Arc of a Vicious Circle

Pathways Activated by *Mycobacterium tuberculosis* That Target the HIV-1 Long Terminal Repeat

James V. Falvo^{1,2}, Shahin Ranjbar^{1,2}, Luke D. Jasenosky¹, and Anne E. Goldfeld^{1,3,4}

¹Immune Disease Institute and Program in Cellular and Molecular Medicine, Children's Hospital Boston; ²Department of Pediatrics and ³Department of Medicine, Harvard Medical School; and ⁴Department of Immunology and Infectious Diseases, Harvard School of Public Health, Boston, Massachusetts

In this review, we examine how a subset of signal transduction cascades initiated by *Mycobacterium tuberculosis* (Mtb) infection modulates transcription mediated by the human immunodeficiency virus type 1 long terminal repeat (HIV-1 LTR). We describe two distinct phases of signaling that target transcription factors known to bind the HIV-1 LTR, and thus drive viral transcription and replication, in cells of the Mtb-infected host. First, Mtb-derived molecules, including cell wall components and DNA, interact with a number of host pattern recognition receptors. Second, cytokines and chemokines secreted in response to Mtb infection initiate signal transduction cascades through their cognate receptors. Given the variation in cell wall components among distinct clinical Mtb strains, the initial pattern recognition receptor interaction leading to direct LTR activation and differential cytokine and chemokine production is likely to be an important aspect of Mtb strain-specific regulation of HIV-1 transcription and replication. Improved understanding of these molecular mechanisms in the context of bacterial and host genetics should provide key insights into the accelerated viral replication and disease progression characteristic of HIV/TB coinfection.

Keywords: HIV/TB coinfection; transcription; signal transduction; innate immunity; cytokines

Although a great deal of research has been devoted to understanding the pathological mechanisms underlying infection by *Mycobacterium tuberculosis* (Mtb) or by human immunodeficiency virus (HIV) separately, relatively little is known about the molecular mechanisms through which these pathogens modulate one another in the setting of HIV/Mtb coinfection (1–4). Here, we combine the current knowledge of signal transduction pathways initiated by Mtb infection and of transcription factors that interact with the HIV-1 long terminal repeat (LTR) with the goal of elucidating the mechanisms underlying Mtb-mediated augmentation of HIV-1 replication in the coinfecting host.

When cells are infected by Mtb bacilli or interact with Mtb-derived molecules, a number of signal transduction cascades are triggered. These include the mitogen-activated protein kinase (MAPK), NF- κ B, and CCAAT/enhancer-binding protein (C/

EBP) pathways, which result in transcriptional activation of the HIV-1 LTR and numerous host genes involved in the innate immune response. Although HIV-1 proteins can also modulate signal transduction pathways in mononuclear phagocytes (5), it is a long-standing observation that infection by HIV-1 does not activate the conventional “antiviral response,” including activation of the TNF and IFN- β genes, in monocytes and T cells (6, 7). Thus, this review focuses on the signal transduction pathways initiated by Mtb infection that subsequently activate transcription through the HIV-1 LTR.

It has long been established that in monocytic cells, Mtb enhances transcription driven by the HIV-1 LTR (8, 9). Macrophages and dendritic cells are major reservoirs for HIV-1 (5), and cells of either lineage are susceptible to concurrent Mtb infection (10). It has also been shown that activation of host gene expression in primary human macrophages coinfecting with HIV-1 and Mtb more closely resembles that of macrophages infected with Mtb alone rather than with HIV-1 alone (11). Based on these data, this review focuses on host–pathogen interactions and cytokine stimulation relevant to these cell types.

We describe transcription factors that interact with the HIV-1 LTR and two phases of signal transduction in response to Mtb infection resulting in LTR activation: (1) the initial direct phase triggered by the interaction of mycobacterial components with host pattern recognition receptors (PRRs) and (2) a subsequent secondary phase initiated by the engagement of cytokines, secreted in response to Mtb infection, with their cognate cell surface receptors. We also discuss how variations in cell wall composition among distinct clinical Mtb strains can correlate with strain-specific effects upon HIV-1 replication.

THE HIV-1 LTR AND ASSOCIATED TRANSCRIPTION FACTORS

After integration of HIV-1 into the host genome, the LTR serves as a promoter region to drive transcription of the approximately 10-kb viral genome. Regulation of LTR activity involves the recruitment of host transcription factors and chromatin remodeling factors (12, 13). The HIV-1 LTR contains binding motifs for a number of transcription factor families, including the Sp, NF- κ B, C/EBP, nuclear factor of activated T cells (NFAT), activator protein (AP)-1, and activating transcription factor (ATF) families, within the U3 and U5 regions (Figure 1). The number and arrangement of these motifs vary among HIV-1 subtypes (14–16).

The HIV-1 LTR contains multiple transcription factor binding sites within a compact regulatory sequence, and there are functionally cooperative interactions between some LTR-bound transcription factors, such as NF- κ B and Sp1 (17). These

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Correspondence and requests for reprints should be addressed to James V. Falvo, Ph.D., Immune Disease Institute, Harvard Medical School and Program in Cellular and Molecular Medicine, Children's Hospital Boston, Boston, MA. E-mail: falvo@idi.harvard.edu

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Figure 1. Transcription factor binding motifs in the human immunodeficiency virus type 1 (HIV-1) long terminal repeat (LTR). *Top:* Approximate positions of κ B (red), Sp1 (blue), AP-1 (purple), and C/EBP (green) binding sites in the context of the HIV-1 subtype B LTR are indicated. *Bottom:* Representative sequences from the LTR core enhancer region (between the RBE III and Sp1-III sites (14, 16, 106) from isolates of the indicated subtypes of HIV-1 between the upstream U3 modulatory region and the conserved Sp1 binding sites of the core promoter region. The highlighted sequences are κ B motifs (red), most of which bind NF- κ B and NFATp (half-sites bound by NFATp [30] indicated by arrows) and some of which are also highly conserved NFAT5 binding motifs (red, with 3' adenine in yellow).

two features are highly reminiscent of the promoters of host immune response genes, including IFN- β (18) and TNF (19). Moreover, certain DNA binding motifs in the LTR can alternatively bind to multiple members of a transcription factor family or even to transcription factors of different families. This is similar to the TNF gene promoter, in which the same series of DNA motifs interacts with different sets of transcription factors in a cell type-specific and stimulus-specific fashion (20–26). In commandeering the host transcription machinery, the HIV-1 LTR has in effect co-opted important components involved in regulation of the host innate immune response, thus recapitulating strategies used by host immune response genes for their own regulation (1, 2).

The Core Promoter and Enhancer: Sp, κ B, and NFAT Motifs

The basal or core promoter of the HIV-1 LTR, which includes approximately 80 nucleotides upstream of the start site of transcription within the U3 region, contains three well-conserved GC-rich Sp motifs. Within the Sp protein family, Sp1, Sp3, and Sp4 can recognize these motifs; however, the ubiquitous activator Sp1 is the predominant factor involved in LTR-mediated transcriptional activation (15).

The overwhelming majority of studies on HIV-1 LTR transcriptional regulation have examined HIV-1 subtype B, in which two κ B motifs are present in the enhancer region. However, enhancer regions from isolates of HIV-1 subtypes C and E, which predominate in regions of Africa and Asia (27), typically contain three κ B motifs and one κ B motif, respectively (Figure 1). Due to the asymmetrical sequence of the HIV-1 enhancer κ B motif (5'-GGGACTTTCC-3'), it is a preferred target of the classical form of NF- κ B, a heterodimer of the subunits p50 and p65 (also known as RelA), the latter of which is a potent transcriptional activator (28).

In T cells, the same κ B motif is also a binding site for proteins of the NFAT family, including NFATp (also known as NFAT1 and NFATc2) and NFATc (also known as NFAT2 and NFATc1) (29). Biochemical and structural data demonstrate that NFATp can recognize the κ B site as a dimer (30, 31),

consistent with the spacing between the half-sites (30). Due to steric constraints at the tandem κ B motifs of the subtype B LTR, however, NFATp concurrently binds the upstream κ B motif as a dimer and the downstream site as a monomer (31). Immediately 3' of the downstream κ B motif, an adenine (5'-GGGACTTTCCA-3') is exquisitely conserved across the LTRs of all major HIV-1 subtypes, as well as in HIV-2 and simian immunodeficiency virus (32). This adenine enables the downstream κ B motif to bind another member of the NFAT family, NFAT5, which is required for maximal levels of basal transcriptional activity of the LTR in human monocytic cells and replication of multiple HIV-1 subtypes in human monocyte-derived macrophages (32). Thus, the occupancy of the HIV-1 LTR κ B motifs by NF- κ B or NFAT proteins is directed by sequence and cell type.

The U5 and U3 Modulatory Regions: AP-1 and C/EBP Motifs

Transcription factor binding sites outside of the core promoter and enhancer region (Figure 1) include AP-1 sites, which are recognized by transcription factors that are targets of the MAPK signal transduction cascade (33). The canonical AP-1 binding factor is a heterodimer of c-fos and c-jun; c-jun is a substrate for MAPKs of the c-jun N-terminal kinase (JNK) family (33). AP-1 sites are found in the U3 or U5 regions, and LTRs with zero to four AP-1 sites, have been reported among the different HIV-1 subtypes (14, 15).

Up to four binding sites for the C/EBP protein family are found in the subtype B LTR: three in the U3 modulatory region and one at the 3' end of the U5 region (15). For cells of the monocyte/macrophage lineage in particular, it has been reported that C/EBP and at least one C/EBP binding site in the LTR are essential for efficient HIV-1 replication (15, 34). In the later stages of monocyte-to-macrophage differentiation, or upon stimulation of macrophages by the cytokines IL-1, TNF, or IFN- γ , the levels of C/EBP β (also known as nuclear factor IL-6) and C/EBP δ increase (15). An inhibitory

16-kD isoform of C/EBP β is also expressed in macrophages after Mtb infection, resulting in suppression of transcription from the HIV-1 LTR in isolated macrophages, but lymphocyte contact inhibits the expression of this C/EBP β isoform and promotes enhanced levels LTR-driven transcription (35, 36).

THE PRR-MEDIATED SIGNAL TRANSDUCTION PHASE: INNATE IMMUNE RESPONSE TO MTB-DERIVED LIGANDS

The innate immune response can be activated by a range of molecular components of Mtb, including lipids, lipoproteins, and glycolipids from its cell wall and membranes, as well as its DNA. These Mtb-derived molecules, or pathogen-associated molecular patterns (PAMPs), serve as ligands that engage PRRs of the host cell. PRRs reside at the plasma membrane; at the membranes of endosomes, lysosomes, endolysosomes, and the endoplasmic reticulum; or in the cytoplasm. Numerous *ex vivo* studies of the activation of macrophages and dendritic cells by molecules isolated from Mtb have revealed several PRRs involved in the recognition of mycobacterial components, which in turn activate intracellular signaling pathways that result in the modification or translocation of transcription factors and the enhancement of transcription mediated by the HIV-1 LTR.

Toll-Like Receptors

Toll-like receptors (TLRs) are a family of transmembrane proteins that are critical mediators of protective immunity against infection by pathogens. TLR homo- and heterodimers interact with specific components derived from bacteria, fungi, viruses, and parasites (37). Mtb-derived PAMPs function as agonists of three TLRs: TLR2, TLR4, and TLR9. TLR4, the first of the TLR family members to be identified and the classical receptor for LPS from gram-negative bacteria (37), was shown to respond to heat-sensitive mycobacterial components (38) and, specifically, to the 38-kD glycolipoprotein and HSP70 from Mtb (39, 40). TLR9, which recognizes the unmethylated CpG motifs that are enriched in bacterial genomes (37), has also been shown to play a role in the response to Mtb infection (41, 42). The TLR principally involved in the host response to Mtb is TLR2, which heterodimerizes with TLR1 and TLR6 (37) and interacts with a range of Mtb cell wall lipoproteins and glycolipids, including lipoarabinomannan (LAM), phosphatidylinositol mannoside (PIM), lipomannan, trehalose dimycolate, and LpqH, also known as the Mtb 19-kD lipoprotein (43) (Figure 2).

At the cell surface, engagement by mycobacterial components of the TLR4 homodimer and TLR2/TLR1 and TLR2/TLR6 heterodimers initiates a signal transduction cascade through the adapter proteins Toll-IL-1R domain-containing adaptor protein (TIRAP, also known as Mal) and myeloid differentiation factor 88 (MyD88). By contrast, engagement by mycobacterial DNA of the TLR9 homodimer in the endosome triggers a cascade mediated directly through MyD88. These MyD88-dependent pathways proceed through IL-1 receptor-associated kinase (IRAK) 4, in association with IRAK1 and IRAK2, followed by TNF receptor-associated factor 6 (TRAF6) (Figure 2). TLR4 also activates a MyD88-independent late-phase signal transduction pathway in which the TLR4 homodimer translocates to the endosome, initiating an activation pathway through the adapter proteins Toll/IL-1 receptor domain-containing adaptor inducing IFN- β (TRIF) and TRIF-related adaptor molecule. Subsequently, activation proceeds via TRAF6 or TNFR1-associated DEATH domain protein (TRADD), Pellino-1, and receptor interacting protein (RIP)1 (Figure 2) (37, 44).

These MyD88-dependent and MyD88-independent cascades converge upon the transforming growth factor (TGF)- β -activated kinase 1 (TAK1), TAK1-binding protein (TAB) 2, and TAB3 kinase complex, which is a critical activator of the MAPK and NF- κ B pathways. TAK1 phosphorylates a range of MAPKs, including JNK and p38, as well as a subunit of the I κ B kinase (IKK) complex, IKK β . The IKK complex, consisting of the NF- κ B essential modulator, IKK α , and IKK β subunits, targets the inhibitory molecule I κ B for degradation, permitting NF- κ B to enter the nucleus and activate transcription, whereas JNK and p38 target transcription factors of the AP-1 and ATF families (Figure 2) (37, 44).

Recent studies have shown that C/EBP β and C/EBP δ expression in macrophages is activated by mycobacterial infection, LpqH, or LPS in a fashion dependent on MyD88 and in some cases IRAK4 (45–48). Given that C/EBP β activity in response to certain stimuli is MAPK-dependent and independent of C/EBP protein expression (45), Mtb-induced TLR engagement can apparently stimulate posttranscriptional modifications of C/EBP proteins, which would in turn promote C/EBP-dependent activation of the HIV-1 LTR (Figure 2).

Nucleotide-Binding Oligomerization Domain Proteins

In addition to the transmembrane TLRs, bacterial components in the cytoplasm are detected by another class of PRR, the nucleotide-binding oligomerization domain (NOD) proteins. Muramyl dipeptide (MDP) derived from Mtb is recognized by NOD2 (49, 50), which appears to function in a synergistic fashion with TLR2 in the Mtb-induced activation of cytokine expression (51). The *N*-glycolyl MDP produced by Mtb has been shown to be a more potent activator of NOD2-mediated responses than the *N*-acetylated MDP found in most bacterial peptidoglycans (49). As is the case with TLR2, TLR4, and TLR9, the MAPK and NF- κ B pathways are activated by NOD2 via the cytosolic adaptor caspase recruitment domain family member 9 (CARD9) and the kinase RIP2 (50, 52) (Figure 2).

C-Type Lectins

Another class of PRRs, the C-type lectins, interact with Mtb cell wall components, subsequently modulating immune responses and activating the NF- κ B pathway (53–55). Dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), which is present on alveolar macrophages and dendritic cells, exhibits high affinity for mannose-capped LAM (manLAM) and hexamannosylated PIM (PIM₆) from Mtb and has been reported to interact with arabinomannan, lipomannan, LpqH, and other PIMs (56, 57). Ligand engagement activates the Ras, Src, and Pak kinases, which subsequently phosphorylate the kinase Raf-1, which in turn enhances the activity of NF- κ B p65 through phosphorylation and subsequent acetylation (Figure 2) (55). An important caveat is that mycobacterial strains that do not express the mannose caps of manLAM or PIM₆ can still interact with DC-SIGN, indicating that other Mtb-derived ligands may induce signaling via DC-SIGN (56, 57).

Another C-type lectin, dectin-1, which is primarily involved in the response to fungi, has been implicated in Mtb-induced innate immune responses, in certain cases operating in conjunction with TLR2 or TLR4 (55, 58). Although an Mtb-derived dectin-1 ligand has not been identified, dectin-1 is known to activate NF- κ B via Raf-1 and to initiate Syk tyrosine kinase-dependent activation of CARD9, which interacts with Bcl-10 and mucosa-associated lymphoid tissue lymphoma translocation protein 1 to drive the activity of the IKK complex (Figure 2) (50, 55).

Figure 2. Signal transduction pathways activated by *Mycobacterium tuberculosis* (Mtb)-derived components. Generalized macrophage/dendritic cell showing intracellular cascades after engagement of Toll-like receptors (TLRs) (top left), C-type lectins (top right), and NOD2 by the indicated ligands derived from Mtb (green text). Receptors are in green; adapter proteins and upstream kinases are in blue; downstream kinases are in orange; and transcription factors are in red. HIV-1 LTR and activated cytokines are indicated at the bottom. Translocation of TLR4 into the endosome after ligand engagement is indicated by the green arrow.

In summary, Mtb-derived PAMPs serve as agonists for a number of PRRs: TLR2, TLR4, TLR9, NOD2, DC-SIGN, and possibly dectin-1. These PRRs activate the NF-κB, MAPK, and, in the case of TLRs, the C/EBP signal transduction pathways, all of which drive transcriptional activation mediated by the HIV-1 LTR.

THE PARACRINE/AUTOCRINE SIGNAL TRANSDUCTION PHASE: MTB-INDUCED CYTOKINE EXPRESSION

Engagement of PRRs by Mtb-derived PAMPs activates signal transduction pathways that up-regulate transcription of a wide

range of host genes. Consistent with the similarity between the HIV-1 LTR and promoters of genes involved in the innate immune response, activation of these genes often proceeds via the NF-κB, MAPK, and C/EBP pathways (Figures 2 and 3). Furthermore, some of the genes that specifically play a role in the response to Mtb infection, such as the TNF, IL-1α, IL-1β, IL-6, monocyte chemoattractant protein (MCP)-1, TGF-β, and IFN-γ genes, encode molecules that bind cognate cell surface receptors that, in turn, activate cascades that result in transcriptional activation of the HIV-1 LTR. With the exception of IFN-γ, which is predominantly secreted by T cells and NK cells, this

Figure 3. Signal transduction pathways activated by Mtb-induced cytokines. Intracellular cascades after association of TNF, IL-1, transforming growth factor (TGF)- β , monocyte chemoattractant protein (MCP)-1, IFN- γ , and IL-6 with their cognate receptors at the cell surface are shown in green and gray. The color scheme for upstream kinases and adaptor proteins, downstream kinases, and transcription factors is as in Figure 2.

phase of Mtb-induced activation of the LTR can proceed in an autocrine or a paracrine fashion in HIV-1-infected macrophages and dendritic cells.

TNF

The proinflammatory cytokine TNF plays a critical role in the host response to Mtb infection. TNF promotes macrophage and dendritic cell activation and subsequent T-cell activation, recruitment of leukocytes to sites of infection, granuloma formation, and suppression of bacterial growth and reactivation of latent TB (54, 59–61). In the setting of Mtb and HIV-1 coinfection, TNF enhances HIV-1 replication (62–64).

Expression of TNF is controlled at a number of transcriptional and posttranscriptional levels in macrophages and dendritic cells, and, unlike most proinflammatory cytokines, its transcriptional initiation is not directly activated by NF- κ B (19, 65). In response to exposure to Mtb, transcriptional

activation of TNF in macrophages is mediated by an enhancosome, a higher-order nucleoprotein complex that includes ATF-2/c-jun, which is targeted by the MAPK pathway (33) and by Sp1, Egr-1, and Ets/Elk proteins (19, 25).

TNF interacts with its two trimeric cognate receptors, TNFR1 and TNFR2, at the cell surface. TNFR1 signals through the adaptor proteins TRADD and RIP1 and subsequently through TRAF2 or TRAF5, whereas TNFR2 signals through TRAF2 or TRAF5 (Figure 3) (44, 66). TRAF2 and TRAF5, in turn, activate the TAB2/TAB3/TAK1 complex, leading to activation of the MAPK and NF- κ B pathways (Figure 3) (44, 66).

IL-1

Like TNF, the proinflammatory cytokines IL-1 α and IL-1 β have been shown to be involved in the control of Mtb infection (67) and in the enhancement of HIV-1 replication (68). In response to Mtb infection, monocytes and macrophages secrete IL-1 α

and IL-1 β , which have been linked to enhancement of transcription driven by the HIV-1 LTR (69). C/EBP β and NF- κ B are involved in the transcriptional regulation of the IL-1 α and IL-1 β promoters, with an additional role for AP-1 at the IL-1 β promoter, similar to the involvement of these factors in the regulation of the HIV-1 LTR (70).

At the cell surface, IL-1 α and IL-1 β interact with their cognate receptor, the type 1 IL-1 receptor (IL1-R1), which subsequently forms a heterodimer with its coreceptor IL-1 receptor accessory protein (IL-1RAcP), which in turn interacts with MyD88. In a similar fashion to its role in TLR signaling, MyD88 propagates a signaling cascade through IRAK4, along with IRAK1, IRAK2, pellino-1, and TRAF6 (Figure 3) (71, 72). As is the case with the TNFR- and TLR-dependent signal transduction cascades, engagement of IL-1R1 targets the TAB2/TAB3/TAK1 complex and thus the MAPK and NF- κ B pathways (Figure 3).

MCP-1

The chemokine MCP-1 (also known as CCL2) promotes HIV-1 replication during Mtb infection, and increased levels of MCP-1 are observed in human monocytes and macrophages coinfecting with HIV-1 and Mtb (62, 63). MCP-1 itself is subject, at least in some contexts, to regulation at the transcriptional level by C/EBP β , NF- κ B, Sp1, and AP-1 (73–78), and the NF- κ B and MAPK pathways have been implicated in the up-regulation of MCP-1 in response to Mtb infection of human monocytes (79).

MCP-1 modulates the MAPK and NF- κ B pathways in a distinct fashion from TNF and IL-1. Upon ligation to CCR2, which is a G-protein-coupled receptor, MCP-1 activates the protein kinase C pathway via phospholipase C. Protein kinase C, in turn, activates the MAPK and NF- κ B pathways independently of the TAB2/TAB3/TAK1 signaling complex (Figure 3) (78).

IL-6

Mtb infection of human macrophages also activates gene transcription and protein secretion of the cytokine IL-6 (69, 80). IL-6 in turn up-regulates HIV-1 replication and transcription in primary human macrophages, and its effect is synergistic with TNF in some monocytic cell types (81). The transcriptional activation of the IL-6 gene by Mtb involves NF- κ B and C/EBP β (69), and AP-1 is also a transcriptional activator of the IL-6 gene in some contexts, including TLR4-, NOD2-, and IL-1R1-dependent activation of IL-6 in human monocytes (82).

IL-6 interacts with the IL-6R α and gp130 receptors (83), and one of the signal transduction cascades triggered by this engagement is the Src-homology tyrosine phosphatase 2–Ras-extracellular signal-related kinase (ERK) pathway (84). C/EBP β , a target of IL-6-dependent signal transduction cascades, is phosphorylated by Ras-dependent MAPKs, including ERK1/2 (85, 86); thus, Ras and ERK1/2 are likely components of the IL-6-induced C/EBP β activation pathway (Figure 3).

TGF- β

The antiinflammatory cytokine TGF- β , which includes the isoforms TGF- β 1, TGF- β 2, and TGF- β 3 (87), is induced by Mtb infection (88). Transcriptional regulation of TGF- β involves AP-1, NF- κ B, C/EBP β , and Sp1 (87, 89, 90). In at least some cell types, including human monocyte-derived macrophages, TGF- β stimulates transcriptional activation from the HIV-1 LTR (89, 91, 92).

At the cell surface, a dimer of TGF- β interacts with two molecules of TGF- β receptor II (T β RII), and upon subsequent

recruitment of two molecules of T β RI, a tetrameric receptor complex is formed. The TGF- β interaction with T β RII/T β RI then activates, via TRAF6, the TAB2/TAB3/TAK1 complex and thus the MAPK and NF- κ B signaling pathways (93) (Figure 3).

IFN- γ

IFN- γ , which is a central cytokine in the host Th1 immune response to Mtb (43, 54, 60), can directly activate transcription from the HIV-1 LTR in synergy with LPS, TNF, or IL-6 (94). Humans with genetic deficiencies in IFN- γ or the α chain of the IFN- γ receptor (IFN- γ R α) are highly susceptible to mycobacterial infection (95).

MyD88 is recruited to IFN- γ R α upon engagement of IFN- γ R by IFN- γ , whereupon it activates the MAP kinase p38 through recruitment of mixed lineage kinase 3 (MLK3) (96). IFN- γ stimulation of macrophages also affects the transcriptional activity of C/EBP β through regulation of its MLK3- and ERK1/2-dependent phosphorylation, which in turn affects its interaction with other transcription factors and with the transcriptional mediator complex (97, 98) (Figure 3).

In summary, although the relative importance of certain signaling pathways, particularly those initiated by TLRs versus IL-1R1 and IFN- γ R, in the innate and adaptive immune responses to Mtb infection remains under investigation (54, 67), it has been shown that Mtb-induced expression of TNF, IL-1, MCP-1, IL-6, TGF- β , and IFN- γ leads to transcriptional activation of the HIV-1 LTR via the NF- κ B, MAPK, and C/EBP pathways.

MTB STRAIN-SPECIFIC EFFECTS UPON HIV-1 REPLICATION

For simplicity, we have thus far treated Mtb as a single, uniform pathogen triggering these two phases of the immune response. In a physiological setting, however, it is critical to consider that a wide range of clinical Mtb isolates have been identified (99). Different clinical isolates of Mtb are known to induce differential host immune responses, including expression of cytokines (100–102) and cytokine receptors (103).

Consider two well-characterized clinical Mtb isolates, CDC1551 and HN878. In a mouse model, CDC1551 elicits a more vigorous proinflammatory cytokine response than HN878 in the lung and in bone marrow-derived macrophages (100–102). To directly test the hypothesis that these Mtb strains can also differentially affect HIV-1 replication, our laboratory coinfecting human peripheral blood mononuclear cells with HIV-1 subtype B, C, or E isolates and CDC1551 or HN878 Mtb bacilli and found that, relative to HN878, CDC1551 infection results in higher levels of replication of all HIV-1 subtypes tested (63). CDC1551 infection leads to enhanced expression and nuclear localization of p65 and to higher levels of TNF, IL-6, and MCP-1 synthesis, and virus replication is inhibited by neutralizing antibodies against these cytokines (63). These results demonstrated for the first time that Mtb strain-specific phenotypic differences differentially affect HIV-1 replication in an *ex vivo* experimental model and indicate that such differences may influence the rate of HIV-1 disease progression in the context of HIV/TB coinfection.

Mtb strain-specific effects upon HIV-1 replication may result from distinct arrays of ligands that engage host PRRs. For example, in the case of HN878, a specific cell wall component, polyketide synthase (*pks15/I*)-derived phenolic glycolipid has been associated with this strain's suppression of the host immune response (102). Even if distinct Mtb cell wall components are not specific ligands of PRRs, they may disrupt or enhance the

host–pathogen interaction. TLR2 and TLR4, for example, localize laterally to lipid rafts at the plasma membrane after cellular exposure to bacterial products such as LPS (104), so it can be imagined that the presence or absence of specific lipid components may affect the diffusion of TLRs and, ultimately, the quality of the ligand–receptor interaction. Moreover, the level and nature of mannosylation of Mtb cell walls has been proposed to influence interactions with different classes of host cell surface receptors (56).

Thus, Mtb strain-specific differences can influence the nature of the initial interaction between PRRs and Mtb-derived ligands and the subsequent host response. The magnitude of these host–pathogen interactions can be further influenced by regulation of PRRs themselves; for example, expression of TLR2 and TLR4 in human monocyte-derived macrophages was shown to be differentially regulated in response to lipids from distinct Mtb strains (105). In this fashion, the initial point of contact between distinct Mtb strains and the cells of the host immune system may play a major role in the eventual transcription and replication of HIV-1 in the setting of HIV/TB coinfection.

CONCLUSIONS

In this review, we have described the intersection between signal transduction pathways initiated by Mtb infection and signal transduction pathways that ultimately activate HIV-1 transcription and replication. As innate immune signaling pathways are dissected in ever greater detail, it is likely that additional cellular components, including kinases, phosphatases, and transcription factors, will be identified that link Mtb-induced signaling to HIV-1 transcriptional activation. Furthermore, the expression levels, trafficking, localization, and stability of the various PRRs, transcription factors, adapter proteins, kinases, and other modifying enzymes that make up the pathways described in this review can potentially be regulated by Mtb, possibly in a strain-specific fashion.

As the public health consequences and human suffering due to HIV/Mtb coinfection are increasingly appreciated, it is critical to consider interactions between the host and HIV and Mtb simultaneously in clinical and basic scientific studies. Through this review, we hope to have provided a framework for future studies aimed at understanding basic molecular mechanisms underlying HIV/Mtb coinfection.

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