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Emerging Roles of Prostaglandins in HIV-1 Transcription

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1. Introduction

Prostaglandins (PG), generated by cyclooxygenase (COX), are a group of lipid mediators formed in response to various stimuli. They include PGD_2, PGE_2, PGF_{2alpha}, and PGI_2. Immediately after synthesis, they are released outside the cell and exert their actions by binding to a G-protein-coupled rhodopsin-type receptor on the surface of target cells. There are seven types of prostaglandin receptors: the PGD receptor, four subtypes of PGE receptor, the PGF receptor, and the PGI receptor. Prostaglandins are involved in host defense against various pathogens. Along with mediating inflammatory symptoms, PGs might suppress some innate immune factors, including nitric oxide (NO) production. These immunomodulatory molecules have been shown to participate in the regulation of virus replication and the modulation of inflammatory responses following infection. Moreover, virus infection also stimulates the expression of a number of proinflammatory gene products, including COX-2, inducible nitric oxide synthase (iNOS) as well as proinflammatory cytokines.

An overproduction of PGE_2 (as high as $10^{-4}M$) is seen in a number of disorders (e.g. allergy, hyper-IgE syndrome, Hodgkin lymphoma, trauma, sepsis, and transplantation), most of which are characterized by elevated Th2 and IgE responses. Elevated levels of PGE_2 have also been reported in individuals infected with HIV-1 and it has been postulated that this may contribute to the immunosuppressive state seen in such virally infected patients. The mechanism(s) responsible for the enhanced prostaglandin formation is still undefined. The initial contact between the virus particle and its target cell might represent the crucial step leading to the production of PGE_2 by macrophages. This concept is supported by the finding that a significant production of endogenous PGE_2 is induced (20- to 40-fold increase) following incubation of primary human monocytes with the HIV-1 external envelope glycoprotein gp120. Given that pro-inflammatory molecules such as PGE_2 are up-regulated during HIV-1 infection, an imbalance in PGJ_2 production is observed in HIV+ individuals.

This book chapter will focus on roles of prostaglandins in HIV-1 replication and their potential therapeutic implications. We propose to review mechanisms by which the pro-inflammatory prostaglandin PGE_2 and the anti-inflammatory prostaglandin PGJ_2 regulate HIV-1 transcription and replication. Specific attention will be placed on how prostaglandins affect the nuclear translocation of NF-κB (nuclear factor kappa B), an essential transcription factor for HIV-1 transcription. In addition, signaling pathways as well as other transcription

factors that are activated or repressed by prostaglandins that regulate HIV-1 gene expression will be reviewed.

2. Prostaglandins: Their synthesis and roles in the regulation of inflammation

2.1 Prostaglandins synthesis

The initial reaction in prostaglandin production is phospholipase A_2 (PLA_2)-mediated liberation of a 20-carbon essential fatty acid, arachidonic acid, from membrane phospholipids. Cyclooxygenase (COX) is the rate-limiting enzymes catalysing oxidation of arachidonic acid to the hydroperoxyendoperoxide, prostaglandin G_2 (PGG_2). Subsequently, PGG_2 is reduced to form the hydroxylendoperoxide, prostaglandin H_2 (PGH_2). Then, prostanoids including prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), prostaglandin F_{2alpha} ($PGF_2\alpha$), prostacyclin (PGI_2), and thromboxane A_2 (TXA_2) are formed by the action of discrete prostaglandins synthases (reviewed in Coleman et al., 1994). Figure 1 reviews the arachidonic cascade.
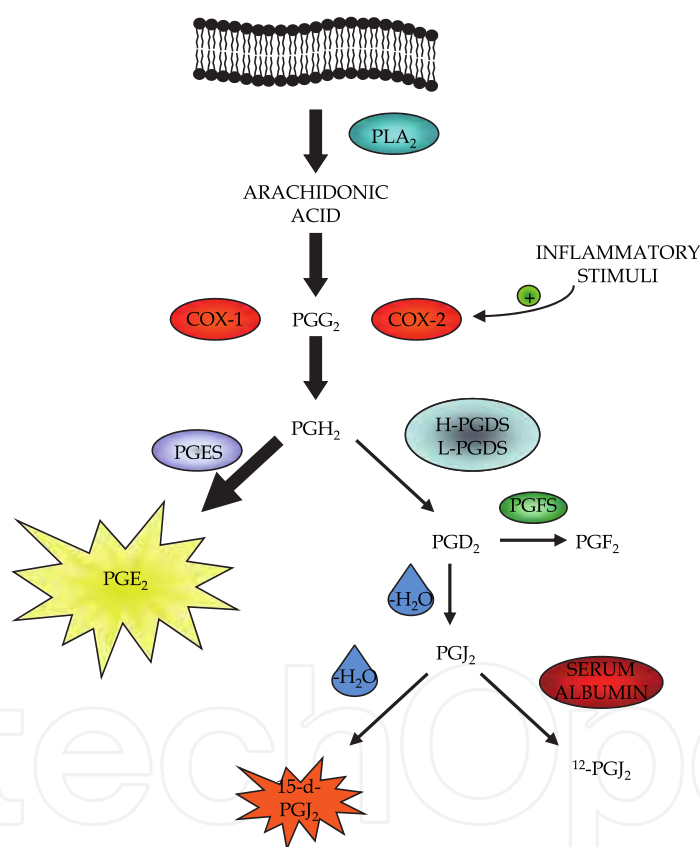

Fig. 1. A model for prostaglandins synthesis.

Prostaglandin E_2 (PGE_2), an oxygenated polyunsaturated fatty acid that contains a cyclopentane ring structure, is present in high concentrations in individuals infected with numerous pathogens (Abel et al., 1992; Ben-Hur et al., 1996; Farrell & Kirkpatrick, 1987; Foley et al., 1992; Griffin et al., 1994a; Henke et al., 1992; Kernacki & Berk, 1994; Midulla et al., 1989; Onta et al., 1993; Ramis et al., 1992; Rastogi et al., 1992; Reiner & Malemud, 1984; Sorrell et al., 1989; Wang & Chadee, 1992, 1995). PGE_2 are molecules that have been shown to modulate the immune response both *in vitro* and *in vivo* (Goodwin & Webb, 1980). Macrophages, follicular dendritic cells, fibroblasts, and vascular endothelial cells synthesize

PGE_2, while lymphocytes do not secrete this major product of arachidonic acid metabolism (Frey et al., 1986; Heinen et al., 1986; Kurland & Bockman, 1978; Phipps et al., 1988). A marked increase in PGE_2 production is generated in response to a variety of immunological stimuli including interleukin (IL)-1, tumor necrosis factor-α (TNF-α), antigen-antibody complexes, and lipopolysaccharide (Roper & Phipps, 1994) in addition to exposition to microorganisms. PGE_2 has been implicated in decreasing T-cell proliferation, IL-2 production, and IL-2 receptor expression (Goodwin et al., 1977; Goodwin & Ceuppens, 1983; Rincon et al., 1988; Roper & Phipps, 1994; Walker et al., 1983). PGE_2 shifts the balance of the cellular immune response away from T-helper type 1 (Th1) favouring a Th2 response which drives humoral responses toward the production of IgE (Fedyk & Phipps, 1996). However, other findings have depicted PGE_2 as a pleiotropic molecule that can act both negatively or positively on the immune system (Phipps et al., 1991). Depending on the cell type, binding of PGE_2 to one of its six described receptors (EP_1, EP_2, EP_{3I}, EP_{3II}, EP_{3III}, and EP_4) can lead to phospholipase C activation, phosphatidylinositol turnover increase, activation of adenylate cyclase through cholera toxin-sensitive $G_{\alpha s}$ proteins and mobilization of intracellular Ca^{2+} concentration (Coleman et al., 1994). PGE_2 facilitates expansion of the Th17 subset of T helper cells of both human and mouse through elevation of cAMP via PGE_2 receptors EP_2 and EP_4 (Sakata et al., 2010).

The balance of opposing prostaglandins produced in tissues profoundly influences inflammatory responses (Harris et al., 2002). The J series of prostaglandins are the end product metabolites of PGD_2 and are abundantly produced by mast cells, platelets, as well as alveolar macrophages (Ito et al., 1989; Straus & Glass, 2001). One of these molecules, 15-d-PGJ_2, is a natural activator of the peroxisome proliferators-activated receptor-γ (PPAR-γ), a nuclear receptor family member that elicits anti-inflammatory activities in macrophages (Hinz et al., 2003; Hortelano et al., 2000; Jiang et al., 1998; Ricote et al., 1998), lymphocytes (Clark et al., 2000; Padilla et al., 2000; Yang et al., 2000), dendritic cells (Faveeuw et al., 2000), and endothelial cells (Imaizumi et al., 2003). Currently, the mechanisms regulating the anti-inflammatory effects of 15-d-PGJ_2 and other PPAR-γ agonists are poorly understood, but it has been suggested to involve the inhibition of the nuclear factor κB (NF-κB) signaling pathway (Daynes & Jones, 2002; Rossi et al., 2000). PPAR-γ is also expressed at high levels both in the colonic epithelium and intestinal epithelial cells (Lefebvre et al., 1998; Saez et al., 2004; Saez et al., 1998; Sarraf et al., 1998; Sarraf et al., 1999), where, depending on the model system studied, it can result in either an increase or a decrease in proliferation (Brockman et al., 1998; Lefebvre et al., 1998).

2.2 Prostaglandins and HIV infection

An overproduction of PGE_2 as high as $10^{-4}M$ is seen in a number of disorders (e.g.allergy, hyper-IgE syndrome, Hodgkin lymphoma, trauma, sepsis, and transplantation), most of which are characterized by elevated Th2 and IgE responses (Fedyk & Phipps, 1996; Haraguchi et al., 1995a; Phipps et al., 1991; Roper & Phipps, 1994). Elevated levels of PGE_2 have also been reported in individuals infected with HIV-1 (Abel et al., 1992; Foley et al., 1992; Griffin et al., 1994a; Ramis et al., 1992) and it has been postulated that this may contribute to the immunosuppressive state seen in such virally-infected patients (Hui et al., 1995). *In vitro*, peripheral blood monocytes and macrophages from AIDS patients exhibit abnormal production of cyclooxygenase products (Coffey et al., 1999; Fernandez-Cruz et al., 1989; Foley et al., 1992; Mastino et al., 1993; Ramis et al., 1991). The mechanism(s)

responsible for the enhanced prostaglandin formation is still undefined. The initial contact between the virus particle and its target cell might represent the crucial step leading to the production of PGE_2 by macrophages. Significant production of endogenous PGE_2 is induced (20- to 40-fold increase) following incubation of primary human monocytes with the HIV-1 external envelope glycoprotein gp120 (Wahl et al., 1989). However, in sharp contrast with this report, a previous study has demonstrated that interaction between gp120 and THP-1, a human monocytoid cell line, does not increase exogenous production of PGE_2 (Hui et al., 1995). It is important to specify that, unlike monocyte/macrophages, promonocytoid THP-1 cells are not at a terminal stage of differentiation. In addition, a monomer form of gp120 was used in this study which might not parallel physiological conditions where gp120 is under a multimeric form (Pinter et al., 1989).

3. PGE_2 and HIV transcription

3.1 Importance of NF-κB in HIV-1 gene transcription

HIV-1 gene expression is regulated in a cell type- and differentiation-dependent manner by the binding of both host and viral proteins to the long terminal repeat (LTR), which serves as the viral promoter. Host transcription factors such as the Sp family, NF-κB family, activator protein 1 (AP-1) proteins, nuclear factor of activated T cells (NFAT), and CCAAT enhancer binding protein (C/EBP) family members play essential roles in the regulation of HIV-1 transcription by binding sites in the LTR that display different levels of sequence conservation (Fig 2). Viral proteins such as HIV Vpr and Tat also bind to the LTR to regulate transcription (Kilareski et al., 2009). Many of these host and viral proteins engage in extensive protein-protein interactions, leading to a complex system of transcriptional regulation.
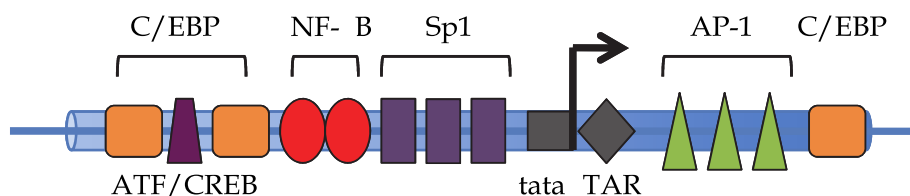

Fig. 2. A schematic representation of a typical HIV-1 LTR.

The transcription factor NF-κB is known to play a central role in the activation of HIV-1 gene expression. The enhancer in the U3 region of LTR contains two NF-κB binding sites (Siebenlist et al., 1994) that are critical for LTR promoter activity and important for optimal HIV-1 replication (Santoro et al., 2003; Siebenlist et al., 1994). NF-κB is an inducible transcription factor that plays an important role in cellular gene expression associated with immune responses, inflammation and cell survival (Ghosh et al., 1998; Viatour et al., 2005). In the host cytoplasm, NF-κB is a heterodimeric molecule (p50/p65) that forms an inactive complex with its inhibitor IκB. Stimulation with inflammatory cytokines, such as TNF-α and IL-1β, viral and bacterial antigens, and stress-inducing agents leads to immediate phosphorylation and subsequent degradation of IκB by the proteasome, resulting in the translocation of NF-κB from the cytoplasm to nucleus.

3.2 Activation of HIV-1 LTR activity by PGE_2

Immune and inflammatory responses are triggered by microorganisms such as bacteria, viruses, and protozoan, all known to be potential opportunistic pathogens in HIV-1-positive

patients. The formation and production of elevated levels of inflammatory mediators such as PGE_2 is a hallmark of the HIV-1 infection (Foley et al., 1992; Griffin et al., 1994a; Ramis et al., 1992). Prostaglandins play a role in disease exacerbation by directly altering T-cell functions or macrophage activation. Although it was thought that PGE_2 is primarily an immunosuppressive molecule that acts as a down-regulator of many aspects of B- and T-cell function and proliferation, other findings support a role for PGE_2 as a potentiator of immunoglobulin class switching and cytokines and cytokine receptors synthesis (Phipps et al., 1991). Moreover, knowing that PGE_2 is a good inducer of cAMP and that a 4-fold increase in intracellular levels of cAMP is seen in asymptomatic HIV-1-seropositive subjects as compared with uninfected controls (Hofmann et al., 1993), it is thus of prime importance to study the putative effect of PGE_2 on the regulatory elements of HIV-1 in T cells considered to be the major cellular reservoir for HIV-1 in the human peripheral blood. As shown in Fig 3, exogenous PGE_2 could further increase the overall positive effect mediated by various HIV-1 LTR-activating agents confirming that PGE_2 could be considered by itself as a potent inducer of HIV-1 LTR transcription in T cells.
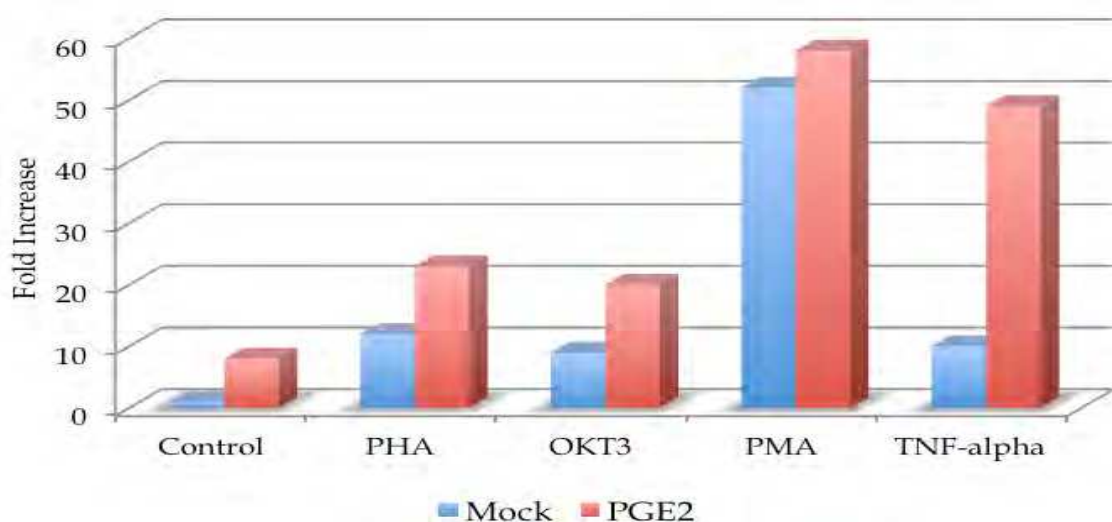

Fig. 3. Activation of HIV-1 LTR by several stimuli in the absence or presence of PGE_2. 1G5 cells, a clonal cell line derived from Jurkat E6.1 cells which has been with stably transfected with a luciferase gene driven by the HIV-1 LTR (Aguilar-Cordova et al., 1994), were either left untreated (control) or treated with PHA (3 μg/ml), OKT3 (1 μg/ml), PMA (20 ng/ml), or TNF-α (2 ng/ml) in the absence or presence of 100 nM PGE_2 for 8 h. Cell lysates were evaluated for luciferase activity and are expressed as fold induction relative to basal luciferase activity in untreated control cells (considered as 1).

Northern blot assays, flow cytometric analyses, and pharmacological studies showed that the EP_4 gene is expressed on T lymphoid cells such as Molt-4, KM-3, IG5 and Jurkat E6.1 (Blaschke et al., 1996; De Vries et al., 1995; Dumais et al., 1998; Mori et al., 1996). It has been demonstrated that EP_4 receptors are coupled to adenylate cyclase via a stimulatory G protein ($G_{\alpha s}$) and that such activation results in an enhancement of intracellular cAMP levels (Coleman et al., 1995; Nishigaki et al., 1995). Interestingly, PGE_2 has been shown to lead to an increase in intracellular cAMP levels partly via the EP_4 receptor (Rodbell, 1980), a finding which lend credence to the potential implication of the EP_4 receptor in the PGE_2-induced up-regulation of HIV-1 LTR activity.

3.2.1 NF-κB-dependent signaling pathways involved in activation of HIV-1 LTR by PGE$_2$ in T cells

The involvement of specific intracellular second messengers in PGE$_2$-mediated up-regulation of HIV-1 LTR activity has been dissected using several signal transduction inhibitors. Only exogenous PGE$_2$ plays a role in the activation of HIV-1 LTR-driven gene expression as shown with experiments using indomethacin, a potent inhibitor of the cyclooxygenase pathway (Dumais et al., 1998). Moreover, it was demonstrated that T cells had a limited capacity to metabolize arachidonic acid to prostaglandins (Auberger et al., 1989; Fu et al., 1990; Goldyne & Rea, 1987). Interaction between PGE$_2$ and an adenylate cyclase-coupled stimulatory receptor leads to activation of adenylate cyclase, hydrolysis of ATP, enhanced turnover of intracellular cAMP and binding to PKA (Kammer, 1988). In T cells, PGE$_2$-induced enhancement of HIV-1 LTR dependent activity requires the participation of adenylate cyclase, cAMP as well as protein kinase A (Dumais et al., 1998) and elevation of cAMP levels resulted in HIV-1 replication (Nokta & Pollard, 1992). It is also well known that cAMP-dependent pathways regulate the immune effector functions of lymphocytes and macrophages. For example, during immune response, cAMP exhibits positive regulatory effects at low concentrations whereas inhibitory effects are seen at high concentrations (Koh et al., 1995). Many of the earlier studies have shown that PGE$_2$ interaction with T cells *in vitro* resulted in an elevation of the cAMP level (Rincon et al., 1988) and that such elevated intracellular cAMP levels were responsible for the proliferative disturbances in T cells (Baker et al., 1981; Lingk et al., 1990; Munoz et al., 1990). In T cells, experiments with the calcium chelator BAPTA/AM and the calcium inhibitor CAI are suggestive of the importance of Ca^{2+} in the PGE$_2$-induced activation of HIV-1 transcription (Dumais et al., 1998). However, given that there is no published report indicating Ca^{2+} influx through the EP$_4$ receptor, our results with BAPTA/AM and carboxyamido-triazole (CAI), two inhibitors of intracellular calcium mobilization, lead us to postulate that PGE$_2$ could generate calcium release from intracellular storage organelles. Up-regulation of HIV-1 LTR requires the implication of cAMP and calcium, as well as the participation of the NF-κB transcription factor.

Several agents known as potent activators of HIV-1 transcription (e.g. PMA, PHA, TNF-α, and anti-CD3 antibody) are all acting through a common mechanism, namely via the nuclear translocation of the transcription factor NF-κB which binds to the enhancer region of the HIV-1 LTR (Nabel, 1991). This transcription factor is sequestered in the cytoplasm due to its physical association with the inhibitor named IκB. NF-κB is a pleiotropic transcription factor that controls the expression of a wide variety of genes, including cytokines such as IL-1, IL-2, IL-6, IL-8, interferon-β, and TNF-α, as well as known genes for some cell adhesion molecules including ICAM-1 and VCAM-1. Its importance in the regulation of HIV-1 gene expression has been stated in numerous studies (Siebenlist et al., 1994). Results from mobility shift assays suggest that the PGE$_2$-mediated effect on HIV-1 LTR activity is due to activation of the transcription factor NF-κB. This is in agreement with the previous demonstration that PGE$_2$ activates NF-κB in the macrophage-like cell line J774 (Muroi & Suzuki, 1993). The fact that we have noticed that both NF-κB and Ca^{2+} are key elements in the PGE$_2$ effect on HIV-1 transcription is of interest considering that calcineurin, a Ca^{2+}/calmodulin-dependent serine/threonine protein phosphatase, has been reported to activate NF–κB through the inactivation of IκB (Frantz et al., 1994). Moreover, researchers had earlier found that cAMP-mediated enhancement of PKA might be involved in the

dissociation of IκB from NF-κB (Nabel and Baltimore, 1987). Recent studies have revealed that NF-κB is regulated through phosphorylation of the p65 subunit by PKA which is directly regulated by intracellular levels of cAMP (Zhong et al., 1997). Experiments in Jurkat E6.1 T cells performed with κB-driven reporter gene constructs (pκB-TATA-LUC and pNF-κB-LUC) and HIV-1 LTR-based vectors (pLTR-LUC and pmκBLTR-LUC), suggest that NF-κB-binding regions and another element(s) in the HIV-1 LTR are involved in the activation of HIV-1 LTR-dependent transcription induced by PGE_2 (fig 4). These results hence support the notion that PGE_2 might be activating the transcription factor NF-κB via cAMP/PKA and calcium signaling pathways in human T lymphoid cells.

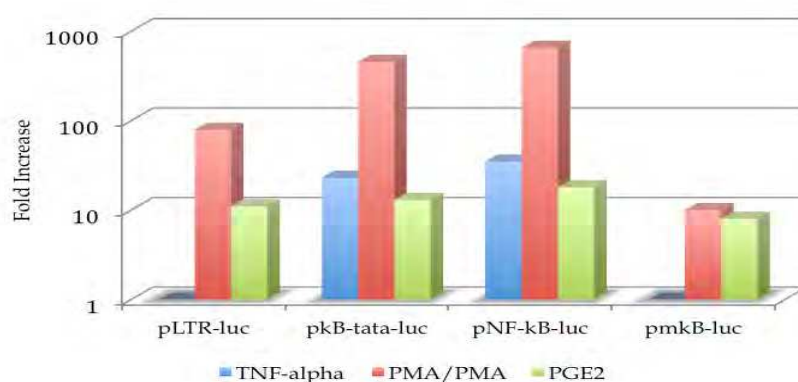Fig. 4. NF-κB-dependent and -independent activation of HIV-1 LTR by PGE_2. Jurkat E6.1 cells were transiently transfected with pLTR-LUC, pmκBLTR-LUC, pNF-κB-LUC or pκB-TATA-LUC and were either left untreated or were treated for 8 h with TNF-α (2 ng/ml), PHA/PMA (3 μg/ml and 20 ng/ml, respectively), or PGE_2 (100 nM). Results shown are expressed as fold induction relative to basal luciferase activity in untreated control cells (considered as 1).

3.2.2 Other transcription factors implicated in the PGE_2-induced HIV-1 gene transcription

PGE_2 could have the capacity to modulate several signal transduction pathways through its effect on transcription factors regulated by cAMP such as the cAMP response-element binding factor, the activating protein-1 (Haraguchi et al., 1995b) and Sp1 (Rohlff et al., 1997). The involvement of these three transcription factors in the observed NF-κB-independent activation of HIV-1 LTR mediated by PGE_2 was further investigated. We have previously discussed that interaction of PGE_2 with EP_4 receptor subtype in human T cells can up-regulate HIV-1 replication via both NF-κB-dependent and –independent pathways (Dumais et al., 1998). In this section, we will address the functional role played by other transcription factors in the PGE_2-induced HIV-1 LTR activation.

Several signal transduction pathways have been shown to regulate the expression of target genes by inducing the phosphorylation of specific transcription factors (Hunter & Karin, 1992). The second messenger cAMP mediates the transcriptional induction of numerous genes through protein kinase A (PKA)-dependent phosphorylation of the CREB at Ser[133] (Gonzalez et al., 1989). CREB is a stimulus-induced 43-kDa basic leucine zipper (b-ZIP) transcription factor that binds to an octanucleotide cAMP-responsive element (CRE) (i.e., TGANNTCA) both as a homodimer and as a heterodimer in

conjunction with other members of the activation transcription factor (ATF)/CREB superfamily of transcription factors (Gonzalez & Montminy, 1989; Habener, 1990; Hoeffler et al., 1988). It is now believed that the transcriptional regulation of genes containing either CCAAT/enhancer binding protein (C/EBP) or ATF/CREB recognition sites may involve the heterodimerization between different members of the b-ZIP family. This is clearly illustrated by the demonstration that transcription of HIV-1 in monocytic cells is regulated by a synergistic interaction between ATF/CREB and C/EBP protein families (Ross et al., 2001). The C/EBP-related family of nuclear transcription factors constitutes a class of proteins characterized by their ability to bind the CCAAT consensus sequence, inducing either transcriptional activation or repression of target genes (Cao et al., 1991; Chodosh et al., 1988; Johnson & McKnight, 1989; Williams et al., 1991). Members of this family include C/EBPα, C/EBPβ (also termed LAP, NF-IL6α, IL-6DBP, AGP/EBP), C/EBPγ, C/EBPδ (NF-IL6) and C/EBPε (Mueller et al., 1990). Interestingly, regulatory sequences of HIV-1, which are located within the LTR, harbor three C/EBP sites that bind C/EBPβ (Tesmer et al., 1993) (Fig 2) and these sites are essential to initiate virus replication in cells of the monocyte/macrophage lineage (Henderson et al., 1995) and in endothelial cells as recently described (Lee et al., 2001). PKA and transcription factors of the ATF/CREB family may be critical for HIV-1 expression and regulation. In this regard, HIV-1 infection has been associated with sustained elevation of cAMP in T cell lines and in normal peripheral blood mononuclear lymphocytes (Nokta & Pollard, 1992). Moreover, HIV-1 replication has been shown to be modulated by intracellular levels of cAMP (Dumais et al., 1998; Nokta & Pollard, 1992). For example, activation of the cAMP/PKA pathway by cholera toxin enhances HIV-1 transcription in latently infected monocytoid U1 cells (Chowdhury et al., 1993). It is still unknown whether the HIV-1 genome, especially the LTR, possesses CRE sequences. However, the downstream sequence elements located in the U5 domain of HIV-1 LTR has been proposed to act as 12-O-tetradecanoylphorbol-13-acetate/phorbol ester responsive element (TRE)-like CRE that bind both AP-1 and CREB/ATF, allowing the induction of HIV-1 LTR activity through both protein kinase C and PKA activation signals (Rabbi et al., 1998).

PGE_2 can act as a potent activator of HIV-1 LTR-driven transcription through effects on both NF-κB-dependent and -independent signaling events (Dumais et al., 1998). More recently, calcium and the CREB transcription factor were also found to be essential second messengers in the PGE_2-mediated up-regulation of LTR activity in T cells (our unpublished observation). Although the binding of a member of the CREB family to the HIV-1 LTR via the CRE consensus sequence has not yet been described, it has been postulated that CREB can act indirectly on the regulatory elements of this retrovirus. For example, it has been shown that CREB interacts with HIV-1 LTR through an association with transcription factors such as TFIID and TFIIB (Ferreri et al., 1994; Rohr et al., 1999; Xing et al., 1995) or with the adapter CBP; the latter is known to interact with the general transcription machinery (Nordheim, 1994). Recently, a recognition sequence for members of the ATF/CREB family was identified within the untranslated leader region of HIV-1 as a novel TRE-like CRE capable of binding both AP-1 and ATF/CREB (Rabbi et al., 1997). However, the U5 region of the HIV-1 LTR is absent from our molecular constructs, rejecting the possible implication of TRE-like CRE in the noticed PGE_2-induced viral activation. A recent report has shown that dopamine treatment of HIV-1-infected T cells leads to the binding of CREB to the COUP-TF sequence that is located at the 5' end of the HIV-1 LTR in a region called the NRE (Rohr et al., 1999). The various LTR constructs used in our study do not bear

the NRE, suggesting that the COUP-TF binding domain is not participating in PGE$_2$-mediated effect.

The C/EBP family of nuclear proteins is a member of a larger superfamily of transcription factors characterized by the b-ZIP motif that also includes the ATF/CREB family (Johnson, 1993). In a number of cell types, C/EBPβ has been shown to function as a cAMP-activated transcription factor (Metz & Ziff, 1991; Roesler et al., 1988; Tae et al., 1995). Treatment of Jurkat cells with PGE$_2$ resulted in a noticeable induction of nuclear translocation and activation of C/EBPβ. Indeed, DNA mobility shift assays provided clear evidence that PGE$_2$ and forskolin treatment of human T cells increases the level of specific protein-DNA complexes when the consensus C/EBP binding site is used as a molecular probe. Although treatment of Jurkat cells with PGE$_2$ did not alter the protein level of C/EBPβ in whole cell extracts, there was a redistribution of this protein from the cytoplasm to the nucleus upon exposure to PGE$_2$ (Dumais et al., 2002).

It has been previously demonstrated that individual C/EBP proteins can homodimerize or heterodimerize with other members of the C/EBP family of b-ZIP domain proteins to elicit specific cAMP-mediated transcriptional stimulation or repression (Metz & Ziff, 1991; Vinson et al., 1989; Williams et al., 1991). Moreover, it is now believed that transcriptional regulation of genes containing the recognition sites of either C/EBP or ATF/CREB may result from heterodimeric formation between different members in each of the C/EBP and ATF/CREB families (Vallejo, 1994). This mechanism may be used to respond to complex signals and transcriptional cues through single sequence elements including a response to cAMP, despite the absence of active CRE, AP1, and AP2 consensus nucleotide sequences (Kagawa & Waterman, 1990; Lund et al., 1990; Pittman et al., 1995). The best example is provided by the CFTR gene promoter that is controlled by interactions between C/EBP and ATF/CREB family members with CREB1 and ATF1 binding to the inverted CCAAT element of this gene to finely regulate its transcription (Pittman et al., 1995). Although the absence of CRE certainly may not preclude ATF or CREB protein from targeting promoters devoid of such cis-acting elements, it is interesting to note that regulation of the somatostatin gene requires protein-protein interaction between C/EBP and ATF/CREB transcription factors to elicit a cAMP-dependent response through the CRE element (Vallejo, 1994). Inversely, C/EBP proteins have been shown to bind specifically to the phosphoenolpyruvate carboxykinase gene CRE with high affinity to promote cAMP-mediated transcriptional activation (Park et al., 1993). In addition, previous studies identified C/EBP as an effector of cAMP-mediated transcription of the phosphoenolpyruvate carboxykinase gene through combined interactions with liver-specific transcription factors (Roesler, 2000; Roesler et al., 1995). Experiments conducted with a vector coding for LIP suggested that C/EBP was playing a crucial role in activation of HIV-1 LTR-driven gene expression that is seen following treatment of human T cells with PGE$_2$ (Dumais et al., 2002). It should be noted that the β-isoform of C/EBP has been intimately linked with the cAMP signaling system, as exemplified by the reported capacity of cAMP to stimulate C/EBPβ gene expression (Park et al., 1993) and translocation of C/EBPβ from the cytosol to the nucleus (1991). Thus, we propose that the PGE$_2$-dependent increase in HIV-1 LTR transcriptional activity is mediated in part by C/EBPβ. The dominant negative form of C/EBP, i.e., LIP, has less impact on PGE$_2$-mediated induction of HIV-1 LTR-driven activity than mutating the C/EBP binding sites, suggesting that factors in addition to C/EBP may be binding to C/EBP sites.

We have identified C/EBPβ as a PGE_2-activated transcriptional regulator of HIV-1 LTR in Jurkat cells and demonstrated that C/EBP binding sites are functionally important for virus transcription. We also suggest that functional and physical association between members of two important transcription factor families, i.e., C/EBPβ and CREB, are required for activation of HIV-1 transcription by PGE_2 (Dumais et al., 2002). Our findings represent a further indication of the high complexity of the molecular mechanisms that regulate HIV-1 gene expression following treatment of human T cells with PGE_2. Fig 5 reviews the effect of PGE_2 on HIV-1 LTR transcription.
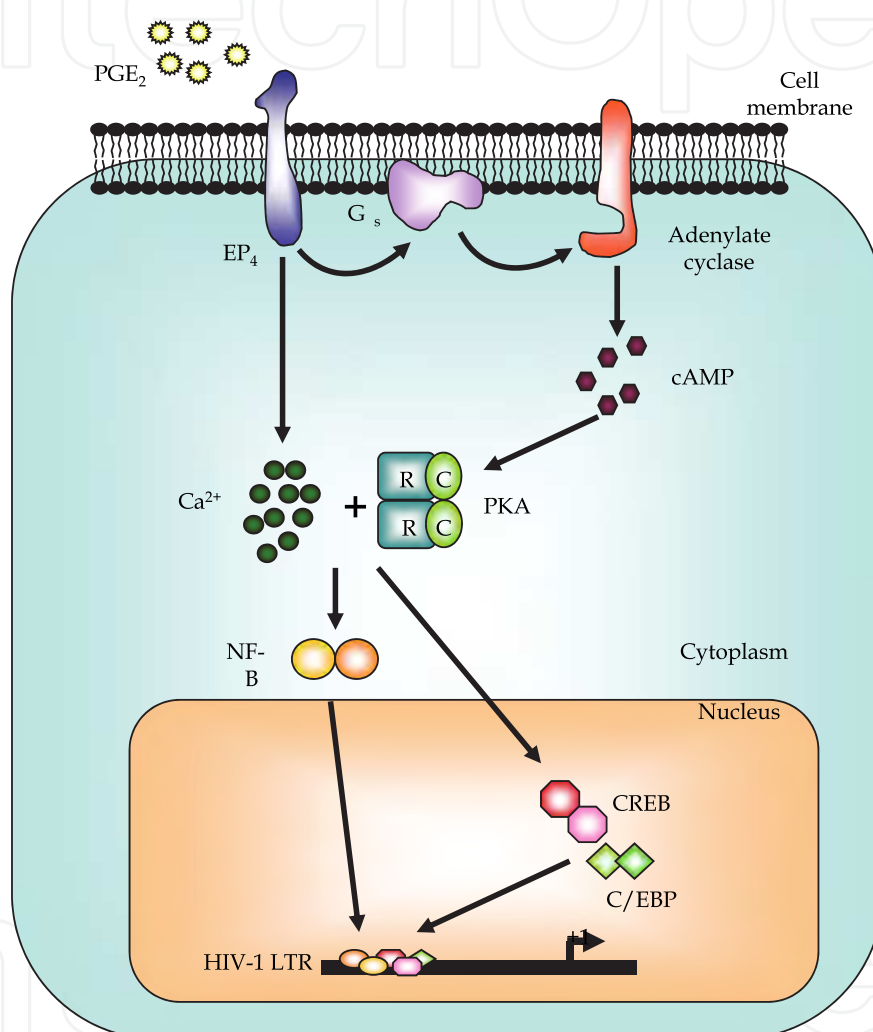

Fig. 5. A model of PGE_2-induced HIV-1 LTR activation in T cells.

3.2.3 Significance

Results from several studies showed that PGE_2 have a major impact in HIV-1 pathogenesis exacerbation. Knowing that HIV-infected individuals have a deficiency in the production of anti-inflammatory molecules, more knowledge are required to fully understand the potential benefit of the resolution of inflammation for people on HAART. Because they are clinically important molecules, a further understanding of the roles that prostaglandins played in host defense and HIV pathogenesis will have great impact on therapeutic research. Detailed characterization of prostaglandins interactions with cells infected with

HIV-1 will help us to understand their mechanism of action and establish their therapeutic potential in the resolution of inflammation in HIV+ individuals.

3.3 15-d-PGJ$_2$ and HIV-1 replication/production in intestinal epithelial cells

Sexual transmission is the predominant mode for epidemic spread of HIV-1 infection worldwide. Because semen contains both free HIV-1 virions and HIV-1-infected cells (Bouhlal et al., 2002; Royce et al., 1997; Shepard et al., 2000), it can lead to both free and cell-associated viral transmission. The intestinal mucosa of the rectum, which serves as a site for virus entry, is known to play a fundamental role in early HIV-1 infection (Belyakov & Berzofsky, 2004; Kozlowski & Neutra, 2003; Neutra et al., 1996). In contrast, the mechanism of HIV-1 transmission across the epithelium is not well understood. While it is known that the penetration of HIV-1 may occur through lesions in the epithelium (Dickerson et al., 1996; Kozak et al., 1997), the existence of lesions is not required (Miller et al., 1990; Spira et al., 1996). Some studies suggest that HIV-1 can be carried to lymphocytes by dendritic cells (Geijtenbeek et al., 2000; Pohlmann et al., 2001). It has been proposed that HIV-1 can cross the epithelium barrier via epithelial cell infection. A quantitative analysis of enhanced green fluorescent protein-tagged HIV infection of cells derived from the female reproductive tract, brain and colon demonstrated that gp120-independent HIV infection occurs in intestinal epithelial cells (Zheng et al., 2006). These results clearly illustrate the importance of such cells in viral latency and transmission during mucosal HIV-1 infection. Earlier *in vitro* studies showed that HIV can infect human intestinal cell lines lacking CD4 (Fantini et al., 1991; Fantini et al., 1993). These studies also demonstrated that galactosylceramide (GalCer), which binds with high-affinity to gp120, can act as a CD4 surrogate HIV-1 receptor (Meng et al., 2002). In fact, Caco-2 cells, a human intestinal cell line, can be infected by HIV-1 via GalCer and CXCR4, one of the two known HIV chemokine coreceptors (Delezay et al., 1997; Fantini et al., 1993). Also, primary human intestinal cells are capable of selectively transferring R5 HIV-1 to CCR5+ cells (cells that express both GalCer and CCR5 on their cell surface) (Meng et al., 2002). Thus, they proposed that infection of epithelial cells might facilitate HIV-1 penetration into the epithelium barrier (Zheng et al., 2006). Following viral replication in the infected epithelial cells, newly formed HIV virions may be discharged into the basolateral side of the epithelium and exposed to immune cells present in the mucosal milieu. This process may ultimately lead to the dissemination of the virus throughout the body. Therefore, it is essential to understand the mechanisms by which HIV replication in epithelial cells can be modulated by the immune system molecules present in the mucosal milieu. Prostaglandins play key roles in inflammation. During the time course of inflammation, the prostaglandins profile shifts from the predominantly pro-inflammatory PGE$_2$ to the anti-inflammatory PGJ$_2$, which is the end product metabolite of PGD$_2$ (Gilroy et al., 1999; Ianaro et al., 2001; Kapoor et al., 2005a; Kapoor et al., 2005b). Pro-inflammatory molecules such as PGE$_2$ are up-regulated during HIV-1 infection (Griffin et al., 1994b; Ramis et al., 1991) leading to an imbalance in PGJ$_2$ production. Given that the cyclopentone prostaglandin PGJ$_2$ has potent anti-inflammatory properties, it is important to determine whether the addition of PGJ$_2$ could inhibit HIV-1 transcription in intestinal epithelial cells.

Cyclopentone prostaglandins such as PGA$_1$ possess potent antiviral activity against a wide variety of viruses such as herpesviruses (Hughes-Fulford et al., 1992; Yamamoto et al., 1987), poxviruses (Santoro et al., 1982), paramyxoviruses (Amici et al., 1992; Santoro et al., 1980), orthomyxoviruses (Santoro et al., 1988), picornaviruses (Ankel et al., 1985), togaviruses

(Mastromarino et al., 1993), rhabdoviruses (Ankel et al., 1985; Santoro et al., 1983) and retroviruses (Hayes et al., 2002; Rozera et al., 1996; Skolnik et al., 2002). In macrophages, rosiglitazone, troglitazone, and PGJ_2 as well as fenofibrate (a PPAR-α agonist) can inhibit HIV-1 replication in U1 cells (Skolnik et al., 2002), while PGA_1 and PGA_2 can inhibit HIV-1 replication in U937 cells and human monocyte-derived macrophages (Hayes et al., 2002). During acute HIV-1 infection in the well-characterized T cell line CEM-SS, treatment with cyclopentone prostaglandins such as PGA_1 and PGJ_2 profoundly alters viral replication (Rozera et al., 1996). Moreover, this antiviral effect does not seem to be mediated by alterations in the expression of α-, β-, or γ-interferon, TNF-α, TNF-β, IL-6 or IL-10 in HIV-infected CEM-SS but rather by a direct, as yet unidentified, mechanism (Rozera et al., 1996).

3.3.1 15-d-PGJ$_2$ inhibition of HIV-1 transcription and viral production

The potent anti-inflammatory molecule 15-d-PGJ$_2$ strongly suppresses HIV-1 replication and particle production in Caco-2 cells, a human intestinal cell line that mimics rectal epithelium susceptible to HIV-1 (Delezay et al., 1997; Fantini et al., 1991; Fantini et al., 1992; Fantini et al., 1993; Zheng et al., 2006). Prophylactic or co-treatment with 15-d-PGJ$_2$ of intestinal epithelial cells significantly reduces HIV replication as well as p24 core antigen production (Boisvert et al., 2008). The 15-d-PGJ$_2$-mediated suppression of HIV-1 replication is a result of the inhibition of promoter activity as shown by the utilization of a pLTR-luc reporter plasmid (Fig 6). This suppression of HIV-1 LTR activity is dose-dependant and is optimal 24h post-treatment. Moreover, 15-d-PGJ$_2$ inhibition of sodium butyrate (NaBut)-induced LTR activity is not specific to Caco-2 cells but can be observed in other intestinal epithelial cell lines such as HT-29 and SW620. Sodium butyrate plays major roles in HIV infection. Indeed, urinary butyrate levels were increased in the AIDS patients with weight loss (2.83±0.67 µmol/l) relative to the controls (1.31±0.13 µmol/l, P<0.05), with the HIV+ patients (1.65±0.18 µmol/l) and AIDS patients without weight loss (1.90±0.22 µmol/l) falling in between (Stein et al., 1997). NaBut is a deacetylase inhibitor that has been shown to activate HIV-1 replication in cells of T-lymphoid and monocytoid origin (Golub et al., 1991). Thus, 15-d-PGJ$_2$, without significantly changing cell viability or the cell cycle by blocking them in G1 phase or altering apoptosis, profoundly affects HIV-1 replication and gene expression in intestinal epithelial cell lines (Boisvert et al., 2008).
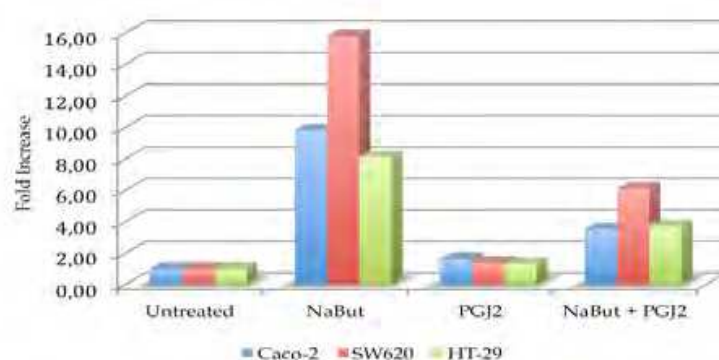

Fig. 6. 15-d-PGJ$_2$-mediated negative effect on HIV-1 LTR activity. Caco-2, SW620 and HT-29 cells were transiently transfected with pLTR-luc and treated with 15-d- PGJ$_2$ (20 µM) used in combination with 2 mM NaBut in a 24 h incubation period. Results shown are expressed as fold induction relative to basal luciferase activity in untreated control cells (considered as 1).

3.3.2 15-d-PGJ$_2$-inhibition of HIV-1 LTR activation is linked to modification to NF-kB signaling pathway

It has been shown previously that 15-d-PGJ$_2$ exerts its effect(s) on cells by activating the PPAR-γ transcription factor via PPAR-γ, the natural ligand of PGJ$_2$ (Schoonjans et al., 1996; Spiegelman, 1998). However, several studies have reported PPAR-γ independent effects of PGJ$_2$ on transcriptional regulation via the modulation of NF-κB (Rossi et al., 2000; Straus et al., 2000). In Caco-2, ciglitazone, a PPAR-γ agonist, failed to mimic the PGJ$_2$-induced suppression of LTR activity, a result that suggests a PPAR-γ-independent mechanism, such as the NF-κB pathway, may play a role in this effect in intestinal epithelial cells (Boisvert et al., 2008). This result is in contrast to those of Skolnik et al. in 2002 (Skolnik et al., 2002) that showed that ciglitazone was able to reduce the HIV-1 promoter activity in monocytes and in peripheral blood mononuclear cells (PBMCs). In contrast, ciglitazone induces luciferase activity in this experimental model. The induction of NF-κB activity in colon cancer cells via p65 phosphorylation has been previously reported (Chen & Harrison, 2005), and this phenomenon may explain why we observed an increase in luciferase expression following the ciglitazone treatment of Caco-2 cells. The blockade of PPAR-γ receptor activation by using a specific human PPAR-γ antagonist (GW9662) confirms that 15-d-PGJ$_2$ repress LTR activity by a mechanism independent of PPAR-γ (Boisvert et al., 2008). Similarly, expression of IL-1β in human chondrocytes is inhibited by 15-d-PGJ$_2$ by a PPAR-γ-independent mechanism (Boyault et al., 2001) as well as IL-8 expression in endothelial cells (Jozkowicz et al., 2001).

The PPAR-γ-independent mechanism by which 15-d-PGJ$_2$ mediates its anti-inflammatory effect can be dependent upon the inhibition of the NF-κB signaling pathway (Daynes & Jones, 2002; Rossi et al., 2000). The NF-κB binding sites within the HIV-1 promoter confer a high level of viral transcription in many cell types (Rabson & Lin, 2000). Previous studies have shown that cyclopentone prostaglandins via their ability to modulate NF-κB activity, significantly alter HIV-1 replication in T cells, monocytes/macrophages and intestinal epithelial cells (Boisvert et al., 2008; Hayes et al., 2002; Rozera et al., 1996; Skolnik et al., 2002). In Caco-2 cells, the functional role of NF-κB was determined using pκB-TATA-luc or pNFκB-luc expression plasmids (Fig 7). The results demonstrated that the NaBut-induced
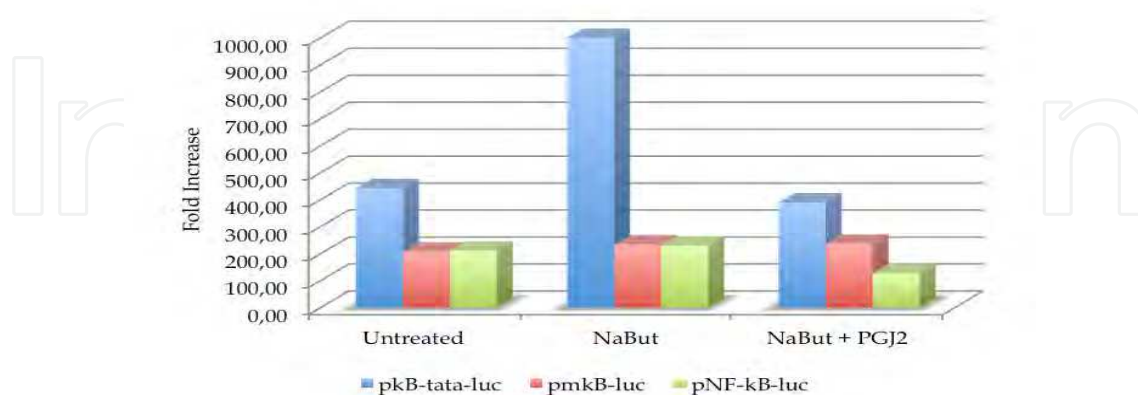

Fig. 7. NF-κB-dependent inhibition of HIV-1 LTR by 15-d-PGJ$_2$. Caco-2 cells were transiently transfected with pκB-TATA-luc, pmκB-luc and pNF-κB-luc. Then, cells were treated with 20 μM 15-d-PGJ$_2$ used in combination with 2 mM NaBut in a 24 h incubation period. Caco-2 cells were lysed and luciferase activity was monitored. Results shown are expressed as fold induction relative to basal luciferase activity in untreated control cells (considered as 1).

luciferase activity of the pκB-TATA-luc construct, which contains the HIV-1 enhancer, is abrogated by 15-d-PGJ$_2$ in a dose-dependent manner. A control construct containing the HIV-1 enhancer with inactivated NF-κB binding sites, pmκB-luc, was used to show that NF-κB is necessary for the NaBut activation of the HIV-1 LTR in Caco-2. Similar results to pκB-TATA-luc were found using the pNFκB-luc construct, which contains five consensus NF-κB binding sites. Together, these data suggest that NF-κB is involved in the 15-d-PGJ$_2$-mediated suppression of HIV-1 LTR activation in Caco-2 cells.

15-d-PGJ$_2$ alters the stability of IκBα proteins thereby altering NF-κB activation. Moreover in human bronchial epithelium, cyclopentone prostaglandin such has PGA$_1$, has been shown to enhance the expression of IκBα, a primary inhibitor of the pro-inflammatory transcription factor NF-κB (Thomas et al., 1998). In intestinal epithelial cells, IKK activity was lower in Caco-2 cells treated with 15-d-PGJ$_2$ and the inhibition of IKK activity was direct without increasing IκBα mRNA expression. Another group (Scher & Pillinger, 2005) reported an inhibitory effect of 15-d-PGJ$_2$ on NF-κB activation and expression of pro-inflammatory genes such as COX-2, IL-1β and TNF-α. Interestingly in human chondrocytes, 15d-PGJ$_2$, but not troglitazone, modulates IL-1β expression by inhibiting NF-κB and AP-1 activation pathways, a mechanism independent of PPAR-γ as observed with 15-d-PGJ$_2$ and NaBut-induced LTR activation. Moreover, it was shown by electrophoretic mobility shift assays that 15-d-PGJ$_2$ represses the nuclear translocation of the ubiquitous transcription factor NF-κB, which also results in the repression of HIV-1 transcription (Boisvert et al., 2008). Taken together results showed that the cyclopentone PGJ$_2$ inhibits NaBut-induced NF-κB binding activity in Caco-2 cells. This effect is caused by a reduction in the activity of IKK which results in reduced NF-κB nuclear translocation but not alterations in IκBα gene expression (Fig 8).
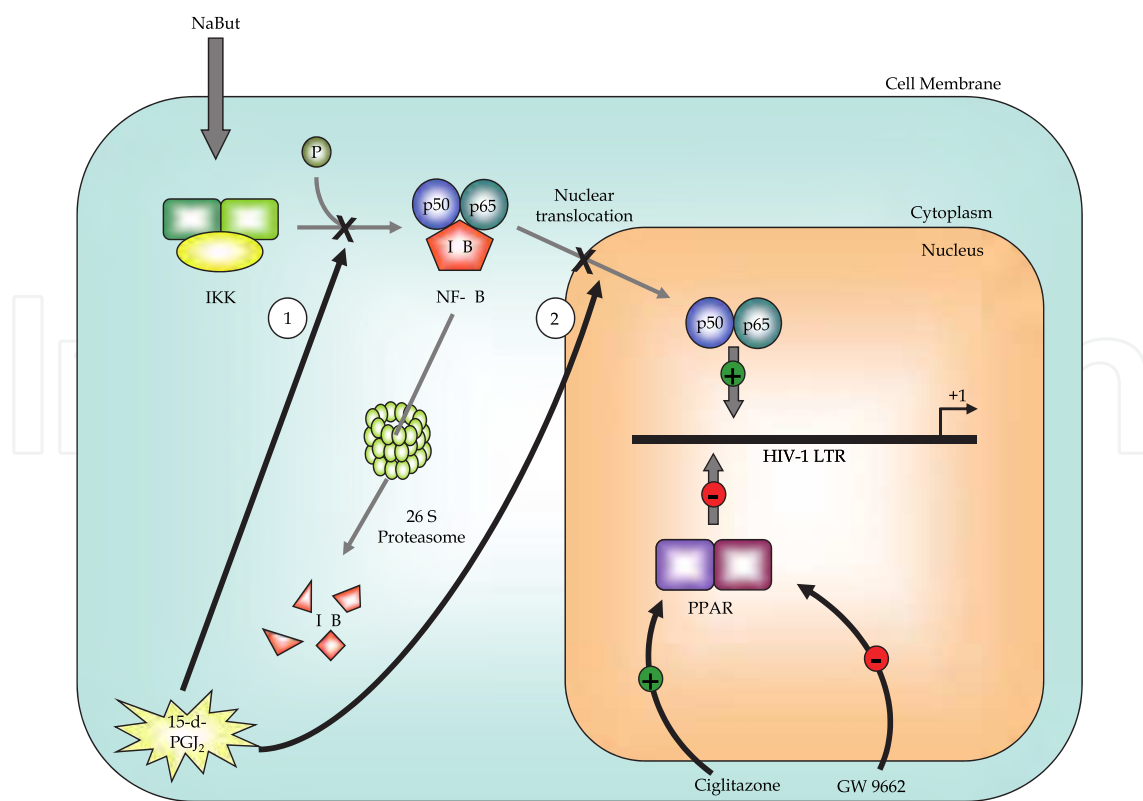

Fig. 8. Effect of 15-d-PGJ$_2$ on NF-κB and impact on HIV-1 transcription.

4. Conclusion

AIDS patients exhibit abnormal production of cyclooxygenase products. Prostaglandins are complex immunomodulatory molecules that shape, on one hand, the immune system and, on the other hand, have an influence on gene transcription by inducing or repressing several transcription factors in cells. Recent studies have led to a better understanding of the unique characteristics and importance of prostaglandins on HIV-1 transcription and replication (Fig 9).
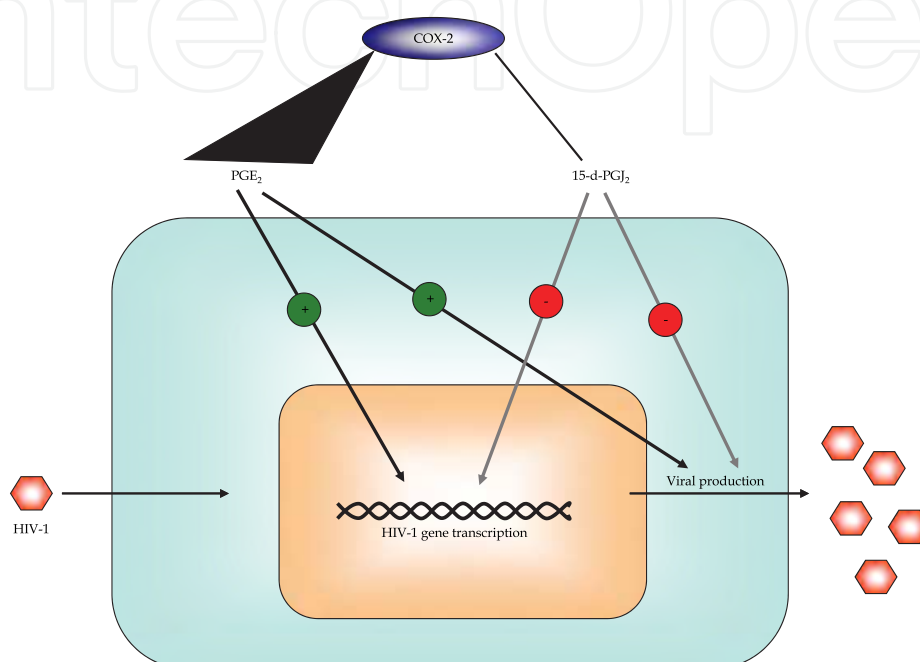

Fig. 9. A model for prostaglandins actions on HIV-1 pathogenesis.

Because of their intrinsic intracellular obligatory parasitic form of life, viruses depend heavily on cell metabolic machinery for their replication. Thus, changes in cellular metabolism might influence the viral life cycle. The data reported in this chapter highlight the positive action of PGE_2, a powerful cAMP-inducing agent, on the regulatory elements of HIV-1. PGE_2 has now emerged as an immuno-activator that acts on the EP_4 receptor that facilitates HIV-1 LTR activation. Elevated levels of PGE_2 detected in HIV-1-infected persons or induced by opportunistic pathogens might actively participate to immunological disturbances associated with AIDS and modify the pathogenesis of this retroviral disease by inducing a higher viral load. High concentrations of PGE_2 (up to 100 μM) found in seminal fluids of HIV-1-infected persons might directly enhance virus replication and facilitate viral transmission during sexual activities. Thus, analysis of the role of the PGE_2 signaling may provide deeper insight into the pathological mechanisms underlying HIV/AIDS exacerbation, which should be fully taken into account in developing an EP_4 antagonist as a therapeutic agent and its clinical application.

Accumulating data from several studies suggest that PGJ_2 has intracellular effects that may suppress inflammation. They include inhibition of NF-κB by multiple mechanisms such as IκB kinase inhibition, blockade of NF-κB nuclear binding and activation of PPAR-γ. The consequences of these activities are complex, but are likely to play a role in the prevention and/or resolution of inflammation. In this chapter, we showed the potentiality of the anti-

inflammatory molecule, PGJ$_2$, to modulate the NaBut effect on HIV-1 LTR in intestinal epithelial cells by a PPAR-γ-independent mechanism via the inhibition of NF-κB translocation to the nucleus. These results suggest that such prostaglandins may have therapeutic value in the treatment of HIV-1 infected individuals where inhibition of NF-κB activity may be required.

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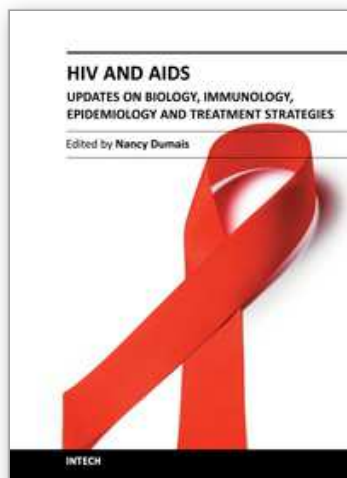
HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies

Edited by Dr. Nancy Dumais

The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

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