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MINIREVIEW

Regulation of HIV-1 Transcription

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Human immunodeficiency virus type-1 (HIV-1) is a highly pathogenic lentivirus that requires transcription of its provirus genome for completion of the viral life cycle and the production of progeny virions. Since the first genetic analysis of HIV-1 in 1985, much has been learned about the transcriptional regulation of the HIV-1 genome in infected cells. It has been demonstrated that HIV-1 transcription depends on a varied and complex interaction of host cell transcription factors with the viral long terminal repeat (LTR) promoter. The regulatory elements within the LTR interact with constitutive and inducible transcription factors to direct the assembly of a stable transcription complex that stimulates multiple rounds of transcription by RNA polymerase II (RNAPII). However, the majority of these transcripts terminate prematurely in the absence of the virally encoded *trans*-activator protein Tat, which stimulates HIV-1 transcription elongation by interacting with a stem-loop RNA element (TAR) formed at the extreme 5′ end of all viral transcripts. The Tat–TAR interaction recruits a cellular kinase into the initiation–elongation complex that alters the elongation properties of RNAPII during its transit through TAR. This review summarizes our current knowledge and understanding of the regulation of HIV-1 transcription in infected cells and highlights the important contributions human lentivirus gene regulation has made to our general understanding of the transcription process.

HIV-1 Transcription factors Long terminal repeat Tat Chromatin Promoter
Nuclear factor kappa B (NF-κB) Activator protein-1

HUMAN immunodeficiency virus type-1 (HIV-1) is a highly pathogenic lentivirus that causes acquired immune deficiency syndrome (AIDS). HIV-1 permanently infects CD4-positive T cells and macrophages by insertion of a DNA copy of its genome into the host cell chromosome (Fig. 1). After integration of the DNA provirus, a threshold burst of genomic length transcription mediated by RNA polymerase II (RNAPII) is required to complete the viral life cycle and produce progeny virions (89,101). The initial transcription of the HIV-1 genome is controlled by the 5′ long terminal repeat (LTR) and is dependent upon host cell transcription factors binding to an array of DNA *cis*-regulatory elements in the LTR promoter (48,78).

Transcriptional studies of the HIV-1 genome indicate that the 636-base pair HIV-1 LTR promoter can be subdivided into four functional domains: a basal core promoter, which is comprised of a specialized initiator element, a canonical TATA element, and three tandem Sp1 binding sites; an upstream enhancer element containing two adjacent binding sites for the inducible transcriptional activator nuclear factor kappa B (NF-κB); an upstream regulatory region containing elements for cell type-specific expression; and a downstream regulatory region containing secondary enhancer elements and an unstable positioned nucleosome. Together, these elements function in concert to determine the level of HIV-1 transcription in a particular cell type.

In addition to the various DNA elements, the LTR also encodes a novel RNA element, the *trans*-activation response (TAR) element, located immediately downstream of the transcription initiation site. TAR

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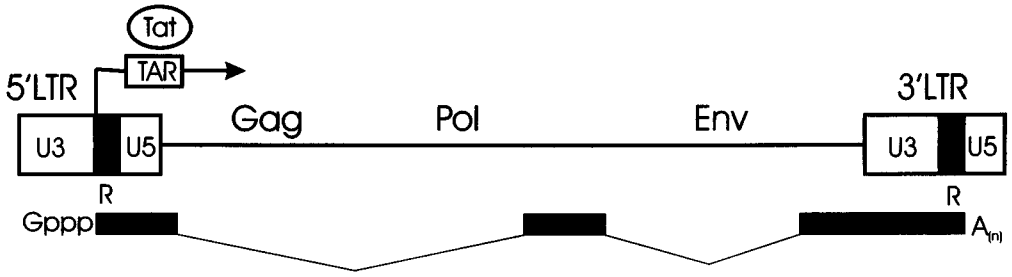

FIG. 1. Structure of the HIV-1 genome. The HIV-1 genome is about 9200 base pairs in length and like all retroviruses contains *Gag*, *Pol*, and *Env* genes, which encode the viral structural proteins. The genome is flanked at the 5′ and 3′ ends by long terminal repeats (LTR) consisting of unique 5′ (U5), unique 3′ (U3), and repeat (R) regions. Transcription, as indicated by the arrow, is initiated at the 5′ LTR and proceeds through the 3′ LTR where transcription termination and polyadenylation occur. Tat is expressed from a multiply spliced transcript (shown below the provirus) and the Tat protein binds a structured RNA element at the 5′ end of all transcripts (TAR).

encodes a 59-nucleotide RNA stem-loop structure that forms a target at the extreme 5′ end of all HIV-1 transcripts for the virally encoded *trans*-activator protein Tat (11,12). Tat is an essential viral regulatory protein that is expressed early in infection from multiply spliced viral mRNAs. By binding to TAR, Tat greatly increases the number of full-length transcripts (75). Tat appears to be critical to bring about the rapid increase in genomic length transcription required for the transition from a quiescent to an active viral infection.

THE HIV-1 PROMOTER

Core Promoter

Although functional studies have shown that the HIV-1 promoter is spread over the entire LTR, only the core promoter is essential for virus transcription (Figs. 2 and 3). The LTR core promoter consists of a TATAA element, an initiator element, and a series of three tandem Sp1 binding sites. Together these elements act in concert to generate basal virus transcription. The core promoter also represents the minimal promoter sequence required for *trans*-activation by Tat.

The TATAA element, located 25 bp upstream of the transcription initiation site, binds the general transcription factor TFIID, which is a large multiprotein complex consisting of the TATA binding protein (TBP) and a number of TBP associated factors (TAF). TAFs function as adapter proteins through protein–protein interactions and are required to mediate the response of transcriptional activator and repressor proteins (187). TBP binding is the first step in the formation of the preinitiation complex and is often the critical rate-limiting step in RNAPII transcribed genes (112). TBP binding to the LTR is essential for the formation of the preinitiation complex and activation of virus transcription (141). TBP also interacts with Tat (83,84,188) and its cooperation with Tat is essential for *trans*-activation of the HIV-1 LTR (113).

Downstream of the TATAA element resides a bipartite initiator element, which determines the transcriptional initiation site (13,116,153,202). The HIV-1 initiator is composed of two elements located between nucleotide positions –6 and +30, both of which are necessary for significant transcription initiation

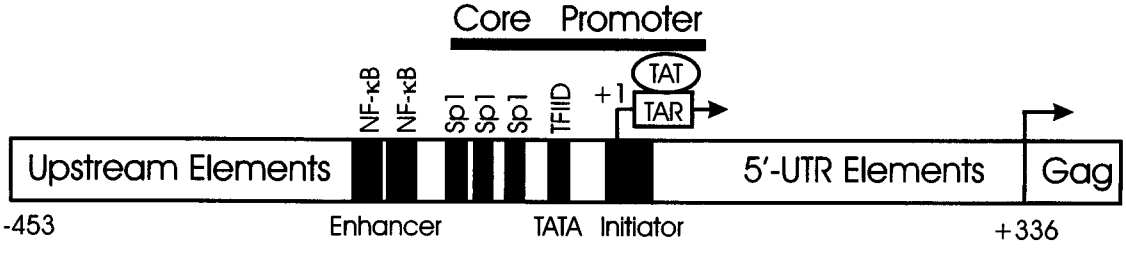

FIG. 2. Stucture of the HIV-1 promoter. The major elements of the HIV-1 promoter are shown. Solid rectangles indicate transcription factor binding sites important for virus transcription. The numbers at the extreme ends of the long terminal repeat (LTR) indicate the nucleotide position relative to the start site of transcription (+1). The four promoter regions important for virus transcription are indicated. The solid bar over the LTR indicates the core promoter, which is essential for basal transcription and Tat *trans*-activation. The core promoter consists of the TATA, initiator, and Sp1 binding sites together with the TAR element. The viral enhancer consists of two binding sites for the transcription factor NF-κB. Tat interacts with TAR, a structured RNA formed at the 5′ end of viral transcripts, to activate HIV-1 transcription.

(202). The HIV-1 initiator differs from other initiator elements, in that the activity of these elements is strictly dependent on the presence and correct position of the TATAA element, suggesting cooperation between the initiator and TATAA elements is critical for proper transcriptional initiation. Furthermore, other TATAA and initiator elements cannot functionally substitute for the HIV-1 elements, indicating that the HIV-1 elements have evolved to specifically promote viral transcription presumably in cooperation with Tat *trans*-activation (10,135).

Immediately upstream of the TATAA element is a GC-rich segment of the promoter containing three binding sites for the ubiquitous transcription factor Sp1 (76). Sp1, a zinc finger transcription factor involved in the transcription of many cellular genes, is critical for both basal transcription and Tat-mediated *trans*-activation of the viral LTR (80,176). Sp1 binds its recognition site through three zinc finger motifs and activates transcription through a Gln-rich hydrophobic activation domain (55). The Sp1 sites cooperate with the TATAA element, and increasing the spacing between the Sp1 sites and the TATAA element abrogates HIV-1 replication (70,159). Sp1 also cooperates with Tat during *trans*-activation (74,196). This interaction with Tat increases the phosphorylation of Sp1 by the DNA-dependent kinase (27). These cooperative interactions indicate that the topological arrangement of the three factors on the HIV-1 promoter are critical for HIV-1 expression, suggesting that Sp1, TFIID, and Tat must correctly interface with each other for optimal virus transcription.

The Sp1 binding sites have also been shown to interact with several other transcription factors. For example, BTEB, a GC binding transcription factor, can bind to the Sp1 motifs and activate the HIV-1 LTR (71). Other members of the Sp1 family can also interact with the Sp1 motifs, but show differential effects (111). Sp4 activates the LTR, while the Sp3 protein represses basal expression of the HIV-1 promoter. Nonetheless, of the Sp1 family members only Sp1 cooperates with NF-κB to activate virus transcription demonstrating a highly specific interaction between NF-κB and the *trans*-acting domain of Sp1 bound to the adjacent site. Embedded within the GC-rich Sp1 binding sites is a thyroid hormone response element, which has been shown to mediate LTR activation by the alpha thyroid receptor (150).

Enhancer Element

Immediately upstream of the Sp1 binding sites are two adjacent binding sites for the inducible transcription factor NF-κB, which function to increase LTR transcription in response to a variety of cellular activation signals (94). Members of the NF-κB family (NF-κB1, RelA, c-Rel, NF-κB2, and RelB) bind as dimers to the HIV-1 enhancer and certain combinations of NF-κB subunits are preferred for Tat *trans*-activation (104). Although binding of NF-κB to the viral enhancer elements results in enhanced expression of HIV-1 in T-cells and macrophages (35,72,92, 120), the NF-κB sites are not essential for HIV-1 replication (25,28,34,97) and appear to serve primarily to increase the rate of HIV-1 transcription during cell activation. The LTR enhancer is activated by proinflammatory cytokines including TNFα, IL-1β, and IL-6 (4,35,41,57,72,99,120,134,146), mitogenic stimuli such as phorbol esters (33), as well as invasion by microorganisms such as *Mycobaterium avium* (50). Antagonistic cytokines such as TGF-β (98) and IL-10 can also stimulate the HIV-1 enhancer under certain conditions and require NF-κB binding activity (7,40). Tat itself can also activate NF-κB forming a positive feedback loop to further enhance and sustain virus transcription (15,29,31).

Enhancer function requires cooperative protein–protein interactions. NF-κB cooperates with the adjacent Sp1 binding site (143) as well as the TATAA element to enhance virus transcription (161). The cooperation with Sp1 is highly specific, involving interactions with the *trans*-acting domain A of Sp1 (111) and the amino-terminal region of RelA (142). The cooperation with the TATAA element is mediated by interactions with TBP and several TAFs that include TAFII250 (58). The HIV-1 enhancer can bind other transcription factors including Ets-1 (8) and E2F-1 (96), which respectively either cooperate with NF-κB to activate transcription synergistically or prevent NF-κB from binding the enhancer downregulating transcription (107).

Upstream and Downstream Regulatory Elements

The LTR regions upstream of the enhancer and downstream of the initiator element contain a variety of transcription factor binding sites that modulate virus transcription (2,48). The upstream region was originally identified as a negative element involved in the downregulation of HIV-1 expression (110, 191), but more recently it has been shown to be capable of both up- and downregulating virus expression depending on the cell type and activation state of the cell. For example, several upstream C/EBP and AP-1 binding sites have been shown to mediate HIV-1 expression in some cell types but not others (22,63–65). Additional binding sites for Ets, LEF-1, COUP, and NF-AT within this upstream region may also contribute to the regulation of HIV-1 transcription in lymphocytes (78).


-453 TGGAAGGGCTAATTTGGTCCCAAAAAAGACAAGAGATCCTTGATCTGTGGATCTACCACA
C/EBP
-393 CACAAGGCTACTTCCCTGATTGGCAGAACTACACACCAGGGCCAGGGATCAGATATCCAC
COUP/AP-1
-333 TGACCTTTGGATGGTGCTTCAAGTTAGTACCAGTTGAACCAGAGCAAGTAGAAGAGGCCA
COUP/AP-1
AP-1
-273 AATAAGGAGAGAAGAACAGCTTGTTACACCCTATGAGCCAGCATGGGATGGAGGACCCGG
GRE
AP-1
-213 AGGGAGAAGTATTAGTGTGGAAGTTTGACAGCCTCCTAGCATTTCGTCACATGGCCCGAG
C/EBP
USF
-153 AGCTGCATCCGGAGTACTACAAAGACTGCTGACATCGAGCTTTCTACAAGGGACTTTCCG
Ets-1
LEF-1
C/EBP
NF-κB
-93 CTGGGGACTTTCCAGGGAGGTGTGGCCTGGGCGGGACTGGGGAGTGGCGAGCCCTCAGAT
NF-κB
Sp1
Sp1
Sp1
U3
R
-1
+1
-33 GCTACATATAAGCAGCTGCTTTTTGCCTGTACTGGGTCTCTCTGGTTAGACCAGATCTGA
TFIID
Oct-1
+28 GCCTGGGAGCTCTCTGGCTAACTAGGGAACCCACTGCTTAAGCCTCAATAAAGCTTGCCT
NF-κB
R
U5
+88 TGAGTGCTCAAAGTAGTGTGTGCCCGTCTGTTGTGTGACTCTGGTAACTAGAGATCCCTC
AP-1/CREB/ATF
AP-1
C/EBP
U5
+148 AGACCCTTTTAGTCAGTGTGGAAAATCTCTAGCAGTGGCGCCCGAACAGGGACTTGAAAG
AP-1/CREB/ATF
C/EBP
NF-AT
IRF
+208 CGAAAGTAAAGCCAGAGGAGATCTCTCGACGCAGGACTCGGCTTGCTGAAGCGCGCACGG
SD
+268 CAAGAGGCGAGGGGCGGCGACTGGTGAGTACGCCAAAAATTTTGACTAGCGGAGGCTAGAA
Sp1
Sp1
Gag Protein
+328 GGAGAGAG ATG GGT GCG AGA
Met Gly Ala Arg

Recent studies indicate the sequences downstream of transcription in the transcribed 5′-untranslated leader region (5′-UTR) are also important for viral expression (2,100,103,154,183). In vivo and in vitro footprinting studies have demonstrated that host cell transcription factors interact extensively with the 5′-UTR (20,38,114). Downstream binding sites for NF-1 and LBP-1 were originally identified by Jones and colleagues (77), but more than a dozen different regulatory elements have now been identified within the 5′-UTR that bind several distinct families of transcription factors (38,79,183). These sequence elements include binding sites for both constitutive (i.e., Sp1) and inducible transcription factors (i.e., AP-1, NF-κB, IRF, NF-AT). Several have been shown to transmit activation signals to the LTR (147–149,155) and some have been shown to be required for efficient HIV-1 expression and replication in T cells (183). In particular, several AP-1 binding sites, which can also bind CREB/ATF proteins, have been shown to mediate cellular activation signals transmitted through the cAMP-dependent protein kinase A (PKA) pathway (147,149). The 5′-UTR also interacts with an unstable positioned nucleosome (Nuc-1) that is displaced during chromatin remodeling of the HIV-1 promoter (184).

Taken together these studies suggest responsive elements in the 5′-UTR may comprise a downstream enhancer domain that can act independent of, or in concert with, the upstream enhancer and promoter to ensure maximal activation of HIV-1 gene expression. Acquisition of a downstream enhancer could broaden the viral response to cellular activation signals and activate LTR transcription in response to a wide variety of cell activation signals. The downstream enhancer could also assist in the displacement of the unstable nucleosome and in the remodeling of proviral chromatin structure.

INDUCIBLE TRANSCRIPTION FACTORS

bZip Transcription Factor Family

Recent studies indicate transcription factors of the basic-leucine zipper (bZip) family play important roles in the regulation of HIV-1 transcription (2,64). bZip transcription factors include the AP-1 (Jun and Fos), CREB/ATF, and C/EBP families. These factors are nuclear phosphoproteins that combine to form homo- or heterodimers through their leucine zipper domains (82). The downstream region of the HIV-1 LTR contains three functional AP-1 binding sites that are important for virus transcription and replication (38,154,183). These AP-1 sites bind purified c-Jun in vitro (38,154), but not purified CREB/ATF protein (149), demonstrating that these elements are genuine AP-1 binding sites.

Interestingly, supershift analyses using nuclear protein extracts indicate the AP-1 complexes are composed of cFos and JunD, as well as CREB, ATF-1, and ATF-2 (149,155), suggesting CREB/ATF proteins bind to the AP-1 sites in cells as cross-family heterodimers with the AP-1 subunits. Certain AP-1 and CREB/ATF family proteins have been shown to cross-dimerize in vitro (59). For example, cJun and ATF-2 dimerize to bind a nonconsensus AP-1 binding site in the c-jun gene promoter (182). Consistent with the cross-dimerization between AP-1 and CREB/ATF subunits, the AP-1 sites were found to mediate cooperativity between TNFα and cholera toxin, a potent activator of the cAMP/PKA pathway (147).

AP-1 binding sites have also been identified in the upstream regulatory region, where they may play a role in cell type-specific expression of HIV-1. A variant AP-1 binding site was recently identified in neurotropic stains of HIV-1 that interact with Jun and Fos (22). AP-1 binding to the variant site is cell type specific because Jun and Fos were detected only with nuclear extracts from glial and HeLa cells and not from neuronal and Jurkat T-cells. Functional analysis further revealed that the variant AP-1 binding site is able to mediate AP-1-dependent transcriptional activation in glial but not neuronal cells.

The LTR also contains several C/EBP binding sites upstream of the enhancer (179,180) that have also been shown to be important for cell type-specific expression of the virus (63–65). The C/EBP sites in the HIV-1 LTR are critical for HIV-1 expression in macrophages but not T cells (63–65), whereas C/EBP inhibits HIV-1 expression in brain-derived cells (124). The C/EBP binding site can also cooperate with the adjacent NF-κB binding site to enhance HIV-1 gene expression (158). This transcriptional synergy may be mediated by cooperative binding of the factors to the HIV-1 promoter because C/EBP has

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FIG. 3. Transcription factor binding sites within the HIV-1 promoter. The nucleotide sequence of the 5′ long terminal repeat of HIV-1 (NL4-3) is shown. The numbers to the left indicate the nucleotide positions relative to the transcription initiation site at the U3–R boundary. Major transcription factor binding sites within the LTR are in bold face type and underlined. The boundaries of the U3, U5, and R regions are indicated by arrows. The translation of the first four amino acids of the Gag protein is shown. SD denotes the 5′ slice site donor.

been shown to physically interact with transcription factors of the NF-κB family (172).

NF-κB Family

NF-κB is a family of inducible proteins that bind as dimers to each of the κB enhancer sites (5). In resting cells, NF-κB resides in the cytoplasm complexed with an inhibitor protein, I-κB (197). In response to cell activation signals, I-κB becomes phosphorylated by a specific kinase and targeted for proteolysis by the 26S proteasome (32,121). Proteolytic degradation of I-κB permits NF-κB to translocate to the nucleus and interact with its recognition sites in the viral LTR. *trans*-Activation of the LTR is conferred primarily through the phosphorylation of the RelA subunit of the NF-κB complex (60,160).

NF-κB binds the HIV-1 enhancer and cooperates with other proteins through specific protein–protein interactions to stimulate HIV-1 transcription (55, 142,143). Recently, a NF-κB binding site was identified in the 5′-UTR that cooperates with the HIV-1 enhancer (115), demonstrating for the first time that upstream and downstream transcription factors can functionally cooperate to activate HIV-1 transcription. NF-κB has also been detected binding to the viral initiator element, suggesting NF-κB may regulate HIV-1 expression not only from the enhancer but also from the initiator (125).

The HIV-1 LTR also contains several NF-AT binding sites. NF-AT is an inducible transcription factor related to the NF-κB family that is regulated by the calcium/calmodulin-dependent phosphatase calcineurin (151). Calcineurin controls the translocation of NF-AT proteins from the cytoplasm to the nucleus of activated cells by interacting with an N-terminal regulatory domain conserved in the NF-AT family. NF-AT is present in most immune cells and can physically interact with AP-1 at NF-AT/AP-1 composite binding sites such as those found in the IL-2 and IL-4 promoters (175). The NF-AT binding site in the HIV-1 5′-UTR was originally identified by DNase I footprinting as an AP-3-like binding site (38) and was subsequently shown to be a NF-AT binding site using antisera raised against NF-AT in gel supershift assays (183). The NF-AT binding site has sequences immediately downstream that resemble the NF-AT/AP-1 composite site in IL-4, suggesting the HIV-1 site may be a composite site in which NF-AT and AP-1 may bind cooperatively, a feature of many cytokine gene promoters. The NF-AT binding sites in the upstream region of the LTR also affect HIV-1 transcription (118,129).

Class II trans-*Activator*

We recently showed that the MHC class II *trans*-activator CIITA activates HIV-1 transcription (Fig. 4). CIITA, a 124-kDa protein first identified by Mach and colleagues in 1993 (170), is required for transcriptional activation of the major histocompatibility complex (MHC) class II genes (23). Mutation of CIITA causes bare lymphocyte syndrome, a combined immunodeficiency disease characterized by the lack of MHC class II gene expression (19,203). The CIITA protein, which contains a strong acidic activation domain, does not bind directly to DNA elements involved in class II expression. Rather, it acts as a transcriptional coactivator integrating interactions with DNA binding proteins such as RFX and CREB with the basal transcriptional machinery (24,42,126, 152). Recent reports demonstrated that CREB binding protein, CBP, also physically interacts with CIITA to synergistically induce transcription of MHC class II genes (43,93). Transfection studies using a human CIITA expression plasmid and HIV-1 provirus or LTR reporter constructs demonstrated an increased stimulation in HIV-1 transcription in response to increasing amounts of CIITA (Fig. 4). These data are the first to suggest that CIITA plays a role in the activation of HIV-1 transcription in infected cells and may explain why HIV-1 is efficiently expressed in class II-positive, but not class II-negative, cells (M. Saifuddin, G. T. Spear, and K. A. Roebuck, unpublished results).

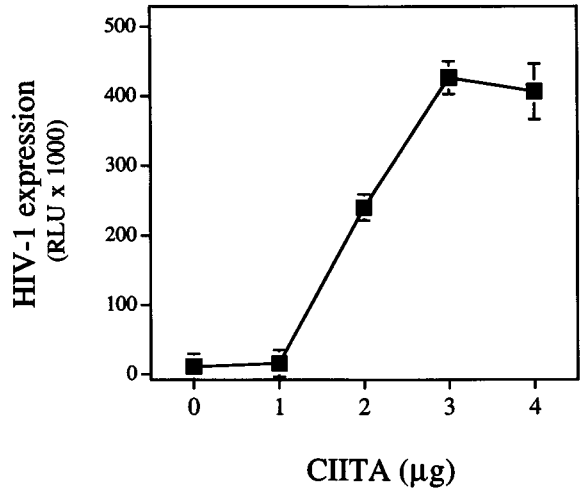

FIG. 4. Class II *trans*-activator CIITA activates HIV-1 expression. HeLa cells were cotransfected with HIV-1 provirus (pNL4-3-LucE⁻) and increasing amounts of the class II *trans*-activator (CIITA) expression plasmid (0–4 μg). At day 3 posttransfection cell lysates were analyzed for luciferase activity. Note that CIITA increases HIV-1 provirus expression in a dose-dependent manner.

Repressive Transcription Factors

In latently infected cells, HIV-1 transcription is minimal and may be actively repressed by a closed chromatin structure and/or binding of repressor proteins. Several DNA binding proteins have been shown to repress HIV-1 transcription and could play a critical role in viral latency. Recently, an Oct-1 binding site was identified between the TATAA and initiator elements that mediated repression of both basal and Tat-induced HIV-1 transcription (106). LBP-1, which binds to multiple sites within the initiator element, has also been shown to repress HIV-1 transcription (85) by itself or in cooperation with YY1 (117,157), suggesting the initiator element may be important for maintaining latent provirus expression in quiescent cells (85,139).

Other Transcription Factors

Computer-generated analyses of the HIV-1 LTR using the TRANSFACT matrix table database and the TFSEARCH program (61,62) revealed a number of other potential transcription factor binding sites within the HIV-1 promoter region. Many of these factors are predicted to interact with the HIV-1 LTR. Of note, we found several binding sites within the core promoter for the myeloid zinc finger (MZF-1) transcription factor. MZF-1 encodes a transcription factor, which is expressed in myeloid cells and recognizes GC-rich sequences (67). MZF-1 contains 13 C_2H_2 zinc fingers arranged in two domains, both of which bind DNA (127).

The promoter search also revealed binding sites for GATA binding transcription factors (GATA-1, -2, and -3). GATA-1 was originally identified as an erythroid-specific factor but is present in most hematopoietic cells including T cell and macrophages. Binding sites for the tumor suppressor protein p53 were also noted. The wild-type p53 protein has been reported to suppress HIV-1 transcription, while oncogenic forms of the protein activate virus transcription (174). The promoter search further revealed several binding sites for inducible transcription factors, including Egr-2, STATx, ELK-1, and HSF-1. It will be of interest to determine whether any of these transcription factors functionally contribute to the activation and regulation of HIV-1 transcription in infected cells.

CHROMATIN REMODELING

After integration into the host chromosome, the HIV-1 provirus is packaged into a chromatin structure that must undergo a defined remodeling process involving histone acetylation prior to activation of LTR transcription [reviewed in (123)]. Structural studies on integrated templates in vivo have identified a set of positioned nucleosomes within the HIV-1 LTR (Fig. 5) (185). An unstable nucleosome (Nuc-1), located at the 5′ end of the 5′-UTR between position +10 and +155, is rapidly displaced in response to TNFα or PMA stimulation (184,186). The disruption of Nuc-1 during transcriptional activation of the HIV-1 LTR promoter produces a large open chromatin region encompassing the upsteam promoter and most of the 5′-UTR. Similar chromatin structures can be duplicated in vitro when chromatin assembly occurs in the presence of Sp1 and NF-κB transcription factors (194).

Transcription factor binding to the 5′-UTR may facilitate Nuc-1 disruption because a DNase I hypersensitive site is associated with downstream transcription factor binding sites and mutation of these sites functionally inactivates the HIV-1 LTR when it is constrained in a chromatin configuration (36). Analysis of the inactive LTR showed that the 5′-UTR was resistant to nuclease digestion (36). The downstream AP-1 binding sites, which partially overlap Nuc-1, may promote disruption of Nuc-1 by binding AP-1 and/or CREB/ATF during cellular activation. AP-1 and CREB transcription factors are capable of altering chromatin structure (130). Phosphorylation of CREB on Ser 119 recruits the CBP coactivator, a histone acetyl transferase that alters chromatin structure by modifying histones (6,56,131). Acetylation of HIV-1 associated histones results in nucleosome remodeling (168) and the displacement of Nuc-1, which in turn permits the activation of LTR transcription (165,184).

The κB enhancer together with the upstream binding transcription factors LEF-1 and Ets-1 also contribute to remodeling of the LTR chromatin structure (140,166,169) and can also recruit CBP (49). LEF-1 is a T-cell-specific architectural transcription factor that enhances assembly and function of enhancer complexes by bending DNA (53,54,108). Assembly of positioned nucleosomes required the prebinding of both NF-κB and Sp1 to the HIV-1 LTR (37,195). Because transcriptional activation of latent provirus is associated with an open chromatin structure in the 5′-UTR (20,185,186), inducible transcription factors such as AP-1 and NF-AT may function to disrupt Nuc-1 independently of, or in concert with, NF-κB binding at the upstream enhancer sites. Unstable nucleosomes such as Nuc-1 can also facilitate transcription by providing the appropriate scaffolding to bring transcription factors bound at distant sites into

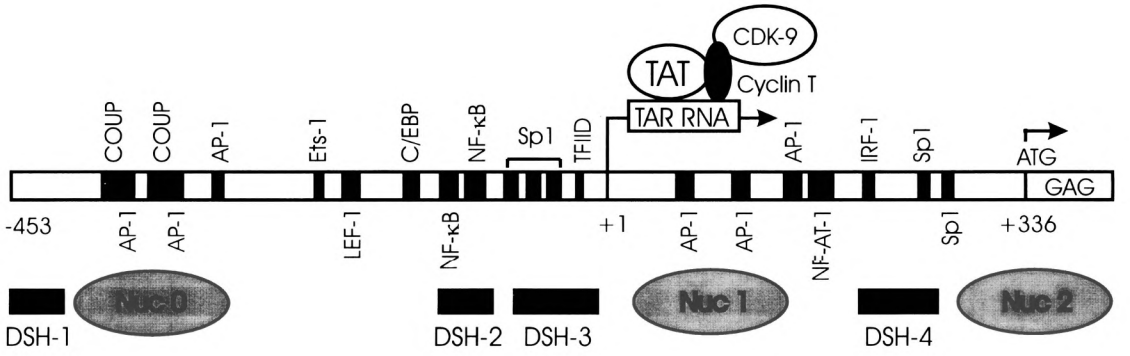

FIG. 5. Nucleosome structure of the HIV-1 promoter. The 5′ end of the HIV-1 provirus is depicted showing the viral long terminal repeat (LTR) and the start of the *Gag* gene. The nucleotide positions are shown relative to the start site of transcription (+1). The *trans*-activation response (TAR) element, present at the 5′ end of all viral transcripts, is indicated as an open rectangle within the mRNA transcript (arrow). An arrow above the *Gag* coding region indicates start of the Gag protein. The relative binding position of the major host cell transcription factors is indicated by solid rectangles along the provirus. The location of four DNase I hypersensitive sites (DHS) are indicated by solid rectangles below the provirus. The three positioned nucleosomes (Nuc) are indicated below the provirus as gray ovals covering 146 base pairs each.

juxtaposition. For example, Nuc-1 could bring the upstream promoter in close proximity to the downstream enhancer, facilitating protein–protein interactions to occur between the various transcription factors bound at these remote sites. In this regard, the upstream and downstream NF-κB binding sites can functionally cooperate (115), and NF-κB can physically interact with AP-1 to activate LTR transcription (171). Tat may also play a role in chromatin remodeling because it can form ternary complexes with histone acetyltransferases (9) and recruit CBP to the HIV-1 promoter (119).

VIRAL TRANSCRIPTION FACTORS

Tat

At least two virally encoded proteins also contribute to HIV-1 transcription: Tat and Vpr. Tat is expressed early in the viral life cycle and is essential for viral replication. Although Tat *trans*-activation has been studied extensively, the precise mechanism of Tat *trans*-activation is still not fully understood. Accumulating evidence indicates that Tat function is similar to that of cellular activator proteins, with the exception that its target is RNA rather than a DNA sequence. Protein fusion experiments have been used to demonstrate the similarities between Tat and conventional transcriptional activators (156). These studies have shown that Tat, when fused to the appropriate DNA binding domain, can function from upstream or downstream DNA binding sites (167). However, in contrast to DNA activators, Tat cannot interact with its binding site until after TAR RNA has been transcribed. Therefore, as the rate of transcription increases so does the number of Tat binding sites, resulting in an increase in the concentration of Tat near the LTR promoter. This unique feature of Tat *trans*-activation may provide a way for the virus to bring about maximal expression of its genome very rapidly, and thereby trigger progression from a quiescent to an active viral infection.

Vpr

In addition to Tat, the 96-amino acid viral protein Vpr has recently been shown to activate HIV-1 transcription (173). Vpr is a virion-associated regulatory protein that has been shown to interact with TFIIB and Sp1 (1,189), and cooperates with the coactivator CBP to activate HIV-1 transcription (39a). Recently, Vpr was shown to contain a functional motif present in cellular nuclear receptor coactivators. Mutations in this region make Vpr a dominant negative inhibitor and abrogate the ability of Vpr to activate transcription (90). Thus, Vpr appears to function as a coactivator protein in concert with the coactivator CBP in the activation of HIV-1 transcription.

Tat trans-*Activation*

Early studies suggested that Tat increases the rate of transcription initiation as well as elongation (16, 86). However, more recent studies indicate that Tat functions primarily to increase the rate of transcription elongation rather than initiation of viral transcription (47,78), most likely through alteration in the transcriptional elongation properties of RNAPII (30, 198). Apparently, the two processes are coupled in HIV-1 transcription with the initiation of transcription being mediated primarily by DNA binding cellular factors and elongation of transcription being dependent on the TAR RNA binding of Tat (105,163).

In contrast to other TATAA element-containing promoters, it has recently been shown that transcription of the HIV-1 promoter has a major rate-limiting step subsequent to the recruitment of TBP to the pro-

moter (199). Thus, in the absence of Tat, the majority of viral transcripts are terminated prematurely at approximately position +59, whereas in the presence of Tat the majority of transcripts reach genomic length. Virus transcription terminates early in response to a DNA element known as the inducer of short transcripts (IST) (81,144,181). IST is a bipartite element in the R region (−5 to +26 and +40 to +59) that binds the cellular factor FBI-1, which associates with Tat, suggesting that Tat repression of IST is mediated through interactions between the two factors (128). The R region of the LTR appears to be a rather complex regulatory region containing both RNA and DNA elements important for the formation of transcription complexes that have different elongation properties (164). Indeed, the HIV-1 LTR may direct the formation of two distinct transcription complexes, only one of which is regulated by Tat (109).

Tat-Associated Factors

Tat *trans*-activation of the HIV-1 LTR requires coactivators that are distinct from those required for basal transcription (177). A number of cellular factors that bind Tat have been identified (102,132, 178,200,205). Recently, Tat has been shown to recruit a 600-kDa cellular protein complex (P-TEFb) containing the cyclin-dependent serine-threonine kinase T1 and CDK9 kinase (73), which phosphorylates the carboxy-terminal domain (CTD) of the large subunit of RNAPII, a prerequisite for transcription elongation (44–46,190,204,206). The CTD of RNAPII has been shown to be essential for Tat *trans*-activation (26,133). There is evidence that Tat and P-TEFb become attached to the elongating transcription complex during its transit through TAR (87,88,145). Tat recruitment of the P-TEFb complex into the transcription initiation–elongation complex, which can also be recruited by DNA binding proteins (192), has been proposed to trigger the transition from transcription initiation to active elongation (138) and is the basis for the species specificity of Tat function (14). Thus, the Tat–TAR interaction has evolved as an efficient way to recruit essential cellular cofactors to the HIV-1 promoter and properly convey them to the transcription initiation–elongation complex.

Exogenous Tat trans-*Activation Effects*

An intriguing feature of Tat is its ability to be released and taken up by cells (39,91). Exogenous Tat had been shown to produce a variety of cellular effects including cell activation and angiogenesis (21, 66,69,136,193). In particular, Tat can activate cellular gene expression through its effects on signal transduction pathways (17,18,122,201) and transcription factors (29,52). For example, Tat has recently been reported to activate AP-1 through the Jun-N-terminal kinase (JNK) (95). Tat can also activate NF-IL-6 (3) and NF-κB through induction of cytokines (137) and can increase CREB activity through stimulation of Ser phosphorylation (51). Tat can even upregulate the expression of the HIV-1 co-receptors, CCR5 and CXCR4 chemokine receptors, making cells more susceptible to infection (68,162).

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, HIV-1 transcription is highly regulated involving a large number of host cell transcription factors, two virally encoded regulatory proteins, and a complex interplay between these cellular and viral factors. It is the intracellular concentrations and activities of these factors along with their DNA–protein and protein–protein cooperative interactions on the HIV-1 promoter that ultimately determine the specific expression pattern of HIV-1 in any given cell type or in response to any particular cellular activation signal. HIV-1 has acquired this large array of regulatory elements most likely to ensure its expression in a wide range of cell types and in response to a large variety of cell activation signals.

Although HIV-1 is one of the most thoroughly studied transcription units in biology, it continues to attract researchers with its fascinating regulatory mechanisms. Indeed, HIV-1 has become an invaluable research tool not only for our understanding of the unique features of lentivirus transcription but also for our understanding of transcriptional mechanisms in general. However, a more complete understanding of HIV-1 transcription will require elucidation of the precise mechanism of Tat function. It will also require a more complete description of the host cell transcription factors involved in HIV-1 transcription and their specific role in chromatin remodeling of the HIV-1 promoter. Given the importance of HIV-1 as a human pathogen, continued molecular studies on the regulation of HIV-1 transcription will be critical for the future hope of developing effective therapeutic strategies and identifying critical targets suitable for antiviral intervention.

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