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Dual Role of Host Cell Factors in HIV-1 Replication: Restriction and Enhancement of the Viral Cycle

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Abstract

Once HIV-1 enters the target cell, the first goal in the viral cycle is to integrate into the cellular chromosomes. The irreversible integration as a provirus allows HIV-1 to persist in the infected cell in a quiescent or latent stage that leads to viral escape from immune response and current antiviral treatment. HIV-1 replication is absolutely dependent on different cellular and viral factors that initiate viral expression, acting at the long terminal repeat of the integrated provirus. Accordingly, HIV-1 induces changes in the cellular environment to make possible an efficient replication and production of viral progeny. One main instigator of HIV-1 replication is the viral regulator Tat, which is absolutely required for efficient transcription and elongation of viral transcripts. For this purpose, Tat recruits several cellular proteins to make the chromatin structure accessible for the transcription machinery, to acquire the posttranslational modifications essential for its function, and to produce efficient viral replication. However, the host cell has also several antiviral mechanisms that may act at different steps of the viral cycle to thwart HIV-1 replication. To level the match, HIV-1 encodes accessory proteins, such as Vif and Vpu, which play important roles in HIV-1 pathogenesis by counteracting cellular antiviral factors. The increasing knowledge of viral protein interactions with host cell factors will be essential for the discovery of new targets that could be used to design new therapeutic strategies. **(AIDS Rev. 2010;12:103-12)**
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Key words

HIV-1. Provirus. Integration. Transcription. Elongation. Tat. NFκB. APOBEC/Vif. BST-2/Vpu.

Introduction

As with other lentiviruses, HIV-1 must be integrated into host cell chromosomes to acquire permanent residence as a provirus. This proviral stage allows HIV-1 to remain silent inside the infected cell, undetectable for the immune response and current antiviral treatment. Once integrated, HIV-1 provirus can subsequently be considered as a host-inducible gene that requires the concerted action of different transcription factors, as well as the RNA polymerase II (RNAPII) and associated transcription machinery, to produce full-length viral mRNA that will be translated into viral proteins. However, efficient viral gene expression represents only the second major step in the viral cycle because an additional process of protein assembly, viral budding, and transmission of fully infective particles is still required to assure viral propagation in the infected host.

Accordingly, highly complex mechanisms of viral and cellular measures and countermeasures have been developed during the virus-host co-evolution. On the one hand, viral proteins such as Tat or Nef can modify cellular gene expression[1] and change host cell responsiveness to extracellular stimuli[2] in order to turn the infected host cells into efficient viral factories. On the other hand, the virus must overcome several cellular antiviral mechanisms that may act at different steps of the viral cycle. The outcome of the match will depend on the imbalance between viral measures and cellular countermeasures.

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In this review, the role of different molecular mechanisms involved in HIV-1 integration, genome expression, and viral infectivity will be examined from a double-sided perspective: their role as mechanisms of viral restriction and their function in facilitating the different steps of the HIV-1 lifecycle.

Cellular mechanism modifying retro-transcription and provirus integration

Once the viral core is released into the cytoplasm, the viral reverse transcriptase (RT) retro-transcribes the viral genome to form linear, double-stranded cDNA (dscDNA)[3] that is included in a pre-integration complex (PIC) along with viral proteins such as integrase, RT, matrix protein, and Vpr (viral protein R)[4]. The PIC transports the lentiviral dscDNA through intact nuclear pores to the nucleus, where the viral DNA lingers until the conditions are optimal to be integrated in the cellular chromosomes[5]. This stage of the viral lifecycle can be overcome by two main mechanisms: the presence of APOBEC (apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like) proteins and the structure of the chromatin at the site of integration.

Efficient retro-transcription is restricted by APOBEC proteins

The APOBEC cytidine deaminases are innate antiviral defenses that potently inhibit HIV-1 replication by inducing lethal hypermutations based on C→U conversion in the viral minus-strand cDNA during reverse transcription[6,7]. APOBEC3G was the first member of this family identified as antiretroviral factor[8] and it displays the most potent anti-HIV-1 activity[9]. Other members such as APOBEC3F[10], 3H[11], and 3B[12] may also inhibit HIV-1 replication. APOBEC3G and 3F expression is highly upregulated by interferon (IFN)-α or IFN-γ in human peripheral blood mononuclear cells (PBMC)[13]. In non-activated CD4+ T-cells, APOBEC3G remains as an enzymatically active low-molecular mass form that hinders the accumulation of reverse transcripts upon viral cellular entry. After T-cell activation, APOBEC3G low-molecular mass complexes assemble into high-molecular mass complexes without cytidine deaminase activity[14,15]. This suggests that active APOBEC low-molecular mass forms would represent a restriction for the progress of the infection in resting CD4+ T-cells, whereas in activated lymphocytes, inactive high-molecular mass APOBEC would allow efficient retro-transcription of viral RNA. Alternation from one to another form would explain the inability of HIV-1 to replicate in resting T-cells, along with low nucleotide pools and adenosine triphosphate levels[5], and its ability to replicate in activated T-cells. Unfortunately, this mechanism has not been further elucidated.

To be fully functional, APOBEC3G should be packaged into the newly synthesized virions from infected cells[16] (Fig. 1 A). Once incorporated in the virions, APOBEC3G remains inactive by the viral genomic RNA because it is enzymatically active only on single-stranded DNA[17]. Following viral entry, reverse transcription is initiated and plus-stranded cDNA is synthesized[18]. At this step, virion-associated APOBEC3G attacks the newly synthesized minus-strand cDNA, inducing non-viable C→U hypermutations all over the length of the viral genome[6,7,10]. However, APOBEC3G may only exert its antiviral activity in the absence of the viral accessory protein Vif (virion infectivity factor)[19] because Vif neutralizes APOBEC3G in the productively infected cell by three major mechanisms[20,21] (Fig. 1 B): first, Vif binds to APOBEC3G and recruits Cul5-E3 ubiquitin ligase complex that mediates the polyubiquitylation of APOBEC3G and its degradation[22-25]. This mechanism is counteracted by protein kinase A-mediated phosphorylation of APOBEC3G, which reduces its binding to Vif and the subsequent degradation in the proteasome[26]. Second, Vif impairs the translation of APOBEC3G mRNA[27-29], likely due to the fact that Vif can bind APOBEC3G mRNA with high affinity[30]. And finally, Vif competes with APOBEC3G for binding to viral components like the nucleocapsid domain of Gag and viral genomic RNA, preventing APOBEC3G from being incorporated in virions.

Cytidine deamination activity is not the only antiviral mechanism of APOBEC3G, 3F, and 3H[11,31-33], as demonstrated by the fact that APOBEC3G-mediated C→U hypermutations do not correlate with viral load or CD4+ T-cell count[34,35]. These cytidine deaminase-independent mechanisms are not well known, but some alternatives have been proposed: first, different allelic variants such as APOBEC3G-H186R have been related to higher viral loads, decreased CD4+ T-cell levels, and worse progression to AIDS[36]. Second, it has been proposed that intracellular APOBEC3G and 3F may somehow interfere with viral assembly, causing morphological changes in the viral core[21]. Finally, Mariani, et al.[27] showed that APOBEC3G-mediated deamination of minus-strand cDNA does not stop viral reverse transcription, but uracil mutations are responsible for viral DNA degradation before its integration occurs through a mechanism still undefined.

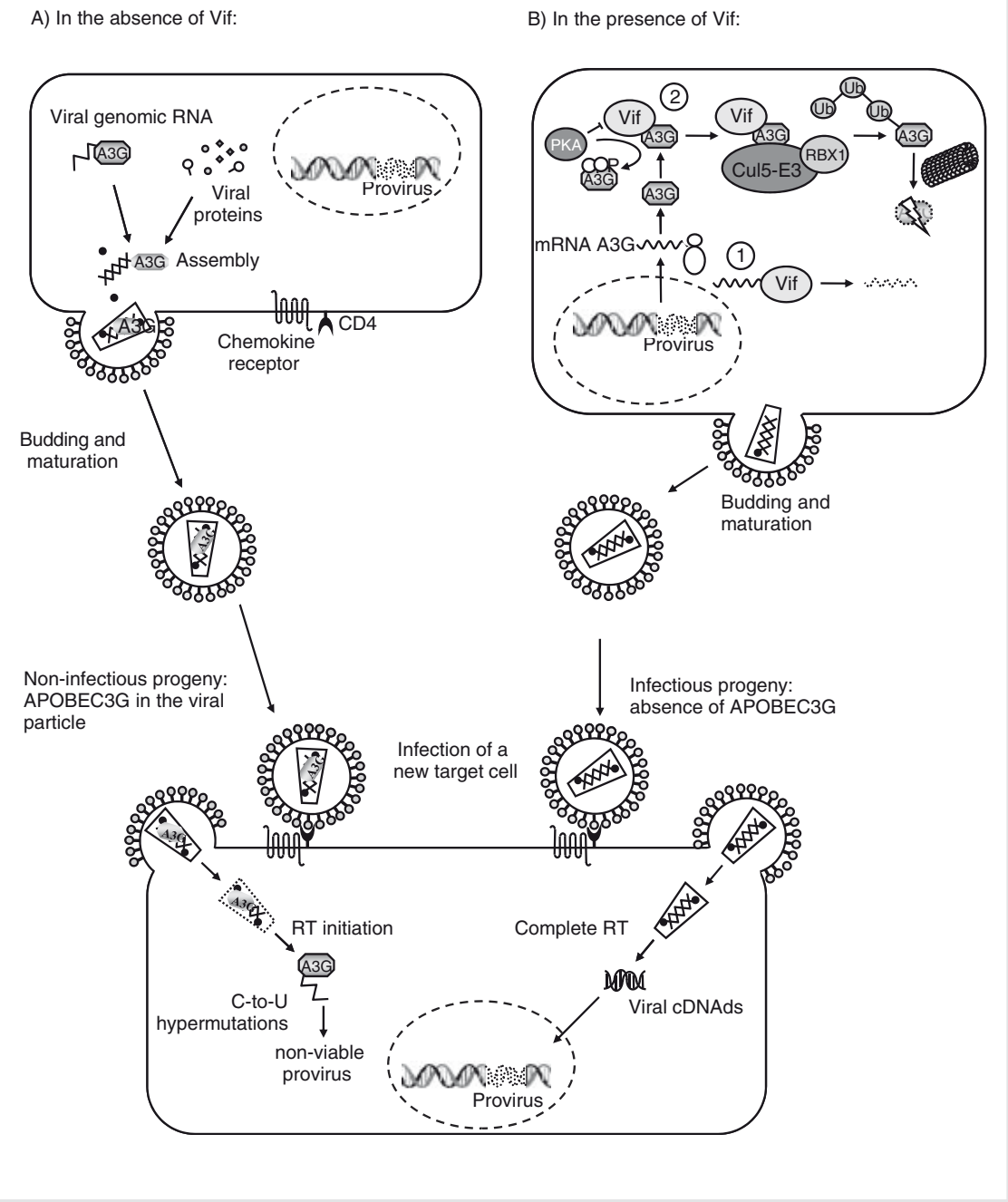

Figure 1. *APOBEC3G and Vif interplay.* ***A:*** *In the absence of Vif, APOBEC3G binds to the 5' end of viral mRNA during virus assembly and is packed into the newly synthesized virions. Following viral entry in a new target cell, reverse transcription is initiated and plus-stranded cDNA is synthesized. APOBEC3G attacks the newly synthesized minus-strand cDNA, inducing non-viable C→U hypermutations all over the length of the viral genome.* ***B:*** *In the presence of Vif, APOBEC3G is inhibited by reducing its levels and half-life. First, Vif may reduce the translation of mRNA encoding for APOBEC3G; and second, Vif interacts with APOBEC3G and recruits the Cul5-E3 ubiquitin ligase complex, which mediates the proteolysis of APOBEC in the proteasome. This mechanism is counteracted by protein kinase A-mediated phosphorylation of APOBEC3G, which reduces its binding to Vif and the subsequent degradation in the proteasome. Viral particle do not encapsidate APOBEC3G and in the newly infected cell retro-transcription is fully completed leading to HIV-1 integration and a productive viral cycle. Vif: virion infectivity factor; APOBEC: apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like protein; PKA: protein kinase A; RT: reverse transcription; dscDNA: double-stranded cDNA.*

Open structure of the chromatin and several cellular factors are necessary for HIV-1 integration

The site of proviral integration is critical to promote efficient transcription. Integration is a highly restrictive process that occurs preferentially into chromosomal regions rich in intronic sequences of expressed genes where the viral transcription may be assured[37]. Host factors such as lens epithelium-derived growth factor (LEDGF/p75), high-mobility group protein B1 (HMG1), and emerin[4,38-40] are necessary to facilitate the provirus integration. The LEDGF/p75 acts as chaperone of the viral integrase to promote viral integration[41]; HMG1 binds to the viral dscDNA, altering its conformation maybe by joining the two ends of the viral cDNA together in the catalytically active PIC[38]. Emerin increases the integration efficiency by improving the viral DNA localization to the chromatin[42]. The opening of the chromatin conformation and nucleosome 1 remodeling near the long terminal repeat (LTR) located at the 5' end of the viral genome, which act as enhancer and promoter sequences, are also indispensable prerequisites for the provirus integration[37,43].

Host cell and viral factors that modulate HIV-1 transcription

After the provirus has been successfully integrated into the cellular chromosome, HIV-1 replication begins when the cellular transcription machinery can be recruited to the LTR once the open chromatin structure allows access to the proviral DNA.

Cellular and viral factors modify accessibility to the chromatin site containing the provirus

The accessibility to the chromatin and to the LTR is greatly dependent on the post-translational modifications of the histone tails such as acetylation and methylation. Hyper-acetylation of histones by cellular acetyltransferases (HAT) induces the opening of the chromatin structure and facilitates the assembly of the basic transcription machinery and viral transcription, whereas hypo-acetylation by histone deacetylase (HDAC) is correlated with transcription repression[44]. Histone methylation by methyltransferase (MTase) has been associated with both activation and repression of HIV-1 replication[45].

The recruitment of HDAC to the LTR can effectively repress HIV-1 replication, and this can be achieved by several host cell factors such as Yin Yang 1 and late SV40 factor, which cooperate in the recruitment of HDAC1 to the LTR[46,47], or the nuclear factor kappa B (NFκB) p50/p50 homodimers and C-promoter binding factor-1, which inhibit viral transcription in a similar way to Yin Yang 1[48,49]. However, HIV-1 can counteract these repressive measures by decreasing HDAC occupancy of the 5'LTR and by inducing hyper-acetylation and rearrangement of nucleosome 1 through its critical regulator Tat. At the beginning of transcription, a stem-loop structure termed transactivation response element (TAR) is formed at the 5' end of the nascent viral transcripts, creating a binding site for Tat[50]. The TAR/Tat complex recruits the binding of the host cell factor positive transcription elongation factor b (P-TEFb, formed by CDK9 and cyclin T1) to increase the functional capacity of RNAPII and to allow the efficient elongation of viral transcripts[51]. To avoid transcriptional repression due to histone hypo-acetylation, Tat recruits to the 5'LTR factors with HAT activity such as p300/CREB binding protein (CBP), CBP/p300-associated factor (PCAF), and human general control of amino acid synthesis protein 5 (hGCN5)[52].

Host cell factors that promote efficient HIV-1 transcription

Once the chromatin around 5'LTR is in a permissive state, several host transcriptional factors, such as NFκB, specific protein 1 (Sp1), activated protein 1 (AP-1), and nuclear factor of activated T-cells (NF-AT), are recruited to their consensus sites, promoting a dynamic viral transcription (Fig. 2). The LTR contains two binding sites for NFκB, a pleiotropic transcription factor essential for inducible HIV-1 gene expression in human T-cells[53]. The NFκB is formed by dimers composed of five Rel proteins (p65/RelA, c-Rel, RelB, NFκB1/p50, and NFκB2/p52) in almost any combination[54,55]. All Rel proteins are regulated by post-translational modifications such as phosphorylation, acetylation, ubiquitination, and isomerization of specific amino acid residues that may alter the functions of NFκB. The most important active NFκB dimer is composed by p65/RelA-NFκB1/p50, which function is mainly regulated by post-translational modifications in p65/RelA, with phosphorylation at S536 being the one that renders a most active p65/RelA[56]. Phosphorylation of p65/RelA is necessary for its association with HAT, such as CBP/p300 or HDAC[57], causing reversible acetylation/deacetylation that further controls NFκB activity[58,59]. The NFκB/DNA complexes are stabilized by cooperative protein-protein

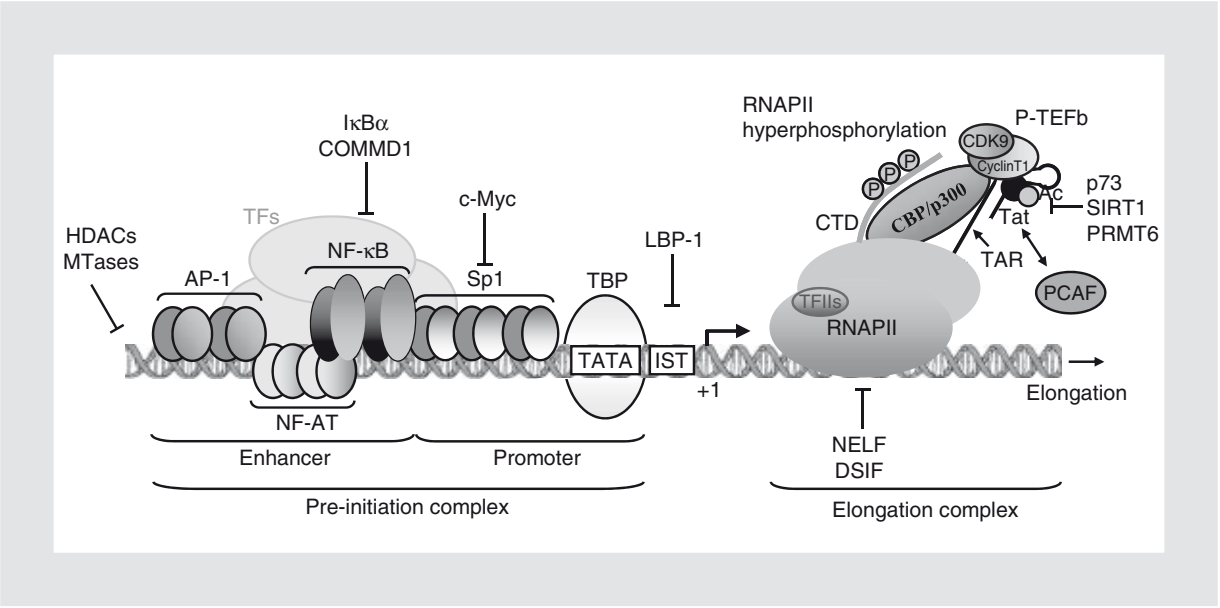

Figure 2. *Binding sites for cellular transcription factors within the HIV-1 LTR and their repressors. Both HIV-1 enhancer and promoter region sites contain several consensus sites for the binding of essential cellular factors such as NFκB, Sp1, NF-AT and AP-1. NFκB is able to form a pre-initiation complex that binds these factors and other transcription factors from the general transcription machinery. The incorporation of RNAPII allows the initiation of transcription, the formation of TAR loop and the binding of the elongation complex formed basically by Tat, P-TEFb and HAT as CBP/p300 and PCAF. Accessibility of transcription factors to the LTR depends on the permissive state of the chromatin after HAT recruitment, whereas recruitment of HDAC and MTase leads to a higher-order chromatin structure responsible for transcriptional silencing. Factors as IκB-α and COMMD1 are responsible for repressing NFκB activity, whereas binding of c-Myc to Sp1 in the LTR leads to transcriptional silencing through recruitment of HDAC. Binding of general TF such as TFIID to the TATA box may be inhibited by LBP-1, which binds strongly to two sequences around the HIV-1 initiation site and weakly over the TATA box. In the elongation complex, factors as p73, SIRT1 or PRMT6 repress Tat activity, avoiding efficient transcription and elongation of viral transcripts. If Tat is inactive, both complexes NELF and DSIF bind tightly to a hypo-phosphorylated RNAPII to inhibit transcription. LTR: long terminal repeat; IκB: inhibitory kappa B; COMMD: copper metabolism gene MURR1 domain; RNAPII: RNA polymerase II; P-TEF: positive transcription elongation factor; HDAC: histone deacetylase; MTase: methyltransferase; TF: transcription factors; NFκB: nuclear factor kappa B; TBP: TATA binding protein; LBP: leader binding protein; IST: initiator of short transcripts; CTD: carboxyl-terminal domain; CBP: p300/CREB binding protein; TAR: transactivation response element; PCAF: CBP/p300-associated factor; PRMT: protein arginine N-methyltransferase; NELF: negative elongation factor; DSIF: DRB sensitivity inducing factor.*

interactions with other transcription factors and structural proteins, forming hyperdynamic protein-DNA complexes called enhanceosomes[60]. The enhanceosome that binds to LTR to begin viral transcription is called pre-initiation complex (Fig. 2).

The HIV-1 LTR also contains three consensus sites for Sp1, a protein member of a multifamily that binds to DNA GC boxes through carboxy-terminal zinc-finger motifs[61]. Sp1 can physically interact and functionally cooperate with TATA box binding protein, several transcription activators such as octamer-binding transcription factor 1 and nuclear factor Y alpha[62,63], and P-TEFb through the binding to cyclin T1[64]. Sp1 activity can be regulated through phosphorylation by the MEK/ERK pathway[65,66] or acetylation by CBP/p300 in response to either T-cell activation or Tat expression[67]. Besides, NF-AT, overlapping with NFκB consensus sites, and AP-1 binding enhancer sites are also represented in the LTR. Activation of NF-AT monomers is tightly regulated by intracellular calcium concentrations. Dephosphorylation of NF-AT by the phosphatase calcineurin induces its translocation to the nucleus, promoting DNA binding and transactivation activities[68]. However, NF-AT is rarely able to bind alone to DNA, but is usually found associated with other factors such as AP-1[69,70] to enhance HIV-1 transcription. The AP-1 dimers are composed by members of Fos/Jun and ATF/CREB families of transcription factors and their activation is regulated by transcriptional and post-transcriptional mechanisms such as specific interactions with transcriptional co-activators[71].

Host cell factors with inhibitory activity against HIV-1 transcription

Despite the virus using several host cell proteins to initiate efficient viral transcription, there are also innate cellular mechanisms to control the activity of own

essential factors as NFκB and Sp1 (Fig. 2). The family of inhibitory proteins IκB tightly control NFκB activity through a non-covalent association that mask the NFκB nuclear localization signal, preventing nuclear translocation and transcription activation[72]. The main inhibitor for NFκB in T-cells is IκB-α, which is continuously shuttling between nucleus and cytosol even in resting $CD4^+$ T lymphocytes[73]. The IκB-α sequesters NFκB in the cytoplasm until, upon T-cell activation, IκB-α is phosphorylated by IκB kinase (IKK) complex and degraded in the proteasome[74], rendering free NFκB that translocates to the nucleus and binds to its consensus sites in the inducible gene promoters[75]. As a result, nuclear accumulation of IκB-α inhibits HIV-1 LTR-dependent transcription, as well as restraining HIV-1 replication in $CD4^+$ T lymphocytes[73]. Besides, p65/RelA phosphorylated at S536 cannot interact with cytosolic IκB-α, being able to translocate directly to the nucleus[56], which supports the importance of post-translational modifications in NFκB activity. The NFκB can be also controlled by other factors such as copper metabolism gene MURR1 domain containing 1 (COMMD1) that interferes with both basal and tumor necrosis factor-induced NFκB activity[76]. The COMMD1 also interacts directly with NFκB and controls the duration of NFκB recruitment to open chromatin by accelerating ubiquitination and degradation of p65/RelA through its interaction with a multimer ubiquitin ligase complex[77]. Besides, there are host cell factors such as c-Myc that may block Sp1 activity. The proto-oncogene Myc/c-Myc regulates the expression of a wide variety of genes through recruiting HAT[78], but it has also been shown to repress the transcription of several genes by recruiting HDAC1[79]. When c-Myc binds Sp1 at the LTR, it promotes the recruitment of HDAC1, repressing viral replication. After exposure to HDAC inhibitors such as valproic acid, c-Myc is noticeably downregulated and remains absent from the promoter, allowing histone acetylation, RNAPII recruitment, and viral transcription[80].

Tat is a viral regulator essential for efficient transcription and elongation

Tat function is highly dependent on specific interactions with a range of cellular proteins. Tat may interact with critical transcription factors from the pre-initiation complex such as Sp1 and NF-AT. Tat binds directly to NF-AT, increasing its association with c-Jun at NF-AT/AP-1 complex[81,82], and with Sp1[83]. However, Sp1 may also activate viral transcription through direct interaction with cyclin T1 in the absence of Tat. Accordingly, blocking the high affinity Sp1-binding site with artificial zinc fingers strongly inhibits both Sp1-cyclin T1-dependent transcription and Tat-dependent transcription, even in the presence of excess expressed Tat[84].

Once the transcription is initiated, RNAPII begins the elongation of the viral genome (Fig. 2). Tat creates a multiprotein elongation complex basically composed by P-TEFb, RNAPII, TAT-SF1 (HIV-1 Tat specific factor 1), hSPT4 and hSPT5/Tat-CT1 (Tat-co-transactivator 1 protein), TFIIF, TCERG1/CA150, and nucleolin[85-87]. Both hSPT4 and hSPT5/Tat-CT1 are components of DRB sensitivity inducing factor (DSIF), which generally exerts a negative function on translation, but may also have a positive effect within a short time-frame from initiation to elongation[88]. The DSIF cooperates with Tat by preventing premature RNA release at terminator sequences[89]. In the absence of Tat, DSIF and negative elongation factor (NELF) bind to RNAPII shortly after initiating RNA synthesis, repressing HIV-1 transcript elongation[90]. Both DSIF and NELF bind tightly to hypophosphorylated RNAPII but not to the hyper-phosphorylated form. After Tat binds to P-TEFb and this complex is tethered to TAR, RNAPII carboxyl-terminal domain (CTD) is hyper-phosphorylated and both repressing DSIF and NELF complexes are released, initiating efficient elongation.

Post-translational modifications such as acetylation and methylation are also essential for regulating Tat activity. First, Tat mostly recruits to the 5'LTR factors with HAT activity in order to achieve an open chromatin structure that permits efficient transcription. Second, Tat function is highly dependent on its own state of acetylation. There are two major sites for acetylation of Tat in its functional domains: K28 and K50. The PCAF binds to the cysteine-rich region of Tat and promotes acetylation on K28[91]. The K28-acetylated Tat shows high affinity for P-TEFb and binds to the nascent TAR RNA, favoring the release of DSIF and NELF from RNAPII and recruiting CBP/p300[92]. Acetylation of Tat by CBP/p300 at K50 in the TAR binding domain leads to the dissociation of Tat from TAR and the binding to PCAF, with the Tat/PCAF association being absolutely necessary to activate sustained HIV-1 transcription. Accordingly, modulation of the Tat acetylation state by cellular factors such as p73 or SIRT1 will result in the inhibition of its activity[93-95]. Tat is a substrate for deacetylase SIRT1, which deacetylates Tat, PCAF and the histone tails in the promoter regions, creating a non-permissive chromatin environment[95]. Deacetylation of Tat by SIRT1 leads to its dissociation from the

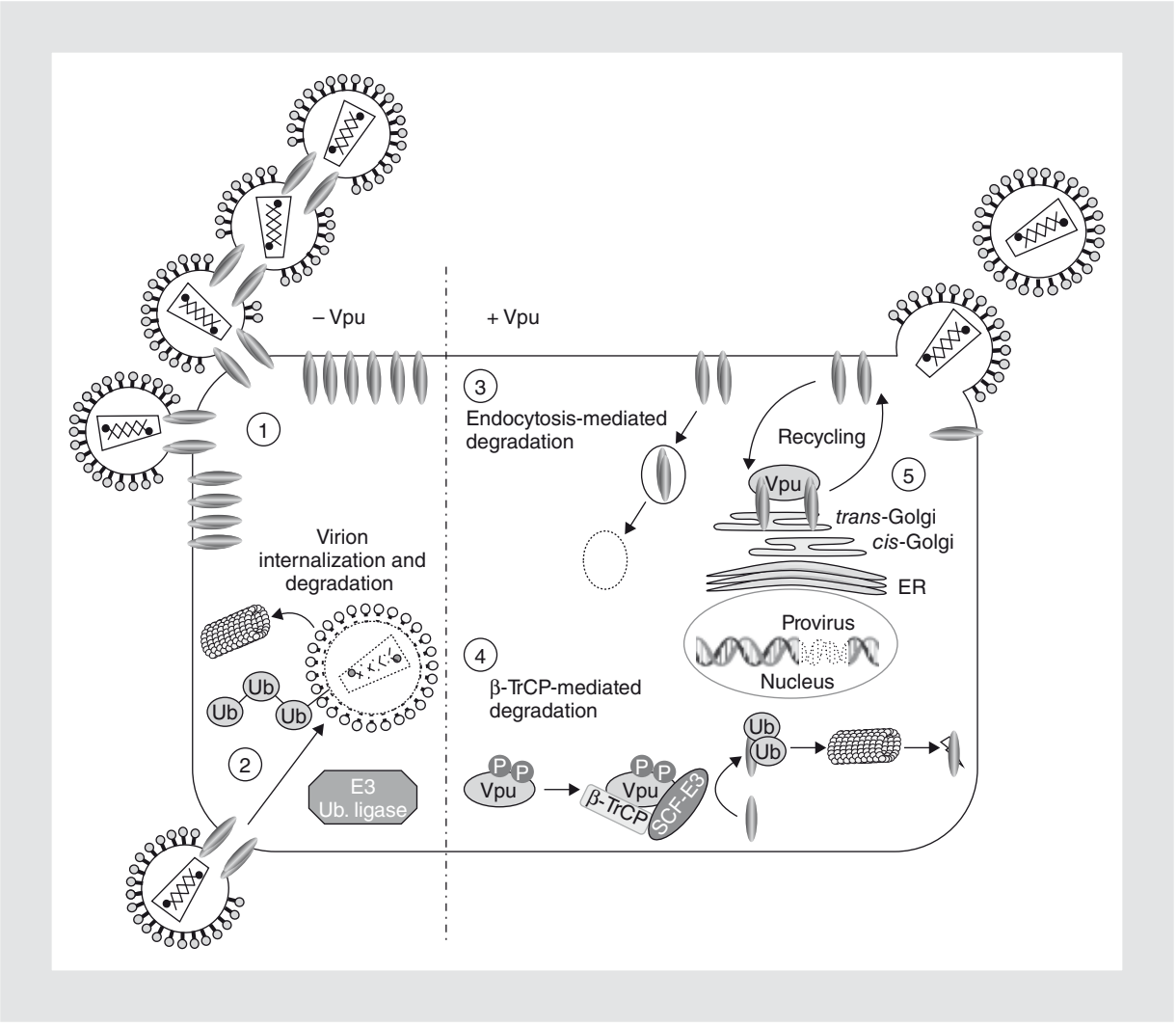

Figure 3. *BST-2 and Vpu interplay. BST-2 is a glycosylated transmembrane protein with a glycosyl phosphatidylinositol anchor that forms homodimers and localizes at the site of viral assembly and budding. In the absence of Vpu, BST-2 attaches virions to the cell surface and among each other (1), inducing the internalization of virions that are subsequently ubiquitinated and degraded in the proteasome (2). In the presence of Vpu, cellular levels of BST-2 are reduced through several mechanisms: endocytosis-mediated degradation (3), E3 ligase-mediated ubiquitination and degradation in the proteasome (4), and retention in the trans-Golgi network, where BST-2 redistributes from early and recycling endosomes to the trans-Golgi network (5). Vpu: viral protein U; BST: bone marrow stromal cell antigen; TrCP: transducing repeat-containing protein; SCF: Skp1/Cullin/F-box protein; Ub: ubiquitin; ER: endoplasmic reticulum.*

elongating polymerase and from PCAF, repressing HIV-1 transcription[94].

Finally, methylation of residues Arg52 and Arg53 of Tat by protein arginine N-methyltransferase 6 (PRMT6) avoids the formation of TAR/Tat/P-TEFb complex[96], thereby annulling viral transcription and elongation.

Host cell factor bone marrow stromal cell antigen 2 modulates the viral infectivity

Once an efficient elongation of the viral transcripts is achieved, viral proteins are translated and virions are assembled and released from the infected cells to infect new targets. At this last stage of the viral lifecycle, there is one last attempt from the infected cell to avoid viral spread that is mediated by an IFN-inducible cell surface protein termed tetherin, CD317 or bone marrow stromal cell antigen 2 (BST-2). The BST-2 is a heavily glycosylated integral membrane protein containing a glycosyl phosphatidylinositol anchor that forms cysteine-linked homodimers[97]. This unusual structure allows BST-2 to act as a cross linker between the virion and the cellular membrane[98], forming a physical bond between the virion and the plasma membrane that keeps the nascent virions attached to the plasma membrane or to each other, impeding their

release[99] (Fig. 3). The BST-2 functions together with other host cell factors such as breast cancer associated gene 2, a RING-type E3 ubiquitin ligase that facilitates the re-internalization of virions bound to the plasma membrane and their degradation in the proteasome[100].

Activity of BST-2 is not restricted to HIV-1, but it is potentially active against many enveloped viruses in several cell types, indicating that the BST-2 mechanism of inhibition does not require specific interactions with viral proteins[101,102]. Besides, although it is essential that BST-2 localizes at the site of viral assembly and budding to produce proper antiviral activity[99,103,104], the functionality of this protein seems unrelated to the intracellular expression level, which is significantly different between cell types: whereas HeLa cells show high a expression level, BST-2 is nearly undetectable in resting primary T-cells and macrophages, although it can be induced by IFN-α[105]. It has also been observed that BST-2 could be incorporated into virions produced from HeLa and 293T-cells[106-108], although it is still unknown whether virions produced from T-cells contain BST-2. In any case, virion tethering activity appears to be also independent of the levels of BST-2 contained in viral particles[108].

The BST-2-mediated restriction of HIV-1 particle release is only completely successful in the absence of the viral accessory protein Vpu (viral protein U), because Vpu may counteract BST-2 activity by several mechanisms (Fig. 3): first, phosphorylation of Vpu at S52 and S56 within its cytoplasmic motif DpSGxxpS promotes the association to beta-transducing repeat-containing protein (β-TrCP), a substrate recognition unit of SCF (Skp1/Cullin/F-box protein)-E3 ubiquitin ligase[104,109-111]. The Vpu/β-TrCP/SCF-E3 complex marks BST-2 for proteasome degradation but, unlike most β-TrCP targets, Vpu itself is not receptive to proteasome degradation[112]. This suggests that Vpu-mediated hijacking of β-TrCP may results in β-TrCP unavailability for stabilizing other targets such as IκBα, β-catherin and absolute free thyroxin 4 (AFT4)[113], which may influence AIDS pathogenesis. Second, Vpu delays the transport of BST-2 to the plasma membrane, inducing its removal from the cell surface and re-localization in a perinuclear compartment[114]. In fact, decrease of BST-2 total levels is not really necessary for Vpu to promote efficient HIV-1 virion release, but only the exclusion of BST-2 from budding sites is required for neutralizing its inhibitory effect[104,111,114]. And third, Vpu induces the redistribution of BST-2 from early and recycling endosomes to the trans-Golgi network, where it can be degraded[103,108,114].

Conclusion

Viral-host interplay is a complex, highly interactive equilibrium developed during their co-evolution. On the one hand, HIV-1 successful infection requires the hijacking of the cellular transcription machinery and transcription factors such as NFκB and Sp1 are essential for efficient viral replication. On the other hand, the host cell has evolved to develop antiviral mechanisms that counteract the attempt by HIV-1 to hijack cellular proteins. First, factors such as IκB-α, COMMD1, or c-Myc may restrain viral transcription by controlling the binding of cellular factors. Second, factors such as p73, SIRT1, or PRMT6 modify the acetylated state of the essential viral regulator Tat, which activity is highly dependent on the acetylation of its functional domains. And third, there are innate antiviral mechanisms that affect viral infectivity, such as APOBEC, which induces hypermutated, non-viable viral particles, or BST-2, which links the new virions to the cell membrane to avoid their release. However, HIV-1 has also evolved to eliminate the effectiveness of these mechanisms by modifying the cellular environment to convert the host cells into efficient viral factories through Tat, or by blocking innate antiviral mechanisms through accessory proteins such as Vif and Vpu, which overcome APOBEC and BST-2 activities, respectively. The outcome of HIV-1-host cell match will depend on the equilibrium between cellular and viral measures and countermeasures. A better understanding of viral/cellular protein interactions is necessary for discovering new targets that could be used to design new therapeutic strategies.

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References

1. López-Huertas M, Callejas S, Abia D, et al. Modifications in host cell cytoskeleton structure and function mediated by intracellular HIV-1 Tat protein are greatly dependent on the second coding exon. Nucleic Acids Res. 2010;38:3287-307.
2. Keppler O, Tibroni N, Venzke S, Rauch S, Fackler O. Modulation of specific surface receptors and activation sensitization in primary resting CD4+ T lymphocytes by the Nef protein of HIV-1. J Leukoc Biol. 2006;79:616-27.
3. Bukrinsky M, Stanwick T, Dempsey M, Stevenson M. Quiescent T lymphocytes as an inducible virus reservoir in HIV-1 infection. Science. 1991;254:423-7.

4. Llano M. An essential role for LEDGF/p75 in HIV integration. Science. 2006;314:461-4.
5. Coiras M, López-Huertas M, Pérez-Olmeda M, Alcamí J. Understanding HIV-1 latency provides clues for the eradication of long-term reservoirs. Nat Rev Microbiol. 2009;7:798-812.
6. Mangeat B, Turelli P, Caron G, Friedli M, Perrin L, Trono D. Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts. Nature. 2003;424:99-103.
7. Zhang H, Yang B, Pomerantz R, Zhang C, Arunachalam S, Gao L. The cytidine deaminase CEM15 induces hypermutation in newly synthesized HIV-1 DNA. Nature. 2003;424:94-8.
8. Sheehy A, Gaddis N, Choi J, Malim M. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein. Nature. 2002;418:646-50.
9. Zennou V, Bieniasz P. Comparative analysis of the antiretroviral activity of APOBEC3G and APOBEC3F from primates. Virology. 2006;349:31-40.
10. Liddament M, Brown W, Schumacher A, Harris R. APOBEC3F properties and hypermutation preferences indicate activity against HIV-1 in vivo. Curr Biol. 2004;14:1385-91.
11. Dang Y, Siew L, Wang X, Han Y, Lampen R, Zheng Y. Human cytidine deaminase APOBEC3H restricts HIV-1 replication. J Biol Chem. 2008;283:11606-14.
12. Doehle B, Schäfer A, Cullen B. Human APOBEC3B is a potent inhibitor of HIV-1 infectivity and is resistant to HIV-1 Vif. Virology. 2005;339:281-8.
13. Chen K, Huang J, Zhang C, et al. Alpha interferon potently enhances the anti-human immunodeficiency virus type 1 activity of APOBEC3G in resting primary CD4 T cells. J Virol. 2006;80:7645-57.
14. Chiu Y, Soros V, Kreisberg J, et al. Cellular APOBEC3G restricts HIV-1 infection in resting CD4+ T cells. Nature. 2005;435:108-14.
15. Kreisberg J, Yonemoto W, Greene W. Endogenous factors enhance HIV infection of tissue naive CD4 T cells by stimulating high molecular mass APOBEC3G complex formation. J Exp Med. 2006;203:865-70.
16. Yamashita T, Nomaguchi M, Miyake A, Uchiyama T, Adachi A. Status ofAPOBEC3G/F in cells and progeny virions modulated by Vif determines HIV-1 infectivity. Microbes Infect. 2010;12:166-71.
17. Suspène R, Sommer P, Henry M, et al. APOBEC3G is a single-stranded DNA cytidine deaminase and functions independently of HIV reverse transcriptase. Nucleic Acids Res. 2004;32:2421-9.
18. Soros V, Yonemoto W, Greene W. Newly synthesized APOBEC3G is incorporated into HIV virions, inhibited by HIV RNA, and subsequently activated by RNase H. PLoS Pathog. 2007;3:e15.
19. Xu H, Chertova E, Chen J, et al. Stoichiometry of the antiviral protein APOBEC3G in HIV-1 virions. Virology. 2007;360:247-56.
20. Caride E, Brindeiro R, Kallas E, et al. Sexual transmission of HIV-1 isolate showing G-->A hypermutation. J Clin Virol. 2002;23:179-89.
21. Henriet S, Mercenne G, Bernacchi S, Paillart J, Marquet R. Tumultuous relationship between the HIV type 1 viral infectivity factor (Vif) and the human APOBEC-3G and APOBEC-3F restriction factors. Microbiol Mol Biol Rev. 2009;73:211-32.
22. Marin M, Rose K, Kozak S, Kabat D. HIV-1 Vif protein binds the editing enzyme APOBEC3G and induces its degradation. Nat Med. 2003;9:1398-403.
23. Sheehy A, Gaddis N, Malim M. The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. Nat Med. 2003;9:1404-7.
24. Yu X, Yu Y, Liu B, et al. Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif-Cul5-SCF complex. Science. 2003;302:1056-60.
25. Liu B, Sarkis P, Luo K, Yu Y, Yu X. Regulation of Apobec3F and HIV type 1 Vif by Vif-Cul5-ElonB/C E3 ubiquitin ligase. J Virol. 2005;79:9579-87.
26. Shirakawa K, Takaori-Kondo A, Yokoyama M, et al. Phosphorylation of APOBEC3G by protein kinase A regulates its interaction with HIV-1 Vif. Nat Struct Mol Biol. 2008;15:1184-91.
27. Mariani R, Chen D, Schröfelbauer B, et al. Species-specific exclusion of APOBEC3G from HIV-1 virions by Vif. Cell. 2003;114:21-31.
28. Kao S, Khan M, Miyagi E, Plishka R, Buckler-White A, Strebel K. The HIV type 1 Vif protein reduces intracellular expression and inhibits packaging of APOBEC3G (CEM15), a cellular inhibitor of virus infectivity. J Virol. 2003;77:11398-407.
29. Stopak K, de Noronha C, Yonemoto W, Greene W. HIV-1 Vif blocks the antiviral activity of APOBEC3G by impairing both its translation and intracellular stability. Mol Cell. 2003;12:591-601.
30. Mercenne G, Bernacchi S, Richer D, et al. HIV-1 Vif binds to APOBEC3G mRNA and inhibits its translation. Nucleic Acids Res. 2010;38:633-46.
31. Shindo K, Takaori-Kondo A, Kobayashi M, Abudu A, Fukunaga K, Uchiyama T. The enzymatic activity of CEM15/Apobec-3G is essential for the regulation of the infectivity of HIV-1 virion but not a sole determinant of its antiviral activity. J Biol Chem. 2003;278:44412-6.
32. Holmes R, Koning F, Bishop K, Malim M. APOBEC3F can inhibit the accumulation of HIV-1 reverse transcription products in the absence of hypermutation. Comparisons with APOBEC3G. J Biol Chem. 2007;282:2587-95.
33. Newman E, Holmes R, Craig H, et al. Antiviral function of APOBEC3G can be dissociated from cytidine deaminase activity. Curr Biol. 2005; 15:166-70.
34. Cho S, Drechsler H, Burke R, Arens M, Powderly W, Davidson N. APOBEC3F and APOBEC3G mRNA levels do not correlate with HIV type 1 plasma viremia or CD4+ T-cell count. J Virol. 2006;80:2069-72.
35. Ulenga N, Sarr A, Thakore-Meloni S, Sankalé J, Eisen G, Kanki P. Relationship between HIV type 1 infection and expression of human APOBEC3G and APOBEC3F. J Infect Dis. 2008;198:486-92.
36. An P, Bleiber G, Duggal P, et al. APOBEC3G genetic variants and their influence on the progression to AIDS. J Virol. 2004;78:11070-6.
37. Schröder A, Shinn P, Chen H, Berry C, Ecker J, Bushman F. HIV-1 integration in the human genome favors active genes and local hotspots. Cell. 2002;110:521-9.
38. Farnet C, Bushman F. HIV-1 cDNA integration: requirement of HMG I(Y) protein for function of preintegration complexes in vitro. Cell. 1997;88:1-20.
39. Jacque J, Stevenson M. The inner-nuclear-envelope protein emerin regulates HIV-1 infectivity. Nature. 2006;441:641-5.
40. Van Maele B, Busschots K, Vandekerckhove L, Christ F, Debyser Z. Cellular co-factors of HIV-1 integration. Trends Biochem Sci. 2006;31:98-105.
41. Shun M, Raghavendra N, Vandegraaff N, et al. LEDGF/p75 functions downstream from preintegration complex formation to effect gene-specific HIV-1 integration. Genes Dev. 2007;21:1767-78.
42. Shun M, Daigle J, Vandegraaff N, Engelman A. Wild-type levels of HIV type 1 infectivity in the absence of cellular emerin protein. J Virol. 2007;81:166-72.
43. Coiras M, Lopez-Huertas M, Alcami J. HIV-1 latency and eradication of long-term viral reservoirs. Discov Med. 2010;9:185-91.
44. Lenasi T, Contreras X, Peterlin B. Transcriptional interference antagonizes proviral gene expression to promote HIV-1 latency. Cell Host Microbe. 2008;4:123-33.
45. Wang G, Ciuffi A, Leipzig J, Berry C, Bushman F. HIV integration site selection: analysis by massively parallel pyrosequencing reveals association with epigenetic modifications. Genome Res. 2007;17:1186-94.
46. Romerio F, Gabriel M, Margolis D. Repression of HIV type 1 through the novel cooperation of human factors YY1 and LSF. J Virol. 1997;71:9375-82.
47. He G, Margolis D. Counterregulation of chromatin deacetylation and histone deacetylase occupancy at the integrated promoter of HIV-1 by the HIV-1 repressor YY1 and HIV-1 activator Tat. Mol Cell Biol. 2002;22:2965-73.
48. Williams S, Chen L, Kwon H, Ruiz-Jarabo C, Verdin E, Greene W. NF-kappaB p50 promotes HIV latency through HDAC recruitment and repression of transcriptional initiation. EMBO J. 2006;25:139-49.
49. Tyagi M, Karn J. CBF-1 promotes transcriptional silencing during the establishment of HIV-1 latency. EMBO J. 2007;26:4985-95.
50. Dingwall C, Ernberg I, Gait M, et al. HIV-1 tat protein stimulates transcription by binding to a U-rich bulge in the stem of the TAR RNA structure. EMBO J. 1990;9:4145-53.
51. Garber M, Wei P, Jones K. HIV-1 Tat interacts with cyclin T1 to direct the P-TEFb CTD kinase complex to TAR RNA. Cold Spring Harb Symp Quant Biol. 1998;63:371-80.
52. Jordan A, Bisgrove D, Verdin E. HIV reproducibly establishes a latent infection after acute infection of T cells in vitro. EMBO J. 2003;22:1868-77.
53. Alcamí J, Laín de Lera T, Folgueira L, et al. Absolute dependence on kappa B responsive elements for initiation and Tat-mediated amplification of HIV transcription in blood CD4 T lymphocytes. EMBO J. 1995;14:1552-60.
54. Hayden M, Ghosh S. Signaling to NF-κB. Genes Dev. 2004;18,2195-224.
55. Gilmore T. Introduction to NF-κB: players, pathways, perspectives. Oncogene. 2006;25:6680-4.
56. Sasaki C, Barberi T, Ghosh P, Longo D. Phosphorylation of RelA/p65 on serine 536 defines an I{kappa}B{alpha}-independent NF-{kappa}B pathway. J Biol Chem. 2005;280:34538-47.
57. Zhong H, May M, Jimi E, Ghosh S. The phosphorylation status of nuclear NF-κB determines its association with CBP/p300 or HDAC-1. Mol Cell. 2002;9:625-36.
58. Chen L, Mu Y, Greene W. Acetylation of RelA at discrete sites regulates distinct nuclear functions of NF-κB. EMBO J. 2002;21:6539-48.
59. Yeung F, Hoberg J, Ramsey C, et al. Modulation of NF-kappaB-dependent transcription and cell survival by the SIRT1 deacetylase. EMBO J. 2004;23:2369-80.
60. Bosisio D, Marazzi I, Agresti A, Shimizu N, Bianchi M, Natoli G. A hyperdynamic equilibrium between promoter-bound and nucleoplasmic dimers controls NF-kappaB-dependent gene activity. EMBO J. 2006;25:798-810.
61. Bouwman P, Philipsen S. Regulation of the activity of Sp1-related transcription factors. Mol Cell Endocrinol. 2002;195:27-38.
62. Suske G. The Sp-family of transcription factors. Gene. 1999;238:291-300.
63. Nicolás M, Noé V, Jensen K, Ciudad C. Cloning and characterization of the 5'-flanking region of the human transcription factor Sp1 gene. J Biol Chem. 2001;276:22126-32.
64. Yedavalli V, Benkirane M, Jeang K. Tat and trans-activation-responsive (TAR) RNA-independent induction of HIV-1 long terminal repeat by human and murine cyclin T1 requires Sp1. J Biol Chem. 2003;278:6404-10.
65. Milanini-Mongiat J, Pouysségur J, Pagès G. Identification of two Sp1 phosphorylation sites for p42/p44 mitogen-activated protein kinases:

their implication in vascular endothelial growth factor gene transcription. J Biol Chem. 2002;277:20631-9.
66. Bonello M, Khachigian L. Fibroblast growth factor-2 represses platelet-derived growth factor receptor-alpha (PDGFR-alpha) transcription via ERK1/2-dependent Sp1 phosphorylation and an atypical cis-acting element in the proximal PDGFR-alpha promoter. J Biol Chem. 2004;279:2377-82.
67. Biggs J, Kraft A. The Role of the Smad3 Protein in Phorbol Ester-induced Promoter Expression. J Biol Chem. 1999;274:36987-94.
68. Im S, Rao A. Activation and deactivation of gene expression by Ca2+/calcineurin-NFAT-mediated signaling. Mol Cells. 2004;18:1-9.
69. Hogan P, Chen L, Nardone J, Rao A. Transcriptional regulation by calcium, calcineurin and NFAT. Genes Dev. 2003;17:2205-32.
70. Macián F, López-Rodríguez C, Rao A. Partners in transcription: NFAT and AP-1. Oncogene. 2004;20:2476-89.
71. Karin M, Liu Z, Zandi E. AP-1 function and regulation. Curr Opin Cell Biol. 1997;9:240-6.
72. Weil R, Israel A. T-cell-receptor- and B-cell-receptor mediated activation of NF-κB in lymphocytes. Curr Opin Immunol. 2004;16:374-81.
73. Coiras M, López-Huertas M, Rullas J, Mittelbrunn M, Alcamí J. Basal shuttle of NF-kappaB/I kappaB alpha in resting T lymphocytes regulates HIV-1 LTR dependent expression. Retrovirology. 2007;4:56.
74. Chen Z, Hagler J, Palombella V, et al. Signal-induced site-specific phosphorylation targets I kappa B alpha to the ubiquitin-proteasome pathway. Genes Dev. 1995;9:1586-97.
75. May M, Ghosh S. Signal transduction through NF-kappa B. Immunol Today. 1998;19:80-8.
76. Burstein E, Hoberg J, Wilkinson A, et al. COMMD proteins, a novel family of structural and functional homologs of MURR1. J Biol Chem. 2005;280:22222-32.
77. Maine G, Mao X, Komarck C, Burstein E. COMMD1 promotes the ubiquitination of NF-κB subunits through a cullin-containing ubiquitin ligase. EMBO J. 2007;26:436-47.
78. Gearhart J, Pashos E, Prasad M. Pluripotency redux--advances in stem-cell research. N Engl J Med. 2007;357:1469-72.
79. Satou A, Taira T, Iguchi-Ariga S, Ariga H. A novel transrepression pathway of c-Myc. Recruitment of a transcriptional corepressor complex to c-Myc by MM-1, a c-Myc-binding protein. J Biol Chem. 2001; 276:46562-7.
80. Jiang G, Espeseth A, Hazuda D, Margolis D. c-Myc and Sp1 contribute to proviral latency by recruiting histone deacetylase 1 to the HIV type 1 promoter. J Virol. 2007;81:10914-23.
81. Macián F, Rao A. Reciprocal modulatory interaction between human immunodeficiency virus type 1 Tat and transcription factor NFAT1. Mol Cell Biol. 1999;19:3645-53.
82. Hidalgo-Estévez A, González E, Punzón C, Fresno M. HIV type 1 Tat increases cooperation between AP-1 and NFAT transcription factors in T cells. J Gen Virol. 2006;87:1603-12.
83. Jeang K, Chun R, Lin N, Gatignol A, Glabe C, Fan H. In vitro and in vivo binding of HIV type 1 Tat protein and Sp1 transcription factor. J Virol. 1993;67:6224-33.
84. Kim Y, Kim J, Jung D, et al. Artificial zinc finger fusions targeting Sp1-binding sites and the trans-activator-responsive element potently repress transcription and replication of HIV-1. J Biol Chem. 2005;280:21545-52.
85. Suñé C, Hayashi T, Liu Y, Lane W, Young R, Garcia-Blanco M. CA150, a nuclear protein associated with the RNA polymerase II holoenzyme, is involved in Tat-activated human immunodeficiency virus type 1 transcription. Mol Cell Biol. 1997;17:6029-39.
86. Li X, Green M. The HIV-1 Tat cellular coactivator Tat-SF1 is a general transcription elongation factor. Genes Dev. 1998;12:2992-6.
87. Parada C, Roeder R. A novel RNA polymerase II-containing complex potentiates Tat-enhanced HIV-1 transcription. EMBO J. 1999;18:3688-701.
88. Zhu W, Wada T, Okabe S, Taneda T, Yamaguchi Y, Handa H. DSIF contributes to transcriptional activation by DNA-binding activators by preventing pausing during transcription elongation. Nucleic Acids Res. 2007;35:4064-75.
89. Bourgeois C, Kim Y, Churcher M, West M, Karn J. Spt5 cooperates with HIV type 1 Tat by preventing premature RNA release at terminator sequences. Mol. Cell. Biol. 2002;22:1079-93.
90. Yamaguchi Y, Takagi T, Wada T, et al. NELF, a multisubunit complex containing RD, cooperates with DSIF to repress RNA polymerase II elongation. Cell. 1999;97:41-51.
91. Col E, Caron C, Seigneurin-Berny D, Gracia J, Favier A, Khochbin S. The histone acetyltransferase, hGCN5, interacts with and acetylates the HIV transactivator, Tat. J Biol Chem. 2001;276:28179-84.
92. Dorr A, Kiermer V, Pedal A, et al. Transcriptional synergy between Tat and PCAF is dependent on the binding of acetylated Tat to the PCAF bromodomain. EMBO J. 2002;21:2715-23.
93. Amini S, Mameli G, Del Valle L, et al. p73 Interacts with HIV type 1 Tat in astrocytic cells and prevents its acetylation on lysine 28. Mol Cell Biol. 2005;25:8126-38.
94. Pagans S, Pedal A, North B, et al. SIRT1 regulates HIV transcription via Tat deacetylation. PLoS Biol. 2005;3:e41.
95. Sartorelli V, Puri P, Hamamori Y, et al. Acetylation of MyoD directed by PCAF is necessary for the execution of the muscle program. Mol Cell. 1999;4:725-34.
96. Xie B, Invernizzi C, Richard S, Wainberg M. Arginine methylation of the HIV type 1 Tat protein by PRMT6 negatively affects Tat Interactions with both cyclin T1 and the Tat transactivation region. J Virol. 2007;81:4226-34.
97. Kupzig S, Korolchuk V, Rollason R, Sugden A, Wilde A, Banting G. Bst-2/HM1.24 is a raft-associated apical membrane protein with an unusual topology. Traffic. 2003;4:694-709.
98. Hammonds J, Wang J, Yi H, Spearman P. Immunoelectron microscopic evidence for Tetherin/BST2 as the physical bridge between HIV-1 virions and the plasma membrane. PLoS Pathog. 2010;6:e1000749.
99. Neil S, Zang T, Bieniasz P. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. Nature. 2008;451:425-30.
100. Miyakawa K, Ryo A, Murakami T, et al. BCA2/Rabring7 promotes tetherin-dependent HIV-1 restriction. PLoS Pathog. 2009;5:e1000700.
101. Neil S, Sandrin V, Sundquist W, Bieniasz P. An interferon-alpha-induced tethering mechanism inhibits HIV-1 and Ebola virus particle release but is counteracted by the HIV-1 Vpu protein. Cell Host Microbe. 2007;2:193-203.
102. Jouvenet N, Neil S, Zhadina M, et al. Broad-spectrum inhibition of retroviral and filoviral particle release by tetherin. J Virol. 2009;83:1837-44.
103. Van Damme N, Goff D, Katsura C, et al. The interferon-induced protein BST-2 restricts HIV-1 release and is downregulated from the cell surface by the viral Vpu protein. Cell Host Microbe. 2008;3:245-52.
104. Mitchell R, Katsura C, Skasko M, et al. Vpu antagonizes BST-2-mediated restriction of HIV-1 release via beta-TrCP and endo-lysosomal trafficking. PLoS Pathog. 2009;5:e1000450.
105. Miyagi E, Andrew A, Kao S, Strebel K. Vpu enhances HIV-1 virus release in the absence of Bst-2 cell surface down-modulation and intracellular depletion. Proc Natl Acad Sci USA. 2009;106:2868-73.
106. Fitzpatrick K, Skasko M, Deerinck T, Crum J, Ellisman M, Guatelli J. Direct restriction of virus release and incorporation of the interferon-induced protein BST-2 into HIV-1 particles. PLoS Pathog. 2010;6: e1000701.
107. Perez-Caballero D, Zang T, Ebrahimi A, et al. Tetherin inhibits HIV-1 release by directly tethering virions to cells. Cell. 2009;139:499-511.
108. Habermann A, Krijnse-Locker J, Oberwinkler H, et al. CD317/tetherin is enriched in the HIV-1 envelope and downregulated from the plasma membrane upon virus infection. J Virol. 2010;84:4646-58.
109. Petroski M, Deshaies R. Function and regulation of cullin-RING ubiquitin ligases. Nat Rev Mol Cell Biol. 2005;6:9-20.
110. Goffinet C, Allespach I, Homann S, et al. HIV-1 antagonism of CD317 is species specific and involves Vpu-mediated proteasomal degradation of the restriction factor. Cell Host Microbe. 2009;5:285-97.
111. Mangeat B, Gers-Huber G, Lehmann M, Zufferey M, Luban J, Piguet V. HIV-1 Vpu neutralizes the antiviral factor Tetherin/BST-2 by binding it and directing its beta-TrCP2-dependent degradation. PLoS Pathog. 2009;5:e1000574.
112. Bour S, Perrin C, Akari H, Strebel K. The HIV type 1 Vpu protein inhibits NF-kappa B activation by interfering with beta TrCP-mediated degradation of Ikappa B. J Biol Chem. 2001;276:15920-8.
113. Besnard-Guerin C, Belaïdouni N, Lassot I, et al. HIV-1 Vpu sequesters beta-transducin repeat-containing protein (betaTrCP) in the cytoplasm and provokes the accumulation of beta-catenin and other SCFbetaTrCP substrates. J Biol Chem. 2004;279:788-95.
114. Dubé M, Roy B, Guiot-Guillain P, Binette J, Mercier J, Chiasson A, Cohen E. Antagonism of tetherin restriction of HIV-1 release by Vpu involves binding and sequestration of the restriction factor in a perinuclear compartment. PLoS Pathog. 2010;6:e1000856.