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Review

Macrophages and HIV-1: dangerous liaisons

Alessia Verani[a], Gabriel Gras[b], Gianfranco Pancino[c,*]

[a] *Human Virology Unit, DIBIT, San Raffaele Scientific Institute, Milan, Italy*
[b] *CEA, Service de Neurovirologie, DSV/DRM, Centre de Recherches du Service de Sante des Armees, EPHE, IPSC, Fontenay aux Roses, France*
[c] *Unité de Biologie des Rétrovirus — Département de Virologie, Institut Pasteur, 25, rue du Dr. Roux — 75724 Paris Cedex 15, France*

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Abstract

HIV-1, like the other lentiviruses, has evolved the ability to infect nondividing cells including macrophages. HIV-1 replication in monocytes/macrophages entails peculiar features and differs in many respects from that in CD4 T lymphocytes. HIV-1 exhibits different tropism for CD4 T cells and macrophages. The virus can enter macrophages via several routes. Mitosis is not required for nuclear import of viral DNA or for its integration into the host cell genome. Specific cellular factors are required for HIV-1 transcription in macrophages. The assembly and budding of viral particles in macrophages take place in late endosomal compartments. Viral particles can use the exosome pathway to exit cells. Given their functions in host defence against pathogens and the regulation of the immune response plus their permissivity to HIV-1 infection, monocytes/macrophages exert a dual role in HIV infection. They contribute to the establishment and persistence of HIV-1 infection, and may activate surrounding T cells favouring their infection. Furthermore, monocytes/macrophages act as a Trojan horse to transmit HIV-1 to the central nervous system. They also exhibit antiviral activity and express many molecules that inhibit HIV-1 replication. Activated microglia and macrophages may also exert a neurotrophic and neuroprotective effect on infected brain regulating glutamate metabolism or by secretion of neurotrophins. This review will discuss specific aspects of viral replication in monocytes/macrophages and the role of their interactions with the cellular environment in HIV-1 infection swinging between protection and pathogenesis.

Keywords: HIV-1; Macrophage; Microglia; Viral replication; Cellular Interactions; Central nervous system; Macrophage antiviral factor

1. Introduction

Lentiviruses can infect and replicate in non-dividing cells, including cells of the monocyte/macrophage lineage. Some non-primate lentiviruses, such as caprine arthritis and encephalitis virus (CAEV) and Maedi-Visna virus, which cause chronic inflammatory diseases, exhibit a restricted tropism for monocytes/macrophages. Conversely, lentiviruses, such as the feline, simian and human immunodeficiency viruses (FIV, SIV and HIV, respectively), have acquired a wider tropism and an expanded range of target cells, primarily CD4+ T lymphocytes. Lentiviruses may cause CD4+ T cell depletion and immunodeficiency. The capacity of lentiviruses to infect macrophages and other antigen-presenting cells (APC) plays a determinant role in the establishment, persistence and pathogenesis of infection. Macrophages greatly contribute to innate responses to pathogens, and are at the interface between innate and adaptive immunity. Thus, they play a central role in defence and in the control of infections, either by directly destroying invading pathogens or by secreting cytokines able to inhibit their replication or to activate other arms of the innate or adaptive immune responses. The infection of macrophages by intracellular pathogens, includ-

Abbreviations: AMM, activated macrophages and microglial cells; APC, antigen-presenting cells; BBB, blood brain barrier; CAF, CD8 antiviral factor; C/EBPβ, CCAAT/enhancer binding protein β; CNF, central nervous system; Cppt, central polypurine tract; EAAT, excitatory amino acid transporter; FcR, Fc receptor; GM-CSF, granulocyte macrophage-colony stimulating factor; HIV, human immunodeficiency virus; IFN, interferon; IN, integrase; ITAM, immunoglobulin gene family tyrosine activation motif; LIF, leukemia inhibitory factor; LPS, lipopolysaccharide; MA, matrix; MCSF, macrophage-colony stimulating factor; MDC, macrophage derived factor; MMR, macrophage mannose receptor; MVB, multivescicular bodies; Nef, negative early factor; NGF, nerve growth factor; NLS, nuclear localisation signal; PIC, preintegration complex; RTC, reverse transcription complex; SDF-1, stromal cell-derived factor; TNF-α, tumour necrosis factor α; Vpr, viral protein R

* Corresponding author. Fax: +33 1 4568 8957.
E-mail address: gpancino@pasteur.fr (G. Pancino)

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ing lentiviruses, may impair their functions and alter the cytokine production pattern, resulting in chronic inflammation and tissue damage. Unlike T cells, HIV-infected macrophages appear to be resistant to the cytopathic effects of the virus and thus serve as a reservoir for persistent infection. The capacity of monocytes and macrophages to migrate in organs and to survive in tissues makes them potential conveyors of HIV-1 infection. Their interplay, as APCs or a source of chemotactic cytokines, with CD4 T cells may favour intercell virus transmission. Therefore, monocytes/macrophages are thought to play an ambiguous, dichotomous role in lentiviral infections, acting either as an antiviral defence system or a virus target, a host cell guardian or a Trojan horse (Herbein et al., 2002). There is increasing interest in several aspects of macrophage infection by HIV, including the mechanisms of HIV replication in monocytes/macrophages, and the roles of these cells in the control of the infection, the pathogenesis of disease and viral escape from antiretroviral therapy. A considerable number of recent reviews have addressed many of these points (Freedman et al., 2003; Gras et al., 2003; Kedzierska et al., 2003a, 2003b) and articles contained in the special issue of November 2003 of J. Leukoc. Biol., no. 74). Thus, this review will summarise current knowledge of some characteristics of HIV infection of macrophages: (a) peculiar features of HIV replication in macrophages, including viral entry, nuclear import of viral DNA, and virus assembly and release, (b) interactions of HIV-1-infected macrophages with the cellular environment, (c) the molecular interactions of brain macrophages with the central nervous system in HIV infection and (d) the range of inhibitory activities exerted by macrophages on HIV replication.

2. Peculiar features of HIV-1 replication in macrophages

The HIV-1 life cycle in macrophages differs in many respects from that in CD4 T lymphocytes (Fig. 1). Indeed, different HIV-1 isolates show different tropism for CD4 T cells and macrophages (Cheng-Mayer et al., 1988; Fenyö et al., 1988; Wu et al., 1997). Unlike T cells, productive HIV-1 infection occurs independently of cellular DNA synthesis in macrophages (Weinberg et al., 1991). The assembly and budding of viral particles take place in cytoplasmic vacuoles in macrophages but not in T cells (Orenstein et al., 1988). Furthermore, HIV-1 accessory genes may have distinct effects in primary macrophages and lymphocytes (Sherman et al., 2002; Subbramanian et al., 1998; Swingler et al., 2003). Some cellular factors required for HIV-1 transcription, such as GATA-3, ETS-1, LEF-1 and NF-ATc, are lymphoid or T cell-specific (Kinoshita et al., 1997; Yang and Engel, 1993), whereas others, such as CCAAT/enhancer binding protein β (C/EBPβ), are necessary for HIV-1 replication in macrophages but not in T cells (Henderson and Calame, 1997; Lee et al., 2002).

2.1. HIV-1 entry in human macrophages

In recent years, there has been much debate regarding the ability of HIV-1 strains that use CXCR4 as a co-receptor to enter target cells (X4 viruses) to infect macrophages. Indeed, although CXCR4 is expressed in both monocytes and mature macrophages (Naif et al., 1998; Valentin et al., 2000; Verani et al., 1998), it is unclear whether X4 viruses can productively infect macrophages. It is generally agreed that most T cell line-adapted laboratory (TCLA) strains of HIV-1, such as the IIIB strain, infect macrophages at best inefficiently. However, conflicting results have been obtained about primary isolates. In particular, some authors observed that macrophages are refractory to X4 HIV-1 isolates (Yi et al., 1998), whereas others found that X4 strains can efficiently enter macrophages but subsequently remain blocked at a post-entry level (Schmidtmayerova et al., 1998). In contrast, several groups have reported that primary isolates that use CXCR4 can enter macrophages and replicate efficiently (Simmons et al., 1998; Valentin et al., 2000; Verani et al., 1998). This is supported by the rigorous demonstration that all the relevant viral isolates are selective CXCR4 users, by the demonstration that CXCR4 is functional in an independent assay (i.e., chemotaxis), and most importantly, by the ability of different ligands for CXCR4, including stromal cell-derived factor (SDF)-1, anti-CXCR4 mAb and the bicyclam derivative AMD3100, to prevent HIV-1 infection. Finally, an HIV-1 primary strain isolated from the central nervous system of an individual with AIDS that is restricted to CXCR4 and induces neuronal apoptosis was reported to replicate efficiently in macrophages (Yi et al., 2003).

The abovementioned discrepancies were probably caused by differences in experimental conditions, such as macrophage isolation and culture methods, assays for measuring co-receptor function or HIV-1 infection, and temporal modulation of CD4 and CXCR4 levels during cell culture. Indeed, the capacity of X4 strains to replicate in macrophages depends largely on how these cells were cultured; different culture conditions may produce macrophages at different stages of activation, which affects the pattern of molecules expressed on the cell surface including proteoglycans and, most importantly, the profile of released cytokines and chemokines (Bakri et al., 2001).

However, peculiar molecular features also contribute to differences between X4 and R5 HIV-1 replication in macrophages. Indeed, western blot analysis of surface proteins from monocytes, macrophages and T cells demonstrated differences in the biochemical properties of CXCR4 molecules in different cell types. CXCR4 was found to be mainly a monomer in monocytes and T cells, but was principally a species of higher molecular weight on the surface of macrophages (Lapham et al., 1999). CD4 co-precipitated with CXCR4 monomers but not with the high molecular weight form, suggesting that this CXCR4 form cannot associate with CD4 (Lapham et al., 1999). In addition, CCR5 and CXCR4 interfere with each other during viral