T cell activation and regulation of HIV-1: Same effectors with distinct outcomes

Jean-François Fortin MSc, Benoit Barbeau PhD, Gilles A Robichaud MSc, Michel J Tremblay PhD


The molecular mechanisms that regulate the function of the immune system and human immunodeficiency virus type-1 (HIV-1) gene expression are diverse and complicated. However, replication of HIV-1 is controlled by many of the same regulatory signals that play a crucial role in the transcriptional regulation of the immune system. For example, the viral promoter, as is the case for the immune system, is subject to complex regulation by combinations of cellular transcription factors that may quantitatively and/or qualitatively differ depending on cell types (eg, macrophages versus T lymphocytes) and cell states (eg, undifferentiated versus differentiated or quiescent versus activated). The present review discusses the regulation of HIV-1 gene expression by nuclear factor-kappa B and nuclear factor of activated T cells, and proposes that selective interference of these two cellular transcription factors may be a route to abrogate virus replication without disrupting normal cellular functions. A better understanding of the regulation of HIV-1 gene expression is of utmost importance for the design of molecular approaches that will effectively abrogate virus replication and, ultimately, disease progression.

Key Words: Activation; HIV-1; T cell; Transcription

Activation des lymphocytes T et régulation du VIH-1 : Les mêmes effecteurs avec des résultats différents

RÉSUMÉ: Les mécanismes moléculaires qui règlent la fonction du système immunitaire et de l'expression des gènes du virus de l'immunodéficience humaine de type 1 (VIH-1) sont divers et complexes. Cependant, la réplication du VIH-1 est contrôlée par plusieurs des mêmes signaux régulateurs qui jouent un rôle primordial dans la régulation de la transcription du système immunitaire. Par exemple, le promoteur viral, comme c'est le cas du système immunitaire, est sujet à une régulation complexe par des combinaisons de facteurs de transcription cellulaire qui peuvent quantitativement et/ou qualitativement varier selon les types de cellules (par exemple, les macrophages par rapport aux lymphocytes T) et les états des cellules (par exemple, indifférenciées par rapport à différenciées ou quiescentes par rapport à activées). La présente synthèse décrit la régulation de l'expression des gènes du VIH-1 par le facteur de transcription NF-Kappa B et le facteur de transcription des lymphocytes T activés (NFAT), et émet l'hypothèse que l'interférence sélective de ces deux facteurs de transcription cellulaire pourrait être une voie pour abroger la réplication virale sans perturber les fonctions cellulaires normales. Une meilleure compréhension de la régulation de l'expression des gènes du VIH-1 revêt la plus grande importance pour la conception d'approches moléculaires qui aboliront réellement la réplication virale et, en fin de compte, la progression de la maladie.
To be specific and effective, T cell activation must be strictly regulated. Many different interactions are required for efficient activation. Although by itself the T cell receptor (TCR)/CD3 complex can induce a cascade of intracellular events, it also needs coreceptors such as CD4 and CD28 for proper T cell activation to proceed (1). The consequences of these interactions are the generation of numerous intracellular messengers and the activation of various signalling pathways, leading to the induction of various transcription factors. These factors ultimately affect the transcription of many different genes involved in the regulation of the immune response, such as cytokines and their receptors, adhesion molecules or chemokines.

One of the earliest events occurring after ligation of the TCR is the activation of the src-family tyrosine kinases p56^ck and p59^6k (2,3). Activated p56^ck then phosphorylates tyrosine residues of the immunoreceptor tyrosine-based activation motifs (ITAM) of the CD3 zeta chain, rendering these tyrosyl phosphorylated ITAM privileged targets for the SH2 domains of the ZAP-70 tyrosine kinase. Upon its phosphorylation by p56^ck, CD3 zeta-targeted ZAP-70 activates various cascades by the phosphorylation of still ill-defined substrates (4).

Many of the proximal events induced following T cell activation involve phosphorylation of proteins on tyrosine residues. Indeed, an increase in the level of intracellular phosphotyrosine content is a hallmark of T cell activation (5). There is, thus, a fairly good correlation between the level of intracellular phosphotyrosine events and the degree of cellular activation. This relation also stands for the human immunodeficiency virus type-1 (HIV-1) because its replication is highly associated with the level of tyrosine phosphorylation (6).

Because tyrosine phosphorylation is an important mediator of T cell activation, the protein tyrosine phosphatases (PTP), responsible for the removal of phosphates on tyrosine residues, are very important modulators of T cell activation cascades (7). In fact, these enzymes are generally seen as inhibitors of T cell activation, exemplified by the study dealing with the PTP SHP-1 (8).

Because the level of tyrosine phosphorylation is regulated by the tight equilibrium between the action of protein tyrosine kinases (PTK) and PTP, PTP inhibitors are widely used as pharmacological agents capable of inducing high levels of tyrosine phosphorylation in T cells (9). In fact, treatment of T cells with PTP inhibitors results in T cell activation that resembles in many aspects what is observed following TCR stimulation, justifying the use of these agents to study T cell activation (9-11).

Activation of T cells is of the utmost importance for the immune system to mount an adequate response. Ironically, activation of T cells results in an effective replication of the causal agent of AIDS, the HIV-1 virus, from which the final outcome is death (12). This tragic issue is preceded by a progressive loss of immune competence, followed by the profound immunodeficiency that characterizes this terrible disease (13). This review focuses on how HIV-1 is able to coordinate its replication with the cellular activation, how it is able to take advantage of the cellular factors needed for a strong immune response and how it uses them in its favour to destroy the immune system. An overview of the HIV-1 life cycle is provided. The genomic region responsible for HIV-1 transcriptional regulation, the long terminal repeat (LTR), followed by the enhancer region, where the binding sites for two of the most powerful cellular transcription factors regulating HIV-1 LTR activity, the nuclear factor-kappa B (NF-κB) and nuclear factor of activated T cell (NFAT) proteins, is found, is discussed in more detail. Current knowledge on the regulation of transcriptional activation by these factors in the context of both T cell genes and HIV-1 LTR is elaborated on, and future work needed in the fields and therapeutic possibilities regarding HIV-1 transcriptional regulation are discussed.

THE HIV-1 LIFE CYCLE

Even though HIV-1 has been isolated and characterized as the etiological agent causing AIDS since 1983, details concerning its mechanism of entry have, until recently, remained poorly known. Since 1984, CD4 has been known to be essential for the attachment of HIV-1 on the surface of target cells, but not sufficient to allow entry (14,15). In the past two years, HIV-1 research has been struck by a whirlwind of optimism generated by the discovery of the long sought cellular coreceptor (16,17). These coreceptors are chemokine receptors, members of the large family of seven-transmembrane G-linked proteins. CCR5 is the main coreceptor used by macrophage-tropic strains of HIV-1, while CXCR4 is mainly used by T-tropic strains (18). Once in the cytoplasm, the viral RNA genome harboured in the nucleocapsid then proceeds through retrotranscription, which results in the formation of a preintegration complex. This complex is then targeted to the nucleus, where the virus-encoded integrase is able to randomly insert the double-stranded viral DNA into one of the cell's chromosomes. Once integrated, the viral DNA is called a provirus. From this step, HIV-1 replication is intimately linked with the cell's fate—HIV-1 transcription depends on the cellular activation state. HIV-1 transcription results in the production of one long mRNA that is reduced by multiple splicing events. The first mRNAs translated are multiply spliced mRNA-encoding early phase proteins, which act to increase the transcription rate of the provirus and to favour the expression of structural, late genes. The late genes code for structural proteins and viral enzymes. The envelope proteins are targeted to the cell surface, while the nucleocapsid and enzyme precursors are targeted to the inner leaflet of the cytoplasmic membrane. By homotypic aggregation, these precursors bud out from the cell. During this step, the forming virions acquire a part of the cellular membrane along with their envelope proteins. The viral life cycle is completed by the cleavage of the precursors by the viral protease, leaving mature virions ready for another cycle of infection.

THE HIV-1 LTRs

At each end of its genome, HIV-1 possesses LTR domains that bear the regulatory elements of this retrovirus. In addition to their important role in the reverse transcription pro-
T cell activation and HIV-1 replication

**Figure 1** Architecture of human immunodeficiency virus type-1 (HIV-1) long terminal repeat (LTR). LEF, Lymphoid-enhancer binding factor; NFAT, Nuclear factor of activated T cells; NF-κB, Nuclear factor-kappa B; NRE, Negative regulatory element; TAR, Trans-activating response; TBP, TATA-box binding protein; Adapted from references 22, 23

In the context of the HIV-1 LTR, the κB-binding complexes having the maximal responding region of the LTR and is primarily responsible for the transcriptional increase observed following T cell activation (19). The HIV-1 enhancer is composed of two NF-κB sites separated by an AP-2 site, which has recently been demonstrated to be a binding site for NFAT (23). NF-κB and NFAT are considered to be the principal effectors linking T cell activation and HIV-1 replication. The HIV-1 LTR is, thus, composed of various motifs found in the regulatory regions of genes induced after activation of a T cell such as interleukin (IL)-2 (19). A direct result of the rather complex architecture of the LTR is an intimate link between T cell activation and HIV-1 transcription due to the overlapping requirement between T lymphokine gene expression and LTR transactivation (24, 25). As in HIV-1, NF-κB and NFAT are similarly important regulators of genes modulated by T cell activation.

**NF-κB**

NF-κB is an eukaryotic transcription factor that was first discovered in 1986 (26). Since then, it has been shown that this factor is present in virtually all cell types (27). NF-κB is a dimer of the REL family of proteins (28). In humans, this family is composed of five members: RelA (p65), RelB, c-Rel, NF-κB1 (p100/p52) and NF-κB2 (p105/p50). Each member contains an N-terminal domain of 500 amino acids known as the rel homology domain (RHD) (27). In the context of the HIV-1 LTR, the κB-binding complexes having the maximal...
transcriptional activation are essentially p50/p65 heterodimers. NF-κB has been attributed with various functions in the development of the immune system. An interesting observation is that, in addition to all previous findings, NF-κB seems to be implicated in the regulation of apoptosis, known as programmed cell death. Indeed, three independent studies have demonstrated that the inhibition of the cascade leading to the activation of NF-κB led to a higher level of apoptosis (29-31). These results were confirmed by the use of gene knock out mice and different cell lines (32).

A tremendous amount of information has been gathered since then, and the mechanism of activation of the NF-κB factor, although complex, has been well described. NF-κB heterodimers, frequently composed of the subunits p50 and p65, are usually retained in the cytoplasm as an inactive complex. The main inhibitory protein of this complex, initially identified as IκB (33), is yet another family of proteins and contains several members, IκBα being the most studied and, thus, the best understood. It is known that IκBα interacts in the cytoplasm with the NF-κB complex and masks its nuclear localization signal. The sudden activation of NF-κB by a wide range of activators typically induces the phosphorylation of IκBα by what is thought to be a large multiprotein complex of 700 kDa (34).

This complex has recently been shown to contain two important kinases termed IKK-α and IKK-β (35). These latter kinases have been suggested to be important in allowing classical phosphorylation of the IκBα inhibitor on serine residues 32 and 36 upon activation of the NF-κB cascade (36). The phosphorylated IκBα polypeptide is then ubiquitinated and targeted to the proteasome for degradation, in turn allowing NF-κB to move freely from the cytoplasm to the nucleus (34,37,38). Two recent publications have demonstrated that the active form of NF-κB requires serine phosphorylation of the complex by protein kinase A (PKA), also leading to the interaction with the important transcriptional activator CREB-binding protein (39,40). This dependency seems to be important for NF-κB to bear optimal transactivation efficiency and to subsequently activate the expression of the multitude of genes that it regulates.

The activation of the NF-κB factor is known to occur through different stimuli such as cytokines and bacterial components. These include several different cytokines and bacterial components such as lipopolysaccharide and mycobacterium-derived membrane components (28,41). Virus infection has also been documented to result in NF-κB translocation. For example, human T cell leukemia-1 and hepatitis B, through their respective viral activators Tax and Hbx, are two viruses known to activate NF-κB upon infection of their target cells (28). It has also been suggested that HIV-1 itself is capable of such activation, although the process seems to have occurred in this case at the cell surface through multimerization of the CD4 receptor (42). Other activators have been described for NF-κB such as hydrogen peroxide, and ultraviolet and x-ray irradiation (28).

All of these activators have been shown to lead to serine phosphorylation of the IκBα. In certain cases, such as for the use of PTP inhibitors (see below), it has been postulated that NF-κB may be turned on by the tyrosine phosphorylation of IκBα in a different mechanistic mode of action (43), although these findings have not been confirmed (6,44).

NF-κB was first discovered through an enhancer region of an intron of the immunoglobulin kappa light chain (26). However, other studies have indicated that the NF-κB factor was a crucial element in the overall immune response. This has become apparent with studies that have made use of transgenic or gene knock out mice of different members of the NF-κB family, especially when investigation focused on the development or the functional efficiency of the T and B cells (45,46). A further indication of the importance of the NF-κB factor in the immune response came with the identification of the targeted genes. Although it is clear that NF-κB acts on the regulation of a wide number of genes, it is apparent that immune response genes are very much modulated by the NF-κB factors. These include a series of cytokines such as IL-1 (alpha and beta), IL-2, IL-3, IL-6, IL-8, tumour necrosis factor (TNF)-alpha and interferon (IFN)-beta. Cell surface proteins are also included in this list and include major histocompatibility complex class (MHC)-I and MHC-II molecules, the alpha and beta TCR chains, as well as the alpha chain of the IL-2 receptor (47).

**IMPORTANCE OF NF-κB IN THE CONTROL OF HIV-1 TRANSCRIPTION**

Several studies have shown a strong correlation between NF-κB activation and the stimulation of the HIV-1 LTR, using either reporter constructs or integrated proviruses (48,49), suggesting that the two κB sites are the main responsive region linking HIV-1 replication to T cell activation. However, the few studies that have investigated the role of the κB sites in viral growth and replication have led to conflicting results regarding their importance during infection of cells, some suggesting that they are largely dispensable (50) and others that they are essential in primary cells (51). In a recent study, Chen et al (52) attempted to further elucidate this issue. Using different cells lines and primary cells, they concluded that NF-κB plays a central role in enhancing HIV-1 growth, even though they were not able to demonstrate an absolute requirement for this factor (52). Some studies were also done on the simian version of HIV-1, simian immunodeficiency virus (SIV), which contains only one κB binding site. As for HIV-1, efficient transcription and replication of SIV strain mac239 were observed in viruses bearing a mutated κB site or even in the absence of a κB site (ΔκB) (53). Moreover, when rhesus monkeys were inoculated with ΔκB, these viruses were able to induce AIDS symptoms similar to those induced by the wild-type viruses, indicating that the NF-κB binding site is not essential for the induction of simian AIDS by SIVmac239 (54). Even though these studies tend to demonstrate a dispensable role for the NF-κB binding sites in HIV-1 replication, evolutionary consideration strongly argues for a prime role of this element. Indeed, almost all HIV-1 strains have the two κB sites in their LTR, while SIV and HIV-2 bear only a single copy of this site. Such a conservation for a virus that is known for its ability to mutate suggests that a strong selective pressure acts to maintain the κB sites in the LTR (52).
Vanadate derivatives are the most commonly used PTP inhibitors. Pervanadate has been demonstrated to activate both NF-κB and AP-1 (55,56). Moreover, the same authors have demonstrated that NF-κB activation by pervanadate may be due to novel mechanism of IkBa inactivation, dependent upon tyrosine phosphorylation and subsequent detachment from the p50/p65 complex, but without the usual degradation through the proteasome (43). Because of its important role in HIV-1 regulation, our group has investigated whether NF-κB activation following treatment with PTP inhibitors could result in HIV-1 LTR activation. Using the bis-peroxovanadium compounds (bpV), the most powerful PTP inhibitors known to date (57), it has been demonstrated that PTP inhibition by these agents, and the subsequent rise in phosphotyrosine content and NF-κB activation result in transcriptional activation of the HIV-1 LTR (6). However, using κB-mutated LTR constructs, it has also been demonstrated that a part of this bpV-mediated HIV-1 LTR activation was independent of NF-κB. By the use of the specific and powerful immunosuppressor cyclosporin A (CsA) and FK506, it has also recently been demonstrated that the bpV-mediated NF-κB-independent activation of HIV-1 LTR was due to NFAT (personal communication).

**NFAT**

NFAT is another family of Rel-related transcription factors that are activated early after T cell activation. Like NF-κB, this factor is sequestered in the cytoplasm. Its translocation to the nucleus results from an increase in the cytoplasmic concentration of calcium (58). As a result, newly formed calcium-calmodulin complexes bind to the serine/threonine phosphatase calcineurin and activate its phosphatase activity by displacement of an autoinhibitory domain from the catalytic site. The activated calcineurin is then able to dephosphorylate the NFAT factor, which results in an uncovering of the nuclear localizing sequence (NLS) and the subsequent migration into the nucleus (58). The critical role of calcineurin in NFAT activation has also been highlighted by the discovery of the mode of action of the powerful immunosuppressors cyclosporin A (CsA) and FK506. These two molecules block NFAT activation by complexing with a cellular factor. The resulting complex was shown to inhibit the catalytic activity of the enzyme calcineurin (59,60).

Once in the nucleus, NFAT usually associates with the newly synthesized AP-1 heterodimer. This complex acquires high transactivating potential upon binding to its consensus sequence 5'-T(A)GGAAA(NN)(A/T/C)-3' (58). Certain types of NFAT binding sites suggested to be cooperative with AP-1 are known to resemble NF-κB binding sites and include the CD28RE element located in the locus of the IL-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF) genes (61,62). Several members of the NFAT family of transcription factors are present in human T cells such as NFATc(NFAT2), NFATc/x and NFATp(NFAT1) (63). NFAT transcription factors are involved in the regulation of numerous T cell-expressed genes. Many of them have been shown to be of prime importance for the immune response. Indeed, potentially functional NFAT binding sites have been identified in the promoter region of the IL-2, IL-3, IL-4, IL-5, GM-CSF, IFN-γ and IL-3 genes, all of which are sensitive in their transcriptional regulation to either CsA or FK506 (58). The importance of NFAT members in T cell function is, thus, very clearly established.

**NFAT AND HIV-1 REPLICATION**

HIV-1 LTR is known to be activated during early T cell activation, suggesting that these events are intimately linked. An increase in NFAT binding precedes the activation of both IL-2 and HIV-1 gene expression in stimulated T cells (64). Previous studies have demonstrated that NFAT-1 can bind the HIV-1 LTR through functional elements (64). The HIV-1 LTR contains two NFAT-binding sites located at positions -283 and -195 upstream of the transcription initiation site, in a region called negative regulatory element (64). Subsequent studies have yielded conflicting results. Even though some reports have demonstrated the implication of NFAT in HIV-1 LTR activation in either an indirect manner (64,65) or in a more direct manner (24), and despite the observation by in vivo footprinting that NFAT-binding sites were occupied in vivo (66), some findings have suggested that NFAT proteins are not involved in HIV-1 LTR activation (67,68). In the early 1990s, Schmidt and co-workers (69) reported the attachment of distinct mitogen-inducible DNA-binding complexes to the HIV-1 enhancer (69). The formation of one of the two complexes was inhibited by CsA when the stimulus was the plant lectin phytohemagglutinin, the phorbol ester phorbol myristate acetate-induced complex being insensitive to CsA. The authors have concluded that two different functionally indistinguishable NF-κB complexes, activated by separate signalling pathways, were responsible for activation of HIV-1 LTR-driven transcription. In 1997, Kinoshita et al (23) reported that the CsA-sensitive complex binding to the HIV-1 enhancer was indeed NFAT. They demonstrated that NFAT was a strong activator of HIV-1 transcription by binding to a nonconventional AP-2 element located in between the two κB binding sites (23). Therefore, this study provided clear and strong evidence of the role played by NFAT in activation of the HIV-1 LTR. This work also suggests a possible explanation for the previous ambiguous results about the role of NFAT because those previous studies focused on the distal NFAT sites for which their role still remains to be defined.

In addition to their important role in transcriptional regulation of HIV-1, NFAT, and particularly the NFATc isoform, have been shown to act in very early events of the replicative cycle, before reverse transcription. Productive HIV-1 infection of primary T cells is blocked depending upon the cells' activation (70,71). However, the reasons for such an arrest were not well understood until recently. Kinoshita et al (72) demonstrated that NFATc expression in quiescent CD4+ T cells was sufficient to allow complete reverse transcription and the continuation of the viral life cycle. NFATc is, thus, acting at both pre- and postintegration steps of the HIV-1 life cycle.

**CONCLUSIONS**

As a parasite of the immune system, HIV-1 has evolved
complex strategies to take full advantage of the extraordinary capacity of this system to be stimulated. By using in its regulatory regions elements that are identical or similar to the ones found in promoter region of genes critical for the immune response, HIV-1 has assured itself of a strong capacity to replicate.

In its enhancer region, HIV-1 has binding sites for two of the most powerful transcription factors found in T cells, namely NF-κB and NFAT. Moreover, the particular arrangement of the binding sites for these factors favours their synergistic action (23). This synergy between NFAT and NF-κB is, however, not restricted to the HIV-1 LTR and has been observed in the context of the IL-2 and IFN-γ promoters (73). The use by HIV-1 of the same activation pathways as the T cell renders the transcriptional regulation of HIV-1 a difficult target for possible therapeutic development. Due to its strong NF-κB-inducing effect and given the importance of this factor in HIV-1 replication, TNF-α is considered to be one of the most potent in vivo activators of HIV-1 replication. Strategies aimed at blocking the action of TNF-α were, thus, the first developed. Pentoxyfilline, a potent inhibitor of TNF-α, has been shown to strongly reduce HIV-1 LTR kB-dependent gene expression (74-76). However, the use of this agent in clinical trials resulted in only minor improvement (77). Other molecules such as thalidomide, which is known to block TNF-α action or secretion, have also been tested in vitro and demonstrated some efficacy (78). The potent anti-inflammatory salicylate-derived drugs are good inhibitors of NF-κB activation and HIV-1 LTR-dependent gene expression (79). Due to their low toxicity, these compounds should be envisaged as good candidates for use as anti-HIV-1 agents. Recently, other molecules have been shown to downregulate HIV-1 transcription. Rolipram, a phosphodiesterase type IV inhibitor, has been demonstrated to diminish both HIV-1 replication, and TNF-α and IL-10 synthesis, by inhibition of NF-κB and NFAT activation (80). Moreover, the carboxyamidotriazole compound, a calcium influx blocking agent, was found to selectively inhibit HIV-1 LTR activity (81). Finally, new therapeutic approaches should be attempted based on the recently discovered role of NFATc as a crucial regulator of the HIV-1 reverse transcription process (72).

There are, therefore, additional avenues for the development of novel therapies aimed at the transcriptional regulation of HIV-1. Even though the targeting of cellular activation pathways may have deleterious effects on the immune system, this strategy renders the emergence of a resistant phenotype for HIV-1 a difficult task.

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