Mechanisms of Polymorphonuclear Neutrophil–Mediated Induction of HIV-1 Replication in Macrophages during Pulmonary Tuberculosis


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Background. Pulmonary tuberculosis (TB) can present with polymorphonuclear neutrophil (PMN)–predominant alveolitis. TB accelerates acquired immunodeficiency syndrome by increasing human immunodeficiency virus type 1 (HIV-1) replication and mutation in alveolar macrophages. A 16-kDa CCAAT/enhancer-binding protein β (C/EBPβ) isoform is a strong transcriptional repressor of the HIV long terminal repeat (LTR) in resting alveolar macrophages, leading to latent viral infection; its expression is lost during TB, derepressing the HIV LTR.

Methods. Lung segments were sampled from HIV/Mycobacterium tuberculosis–coinfected patients by means of bronchoalveolar lavage. In vitro coculture experiments defined the mechanism of induction of HIV-1 infection in macrophages by PMNs.

Results. Lung segments from patients with PMN-predominant TB had a markedly elevated viral load. Direct contact between activated PMNs and macrophages stimulated HIV-1 replication and LTR transcription and down-regulated inhibitory C/EBPβ. Isolated PMN membranes substituted for PMN contact, derepressing the HIV-1 LTR. The lipid raft fraction of PMN membranes expressed CD40 ligand (CD40L), CD28, and leukocyte function–associated antigen 1 (LFA-1 [i.e., CD11a and CD18]), and PMN activation increased lipid raft expression of CD40L and CD28. Blocking antibodies to CD40L, CD28, and LFA-1 inhibited PMN membrane–mediated HIV-1 LTR derepression. Alternately, cross-linking of macrophage receptors for CD40L, CD28, and LFA-1 (CD40, CD80/86, and intercellular adhesion molecule 1) abolished inhibitory C/EBPβ expression.

Conclusion. PMN-macrophage contact derepresses the HIV-1 LTR and enhances HIV-1 replication in alveolar macrophages during pulmonary TB. Derepression is mediated through costimulatory molecule signaling.

There are 40 million persons infected with HIV-1, and one-third of the world’s population has been infected with Mycobacterium tuberculosis; the intersection of HIV and M. tuberculosis in developing countries has become a public health crisis [1, 2]. There is a reverberating interaction between these 2 pathogens [3]. HIV-1–infected patients are unable to control latent tuberculosis (TB) and almost invariably experience progression to active TB. In addition, TB is also associated with an acceleration of AIDS [4, 5]. TB markedly increases replication of HIV-1 in the lungs and produces virus with mutations in the gp120 V3 loop sequences, suggesting a more virulent phenotype [6, 7]. Enhanced HIV-1 replication and mutation likely underlie the deleterious effect of TB on immune function in persons with AIDS.

Alveolar macrophages are the major source of HIV-1 in the lungs of persons with TB [8, 9], leading to the possibility that alveolar macrophages are a reservoir for viral reactivation after prolonged treatment with highly active antiretroviral therapy [10]. Bronchoalveolar lavage (BAL) has identified significant increases in in-
flammatory cells, such as polymorphonuclear neutrophils (PMNs) or lymphocytes, in the lungs of persons with TB [6, 11].

Transcriptional initiation in the HIV-1 long terminal repeat (LTR) is a major regulator of HIV-1 replication. The HIV-1 LTR binds CCAAT/enhancer-binding protein (C/EBP), and mutation of the C/EBP-binding sites abolishes HIV replication in monocytes [12, 13]. There are 2 C/EBPβ isoforms expressed from the same transcript through a process of translational state site selection. The short 16-kDa isoform is a dominant negative transcription factor repressing C/EBP-containing promoters when expressed at 20% of the level of the 37-kDa stimulatory isoform. Overexpression of the inhibitory 16-kDa C/EBPβ inhibits HIV-1 replication and LTR promoter function [14]. During active TB, alveolar macrophages lose the inhibitory isoform, leading to increased viral replication [9]. When expression of the inhibitory 16-kDa C/EBPβ is specifically inhibited by an antisense oligonucleotide, HIV-1 replication in macrophages is enhanced [15]. We have previously demonstrated that contact between activated T cells and macrophages leads to HIV-1 LTR activation and loss of inhibitory C/EBPβ [9, 16].

PMNs may have important roles in the control of mycobacterial infection [11, 17]. In addition, bacterial pneumonia presents with PMN-predominant inflammation, and it accelerates AIDS by increasing HIV-1 replication in macrophages [18, 19]. However, the influence of PMNs on viral replication in macrophages is poorly understood. Therefore, we evaluated the role of PMNs in regulating HIV-1 replication in alveolar macrophages, using TB pneumonia as a model system. In the present article, we report that contact between PMNs and macrophages leads to loss of C/EBPβ, enhancement of HIV-1 LTR transcription, and increased HIV-1 replication.

**PATIENTS AND METHODS**

**Study population.** Research bronchoscopy was performed for 16 HIV-1–infected patients with pulmonary TB. Six of these patients were found to have PMN-predominant alveolitis (>20% PMNs). The BAL protocol was approved by the human subjects review committees of New York University Medical Center and Bellevue Hospital Center and was performed as described elsewhere [6, 7]. All patients provided written, informed consent. HIV-1 load was quantified in a clinical laboratory (Ultrasonic Roche Molecular Systems).

**Purification of PMN- and monocyte-derived macrophages.** Whole blood was separated into peripheral blood mononuclear cells (PBMCs) and red blood cells (RBCs) containing PMNs, by means of ficoll-hypaque (Amersham Pharmacia Biotech) sedimentation. PMNs (>99.9% granulocytes, of which >95% were PMNs) were separated from RBCs by means of dextran sedimentation (3% dextran in 0.9% NaCl solution at 1 g for 30 min). Primary granulocytes were also negatively selected from whole blood of healthy volunteers, by use of RosetteSep Granulocyte enrichment (StemCell Technology). The purified PMNs were >95% viable, as judged by trypan blue exclusion. PMNs were activated by 100 ng/mL mannose (Man)–lipopolysaccharide (LAM) (provided by Dr. J. Belisle at Colorado State University, Fort Collins) for 2–24 h.

**Cell culture.** Monocyte-derived macrophages, alveolar macrophages, THP-1 cells (ATCC TIB-202), or BF-24 cells (AIDS Research and Reference Reagent Program 1296) were cultured in RPMI 1640 with 10% fetal calf serum. THP-1 and BF-24 cells were differentiated with 20 ng/mL phorbol myristate acetate (PMA) for 48 h and were incubated with interferon (IFN)–β (Biosource) at 1 U/mL for 24 h to use as macrophages [9, 16]. Where noted, activated PMNs and alveolar macrophages, monocyte-derived macrophages, or THP-1 cells were separated by means of a 0.4-μm pore cell culture insert (Millipore). Nuclear extracts were prepared by NP-40 lysis as described elsewhere [19]. Immunoblot assays were performed as described elsewhere [9]. Protein extracts for chloramphenicol acetyltransferase (CAT) ELISA (Roche Molecular Biochemicals) were processed according to the manufacturer’s instructions.

**HIV-1 and M. tuberculosis infection.** THP-1 macrophages were infected with R5 strains of either HIV-1 Ba-L or HIV-1 NLHxADA (1–10 ng of p24 antigen per milliliter) at 37°C for 4 h. The R5 strains were provided by Dr. A. Pinter (Public Health Research Institute [PHRI], Newark, NJ). They were washed 3 times with PBS and were incubated with and without *M. tuberculosis* TN913 (a clinical isolate obtained from the PHRI Tuberculosis Center) at an MOI of 3, with and without fresh PMNs (PMN:THP-1, 3:1) and with and without an insert. After 3 days’ incubation, HIV-1 RNA was extracted from the supernatants and was assayed as an HIV-1 load by measurement of HIV-1 complementary DNA by use of real-time quantitative polymerase chain reaction assay performed using ABI Prism 7770, as described elsewhere [20, 21].

**Detergent-resistant membrane and lipid raft isolation.** Cells were lysed on ice with 200 μL of 1% Triton X-100 and 3 μg/mL aprotinin, 2 μg/mL leupeptin, 2 μg/L pepstatin, 1 mmol/L dithiothreitol, 1 mmol/L phenylmethylsulfonyl fluoride, and 1 mmol/L Na3VO4 in MNE buffer (25 mmol/L MES [pH 6.5], 150 mmol/L NaCl, and 5 mmol/L ethylenediaminetetraacetic acid). The sample was then overlaid with 1000 μL of 30% sucrose and 600 μL of 5% sucrose in MNE buffer and was spun for 16–24 h at a mean of 130,000 g at 4°C in a Beckman TLS 55 swing rotor by use of a Beckman Optima TLX Ultracentrifuge (Beckman). Two hundred–microliter fractions were harvested serially from the top of the gradient. The detergent-resistant membrane/raft fraction was usually obtained in fractions 1–4.

**Immunofluorescence confocal laser microscopy.** Fresh PMNs were isolated as described above, were activated with lipopolysaccharide (LPS) or Man-LAM for several hours, and
then were attached to poly-L-lysine–coated coverslips and fixed in 4% paraformaldehyde/PBS. Cells were then fixed in acetone/methanol (vol/vol, 1:1). After undergoing blocking in nonspecific IgG for 30 min and washing by PBS with Tween 20, the cells were incubated with primary antibody (1:1000) overnight. After washing in PBS, the cells were incubated with appropriate secondary antibodies containing Alexa-Fluor–labeled 488, 563, or 633 IgG (H+L) antibodies (Molecular Probes) (1:500) for 30 min. After a final wash, the samples were mounted with VectraShield mounting medium (Vector Laboratories), and images were obtained and quantified by Leica TCS NT imaging software for a Leica DM RBE confocal microscope. All data were collected by sequential image recording mode, to prevent 2-photon combination [21].

**Data analysis.** Nonparametric data, including differences between 2 groups, were evaluated using the Wilcoxon signed rank test. Paired Student’s *t* tests were used for in vitro viral load and reporter construct assays. *P*<.05 was considered to be statistically significant.

**RESULTS**

**Stimulation of HIV-1 replication by activated PMNs.** Patients with TB with >20% PMNs had a significantly higher HIV-1 burden in the involved lobe, compared with the uninvolved lobe (figure 1A). When data for all lobes were pooled, there was a trend toward a correlation between HIV load and PMN content (*r* = 0.49; *P* = .08). These data demonstrate that PMN infiltration of the alveolar space is associated with increased HIV-1 replication in vivo. To test this association in vitro, alveolar macrophages from an HIV-1–infected patient without lung disease were cocultured with Man-LAM–activated PMNs. In the absence of stimulation, no measurable virus was released from the alveolar macrophages, suggesting that the cells from this patient were latently infected. Within 6 h of the addition of activated PMNs, the HIV-1 load increased 12-fold (figure 1B).

To model enhanced HIV-1 replication in vitro, we used THP-1 macrophages infected with HIV-1, which accurately recapitulate viral replication in macrophages [9, 16]. HIV-1–infected macrophages cocultured with either *M. tuberculosis* or unstimulated PMNs released minimal HIV-1 virions (figure 1G, rows 2 and 3). However, the combination of both *M. tuberculosis* and PMNs resulted in a 2.3-fold increase in HIV-1 replication (*P*<.05, compared with medium control). This was dependent on direct PMN-macrophage contact, because a 0.4-μm insert, which prevented contact but which allowed soluble factors to cross, did not significantly change HIV-1 production. Together, these results suggested that TB-activated PMNs may increase HIV-1 replication in macrophages and by a contact-dependent pathway.

**Requirement of PMN contact for activation of the HIV-1 LTR.** The functional effect of PMN coculture on LTR pro-
moter activity was assayed using THP-1 cells with an integrated HIV-1 LTR CAT promoter reporter (BF-24 cells). Coculture of activated PMNs with THP-1 macrophages produced a 5-fold increase in HIV-1 LTR promoter activity within 6 h (figure 1D, row 1). Similar to what was observed in the HIV-1 replication experiments, PMN-mediated induction of the HIV-1 LTR was contact dependent, because a 0.4-μm insert reduced HIV-1 LTR activity by 50% (figure 1D, row 2) ( \( p = .025 \), for the comparison of direct contact with filter insert). To better understand the nature of the contact requirement, experiments were repeated with membrane fractions isolated from PMNs by sucrose sedimentation. The membrane fractions were used as a surrogate of the contact component of PMN-macrophage interaction. The membrane fractions of PMNs produced a 4-fold activation of the HIV-1 LTR ( \( p = .02 \), compared with unstimulated THP-1 macrophages). Macrophage membrane preparations did not significantly induce HIV-1 LTR activity ( \( p = .43 \), compared with unstimulated THP-1 macrophages).

**Abolishment of C/EBPβ expression in macrophages by activated PMNs.** The ability of PMN contact to activate the HIV-1 LTR in macrophages is similar to the ability of lymphocytes to activate the LTR in macrophages. Because lymphocyte contact leads to loss of inhibitory C/EBPβ, we tested whether PMN contact also produced derepression. Unstimulated monocyte-derived macrophages express high levels of the 16-kDa inhibitory isoform of C/EBPβ (figure 2A, lane 1). Unstimulated PMNs had no effect on inhibitory C/EBPβ (figure 2A, lane 2). Coculture of Man-LAM–activated PMNs with monocyte-derived macrophages resulted in the loss of both isoforms of C/EBPβ within 30 min (figure 2A, lane 3). Because the short inhibitory isoform is dominant negative, this should derepress the system. Equal loading in each lane was assured by reprobing the filter with actin antibodies. The addition of apoptotic UV-irradiated PMNs did not result in the loss of the inhibitory C/EBPβ (figure 2A, lane 4).

Similar to monocyte-derived macrophages, resting alveolar macrophages expressed inhibitory C/EBPβ. Man-LAM–activated PMNs were capable of abolishing both C/EBPβ isoforms in human alveolar macrophages (figure 2B, lane 2). This result was abolished with a 0.4-μm insert separating PMNs from the macrophages (figure 2B, lane 3). These results demonstrate that direct contact between activated PMNs and macrophages is required for the loss of C/EBPβ and subsequent promoter derepression.

**Requirement of engagement of CD40, CD80/86, and intracellular adhesion molecule (ICAM)–1 for contact-mediated PMN activation of macrophages.** The requirement of cell-to-cell contact for PMN-mediated loss of C/EBPβ and an increase in LTR promoter activity led us to focus on the mechanism of contact-mediated PMN activation of macrophages. First, we evaluated whether aggregation of macrophage-expressed costimulatory molecules with antibodies attached to agarose beads could reproduce the effects of PMN contact. Inhibitory 16-kDa C/EBPβ expression was abolished within 30 min when a combination of antibodies against CD40, vascular cell adhesion molecule–1, and B7 (stimulating antibodies) was added to THP-1 macrophages attached to agarose protein A/G beads (figure 3, lane 2). This required the scaffolding effect of protein A/G beads, because antibodies added without protein A/B beads did not abolish C/EBPβ expression (data not shown). Any combination of 2 stimulatory antibodies did not abolish inhibitory C/EBPβ expression (figure 3, lanes 3–5). In addition,
Expression of CCAAT/enhancer-binding protein β (C/EBPβ) expression in THP-1 macrophages after ligation of costimulatory molecules by antibodies. Untreated cells have strong C/EBPβ expression (lane 1). Expression of 16-kDa inhibitory C/EBPβ after cross-linking of intercellular adhesion molecule (ICAM)-1, CD80, and CD40 by antibodies attached to protein A/G beads (lane 2). Combinations of any 2 antibodies did not abolish inhibitory C/EBPβ expression (lanes 3–5).

Expression of ligands for CD40, CD80/86, and ICAM-1 in lipid rafts by PMNs. The requirement for ligation of CD40, CD80/86, and ICAM-1 on the macrophage for loss of inhibitory C/EBPβ suggested the presence of corresponding ligands in PMNs. CD40 ligand (CD40L) activates CD40, CD28 activates CD80/86, and LFA-1 activates ICAM-1. PMNs were assayed with dual-color immunofluorescent confocal microscopy to test whether CD40L, CD28, and LFA-1 were expressed in activated PMNs. We observed strong CD40L expression in PMNs (figure 4A, row 1). CD40L was localized to the lipid raft portion of the PMN membrane, as determined by colocalization with the protein Lyn, which is a molecule known to be localized to PMN lipid rafts (Lyn is colored red, CD40L is colored green, and yellow shows where Lyn and CD40L are colocalized in figure 4A). In similar fashion, CD11a, a component of LFA-1 (CD11a/CD18), was expressed in a punctate pattern on the surface of activated PMNs (figure 4A, row 2). Colocalization of CD11a with Lyn confirmed its presence in the lipid raft portion of PMN membranes (figure 4A, row 2). CD18, the other component of LFA-1, was also found in the lipid rafts of activated PMNs (data not shown). CD28 was strongly expressed on ac-

tivated PMNs and was colocalized with both CD40L and CD11a in the lipid rafts of PMNs (figure 4B).

We then used sucrose density gradient centrifugation to confirm that CD40L, CD28, DC18, and CD11a were expressed in the lipid raft fraction of PMN membranes. Proteins located in the lipid raft fraction will have low buoyant density because of their association with lipids and will float to the top of the gradient. Western blots were used to confirm the presence of costimulatory molecules in the buoyant fractions of membrane preparations. CD40L, CD28, CD18, and CD11a were present in buoyant fractions of sucrose gradients, along with Lyn and Gα-i, which are proteins that localize in lipid rafts (figure 4C, fractions 2–6). These data suggested that the lipid raft portion of activated PMNs expressed the 3 costimulatory molecules CD40L, CD28, and LFA-1.

It is possible that alteration of the location or content of the costimulatory molecules occurred during PMN activation. To test this possibility, sucrose gradients of unstimulated and LPS-stimulated PMNs were probed for CD40L and CD28. LPS stim-
Figure 5. Mobilization of costimulatory molecules to the lipid raft fraction of polymorphonuclear neutrophils (PMNs) by lipopolysaccharide (LPS), mannose (Man)–lipoarabanomannan (LAM), and intercellular adhesion molecule (ICAM)–1. A, Immunoblot of sucrose gradient fractions probed with antibody to CD40 ligand (CD40L). CD40L is expressed in both resting and LPS-stimulated PMNs (Input). The distribution of CD40L in resting PMNs is in fractions 2–5. After LPS stimulation, CD40L is expressed in fractions 1–3. Fractions 1–3 contain lipid rafts. B, Immunoblot of lipid rafts for CD40L. CD40L was not expressed in the lipid raft fraction of unstimulated PMNs (lane 1) but was weakly expressed at the bottom of the gradient (lane 2). Thirty minutes after LPS stimulation, CD40L was strongly expressed in the lipid raft fraction (lane 3). CD40L was mobilized to the lipid raft fraction by the mycobacterial cell wall product Man-LAM (lane 5) and by soluble ICAM-1 (lane 7). C, Immunoblot of lipid rafts for CD28. CD28 was weakly expressed in whole-cell homogenates of PMN (lane 1). There was marked up-regulation of CD28 after LPS stimulation (lane 2).

Requirement of CD40L, CD28, and LFA-1 for down-regulation of inhibitory C/EBPβ and derepression of the HIV-1 LTR in alveolar macrophages. We next evaluated whether purified PMN lipid rafts activated macrophages similar to intact PMNs. As with whole PMNs, activated PMN lipid rafts down-regulated C/EBPβ expression in macrophages (figure 6A, lane 2). The lipid raft fraction of PMNs also increased HIV-1 LTR activity 10-fold in THP-1 macrophages (data not shown). Antibody to CD40L (CD154), CD28, and CD11a partially blocked the activity of the lipid raft fraction to down-regulate inhibitory 16-kDa C/EBPβ (figure 6A, lanes 3–5). To ascertain the functional significance of the lipid rafts, experiments were repeated with BF-24 cells. When anti-CD28 antibody was added to the lipid raft fractions, there was a 20% inhibition of LTR activity (figure 6B). Anti-CD40L (CD154) antibody produced a 60% inhibition in LTR activity, and anti-CD11a antibody produced a 30% inhibition.
DISCUSSION

We found that HIV-1/M. tuberculosis–coinfected patients with >20% PMNs have a marked increase in HIV-1 replication. Stimulated PMNs were capable of activating HIV-1 replication in macrophages through direct contact in vitro, with resultant induction of HIV LTR promoter activity. This is mediated, in part, by abolishing inhibitory C/EBPβ, leading to derepression of the HIV-1 LTR. Contact-mediated activation of macrophages is dependent on cross-linking of 3 costimulatory receptors (CD40, CD80/86, and ICAM-1) by their respective ligands (CD40L, CD28, and LFA-1) expressed in the lipid raft fraction of PMN membranes.

We recently described a role for lymphocyte contact in inducing HIV-1 replication in macrophages. This process is dependent on engagement of macrophage costimulatory receptors [16]. However, many HIV-1/M. tuberculosis–coinfected patients with bilateral, cavity TB have PMN-predominant alveolitis. These individuals have a similar increase in HIV-1 replication, and Man-LAM–stimulated PMNs in vitro were capable of increasing HIV-1 replication and HIV-1 LTR activity in macrophages. Similar to what was observed in alveolar macrophages in vivo, stimulated PMNs in contact with macrophages result in loss of inhibitory C/EBPβ.

The ability of PMNs to derepress the HIV-1 LTR in macrophages is dependent on the state of activation of the PMNs. Apoptotic PMNs down-regulated inflammatory cytokine production [22]. In our experiments, PMNs made apoptotic by UV irradiation failed to alter expression of the dominant negative C/EBPβ transcription factor. In contrast, live and/or necrotic PMNs can have the opposite effect, stimulating inflammatory cytokine release [23, 24]. Our results are consistent with these observations, because only PMNs stimulated with bacterial cell wall components were capable of contact-mediated macrophage activation. Our results extend these findings by identifying cell surface coreceptors and transcriptional repressors that mediated macrophage activation by stimulated PMNs.

The predominant component of PMN-mediated HIV-1 induction is dependent on cell-to-cell contact, because separation of PMNs and macrophages by a 0.4-μm insert prevents loss of inhibitory C/EBPβ, full HIV-1 LTR activity, and enhanced HIV-1 replication. Ligation of CD40, B7, and ICAM-1 on macrophages by antibodies attached to protein A/G beads reproduced the effects of PMN contact on the loss of inhibitory C/EBPβ.

Stimulated PMNs express CD40L, CD28, and LFA-1 in the lipid raft fraction of PMN membranes. Although previous investigations reported the presence of LFA-1 and CD28 on the surface of PMNs [25–30], this is, to our knowledge, the first description of CD40L on PMNs. The presence of CD40L is essential, because all 3 ligands must be engaged for macrophage activation to occur, and because blocking antibodies to CD40L markedly inhibit the stimulatory activity of PMN membranes.

The ability of isolated PMN lipid rafts to reduce inhibitory C/EBPβ and enhance HIV-1 LTR activity make it unlikely that PMN-derived soluble factors or intracellular proteins lead to macrophage activation by derepression. Finally, stimulation of PMNs with bacterial products or soluble ICAM-1 increased expression of CD40L in the PMN lipid rafts. Much of the data on the role of lipid rafts in costimulatory molecule function has focused on antigen-presenting cell (APC)/lymphocyte interaction during formation of the immunological synapse. There are increasing data that costimulatory molecules are important for mediating the innate immune response and modulating HIV-1 replication. The induction of CD40L in PMNs may explain why deletion of CD40 impairs the innate immune response [26]. CD40L also appears to be important for the ability of HIV to infect macrophages [31]. CD28 has been reported on PMNs [32] and mediates induction of HIV-1 replication in vitro [33]. The requirement of costimulatory molecule engagement for PMN-mediated macrophage activation implies an important role for costimulatory molecules in the innate immune response.

Our data detail that ≥3 receptor-ligand dyads are required for contact-mediated macrophage activation by PMNs. CD40L interacts with CD40, CD28 interacts with CD80/86 (B7), and LFA-1 interacts with ICAM-1. PMNs can down-regulate transcriptional inhibitors within 30 min in vitro. The rapidity of derepression is consistent with the role of PMN-expressed costimulatory ligands as a membranous cellular component of the innate immune response. Macrophage activation via PMN-expressed costimulatory ligands, in turn, results in further amplification of the host immune response. Our data also suggest that ICAM-1 is able to activate PMNs by recruiting CD40L to the lipid raft fraction of PMN membranes. In this way, macrophages may further activate PMNs.

Although the present study principally examined HIV-1 replication and HIV-1 LTR activity, the presence of C/EBPβ sites within the promoters of most inflammatory cytokines/chemokines suggests that proinflammatory cytokine production and HIV-1 replication are coordinately regulated during inflammation. We previously documented that TNF-α correlates closely with HIV-1 LTR activity in vivo [7]. This form of regulation may also extend to other myeloid cell types, because inhibitory C/EBPβ produces HIV latency in glial cells [34] and in macrophages in a simian immunodeficiency virus model [35]. The data from the present investigation support a novel role for PMNs as a component of the innate immune response that provides signals leading to loss of a dominant negative transcription factor. This, in turn, derepresses the HIV-1 LTR in macrophages through cell-to-cell contact. A reverberating interaction between PMNs and macrophages is likely. It is likely that the increase in viral burden produced by PMN-macrophage contact underlies the acceleration of AIDS produced by
TB and other forms of pneumonia. An important clinical correlate of these observations is that prevention of secondary infections will slow the progression of AIDS.

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References