The macrophage in HIV-1 infection: from activation to deactivation?

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Georges Herbein[1*], Audrey Varin[1,2]

Abstract

Macrophages play a crucial role in innate and adaptative immunity in response to microorganisms and are an important cellular target during HIV-1 infection. Recently, the heterogeneity of the macrophage population has been highlighted. Classically activated or type 1 macrophages (M1) induced in particular by IFN-γ display a pro-inflammatory profile. The alternatively activated or type 2 macrophages (M2) induced by Th-2 cytokines, such as IL-4 and IL-13 express anti-inflammatory and tissue repair properties. Finally IL-10 has been described as the prototypic cytokine involved in the deactivation of macrophages (dM). Since the capacity of macrophages to support productive HIV-1 infection is known to be modulated by cytokines, this review shows how modulation of macrophage activation by cytokines impacts the capacity to support productive HIV-1 infection. Based on the activation status of macrophages we propose a model starting with M1 classically activated macrophages with accelerated formation of viral reservoirs in a context of Th1 and proinflammatory cytokines. Then IL-4/IL-13 alternatively activated M2 macrophages will enter into the game that will stop the expansion of the HIV-1 reservoir. Finally IL-10 deactivation of macrophages will lead to immune failure observed at the very late stages of the HIV-1 disease.

Introduction

Macrophages (Ms) are the first line of defence of the organism against pathogens and, in response to the microenvironment, become differentially activated. The classical pathway of interferon-γ-dependent activation of macrophages (M1) by T helper 1 (Th1)-type responses is a well-established feature of cellular immunity to infection with HIV-1. In the presence of cytokines that are produced in a Th-2 type response, such as IL-4 and IL-13, macrophages become differentially activated (M2) and play an important role in HIV-1 pathogenesis. Although it is superficially similar to a Th2-type cytokine and is often co-induced with Th2 cytokines in the course of an immune response, it is not appropriate to classify IL-10 together with IL-4 and IL-13 as an alternative activator of macrophages. IL-10 acts on a distinct plasma membrane receptor to those for IL-4 and IL-13 [1], and its effects on macrophage gene expression are different, involving a more profound inhibition of a range of antigen-presenting and effector functions, leading to a deactivation stage of macrophages [2]. Following this line of reasoning, it seems appropriate to classify macrophages in IFN-γ classically activated macrophages (M1), IL-4/IL-13 alternatively activated macrophages (M2), and IL-10 deactivated macrophages (dM). In addition, T cells themselves are more heterogeneous than was thought originally [3,4], including not only Th0, Th1 and Th2 type cells, but also among other regulatory (Treg) and Th17 cells [5]. In addition, a wide variety of stimuli, both endogenous and exogenous, influence the susceptibility of macrophages to infection by HIV-1. The differentiation stage of monocytes/macrophages also modulates permissiveness to HIV-1: primary monocytes are less susceptible to the virus than differentiated macrophages [6-9]. The localization of macrophages in different tissues results in cells with distinct activation status and susceptibility to HIV-1 infection. Addressing the effects of macrophage differentiation and/or activation on HIV-1 replication provides some insight into the impact of specific microenvironments on macrophage infection *in vivo*. Modulation of HIV-1 replication induced by diverse stimuli have however been addressed using monocytic cell lines, primary monocytes or macrophages differentiated *in vitro* from primary monocytes. Keeping these data in mind, the present review will focus on the distinctive patterns of macrophage activation (classically activated M1, alternatively

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activated M2, and deactivated dM) in HIV-1 pathogenesis.

Classical Activation of Macrophages and HIV-1 Infection

Classically activated or type 1 macrophages induced in particular by IFN-γ [10], display a pro-inflammatory profile (Figure 1). In addition pro-inflammatory cytokines modulate HIV-1 replication in macrophages and could depend on the maturation and/or activation stages of monocytes/macrophages [7,8]. High levels of proinflammatory cytokines, such as tumor necrosis factor α (TNFα), interleukin (IL)-1β and IL-6 in both plasma and lymph nodes are observed from the early stages of HIV-1 infection [11-15]. The secretion of chemokines such as macrophage inflammatory protein (MIP)-1α, MIP-1β and RANTES (CCL3, CCL4 and CCL5 respectively) is increased in these patients [16,17]. Immune activation also reflects the mounting of antiviral immunity with enhanced Th1 activity and increased levels of IFNγ, IL-12, IL-2 and IL-18, especially in lymph nodes of HIV-infected subjects [18]. In addition these cytokines and their receptors have validated the importance of this pathway in cellular immunity, immunodeficiency syndromes, delayed hypersensitivity responses and tissue damage [2]. In classically activated macrophages, the following steps of the HIV-1 life cycle are modulated (Table 1).

Entry

HIV-1 infects monocytes/macrophages via interaction of gp120 with CD4 and either coreceptor CXCR4 or CCR5 which determines the cellular tropism [19-31]. HIV-1 envelope glycoprotein gp120 down-regulates CD4 expression in primary human macrophages through induction of endogenous TNFα [32-37]. TNFα, IL-1β and IFN-γ down-regulate both surface and total CD4 expression in primary human macrophages at the level of transcription [36,38-41]. TNFα, IFN-β, and IFN-γ inhibit R5 and R5/X4 HIV-1 entry into primary macrophages via down-regulation of both cell surface CD4 and CCR5 and via enhanced secretion of C-C chemokines, MIP-1α, MIP-1β, and RANTES [37,38,40,42-46]. An iterative pre-treatment of primary macrophages with TNFα prior to HIV infection inhibits HIV-1 replication [43]. The inhibition of HIV-1 entry into primary macrophages by TNFα involves the 75-kDa TNFR2 [43]. Another explain could be that TNFα triggers the release

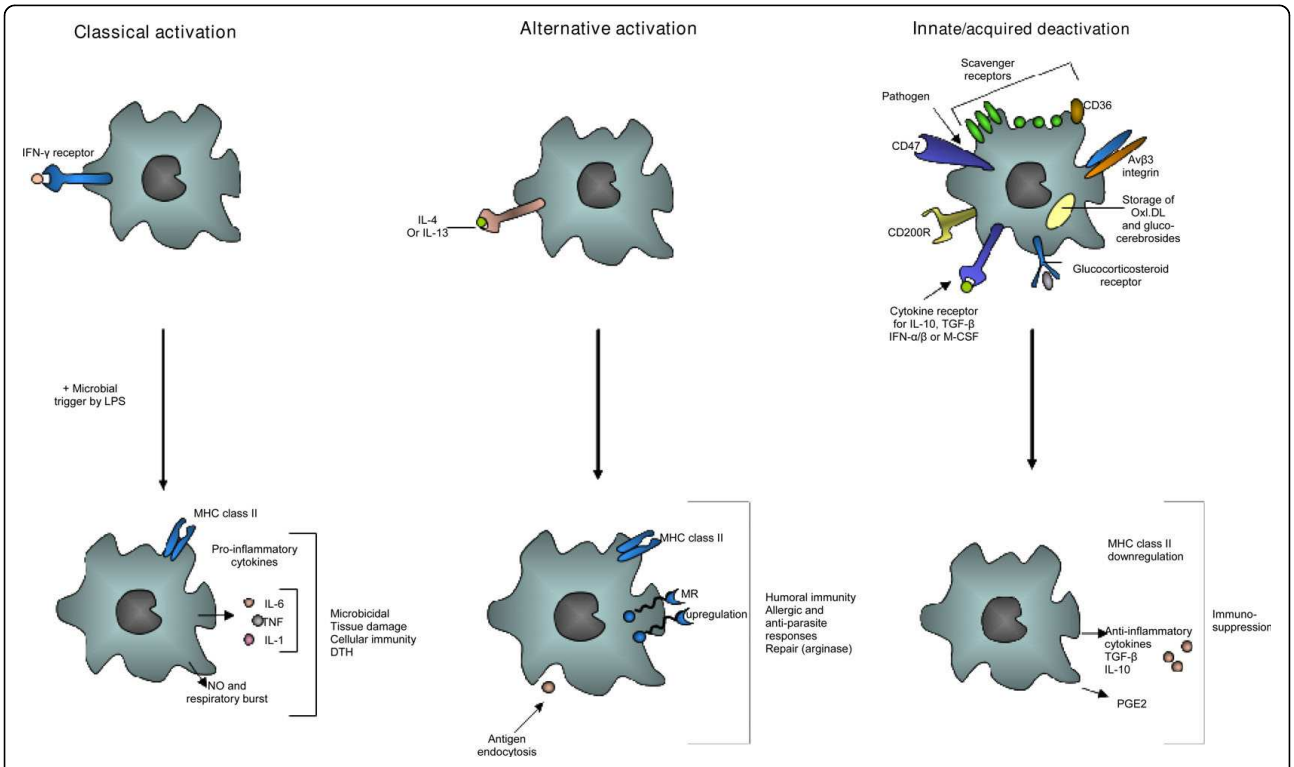

Figure 1 Classical activation (M1), alternative activation (M2) and deactivation of macrophages. Classical activation is mediated by the priming stimulus IFN-γ, followed by a microbial trigger (lipopolysaccharide, LPS). Alternative activation is mediated by IL-4 and IL-13, acting through a common receptor chain (IL-4Rα). Deactivation can be innate or acquired in origin. The uptake of apoptotic cells or lysosomal storage of host molecules generates anti-inflammatory responses. Cytokines (IL-10, TGF-β, M-CSF, IFNα/β) and glucocorticoids are potent modulators of activation. Pathogens can deactivate macrophages by various mechanisms.

Table 1 HIV-1 viral cycle in classically activated M1, alternatively activated M2 and deactivated macrophages

Viral cycle target	M1 macrophages		M2 macrophages		Deactivated macrophages	
Entry	*Decreased*	* CD4 downregulation: TNFα, IL1β, IFNγ, IL-2, IL-18	*Decreased*	* CXCR4 downregulation: IL-4, IL-13	*Decreased*	* CCR5 downregulation: IFNβ
		* CCR5 downregulation: TNFα, MIP-1α, MIP-1β, MCP-2, RANTES, IFNγ, GM-CSF, IL-2, IL-16, IL-15		* CCR5 downregulation IL-13	*Increased*	* CCR5 upregulation: IL-10, M-CSF
		* fusion block: RANTES		* CD4 downregulation IL-13		
Reverse transcription	*No effect reported*		*Decreased*	* Block of RT: IL-13	*Decreased*	* Block of RT: IL-10, IFNα/β
						* Inhibition of RT synthesis: TGFβ
Transcription	*Increased*	*Transactivation of HIV-1 LTR: TNF, IL-1β, IL-6, GM-CSF, IL-18	*Decreased* +	* Block of HIV-1 LTR transactivation: IL-4, IL-13	*Decreased*	* Block of HIV-1 LTR activation ++
Post transcription	*Decreased*	* Inhibition of viral assembly and budding: IFNγ, IL-18 (via IFNγ release),	*No effect reported*		*Decreased*	* Inhibition of viral assembly: IL-10
						* Inhibition of viral budding: IFNα/β, IL-27 (via IFNα release)

+ inhibition in differentiated macrophages

++ depends on IL-10 concentration

of granulocyte-macrophage colony-stimulating factor (GM-CSF) that has been reported to down-regulate CCR5 and subsequently block entry of R5 HIV into macrophages [47]. Interestingly, TNFR2 stimulation triggers GM-CSF secretion that has been shown to block R5 HIV-1 entry via CCR5 downregulation [47]. The inhibition of HIV-1 entry into macrophages observed following TNFα pre-treatment could be mediated via the secretion of C-C chemokines, such as RANTES, MIP-1α and MIP-1β. TNFα induces the production of RANTES, MIP-1α, and MIP-1β which in turn down-regulate cell surface CCR5 expression on primary macrophages resulting in inhibition of R5 HIV-1 entry [48-53]. In agreement with this observation, RANTES inhibits HIV-1 envelope-mediated membrane fusion in primary macrophages [54] and the activity of RANTES promoter that contains four NF-kB binding sites is up-regulated by TNFα [55]. Nevertheless, some authors report an enhancement of HIV-1 replication by RANTES in primary macrophages [27,56]. The enhancing effect of RANTES on HIV-1 infectivity may be independent of the route of virus-cell fusion and could involve two different mechanisms: one mediated via cellular activation, and the other mediated via increased virion attachment to target cells [56]. Another explanation for this discrepancy is the activation and/or differentiation status of macrophages with a more potent inhibitory effect of RANTES on monocyte-derived macrophages cultivated *in vitro* in absence of additional cytokines such as M-CSF [57].

The monocyte chemotactic protein-2 (MCP-2), but not MCP-1, has been shown to bind to CCR1, CCR2b, and CCR5 and to inhibit CD4/CCR5-mediated HIV-1 entry/replication [58]. Pretreatment of macrophages with IL-16 also inhibits R5 and R5/X4 HIV-1 replication in primary macrophages at the level of entry, although the secretion of CC-chemokines does not seem to be involved in this phenomenon [59].

IL-2 has been reported to inhibit HIV-1 replication in macrophages by down-regulating CD4 and CCR5 expression [60]. IL-15 is a Th1 cytokine produced by mononuclear phagocytes and shares many activities with IL-2, such as T-cell proliferation and activation. In addition IL-15 is more potent than IL-2 in stimulating NK cell function, including secretion of IFN-γ and of CCR5-binding chemokines [61]. *Ex vivo*, increased levels of IL-15 were detected in histocultures established from lymph nodes of individuals who were HIV positive in comparison to their uninfected counterparts [62]. Supernatants of NK cells stimulated with IL-12 and IL-15 inhibited both macrophage-tropic HIV-1_{NFN-SX} and T cell-tropic HIV-1_{NL4-3} replication *in vitro*, but not dual-tropic HIV-$1_{89.6}$ due to the use of multiple coreceptors for entry by this latter, including CXCR4, CCR5, but also CCR3 and CCR2b [24,63]. Importantly, the C-C chemokines MIP-1α, MIP-1β, and RANTES were responsible only for a fraction of the HIV-1-suppressive activity exhibited by NK cell supernatants against macrophage-tropic HIV-1. Collectively these data indicate that NK cells from normal and HIV-1^+ donors

produce C-C chemokines and other unidentified factors that can inhibit both macrophage- and T cell-tropic HIV-1 replication *in vitro* [63].

IL-18 is a pro-inflammatory cytokine related to the IL-1 family of cytokines that plays an important role in both innate and adaptative immune responses against viruses [64,65]. Increased levels of circulating IL-18 from HIV-1 infected patients have been reported especially in the advanced and late stages of the disease [65]. IL-18 reduces cell surface expression of the HIV-1 receptor CD4 [66]. In the advanced stages of the disease, strong activation of IL-18 production along with persistent decreased production of IFN-γ, IL-12 and IL-2 may promote a Th2 immune response, which leads to persistent viral replication [65].

CD40 ligand (CD40L) is a cell surface molecule of $CD4^+$ T cells that interacts with its receptor CD40 on antigen-presenting cells (APC) to mediate thymus-dependent humoral immunity and inflammatory reactions. The stimulation of macrophages by CD40L has been shown to trigger the release of TNFα and CC-chemokines which results in down-regulation of cell surface CD4 and CCR5 and subsequent inhibition of HIV-1 entry into macrophages [17,67-69]. An in situ hybridization study showed that macrophages in lymph nodes of HIV-1 infected individuals produce MIP-1α and MIP-1β, and to a lesser extent RANTES, suggesting that HIV-1 infection might be modulated *in vivo* by activated macrophages [70]. It is interesting to note that the CD40/CD40L interaction triggers signalling through TNF receptor-associated factor 6 (TRAF6) in antigen presenting cells. TRAF6 has also been involved in innate immune responses mediated by TLR-4, such as the response to lipopolysaccharide (LPS) [68]. Like CD40L activation, LPS stimulation also induces high secretion of C-C chemokines and TNFα and inhibits infection of macrophages and $CD4^+$ T cells with R5 HIV-1 strains. Thus, during opportunistic infections, LPS might also be produced that, either directly or indirectly via TNFα production, might block HIV-1 entry into macrophages [71,72]. In human blood monocyte tissue culture-derived macrophages (TCDM), endogenous TNFα and IL-1β induced by LPS, down-regulate surface and total CD4 expression in primary macrophages [41]. Conversely, neither LPS nor TNFα/IL-1β were able to modulate surface CD4 expression on quiescent or PHA-activated lymphocytes [41]. Thus, opportunistic infections during HIV disease can result in a sustained but controlled viral production within infected macrophages.

Transcription

TNFα has been reported to stimulate HIV-1 replication in chronically infected promonocytic U1 cell line through NF-kB activation and subsequent transactivation of the proviral LTR [73-76]. The stimulation of HIV-1 replication in U1 cell line with TNFα is mediated through the TNFR1, and not via TNFR2 [77]. Similarly, IL-1β binding to the IL-1 receptor 1, but not to the IL-1 receptor 2, stimulates HIV-1 transcription through activation of NF-kB or by an independent mechanism [75,78]. IL-1 can act alone or in synergy with IL-6 to stimulate viral replication in chronically infected promonocytic U1 cell line [78]. In addition IL-6 alone stimulates HIV-1 replication in U1 cells and primary macrophages infected with R5 AD-87 strain, but not in T cell lines [76]. Nuclear factor IL-6 (NF-IL6) is a nuclear factor that activates gene expression in response to IL-6. A consensus binding site for NF-IL6 is present in the LTR of many HIV-1 variants and the regulation of HIV-1 LTR by NF-IL6 and NF-kB/Rel transcription factors has been reported [79-81]. IL-6 stimulates HIV replication by activating viral transcription in synergy with TNFα and also by targeting a post-transcriptional step [76]. In addition, endothelial cells enhance C/EBPbeta binding activity and HIV-1 replication in macrophages. This increase in HIV-1 transcription is due in part to the production of soluble factors, such as IL-6 and also is mediated by ICAM-1 activation [82], indicating that endothelial cells, through the activation of C/EBPβ, provide a microenvironment that supports HIV-1 replication in monocytes/macrophages. The stimulation of HIV-1 replication in primary macrophages by GM-CSF is primarily due to enhanced viral transcription rather than increased viral entry [76]. GM-CSF stimulates HIV-1 replication in promonocytic U1 cells [83] and in primary human macrophages infected with the R5 HIV-1 JR-FL strain [84] by targeting HIV LTR at a site different from NF-κB [76].

In vitro, both acute HIV infection and incubation of the THP-1 monocytoid cell line with the accessory viral protein Nef induced expression of IL-18 [85]. Like most proinflammatory cytokines, IL-18 induces HIV expression in chronically infected monocytic cell lines via induction of the release of endogenous TNFα and IL-6 [86]. IL-18 stimulates HIV-1 replication in the chronically infected U1 monocytic cells, mediated in part via TNFα and IL-6 since the addition of anti-TNFα and anti-IL-6 antibodies reduced IL-18 increased HIV-1 production by 48% and 63%, respectively [86]. IL-18 stimulation of HIV-1 replication in U1 cells involves NF-kB and p38 MAPK activation [86].

Posttranscription

The effect of IFN-γ on HIV-1 replication might be more complex. Pretreatment of human primary macrophages with IFN-γ before viral input has been reported either to stimulate or to inhibit HIV-1 replication [45,46,84]. In addition, IL-18 has been reported as an

IFN-γ-inducing factor which inhibits HIV-1 production in PBMC through IFN-γ [66].

Altogether classically activated macrophages M1 are in contact with Th1 cytokines (IFN-γ, IL-2, IL-12), proinflammatory cytokines (TNFα, IL-1β, IL-6, IL-18) and chemokines (MIP-1α, MIP-1β, RANTES) that favor the formation of viral reservoirs with inhibition of HIV-1 entry, assembling and budding parallel to increased viral transcription within the infected macrophages (Figure 2).

Alternative Activation of Macrophages and HIV-1 Infection

The alternatively activated or type 2 macrophages (M2) induced by Th-2 cytokines, express anti-inflammatory and tissue repair properties [2] (Figure 1). Alternative activation of macrophages is induced by IL-4 and IL-13, cytokines that are produced in a Th-2 type response, particularly during allergic, cellular and humoral responses to parasitic and selected pathogen infections. The alternative activation of macrophages is mediated by IL-4 and IL-13, acting through a common receptor chain (IL-4Rα) [87]. IL-4 is a pleiotropic cytokine produced by a subpopulation of $CD4^+$ T cells, designated Th-2 cells, and by basophiles and mast cells. IL-4 modulates other lymphoid cell activities such as regulation of the differentiation of antigen-stimulated T lymphocytes [88,89] and control of immunoglobulin class switching in B lymphocytes [90-93]. IL-13 is a cytokine secreted by activated T cells which has been shown to be a potent *in vitro* modulator of human monocytes and B cell functions [94-96]. Among its pleiotropic activities, IL-13 induces significant changes in the phenotype of human monocytes, up-regulating their expression of multiple cell surface molecules and increasing their antigen presenting capabilities. IL-4 and IL-13 upregulate expression of the mannose receptor and MHC class II molecules by macrophages which stimulate endocytosis and antigen presentation, and they induce the expression of macrophage-derived chemokine (MDC, also known as CCL22). IL-4 and IL-13 augment expression of IL-1 decoy receptor and the IL-1 receptor α-chain *in vitro* and *in vivo*, thereby counteracting the proinflammatory actions of IL-1 [97,98]. In alternatively activated macrophages, the following steps of the HIV-1 life cycle are modulated (Table 1).

Entry

Infection of macrophages by primary R5X4 and X4 isolates of HIV-1 is inhibited by IL-4 and IL-13, an effect that is associated with down-regulation of surface CXCR4, CCR5 and CD4 expression [38,99].

Reverse transcription

Upon cell infection by HIV-1, the reverse transcriptase copies the genomic RNA to generate the proviral DNA flanked by two LTRs [100]. IL-13 has been shown to inhibit HIV-1 replication in blood-derived monocytes

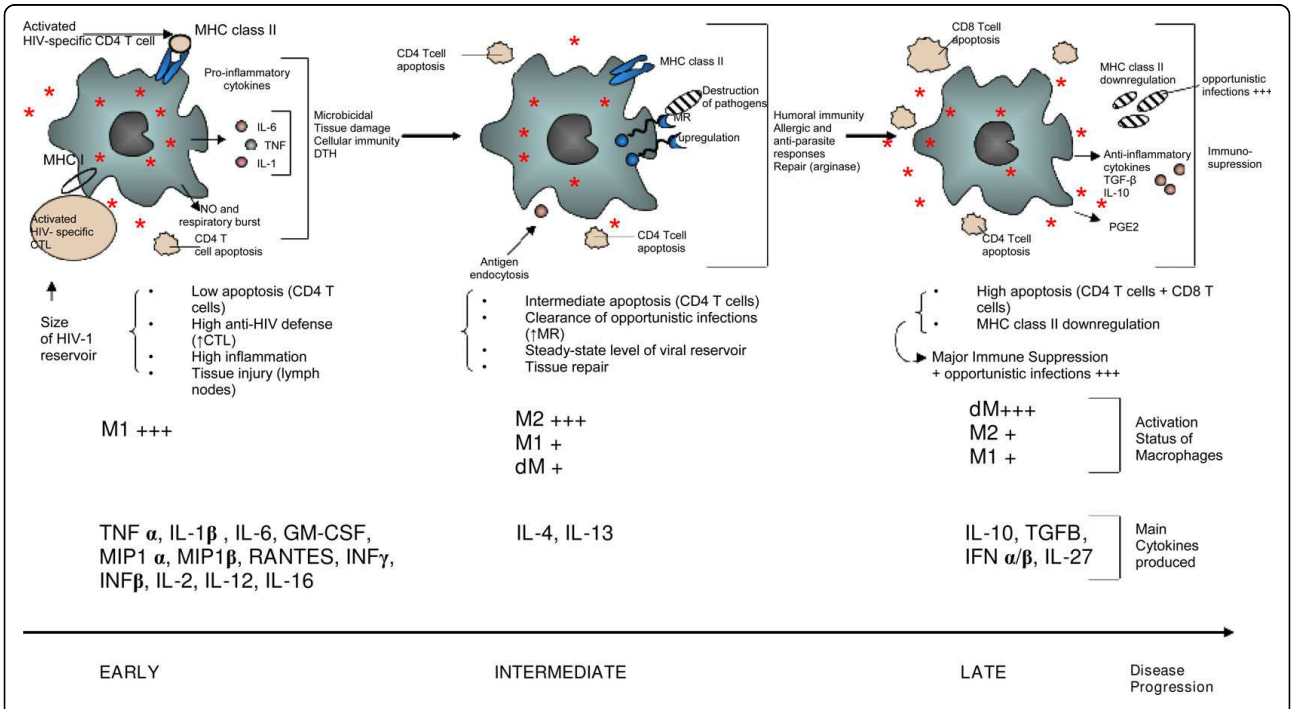

Figure 2 A model of HIV-1 pathogenesis based on the activation status of macrophages.

and mature lung macrophages, but not in T cells [95,101]. The mechanism by which IL-13 inhibits HIV-1 is not yet clear. IL-13 has been reported either not to modulate reverse transcription [102] or to block the completion of reverse transcription in macrophages [103].

Transcription

IL-13 has been reported to block HIV-1 replication at the level of transcription in human alveolar macrophages [102]. In fact, the state of maturation of monocytes into macrophages determines the effects of IL-4 and IL-13 on HIV-1 replication. In freshly isolated monocytes, IL-4 up-regulates the expression of both genomic and spliced HIV mRNA [104,105]. IL-4 stimulates NF-κB translocation and binding resulting in enhanced HIV RNA expression [105]. IL-4 up-regulates the expression of HIV mRNA within the first two days after infection of promonocytic U937 cells and 3 to 4 days after infection of plastic-adherent blood-derived macrophages with HIV-1 [104,106]. Conversely, IL-13 and IL-4 inhibit HIV-1 replication at the transcriptional level in differentiated macrophages, but not in peripheral blood lymphocytes [95,104,105]. In addition, exposure to IL-13 inhibits the transcription of many other cytokines in monocytes, including IL-1α, IL-1β, IL-6, TNF, and GM-CSF [96], all of which have been implicated in enhancing HIV-1 replication *in vitro* [107-110].

Altogether alternatively activated macrophages are in contact with IL-4/IL-13 producing Th2 cells that will curtail the formation of HIV-1 reservoirs in the macrophages (Figure 2).

Deactivation of Macrophage and HIV-1 Infection

The prototypic cytokine involved in the deactivation of macrophages is IL-10. Although it is superficially similar to a Th2-type cytokine and is often co-induced with Th2 cytokines in the course of an immune response, it is not appropriate to classify IL-10 together with IL-4 and IL-13 as an alternative activator of macrophages [2]. IL-10 acts on a distinct plasma membrane receptor to those for IL-4 and IL-13 [1]. Similar to IL-10, other cytokines such as TGF-β, M-CSF and IFNα/β result in macrophage deactivation [2] with strong anti-inflammatory properties, down-regulation of MHC class II molecules on the plasma membrane (Figure 1). Deactivation of macrophages leads to immune suppression through at least two independent mechanisms: diminished MHC class II expression and increased uptake of apoptotic cells generating an anti-inflammatory response [111-115]. In deactivated macrophages, the following steps of the HIV-1 life cycle are modulated (Table 1).

Entry

IL-10 up-regulates cell surface CCR5 expression on monocytes and thereby enhances viral entry [116]. M-CSF has been shown to favor HIV-1 replication in human macrophages, probably via an increased maturation stage and increased CCR5 expression, also resulting in enhanced viral entry [29,117]. By contrast, IFN-β inhibit R5 HIV-1 entry into primary macrophages via down-regulation of both cell surface CD4 and CCR5 and via enhanced secretion of C-C chemokines, MIP-1α, MIP-1β, and RANTES [37,40,42-46].

Reverse transcription

IL-10 suppresses HIV-1 replication in primary human macrophages by inhibiting the initiation of reverse transcription; therefore, IL-10 mediates a virostatic latent stage in cells of the monocyte/macrophage lineage [118-120]. TGF-β inhibits the synthesis of different viral proteins especially reverse transcriptase in U1 promonocytic cells activated by phorbol ester or IL-6 [121]. Members of the APOBEC (acronym for apolipoprotein B editing catalytic polypeptide) family of cellular cytidine deaminases represent a recently identified group of proteins that provide immunity to infection by retroviruses [122-125]. The cytidine deaminases APOBEC exert anti-HIV-1 activity that is countered by the HIV-1 vif protein [122]. Tripartite motif (TRIM) proteins constitute a family of proteins that share a conserved tripartite architecture [126-128]. Interferons, especially type I IFNα/β bolster innate defence against HIV-1 via the up-regulation of APOBEC/TRIM proteins which blocks retroviral replication, especially reverse transcription [129-131].

Transcription

High concentrations of IL-10 inhibit the production of proinflammatory cytokines such as TNFα, IL-1β, IL-6, and thereby IL-10 inhibits HIV-1 transcription [132]. By contrast, low concentrations of IL-10 have been reported to enhance HIV replication in macrophages induced by TNF-α and IL-6 via an increase in HIV mRNA accumulation and stimulation of phorbol ester-induced LTR-driven transcription that is independent of the NF-κB and Sp1 transcription factors [133].

Posttranscription

Primary macrophages treated with IL-10 after HIV-1 inoculation show an accumulation of Gag protein suggestive of an inhibitory effect at the level of virus assembly [134]. IFNα and IFNβ reduce HIV-1 replication in primary macrophages although inhibition by IFNα has been reported to be more efficient [45,135]. Anti-HIV effects of IFNα/β are mediated by both inhibition of viral assembly and budding [136,137]. IL-27 inhibits

HIV replication in monocyte-derived macrophages like IFN-α and IFN-β[138]. IL-27 suppresses the transcription of HIV-1 and preferentially inhibits HIV-1 replication in macrophages compared with $CD4^+$ T cells and activates multiple IFN-inducible genes (ISG) in macrophages like IFN-α, suggesting that IL-27 inhibits HIV-1 replication in macrophages via a mechanism similar to that of IFN-α [138-140]. Recently, of the hundred of IFN-inducible genes discovered to date, ISG15 and ISG20 have been reported to inhibit assembly and release of HIV-1 virions [141-144]. In addition the IFN-inducible tripartite motif protein TRIM22 inhibits the budding of HIV-1 with diffuse cytoplasmic distribution of Gag rather than accumulation at the plasma membrane [145]. The effects of TGF-β on the post-transcriptional steps of HIV-1 replication are more complex. In primary human macrophages, both inhibition and stimulation of HIV-1 replication have been reported following a posttreatment with TGF-β[121,146].

Altogether in deactivated macrophages, HIV-1 replication is strongly blocked at several steps of the viral life cycle especially reverse transcription, transcription and viral budding and assembly (Figure 2).

Activation Status of Macrophages and HIV-1 Pathogenesis

Because of the various behaviours of macrophages reported (classically activated M1, alternatively activated M2, deactivated dM), we would like to present a new model that highlights the role of macrophage activation status in the modulation of viral persistence and T-cell apoptosis and could thereby further enhance our understanding of pathogenesis of HIV-mediated disease (Figure 2). We will first propose a model that applies to the monocytes/macrophages present in the blood and in the lymph nodes of HIV-1-infected patients. We will then discuss this HIV model in light of the different populations of macrophages present in distinct tissues and highlight the critical role of the microenvironment in tissues such as mucosal tissue and the central nervous system (CNS).

Activation status of monocytes/macrophages in peripheral blood and in lymph nodes of HIV-1-infected subjects

Early in the disease, when the levels of proinflammatory cytokines, C-C chemokines and type I IFN are low and chronic immune activation is not yet predominant viral proteins are crucial for establishing a productive infection and for the activation of macrophages [147-149]. Viral proteins expressed early in the viral cycle, such as Nef, Tat, and virion-associated Vpr, activate the TNFR pathway to partially mimic TNFα biological effects, suggesting that these viral proteins can fuel the progression of the disease even in the absence of proinflammatory cytokines, especially in macrophages [9,148,150]. These viral proteins play a role in the formation of viral reservoirs in macrophages by activating transcription from the LTR and interfering with apoptotic machinery [6,151]. The classically activated macrophages M1 are in contact with high levels of Th1 cytokines (IFN-γ, IL-2, IL-12), proinflammatory cytokines (TNFα, IL-1β, IL-6, IL-18) and chemokines (MIP-1α, MIP-1β, RANTES) that favor the formation of viral reservoirs with strongly increased viral transcription and inhibition of HIV-1 entry to block superinfection within infected macrophages. In addition type I interferon production is impaired in primary HIV-1 infection with only limited inhibition of viral assembling and budding [147,152,153]. During this stage of the disease M1 macrophages are predominant, tissue injury especially in lymph nodes is observed and the rate of T-cell apoptosis is increasing [148].

At a later stage of the disease, a M1 toward M2 shift is observed with IL-4/IL-13 as pleiotropic modulators of macrophage activation that induce distinctive programmes of altered macrophage gene expression after the engagement of their specific cytokine receptors [154]. At this intermediate stage M2 macrophages appear and will favor tissue repair, the MHC class II-mediated antigen presentation and T-cell activation, the stimulation of bacterial endocytosis via the up-regulation of the mannose receptor on the cell surface [2,155]. Alternative activation of macrophages might help to favor the clearance of opportunistic infections during HIV-1 disease [156,157]. Intermediate levels of T-cell apoptosis are observed that does not totally block the production of proinflammatory cytokines [111,158]. The combination of IL-4/IL-13 cytokines and proinflammatory cytokines in the microenvironment present in the vicinity of infected macrophages will curtail the expansion of macrophage HIV-1 reservoirs [38,159].

At the onset of AIDS, T-cell apoptosis is dramatically increased and opportunistic infections are very frequent [148,158,160], resulting in an enhanced apoptotic cell clearance by IL-10-deactivated macrophages [161,162]. An imbalance in the TH1-type and TH2-type responses has been proposed to contribute to the immune dysregulation associated with HIV infection, and that progression to AIDS is dependent on a TH1/TH2 shift [163]. This hypothesis was based on the following facts: (1) progression to AIDS is characterized by loss of IL-2- and IFN-gamma production concomitant with increases in IL-10; and (2) many seronegative, HIV-exposed individuals generate strong TH1-type responses to HIV antigens. Recently, haplotypes of the IL-4 and IL-10 genes associated with AIDS progression have been reported [164,165]. In HIV-infected patients, the amount

of IL-10, but not IL-4, increases significantly in patients with AIDS [166]. Opportunistic infections, especially present at the late stages of the disease, trigger IL-10 production [167] and IL-10 production from patients with AIDS has been reported to decrease *in vitro* HIV-1 replication and TNFα production [168]. In addition, IL-10 has been reported to suppress antiviral T-cell activity during persistent viral infection [169] and Tat-induced IL-10 mediates immune suppression during HIV-1 infection [170]. In addition, the IL-10 deactivated macrophages inhibit the production of proinflammatory cytokines such as TNFα and C-C chemokines that were produced abundantly due to chronic immune stimulation during the previous stages of the disease [171,172]. IL-10 inhibits HIV-1 LTR-driven gene expression in human macrophages through the induction of cyclin T1 proteolysis [173]. At the late stages of the disease the decreased levels of proinflammatory cytokines result in a strong reduction of viral transcription. In addition high expression of IFNα/β inducible proteins such as APOPEC and TRIM proteins inhibit strongly the HIV-1 reverse transcription and assembly/budding (Table 1). The deactivation of macrophages also results in a profound immune suppression resulting from the decreased expression of MHC class II expression on the plasma membrane of macrophages with diminished Ag-mediated T cell response and the depletion of both CD4 + and CD8+ T cell by accelerated apoptosis. Thus, IL-10 and type I IFN restrict strongly HIV-1 replication in macrophages parallel to the immune failure observed at the very late stages of the HIV-1 disease.

Activation status of macrophages in mucosal tissues and in the CNS

The localization of macrophages in distinct tissues has been reported to modulate their susceptibility to HIV-1 infection. In human and macaque gastrointestinal mucosa, most attention has been focused on the small intestine, where lamina propria CD4+ T cells are prominent HIV-1 and SIV target cells and undergo profound depletion shortly after infection [174-182]. In contrast, macrophages in the gastrointestinal mucosa, unlike monocyte-derived macrophages, are rather resistant to infection with HIV-1 [183-185]. In contrast to monocytes and monocyte-macrophages, intestinal macrophages do not express many innate response receptors [186,187], are downregulated for triggering receptor expressed on monocytes (i.e., TREM-1) [188,189] and costimulatory molecules [187,190], and display markedly reduced CD4 and CCR5 cell surface protein and mRNA [191]. Thus, the striking and well-defined phenotypic and functional differences between blood monocytes and mucosal macrophages, in particular macrophages in the gastrointestinal mucosa [186,187,192], preclude the simple extrapolation from findings in HIV-1-infected monocytes to HIV-1 infection of mucosal macrophages. Human vaginal macrophages have been reported recently to support R5 virus entry in explanted vaginal mucosa, and purified vaginal macrophages support substantial levels of R5 HIV-1 replication [193]. Vaginal macrophages display the innate response receptors CD14, CD89, CD16, CD32 and CD64, and the CD4 receptor and CCR5 and CXCR4 coreceptors [193]. The difference in phenotype and HIV-1 permissiveness between vaginal and intestinal macrophages may reflect differences in the local microenvironment, since mucosa-derived cytokines, including TGF-β, regulate the phenotype and function of blood monocytes after their recruitment to the mucosa, at least in the intestinal mucosa [187]. In agreement with this hypothesis, intestinal macrophages are threefold less frequently CD4+ CCR5+ than vaginal macrophages, and yet virus is detected in intestinal macrophages, indicating low-level receptor mediated entry, but intestinal macrophages do not support viral replication suggesting a post-entry block such as described for TGF-β [193].

Macrophages of the central nervous system (CNS) are permissive to HIV-1 infection. Two models have been proposed: the Trojan horse model and the late invasive model [194]. In the Trojan horse model, the virus enters the CNS early, and replicates at low levels as a reservoir separated from the periphery. A viral phenotype that is more virulent in the context of the CNS emerges, leading to the development of disease. In the late invasion model, uncontrolled virus replication and resulting immune deficiency lead to alterations in the myeloid differentiation pathway, promoting the expansion of an activated monocyte subset that is capable of tissue invasion. The hallmark of the brain histopathology is productive infection in macrophages (perivascular macrophages and microglia) [195]. HIV encephalitis (HIVE) is characterized by monocyte/macrophage infiltration into the brain, multinucleated giant cell formation (fusion of several macrophages), and presence of microglial nodules [196]. There is little evidence for infection in neurons, endothelial cells, or macroglia (astrocytes and oligodendrocytes) [197-199]. In the Trojan horse model, it has been hypothesized that the virus enters the CNS mainly through infected monocytes and macrophages destined to become brain-resident macrophages or perivascular macrophages [200]. It is assumed that HIV-1 enters early after primary infection (at a peak of primary viremia), and HIV-1 infection persists at low levels due to the immune-privileged status of the CNS. In addition there is an uniqueness of the brain microenvironment with several anatomic/structural, physiological, and immunoregulatory mechanisms that ensure the immune priviledge of the brain, preventing

recognition of foreign antigens, to minimize/deviate and block inflammatory responses [201]. Soluble anti-inflammatory molecules have been shown to play a role in immune privilege in the CNS. TGF-β has the ability to inhibit activation of macrophages, T lymphocytes, and NK cells [202], and TGF-β has been shown to possess neuroprotective capabilities [203]. Upregulation of TGF-β is observed during HIV-1 infection and is correlated with the magnitude of inflammatory responses during HIV-1 brain infection [204]. High concentrations of gangliosides downregulate expression of MHC class II on astrocytes [205] and could contribute to generally low levels of MHC class II on microglia. In contrast, a significant increase in MHC class II has been reported in the context of HIVE on activated microglia [206,207] and it is considered the best neuropathologic correlate of cognitive impairment [208]. TGF-β, IL-10, and TRAIL have been reported to contribute significantly to the CNS-DC-mediated inhibition of allo-T-cell proliferation [209] and to participate in the control of viral CNS infections [210]. In agreement with this observation, only few DC-like cells were found in perivascular spaces in SIV-infected macaques [211]. Although invasion of the CNS by HIV-1 occurs at the time of primary infection and induces a transitory inflammatory process with increased number of microglial cells, upregulation of MHC class II antigens, and local production of cytokines [212], viral replication remains very low during the asymptomatic stage of HIV-1 infection. Specific immune responses including Th2 cytokines and CTLs continuously inhibit viral replication at this stage of infection [213-216]. While HIV-1 enters the brain early following viral infection [200], detectable productive viral replication and brain macrophage infiltration occur years later and only in some infected patients [217]. The replication of HIV-1 in microglia depends on the microenvironment in the CNS. Recently, it has been reported astrocyte-mediated regulation of microglial function and its influence on the onset and the progression of neuroAIDS [218]. HIV-1, recombinant gp120, and viral transactivator Tat activate astrocytes to secrete pro-inflammatory cytokines TNFα, IL-6, and IL-1β and the pro-inflammatory chemokines MCP-1 and IP-10 [195,219-224], all of which could contribute to the overall inflammatory environment in the brain. To further contribute to the inflammatory environment in the CNS, microglia and macrophages release proinflammatory cytokines such as IL-1β and TNFα which play a role in CNS injury [225,226]. In agreement with these data, *in vivo* expression of proinflammatory cytokines in HIV-1 encephalitis has been reported and the macrophage/microglia lineage is the main cell type reported to release cytokines in HIVE [227]. Altogether, after an early and transitory stage of macrophage/microglia activation at the time of primary infection, a stage of deactivation of macrophage/microglia is observed parallel to the presence of "deactivating" cytokines such as TGF-β and IL-10 in the CNS microenvironment. In some patients, detectable productive viral infection and brain macrophage infiltration occur years later parallel to increased levels of pro-inflammatory cytokines in the context of HIVE.

A M1/M2/Md macrophage polarization model and vice versa

Altogether, in the lymph nodes of HIV-1-infected patients a shift from activated to deactivated macrophages throughout the disease is observed parallel to a Th1 pro-inflammatory/Th2 anti-inflammatory switch. In some tissue such as the intestinal mucosal tissue, the macrophages are mostly in a deactivated stage with a local microenvironment curtailing the viral replication through the release of anti-inflammatory cytokines such as TGF-β. In contrast to the intestinal mucosa, macrophages from the vaginal mucosa are more permissive to HIV-1 replication and are activated by proinflammatory cytokines. In the CNS of HIV-infected patients, the macrophage/microglia are mostly deactivated under the control of cytokines such as TGF-β, although in some cases HIVE occurs parallel to the production of proinflammatory cytokines and high viral production at advanced stage of the disease. Thus the shift of macrophage/microglia from activation to deactivation and vice-versa depends on the tissue infected by HIV-1 and on the local microenvironment. In agreement with this hypothesis, the reversion of M2/Md macrophages to M1 polarization has been recently reported *in vitro*, and was associated with a renewed capacity to support HIV-1 replication [228]. M1/M2/Md macrophage polarization may represent a mechanism that allows macrophages to cycle between productive and latent HIV-1 infection and vice-versa, parallel to the critical role of the tissue microenvironment which can drive the macrophage polarization either way and thereby can modulate HIV-1 replication specifically in distinct tissues at different stages of the disease.

Conclusion

The concept of macrophage heterogeneity and differentiation has been recently highlighted by the description of at least three types of macrophage activation: M1, M2 and deactivated macrophages. Based on the activation status of macrophages we propose a model starting with M1 classically activated macrophages with accelerated formation of viral reservoirs in a context of Th1 and proinflammatory cytokines. Then IL-4/IL-13 alternatively activated M2 macrophages will enter into the game that will be concomitant to tissue repair, enhanced

MHC class II-mediated antigen presentation, increased T-cell activation, and enhanced clearance of opportunistic pathogens via bacterial endocytosis. At this stage of the disease, the expansion of the HIV-1 reservoir in IL-4/IL-13 alternatively activated M2 macrophages will be stopped [228]. The M2 macrophages will be in the vicinity of Th2 cells with the appearance of IL-10 deactivation of macrophages leading to immune failure observed at the very late stages of the HIV-1 disease with diminished Ag-mediated T cell response and accelerated depletion of both CD4+ and CD8+ T cells by apoptosis [229]. A better understanding of the macrophage activation status during the progression of HIV-1 infection could lead to the development of new therapeutic approaches.

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Authors' contributions
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