HIV-1 infection in macrophages and genes involved throughout: Big eaters versus small invaders

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GENERAL INTRODUCTION

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And
MONOCYTES AND MACROPHAGES

Macrophages are effector cells of the innate immune response, and are responsible for sensing and clearing pathogens, thus playing an important role in establishing primary as well as adaptive immune responses. These cells also contribute to regulation of tissue homeostasis, inflammation and repair. Derived from a common myeloid progenitor, monocytes that originate in the bone marrow are released into the bloodstream. Monocytes subsequently migrate to the tissues, where they mature into macrophages and can encounter a number of stimuli that can shape their physiology (Figure 1). Cytokines that are produced by either innate or adaptive immune cells are responsible for skewing macrophages into two main phenotypic subpopulations: M1 or M2, with M1 macrophages typically producing high levels of IL-12 and low levels of IL-10, and M2 macrophages producing high levels of IL-10 and low levels of IL-12. M1 macrophages are generated by stimulation with IFN-γ and TNF-α or LPS, and have a pro-inflammatory profile. These classically activated macrophages are characterized by high production of pro-inflammatory cytokines (IL-1, IL-6, IL-12, and TNF-α) and a high microbicidal activity. M2 or alternatively activated macrophages comprise a broad variety of cells with different characteristics. However, they are all mediators of Th2 or anti-inflammatory responses and may be involved in tumorigenesis. M2 macrophages can be divided into three main groups: M2a, M2b and M2c. M2a macrophages are induced by exposure to IL-4 or IL-13, produce high levels of anti-inflammatory cytokines IL-10 and IL-1ra (receptor antagonist), and are involved in wound healing, tissue repair and, in some cases, killing and encapsulation of parasites. They are also involved in allergic responses and recruit other immune cells to inflammation sites. M2b macrophages are primed by stimulation with IgG immune complexes and are further activated by TLR ligands. These cells produce pro-inflammatory cytokines (IL-1, IL-6, TNF-α), but in contrast to M1 macrophages they also produce IL-10. This subpopulation of activated macrophages plays an important role in mediating anti-inflammatory responses, and development of humoral responses. In these macrophages, binding of the FcγR to an antigen-IgG complex will elicit IL-10 production, which will prompt T cells to produce IL-4, thus stimulating B cells to produce antibodies against such antigen. M2c macrophages are generated by stimulation with IL-10 or glucocorticoids, are involved in immune suppression and regulation of inflammation, and produce IL-10 and TGF-β (Figure 1). It has been proposed that the activation process of macrophages occurs in a successive manner, instead of being a single-step stimulation event, and goes from initial priming, full activation into effector cells and subsequent deactivation by anti-inflammatory mediators.
Macrophages are important target cells for HIV-1, and due to their ubiquitous distribution and their capacity to migrate to other tissues, they contribute greatly to the spread of the viral infection to CD4+ T cells and the establishment of the viral reservoir. Although the introduction of combined antiretroviral therapy (cART) has contributed to the control of viral load in infected patients, residual viremia can still be detected when using highly sensitive methods. Macrophages are long lived cells that are resistant to the cytopathic effects of viral infection. Additionally, HIV-1 induces anti-apoptotic mechanisms in macrophages that allow for continuous production of viral particles for long periods of time. Poor tissue penetration of antiretroviral drugs prevents inhibition of viral replication in these cells, allowing them to reside in sanctuary sites, such as the testis, gut associated lymphoid tissue, the brain, and the bone marrow.

Furthermore, it has been shown that HIV-1 infected macrophages render resting T cells permissive for infection, which indicates that both the resting T cell and the macrophage reservoirs are connected. Viral reservoirs such as macrophages contribute to the development of HIV-1 associated diseases and make eradication of the virus from the host a challenging task.
ROLE OF MACROPHAGES IN TRANSMISSION OF HIV-1

Macrophages are of great importance in the spread of the virus from host-to-host, during mucosal transmission, and are also central players during cellular transmission of HIV-1 from cell-to-cell.

Host-to-host transmission
HIV-1 transmission occurs mainly through mucosal tissue after translocation of the virus across the epithelium. Since macrophages constitute the largest population of immune cells in the subepithelial lamina propria, it is thought that macrophages play a role in transmission of the virus from host-to-host\(^1\). Organ culture systems derived from cervical tissue allowed for the identification of CD4\(^+\) T cells as the first cells being infected after contact with cell-free CCR5-using HIV-1, but also helped to identify Langerhans cells and macrophages as early target cells for HIV-1 infection\(^1\). In addition, macrophages were found to be present in the mucosa and submucosa of human vagina and foreskin, which are also early sites of HIV-1 replication before the virus disseminates\(^1,2\). Finally, the predominant infection of macrophages by CCR5-using HIV-1 may be one of the factors contributing to the predominant transmission of these variants from host-to-host\(^2,3\).

Cell-to-cell transmission
Transmission of HIV-1 can occur from infected macrophages to CD4\(^+\) T cells upon cell-to-cell contact and it is accompanied by activation of the T cells. Cell-to-cell transmission is more efficient than infection by cell-free virus\(^2\). The virological synapse, the structure between the infected cell and an uninfected permissive target cell, is used for the transfer of HIV-1\(^2\). In macrophages, HIV-1 induces the formation of tunnelling nanotubes which the virus uses for transfer to the connected cell\(^2\). In addition, macrophages and microglia express mannose-receptors that can bind and endocytose HIV-1, allowing subsequent transmission to CD4\(^+\) T cells without infection of the macrophage\(^2\). Expression of DC-SIGN plays a role in the transmission of HIV-1 from macrophages in colostrum (early breast milk) to recipient cells in the new born child\(^2,3\).

CELLULAR FACTORS INVOLVED IN HIV-1 REPLICATION IN MACROPHAGES
Monocytes are refractory to HIV-1 infection in vitro, yet become susceptible to infection during differentiation into macrophages\(^2,3\). For efficient replication, HIV-1 continuously interacts with the cellular machinery of macrophages, and several studies have identified cell type-specific factors, including miRNAs, that are involved at different steps of the replication cycle of the virus.
Monocytes

Although freshly isolated monocytes express reasonably high levels of CD4\(^{30}\), expression of CCR5 is low\(^{31,32}\). Still, HIV-1 is able to efficiently enter the cells, however the process of reverse transcription is not completed\(^{28,29}\) probably due to the low levels of dNTP in non-dividing cells\(^{33,34}\). A 32 base pair deletion in the gene encoding for CCR5 influences macrophage susceptibility to HIV-1; donors with a heterozygous genotype \((\text{CCR}5 \text{ wt}/\Delta32)\) are less permissive to infection\(^ {35,36}\), whereas the absence of CCR5 on the cell surface \((\text{CCR}5 \Delta32/\Delta32)\) results in complete resistance to infection with a CCR5-using virus\(^ {36,37}\).

Monocyte-derived macrophages

HIV-1 susceptibility of macrophages in vitro is enhanced by growth factors like M-CSF or GM-CSF\(^ {38-40}\). The increase in susceptibility of macrophages to HIV-1 infection during differentiation correlates with enhanced CCR5 expression\(^ {31,32,41}\). Despite expression of CXCR4 on macrophages, these cells are refractory to infection with most CXCR4-using HIV-1 isolates \(\text{in vitro}\)\(^ {42}\), perhaps because of lack of an association between CXCR4 and CD4 on the cellular membrane\(^ {43}\). Furthermore, additional to binding to the co-receptor, the subsequent intracellular signalling also influences the ability of HIV-1 to replicate in macrophages\(^ {44}\).

The ability of primary macrophages to support HIV-1 replication \(\text{in vitro}\) was found to be highly variable and dependent on the donor, suggesting that genetic variations may contribute to susceptibility to HIV-1 infection\(^ {36}\). A genome-wide association study identifying genetic polymorphisms allowed identification of factors like PDE8A and DYRK1A that play a role in HIV-1 susceptibility of primary macrophages\(^ {45,46}\).

During the replication cycle, HIV-1 utilizes the cellular machinery of macrophages in order to produce new viral progeny. Differential expression of cellular factors during macrophage differentiation, activation and polarization might explain changes in susceptibility of these cells to HIV-1 infection, despite the variation between individuals. Several studies have identified cellular proteins that interact with HIV-1 at different steps in the replication cycle in primary macrophages. HIV-1 infects macrophages through binding of the HIV-1 envelope protein gp120 to CD4 and CCR5, followed by viral uptake and entry into the cell. Other cellular factors that contribute to viral entry are the integrin \(\alpha_v\beta_5\)\(^ {47}\) and a novel endocytic entry pathway, which is dependent on actin rearrangements, \(\text{Na}^+/\text{H}^+\) exchange, Rac GTPase, N-WASP, Pak1, and dynamin GTPase\(^ {48}\).

In the cytoplasm, the viral RNA is reverse transcribed into a double-stranded DNA genome. In macrophages, reverse transcription and subsequent integration were restricted by Trim5\(\alpha\)\(^ {49}\), Cyclophilin A\(^ {50}\) and APOBEC3G\(^ {51,52}\). In contrast, CD63, supports reverse transcription and subsequent steps of the viral replication cycle\(^ {53}\).

Furthermore, nuclear translocation and integration of the viral genome requires phosphorylation of the emerin protein by virion-associated ERK/MAPK in...
non-dividing cells\textsuperscript{54}. NAMPT is able to decrease the levels of integrated proviral DNA in MDM\textsuperscript{55}. After integration, the viral genome is transcribed by the cellular machinery, leading to protein production and assembly of new viral particles. Early in infection mainly non-full length HIV-1 transcripts are generated, resulting in the translation of the HIV-1 protein Tat. HIV-1 Tat recruits the host proteins Cyclin-T1, NL-IL6 and CDK9 to form a complex that binds the HIV-1 LTR and enhances elongation of HIV-1 transcripts\textsuperscript{56,57}. However, the small isoform of the C/EBP\(\beta\) gene is a dominant negative transcription factor that blocks viral DNA transcription\textsuperscript{58-60}. Trim22 and OTK18 (ZNF175) can also suppress HIV-1 LTR promoter activity\textsuperscript{61,62}. In microglia, the DNA repair protein Rad51 enhances NF-\(\kappa\)B-induced transcription\textsuperscript{63}.

Late in the viral replication cycle, TIP47 is essential for the production of infectious new viral particles and Anexin2 maintains infectivity of the viral progeny in infected primary macrophages\textsuperscript{64,65}. Tetherin (BST2) and Alix (AIP1) block viral release from the cellular membrane of macrophages\textsuperscript{66,67}.

Role of microRNAs in HIV-1 infected macrophages

Cellular microRNA (miRNA) pathways have been described to interfere with HIV-1 replication and contribute to viral latency by targeting HIV-1 transcripts or cellular RNAs encoding for proteins essential for replication. Expression of cyclin T1 can be regulated by miR-198, abundantly expressed in monocytes, and therefore regulates Tat-dependent gene expression\textsuperscript{68}.

Expression of a number of cellular miRNAs that directly target HIV transcripts (miR-28, miR-150, miR-223, and miR-382), decreases during differentiation of monocytes into macrophages\textsuperscript{69} and it is inversely correlated with the susceptibility to HIV-1 infection\textsuperscript{70}.

HIV-1 can modulate the host RNA interference pathways to promote either viral latency or suppress the innate responses against viruses. The HIV-1-accessory proteins Vpr and, to a lesser extent, Nef down-regulated DICER expression, thus suppressing the complete miRNA pathway in PMA- or M-CSF-treated macrophages derived from U937 cells\textsuperscript{71}. In microglial cells, the resident macrophages in the Central Nervous System (CNS), HIV-1 induced expression of miRNA-146a, which targets MCP-2, a potent inhibitor of CD4/CCR5-mediated HIV-1 entry\textsuperscript{63}.

**HIV-1 INFECTION OF POLARIZED MACROPHAGES**

Several studies have reported the effects of cytokine stimulation on HIV-1 infection of macrophages and determined that HIV-1 is inhibited in M1 or M2 polarized macrophages\textsuperscript{72-75}.

**M1 Macrophages**

HIV-1 inhibition has been attributed to low expression of CD4 and up regulation of CCR5 binding chemokines and also inhibition of early (in M1) or late (M2) steps of the
replication cycle\textsuperscript{72,76,77}. Additionally, IFN-γ treatment alone also blocks HIV-1 replication in macrophages and in most studies a decrease in proviral DNA is observed\textsuperscript{78-80}. Other proinflammatory cytokines produced by M1 activated macrophages may also modulate HIV-1 infections in these cells. Studies have shown that HIV-1 replication is inhibited at an early step by IL-6\textsuperscript{81} and IL-12\textsuperscript{82}, but is enhanced by CXCL10\textsuperscript{83} and CCL2\textsuperscript{84}, at early and late steps in the replication cycle, respectively.

**M2 Macrophages**

In M2a macrophages, a more sustained inhibitory effect at a late stage in the virus life cycle is observed\textsuperscript{72}. Treatment of HIV-1 infected monocyte-derived macrophages (MDM) with IL-4 alone stimulates HIV-1 reverse transcription, p24 production, and HIV-1 transcription by accelerating nuclear import of NF-κB\textsuperscript{85-88}. However, treatment of MDM prior to viral inoculation significantly reduces reverse transcription and p24 production\textsuperscript{40,89-91}, and is associated with the reduced proliferative capacity, advanced maturation state\textsuperscript{90}. Treatment with IL-13 also inhibits HIV-1 replication, similar to IL-4\textsuperscript{40,91}.

HIV-1 replication in M2b macrophages generated using human IgG to cross-link FcγRs, either before or after viral inoculation, is strongly inhibited at the level of proviral integration into the host genome\textsuperscript{74,75}. Reversed transcription is also restricted in these macrophages by the cyclin-dependent kinase inhibitor p21-Cip1/Waf\textsuperscript{92}.

Induction of M2c macrophages by IL-10 results in inhibition of viral replication at a late step during infection, probably at the level of viral assembly\textsuperscript{93,94}. However, others show treatment of infected monocyte-derived macrophages with IL-10 and TNF-α increases HIV-1 replication, probably due to a synergistic effect\textsuperscript{95}. Additionally, IL-10 induces proteosomal degradation of Cyclin-T1, which in turn has a suppressive effect on HIV-1 replication in macrophages\textsuperscript{96}.

**INNATE IMMUNITY TO HIV-1 AND EVASION STRATEGIES OF THE VIRUS**

Recent studies revealed contrasting roles for Toll-like receptor (TLR) ligands, derived from different microbial invaders, in either suppressing or enhancing HIV-1 replication in macrophages. Activation of TLR3, TLR4 and TLR9 leads to inhibition of HIV-1 replication mostly by stimulation with type I interferon responses and other proinflammatory mediators\textsuperscript{97-100}. However TLR5 activation has been associated with enhanced virus production, and TLR8 stimulation activates HIV from latently infected monocytic cell lines\textsuperscript{101,102}.

Upon viral infection, receptors that recognize viral nucleic acids initiate a cellular innate immune response. Central to this response are type I IFNs that potently inhibit the early stage of HIV-1 replication\textsuperscript{103,104}. Notably, HIV-1 infection in macrophages neither triggeres NF-κB nor IRF3 pathways nor does it induce type I IFN gene
expression\textsuperscript{105}. The molecular basis behind the lack of functional recognition of HIV-1 in macrophages is not completely understood. TREX1 might be one of the cellular factors responsible for impeding type I IFN responses. This DNase binds to HIV-1 DNA copies in the cytoplasm, and digests excess of proviral DNA\textsuperscript{106}. Additionally, the phosphohydrolase SAMHD1 is capable to restricting reverse transcription of HIV-1 in myeloid cells, by limiting the pool of nucleotides available to viral cDNA synthesis\textsuperscript{107,109}. Together, TREX1 and SAMHD1 prevent viral DNA to be abundant in the cytoplasm, making it invisible to cytoplasmic DNA sensors that otherwise are capable of triggering an innate antiviral response through IFN-\(\beta\) production, thus enabling HIV-1 to escape this antiviral responses and be transmitted to T cells\textsuperscript{110}.

In spite of the muted changes to the macrophage transcriptome upon HIV-1 infection\textsuperscript{105}, different effects of HIV-1 have been reported. The HIV-1 accessory protein Nef was shown to induce MIP-1\(\alpha\) and MIP-1\(\beta\) production in macrophages, thereby enhancing viral replication and dissemination by recruitment of T cells\textsuperscript{111}. HIV-1-infected monocytes and macrophages exhibit upregulation of programmed death-1 (PD-1) and its ligands PD-L1 and PD-L2\textsuperscript{112,113}. When engaged in combination with the T-cell receptor, PD-1/ligand signaling results in an inhibitory signal affecting proliferation and cytokine production, T-cell activation and recognition of the infected macrophage. HIV-1 infection also impairs the ability of macrophages to phagocytose pathogens opsonized by antibodies or complement\textsuperscript{114}.

During HIV-1 replication in macrophages, Nef induces formation of autophagosomes, although it inhibits their maturation in order to protect the virus from degradation and limit presentation of viral peptides by MHC\textsuperscript{115}. HIV-1 also inhibits autophagy activity of uninfected bystander cells in adjacent cells through Src-Akt and STAT3 activation\textsuperscript{116} and inhibition of IFN\(\gamma\)-induced STAT1 phosphorylation\textsuperscript{117}. Disruption of autophagy by HIV-1 interferes with the host defense mechanisms against invading pathogens, thereby creating a favorable environment for opportunistic infections.

In conclusion, HIV-1 does not evoke a strong innate immune response, involving for instance type I IFN and NF-\(\kappa\)B, upon infection of primary macrophages. Although HIV-1-infected macrophages are dysfunctional, they are able to evade recognition by the immune system and serve as viral reservoir, disseminating the virus to various tissues.

**PATHOLOGIES ASSOCIATED WITH HIV-1 INFECTION IN MACROPHAGES**

HIV-1-infected macrophages are involved in the development of different pathologies, like AIDS-related lymphomas, cardiovascular diseases, and HIV-1-associated neurocognitive disorders (HAND), of which HIV-1-associated dementia (HAD) is the most severe complication\textsuperscript{118}. 


Neurocognitive disorders

Early in the course of infection, HIV-1 transits to the CNS via infected macrophages and lymphocytes where it settles in perivascular macrophages, microglia, and astrocytes\textsuperscript{119-121}. Although astrocytes are not productively infected, they form the majority of cells in the brain and are critical for maintaining essential brain functions.

Production of proinflammatory chemokines, like CCL2, by infected macrophages, microglia, and astrocytes increases transmigration of circulating infected monocytes and macrophages over the blood-brain barrier (BBB)\textsuperscript{122}. Once infected, the CNS acts as a viral reservoir and is capable of re-seeding the periphery with HIV-1, most likely via the meninges as primary transport tissue\textsuperscript{123}. Replication in macrophages and activated microglia leads to production of viral and proinflammatory proteins creating a neurotoxic environment. Viral proteins, such as gp120, gp41, and Tat, have strong neurotoxic effects and have been implicated in the development of HAD\textsuperscript{124}. HIV-1 Tat has a direct toxic effect on neurons and can induce expression of adhesion molecules and chemokines in astrocytes and microglia attracting monocytes/macrophages to the brain\textsuperscript{125}. Tat also induces suppressor of cytokine signaling 3 (SOCS3), thereby inhibiting IFN-\(\beta\) signaling, thus enhancing viral replication in macrophages and promoting HAD development\textsuperscript{126}.

Treatment of HIV-1-infected individuals with combined antiretroviral therapy (cART) has diminished the prevalence of severe AIDS-related complications, like HAD. However, milder forms of HAND are increasingly recognized in a substantial number of aging HIV-1-infected individuals on cART and are now one of the most feared complications of the infection\textsuperscript{118,127}.

AIDS related lymphomas

Macrophages might also indirectly contribute to the onset of AIDS related cancers. The occurrence of non-Hodgkin lymphomas in HIV-1 infected patients has decreased since cART, but is thought to remain too frequent to only be associated with poor immunity caused by the virus\textsuperscript{128,129}. Excessive cytokine production by macrophages could result in overstimulation of B cells with subsequent DNA modifications, resulting in malignancy\textsuperscript{130,131}. Cell-to-cell transmission from infected macrophages to B cell through tunnelling nanotubes may contribute to the formation of AIDS-related lymphomas (ARL)\textsuperscript{132,133}. HIV-1 has not been found in malignant B cells, but was present in tumor associated macrophages in the stroma\textsuperscript{128,134}. Additionally, 40% of the ARL tissues were found to harbour HIV-1 infected macrophages\textsuperscript{135}.

Cardiovascular disease

HIV-1 infected patients have a greater risk to develop cardiovascular disease, independent of the use of cART or of dyslipidemia\textsuperscript{136-139}. Multiple studies have shown that there is a direct effect of HIV-1 on plasma lipid levels, resulting in an atherogenic lipoprotein profile\textsuperscript{136,140,141}. HIV-1 induces systemic inflammation and expression of
cytokines, which recruits monocytes and macrophages to the damaged arterial wall, promoting local differentiation and activation of the macrophages. This results in increased uptake of lipids by macrophages, leading to the formation of foam cells and of plaque at the inner lining of the inflamed artery\textsuperscript{142}. In addition, expression of the viral protein Nef in infected macrophages leads to higher production, uptake and accumulation of cholesterol\textsuperscript{143-146}. Therefore, through the increased cytokine production and recruitment of infected monocytes and macrophages, HIV-1 may contribute to the development of cardiovascular diseases\textsuperscript{143,146,147}.

CONCLUSION

HIV-1 interacts with numerous cellular factors expressed in macrophages, during the viral replication cycle. The effect of such cellular factors can be beneficial as well as detrimental for viral replication, yet HIV-1 is capable to efficiently infect macrophages and at the same time avoid triggering of immune responses that may eliminate the virus or the infected cells. Due to this efficient evasion from immunity, and wide tissue dissemination, virus-infected macrophages function as cellular reservoir for the virus, becoming the main hurdle for the eradication of HIV-1.

It is still unclear how HIV-1 replication in macrophages is regulated, especially upon cytokine polarization, and which mechanisms and cellular factors are involved. It is of great importance to identify these factors in the macrophages, present at the moment of infection, in non-activated as well as polarized/activated macrophages, to reveal the exact mechanism of HIV-1 infection in these cells. Identification of cellular factors involved in HIV-1 replication in macrophages will increase the understanding of both virus- and cell-type-specific aspects of viral replication and may identify new therapeutic alternatives that specifically target HIV-1 reservoirs.

SCOPE OF THIS THESIS

In this thesis we have studied the infectious process of HIV-1 in differently polarized macrophages. The purpose of this research was to identify cellular factors that are involved in HIV-1 infection of macrophages, how these factors affect viral replication and whether their function or expression is affected by stimulatory signals that macrophages encounter during their differentiation in the tissues.

In order to better understand the process of macrophage polarization, in chapter 2, we have characterized expression of miRNAs in cytokine-polarized macrophages, and identified specific miRNA expression signatures that are associated with the macrophage physiology. In chapter 3, we have demonstrated that HIV-1 infection is inhibited in M1 and M2 polarized macrophages. Analyses of expression of cellular factors known to interact with HIV-1 during infection indicated that the known factors are not associated with HIV-1 inhibition in M1 and M2 macrophages. These data suggested that novel cellular factors are involved,
and in chapter 4, we have indeed identified a novel HIV-1 restriction factor expressed in macrophages and T cells, through the analysis of gene expression profiles in M1 and M2 macrophages. We found that the GTPase Binding Protein (SH3 domain) Binding Protein 1 (G3BP1) restricts HIV-1 replication by binding to HIV-1 RNA transcripts, which delays mRNA translation and viral protein production, therefore reducing production of new viral particles. In chapter 5 we have investigated the role of a recently described cellular factor PDE8A, in HIV-1 replication in macrophages. We have identified the mechanism of HIV-1 restriction by PDE8A and show that PDE8A expression is regulated by cellular miRNAs during maturation of monocytes into macrophages. In chapter 6 we have analyzed how HIV-1 influences gene expression in macrophages upon infection, and how this relates to gene expression in macrophage polarization by cytokines. The findings of this work and its implications are discussed in chapter 7.

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