MINIREVIEWS

Impaired Regulation of HLA-DR Expression in Human Immunodeficiency Virus-Infected Monocytes

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Although direct cytopathic effects have a major role in human immunodeficiency virus type 1 (HIV-1) infection, immune defects that disrupt normal immune function also contribute to HIV-1 pathogenesis. HIV-1 infection has been associated with a number of immunodysfunctional defects that lead to dysregulation of normal immune responses (2, 16, 17, 39, 40, 74). HIV-1 infects antigen-presenting cells, including monocytes, causing several abnormalities involving cytokine secretion, chemotaxis, and antigen presentation (1, 33, 34, 48, 51, 54, 60, 61, 66, 81). Moreover, these defects have been shown in vitro and in vivo to be associated with disease progression (41).

The monocyte, one of the first cells infected with HIV-1, plays a key role in determining future immune responses (76). However, studies of macrophage and monocyte infection by HIV-1 have been hampered, since primary monocytes show variable levels of infection, which confounds efforts to standardize assay systems. On the other hand, existing monocytic cell lines often do not possess many of the normal functions that are characteristic of monocytes in vivo. In order to overcome these obstacles, our laboratory generated a series of human monocyte and macrophage hybridomas by fusing a mutant promonocytic U937 cell line with gamma interferon-stimulated monocytes and macrophages obtained by allowing monocytes to mature into macrophages (52, 67, 68, 69, 88). As a result of these fusions, we generated a series of 11 monocytic and 15 macrophagic cell lines that exhibited normal monocyte and macrophage function and, importantly, could be uniformly infected with HIV-1. Furthermore, our human macrophage hybridomas recapitulate many characteristics found in primary monocytes from HIV-1-infected individuals (Table 1).

Multiple defects in accessory cell functions have been previously described for HIV-positive patients (3, 4, 51, 54, 60, 61, 66). Blauvelt and colleagues compared monocytes derived from HIV-1-infected individuals and uninfected controls, including three pairs of monozygotic twins discordant for HIV-1 infection (4). In this study, monocytes from HIV-1-infected individuals were incapable of stimulating primary T-cell responses to alloantigens, as well as mitogen-induced (phytohemagglutinin) proliferation, as measured by interleukin-2 (IL-2) responses to alloantigens, as well as mitogen-induced (phytohemagglutinin) proliferation, as measured by interleukin-2 (IL-2) production. In contrast, in the monozygotic twins, it was found that primary monocytes from the HIV-1-infected twin retained the ability to generate recall antigen responses in the T cells of the uninfected twin to the model influenza A antigen, again, measured by IL-2 production.

In concert with these earlier results, our human macrophage hybridomas showed impaired T-cell proliferation in response to phytohemagglutinin, pokeweed mitogen, and concanavalin A and anti-CD3 cross-linking when the macrophage hybridomas of HIV-1-infected humans were used as accessory cells (88). Cytokine profiles of T cells cocultured with infected hybridoma cells in the presence of mitogens revealed a complete absence of IL-2 secretion. Antigen-specific immune responses, however, were found to be diminished when HIV-1-infected macrophage hybridomas were used as antigen-presenting cells (52, 68). Exogenous IL-2 restored the capacity of the T cells to be stimulated in response to mitogens but not to specific antigen (88). The diminished T-cell responses to recall antigens are in contrast to earlier studies using primary monocytes derived from HIV-1-infected patients as accessory cells. Similarly, studies using primary monocytes have found increased IL-1 secretion (61), whereas the macrophage hybridomas used in our laboratory previously exhibited decreased IL-1 production (68). One possible explanation may be the different frequencies of actual HIV-1 infection in monocytes from the peripheral blood of infected individuals versus rates of infection in our macrophage hybridomas. Although difficult to quantitate, rates of infection in peripheral blood monocytes are less than 1% of total monocytes. Thus, in studies using primary monocytes, it is possible that normal, uninfected monocytes may mask defects in the infected subpopulation. In contrast, our human macrophage hybridomas were nearly uniformly infected with HIV-1, as measured by reverse transcriptase activity, in situ hybridization, intracytoplasmic staining, and electron microscopic studies, as well as by p24 assays (68).

In order to characterize the phenotypic changes in monocytes after HIV-1 infection, we determined the expression of various regulatory elements by flow cytometry. Major histocompatibility complex class I (MHC-I) defects have been well described in HIV-1-infected primary monocytes. Extensive work has elucidated the mechanisms by which HIV-1 viral proteins interact and interfere with the normal surface expression of and antigen presentation by MHC-I (24). Consonant with these results, our macrophage hybridomas showed reduced MHC-I surface expression after infection with HIV-1 (55, 68).

Further phenotypic analysis of the human macrophage hybridomas yielded an intriguing result. A subpopulation of hu-
man primary monocytes and our human macrophage hybridomas—including human macrophage cell line clone 43, a representative cell line chosen because of its stability in long-term culture—lost expression of HLA-DR after HIV-1 infection (52). Recent studies have attempted to clarify the mechanisms underlying this defect, which could potentially contribute to the observed defects in accessory cell function. This paper will discuss the molecular mechanisms elucidated in our laboratory as well as others that may explain the alterations in MHC-II processing and presentation pathways observed in vivo and in vitro.

HIV-1 AFFECTS HLA-DR TRANSCRIPTION

Earlier experiments demonstrated a loss of HLA-DR expression in our model system which was associated with absent HLA-DR mRNA (88). These observations could be attributed to either a lack of transcription or, alternatively, to mRNA instability. The loss of HLA-DR expression in the human monocyctic hybridomas after HIV-1 infection could be overcome by transfection of HLA-DR genes driven by a nonphysiologic cytomegalovirus promoter, suggesting that HIV-1 was having an effect on transcriptional regulation through DNA binding proteins (52).

Much of our knowledge of the regulation of MHC-II gene transcription comes from the study of a rare immunodeficiency known as bare lymphocyte syndrome (BLS) (57). BLS is characterized by a loss of expression of all MHC-II antigens, resulting in general susceptibility to infection and increased mortality (19). Genetic analysis of patients with this disease has revealed heterogeneous mutations that segregate outside of the MHC locus (8). The subsequent identification and characterization of the mutated factors responsible for BLS later explained these findings.

Two groups of BLS patients were defined based on their molecular defects (Fig. 1). The first group of patients had mutations in the DNA binding proteins that recognize a conserved nucleotide sequence known as the X-box. This X-box binding complex consists of three factors, RFX5, RFXAP, and RFXANK, all of which have been shown to be mutated in distinct subgroups of BLS patients (11, 12, 38, 43, 47, 70, 79). Importantly, these regulatory factors show not only cooperative binding among themselves but the ability to promote the assembly of a macromolecular enhanceosome (7, 30, 42, 56, 58, 80, 87). Critically important within the enhanceosome are other factors, including Y-box and W/S/Z-box binding proteins that recognize their consensus DNA motifs, stabilize the transcriptional complex, and help to confer specificity in gene regulation (35, 58, 77, 78).

The second group of BLS patients exhibited a defect in a protein that did not bind DNA but was still crucial for class II expression (71). Subsequent work identified a gene now called the class II transactivator (CIITA). In addition to its interactions with the promoter-proximal X-, Y-, and W/S/Z-box binding proteins, CIITA can recruit basal transcription factors, elongation factors, and chromatin remodeling agents, which ultimately drives MHC-II gene expression (14, 15, 25, 29, 32, 84).

Thus, we first surveyed for the presence of X-, Y-, and W/S/Z-box binding proteins in nuclear lysates by a gel shift assay of macrophage hybridomas that had been infected with HIV-1. In contrast to uninfected clone 43 cells, HIV-1-infected clone 43 (43HIV) cells showed a lack of proteins binding to MHC-II promoter-derived probes (55). However, because of the synergistic binding exhibited by the factors discussed above, it was impossible to determine from this experiment which proteins, if any, were affected by HIV-1 infection. Other investigations examined mRNA expression by reverse transcription-PCR for specific X-, Y-, and W/S/Z-box binding proteins as well as CIITAs that have been associated with HLA-DR loss in vivo. These studies demonstrated a selective loss of a Y-box binding protein, nuclear factor NF-YA (55).

Indeed, reintroduction of NF-YA in 43HIV cells restored MHC-II expression, showing that NF-YA was the target of HIV-1 responsible for defective class II transcription in our model system as well as in primary HIV-1-infected monocytes that lost HLA-DR expression.

The Y-box proteins are necessary for class II expression and are comprised of two protein chains, NF-YA and NF-YB,
which are highly homologous to the HAP2 and HAP3 transcription factors of *Saccharomyces cerevisiae* (9, 22, 58, 64, 65, 72). The loss of the NF-YA DNA binding protein as it relates to HLA-DR expression appears to be unique to our system. Others have reported that the absence of NF-YA increases HLA-DR expression and increases the susceptibility to rheumatoid arthritis (20, 64). Interestingly, the NF-YA protein binds to the long terminal repeat of HIV-1 and human T-cell leukemia virus type 1, can activate transcription of viral gene products, and is related to Rous sarcoma virus enhancer factor I (13, 26, 63).

One of the interesting features of our system is that there is a selective loss of mRNA for HLA-DR, while mRNAs for HLA-DM and Ii are transcribed. Although HLA-DR, HLA-DM, and Ii have been reported by some investigators to be transcribed coordinately (28), more recent studies have shown that HLA-DR and Ii genes are not always coordinately transcribed (21, 31, 89). The HLA-DR and Ii promoters differ in spacing between the X and Y boxes (85, 86), and mutational analysis of HLA-DR and Ii promoters has demonstrated differences in the contribution of W/Z/S-box binding (23). Subtle differences in promoter occupancy have also been noted between HLA-DR and Ii (31). Because differences in the stability of the class II transcription complex have been observed (10, 73, 77), it is conceivable that the lack of NF-YA binding protein in vivo may alter the stability of this complex, accounting for the selective loss of HLA-DR transcription (Fig. 2).

The loss of class II mRNA expression in monocytes after HIV-1 infection, associated with defects in transcription factors, has also been reported by other researchers. Kanazawa et al. (25) have demonstrated that the Tat protein competed with CIITA for binding to P-TEFb, an activation factor that is required for class II transcription, and blocked the expression of class II genes in THP-1 cells (Fig. 2). Tat inhibition of the binding of CIITA to P-TEFb could occur to impair class II mRNA transcription. However, because we observed a selective loss of HLA-DR, it is uncertain what role this may be playing in our system. It is possible that HIV-1 infection has multiple effects on the regulation of class II expression in different subpopulations of monocytic cells.

![Diagram](http://cvi.asm.org/Downloaded from http://cvi.asm.org/)

**FIG. 1.** Regulation of transcription of MHC-II, Ii, HLA-DMA, and HLA-DMB. (A) A combination of RFX, hX-2BP, and NF-Y proteins bind cooperatively to their respective DNA consensus sequences. The presence of RFX, hX-2BP, and NF-Y proteins is required to recruit the coactivator CIITA. This macromolecular assembly leads to the initiation of gene transcription. (B) In BLS patients deficient in the RFX proteins, CIITA does not bind, leading to a defect in gene transcription. (C) An identical phenotype is observed in BLS patients deficient in CIITA.
HIV-1 IMPAIRS INTRACELLULAR SORTING

While the introduction of exogenous Y-box binding protein, NF-YA, rescued HLA-DR expression, there remained a persistent defect in HIV-1-infected monocytes functioning as accessory cells. It was previously shown that the kinetics of antigen trafficking were altered in monocytes after HIV-1 infection. Furthermore, in these studies, HLA-DR did not colocalize with endocytosed antigen (52). We therefore hypothesized that HIV-1 infection may impair HLA-DR sorting into antigen-processing pathways, leading to the observed defects in T-cell responses.

After translation, HLA-DR associates with invariant chain (Ii) in the endoplasmic reticulum (ER). This association serves two important functions: the targeting of MHC-II to late endosomes and the prevention of endogenous peptides from loading MHC-II in the ER. In human cells, two forms of Ii target HLA-DR molecules to endosomal processing compartments, a 33-kDa isoform and a 35-kDa isoform (10). The 33-kDa isotype constitutes 80% of the Ii pool and traffics to the antigen-processing compartments via the cell surface, whereas the 35-kDa Ii targets endosomal compartments by a strictly intracellular route (77). Following internalization, the 33-kDa form of Ii, in association with HLA-DR, is targeted to late endosomes and lysosomes via dileucine-based motifs present in the cytoplasmic tail of Ii (75). After Ii reaches the late endosomes, the action of a combination of cathepsin proteases catalyzes the cleavage of Ii into its proteolytic products, class-II-associated invariant chain peptide (CLIP) and leupeptin-induced peptide (LIP). These small peptides remain in the antigen-binding groove of MHC-II until they are exchanged

FIG. 2. Mechanism of HIV-1-induced defects in HLA-DR expression. (A) Normal expression of HLA-DR requires the cooperative binding of RFX, hX-2BP, and NF-Y proteins to their respective promoter-proximal elements. Subsequent binding of CIITA leads to the recruitment of transcription initiation, elongation, and chromatin remodeling proteins, ultimately activating RNA polymerase II (POLII) via phosphorylation of its carboxy-terminal domain (CTD). (B) In 43HIV cells and in a subpopulation of primary human macrophages derived from HIV-1-infected patients (MHIV DR/), a selective defect in NF-YA protein production prevents the cooperative binding of HLA-DR promoter-proximal elements, including CIITA. (C) In THP-1 cells, a monocytic cell line that loses HLA-DR expression after HIV-1 infection, HIV-1 Tat protein competes with CIITA for the binding of a transcriptional elongation factor P-TEFb. This prevents the activation of RNA polymerase II through its carboxy-terminal domain.
for peptide antigen in a reaction mediated by HLA-DM (Fig. 3).

In order to dissect out the pathway responsible for the defects in T-cell proliferative responses, we performed a series of PCR experiments for nonpolymorphic HLA gene products that are involved in antigen processing. Reverse transcription-PCR experiments involving Ii and HLA-DM showed normal mRNAs for these components. However, there was a marked reduction in the CLIP and LIP peptides in 43HIV cells (55). In addition, we examined the subcellular localization of HLA-DR by colocalization with well-characterized markers of different endosomal compartments (Fig. 4). HLA-DR failed to localize to early endosomes (cathepsin D positive), acidic endosomes (DAMP positive), late endosomes (M6PR positive), or lysosomal structures (CD63 positive) (55).

In an attempt to determine the nature of the sorting defect, we transfected segments of the HIV-1 genome via a vaccinia virus vector. Other groups have shown that various HIV-1 proteins can alter normal cell surface protein expression. HIV-1 proteins Nef and Vpu are well known to interact with both CD4 and MHC-I restriction elements, targeting them for premature degradation (27, 36, 49, 50, 59, 83). Using our human macrophage hybridomas transfected with vaccinia virus carrying either the gag, pol, env, or nef genes for HIV-1, we found that HLA-DR failed to localize to the acidic compartments, late endosomes, or lysosomes of cells transfected with the HIV-1 env gene (55). While it is unclear how the Env protein could inhibit Ii and HLA-DR targeting, a possible explanation may lie in the way cell surface proteins are internalized (Fig. 4).

As mentioned above, the leucine motifs present in the cytoplasmic domains of both the 33- and 35-kDa isoforms target the antigen-processing compartments. Proteins like the 33-kDa isoforms of Ii and HIV-1 Env protein that are internalized from the cell surface before delivery into the late endosomes or lysosomes cluster into regions on the cell membrane that are

FIG. 3. Intracellular trafficking of HLA-DR and invariant chain (Ii). HLA-DR and Ii protein associate within the ER and are first sent to the Golgi apparatus. From the trans-Golgi network, 80% of HLA-DR is first sorted to the cell surface. Internalization of the HLA-DR–Ii complex is mediated by clathrin-coated pits through the adapter protein AP-2. HLA-DR and Ii are sorted to the late endosomes and lysosomes via dileucine-based motifs in the cytoplasmic tail of Ii. Inset: (1) Cleavage of Ii is mediated by cathepsin proteases. (2) The CLIP and LIP peptides, proteolytic products of Ii, remain in the antigen binding groove of HLA-DR until they are exchanged for antigen in a reaction catalyzed by HLA-DM (2a). (3) After antigens are loaded into the binding pocket within the late endosomes and lysosomes, HLA-DR is sorted to the surface.
underlain with the coat protein clathrin (6, 53, 82). After internalization, an adapter complex is formed (62). One well-characterized adapter complex, activator protein 2 (AP-2), mediates the association of clathrin with the plasma membrane (62). The AP-2 complex consists of four protein subunits: two approximately 100-kDa large-chain proteins (α-adapter and either β-2 or β-1 adapter), a 50-kDa medium-chain protein (μ2), and a 17-kDa small-chain protein (σ2). Early experiments indicate that the cytosolic domains of internalized proteins could be bound with low affinity by the AP-2 adapter complex (37, 46). Evidence from several laboratories has established that the AP-2 adapter complex recognizes both tyrosine-based and dileucine-based sorting signals (5, 18, 45). Ohno et al. (44) have demonstrated that the HIV-1 Env protein can bind to members of the AP-2 adapter complex and that overexpression of the Env protein saturates the AP-2-dependent pathway and impairs protein sorting into different subcellular compartments. Competition between Env protein and Ii may inhibit the localization of HLA-DR to the late endosomes, lysosomes, and acidic compartments in the monocyte hybridomas infected with HIV-1 or vaccinia virus expressing the Env protein (Fig. 4).

FIG. 4. HIV-1 Env protein competes with HLA-DR–Ii complexes for AP-2. Expression of HIV-1 Env protein is sufficient to block the sorting of HLA-DR and Ii. After translation, HIV-1 Env protein is sorted to the cell surface and then internalized into endocytic compartments via clathrin-coated pits. Env protein effectively competes for the adapter protein AP-2 that can recognize the leucine-based motifs on the Ii and the tyrosine-based motifs on gp120, preventing HLA-DR and Ii entry into the endocytic compartments.

CONCLUSION

Elucidating the mechanisms of altered macrophage function remains a major goal for understanding HIV-1 pathogenesis and may potentially provide targets for future rational HIV-1 therapies. To this end, our laboratory has generated a series of human monocyte and macrophage hybridomas that are valuable in the study of HIV-1 infection. Using these hybridomas in conjunction with primary monocytes, we defined and characterized defects in accessory cell function in HIV-1-infected cells. HIV-1 prevents the transcription of HLA-DR by interfering with the transcription factor NF-YA. Alternatively, HIV-1 may prevent the association of the elongation factor P-TEFb with CIITA through its Tat protein (25). The question of how HIV-1 inhibits NF-YA has yet to be determined. HIV-1 is also capable of interfering with normal MHC-II sorting through its envelope protein. After infection, HLA-DR failed to localize in the antigen-processing compartments, including acidic compartments, late endosomes, and lysosomes. Overall, it is clear that HIV-1 infection has a profound impact on the normal function of monocytes, which almost certainly contributes to the immune dysregulation seen in HIV-1-infected patients.
ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants CA-29-256990, PO-1-AI-44236, and AI-45343 and the Irma T. Hirs- chel Career Development Trust.

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