JLB

Review

Macrophage polarization and HIV-1 infection

Edana Cassol,*[,†,‡] *Luca Cassetta*,* *Massimo Alfano*,* *and Guido Poli*[*,†,1]

*AIDS Immunopathogenesis Unit, Division of Immunology, Transplantation and Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy; †Vita-Salute San Raffaele University, School of Medicine, Milan, Italy; and ‡Medical Research Council Unit of Inflammation and Immunity, Department of Immunology, Faculty of Health Sciences, University of Pretoria and Tshwane Academic Division of the National Health Laboratory Service, Pretoria, South Africa

RECEIVED OCTOBER 11, 2009; REVISED NOVEMBER 13, 2009; ACCEPTED NOVEMBER 30, 2009. DOI: 10.1189/jlb.1009673

ABSTRACT

Polarization of MP into classically activated (M1) and alternatively activated (M2a, M2b, and M2c) macrophages is critical in mediating an effective immune response against invading pathogens. However, several pathogens use these activation pathways to facilitate dissemination and pathogenesis. Viruses generally induce an M1-like phenotype during the acute phase of infection. In addition to promoting the development of Th1 responses and IFN production, M1 macrophages often produce cytokines that drive viral replication and tissue damage. As shown for HIV-1, polarization can also alter macrophage susceptibility to infection. In vitro polarization into M1 cells prevents HIV-1 infection, and M2a polarization inhibits viral replication at a post-integration level. M2a cells also express high levels of C-type lectins that can facilitate macrophage-mediated transmission of HIV-1 to CD4$^+$ T cells. Macrophages are particularly abundant in mucosal membranes and unlike DCs, do not usually migrate to distal tissues. As a result, macrophages are likely to contribute to HIV-1 pathogenesis in mucosal rather than lymphatic tissues. In vivo polarization of MP is likely to span a spectrum of activation phenotypes that may change the permissivity to and alter the outcome of HIV-1 and other viral infections. *J. Leukoc. Biol.* 87: 599–608; 2010.

INTRODUCTORY REMARKS: POLARIZED IMMUNE RESPONSES

Recent studies have highlighted the importance of immune activation in the resolution and promotion of infectious diseases [1–5]. Of particular interest are studies of SIV infection, suggesting that the main difference between natural (nonpathogenic) and pathogenic SIV infection is that the latter is characterized by excessive and prolonged activation of the host immune system [6, 7]. However, immune activation is also needed to induce polarization of the immune system along pro- or anti-inflammatory pathways and to mount an effective host response against invading pathogens [8]. Immunologically driven polarization has been studied most extensively in murine models [9–11] and in the setting of CD4$^+$ Th cell responses [1, 12, 13]. In humans, proinflammatory Th1 cells are important in mediating resistance to mycobacteria and in providing protection from *Leishmania major* infection [14, 15]. On the downside, Th1 cells are involved in the induction of autoimmunity. Conversely, helminthic infections typically orient immune responses toward a Th2 pathway associated with anti-inflammatory effects, and the maturation of antibodies toward specific IgA and IgE types that are effective in the clearing of microbial agents [2, 16].

In addition to T cells, recent evidence (obtained primarily in the mouse) suggests that MP may also undergo functional polarization, and such a process may play a role, not only in the initiation and orchestration of inflammatory responses but also in the regulation of innate and adaptive immune responses to viral pathogens [17–19]. This review provides a brief overview of human macrophage polarization and its impact on the pathogenesis of HIV-1. A clear understanding of the importance of macrophage polarization may reveal novel strategies for controlling the replicative and pathogenic potential of HIV-1.

THE MP SYSTEM

Cells belonging to the MP system include circulating monocytes, tissue macrophages, and DCs and are characterized by a high level of plasticity, widespread tissue distribution, and an ability to respond to a wide range of environmental stimuli, most notably, microbial products and host cytokines [20–22]. These different stimuli interact with cell membrane receptors, resulting in activation of distinct intracellular signaling pathways and downstream gene activation. This, in turn, leads to changes in functional properties, such as cellular adhesion and

Abbreviations: APOBEC=apolipoprotein B mRNA editing enzyme, catalytic polypeptide, DC=dendritic cell, DC-SIGN=dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin, H3K27=histone H3 lysine 27, IL-1ra=IL-1R antagonist, Jmjd3=jumonji domain-containing 3, histone lysine demethylase, MDM=monocyte-derived-macrophages, MP=mononuclear phagocyte(s), MRC1=mannose receptor, C type 1, Mtb=*Mycobacterium tuberculosis*, PRR=pattern recognition receptor, SR-A=scavenger receptor-A, TAM=tumor-associated macrophage

1. Correspondence: P2/P3 Laboratories, DIBIT, Via Olgettina n. 58, 20132 Milano, Italy. E-mail: poli.guido@hsr.it

migration, cytokine/chemokine production, and antigen processing [23–26].

CIRCULATING MONOCYTES

Monocytes, the progenitors of most tissue macrophages, represent 10–30% of all circulating mononuclear leukocytes. Peripheral blood monocytes originate in the bone marrow from a common myeloid progenitor [22] and circulate for only 1–2 days before migrating into peripheral tissues and differentiating into fully mature, resident macrophages, including liver Kupffer cells and brain microglial cells. During their short circulatory life, monocytes are exposed to cytokines such as M-CSF, which can alter their phenotypic and functional properties [27, 28]. As a result, monocytes can be classified into at least three distinct subsets based on their expression of the functional cell surface receptors CD14 and CD16 (i.e., $CD14^+CD16^-$, $CD14^+CD16^+$, and $CD14^{dim}CD16^+$) as well as on their capacity of secreting proinflammatory cytokines [21, 29–32]. It is unclear, however, whether these phenotypically distinct monocyte subsets represent cells already precommitted to differentiate into polarized M1 or M2 macrophages or DCs. In this regard, Martinez et al. [28] have suggested that under normal conditions blood monocytes are likely predisposed toward an M2 phenotype, mostly devoted to tissue repair, as a result of their stimulation by relatively high levels of M-CSF present in the plasma (estimated to range from 187 to 7604 pg/ml [27]). A transcriptome analysis supports this hypothesis, showing that M2 polarization involves only minimal alterations of macrophage steady-state mRNA in comparison with M1 polarization [28]. It is unclear, however, if tissue-specific signals are required to maintain the M2 phenotype.

TISSUE MACROPHAGES

At the tissue level, terminally differentiated macrophages are exposed to and are profoundly affected by tissue-specific immune-modulating cytokines, chemokines, and microbial byproducts [22, 24, 33]. As a result, when compared with circulating monocytes, lung alveolar macrophages express higher levels of PRRs and scavenger receptors involved in clearing viruses as well as other microorganisms and environmental particles [22, 33]. Osteoclasts, on the other hand, acquire determinants fundamental for bone remodeling [22, 34, 35]. Macrophages located at sites of pathogen entry, such as the intestine, display high phagocytic and antibacterial activities but produce only low levels of proinflammatory cytokines to prevent unnecessary overstimulation of the immune system as a result of constant exposure to commensal and pathogenic microbes [36–38]. Interestingly, some intestinal macrophages, such as those present in the lamina propria of the gastrointestinal tract, survive for a few weeks before undergoing programmed cell death [22]. Such cells are continually replenished by newly recruited blood monocytes that rapidly differentiate into gut macrophages. Other macrophage populations are characterized by a prolonged half-life, ranging from several months (lung alveolar macrophages) to decades (microgial cells). These cells may be renewed, at least in part, by local proliferation [22, 39, 40]. In contrast, M1 macrophages recruited to sites of acute inflammation typically have short half-lives and exert potent proinflammatory effects that may cause tissue damage [22].

Although polarized macrophages contribute to the pathogenesis of various diseases, little is known about the molecular mechanisms underlying the acquisition and maintenance of macrophage programming. In mice, SHIP-1 dampens LPS-induced M1 activation in vitro. Alternatively, in vivo, SHIP knockout mice display a profound skewing of peritoneal and alveolar macrophages toward an M2 phenotype [41]. In addition to SHIP and Lyn/Hck, increased STAT5 activity may play an important role in M2 programming [42]. Recent studies show alternative activation may also be regulated by epigenetic mechanisms [43]. Specifically, in mice, IL-4 induces an upregulation of H3K27 demethylase Jmjd3 (in a STAT6-dependent manner), increasing H3K27 methylation at the promoters of M2 genes (arginase 1, mannose receptor) [43]. Similarly, Jmjd3 is also induced in macrophage cell lines stimulated with LPS, suggesting it may play a common role in both phenotypes [44]. Although not yet investigated in humans, these results suggest that chromatin remodeling may play an important role in polarization responses, as reviewed [45].

POLARIZATION OF HUMAN MACROPHAGES ALONG M1 AND M2 PATHWAYS

Macrophages undergo activation in response to a broad spectrum of environmental signals. The type, timing, and concentration of these stimuli determine the range of immune responses. As a result of exposure to different tissue environments, macrophage polarization is likely to span a continuum of functional states. One implication of these features is that unlike T cell activation, macrophage polarization is transient and highly reversible [17, 46]. Recent results also suggest that macrophages, like T cells, may require at least two signals to become fully and functionally polarized [47]. The first signal, usually driven by pathogen interactions with PRRs, such as TLR, cytosolic proteins of the nonobese diabetic-like receptor family, or C-type lectins, primes the resting macrophage. PRR activation also increases chemokine production and the recruitment of different immune cells, including NK cells, naïve T lymphocytes, eosinophils, and basophils, which deliver the second signal required for M1 (IFN-γ) or M2a (IL-4) polarization, respectively [47]. For example, early IFN-γ and PRR activation induces a first wave of classical macrophage activation that stimulates IL-12 production, a cytokine crucial for the induction of Th1 responses. The resultant Th1 $CD4^+$ T cells then produce more IFN-γ, inducing a long-lasting M1 phenotype and an effective $CD8^+$ cytotoxic T lymphocyte response [47]. With the exception of LPS, little is known about the impact of past stimulations on future responses. In the case of LPS, it is known that previous stimulations can lead to TLR tolerance [48–50].

By analogy to the Th1/Th2 classification of $CD4^+$ helper lymphocytes, it has been proposed that mononuclear phago-

cytes can also be polarized along proinflammatory (M1) or alternatively activated, anti-inflammatory (M2) pathways [18, 19, 51–53]. In healthy tissues, particularly mucosal membranes, M2 activation may represent a default phenotype that serves to maintain a balanced microenvironment in anatomical sites under constant microbial assault [17, 28]. For example, macrophages in the lung, placenta, and gastrointestinal tract express high levels of C-type lectins [54, 55] and exhibit a decreased capacity to produce proinflammatory cytokines, thereby limiting tissue damage [36, 38]. In contrast, M1 macrophages express high levels of classical proinflammatory cytokines, including IL-1β, IL-12, IL-23, and TNF-α. Furthermore, they produce effector molecules such as reactive oxygen and nitrogen intermediates, participate in the induction of polarized Th1 responses, and have been associated to resistance to intracellular pathogens such as viruses and to some forms of tumors [19, 52, 53]. M1 cells also express high levels of MHC class I and class II antigens and secrete complement factors that facilitate complement-mediated phagocytosis [19].

Different stimuli can lead to the polarization of macrophages into M2 cells. To reflect these different forms of activation, M2 macrophages have been subdivided further into M2a, M2b, and M2c cells [19]. M2a cells are induced by exposure of macrophages to IL-4 or IL-13, and M2b macrophages are induced by immune complexes, TLR stimulation, or by the IL-1ra. These cells exert immune regulatory functions and drive Th2 responses. Finally, M2c macrophages are generated by stimulation with the immunosuppressive cytokine IL-10 and play a predominant role in suppressing immune responses and in promoting tissue remodeling [19]. M2 macrophages are, therefore, more heterogeneous than M1 cells and depending on their state of activation, participate in a number of diverse activities aimed at suppressing inflammation, enhancing phagocytosis, promoting tissue repair and eliminating of parasites [18, 19, 47].

Although activation is critical for the induction of an effective immune response, inappropriate and sustained activation/polarization of macrophages can lead to tissue damage, immune dysfunction, and disease pathology. For example, M1 responses, important in mediating resistance against acute viral and mycobacterial infections, may also contribute to the induction of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [56–59]. Alternatively, M2 polarization, important in controlling helminthic infections, has been linked to the development and persistence of asthma and allergic diseases [60, 61]. Interestingly, TAM, including tyrosine kinase with Ig-like and EGF-like domains 2 (Tie2)-derived macrophages [62, 63], closely resembles M2 macrophages when analyzed for function and transcriptome expression [64, 65]. M2 macrophages produce anti-inflammatory and immunosuppressive cytokines such as IL-10 and TGF-β that promote tumor growth and progression [64, 65]. Several lines of evidence suggest that pharmacological skewing of TAM from an M2 toward an M1 phenotype may help preserve anti-tumor activity, as reviewed in ref. [64]. One study reported that the combination of CpG plus anti-IL-10R antibody induces a switch in tumor-infiltrating macrophages from an M2 to an M1 phenotype, triggering innate responses that lead to a rapid decrease in tumor size [66, 67].

In vitro, MDM are the most commonly used tool to investigate macrophage phenotype and function, particularly in humans. MDM can be induced to differentiate into M1 cells through exposure to proinflammatory stimuli, such as GM-CSF or IFN-γ, alone or in combination with TNF-α or LPS, a component of the cell wall of Gram-negative bacteria [19]. In vitro-derived M2-MDM secrete anti-inflammatory molecules, including IL-1ra, IL-10, and TGF-β, thereby inhibiting respiratory bursts and the production of IL-1β and IL-8 [68]. Furthermore, M2-MDM express high levels of the scavenger and MRC1, SR-A, hemoglobin scavenger receptor (CD163) Dectin-1, and DC-SIGN [18, 47] (**Table 1**).

As only meager information is currently available for M2b and M2c cells under different pathological conditions, we will focus on the role of M1 and M2a (IL-4/IL-13-induced) macrophage polarization in HIV and associated coinfections.

MACROPHAGE POLARIZATION AND HIV-1 INFECTION

A large number of studies have investigated the effects of individual cytokines and bacterial products on macrophage susceptibility to HIV-1 and other viruses and on the capacity of these cells to support productive or latent infection, as reviewed in refs. [69–71]. These studies have used different model systems and cell lines [72], as well as different viral strains and infection protocols. A consistent finding emanating from these investigations is that the ultimate outcome of host-viral interactions depends frequently on the timing of infection relative to the timing of the stimulus (before, simultaneously, or after) and on the stage of macrophage differentiation (precursor cells, as exemplified by cell lines, monocytes vs. macrophages). To date, only a few studies have examined thoroughly the consequences of M1 versus M2 polarization on viral infections [17, 73–75].

Although important in driving immune responses, increased secretion of inflammatory cytokines as a consequence of viral infection can result in severe tissue damage. Alveolar macrophages, for example, produce large amounts of inflammatory cytokines during infection with respiratory viruses such as human metapneumovirus and respiratory syncytial virus [76, 77]. Cytokines produced by macrophages infected with influenza A virus mediate the typical constitutional and inflammatory effects observed with this disease [78]. Rhinovirus infections increase the level of TNF-α and IL-8 secretion by lung alveolar macrophages [79, 80]. Interestingly, macrophages exposed previously to rhinoviruses show a reduced capacity to mount an antibacterial response, suggesting that these viruses may facilitate secondary infections indirectly [81]. An analytical analysis of viral infection of MP is beyond the scope of the present paper. However, excellent reviews about the subjects are readily available [82–84].

Cells of the MP lineage are the targets of several retroviruses belonging to the lentiviral subfamily and depending on their state of differentiation and activation, can serve as reservoirs of latent or productive infection. Most lentiviruses, with the ex-

TABLE 1. Differentially Expressed Markers of Human Macrophage Polarization

	M1	M2a
Receptors		
	CCR7	DC-SIGN
	IL-1R1	DCIR
	IL-2ra	MRC1
	IL-15ra	CD36
	IL-7R	DECTIN 1
	CD80	DCL-1
	CD86	SR-A
	MHC class II	CD163
	TLR2	CXCR1
	TLR4	CXCR2
Chemokines		
	CXCL8	CCL13
	CXCL9	CCL14
	CXCL10	CCL17
	CXCL11	CCL18
	CXCL16	CCL20
	CCL2	CCL22
	CCL3	CCL23
	CCL4	CCL24
	CCL5	
Cytokines		
	TNF-α	IL-10
	IL12	IL-1ra
	TRAIL	
	IL-6	
Other factors		
	Homeobox expressed in ES cells 1	Growth arrest-specific 7
	IFN regulatory factor 1 (IRF1)	Early growth response 2
	Activation transcription factor 3	v-MAF
	IRF7 [28]	Cathepsin C
	Indoleamine-pyrrole 2,3 dioxygenase	Hexosaminidase
	Proteasome activator subunit 2	Lipase A cholesterol esterase
	Hydroxysteroid (11-β) dehydrogenase	Adenosine kinase
	2′–5′-oligodenylate synthase-like	Ceramide kinase
	Proteasome subunit β type 9	Heparan sulfate 3-O-sulfotransferase
	Proteasome subunit α type 2	Leukotriene A4 hydrolase

DCIR, DC immunoreceptor; DCL-1, DC ligand 1; ES, embryonic stem; v-MAF, viral macrophage-activating factor.

ception of HIV-1, infect cells of MP lineage preferentially or exclusively. However, the level of viral replication and the outcome of these infections are related intimately to the host immune response and the type of infection. During HIV-1 infection, circulating monocytes and tissue macrophages contribute to the initial seeding and establishment of viral reservoirs [85–87] playing a pivotal role in the infection of certain organs, such as the brain, as reviewed in refs. [88–90]. Although human macrophages can support high levels of HIV-1 replication, particularly in late-stage HIV disease, i.e., AIDS, when CD4 cells are depleted severely and in the context of opportunistic infections [91], they also serve as reservoirs of latent or poorly replicative infection [92–94]. It should be underscored that HIV-1 latency and the persistence of viral reservoirs (eventually harboring antiretroviral-resistant viruses) are the major obstacles nowadays preventing the eradication of this infection [93, 95]. MP and memory $CD4^+$ T cells latently infected with HIV-1 are not recognized efficiently by the host immune system and can persist for prolonged periods in the face of the administration of antiretroviral therapy [96, 97].

At the functional level, monocytes as well as lung alveolar macrophages isolated from HIV-infected individuals have all shown reduced phagocytic activity [98, 99] in association with decreased phagosome-lysosome fusion and decreased intracellular killing of opportunistic pathogens [100, 101]. Monocytes isolated from patients with AIDS also have defective migratory responses [102, 103], a phenotype that has been linked to a down-regulation of receptors for chemotactic ligands (i.e., C5a and bacterial tripeptides, such as fMLP) [104, 105]. These functional defects, in turn, result in the inefficient control of opportunistic pathogens and further enhancement of activation and disease pathogenesis. Chronic HIV-1-associated immune activation also leads to altered secretion of pro- and anti-inflammatory cytokines and chemokines and ultimately, to dysregulation of the host immune system and the killing of bystander $CD4^+$ T cells. In addition, HIV-infected macrophages have been implicated in the elimination of effector $CD8^+$ T cells through interactions between TNF bound to the surface of macrophages and TNFRII expressed on $CD8^+$ T cells [106].

The transmission and pathogenesis of HIV-1 are linked intimately to the activation status of the immune system [107–109]. Prolonged immune activation during chronic infection provides an environment that drives viral replication and disease progression, even in the face of combination antiretroviral therapy [3]. Indeed, the state of immune activation is a stronger predictor of disease progression in patients with advanced HIV-1 disease than the levels of plasma viremia [107].

Recent evidence suggests that increased translocation of bacteria and bacterial byproducts from the gastrointestinal tract, a consequence of HIV-1-induced damage to the gut during acute infection, may drive systemic immune activation and progression to AIDS [110–112]. Given that cells of the MP lineage are the primary targets of LPS-induced activation and that they are key regulators of inflammatory and anti-inflammatory responses, it is important to understand the relationships among immune activation, macrophage polarization, and HIV-1 disease. In this regard, the factors driving macrophage polarization in HIV-1 pathogenesis are complex. Macrophages respond not only to HIV-1 but also to a spectrum of opportunistic coinfections and can be activated sequentially (or simul-

taneously) by different bacterial, fungal, and viral products. The timing and order of these synergistic or competing stimulations will determine the dominant polarization profile.

In vitro, HIV-1 drives macrophages toward an M1-like phenotype [73, 113]. However, unlike LPS, HIV-1-related polarization does not involve a TLR-dependent pathway and does not result in the production of TNF, IL-1β, or IL-6. Instead, HIV-1-primed MDM become hyper-responsive to TLR agonists such as LPS, polyinosinic:polycytidylic acid, and CL097 (TLR7/8 agonist), resulting in a three- to fivefold increase in cytokine production compared with TLR agonists alone [73]. Viral replication in MDM also correlates with increased production of M1 chemokines, such as CCL3, CCL4—up-regulated directly by the viral gene Nef [114]—and CCL5 and a down-regulation of the M2 determinants, such as the scavenger receptor CD163, the mannose receptor CD206, IL-10, and CCL18 [113]. Furthermore, a transcriptional profiling study suggests that these HIV-1-associated alterations may involve the transient expression of genes that regulate the cell cycle, calcium fluxes, apoptosis, and mitogen-activated kinase-dependent pathways [73] (**Table 2**).

The capacity of macrophages to support HIV-1 infection is dependent on the local tissue environment. Alveolar and vaginal macrophages are susceptible to HIV-1, whereas intestinal macrophages are typically resistant [85, 115]. Intestinal resistance is the result of high levels of IL-10 and TGF-β. These cytokines down-regulate the expression of coreceptors required for HIV-1 entry (namely, CCR5 and CXCR4), as well as innate response receptors and costimulatory molecules [115–117]. In vitro, we observed that short-term (18 h) exposure of human MDM to M1 (IFN-γ plus TNF-α) or M2a (IL-4) cytokines prior to infection with HIV-1 resulted in a decreased capacity to support productive HIV-1 infection in comparison with unpolarized MDM [17]. These restrictions occurred at different levels of the viral life cycle (i.e., at an early, preintegration step in the case of M1-MDM and at a post-transcriptional/post-translational step in M2a-MDM). M1 restriction was associated with a more profound down-regulation of CD4 and a greater suppression of HIV-1 replication compared with M2-MDM. M1 polarization also resulted increased secretion of CCR5-binding chemokines (CCL3, CCL4, and CCL5) and a significant decrease in the synthesis of HIV-1 DNA [17]. M2a polarization, on the other hand, was associated with a more prolonged, although less profound suppression of infection. In contrast to M1 polarization, there was no detectable impairment of HIV-1 DNA synthesis in M2a cells [17]. Other studies have reported that APOBEC-3G mRNA levels are increased in MDM stimulated with IFN-α and to a lesser extent, IFN-γ [118] (Table 2 and **Fig. 1**).

It is still unclear whether macrophage polarization is reversible and whether individual tissue macrophages can switch from an M1 to an M2 activation state as a consequence or a cause of disease progression or whether such a switch requires the differentiation and polarization of newly recruited blood monocytes [20, 46]. We have reported recently that M1- and M2a-MDM reverted to a prepolarization phenotype 3–7 days after removal of the inductive stimulus, although some molecules such as CXCL10 (M1) and CCL22 (M2a) remained elevated after 7 days of culture in the absence of the polarizing cytokines [17]. We also described a contra-modulatory effect of polarization on the secretion of cytokines and chemokines associated with the opposite phenotype—a process that typically peaked 3 days after the initial stimulation. For most phenotypic determinants, reversion to a prepolarization state was associated with a renewed capacity to support productive HIV-1 infection. M1 cells were able to support HIV-1 replication 3 days after removal of the polarizing cytokines. In contrast, M2a cells recovered their ability to produce virus at con-

Table 2. Factors Related to HIV-1 Infection Differentially Expressed in Polarized Human MDM

	M1		M2a		
	mRNA	Protein	mRNA	Protein	Role in HIV-1 pathogenesis
Cytokines, chemokines					
IL-12	⇑⇑⇑	N.D.	⇑	N.D.	⇓ HIV-1 replication
IL-10	n.a.	⇑	n.a.	–	⇓ HIV-1 replication
TNF-α	⇑⇑⇑⇑	n.a.	⇑⇑	n.a.	⇑ HIV-1 replication
IL-6	⇑⇑⇑⇑	⇑	⇑⇑	–	⇑ HIV-1 replication
IL-8	n.a.	⇑	n.a.	–	⇑ HIV-1 replication
CCL2	n.a.	⇑	n.a.	⇓	⇑ HIV-1 replication; ⇓ virion release
CCL3	n.a.	⇑⇑		⇑	CCR5 ligand; ⇓ HIV-1 replication
CCL4	n.a.	⇑	n.a.	–	CCR5 ligand; ⇓ HIV-1 replication
CCL5	⇑⇑⇑⇑	⇑⇑	⇑⇑	N.D.	CCR5 ligand; ⇓ HIV-1 replication
CXCL10	⇑⇑⇑⇑	⇑⇑⇑	⇑⇑	–	⇑ HIV-1 replication
CCL22	n.a.	–	n.a.	⇑	⇓ HIV-1 replication
Membrane receptors					
CD4	n.a.	⇓	n.a.	⇓	Primary HIV entry receptor
CCRS	n.a.	–	n.a.	–	HIV entry coreceptor
DC-SIGN	⇑⇑	⇓	⇑⇑⇑⇑	⇑	HIV attachment and transfer rececptor

⇓, 0 to 25-Fold decrease; –, no change; ⇑, 0 to 25-fold increase; ⇑⇑, 25 to 200-fold increase; ⇑⇑⇑, 200 to 500-fold increase; ⇑⇑⇑⇑, >500-fold increase; N.D., not detectable; n.a., not available.

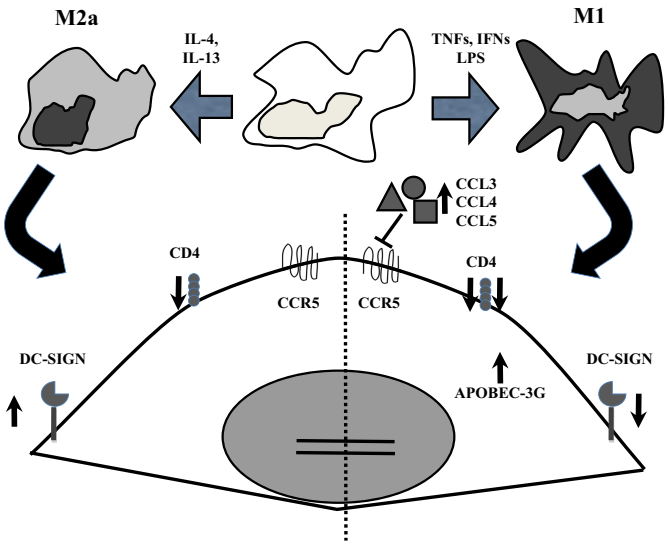

Figure 1. Impact of human MDM polarization on HIV-1 infection and replication. M1- and M2a-polarized MDM have shown decreased levels of CCR5-dependent HIV-1 replication in comparison with unpolarized cells [17]. However, this ultimate effect is likely a result of differential and multifactorial effects triggered by cell polarization, including up-regulation of CCR5-binding chemokines, APOBEC-3G, and profound down-regulation of CD4 in M1- but not M2-MDM [17]. A divergent regulation of DC-SIGN in M1- versus M2-MDM might differentially contribute to spreading of bound HIV-1 to T lymphocytes and other target cells.

trol levels 7 days after polarization [17]. These findings are in agreement with a recent study reporting that macrophages retain the capacity to switch from one activation state to another based on the expression of CD163 and CD206 and the secretion of CCL3 and CCL18 [20]. Collectively, these findings suggest that functional polarization may be an important regulator of susceptibility to HIV-1 infection and efficiency of viral replication in human macrophages. The transient and reversible nature of polarization may represent a mechanism through which infected tissue macrophages, typically resistant to viral-induced cytopathic effects [91, 119, 120], can cycle between a state of inefficient versus productive viral expression. An improved understanding of these events may lead to new insights for suppressing virus replication or alternatively, for unleashing HIV-1 production in latently and poorly, productively infected cells, rendering them more visible to immune recognition in the perspective of viral eradication [121–123].

An important determinant discriminating between M1 and M2 polarization is the hemoglobin scavenger receptor, CD163. This receptor is expressed at high levels on M2 and at low levels on M1 cells [17] and has proven particularly useful for the identification and characterization of perivascular macrophages in the brain tissue of humans, monkeys, and mice [124]. Several studies have reported significant accumulations of CD163 within the perivascular cuff and nodular lesions of the CNS of humans and nonhuman primates with HIV-1 and SIV encephalitis [124, 125], suggesting that alternatively activated M2 macrophages may contribute to the pathology and immune dysfunction observed in these disorders [126]. Another recent study observed an increased accumulation of $CD163^+$ macrophages in uninflamed hearts from SIV-infected animals compared with hearts from SIV-infected animals with myocarditis or uninfected controls [127]. Furthermore, in this study, CD163 expression was correlated positively with the number of SIV-infected cells, suggesting that the CD163 population of macrophages was associated with decreased inflammatory infiltration and an increased myocardial viral burden [127].

A subset of proinflammatory monocytes expressing high levels of CD16 (the FcRγIII) is markedly up-regulated in HIV-1^+ patients, especially in patients with advanced disease [128, 129]. In vitro and in vivo $CD14^+CD16^+$ monocytes are more susceptible to HIV-1 infection than CD16-negative cells [130, 131], and they are an important source of the proinflammatory cytokine TNF-α [132]. Furthermore, $CD14^+CD16^+$ MDM are more efficient at activating resting T cells, and in vitro conjugates formed between $CD14^+CD16^+$ MDM and T cells are major sites of virus production [133, 134]. $CD16^+CD163^+$ monocytes, a potential precursor of alternatively activated populations, have also been described as expanded during HIV-1 infection [135]. Unlike $CD16^+CD163^-$ cells, the frequency of $CD16^+CD163^+$ monocytes is positively correlated with HIV-1 viremia and negatively with peripheral $CD4^+$ T cell counts (in patients with CD4, <450 cells/μl), reinforcing the hypothesis that a switch to Th2 immune responses and toward an M2-like phenotype is associated with disease progression [135].

Mucosal macrophages are located at the interface with the external environment, where they serve as one of the first lines of defense against microorganisms that have breached the epithelial barrier [37, 38, 115]. Yet, several viruses are able to gain entry and exploit these cells for purposes of virus transmission and dissemination, often by exploiting C-type lectins [136–139]. In this regard, M2-MDM express high levels of several C-type lectins, including DC-SIGN [18, 47]. Studies in our laboratory have demonstrated that DC-SIGN is strongly up-regulated on the surface of M2a-MDM and that these DC-SIGN-expressing MDM can transfer CXCR4-dependent HIV-1_{IIIB} efficiently (not efficiently replicating in polarized and unpolarized MDM) to IL-2 PBMC (E. Cassol et al., submitted; Fig. 1). Our findings are consistent with an independent study, demonstrating that an IL-4-enriched environment is associated with increased capture, integration, production, and transfer of CCR5-dependent HIV-1 by MDM [140]. Collectively, these observations suggest that similar to DC [141–143], DC-$SIGN^+$ M2a macrophages may play a pivotal role in HIV-1 transmission. However, in contrast to DC-$SIGN^+$ DC that bind and transport HIV-1 to lymphatic tissues for presentation to T cells [55], resident tissue macrophages are nonmigratory cells that are likely to play an important role in the pathogenesis of mucosal infection and in sexual transmission.

IMPACT OF MICROBIAL COINFECTIONS ON MACROPHAGE POLARIZATION

In Africa and other areas of the developing world, Mtb [144, 145] and parasitic infections [146, 147] contribute to the mod-

ulation of macrophage activation in persons coinfected with HIV-1. As with most microbes, acute Mtb infection drives these cells toward an M1 phenotype [148, 149]. Experimentally, macrophages activated by Mtb secrete high levels of TNF-α, IL-6, IL-12, IL-1β, CCL2, CCL5, and CXCL18 [148]. In the absence of effective therapy, prolonged secretion of these molecules in vivo can result in a cytokine storm similar to that observed in patients with systemic inflammatory response syndrome (sepsis) and multiple organ failure [150]. As observed in other bacterial infections such as chronic brucellosis, chronic Mtb infection is associated with a switch from an M1 toward and M2 phenotype [148]. These alternatively activated macrophages are a major source of IL-10 and can promote Mtb recrudescence without activating and inducing anti-Mtb T cell immunity [151–153]. In contrast to Mtb and HIV-1, helminths are extremely efficient at triggering M2 activation in tissue macrophages [154–156]. In patients coinfected with HIV-1, a helminth-induced switch toward an M2 response can accelerate disease progression [157, 158]. Paradoxically, M2 responses, which are required for wound healing and worm expulsion, also increase HIV-1 replication [159–161]. Unexpectedly, treatment of intestinal helminths in African populations is not associated with a reduction in HIV-1 viremia (i.e., the number of copies of HIV RNA measured in 1 ml plasma, with a single virion containing two copies of genomic RNA on average) [162].

CONCLUSIONS

The concept of immune cell polarization, including the polarization of tissue macrophages, provides a valuable but somewhat simplistic framework for unraveling the complexity of host-viral interactions. Continued investigation of this complex network of inter-related interactions may lead to new insights for controlling HIV-1, as well as other microbial diseases, causing a great burden on human health in the underdeveloped and industrialized world.

AUTHORSHIP

All authors contributed equally to the writing of this review.

ACKNOWLEDGMENTS

This study was supported in part by the Fondation Dormeur and by Europrise (grant no. LSHP CT-2006-037611 to G. P.), European Union (SANTE 2007 147-790), and the National Research Foundation of South Africa (grant no. 61509). E. C. performed this study as partial fulfillment of her joint Ph.D. in "Molecular and Cellular Biology" of the Vita-Salute University of Milan (Milan, Italy) and the Open University of London (UK). L. C. also performed some aspects of the study as partial fulfillment of his Ph.D. in "Molecular Medicine-Section of Basic and Applied Immunology" of the Vita-Salute University of Milan.

REFERENCES

1. Zhu, J., Paul, W. E. (2008) CD4 T cells: fates, functions, and faults. *Blood* **112,** 1557–1569.
2. Urban Jr., J. F., Noben-Trauth, N., Donaldson, D. D., Madden, K. B., Morris, S. C., Collins, M., Finkelman, F. D. (1998) IL-13, IL-4Rα, and Stat6 are required for the expulsion of the gastrointestinal nematode parasite *Nippostrongylus brasiliensis*. *Immunity* **8,** 255–264.
3. Lawn, S. D., Butera, S. T., Folks, T. M. (2001) Contribution of immune activation to the pathogenesis and transmission of human immunodeficiency virus type 1 infection. *Clin. Microbiol. Rev.* **14,** 753–777.
4. Balagopal, A., Philp, F. H., Astemborski, J., Block, T. M., Mehta, A., Long, R., Kirk, G. D., Mehta, S. H., Cox, A. L., Thomas, D. L., Ray, S. C. (2008) Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. *Gastroenterology* **135,** 226–233.
5. Ancuta, P., Kamat, A., Kunstman, K. J., Kim, E. Y., Autissier, P., Wurcel, A., Zaman, T., Stone, D., Mefford, M., Morgello, S., Singer, E. J., Wolinsky, S. M., Gabuzda, D. (2008) Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. *PLoS One* **3,** e2516.
6. Sodora, D. L., Allan, J. S., Apetrei, C., Brenchley, J. M., Douek, D. C., Else, J. G., Estes, J. D., Hahn, B. H., Hirsch, V. M., Kaur, A., Kirchhoff, F., Muller-Trutwin, M., Pandrea, I., Schmitz, J. E., Silvestri, G. (2009) Toward an AIDS vaccine: lessons from natural simian immunodeficiency virus infections of African nonhuman primate hosts. *Nat. Med.* **15,** 861–865.
7. Paiardini, M., Pandrea, I., Apetrei, C., Silvestri, G. (2009) Lessons learned from the natural hosts of HIV-related viruses. *Annu. Rev. Med.* **60,** 485–495.
8. Appay, V., Sauce, D. (2008) Immune activation and inflammation in HIV-1 infection: causes and consequences. *J. Pathol.* **214,** 231–241.
9. Hoffmann, K. F., Cheever, A. W., Wynn, T. A. (2000) IL-10 and the dangers of immune polarization: excessive type 1 and type 2 cytokine responses induce distinct forms of lethal immunopathology in murine schistosomiasis. *J. Immunol.* **164,** 6406–6416.
10. Gazzinelli, R. T., Wysocka, M., Hieny, S., Scharton-Kersten, T., Cheever, A., Kuhn, R., Muller, W., Trinchieri, G., Sher, A. (1996) In the absence of endogenous IL-10, mice acutely infected with *Toxoplasma gondii* succumb to a lethal immune response dependent on CD4+ T cells and accompanied by overproduction of IL-12, IFN-γ and TNF-α. *J. Immunol.* **157,** 798–805.
11. Baenziger, S., Heikenwalder, M., Johansen, P., Schlaepfer, E., Hofer, U., Miller, R. C., Diemand, S., Honda, K., Kundig, T. M., Aguzzi, A., Speck, R. F. (2009) Triggering TLR7 in mice induces immune activation and lymphoid system disruption, resembling HIV-mediated pathology. *Blood* **113,** 377–388.
12. Mosmann, T. R., Sad, S. (1996) The expanding universe of T-cell subsets: Th1, Th2 and more. *Immunol. Today* **17,** 138–146.
13. Weaver, C. T., Hatton, R. D., Mangan, P. R., Harrington, L. E. (2007) IL-17 family cytokines and the expanding diversity of effector T cell lineages. *Annu. Rev. Immunol.* **25,** 821–852.
14. Darrah, P. A., Patel, D. T., De Luca, P. M., Lindsay, R. W., Davey, D. F., Flynn, B. J., Hoff, S. T., Andersen, P., Reed, S. G., Morris, S. L., Roederer, M., Seder, R. A. (2007) Multifunctional TH1 cells define a correlate of vaccine-mediated protection against *Leishmania major*. *Nat. Med.* **13,** 843–850.
15. Sutton, C., Brereton, C., Keogh, B., Mills, K. H., Lavelle, E. C. (2006) A crucial role for interleukin (IL)-1 in the induction of IL-17-producing T cells that mediate autoimmune encephalomyelitis. *J. Exp. Med.* **203,** 1685–1691.
16. Wynn, T. A. (2003) IL-13 effector functions. *Annu. Rev. Immunol.* **21,** 425–456.
17. Cassol, E., Cassetta, L., Rizzi, C., Alfano, M., Poli, G. (2009) M1 and M2a polarization of human monocyte-derived macrophages inhibits HIV-1 replication by distinct mechanisms. *J. Immunol.* **182,** 6237–6246.
18. Gordon, S. (2003) Alternative activation of macrophages. *Nat. Rev. Immunol.* **3,** 23–35.
19. Mantovani, A., Sica, A., Sozzani, S., Allavena, P., Vecchi, A., Locati, M. (2004) The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.* **25,** 677–686.
20. Stout, R. D., Suttles, J. (2004) Functional plasticity of macrophages: reversible adaptation to changing microenvironments. *J. Leukoc. Biol.* **76,** 509–513.
21. Grage-Griebenow, E., Flad, H. D., Ernst, M. (2001) Heterogeneity of human peripheral blood monocyte subsets. *J. Leukoc. Biol.* **69,** 11–20.
22. Gordon, S., Taylor, P. R. (2005) Monocyte and macrophage heterogeneity. *Nat. Rev. Immunol.* **5,** 953–964.
23. Bach, E. A., Aguet, M., Schreiber, R. D. (1997) The IFN γ receptor: a paradigm for cytokine receptor signaling. *Annu. Rev. Immunol.* **15,** 563–591.
24. Bonecchi, R., Sozzani, S., Stine, J. T., Luini, W., D'Amico, G., Allavena, P., Chantry, D., Mantovani, A. (1998) Divergent effects of interleukin-4 and interferon-γ on macrophage-derived chemokine production: an amplification circuit of polarized T helper 2 responses. *Blood* **92,** 2668–2671.

25. Martinez-Pomares, L., Hanitsch, L. G., Stillion, R., Keshav, S., Gordon, S. (2005) Expression of mannose receptor and ligands for its cysteine-rich domain in venous sinuses of human spleen. *Lab. Invest.* **85,** 1238–1249.
26. De Waal Malefyt, R., Figdor, C. G., Huijbens, R., Mohan-Peterson, S., Bennett, B., Culpepper, J., Dang, W., Zurawski, G., de Vries, J. E. (1993) Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. Comparison with IL-4 and modulation by IFN-γ or IL-10. *J. Immunol.* **151,** 6370–6381.
27. Trofimov, S., Pantsulaia, I., Kobyliansky, E., Livshits, G. (2004) Circulating levels of receptor activator of nuclear factor-κB ligand/osteoprotegerin/macrophage-colony stimulating factor in a presumably healthy human population. *Eur. J. Endocrinol.* **150,** 305–311.
28. Martinez, F. O., Gordon, S., Locati, M., Mantovani, A. (2006) Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression. *J. Immunol.* **177,** 7303–7311.
29. Auffray, C., Sieweke, M. H., Geissmann, F. (2009) Blood monocytes: development, heterogeneity, and relationship with dendritic cells. *Annu. Rev. Immunol.* **27,** 669–692.
30. Passlick, B., Flieger, D., Ziegler-Heitbrock, H. W. (1989) Identification and characterization of a novel monocyte subpopulation in human peripheral blood. *Blood* **74,** 2527–2534.
31. Grage-Griebenow, E., Flad, H. D., Ernst, M., Bzowska, M., Skrzeczynska, J., Pryjma, J. (2000) Human MO subsets as defined by expression of CD64 and CD16 differ in phagocytic activity and generation of oxygen intermediates. *Immunobiology* **202,** 42–50.
32. Ziegler-Heitbrock, H. W. (2000) Definition of human blood monocytes. *J. Leukoc. Biol.* **67,** 603–606.
33. Hume, D. A. (2006) The mononuclear phagocyte system. *Curr. Opin. Immunol.* **18,** 49–53.
34. Fox, S. W., Fuller, K., Bayley, K. E., Lean, J. M., Chambers, T. J. (2000) TGF-β 1 and IFN-γ direct macrophage activation by TNF-α to osteoclastic or cytocidal phenotype. *J. Immunol.* **165,** 4957–4963.
35. Chambers, T. J. (2000) Regulation of the differentiation and function of osteoclasts. *J. Pathol.* **192,** 4–13.
36. Schenk, M., Mueller, C. (2007) Adaptations of intestinal macrophages to an antigen-rich environment. *Semin. Immunol.* **19,** 84–93.
37. Smythies, L. E., Sellers, M., Clements, R. H., Mosteller-Barnum, M., Meng, G., Benjamin, W. H., Orenstein, J. M., Smith, P. D. (2005) Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity. *J. Clin. Invest.* **115,** 66–75.
38. Smith, P. D., Ochsenbauer-Jambor, C., Smythies, L. E. (2005) Intestinal macrophages: unique effector cells of the innate immune system. *Immunol. Rev.* **206,** 149–159.
39. Lassmann, H., Schmied, M., Vass, K., Hickey, W. F. (1993) Bone marrow derived elements and resident microglia in brain inflammation. *Glia* **7,** 19–24.
40. Tarling, J. D., Lin, H. S., Hsu, S. (1987) Self-renewal of pulmonary alveolar macrophages: evidence from radiation chimera studies. *J. Leukoc. Biol.* **42,** 443–446.
41. Rauh, M. J., Ho, V., Pereira, C., Sham, A., Sly, L. M., Lam, V., Huxham, L., Minchinton, A. I., Mui, A., Krystal, G. (2005) SHIP represses the generation of alternatively activated macrophages. *Immunity* **23,** 361–374.
42. Xiao, W., Hong, H., Kawakami, Y., Lowell, C. A., Kawakami, T. (2008) Regulation of myeloproliferation and M2 macrophage programming in mice by Lyn/Hck, SHIP, and Stat5. *J. Clin. Invest.* **118,** 924–934.
43. Ishii, M., Wen, H., Corsa, C.A., Liu, T., Coelho, A.L., Allen, R.M., Carson IV, W. F., Cavassani, K. A., Li, X., Lukacs, N. W., Hogaboam, C. M., Dou, Y., Kunkel, S. L. (2009) Epigenetic regulation of the alternatively activated macrophage phenotype. *Blood* **114,** 3244–3254.
44. De Santa, F., Totaro, M. G., Prosperini, E., Notarbartolo, S., Testa, G., Natoli, G. (2007) The histone H3 lysine-27 demethylase Jmjd3 links inflammation to inhibition of polycomb-mediated gene silencing. *Cell* **130,** 1083–1094.
45. Mantovani, A., Locati, M. (2009) Orchestration of macrophage polarization. *Blood* **114,** 3135–3136.
46. Porcheray, F., Viaud, S., Rimaniol, A. C., Leone, C., Samah, B., Dereuddre-Bosquet, N., Dormont, D., Gras, G. (2005) Macrophage activation switching: an asset for the resolution of inflammation. *Clin. Exp. Immunol.* **142,** 481–489.
47. Martinez, F. O., Helming, L., Gordon, S. (2009) Alternative activation of macrophages: an immunologic functional perspective. *Annu. Rev. Immunol.* **27,** 451–483.
48. Sinistro, A., Ciaprini, C., Natoli, S., Sussarello, E., Carducci, F. C., Almerighi, C., Capozzi, M., Bolacchi, F., Rocchi, G., Bergamini, A. (2007) Lipopolysaccharide desensitizes monocytes-macrophages to CD40 ligand stimulation. *Immunology* **122,** 362–370.
49. Medvedev, A. E., Piao, W., Shoenfelt, J., Rhee, S. H., Chen, H., Basu, S., Wahl, L. M., Fenton, M. J., Vogel, S. N. (2007) Role of TLR4 tyrosine phosphorylation in signal transduction and endotoxin tolerance. *J. Biol. Chem.* **282,** 16042–16053.
50. Medvedev, A. E., Sabroe, I., Hasday, J. D., Vogel, S. N. (2006) Tolerance to microbial TLR ligands: molecular mechanisms and relevance to disease. *J. Endotoxin Res.* **12,** 133–150.
51. Mantovani, A., Sica, A., Locati, M. (2005) Macrophage polarization comes of age. *Immunity* **23,** 344–346.
52. Goerdt, S., Politz, O., Schledzewski, K., Birk, R., Gratchev, A., Guillot, P., Hakiy, N., Klemke, C. D., Dippel, E., Kodelja, V., Orfanos, C. E. (1999) Alternative versus classical activation of macrophages. *Pathobiology* **67,** 222–226.
53. Mills, C. D., Kincaid, K., Alt, J. M., Heilman, M. J., Hill, A. M. (2000) M-1/M-2 macrophages and the Th1/Th2 paradigm. *J. Immunol.* **164,** 6166–6173.
54. Soilleux, E. J., Morris, L. S., Leslie, G., Chehimi, J., Luo, Q., Levroney, E., Trowsdale, J., Montaner, L. J., Doms, R. W., Weissman, D., Coleman, N., Lee, B. (2002) Constitutive and induced expression of DC-SIGN on dendritic cell and macrophage subpopulations in situ and in vitro. *J. Leukoc. Biol.* **71,** 445–457.
55. Gurney, K. B., Elliott, J., Nassanian, H., Song, C., Soilleux, E., McGowan, I., Anton, P. A., Lee, B. (2005) Binding and transfer of human immunodeficiency virus by DC-SIGN+ cells in human rectal mucosa. *J. Virol.* **79,** 5762–5773.
56. Christophi, G. P., Panos, M., Hudson, C. A., Christophi, R. L., Gruber, R. C., Mersich, A. T., Blystone, S. D., Jubelt, B., Massa, P. T. (2009) Macrophages of multiple sclerosis patients display deficient SHP-1 expression and enhanced inflammatory phenotype. *Lab. Invest.* **89,** 742–759.
57. Dheen, S. T., Kaur, C., Ling, E. A. (2007) Microglial activation and its implications in the brain diseases. *Curr. Med. Chem.* **14,** 1189–1197.
58. Behrens, E. M. (2008) Macrophage activation syndrome in rheumatic disease: what is the role of the antigen presenting cell? *Autoimmun. Rev.* **7,** 305–308.
59. Szekanecz, Z., Koch, A. E. (2007) Macrophages and their products in rheumatoid arthritis. *Curr. Opin. Rheumatol.* **19,** 289–295.
60. Suarez, C. J., Parker, N. J., Finn, P. W. (2008) Innate immune mechanism in allergic asthma. *Curr. Allergy Asthma Rep.* **8,** 451–459.
61. Burke, L. A., Wilkinson, J. R., Howell, C. J., Lee, T. H. (1991) Interactions of macrophages and monocytes with granulocytes in asthma. *Eur. Respir. J. Suppl.* **13,** 85s–90s.
62. De Palma, M., Murdoch, C., Venneri, M. A., Naldini, L., Lewis, C. E. (2007) Tie2-expressing monocytes: regulation of tumor angiogenesis and therapeutic implications. *Trends Immunol.* **28,** 519–524.
63. Lewis, C. E., De Palma, M., Naldini, L. (2007) Tie2-expressing monocytes and tumor angiogenesis: regulation by hypoxia and angiopoietin-2. *Cancer Res.* **67,** 8429–8432.
64. Sica, A., Larghi, P., Mancino, A., Rubino, L., Porta, C., Totaro, M. G., Rimoldi, M., Biswas, S. K., Allavena, P., Mantovani, A. (2008) Macrophage polarization in tumor progression. *Semin. Cancer Biol.* **18,** 349–355.
65. Mantovani, A., Sica, A., Allavena, P., Garlanda, C., Locati, M. (2009) Tumor-associated macrophages and the related myeloid-derived suppressor cells as a paradigm of the diversity of macrophage activation. *Hum. Immunol.* **70,** 325–330.
66. Guiducci, C., Vicari, A. P., Sangaletti, S., Trinchieri, G., Colombo, M. P. (2005) Redirecting in vivo elicited tumor infiltrating macrophages and dendritic cells towards tumor rejection. *Cancer Res.* **65,** 3437–3446.
67. Colombo, M. P., Mantovani, A. (2005) Targeting myelomonocytic cells to revert inflammation-dependent cancer promotion. *Cancer Res.* **65,** 9113–9116.
68. Abramson, S. L., Gallin, J. I. (1990) IL-4 inhibits superoxide production by human mononuclear phagocytes. *J. Immunol.* **144,** 625–630.
69. Alfano, M., Crotti, A., Vicenzi, E., Poli, G. (2008) New players in cytokine control of HIV infection. *Curr. HIV/AIDS Rep.* **5,** 27–32.
70. Herbein, G., Khan, K. A. (2008) Is HIV infection a TNF receptor signaling-driven disease? *Trends Immunol.* **29,** 61–67.
71. Kedzierska, K., Crowe, S. M. (2001) Cytokines and HIV-1: interactions and clinical implications. *Antivir. Chem. Chemother.* **12,** 133–150.
72. Cassol, E., Alfano, M., Biswas, P., Poli, G. (2006) Monocyte-derived macrophages and myeloid cell lines as targets of HIV-1 replication and persistence. *J. Leukoc. Biol.* **80,** 1018–1030.
73. Brown, J. N., Kohler, J. J., Coberley, C. R., Sleasman, J. W., Goodenow, M. M. (2008) HIV-1 activates macrophages independent of Toll-like receptors. *PLoS One* **3,** e3664.
74. Chan, G., Bivins-Smith, E. R., Smith, M. S., Smith, P. M., Yurochko, A. D. (2008) Transcriptome analysis reveals human cytomegalovirus reprograms monocyte differentiation toward an M1 macrophage. *J. Immunol.* **181,** 698–711.
75. Chan, G., Bivins-Smith, E. R., Smith, M. S., Yurochko, A. D. (2009) NF-κB and phosphatidylinositol 3-kinase activity mediates the HCMV-induced atypical M1/M2 polarization of monocytes. *Virus Res.* **144,** 329–333.
76. Kukavica-Ibrulj, I., Hamelin, M. E., Prince, G. A., Gagnon, C., Bergeron, Y., Bergeron, M. G., Boivin, G. (2009) Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia. *J. Virol.* **83,** 1341–1349.
77. Pribul, P. K., Harker, J., Wang, B., Wang, H., Tregoning, J. S., Schwarze, J., Openshaw, P. J. (2008) Alveolar macrophages are a major determi-

nant of early responses to viral lung infection but do not influence subsequent disease development. *J. Virol.* **82,** 4441–4448.
78. Van Reeth, K., Adair, B. (1997) Macrophages and respiratory viruses. *Pathol. Biol. (Paris)* **45,** 184–192.
79. Laza-Stanca, V., Stanciu, L. A., Message, S. D., Edwards, M. R., Gern, J. E., Johnston, S. L. (2006) Rhinovirus replication in human macrophages induces NF-κB-dependent tumor necrosis factor α production. *J. Virol.* **80,** 8248–8258.
80. Berg, K., Andersen, H., Owen, T. C. (2004) The regulation of rhinovirus infection in vitro by IL-8, HuIFN-α, and TNF-α. *APMIS* **112,** 172–182.
81. Oliver, B. G., Lim, S., Wark, P., Laza-Stanca, V., King, N., Black, J. L., Burgess, J. K., Roth, M., Johnston, S. L. (2008) Rhinovirus exposure impairs immune responses to bacterial products in human alveolar macrophages. *Thorax* **63,** 519–525.
82. Maines, T. R., Szretter, K. J., Perrone, L., Belser, J. A., Bright, R. A., Zeng, H., Tumpey, T. M., Katz, J. M. (2008) Pathogenesis of emerging avian influenza viruses in mammals and the host innate immune response. *Immunol. Rev.* **225,** 68–84.
83. Frieman, M., Heise, M., Baric, R. (2008) SARS coronavirus and innate immunity. *Virus Res.* **133,** 101–112.
84. Ryman, K. D., Klimstra, W. B. (2008) Host responses to αvirus infection. *Immunol. Rev.* **225,** 27–45.
85. Carter, C. A., Ehrlich, L. S. (2008) Cell biology of HIV-1 infection of macrophages. *Annu. Rev. Microbiol.* **62,** 425–443.
86. Morrow, G., Vachot, L., Vagenas, P., Robbiani, M. (2007) Current concepts of HIV transmission. *Curr. HIV/AIDS Rep.* **4,** 29–35.
87. Wahl, S. M., Greenwell-Wild, T., Vazquez, N. (2006) HIV accomplices and adversaries in macrophage infection. *J. Leukoc. Biol.* **80,** 973–983.
88. Kaul, M., Lipton, S. A. (2006) Mechanisms of neuroimmunity and neurodegeneration associated with HIV-1 infection and AIDS. *J. Neuroimmune Pharmacol.* **1,** 138–151.
89. Rock, R. B., Peterson, P. K. (2006) Microglia as a pharmacological target in infectious and inflammatory diseases of the brain. *J. Neuroimmune Pharmacol.* **1,** 117–126.
90. Kaul, M., Lipton, S. A. (2006) Mechanisms of neuronal injury and death in HIV-1 associated dementia. *Curr. HIV Res.* **4,** 307–318.
91. Orenstein, J. M., Fox, C., Wahl, S. M. (1997) Macrophages as a source of HIV during opportunistic infections. *Science* **276,** 1857–1861.
92. Perno, C. F., Svicher, V., Schols, D., Pollicita, M., Balzarini, J., Aquaro, S. (2006) Therapeutic strategies towards HIV-1 infection in macrophages. *Antiviral Res.* **71,** 293–300.
93. Alexaki, A., Liu, Y., Wigdahl, B. (2008) Cellular reservoirs of HIV-1 and their role in viral persistence. *Curr. HIV Res.* **6,** 388–400.
94. Shehu-Xhilaga, M., Tachedjian, G., Crowe, S. M., Kedzierska, K. (2005) Antiretroviral compounds: mechanisms underlying failure of HAART to eradicate HIV-1. *Curr. Med. Chem.* **12,** 1705–1719.
95. Geeraert, L., Kraus, G., Pomerantz, R. J. (2008) Hide-and-seek: the challenge of viral persistence in HIV-1 infection. *Annu. Rev. Med.* **59,** 487–501.
96. Shen, L., Siliciano, R. F. (2008) Viral reservoirs, residual viremia, and the potential of highly active antiretroviral therapy to eradicate HIV infection. *J. Allergy Clin. Immunol.* **122,** 22–28.
97. Peterson, S., Reid, A. P., Kim, S., Siliciano, R. F. (2007) Treatment implications of the latent reservoir for HIV-1. *Adv. Pharmacol.* **55,** 411–425.
98. Kedzierska, K., Ellery, P., Mak, J., Lewin, S. R., Crowe, S. M., Jaworowski, A. (2002) HIV-1 down-modulates γ signaling chain of Fc γ R in human macrophages: a possible mechanism for inhibition of phagocytosis. *J. Immunol.* **168,** 2895–2903.
99. Musher, D. M., Watson, D. A., Nickeson, D., Gyorkey, F., Lahart, C., Rossen, R. D. (1990) The effect of HIV infection on phagocytosis and killing of *Staphylococcus aureus* by human pulmonary alveolar macrophages. *Am. J. Med. Sci.* **299,** 158–163.
100. Kedzierska, K., Crowe, S. M. (2002) The role of monocytes and macrophages in the pathogenesis of HIV-1 infection. *Curr. Med. Chem.* **9,** 1893–1903.
101. Pittis, M. G., Prada, F., Mangano, A., Perez, L., Sternik, G., Redondo, J., Bologna, R., Sen, L. (1997) Monocyte phagolysosomal fusion in children born to human immunodeficiency virus-infected mothers. *Pediatr. Infect. Dis. J.* **16,** 24–28.
102. Smith, P. D., Ohura, K., Masur, H., Lane, H. C., Fauci, A. S., Wahl, S. M. (1984) Monocyte function in the acquired immune deficiency syndrome. Defective chemotaxis. *J. Clin. Invest.* **74,** 2121–2128.
103. Poli, G., Bottazzi, B., Acero, R., Bersani, L., Rossi, V., Introna, M., Lazzarin, A., Galli, M., Mantovani, A. (1985) Monocyte function in intravenous drug abusers with lymphadenopathy syndrome and in patients with acquired immunodeficiency syndrome: selective impairment of chemotaxis. *Clin. Exp. Immunol.* **62,** 136–142.
104. Mastroianni, C. M., Lichtner, M., Mengoni, F., D'Agostino, C., Forcina, G., d'Ettorre, G., Santopadre, P., Vullo, V. (1999) Improvement in neutrophil and monocyte function during highly active antiretroviral treatment of HIV-1-infected patients. *AIDS* **13,** 883–890.
105. Wahl, S. M., Allen, J. B., Gartner, S., Orenstein, J. M., Popovic, M., Chenoweth, D. E., Arthur, L. O., Farrar, W. L., Wahl, L. M. (1989) HIV-1 and its envelope glycoprotein down-regulate chemotactic ligand receptors and chemotactic function of peripheral blood monocytes. *J. Immunol.* **142,** 3553–3559.
106. Herbein, G., Mahlknecht, U., Batliwalla, F., Gregersen, P., Pappas, T., Butler, J., O'Brien, W. A., Verdin, E. (1998) Apoptosis of CD8+ T cells is mediated by macrophages through interaction of HIV gp120 with chemokine receptor CXCR4. *Nature* **395,** 189–194.
107. Giorgi, J. V., Hultin, L. E., McKeating, J. A., Johnson, T. D., Owens, B., Jacobson, L. P., Shih, R., Lewis, J., Wiley, D. J., Phair, J. P., Wolinsky, S. M., Detels, R. (1999) Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J. Infect. Dis.* **179,** 859–870.
108. Hazenberg, M. D., Otto, S. A., van Benthem, B. H., Roos, M. T., Coutinho, R. A., Lange, J. M., Hamann, D., Prins, M., Miedema, F. (2003) Persistent immune activation in HIV-1 infection is associated with progression to AIDS. *AIDS* **17,** 1881–1888.
109. Deeks, S. G., Kitchen, C. M., Liu, L., Guo, H., Gascon, R., Narvaez, A. B., Hunt, P., Martin, J. N., Kahn, J. O., Levy, J., McGrath, M. S., Hecht, F. M. (2004) Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. *Blood* **104,** 942–947.
110. Brenchley, J. M., Price, D. A., Douek, D. C. (2006) HIV disease: fallout from a mucosal catastrophe? *Nat. Immunol.* **7,** 235–239.
111. Brenchley, J. M., Price, D. A., Schacker, T. W., Asher, T. E., Silvestri, G., Rao, S., Kazzaz, Z., Bornstein, E., Lambotte, O., Altmann, D., Blazar, B. R., Rodriguez, B., Teixeira-Johnson, L., Landay, A., Martin, J. N., Hecht, F. M., Picker, L. J., Lederman, M. M., Deeks, S. G., Douek, D. C. (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat. Med.* **12,** 1365–1371.
112. Douek, D. C., Picker, L. J., Koup, R. A. (2003) T cell dynamics in HIV-1 infection. *Annu. Rev. Immunol.* **21,** 265–304.
113. Porcheray, F., Samah, B., Leone, C., Dereuddre-Bosquet, N., Gras, G. (2006) Macrophage activation and human immunodeficiency virus infection: HIV replication directs macrophages towards a pro-inflammatory phenotype while previous activation modulates macrophage susceptibility to infection and viral production. *Virology* **349,** 112–120.
114. Swingler, S., Mann, A., Jacque, J., Brichacek, B., Sasseville, V. G., Williams, K., Lackner, A. A., Janoff, E. N., Wang, R., Fisher, D., Stevenson, M. (1999) HIV-1 Nef mediates lymphocyte chemotaxis and activation by infected macrophages. *Nat. Med.* **5,** 997–1103.
115. Shen, R., Richter, H. E., Clements, R. H., Novak, L., Huff, K., Bimczok, D., Sankaran-Walters, S., Dandekar, S., Clapham, P. R., Smythies, L. E., Smith, P. D. (2009) Macrophages in vaginal but not intestinal mucosa are monocyte-like and permissive to human immunodeficiency virus type 1 infection. *J. Virol.* **83,** 3258–3267.
116. Smith, P. D., Meng, G., Salazar-Gonzalez, J. F., Shaw, G. M. (2003) Macrophage HIV-1 infection and the gastrointestinal tract reservoir. *J. Leukoc. Biol.* **74,** 642–649.
117. Smith, P. D., Meng, G., Sellers, M. T., Rogers, T. S., Shaw, G. M. (2000) Biological parameters of HIV-1 infection in primary intestinal lymphocytes and macrophages. *J. Leukoc. Biol.* **68,** 360–365.
118. Peng, G., Lei, K. J., Jin, W., Greenwell-Wild, T., Wahl, S. M. (2006) Induction of APOBEC3 family proteins, a defensive maneuver underlying interferon-induced anti-HIV-1 activity. *J. Exp. Med.* **203,** 41–46.
119. Embretson, J., Zupancic, M., Ribas, J. L., Burke, A., Racz, P., Tenner-Racz, K., Haase, A. T. (1993) Massive covert infection of helper T lymphocytes and macrophages by HIV during the incubation period of AIDS. *Nature* **362,** 359–362.
120. Martin, J. C., Bandres, J. C. (1999) Cells of the monocyte-macrophage lineage and pathogenesis of HIV-1 infection. *J. Acquir. Immune Defic. Syndr.* **22,** 413–429.
121. Bowman, M. C., Archin, N. M., Margolis, D. M. (2009) Pharmaceutical approaches to eradication of persistent HIV infection. *Expert Rev. Mol. Med.* **11,** e6.
122. Richman, D. D., Margolis, D. M., Delaney, M., Greene, W. C., Hazuda, D., Pomerantz, R. J. (2009) The challenge of finding a cure for HIV infection. *Science* **323,** 1304–1307.
123. Marsden, M. D., Zack, J. A. (2009) Eradication of HIV: current challenges and new directions. *J. Antimicrob. Chemother.* **63,** 7–10.
124. Kim, W. K., Alvarez, X., Fisher, J., Bronfin, B., Westmoreland, S., McLaurin, J., Williams, K. (2006) CD163 identifies perivascular macrophages in normal and viral encephalitic brains and potential precursors to perivascular macrophages in blood. *Am. J. Pathol.* **168,** 822–834.
125. Roberts, E. S., Masliah, E., Fox, H. S. (2004) CD163 identifies a unique population of ramified microglia in HIV encephalitis (HIVE). *J. Neuropathol. Exp. Neurol.* **63,** 1255–1264.
126. Fischer-Smith, T., Bell, C., Croul, S., Lewis, M., Rappaport, J. (2008) Monocyte/macrophage trafficking in acquired immunodeficiency syndrome encephalitis: lessons from human and nonhuman primate studies. *J. Neurovirol.* **14,** 318–326.
127. Yearley, J. H., Pearson, C., Shannon, R. P., Mansfield, K. G. (2007) Phenotypic variation in myocardial macrophage populations suggests a role for macrophage activation in SIV-associated cardiac disease. *AIDS Res. Hum. Retroviruses* **23,** 515–524.

128. Thieblemont, N., Weiss, L., Sadeghi, H. M., Estcourt, C., Haeffner-Cavaillon, N. (1995) CD14lowCD16high: a cytokine-producing monocyte subset which expands during human immunodeficiency virus infection. *Eur. J. Immunol.* **25,** 3418–3424.
129. Pulliam, L., Gascon, R., Stubblebine, M., McGuire, D., McGrath, M. S. (1997) Unique monocyte subset in patients with AIDS dementia. *Lancet* **349,** 692–695.
130. Jaworowski, A., Kamwendo, D. D., Ellery, P., Sonza, S., Mwapasa, V., Tadesse, E., Molyneux, M. E., Rogerson, S. J., Meshnick, S. R., Crowe, S. M. (2007) CD16+ monocyte subset preferentially harbors HIV-1 and is expanded in pregnant Malawian women with *Plasmodium falciparum* malaria and HIV-1 infection. *J. Infect. Dis.* **196,** 38–42.
131. Ellery, P. J., Tippett, E., Chiu, Y. L., Paukovics, G., Cameron, P. U., Solomon, A., Lewin, S. R., Gorry, P. R., Jaworowski, A., Greene, W. C., Sonza, S., Crowe, S. M. (2007) The CD16+ monocyte subset is more permissive to infection and preferentially harbors HIV-1 in vivo. *J. Immunol.* **178,** 6581–6589.
132. Belge, K. U., Dayyani, F., Horelt, A., Siedlar, M., Frankenberger, M., Frankenberger, B., Espevik, T., Ziegler-Heitbrock, L. (2002) The proinflammatory CD14+CD16+DR++ monocytes are a major source of TNF. *J. Immunol.* **168,** 3536–3542.
133. Ancuta, P., Autissier, P., Wurcel, A., Zaman, T., Stone, D., Gabuzda, D. (2006) CD16+ monocyte-derived macrophages activate resting T cells for HIV infection by producing CCR3 and CCR4 ligands. *J. Immunol.* **176,** 5760–5771.
134. Ancuta, P., Kunstman, K. J., Autissier, P., Zaman, T., Stone, D., Wolinsky, S. M., Gabuzda, D. (2006) CD16+ monocytes exposed to HIV promote highly efficient viral replication upon differentiation into macrophages and interaction with T cells. *Virology* **344,** 267–276.
135. Fischer-Smith, T., Tedaldi, E. M., Rappaport, J. (2008) CD163/CD16 coexpression by circulating monocytes/macrophages in HIV: potential biomarkers for HIV infection and AIDS progression. *AIDS Res. Hum. Retroviruses* **24,** 417–421.
136. Baribaud, F., Doms, R. W., Pohlmann, S. (2002) The role of DC-SIGN and DC-SIGNR in HIV and Ebola virus infection: can potential therapeutics block virus transmission and dissemination? *Expert Opin. Ther. Targets* **6,** 423–431.
137. Feng, Z. H., Wang, Q. C., Nie, Q. H., Jia, Z. S., Zhou, Y. X. (2004) DC-SIGN: binding receptor for HCV? *World J. Gastroenterol.* **10,** 925–929.
138. Han, D. P., Lohani, M., Cho, M. W. (2007) Specific asparagine-linked glycosylation sites are critical for DC-SIGN- and L-SIGN-mediated severe acute respiratory syndrome coronavirus entry. *J. Virol.* **81,** 12029–12039.
139. Lozach, P. Y., Burleigh, L., Staropoli, I., Navarro-Sanchez, E., Harriague, J., Virelizier, J. L., Rey, F. A., Despres, P., Arenzana-Seisdedos, F., Amara, A. (2005) Dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN)-mediated enhancement of dengue virus infection is independent of DC-SIGN internalization signals. *J. Biol. Chem.* **280,** 23698–23708.
140. Saidi, H., Carbonneil, C., Magri, G., Eslahpazire, J., Sekaly, R. P., Belec, L. (2010) Differential modulation of CCR5-tropic human immunodeficiency virus-1 transfer from macrophages towards T cells under interleukin-4/interleukin-13 microenvironment. *Hum. Immunol.* **71,** 1–13.
141. De Witte, L., Nabatov, A., Geijtenbeek, T. B. (2008) Distinct roles for DC-SIGN+-dendritic cells and Langerhans cells in HIV-1 transmission. *Trends Mol. Med.* **14,** 12–19.
142. Requena, M., Bouhlal, H., Nasreddine, N., Saidi, H., Gody, J. C., Aubry, S., Gresenguet, G., Kazatchkine, M. D., Sekaly, R. P., Belec, L., Hocini, H. (2008) Inhibition of HIV-1 transmission in trans from dendritic cells to CD4+ T lymphocytes by natural antibodies to the CRD domain of DC-SIGN purified from breast milk and intravenous immunoglobulins. *Immunology* **123,** 508–518.
143. Arrighi, J. F., Pion, M., Garcia, E., Escola, J. M., van Kooyk, Y., Geijtenbeek, T. B., Piguet, V. (2004) DC-SIGN-mediated infectious synapse formation enhances X4 HIV-1 transmission from dendritic cells to T cells. *J. Exp. Med.* **200,** 1279–1288.
144. Pepper, D. J., Rebe, K., Morroni, C., Wilkinson, R. J., Meintjes, G. (2009) Clinical deterioration during antitubercular treatment at a district hospital in South Africa: the importance of drug resistance and AIDS defining illnesses. *PLoS One* **4,** e4520.
145. Harries, A. D. (1990) Tuberculosis and human immunodeficiency virus infection in developing countries. *Lancet* **335,** 387–390.
146. Borkow, G., Bentwich, Z. (2006) HIV and helminth co-infection: is deworming necessary? *Parasite Immunol.* **28,** 605–612.
147. Idemyor, V. (2007) Human immunodeficiency virus (HIV) and malaria interaction in sub-Saharan Africa: the collision of two Titans. *HIV Clin. Trials* **8,** 246–253.
148. Benoit, M., Desnues, B., Mege, J. L. (2008) Macrophage polarization in bacterial infections. *J. Immunol.* **181,** 3733–3739.
149. Ehrt, S., Schnappinger, D., Bekiranov, S., Drenkow, J., Shi, S., Gingeras, T. R., Gaasterland, T., Schoolnik, G., Nathan, C. (2001) Reprogramming of the macrophage transcriptome in response to interferon-γ and *Mycobacterium tuberculosis*: signaling roles of nitric oxide synthase-2 and phagocyte oxidase. *J. Exp. Med.* **194,** 1123–1140.
150. O'Reilly, M., Newcomb, D. E., Remick, D. (1999) Endotoxin, sepsis, and the primrose path. *Shock* **12,** 411–420.
151. Schreiber, T., Ehlers, S., Heitmann, L., Rausch, A., Mages, J., Murray, P. J., Lang, R., Holscher, C. (2009) Autocrine IL-10 induces hallmarks of alternative activation in macrophages and suppresses antituberculosis effector mechanisms without compromising T cell immunity. *J. Immunol.* **183,** 1301–1312.
152. Almeida, A. S., Lago, P. M., Boechat, N., Huard, R. C., Lazzarini, L. C., Santos, A. R., Nociari, M., Zhu, H., Perez-Sweeney, B. M., Bang, H., Ni, Q., Huang, J., Gibson, A. L., Flores, V. C., Pecanha, L. R., Kritski, A. L., Lapa e Silva, J. R., Ho, J. L. (2009) Tuberculosis is associated with a down-modulatory lung immune response that impairs Th1-type immunity. *J. Immunol.* **183,** 718–731.
153. Raju, B., Hoshino, Y., Belitskaya-Levy, I., Dawson, R., Ress, S., Gold, J. A., Condos, R., Pine, R., Brown, S., Nolan, A., Rom, W. N., Weiden, M. D. (2008) Gene expression profiles of bronchoalveolar cells in pulmonary TB. *Tuberculosis (Edinb.)* **88,** 39–51.
154. Mylonas, K. J., Nair, M. G., Prieto-Lafuente, L., Paape, D., Allen, J. E. (2009) Alternatively activated macrophages elicited by helminth infection can be reprogrammed to enable microbial killing. *J. Immunol.* **182,** 3084–3094.
155. Siracusa, M. C., Reece, J. J., Urban Jr., J. F., Scott, A. L. (2008) Dynamics of lung macrophage activation in response to helminth infection. *J. Leukoc. Biol.* **84,** 1422–1433.
156. Donnelly, S., Stack, C. M., O'Neill, S. M., Sayed, A. A., Williams, D. L., Dalton, J. P. (2008) Helminth 2-Cys peroxiredoxin drives Th2 responses through a mechanism involving alternatively activated macrophages. *FASEB J.* **22,** 4022–4032.
157. Modjarrad, K. (2009) Which helminth coinfections really affect HIV disease progression? *AIDS* **23,** 276–277, author reply 277–278.
158. Walson, J. L., Herrin, B. R., John-Stewart, G. (2009) Deworming helminth co-infected individuals for delaying HIV disease progression. *Cochrane Database Syst. Rev.* CD006419.
159. Hewitson, J. P., Grainger, J. R., Maizels, R. M. (2009) Helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity. *Mol. Biochem. Parasitol.* **167,** 1–11.
160. Hopkin, J. (2009) Immune and genetic aspects of asthma, allergy and parasitic worm infections: evolutionary links. *Parasite Immunol.* **31,** 267–273.
161. Bentwich, Z. (2003) Concurrent infections that rise the HIV viral load. *J. HIV Ther.* **8,** 72–75.
162. Modjarrad, K., Zulu, I., Redden, D. T., Njobvu, L., Lane, H. C., Bentwich, Z., Vermund, S. H. (2005) Treatment of intestinal helminths does not reduce plasma concentrations of HIV-1 RNA in coinfected Zambian adults. *J. Infect. Dis.* **192,** 1277–1283.

KEY WORDS:
cytokines · chemokines · HIV-1 · DC-SIGN · tuberculosis