HIV-1 infection of mononuclear phagocytic cells: the case for bacterial innate immune deficiency in AIDS

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HIV-1 infection of mononuclear phagocytic cells, comprising monocytes, macrophages, and dendritic cells, has been the subject of extensive research over the past 20 years. The roles of mononuclear phagocytic cells in transmission of HIV-1 infection and as reservoirs of actively replicating virus have received particular attention. Experimental data have also accumulated about the effects of HIV-1 on the physiological function of mononuclear phagocytic cells, particularly their role in innate immunity to bacteria. The effects of HIV-1 on bacterial innate immune responses by mononuclear phagocytic cells are discussed here together with reports of direct interactions between HIV-encoded products and bacterial innate immune signalling pathways. These reports demonstrate mechanisms for HIV-mediated disruption of innate immune responses by mononuclear phagocytic cells that could provide novel therapeutic targets in HIV-infected patients. The clinical urgency is highlighted by greatly increased risk of invasive bacterial disease in this population, even in the era of highly active antiretroviral therapy. HIV-mediated injury to bacterial innate immunity provides an experimental paradigm that could broaden our overall understanding of innate immunity and be used to study responses to pathogens other than bacteria.

Introduction

Immune deficiency in AIDS is predominantly attributed to HIV-1 infection of CD4 T cells, consequent cell death causing CD4 lymphopenia, and therefore deficiency of the adaptive immune system, which is dependent on T-helper cell function. However, the potential effects of HIV-1 on innate immunity to other pathogens has been comparatively neglected. Since the discovery of Toll-like receptor (TLR)-4 as the primary signal-transducing element for lipopolysaccharide recognition in 1998, our understanding of bacterial innate immune pathways has vastly improved. With it, an appreciation of mononuclear phagocytic cells as sentinels of bacterial innate immunity—which also provide a bridge to adaptive immune responses by virtue of their role as antigen-presenting cells—has also developed. There have been numerous reports of immunological dysfunction in mononuclear phagocytic cells from HIV-infected patients. The ability of HIV-1 to infect these cells, interact with components of the innate immune pathway, and inhibit bacterial innate immune responses, coupled with the substantial prevalence of bacterial disease in HIV-infected patients, strongly supports the proposal that HIV-1 infection of mononuclear phagocytic cells causes bacterial innate immune deficiency. The purpose of this review is to examine the experimental and clinical data that suggest that HIV-1 infection of mononuclear phagocytic cells might impair cellular innate immune responses and contribute to invasive bacterial disease in AIDS.

HIV-1 infection of mononuclear phagocytic cells

The mononuclear phagocytic cell family includes monocytes, derived from myeloid progenitor cells within the bone marrow, which develop into macrophages on migration from the circulation into tissues. Macrophages are found in all tissues and display phenotypic variability, which has resulted in diverse nomenclature. Although dendritic cells are a heterogeneous population, they are also mostly derived from common myeloid progenitor cells.1 Immature dendritic cells resident in epithelial tissues are called Langerhans cells and those in non-epithelial tissues are described as interdigitating or interstitial dendritic cells. The association between dendritic cells and myeloid cells is shown by in-vitro differentiation of monocytes into dendritic cells in response to granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 4, or by transendothelial migration and phagocytosis of particulate material.2,3

Monocytes are therefore considered as common precursors of macrophages and myeloid dendritic cells. Both of these are professional phagocytic cells, the major differences being the ability of dendritic cells to mature to CD11b+CD11c+ antigen-presenting cells that can activate naive T cells with predominant T-helper (Th)-1 polarisation.4 This contrasts with macrophages, which mainly orchestrate the amplification of immune responses within their resident tissue and can activate memory T cells.

HIV-1 can infect a variety of myeloid cells through interaction of gp120 envelope glycoprotein V3 hypervariable loop, predominantly with the chemokine receptor CCR5;5 hence the description of macrophage-tropic and R5 HIV-1 strains. These strains represent the predominant isolates in HIV transmission,6 mononuclear phagocytic cells being carriers of HIV in semen, vaginal, and cervical secretions,6 and providing permissive cells at epithelial surfaces or within blood. The importance of this route of transmission is highlighted by the discovery of CCR5 mutations associated with relative resistance to HIV-1 infection,6,7 and dendritic-cell mediated transfer of virus to regional lymph nodes in animal models of infection.8

In vitro, proliferating monocytes can be infected by HIV-1 and become increasingly susceptible to infection during maturation into macrophages, correlating with quantitative expression of CCR56,9 and possibly changes...
to transcriptional regulation. R5 HIV-1 can infect monocyte-derived and circulating immature dendritic cells, and viral replication within these cells is enhanced in the presence of T cells, possibly in response to CD40/CD40 ligand interaction, thereby enhancing T-cell infection. Dendritic cells can also enhance T-cell infection without becoming infected themselves by capturing HIV-1 on DC-SIGN, a cell surface receptor expressed by circulating immature dendritic cells and Langerhans cells. In vivo, HIV-1 can be isolated from monocytes of infected patients, albeit only in small (<1%) subpopulations. Similarly, HIV-1 infection has been shown within Langerhans cells, peripheral blood mononuclear phagocytic cells harbouring HIV-1 infection within mononuclear phagocytic cells is important for transmission of virus and subsequent infection of CD4 T cells. It might also contribute to viral persistence and transmission despite HAART. However, whether HIV-1 infection within mononuclear phagocytic cells is latent or subject to active replication has not been proven of tissue macrophages.

By contrast with the cytopathic effects of HIV-1 on T cells, mononuclear phagocytic cells can accumulate large numbers of virions without cell death, and infected macrophage populations are preserved despite progressive T-cell depletion. Accordingly, HIV-infected monocytes are found in patients receiving highly active antiretroviral therapy (HAART) and proviral DNA can be measured in monocytes despite suppression of viral load below the limit of detection. HIV-1 resistance to HAART within macrophages might reflect differences in intracellular penetration of these drugs and dynamics of viral replication. Therefore, HIV-1 infection of mononuclear phagocytic cells is important for transmission of virus and subsequent infection of CD4 T cells. It might also contribute to viral persistence and transmission despite HAART. However, whether HIV-1 infection within mononuclear phagocytic cells is latent or subject to active replication has not been proven in vivo, and an accurate estimation of the proportions of mononuclear phagocytic cells harbouring HIV-1 infection still requires further study.

**Bacterial innate immune responses by mononuclear phagocytic cells**

Mononuclear phagocytic cells are the most potent cellular mediators of innate immune responses to bacteria, by virtue of abundant expression of germ-line encoded innate immune pattern recognition receptors (PRRs) for ubiquitous bacterial moieties described as pathogen-associated molecular patterns (PAMPs). The lipid A component of lipopolysaccharide, peptidoglycan and its derivatives, and CpG deoxyoligonucleotides (ODN) are the best characterised bacterial PAMPs. Structurally diverse innate immune receptors have been described, but transmembrane TLRs and intracellular nucleotide-binding oligomerisation domain (Nod) molecules have emerged as the primary signal-transducing elements of host-microbial interactions (figure 1). Despite the specificity of innate immune receptors and the potential for diversity of intracellular signalling pathways, highly conserved downstream cellular responses are recognised, the most promiscuous of which is activation of the pro-inflammatory transcriptional regulator nuclear factor kappa B (NFκB) by degradation of its cytoplasmic inhibitor IκB (inhibitory kappa B) and translocation into the nucleus (figure 1). There, NFκB regulates the expression of cytokines, inducible intracellular enzymes, cell surface molecules, and plasma proteins, and also mediates

**Figure 1: Current paradigm for major cellular activation pathways for bacterial innate immune stimuli**

Specificity and diversity is introduced by variations in heteromeric receptor complexes at the cell surface, variability in use of adaptor proteins (MyD88, TIRAP, TRIF, TRAM), nuclear transcription factors other than NFκB (Elk-1 and AP-1 family), and complex regulatory elements in the intracellular signalling pathways (not shown). TLR=Toll-like receptor; LRR=leucine rich repeats; TIR=Toll/interleukin-1 receptor domain; CARD=caspase activation and recruitment domain; Rip2=receptor interacting protein; P=phosphate moiety; Nod=nucleotide-binding oligomerisation domain; NFκB=nuclear factor kappa B; IκB=inhibitory kappa B.

**Figure 2: Mononuclear phagocytic cells: sentinel cells in innate immunity and a target for HIV**

Innate immune activation of mononuclear phagocytic (MP) cells initiates a cascade of amplification and recruitment of non-specific host defences locally and systemically, and augments activation of specific adaptive immune responses. The role of HIV infection of T cells in AIDS is well documented. HIV also infects mononuclear phagocytic cells, but the significance of this on innate immune responses by mononuclear phagocytic cells is not known and needs further study.
changes to the cell cycle, typically inhibition of cellular apoptosis. In so doing, innate immune activation of mononuclear phagocytic cells initiates local and systemic pro-inflammatory cascades that activate non-specific and specific host defences (figure 2). The broad repertoire of innate immune response genes and the complexity of this response are highlighted in microarray expression analyses of macrophages and dendritic cells, which show changes to 1000–1500 genes following stimulation.26,27

Innate immune pathways protect the host from bacterial infection but might also contribute to the immunopathogenesis of bacterial diseases. The evidence for this is derived from targeted deletions of various components in animal models, summarised in table 1.58–63 These data have led to the hypothesis that variations in components of innate immune pathways might underlie human susceptibility to infection and immunopathogenetic sequelae, such as severe sepsis.56 Some data to support this hypothesis are already available. TLR4 mutations are associated with hyporesponsiveness to lipopolysaccharide and possible correlations have been reported with susceptibility to meningococcal disease, Gram-negative pathogens, and Gram-negative septic shock. TLR2 gene polymorphisms might be associated with susceptibility to Gram-positive bacterial infection and a polymorphism within the coding sequence of lipopolysaccharide-binding protein is associated with mortality from sepsis.57 Inherited deficiency of interleukin-1 receptor-associated kinase (IRAK)-4, a component of the TLR-dependent intracellular signalling pathway for NFKB activation, is associated with increased susceptibility to pyogenic bacterial infections.58 Additionally, monocytes from patients with a frameshift mutation within Nod2 associated with Crohn’s disease show impaired innate immune cellular responses in vitro.59 Interestingly, clinical trials of therapeutic interventions that antagonise these innate immune pathways or downstream pro-inflammatory signals for the treatment of severe sepsis have failed. Accepting the heterogeneity of such patients as a confounding factor in the outcome of these trials,60 therapeutic failure could also reflect the conflict of interest between inhibiting innate immunity to control pathogenesis in sepsis while compromising the defence against bacterial infection.

Interaction of innate and adaptive immunity

The adjuvant effect of lipopolysaccharide, the peptidoglycan derivative muramyl dipeptide, and CpG ODN, and the need for mononuclear phagocytic cells to optimise antigenic lymphoid responses represented early clues to the interface between innate and adaptive immunity.54 The elucidation of innate immune signalling pathways has provided the mechanism by which innate immunity might exert pluripotent regulation of adaptive immunity. Since most bacterial innate immune receptors recognise bacterial moieties exclusively, innate host–microbial interactions provide a mechanism for self/non-self discrimination. There is also accumulating evidence that shows TLR-dependent effects on dendritic cell and T-cell function in adaptive immunity. TLR ligands evidently contribute to maturation of dendritic cells, by upregulating expression of MHC class I and class II molecules as well as co-stimulatory cell surface molecules (CD40, CD80, and CD86) and cytokines.52 TLR ligands enhance MHC recruitment to phagolysosomes during antigen processing52 and stimulate changes to chemokine receptor expression that favour migration of dendritic cells to lymph nodes.62 Furthermore, innate immune dendritic-cell stimulation induces Th1 responses, suggesting that they provide critical polarising signals for adaptive immunity.25–28 This observation is supported by experiments that show that Th2 responses are inhibited by TLR ligands.63 The physiological significance of these findings is highlighted by reports of impaired vaccine responses in TLR or Nod-deficient hosts.57,61

Interactions between HIV-1 and innate immune components

The interaction between innate immunity and regulation of HIV-1 replication has already attracted interest. This is because HIV-1 gene expression can be induced by innate immune stimuli and is attributable to NFKB binding to transcriptional enhancer elements on the 5’ long-terminal repeat of the integrated HIV-1 provirus.50 This interaction provides a target for therapeutic inhibition of HIV-1 replication. However, in view of the central role of mononuclear phagocytic cells in innate immune responses, HIV-1 infection of these cells could also contribute to immunodeficiency in AIDS (figure 2). The evidence for HIV-mediated disruption of cellular innate immunity to bacteria is examined here. Typically this disruption includes effects on innate immune receptor expression and cellular responses to innate immune stimuli, as summarised in table 2.51–54 Additional evidence is derived from immunological dysfunction such as impaired antigen-presenting cell maturation or antibacterial effectors that might be under regulatory

### Table 1: Associations between deletions in innate immune pathway components and susceptibility to infection or resistance to innate immune inflammatory stimuli

<table>
<thead>
<tr>
<th>Targeted gene deletion of innate immune component</th>
<th>Increased susceptibility to infection</th>
<th>Enhanced resistance to innate immune inflammatory stimuli</th>
<th>References</th>
</tr>
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<tr>
<td>LPS binding protein, CD14, MD-2, TLR4</td>
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<td>38–42</td>
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<tr>
<td>TLR2</td>
<td>Gram-positive bacteria ...</td>
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<tr>
<td>TLR9</td>
<td>...</td>
<td>44</td>
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</tr>
<tr>
<td>MyD88, IRAK-4, NFKB</td>
<td>Wide ranging bacteria LPS</td>
<td>35; 43, 45, 46–48</td>
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</tr>
<tr>
<td>Nod2</td>
<td>Gram-positive bacteria MDP</td>
<td>49</td>
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*–not reported; LPS=lipopolysaccharide; TLR=Toll-like receptor; IRAK=interleukin-1 receptor-associated kinase; NFKB=nuclear factor kappa B; ODN=deoxyoligonucleotides; Nod=nucleotide-binding oligomerisation domain. MDP=muramyl dipeptide.*
control of innate immunity. Data showing the effect of individual HIV-1 components are described here first because they provide the most direct evidence and suggest putative mechanisms by which HIV-1 could inhibit innate immunity (figure 3).

The transcriptional transactivator (Tat), essential for production of full-length HIV-1 transcripts, can bind promoter sequences of pro-inflammatory cytokines such as tumour necrosis factor (TNF) α with biologically striking effects, enhancing transendothelial migration of monocytes, monocyte-derived dendritic-cell maturation, and the Th1-type cytokine response that is typically promoted by innate immunity. Despite these observations, recombinant Tat inhibited production of the prototypic Th1 cytokine interleukin 12 by human monocytes stimulated with Staphylococcus aureus. This inhibitory effect of Tat was further supported by the finding that expression of HIV-1 Tat in human monocyte-derived dendritic cells, using an adenoviral vector, inhibited dendritic-cell maturation.

Nef (negative factor, so-called following its original description as an inhibitor of HIV-1 transcription) is not essential for HIV-1 replication but its contribution to HIV-1 pathogenesis has been shown in experimental models by diminished virulence of Nef-defective mutants and in patients. Nef reduces cell surface expression of CD4 and MHC class I by increasing endocytosis and evidently increases HIV-1 infectivity. Nef also induces secretion of chemokines by macrophages, which could serve to attract other susceptible cells. Its potential effect on innate immune responses was alluded to in a report that expression of Nef in T-cell lines might inhibit NFκB activation in response to T-cell mitogens, but this effect was not reproduced in other studies following stimulation with lipopolysaccharide and was further undermined in experiments reporting preserved TNFα, interleukin 1, and interleukin 6 responses by lipopolysaccharide-stimulated monocyte-derived macrophages transfected with an adenoviral-Nef expression system. Nonetheless,
In view of the downstream control of innate immune responses on adaptive immunity, experimental data showing the inhibitory effect of Vpr on antigen-presenting cell maturation and Th1-type responses further support inhibition of innate immune responses by Vpr. This is shown by inhibition, by recombinant Vpr, of costimulatory markers in monocyte-derived macrophages/dendritic cells and suppression of antigen-specific T-cell responses following stimulation with TNFα. Similarly, HIV-1-infected human monocyte-derived dendritic cells have impaired maturation compared with cells infected with an isogenic vpr-deficient strain. In vivo, co-immunisation of mice with HIV-1 plasmid-encoded antigens in addition to a vpr plasmid is associated with a Th2 cytokine and immunoglobulin bias, as well as reduced local inflammation.

There is also evidence that HIV-1 can affect innate immune responses by mononuclear phagocytic cells without viral infection and integration. This might be an indirect effect of changes to intercellular signalling cascades from adjacent HIV-infected cells, but HIV-1 components that are detectable in the circulation of patients can also mediate direct effects. Notably, this is shown by the effects of recombinant Vpr on monocytes, monocyte-derived macrophages, and dendritic cells discussed above. Additionally, gp120 and gp41 inhibit monocyte chemotaxis and activation by chemokines, transient exposure of macrophages to gp120 induces inhibition of phagosome-lysosome fusion, lipopolysaccharide induced interleukin 12 production, and allostimulatory capacity of monocyte-derived dendritic cells was diminished by exposure to gp120. The physiological significance of the effects of individual components is supported by the repertoire of immunological dysfunction associated with HIV-1 infection in vitro and in vivo. Microarray gene expression profiling in monocytes from macaques, following acute infection with a simian immunodeficiency virus/HIV-1 chimaeric virus, showed downregulated expression of components of the lipopolysaccharide receptor complex, CD14 and TLR4. HIV-1 infection of a myeloid cell line impaired lipopolysaccharide-induced interleukin 12 production by reducing NFκB binding to the interleukin 12 promoter. In a monocytic cell line, HIV-1 infection inhibited lipopolysaccharide-induced TNFα release via a TLR4-dependent pathway and parallel observations were made in alveolar macrophages from HIV-infected patients. Furthermore, monocytes from HIV-infected patients show impaired maturation and interferon α/β responses when stimulated with CpG ODN. This finding correlates with HIV-1 plasma viral load and is further supported by a report of impaired ex-vivo interferon γ responses to CpG ODN in peripheral blood mononuclear cells from HIV-infected progressor patients compared with long-term non-progressors or healthy controls.

Inhibition of innate immunity could underlie the widely reported Th1 to Th2 switch associated with AIDS...
as well as consequent inhibition of cellular maturation and allostimulatory capacity of macrophages and dendritic cells.\(^{18,20}\) Interestingly, a persistent Th2 bias that correlates with HIV viral load has also recently been reported in HIV-infected patients on HAART.\(^{20}\) However, it is important to acknowledge that defective antigen presentation in HIV-infected patients is still a contentious issue. For example, it has recently been reported that T-cell stimulation by monocyte-derived dendritic cells from HIV-infected patients who have either normal CD4 counts, or severe CD4 lymphopenia, or are on HAART, is equivalent to T-cell stimulation by monocyte-derived dendritic cells from uninfected healthy controls.\(^{20}\) This effect could, of course, be caused by very small numbers of cells harbouring virus. Other researchers have reported highly purified dendritic cell populations from HIV-infected patients with integrated virus that show impaired T-cell stimulation,\(^{20}\) but the true physiological significance of these small subsets is not known and requires further study.

HIV-mediated inhibition of phagocytosis, intracellular killing, cellular recruitment, and production of inflammatory mediators have been described.\(^{10,11,21}\) Again, whereas some of these data are derived from HIV-1 infected cells, they are also described in cellular populations from HIV-infected patients, most of which do not themselves host integrated virus. In part, these abnormalities might reflect abnormal signalling from infected mononuclear phagocytic cells. This possibility is supported by reports such as inhibition of fungicidal activity in polymorphonuclear leucocytes from HIV-infected patients exposed to interleukin 4 and interleukin 10,\(^{22}\) representing the Th2 cytokine bias that results from HIV-1-infected mononuclear phagocytic cells. Similarly, impaired interleukin 12 production in AIDS is attributed to a Th1 to Th2 switch\(^{20}\) and cell-mediated immune responses can be restored by interleukin 12.\(^{23}\)

**Invasive bacterial infection in HIV-infected patients**

Invasive bacterial infection has long been a recognised feature of underlying HIV-1 infection.\(^{24,25}\) Diseases associated with non-typhoidal Salmonella spp and Streptococcus pneumoniae are the most commonly reported infections, and as a result were included as AIDS-defining illnesses.\(^{26}\) Bacterial infections featured prominently in the WHO clinical staging system for HIV infection in resource-poor countries before the availability of CD4 counts and HIV viral load measurements.\(^{27}\) It was recognised that pneumococcal disease could complicate HIV-1 infection relatively early in the course of the disease,\(^{28,29}\) and a 100-fold increased risk of pneumococcal bacteraemia was reported in HIV-infected patients.\(^{29}\) A similarly strong association between HIV-1 and bacteraemia caused by non-typhoidal Salmonella spp has also been evident, particularly across Africa.\(^{31,32}\) Increased risk of infection with other enteric pathogens such as *Shigella* spp campylobacter, and enteroinvasive *Escherichia coli* are also reported.\(^{33}\)

In selected populations, increased risk of bacterial disease attributable to HIV-1 has been reported for a wide range of other bacteria. In a study of South African children with lower respiratory tract infections, HIV-1 infection was associated with relative risk (RR) ratios of 21, 49, and 98 for *Haemophilus influenzae* type B, *S aureus*, and *E coli* bacteraemia, respectively.\(^{24}\) A similarly wide range of bacteria is reported in European children with sepsis.\(^{35}\) Among adults in industrialised countries, HIV-infected patients are at greater risk of *S aureus* bacteraemia and Gram-negative bacteria such as *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*. These observations are strongly associated with nosocomial and indwelling catheter infections, and among injecting drug users.\(^{26,37}\) Bacteria that are uncommon in the general population, such as *Rhodococcus* spp or *Nocardia* spp, show greater pathogenicity in HIV-infected patients.\(^{38}\) New diseases have also been described. The recognition of bacillary angiomatosis associated with AIDS led to identification of a new bacterial pathogen, *Bartonella* (formerly *Rochalimaea*) *henselae*, and to the definition of its association with other *Bartonella* spp and the spectrum of clinical consequences of infection.\(^{39}\)

Despite this wealth of epidemiological data, the mechanisms by which HIV-1 infection increases susceptibility to bacterial infection are not established. HIV-induced depletion of CD4 T cells and associated B-cell dysfunction\(^{19}\) have been assumed to be the predominant cause. Emerging data, however, suggest that in stark contrast to other opportunistic infections in AIDS, the risk of invasive bacterial disease might not be alleviated by HAART and the consequent recovery of CD4 T cells. In a North American cohort of over 5000 HIV-infected patients between 1990 and 2003, there was no substantial change to the incidence of invasive pneumococcal disease and no effect attributable to HAART.\(^{15}\) In a study from Barcelona, the incidence of invasive pneumococcal disease in HIV-infected patients did not change over the study period (1996–2002). Interestingly, clinical disease and number of recurrent episodes were similar in patients with CD4 lymphocyte counts of greater than 200 or less than 200 cells per μL.\(^{40}\)

In this study the overall incidence of invasive pneumococcal disease was 677 per 100 000 patient-years in HIV-infected patients compared with 11·3 per 100 000 patient-years in the general population. A North American multicentre surveillance study of invasive pneumococcal disease in HIV-infected patients, albeit limited by the lack of CD4 count or HAART data, did report a significant fall in the annual incidence between 1995 and 2000, but the incidence of pneumococcal infection remained 35 times higher in HIV-infected patients than in non-HIV-infected patients.\(^{40}\) In a survey of the causes of pulmonary infiltrates in HIV-infected patients, 68% were attributed to bacterial infection with
no difference attributable to the use of HAART, and Gram-positive bloodstream infections in injecting drug users remained a significant problem.

In view of the increasing availability of HAART and migration of HIV-infected patients from resource-poor settings, the epidemiology of fever in a specialist inpatient HIV care facility was investigated from 2001 to 2003. In this study, approximately 50% of cases were attributable to bacterial infection. Importantly, susceptibility to bacterial disease in HIV-infected patients was independent of CD4 lymphopenia and not alleviated by HAART, at least when compared with other opportunistic infections in AIDS. It is also important to highlight that the early literature from the pre-HAART era on the burden of bacterial disease in African populations, which harbour the major share of the global HIV-1 epidemic, remains relevant while there is limited access to HAART in these areas. It will be imperative to monitor the effect of HAART on bacterial disease in African HIV-infected cohorts as HAART becomes increasingly used, so it can be compared with US and European studies, which suggest that HAART might not have as pronounced an effect on bacterial disease as it has had on other opportunistic infections.

Because of the global burden of bacterial disease associated with HIV-1, the mechanisms of HIV-induced immunodeficiency to bacteria merit urgent and systematic investigation. The established role of mononuclear phagocytic cells in protective cellular innate immune responses to bacteria, the ability of HIV-1 to infect these cells, and experimental data that show HIV-dependent inhibition of innate immunity, strongly support the proposal that HIV-1 infection of mononuclear phagocytic cells contribute to bacterial infection.

Opportunities for translational research
Greater understanding of the mechanisms by which HIV-1 infection of mononuclear phagocytic cells affects innate immune responses to bacteria could provide new opportunities for therapeutic intervention in the prevention and treatment of bacterial diseases in HIV-infected patients. Examples in which identification of macrophage and dendritic cell dysfunction in HIV-infected patients has already led to therapeutic applications include the clinical use of cytokines such as granulocyte-colony stimulating factor (G-CSF), GM-CSF, and interferon γ. G-CSF, normally produced by myeloid mononuclear cells, is involved in homeostasis of production and release of neutrophils from bone marrow. HIV-1 related neutropenia has been associated with diminished G-CSF production and increased risk of bacterial infection. Administration of G-CSF is now widely used to reverse this risk and correct neutropenia. GM-CSF, derived from a wider range of cellular sources as well as macrophages, stimulates differentiation of the myeloid cell lineage and enhances their antimicrobial activity. GM-CSF has been shown to enhance phagocytosis of atypical mycobacteria by HIV-infected macrophages, and reduce associated bacteraemia in an HIV-infected patient. Interferon γ is mainly produced by T cells and natural killer cells in response to Th1 signals from stimulated macrophages and induces a paracrine Th1 amplification loop. Hence, administration of interferon γ to HIV-infected patients with diminished Th1 responses is an attractive strategy. Interferon γ enhances oxidative burst responses and intracellular killing within HIV-infected macrophages in vitro, and has been subjected to a clinical trial to reduce opportunistic infections in AIDS.

The range of translational applications that could be derived from studying the effect of HIV-1 infection on innate immunity to bacteria extends beyond the management of bacterial infections. In view of the regulatory influence of innate immunity on adaptive immune responses, understanding the mechanisms by which HIV-1 disrupts innate immune pathways in mononuclear phagocytic cells could provide novel therapeutic targets to enhance adaptive immunity and hopefully vaccine responses in HIV-infected patients. CpG ODNs are emerging as potentially valuable adjuvants for vaccines as a result of inducing a Th1-biased immune response through the TLR9 signal transduction pathway, but this strategy is unlikely to be successful in HIV-infected patients if HIV-1 inhibits innate immune pathways. Assuming that HIV-1 disrupts innate immune pathways in mononuclear phagocytic cells to its own teleological advantage, interventions that restore normal function might promote host immunity against HIV-1. Encouraging results have emerged from animal models of retroviral infection in which immunostimulatory CpG ODN substantially enhances viral clearance to suggest that this could be possible. Therapeutic targeting of the interaction between HIV-1 and innate immune components could, therefore, contribute to clearance of HIV-1 from reservoirs that are resistant to HAART, and hence contribute to finding a cure for AIDS.

Finally, systematic investigation of the effect of HIV-1 infection of mononuclear phagocytic cells on cellular innate immune responses to bacteria will provide a paradigm to investigate the effect of HIV-1 infection on innate responses to other pathogens and the role of pathogen–pathogen interactions in infectious diseases. In particular, identification of the specific host–microbial interactions that lead to impaired innate immunity could lead to the discovery of novel components of cellular innate immune pathways, and in turn, provide new insights into the heterogeneity of host responses to infection and new therapeutic targets in the management of infectious diseases generally. The interaction of HIV-1 with cellular innate immunity provides exciting new opportunities for translational research in infectious diseases with broad and ambitious objectives.
Search strategy and selection criteria

Several English language literature searches were done using the Medline database. The keywords used were combinations of the following terms: "HIV", "AIDS", "bacteria", "macrophage", "dendritic cell", "monocyte", "mononuclear phagocyte", "mononuclear phagocytosis", "myeloid", "innate", "innate immunity". Searches were complete up to the end of September, 2006.

Conflicts of interests

We declare that we have no conflicts of interest.

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Review


