereby reduces the integration of proviral DNA into the cell genome in [16–18, 96].

In contrast to MxA, MxB has an extended N-terminal domain necessary for HIV-1 restriction in addition to the GTPase domain in [16, 96, 97]. This domain carries a nuclear localization signal (NLS) and can bind to the viral capsid after homodimerization (2 MxB molecules bind to each other in antiparallel directions). The Arg-rich motif of this domain directly binds to the HIV-1 capsid and determines the ability of MxB to restrict the virus in [98]. It supposedly leads to the inhibition of virus “uncoating” similar to TRIM5 α restriction in [99].

Thus, MxB influences HIV-1 replication in two cellular compartments and, accordingly, at the subsequent stages of virus replication cycle: “uncoating” in the cytoplasm, import of the pre-integration complex to the nucleus, and integration of the provirus into the cell genome. Clinical HIV-1 isolates carrying H87Q and G116A mutations in the capsid protein have lower sensitivity to MxB-mediated restriction and enhanced replicative activity compared to other circulating strains in [100, 101]. These data can be considered evidence in favor of the hypothesis of the inhibitory pressure of the MxB factor on HIV-1.

SCHLAFEN11 (SLFN11)

SLFN11 is a member of the Schlafen family of ISG-proteins regulating cell proliferation, immune response and viral replication in [102]. The involvement of SLFN11 in HIV restriction was shown in [19]. SLFN11 proved to have no effect on early stages of the cycle of retroviral infection, including reverse tran-

scription, integration, and transcription. SLFN11 acts at the late stage of virus replication, selectively inhibiting the translation of viral proteins. SLFN11 binds tRNA and counteracts the changes in the cellular pool of tRNA caused by the presence of HIV. This is a new antiviral mechanism of innate immune response, where SLFN11 selectively inhibits the synthesis of viral proteins in HIV-infected cells.

The reduced translation of viral proteins under type-I IFN stimulation was observed 18 years before this discovery, as early as in 1994, but the regulation mechanism was not studied in [103]. SLFN11, under the conditions of type-I IFN stimulation, inhibits the translation of not only viral but also other codon-optimized transcripts in a cell in [104]; hence, this protein apparently should not be considered as a specific HIV restriction factor. Most likely, SLFN11 is involved in the total antiviral response of cells.

MARCH8 (c-MIR)

The involvement of MARCH8 (membrane-associated RING-CH8) protein in HIV-1 restriction has been shown lately in [105]. MARCH8 is an E3-ubiquitin ligase with a high level of expression in differentiated myeloid cells: macrophages and dendritic cells. At the moment of revealing the antiviral function of the protein, MARCH8 was known to reduce the expression of some cellular transmembrane proteins, in particular, MHC class II and TRAIL-R1 (TNF-related apoptosis-inducing ligand receptor 1) in [106, 107]. MARCH8 is supposed to recognize the three-dimensional structure of transmembrane domains of proteins but not specific motives; however, there is no reliable experimental evidence in favor of this fact.

Tada et al. have shown in [105] that the ectopic expression of MARCH8 in virus-producing cells does not influence the level of virus production but reduces the infectivity of viral particles. MARCH8 blocks the entry of viral envelope protein into virions by reducing the expression of Env at the cell surface, possibly by interacting with it. As a result, there is a substantial decrease in the efficiency of virus–cell fusion. At the moment, the exact strategy of HIV counteracting the MARCH8-mediated restriction HIV is unknown, however, it has been shown that accessory proteins Vpr, Vpu, and Nef do not interfere with MARCH8 in [105].

SERINC3 AND SERINC5

There was no understanding of how viral protein Nef increases the infectivity of viral particles in [106, 107]. Usami et al. in [108] supposed that Nef counteracted a certain restriction factor by decreasing its density at the cell surface and preventing incorporation into virions. The proteomic analysis of Nef⁺ HIV-1 and Nef⁻ HIV-1 virions showed that they possessed membrane proteins SERINC3 and SERINC5 (SERin INCorporator). The incorporation of SERINC3 and

SERINC5 into HIV virions actually decreased their ability to infect host cells in [108].

The SERINC family consists of five proteins characterized by the presence of 10–11 transmembrane domains. SERINC proteins are involved in the biosynthesis of sphingolipids and phosphatidylserine in [109]. However, only SERINC3 and SERINC5 are considered to be HIV-1 restriction factors, and SERINC5 has a more marked antiviral effect in [110, 111]. The supposed mechanism of action of SERINC5 consists in the formation of oligomers on the membranes of viral particles, which leads to the lower efficiency of viral–cell membrane fusion in [112]. In addition, the penetration of SERINC5 into viral particles results in their enhanced sensitivity to the broadly neutralizing antibodies recognizing conservative domain gp41 of the envelope protein in [112, 113].

The HIV-1 accessory protein Nef effectively removes SERINC3 and SERINC5 from the cell surface, preventing their penetration into virions in [108, 111, 114]. The mechanism of negative regulation of SERINC3 and SERINC5 is analogous to reduction of CD4 expression at the cell surface: in each case, Nef uses the cellular transport system to provide endolysosomal degradation of target cell proteins. The sensitivity of SERINC5 to Nef-mediated degradation is determined via the structure of its intracellular domain ICL4 (intracellular loop 4). With the substitution of a resistant variant of ICL4 for the Nef-sensitive variant, SERINC5 becomes resistant to Nef, which no longer prevents SERINC5-induced HIV restriction in [115].

BST-2 (CD317, TETHERIN)

One of the causes of why HIV-1 group M has become widespread in humans and became pandemic was the high resistance to cellular factor BST-2 acquired as a result of evolution and adaptation of viral protein Vpu to BST-2-induced restriction in [116]. Other HIV-1 groups, as well as HIV-2 and SIV, have not evolved in this direction and are supposed to protect themselves from the effect of BST-2 via a more ancient and less effective method: using accessory protein Nef in [117–120]. Accessory viral protein Vpu is encoded in the HIV-1 genome without being in HIV-2 and in most SIV strains. *vpu*-defective virus Δ vpu-HIV-1 has definite characteristics that differentiate it from the wild-type virus: the smaller number of “spikes” at the virion surface and the agglomeration of viral particle “clusters” near the cell surface in [121–123]. The decreased number of spikes at the viral envelope is due to the interaction between CD4 molecule and viral envelope protein gp160 in the Golgi apparatus. Vpu binds to CD4, thereby releasing the envelope protein that can be easily transported to the cell plasma membrane in [124].

It was more difficult to understand the cause of the Δ vpu-HIV-1 viral particle clustering near the cell sur-

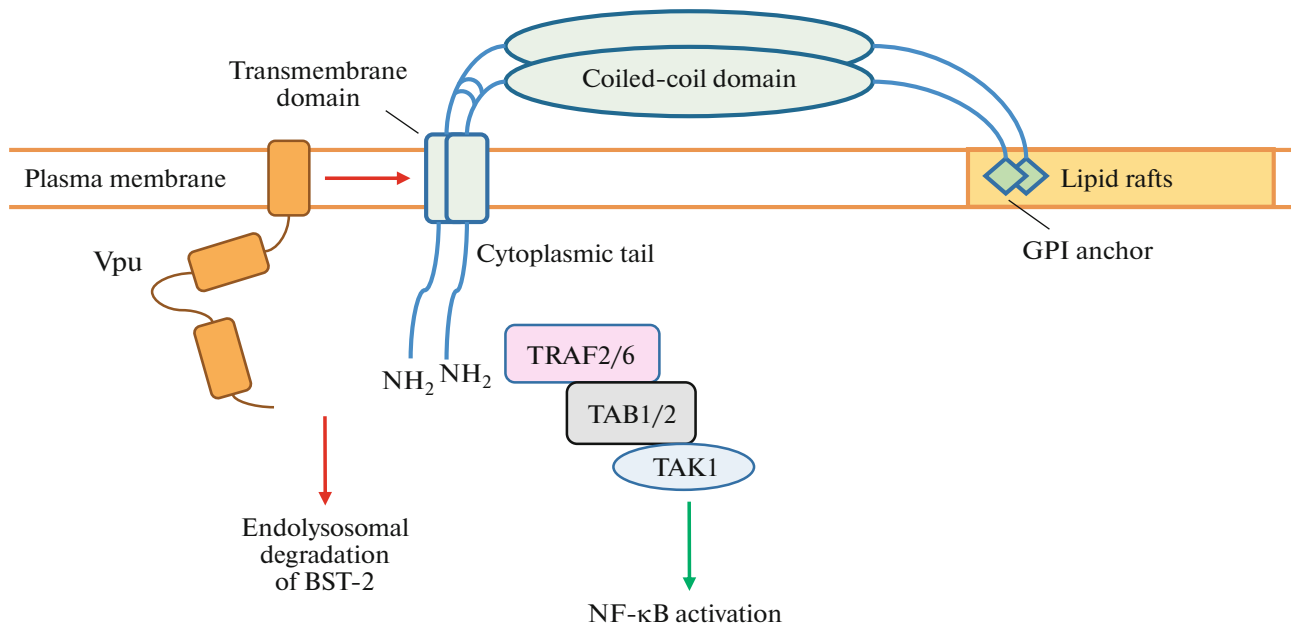


Fig. 3. The topology of BST-2, the interaction with Vpu, and the activation of the NF- κ B pathway.

face. The site-directed mutagenesis in the *vpu* gene has shown that the release of gp160 and the clustering of virions near the cell surface involve different Vpu domains. Thus, the assembly of Δ vpu-HIV-1 virions was observed only in particular types of cells and could be intensified with type-I IFN in [125, 126]. The Vpu-defective virus also proved more sensitive to the suppression of replication under the influence of IFN- α . In addition, these viral particles were mature and could be removed from the surface of infected cells via protease treatment. Consequently, there is a cellular protein capable of retaining Δ vpu-HIV-1 virions on the cell surface, thereby preventing budding. According to data from electron microscopy, Δ vpu-HIV-1 viral particles not only attach to the surface of infected cells but also “adhere” to each other in [23]. This means that the molecule involved in this process can be incorporated into a viral envelope and prevent virus distribution by retaining viral particles on the surface of infected cells. All the above gives grounds to believe that the Vpu protein originated and was established during the coevolution of HIV-1 with humans as a tool for counteracting IFN-mediated cell defense.

Neil et al. in [23] proposed the name “tetherin” (from “tether”: to tie, to restrict) for the cell surface protein responsible for this process. The specific molecule performing this function was identified by the microchip analysis of cell transcriptome before and after the stimulation with IFN- α . The candidates were BST-2 (bone marrow stromal antigen 2) and three IFN-induced transmembrane proteins: IFITM1, IFITM2, and IFITM3. The ability of BST-2 to “tether” the virus to the membrane was confirmed experimentally. BST-2 had no effect on the expression

and processing of viral protein Gag, inhibiting only the release of formed viral particles from the cell.

BST-2 has a unique structure: the N-terminus with the cytoplasmic domain merges into the transmembrane domain; next there is an external coiled-coil domain and C-terminal glycosylphosphatidylinositol (GPI) anchor often referred to as second transmembrane domain in [127, 128] (Fig. 3). BST-2 is localized in lipid rafts of the plasma membrane, the trans-Golgi network, and endosomes in [127, 129, 130]. Two membrane-associated domains determine the ability of the protein to retain viral particles close to the membrane and bind them with each other: when the virions bud, one of the domains remains on the membrane, while the other is incorporated into the lipid envelope of the virus in [131–134] (Fig. 4). BST-2 functions as homodimers and homotetramers covalently bound via cysteine residues localized in the coiled-coil external domains of BST-2 in [129, 131, 135, 136] (Fig. 3).

The attachment of the virus to the membrane of infected cell reduces infection by the cell-free virus. HIV-1 is more effectively transmitted through intercellular junctions, especially through virological synapses attracting adhesion molecules, viral proteins, and cell receptors in the area of contact in [137, 138]. The question on the function of BST-2 in HIV cell-to-cell transmission is interesting and still open. There are contradictory data. The inhibitory effect of BST-2 on the cell-to-cell transmission of infection has been shown in [139–142]; contrariwise, BST-2 does not function as a restriction factor of HIV during its cell-to-cell transmission but even facilitates more effective infection of neighboring cells due to retaining viral particles in the infected/uninfected cell contact area in

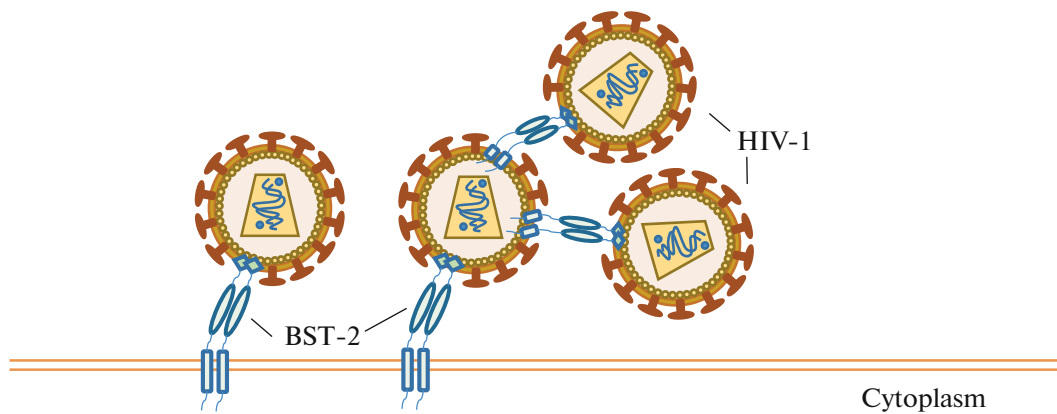


Fig. 4. The scheme of BST-2-mediated retention of HIV-1 virions near the surface of infected cells.

[143–145]. The development of methods for the quantitative measurement of cell-to-cell infection, making it possible to separate producer cells from infected cells in a single culture, can resolve this contradiction and elucidate the role of BST-2 in HIV-1 cell-to-cell transmission in [146, 147].

The cytoplasmic tail of BST-2 determines the protein involvement in intracellular signal transduction. BST-2 has been found among the proteins activating the NF- κ B signaling pathway in [148]. Retention of the virus near the surface and activation of the NF- κ B signaling pathway are two independent functions of the protein performed via different domains; at the same time, virion binding and BST-2 dimerization induce NF- κ B-signaling in [149, 150]. TRAF2 and TRAF6 are attracted to the supposed TRAF-binding site at the BST-2 molecule, which leads to the activation of TAK1 and, accordingly, the triggering of the canonical NF- κ B-signaling pathway, followed by the expression of proinflammatory cytokines IL-6, CXCL10, and IFN- β .

Accessory protein Vpu of the HIV-1 virus binds to the transmembrane domain of BST-2 in [151] and attracts SCF E3-ubiquitin ligase, which leads to ubiquitination and endolysosomal degradation of BST-2 in [151, 152]. SIV Nef protein effectively counteracts BST-2 in monkeys in [116, 117], while HIV Nef is not considered a factor interfering with BST-2 in humans.

METHODS FOR REVEALING NEW HIV RESTRICTION FACTORS

Most of the currently known (IFITM, BST-2, APOBEC3) HIV restriction factors have been found among ISGs. The triggering of IFN and NF- κ B signaling pathways in the infected cell due to viral sensors (TLR, RLR, etc.) leads to the expression of proteins of cell protection against viral infection. It is not surprising that HIV restriction factors have been found among them.

One more efficient strategy for studying restriction factors consists in the search of partner proteins for accessory proteins of the virus. HIV is able to infect cells without expression of Vif, Vpr, Vpu, and Nef (Vpx in HIV-2); however, their presence in the viral genome is functionally justified. It is believed that the main function of accessory proteins is to counteract cell defense. The identification of SAMHD1 and SERINC3/5 restriction factors as the targets of Vpx and Nef, respectively, confirms this hypothesis.

The development of high-throughput sequencing techniques has opened up new prospects for searching restriction factors. Even now there is a large body of data accumulated as a result of siRNA-, shRNA-, and CRISPR/Cas9-screening for the search of restriction factors in [153] and HIV-1 replication factors in [154–158]. These data arrays still “wait in the wings”: they require systematization in [159] and interpretation in accordance with the results of experimental studies; but even now they stimulate and accelerate the search of new, clinically interesting cellular proteins involved in HIV infection.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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