



## Review

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## Macrophages and their relevance in Human Immunodeficiency Virus Type I infection

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### Abstract

Macrophages are important target cells for the Human Immunodeficiency Virus Type I (HIV-1) *in vivo*. Several studies have assessed the molecular biology of the virus in this cell type, and a number of differences towards HIV-1 infection of CD4+ T cells have been described. There is a broad consensus that macrophages resist HIV-1 infection much better than CD4+ T cells. Among other reasons, this is due to the presence of the recently identified host cell restriction factor SamHD1, which is strongly expressed in cells of the myeloid lineage. Furthermore, macrophages produce and release relatively low amounts of infectious HIV-1 and are less sensitive to viral cytotoxicity in comparison to CD4+ T cells. Nevertheless, macrophages play a crucial role in the different phases of HIV-1 infection. In this review, we summarize and discuss the significance of macrophages for HIV-1 transmission, the acute and chronic phases of HIV-1 infection, the development of acquired immunodeficiency syndrome (AIDS) and HIV-associated diseases, including neurocognitive disorders. We propose that interaction of HIV-1 with macrophages is crucial during all stages of HIV-1 infection. Thus, long-term successful treatment of HIV-1 infected individuals requires potent strategies to prevent HIV-1 from entering and persisting in these cells.

### Review

#### Introduction

HIV-1 infects various cell types of the immune system. CD4+ T helper cells are major target cells for HIV-1 in the blood, since they can express high levels of the HIV-1 receptor CD4 on their surface and are highly permissive for HIV-1 production [1,2]. However, other immune cells also express CD4 and HIV-1 co-receptors at the cell surface and thus also serve as viral targets. Among them macrophages were described, more than twenty five years ago, to carry markers of productive HIV-1 infection *in vivo*[3], although they express only low levels of CD4.

Macrophages are terminally differentiated, non-dividing cells, derived from circulating monocytes [4]. They represent a distinct population of phagocytes which are found under different names in various tissues (e.g. microglia in the brain, alveolar macrophages in the lung, or Kupffer cells in the liver) [4,5]. Macrophages play an important role in the innate and adaptive immune response. They phagocytose cellular debris and pathogens, but also act as professional antigen presenting cells (APC), triggering antibody responses by the presentation of pathogen derived peptides via the MHC-II pathway to CD4+ T cells [5] and activating CD8+ cytotoxic T-cells (CTL) by cross-presentation of HIV-1 antigens [6]. The life spans of macrophages can differ greatly, depending on their immunological roles and tissue localizations. Thus inflammatory macrophages derived from circulating monocytes die after a few days [7], whereas microglia or alveolar macrophages can live from several weeks up to years [8-10]. Due to their dissemination over different tissues and their capacity to infiltrate virtually all organs including the brain, macrophages might critically contribute to the spread of HIV-1 within a patient [11-13]. Furthermore, next to human mammary epithelial cells [14,15], macrophages have been implicated as key cells responsible for mother-to-child transmission due to breast feeding [16].

The progressive loss of CD4+ T cells and high-level virus production by these cells are the irrefutable cause of immune deficiency [17]. However, the relevance of macrophages for the transmission, spread and pathogenicity of HIV-1 is less clear. One reason for this is the large diversity of possible interactions of macrophages with HIV-1. For example macrophages can differ both in their capacity to permit HIV-1 entry as well as their capacity to support the HIV-1 replication cycle [18-20]. Infection frequently results in only limited virus production, and *in vivo* infection may be apparent in only a minor proportion of macrophages within certain macrophage subpopulations [19,21,22]. In addition, macrophages are much more resistant to cytopathic effects of lentiviral replication than for example activated CD4+ T cells [23-25], and HIV-1 has evolved sophisticated mechanisms to prolong the life span of infected macrophages [24,26]. Especially long-lived macrophages using a major obstacle to virus eradication from infected individuals. of macrophages throughout the different phases of HIV-1 infection.

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#### at mucosal surfaces

Worldwide, the predominant mode of primary HIV-1 infection is through heterosexual intercourse [27]. HIV-1 and other sexually transmitted pathogens have to pass the genital mucosal barrier, which strongly hinders infection due to its low pH, the closed epithelium and antiviral factors present in vaginal secretions [28,29]. Nevertheless, pathogens are able to cross the mucosal barrier, especially through small mucosal lesions that occur during sexual intercourse and impair epithelial integrity. Macrophages, dendritic cells (DC) and CD4+/CCR5+ memory T cells patrolling the mucosal surface are the first immune cells facing the virus [21]. Most