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# Innate Immune Responses in HIV-Infection

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## 1. Introduction

The immune system comprises complex cellular and humoral systems, which are forming an interactive network to recognize and eradicate invading pathogens. Foreign molecules present on viruses, bacteria and parasites, but not on host cells, are discriminated from self through pathogen-associated molecular patterns. Upon entry of the pathogen into the body immediate non-specific immune responses are triggered and within a short time the innate immune system is completely activated. The innate immune system is composed of multiple humoral and cellular players, including cytokines, complement proteins, acute-phase proteins, dendritic cells, macrophages, NK cells, that co-operate in a complex to generate an efficient defense against infection (Figure 1). At best, these immediate innate immune responses are able to clear infection or bridge the period until the adaptive, specific immune response is taking effect.

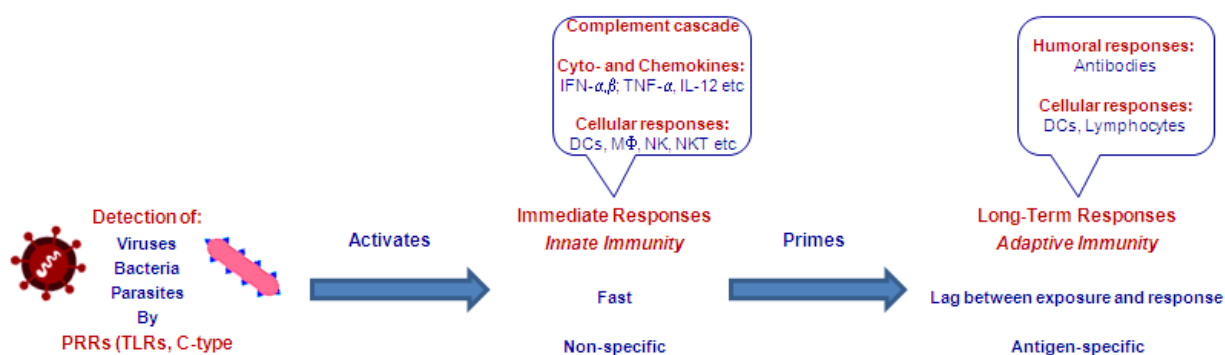


Fig. 1. Induction of Immune responses

Among the first components activated during the innate immune response is the complement system that together with interferons, cytokines and chemokines stimulate innate immune cells, such as dendritic cells (DCs), natural killer (NK) cells, natural killer T (NKT) cells, monocytes, or macrophages. These factors act in concert until the adaptive arm of immunity is established. Thus, to control the infection process in the acute phase a coordinated action of the innate immune elements is essential.

In the beginning of an infection viruses and microbes developed different strategies to avoid the attack of the innate immune system. Also the human immunodeficiency virus (HIV) is able to overcome innate and adaptive immune responses in infected individuals and

thereby attenuates the immunity of the host. In the last years the interest in innate immune responses to control HIV infection significantly increased and this book chapter will describe various interactions and evasion strategies of HIV and innate immune elements with a special focus on complement and dendritic cells.

## **2. Interactions of HIV with humoral components of the innate immune system**

Following entry of HIV into the host, humoral components of the innate immune system, such as complement system, interferons, cyto- and chemokines, are spontaneously activated and will be discussed here. Together with dendritic cells, which are among the first cells of the immune system to interact with HIV, the innate humoral components attract other cells of the immune system, e.g. NK cells or macrophages, to the sites of infection and a first line of defense is established. To ensure a logical configuration of the chapter, we will first summarize interactions of HIV with humoral components of the innate system and subsequently with cellular responses, although these actions cannot be separated and are proceeding in parallel at mucosal surfaces.

### **2.1 Interactions of HIV with the complement system**

The complement system plays a crucial role during viral infection respecting both innate and adaptive immune responses. It constitutes the first barrier to control HIV propagation and can be activated via three different biochemical pathways: the classical, the MBL, and the lectin pathway (Fig. 2). The classical complement pathway was the first way to be identified, and activation of the classical pathway occurs when the first component of the pathway, C1, binds the Fc region of either natural or specific IgG antibody immune-complexed with viral antigen. The classical pathway is also triggered in an antibody-independent manner when C1 directly binds to virions or infected cells.

The alternative pathway is activated by direct recognition of certain microbial structures and the (mannan-binding) lectin (MBL) pathway is triggered by binding of terminal mannose residues on microbial glycoproteins and glycolipids (Fig. 2). All three pathways converge in the cleavage of C3, the main complement component, to the anaphylatoxin C3a and the opsonin C3b. This cleavage initiates a cascade of further activation events. C3b is covalently deposited on the microbial surface and joins with the C3 convertase to generate the C5 convertase. This convertase again cleaves C5 into C5a (anaphylatoxin) and C5b. C5b triggers the formation of the membrane attack complex (MAC), that consists of C5b, C6, C7, C8 and polymeric C9 molecules (Fig. 2). The formation of the MAC disrupts the microbial membrane, resulting in lysis of infected cells or pathogens (Stoiber et al., 2007; Speth et al., 2008). Figure 2 summarizes the activation events of the complement cascade using the example of a viral particle.

An appropriate control of the over 30 complement proteins, that are participating in the activation of the three different complement pathways, is crucial to prevent spontaneous activation and destruction of bystander cells. Thus, the complement system is tightly controlled by the 'regulators of complement activation' or RCAs. RCAs are present in fluid phase and also membrane-bound on the surface of host cells. Among the most important RCAs are secreted fH (factor H), C4bp (C4-binding protein), MCP (membrane-cofactor protein), CD55 (DAF), CD59, and CR1 (Spear et al., 1995; Spiller et al., 1997; Da Costa et al., 1999; Carroll, 2000).

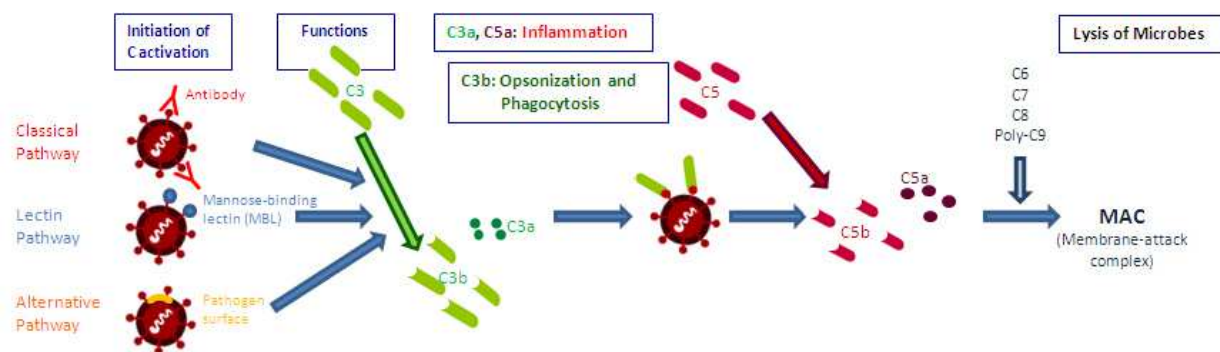


Fig. 2. Activation of Complement (C)

Upon entering the host HIV-1 spontaneously activates the complement system via gp120 and gp41, even in the absence of HIV-specific antibodies, and is hence already coated with complement fragments at the initial stages of infection. After seroconversion, adaptive immunity is fully activated, as reflected by the generation of specific anti-HIV-1 antibodies and activated T cells. Activation of complement is strongly enhanced due to the Ab-C1 interactions, and deposition of complement fragments on virions dramatically increased by virus-bound Abs. Accordingly, opsonized infectious viral particles accumulate in HIV-1-positive individuals during the acute and chronic phase of infection and complement activation results in multifaceted outcomes. Despite the clearance and neutralization of HIV-1 virions by action of complement, it also accounts for the spread and maintenance of HIV during the infection. During the budding process, HIV acquires membrane-anchored RCAs such as CD59, CD55 and binds fH in fluid-phase (Frank et al., 1996). Therefore the virus is efficiently protected from complement-mediated lysis (CoML). Only at early stages of infection, CoML is suggested to contribute to the control of the virus before the adaptive immunity is fully activated. At later stages of infection, CoML seems to play a minor role in reducing the viral burden in infected individuals (Stoiber et al., 2007; Huber et al., 2008).

HIV that is not killed by complement-mediated lysis, persists covered with C3 fragments in the host. Thus, opsonized HIV accumulates in all so far tested compartments of the host, such as blood, lymphatic tissue (LT), brain, mothers milk, or seminal fluid and is able to interact with complement receptor (CR)-positive cells, e.g. DCs, macrophages, NK cells, B cells or follicular dendritic cells (FDCs). Opsonized virions were found to bind to complement receptor-expressing cells, which can promote enhanced viral infectivity and transmission *in vitro*.

Furthermore, it was shown that complement by itself or together with dendritic cells is involved in priming antiviral T cell immunity, therefore suggesting that complement not only triggers CoML but mediates adaptive immune responses (Kopf et al., 2002; Banki/Posch et al., 2010). C3-deficiency impeded priming of CD4<sup>+</sup> and CD8<sup>+</sup> T cells in an influenza virus model (Kopf et al., 2002), thus supporting this thesis. The exact mechanisms of complement-mediated T cell priming have not yet been resolved, but as recently shown, priming of naive CD8<sup>+</sup> T cells was significantly enhanced when DCs were exposed to complement-opsonized HIV compared to DCs stimulated with non-opsonized HIV (Banki/Posch et al., 2010). This was also confirmed *in vivo* using the Friend Murine Leukemia Virus model (Banki/Posch et al., 2010). Therefore, the failure to induce efficient T cell responses in the absence of complement can be explained by the fact that dendritic cells (DCs), which ingest C3-coated pathogens via CR3 or CR4, efficiently prime CD8<sup>+</sup> T cells,

resulting in efficient activation of the adaptive immunity. Without C3 the antigen-presenting capacity of DCs, and consequently T cell priming, could be defective, which has to be further investigated. In addition, the appropriate cytokine environment for T cell priming could be altered in the absence of C3 and therefore weaken antigen-presentation.

Beside inducing T cell immunity, complement opsonization of HIV particles also accounts for the generation of a huge viral reservoir in infected individuals. This can be explained by the extracellular binding of C3d-opsonized HIV-particles to follicular dendritic cells (FDCs) in germinal centers (Kacani et al., 2000). Up to 90% of viral particles were shown to bind via C3d-CR2 interactions on FDCs, creating an additional reservoir for infectious HIV (Pantaleo, 1995; Haase, 1999).

In summary, HIV-complement interactions are very complex and contribute on the one hand to reduction of the viral load by lysis or neutralization due to opsonization, and on the other hand to spread of the virus by allowing attachment and maintenance to and on CR-expressing cells.

## 2.2 Induction of type I interferons and cytokines in acute HIV-infection

During the early stages of HIV infection, high-level viral replication, loss in CD4<sup>+</sup> T cell number and function, and an up-regulation of proinflammatory and immunoregulatory cytokines can be measured. As recently described, an ordered increase in plasma levels of multiple cytokines and chemokines was observed in acute HIV-infection (Stacey et al., 2009):

- Rapid and transient elevations in IFN $\alpha$  and IL-15 levels were succeeded by
- a large increase in inducible protein 10 (IP-10),
- rapid and sustained increases in tumor necrosis factor alpha (TNF- $\alpha$ ) and monocyte chemotactic protein-1 (MCP-1),
- a more slowly induction of proinflammatory cytokines such as IL-6, IL-8, IL-12, and IFN- $\gamma$  and
- late up-regulation of the immunoregulatory cytokine IL-10.

Plasmacytoid DCs (pDCs) act as the principal source of systemic IFN $\alpha$  production in many viral infections. pDCs were shown *in vitro* to produce cytokines following the endocytosis of HIV virions (Beignon et al., 2005) and they are responsible for early elevations in plasma IFN $\alpha$ , and together with myeloid dermal dendritic cells (DCs) in an early increase of IL-15, and TNF $\alpha$  levels. Myeloid DCs are made responsible for the slower and more-prolonged secretion of an array of cytokines including IL-6, IL-8, IL-12, IL-18, TNF $\alpha$ , and IL-10. This part of the chapter will review the most important facts about some of the cytokines and their functions in acute HIV infection.

### Type I interferons and APOBEC3G in acute HIV infection

Interferons inhibit viral replication within host cells ("interfere"), but they do also have other functions, like activating immune cells, such as NK cells or macrophages, or up-regulating antigen-presentation to T cells. IFN $\alpha/\beta$  elicit potent antiviral activities in both virally infected and non-infected cells (Katze et al., 2002) and they additionally enhance the antiviral activity of NK cells and macrophages. Furthermore, IFN $\alpha/\beta$  induce maturation of immature pDCs, which is associated with increased expression of CD83, co-stimulatory molecules and enhanced secretion of cytokines, e.g. IFN $\alpha/\beta$ , TNF $\alpha$  and IL-6 (Cella et al., 1999). IFN-secretion during infection causes symptoms like fever or aching muscles.

IFN $\alpha$  inhibits HIV replication, the mechanism by which it blocks replication of HIV *in vivo* are not known. The anti-HIV effects of IFN $\alpha$  were ascribed to a number of functions



mediated by this cytokine, including inhibition of early steps in viral replication, inhibition of HIV gene expression, and effects on viral assembly and budding. HIV-1 activates plasmacytoid dendritic cells (pDCs) via toll like receptors (TLRs) and induces the secretion of IFN $\alpha$ . IFN $\alpha$  secretion is triggered from pDCs in acute HIV-infection via TLR7, TLR8 or TLR9 signaling (Beignon et al., 2005; Lee et al., 2006; Meier et al., 2007; Mandl et al., 2008; Zhang et al., 2009). TLRs are pattern recognition receptors (PRRs), which recognize conserved motifs specific for microorganisms. Certain viral proteins and viral single- or double-stranded RNAs are detected mainly by TLRs 7 [ssRNA]/8 [ssRNA]/9 [dsRNA] (Kadowaki et al., 2001; Diebold et al., 2004; Mandl et al., 2008). In acute HIV infection IFN $\alpha$  has a protective role, while chronic immune activation and inflammation associated with the production of type I interferon are major determinants of disease progression in primate lentivirus infections (Stoddard et al., 2010). IFN $\alpha$  drives the expression of several IFN regulatory factors (IRFs), and the induction of IFN-stimulated genes (ISGs) by an autocrine positive feedback loop. In turn, ISGs promote proliferation of immune cells and induce an antiviral state in cells.

IFN $\alpha$  was also demonstrated to potently induce APOBEC3G (Apolipoprotein B mRNA-editing enzyme-catalytic polypeptide-like 3G) to abrogate HIV Vif neutralization of APOBEC3 proteins (Peng et al., 2006). APOBEC3G, a cytidine deaminase, is an innate intracellular protein with lethal activity against HIV and exerts this intrinsic anti-HIV activity by introducing lethal G-to-A hypermutations in the viral genome (Casartelli et al., 2010). While HIV<sup>+</sup> patients with progressive disease show a significant decline in pDCs over time, long term non-progressors (LTNPs) maintain high levels of these cells and this may be of importance in the innate response in these patients.

#### **TNF- $\alpha$ in acute HIV infection**

TNF- $\alpha$  is a pro-inflammatory cytokine that mediates many inflammatory and immune functions (rev. in Armitage, 1994). It is produced by NK cells, macrophages, monocytes, T cells, B cells and neutrophils and exerts its actions via binding to TNF-R1 and TNF-R2. Attachment of HIV to TNF-R1 and subsequent activation of NF $\kappa$ B were demonstrated to significantly increase HIV-1 replication in cells of the macrophage lineage (Griffin et al., 1991; Naif et al., 1994; Herbein and Gordon, 1997). This enhancement was further amplified by IFN- $\gamma$  (Han et al., 1996) and a positive autocrine TNF- $\alpha$  loop initiated by HIV-1 infection of monocyte-derived macrophages resulted in increased HIV-1 production (Esser et al., 1991, 1996, 1998). In contrast, ligation of TNF- $\alpha$  to TNF-R2 resulted in inhibition of HIV-1 replication (Herbein and Gordon, 1997).

#### **Interleukins**

##### **IL-15 in acute HIV-infection**

The activation of DCs by HIV determines a progressive accumulation of various cytokines, including IL-15, which subsequently acts as potent inducer of NK cell activation and cytotoxicity. DC-NK cell cross-talk represents a key mode of the cellular network regulating the links between innate and the adaptive immune response (Moretta, 2002; Moretta et al., 2006). IL-15 is produced during acute HIV-1 and SIV (simian immunodeficiency virus) infection and exerts an influence on viremia and viral set point. The viral set point was significantly increased during acute SIV-infection upon administration of IL-15. To identify cytokine biomarkers in plasma during acute HIV-1 infection that predict HIV disease progression, 30 cytokines were tested in 40 South African women in acute infection and 12

months post infection. Only a small panel of plasma cytokines during acute HIV-1 infection was predictive of long-term HIV disease prognosis in this group, namely IL-12p40, IL-12p70, IFN- $\gamma$ , IL-7 and IL-15. While IL-12p40, IL-12p70 and IFN- $\gamma$  were significantly associated with lower viral load, IL-7 and IL-15 were associated with higher viral load (Roberts et al., 2010).

#### **IL-6 in acute HIV-infection**

IL-6 is a pro-inflammatory cytokine produced by macrophages, DCs, T and B cells in response to bacterial and viral infections. IL-6 mediates B cell stimulation, monocyte differentiation and induction of IL-4-producing cells (Rincon et al., 1997). It helps augmenting HIV-1 replication in macrophages and U1 cells (macrophage lineage) and enhances TNF- $\alpha$ -induced up-regulation of HIV-1 production (Poli et al., 1990; Poli and Fauci, 1992).

#### **IL-10 in acute HIV-infection**

IL-10 is an anti-inflammatory cytokine produced by monocytes/macrophages, DCs and activated T and B cells. This cytokine blocks macrophage activation and inhibits secretion of the pro-inflammatory cytokines IL-1, IL-6, IL-8, IL-12 or TNF- $\alpha$  (rev. in Moore et al, 2002). IL-10 was shown to interfere with HIV-infection at the early stages of HIV-1 infection although it does not alter CCR5 surface expression (Montaner et al., 1994; Wang et al., 1998). Pre-treatment of monocytes with IL-10 significantly decreased HIV-1 RNA expression and this inhibition of HIV replication was associated with down-modulation of IL-6- and TNF- $\alpha$  production by IL-10 (Weissman et al., 1994; Naif et al., 1994).

### **2.3 Induction of $\beta$ -chemokines (MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES) in acute HIV-infection**

MIP-1 $\alpha$  (CCL3), MIP-1 $\beta$  (CCL4) and regulated upon activation normal T-cell expressed and secreted (RANTES, CCL5) were the first three factors of the  $\beta$ -chemokine family identified as suppressors of HIV infection (Cocchi et al., 1995). These chemokines have been identified to bind the G-protein coupled receptors CCR5, which acts as co-factor for macrophage-(R5) and dual-(R5X4)-tropic HIV-1 strains. Similarly, the ligand of CXCR4, SDF-1 (CXCL12) was shown to suppress infection with T cell-(X4)-tropic HIV strains (Bleul et al., 1996; Oberlin et al., 1996). Polymorphisms in the CCR5 locus, in particular a 32 bp gene deletion (CCR5 $\Delta$ 32) results in a decreased susceptibility to infection with macrophage-(R5)-tropic HIV-1 strains (Kramer et al., 2005). CCR5 $\Delta$ 32- heterozygotic individuals can be infected with R5-tropic HIV, but exhibit a significantly slower disease progression, whereas CCR5 $\Delta$ 32-homozygotic individuals are susceptible to infection with X4-tropic HIV-1 strains.

## **3. Interactions of HIV with cellular components of the innate immune system**

Very little is known respecting the earliest events after HIV transmission in the genital tract or the rectal mucosa and most findings about these early events were acquired from *in vivo* models of SIV-infected macaques (Haase, 2005). The *in vivo* SIV models and *ex vivo* analyses in the human system pursue to identify cells and soluble factors involved in HIV-transmission (Haase, 2005; Hladik and McElrath, 2008). R5-tropic HIV-1 particles are selectively captured by epithelial cells and subsequently transferred to CCR5-expressing target cells underneath the epithelia. This could be responsible for the selective preferential transmission of R5-tropic HIV-1 strains (Meng et al., 2002). Langerhans cells (LCs) or other

dendritic cells are present at the port of the mucosal entry site (in the underlying tissues of the vagina and cervix) and trap pathogens with their processes that extend to the luminal surface. Thus, viruses cross the mucosal barrier by attachment or infection of DCs, by transcytosis (M cells) or by infection of intraepithelial lymphocytes and macrophages (Fig. 3). Various cells of the innate immune system account for building the first line defense against HIV until the adaptive immune response is fully developed. Among those are LCs, myeloid DCs, pDCs, that recruite and activate NK cells (Fig. 3), macrophages, and NKT cells, which will be discussed in this part of the chapter.

3.1 Dendritic cells in acute HIV infection

Dendritic cells are the most potent antigen-presenting cells and can be divided into conventional myeloid DCs (LCs, dermal DCs, blood DCs) and plasmacytoid DCs (Table 1, adapted from *Altfeld et al., 2011*). They differ respecting their location, their C-type lectin and TLR expression, their role in HIV-infection, their cytokine production and their function (Table 1, *Altfeld et al., 2011*). As described very recently (*Sabado et al., 2010*), depletion of both, myeloid and plasmacytoid DCs from the circulation already occurs during the early

	Conventional DCs (CD11c <sup>+</sup> HLA-DR <sup>+</sup> )		Plasmacytoid DCs (CD123 <sup>+</sup> HLA-DR <sup>+</sup> )
	Langerhans Cells	Dermal Dendritic Cells	
		CD103 <sup>-</sup> CD103 <sup>+</sup>	
Location	Stratified squamous epithelium of the skin and oral and ano-genital mucosa	Dermis	Blood Secondary lymphoid organs Peripheral tissues (Skin, Lungs)
C-type lectin expression	Langerin	DC-SIGN DEC-205    Langerin DEC-205	BDCA-2
TLR expression	TLR2,3,5	TLR2,3,4,5	TLR7, 8, 9
Role in HIV-infection	Degradation of HIV in Birbeck granules	HIV shuttle and transfer    Unknown	•Production of type I interferons: antiviral and induction of bystander T cell death •Induction of Treg cells by HIV-induced IDO up-regulation •Recruitment of T cells to sites of HIV-infection, thus facilitating viral spread
Cytokine production	IL-1β, IL-6, IL-8, IL-12, IL-15, IL-23	IL-1β, IL-6, IL-8, IL-12, IL-15, IL-23	IFNα, IFNβ, IL-6, TNF
Function	•Prime Ag-specific T cells and B cells •NK cell activation by IL-12	•Prime Ag-specific T cells and B cells •NK cell activation by IL-12	•Treg induction •Plasma cell induction •NK cell activation by IFNs
Pathology during HIV-infection	•Reduced frequency in peripheral blood •Conflicting results respecting dysfunction and functionality	•Reduced frequency in peripheral blood •Conflicting results respecting dysfunction and functionality	•Reduced frequency in peripheral blood •Conflicting results respecting dysfunction and functionality

Table 1. DC-subsets and functions during HIV-infection (adapted from *Altfeld et al., 2011*, blood DCs not portrayed)



phases of HIV infection. The depletion from the circulation is suggested to be due to preferential re-distribution of both DC types from blood to lymphoid organs. This re-distribution is based on the ability of the DCs to up-regulate chemokine-receptor 7 (CCR7), that causes migration of DCs to the lymph nodes along a CCL19/CCL21 gradient. The reduction in circulating DC numbers was shown not to be transient, but also detectable in the chronic phase of infection and under highly-active antiretroviral therapy (Sabado et al., 2010). Restoration of circulating DCs might represent a key factor in providing an improved immune response against the virus.

### 3.1.1 Langerhans cells and HIV

Langerhans cells (LCs) build the first line defense against mucosal infections because they are situated ideally in mucosal tissues to catch pathogens (Fig. 3). LCs survey the basal and suprabasal layers of the stratified squamous epithelium of the skin and oral and ano-genital mucosa for invading pathogens (Katz et al., 1979; Romani et al., 1985; rev. in DeJong and Geijtenbeek, 2010). Upon capture of Ags, LCs start to mature, which is represented by up-regulation of CCR7, co-stimulatory molecules CD80/CD86/CD40, MHC class I and class II molecules and CD83 and by down-regulation of Langerin and E-cadherin (Merad et al., 2008). These mature LCs migrate to the lymph node to present the captured Ag to T cells, thus inducing an efficient immune response (Merad et al., 2008). Despite their important function in initiating adaptive immune responses, LCs additionally exert innate immune functions as recently shown (De Witte et al., 2007). LCs characteristically express a specific set of TLRs (TLR2, 3, 5), high levels of CD1a, the C-type lectin Langerin and intracellular Birbeck granules that might be crucial to their innate function (Valladeau et al., 2000; Liu, 2001; Flacher et al., 2006; Fahrbach et al., 2007; Romani et al., 2010). Langerin interacts with HIV-1 and other pathogens like fungi and bacteria. After heterosexual contact with an HIV-infected individual, the chance to acquire HIV-1 is very low (0.01-0.1%) (Wu and KewalRemani, 2006) and LCs are the first cells to encounter HIV due to their location in the mucosal stratified epithelium. Attachment of HIV-gp120 to Langerin leads to internalization of the viral particle and subsequent degradation in the Birbeck granules, that are characteristic for LCs (De Witte et al., 2007). Thus, LCs are protected from infection with incoming, non-opsonized HIV particles and HIV-1 is not disseminated through the host (De Witte et al., 2007). Although LCs express the primary receptor for HIV-1, CD4, and the chemokine co-receptor CCR5, they are not productively infected by the virus. This is probably due to efficient capture of the virus by Langerin and targeting of HIV-1 to Birbeck granules, where it is degraded (De Witte et al., 2007). The rapid internalization of HIV-1 into LCs prevents also transmission to the main target cells of the virus, CD4<sup>+</sup> T cells. The degradation of HIV in Birbeck granules and the prevention of virus transfer to CD4<sup>+</sup> T cells renders Langerin as a protective anti-HIV barrier. When, in addition, sexually transmitted infections (STIs) are present, the anti-HIV-1-barrier of LCs is abrogated and HIV-1 transmission to CD4<sup>+</sup> T cells by LCs is promoted (DeJong et al., 2008, 2010; Ogawa et al., 2009). The by-passing of the anti-HIV-effect due to additional STIs results from direct interaction of the STIs with Langerin and therefore competition for HIV-1 binding, Langerin inhibition by high viral loads, lower Langerin surface expression by Poly(I:C) or HSV2 (DeJong et al., 2010), up-regulation of HIV entry receptors and down-regulation of restriction factors (Ogawa et al., 2009), or inflammation-induced TNF- $\alpha$  production by

*Candida albicans* or *Neisseria gonorrhoea* (DeJong et al., 2008). In summary, during acute co-infection the anti-viral function of LCs is significantly reduced due to competition for Langerin. This facilitates HIV-1 infection of LCs and thereby promotes HIV-1 transfer to and infection of CD4<sup>+</sup> T cells.

### 3.1.2 Dermal dendritic cells and HIV

In addition to LCs, interstitial dendritic cells are among the first cells to encounter HIV at mucosal surfaces (Fig. 3). They are underlying the epithelium and differ from LCs, since they do not contain Birbeck granules and express heterogeneous amounts of CD1a (Bell et al., 1999). Interstitial DCs are localized in the dermis and oral, vaginal and colonic lamina propria (Pavli et al., 1990, 1993; Lenz et al., 1993; Nestle et al., 1993; McLellan et al., 1998). They are characterized by the expression of CD11c, high concentrations of various C-type lectin receptors, TLRs 2, 3, 4 and 5 and secretion of IL-1 $\beta$ , IL-6, IL-10, IL-12, IL-15, and IL-23 upon pathogenic stimulation (Liu, 2001). Also dermal dendritic cells can be functionally divided in immature and mature DCs (iDCs, mDCs) based on their T cell stimulatory capacity (Banchereau and Steinman, 1998). Following antigen exposure, iDCs undergo major changes and mature (described under 3.1.1). Upon entry of HIV into the host, the virus has to be transported from mucosal surfaces to lymphatic tissues, where it is transmitted to its primary targets, CD4<sup>+</sup> T lymphocytes. As mentioned above, this process is thought to be contrived by DCs. By clustering T cells, DCs may both activate antiviral immunity as well as facilitate spread of the virus. *In vitro* experiments showed that DCs efficiently capture and transfer HIV to T cells and initiated a vigorous infection (Pope et al., 1995; McDonald et al., 2003; Pruenster/Wilflingseder et al., 2005; Wilflingseder et al., 2007). These experiments imply that *in vivo* HIV exploits DCs at mucosal sites as shuttles to CD4<sup>+</sup> T cells in the lymph nodes. Preferential expression of CCR5 on immature LCs and DCs restricts the transmission of X4-tropic isolates at the site of infection. Additionally, *ex vivo* analyses revealed that X4-tropic HIV replicate worse in DCs and LCs compared to R5-tropic viruses (Granelli-Piperno et al., 1998; Kawamura et al., 2000; Ganesh et al., 2004). Productive infection of DCs and LCs with HIV is relatively inefficient compared to HIV-infection of CD4<sup>+</sup> T cells and HIV- or SIV-infected DCs are rarely detected *in vivo* (rev. in Piguet and Steinman, 2007). Virus is very efficiently transmitted to T cells either via de novo ('*cis*'-transfer) or without ('*trans*'-) infection despite the low-level productive infection of DCs (Turville et al., 2004). Especially C-type lectins such as Dendritic cell-specific ICAM-3-grabbing non-integrin (DC-SIGN) on dermal DCs was implicated in the transfer of HIV to T cells in the lymph nodes (Geijtenbeek et al., 2003; Turville et al., 2004). Similar to Langerin, DC-SIGN has high affinity for mannose and fucose structures. Dermal iDCs express the C-type lectin DC-SIGN and recently a second dermal DC subtype, expressing CD103 and Langerin, but no Birbeck granules, was described (Ginhoux et al., 2009). DC-SIGN captures low titres of HIV-1 through its interaction with the HIV-1 glycoprotein gp120 (Geijtenbeek et al., 2000) and this DC-SIGN/virus interaction protects HIV from degradation within the cells in contrast to the anti-viral action of Langerin on LCs (Geijtenbeek et al., 2000). DC-SIGN-complexed HIV-1 is stable and retains the infectivity for prolonged periods in contrast to DC-SIGN-bound antibody and probably other ligands that are internalized into lysosomal compartments for processing (Geijtenbeek et al., 2000; Engering et al., 2002). These studies suggest that DC-SIGN-bound HIV-1 particles hide near the cell membrane in DCs and are not degraded. After ligating DC-SIGN, HIV is indeed transported into non-lysosomal acidic organelles. Thereby, DC-SIGN effectively transmits HIV

to CD4<sup>+</sup> T cells and also leads to enhancement of infection in these co-cultures and facilitates 'trans'-infection of the T cells (Geijtenbeek et al., 2000).

Besides C-type lectins, other molecules, such as adhesion molecules e.g. ICAM-1 (Pruenster/Wilflingseder et al., 2005) are described to further contribute to DC-HIV interaction. In all compartments tested so far (plasma, seminal fluid, lymphatic tissues), HIV is opsonized with C3 complement fragments and after seroconversion additionally with HIV-specific IgGs. Similar to the interaction of non opsonized HIV with C-type lectin receptors on DCs, receptors such as complement receptors (CRs) or Fc receptors (FcR) contribute to the attachment of the complement- or IgG-coated virus. If the virus is opsonized, the DC-SIGN- or ICAM-dependent interactions play a minor role for the attachment of HIV to DCs as well as the DC-mediated *cis* and *trans* HIV-infection (Pruenster/Wilflingseder et al., 2005). Complement-opsonization of HIV significantly enhanced the productive infection of DCs compared to non-opsonized HIV and also acted as an endogenous adjuvant for the DC-mediated induction of virus-specific CTLs (Wilflingseder et al., 2007; Banki/Posch et al., 2010). These results emphasize a role of DCs in combination with complement-coating of the virus in priming adaptive T cell responses. Vigorous *trans*-infection of CD4<sup>+</sup> T cells by DCs was shown to be promoted by infectious synapse formation independent on the attachment mechanism (C-type lectin receptors, adhesion molecules, CRs [own unpublished observations]) (rev. by Piguet and Sattentau, 2004). The receptors involved in the HIV attachment have to be re-arranged and are recruited to the DC-T cell junctions (McDonald et al., 2003). Microscopic analyses of DC-CD4<sup>+</sup> T cells revealed re-arrangement and recruitment of CD4 and chemokine-co-receptor to the infectious synapse on the T cell site and of HIV on the DC site (McDonald et al., 2003). Thereby, dermal DCs contribute not only to shuttle HIV from the mucosal site to the lymphatic tissue but also to efficiently transmit of HIV to its main targets, CD4<sup>+</sup> T cells.

Beside the support of DCs in HIV dissemination, DCs produce high amounts of cytokines, such as IL-12 or interferons, which belong to the first line of the host defense against invading organisms. They are also able to activate NK cells via secretion of pro-inflammatory cytokines (IL-12, IL-15, IL-18) and other factors, thus enhancing their cytotoxicity to virally infected cells (Chehimi et al., 1989; Mellman and Steinman, 2001; Yu et al., 2001).

In terms of modulation of DC function by HIV infection *in vivo*, it is not clear if DC defects are resulting from the direct exposure to HIV or if they are due to production of host cell factors during infection. Circulating lipopolysaccharide (LPS) or other pathogen-derived factors were also implicated in chronic immune activation, which is monitored during HIV infection (Brenchley et al., 2006). Bacterial stimuli like LPS could result in maturation of iDCs thus rendering these cells tolerant to subsequent stimuli. *Ex vivo* tests of DCs from chronically infected individuals demonstrated that they were less potent in responding to other TLR stimuli as well as in stimulating T cell responses compared to DCs from non-infected individuals (Donaghy et al., 2003; Martinson et al., 2007).

DCs are furthermore involved in the generation of regulatory T cells and thus induce both, immunity and tolerance. DCs shown to induce tolerance are plasmacytoid DCs (pDCs). (Steinman, 2000).

### 3.1.3 pDCs and HIV

Plasmacytoid DCs or type 1 IFN-producing cells, are innate immune cells specialized in releasing massive amounts of IFN $\alpha$  and IFN $\beta$  upon viral challenge, including HIV (Fig. 3)

(Siegal et al., 1999). This blood DC population expresses high levels of HLA-DR and the characteristic markers BDCA-2 and CD123 (Table 1), but not CD11c, a marker of myeloid DCs (Table 1) (O'Doherty et al., 1994; Dzionek et al., 2001). pDCs are key initiators of the innate immune response *in vivo* and they can prime adaptive immunity due to the aforementioned production of high type I interferon levels, especially upon exposure to viral products (Cella et al., 1999; Siegal et al., 1999). pDCs recognize pathogenic single-stranded RNA or unmethylated DNA mainly by TLR7 and TLR9. Due to the intracellular localization of these TLRs, the viruses have to be ingested by the cells and endosomal maturation must occur to activate NF $\kappa$ B- and MAPK-signals through MyD88. Once activated, pDCs mature and produce large amounts of pro-inflammatory and antiviral cytokines (Kadowaki et al., 2000; Ito et al., 2002; Colonna et al., 2004). pDCs do not only act as pro-inflammatory cells, but also provide negative regulatory signals and thereby induce tolerance (Ochando et al., 2006). pDCs express indoleamine 2,3-dioxygenase (IDO) and programmed death ligand 1 (PDL-1) that are associated with the negative modulation of T cell responses and regulatory T cell induction (Boasso et al., 2007, 2008; Chen et al., 2008). As shown, constant exposure of pDCs to HIV results in their chronic hyperactivation coming along with production of type I interferon and IDO, which exerts cytotoxic as well as suppressive effects on T cells (Herbeuval and Shearer, 2007). In acute HIV-infection pDCs recruit and activate NK cells to the sites of infection as well as to the lymph nodes (Gerosa et al., 2002; Megjugorac et al., 2004). The activation is due to IFN $\alpha$  released from pDCs, which was demonstrated to induce increased perforin expression in NK and CD8<sup>+</sup> T cells. The pDC-NK cell activation is bi-directional, since activated NK cells deplete immature pDCs to possibly select the more immunogenic mature pDCs at the sites on infection (Pertales et al., 2003a, 2003b; Ferlazzo and Munz, 2004). This process is called 'DC-editing' (Ferlazzo et al., 2002). Beside NK cell recruitment and activation, pDC-produced IFN $\alpha$  promotes maturation and migration of DCs. pDCs are not as efficient in antigen-presentation as myeloid DCs and they are not located in high amounts at the site of pathogen entry. Due to their spontaneous antiviral and NK priming activity they are supposed to control the virus in the acute phase of infection and it is unlikely that they are involved in HIV capture, transport and transmission.

Deficiencies in pDC function were among the earliest observations of immune dysfunction in HIV-1 infection. Loss of pDCs in blood of chronically infected individuals has been ascribed to cell death and/or to a failure of bone marrow progenitors to differentiate into pDCs. Additionally, a low productive virus replication of IFN $\alpha$ -producing pDCs has been shown *in vivo* and *in vitro* by R5- and X4-tropic HIV variants (Donaghy et al., 2003; Schmidt et al., 2004). It is not known so far, if infection of pDCs plays a role for IFN $\alpha$ -secretion.

### 3.2 NK and NK T cells in acute HIV infection

Natural killer (NK) cells are lymphocytes deriving from bone marrow precursors. They circulate as mature populations in blood and spleen and are activated by type I interferons (Fig. 3). Classical NK cells do not express T cell antigen receptors (TCR) and are CD3-negative. They produce high levels of certain cyto- and chemokines, such as MIP-1 $\alpha$ , MIP-1 $\beta$ , RANTES, TNF $\alpha$ , GM-CSF or IFN- $\gamma$  and mediate significant levels of cytotoxic activity by exocytosis of granules containing perforin and granzymes. NK cells thus efficiently contribute to innate immune responses due to their spontaneous cytotoxic action against tumor and virus-infected targets. The direct cytotoxic activity of NK cells is regulated by the



balance of activating and inhibitory NK cell receptors (Moretta et al, 2001; Moretta, 2002; Lanier, 2005) and they are able to kill HIV-infected target cells by direct lysis or by antibody-dependent cell-mediated cytotoxicity (ADCC) (Tasca et al, 2003; Bonaparte and Barker, 2004). ADCC is mediated in classical NK cells through their cell surface receptors for immunoglobulins (FcR). Additionally, NK cells initiate priming of the adaptive immunity due to their cross-talk with DCs. As mentioned above, NK cells activate DCs by cell-cell contact or secretion of cytokines and vice versa, DC-derived cytokines and membrane-bound molecules play a key role in NK cell activation (Zitvogel, 2002; Andrews et al, 2003; Ferlazzo et al, 2004; Cooper et al., 2004; Moretta et al, 2006; Newman et al, 2006). Their killer inhibitory receptors (KIRs), which transmit an inhibitory signal, if they encounter MHC class I molecules on a cell surface, are crucial in killing virus-infected cells. Two subsets of classical NK cells can be distinguished by their expression of CD16 and CD56. >95% of the NK cells belong to the CD16<sup>high</sup>CD56<sup>low</sup> subset, which is responsible for the direct lysis of cells and the ADCC (Nagler et al, 1989; Caligiuri et al, 1990). The remaining 5% CD16<sup>low/-</sup>CD56<sup>high</sup> subset produces high concentrations of IFN- $\gamma$  and TNF- $\alpha$ , but this sub-population exerts a very low cytotoxic potential (Ahmad and Menezes, 1996). In HIV-infected individuals NK cell responses were shown to be impaired and the defects comprised cytotoxic activity of NK cells as well as secretion of CCR5-ligands MIP1 $\alpha$ , MIP1 $\beta$  and RANTES (Scott-Algara et al, 1992; Mavilio et al, 2003; Kottlilil, 2003). The HIV-mediated impairment of NK cells becomes manifest early after infection and continues during HIV progression and can be attributed to several factors:

HIV-infected individuals might have a down-regulation in intracellular perforin and granzyme A stores, which would account for the decreased cytotoxic capacity of NK cells in HIV-infection (Portales et al., 2003).

Another explanation might be the change in the expression patterns of various activating and inhibitory NK cell receptors during HIV-infection (DeMaria et al., 2003).

Chronic viral stimulation may also lead to inappropriate activation of peripheral NK cells, thus resulting in NK cell exhaustion or anergy (Alter et al., 2005; Mavilio et al., 2005).

Finally, CD4<sup>+</sup> NK cells may be a reservoir for HIV-1 *in vivo* and further investigation is necessary to explore this possibility.

A population of T cells sharing characteristics with classical NK cells has been identified based on expression of NK cell markers, and this population was named NK T cells (McDonald, 1995). NK T cells, a rare population of T lymphocytes, comprise only 0.01 ~ 1% of human peripheral blood mononuclear cells and play an important role in the innate immune defense (Motsinger et al, 2002). NK T cells are important immunoregulatory cells, producing both, high amounts of IFN- $\gamma$  ( $\Rightarrow$  double-negative NK T cells), a major T<sub>H</sub>1 cytokine, and IL-4 and IL-13 ( $\Rightarrow$  CD4<sup>+</sup> NK T cells), the major T<sub>H</sub>2 type cytokines (Gumperz et al, 2002; Lee et al, 2002). Thus NK T cells may provide quicker help for a cell- (IFN- $\gamma$ ) or antibody-mediated (IL-4) response than conventional T cells through recruiting and stimulating other effector cells, such as NK cells, macrophages, DCs and conventional T cells. NK T cells can in addition act directly cytolytic through involving the perforin/granzymes and the Fas/FasL pathway (Metelitsa et al., 2001).

A semi-invariant TCR (NK T TCR) is expressed on NK T cells consisting of an invariant  $\alpha$ -chain, and a restricted TCR- $\beta$ -chain repertoire (rev. in Godfrey and Kronenberg, 2004). NK T cells recognize self or foreign glycolipids presented by the non-polymorphic MHC class I-

like molecule CD1d (Bendelac et al, 1997; Joyce, 2001). NK T cells are stimulated by type I interferons or pro-inflammatory cytokines (IL-15, IL-12, IL-18). Therefore, also NK T cells need a cross-talk with DCs to be fully activated (pDCs  $\Rightarrow$  type I IFNs, DCs  $\Rightarrow$  IL-12).

Upon HIV-1 infection NK T cells are rapidly and selectively depleted from the circulation. The NK T cell numbers are dramatically reduced in HIV-infected individuals compared to healthy donors (Motsinger et al., 2002; Van der Vliet et al, 2004). *In vivo* studies showed that the decrease in NK T cell numbers significantly correlated with higher viral loads in infected individuals (Motsinger et al., 2002) and that these HIV-susceptible cells were rapidly destroyed *in vitro* by R5-tropic HIV-strains (Motsinger et al., 2002). The mature NK T phenotype is induced by persistent stimulation of the cells with unidentified self-Ags or Ag-independent mechanisms and the high expression of CCR5 on the surface renders NK T cells permissive for HIV. They are not only efficiently infected by HIV but also contribute to the viral spread due to activating resting by-stander CD4<sup>+</sup> T cells (Unutmaz et al., 1999).

The rapid loss of NK T cells during early HIV-infection causes subsequent depletion of important immunoregulatory functions, which are involved in tumor immunity, defense against other invading pathogens and autoimmune diseases. This might facilitate establishment of other opportunistic infections or tumor development frequently detected at later stages of the disease. NKT cells are important cells of the innate immune system, which are selectively and rapidly depleted by HIV-1 infection. Stimulation of the surviving NK T cells is additionally impeded due to down-regulation of CD1d on antigen-presenting cells.

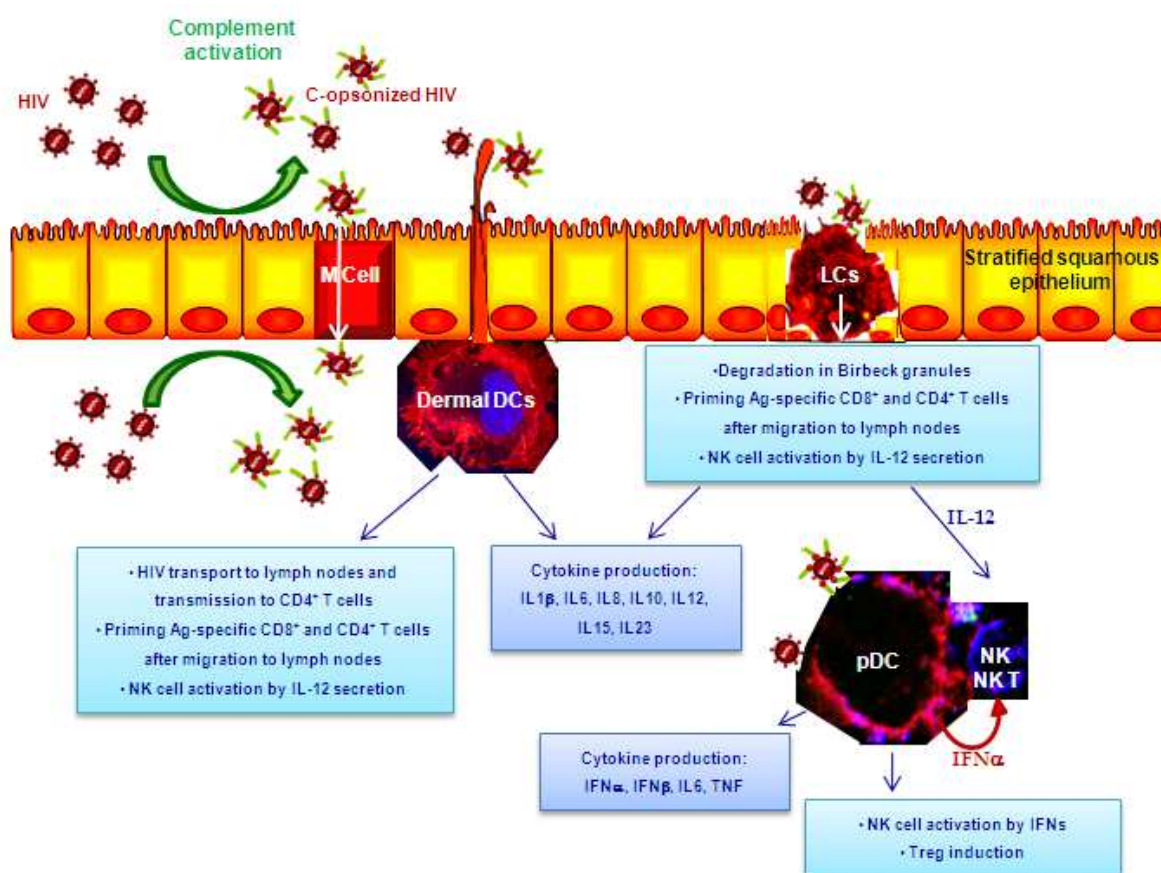


Fig. 3. Functions of DCs and NK/NK T cells during acute HIV infection

### 3.3 Macrophages in acute HIV infection

Macrophages resident at mucosal sites are proposed to play an important role during HIV-1 pathogenesis. Macrophages bridge innate and adaptive immunity similar to DCs, NK and NK T cells. They are recognizing, internalizing and degrading microorganisms and clear cell debris via TLRs, C-type lectins (Dectin-1), Fc receptors and complement receptor 3. Furthermore, macrophages present pathogen-derived peptides via MHC class II, thus initiating adaptive immune responses, and secrete pro-inflammatory cytokines. Upon HIV-infection they are among the first cells encountered by the virus, but they are able to resist to HIV-mediated cytopathic effects. Therefore, macrophages are thought to serve as major cellular HIV reservoir together with latently infected resting CD4<sup>+</sup> T cells for long-term infection. Productively infected macrophages were detected in both untreated patients and those receiving antiretroviral therapy (ART), but the HIV infection within macrophages was not associated with virus-induced cytopathic effects (Koenig et al, 1986; Sharkey et al, 2000). The infectious virus is retained in macrophages for a prolonged period of time and the virus may be released from macrophages delayed and in a different compartment – thus macrophages contribute to persistence and spread of the virus (Crowe et al., 2003; Montaner et al., 2006; Carter and Ehrlich, 2008). As detected in NK or NK T cells, the functions of macrophages were found to be impaired by HIV-1 infection *in vitro* and *in vivo*. *In vivo* macrophages from HIV-infected individuals were found to be defective for phagocytosis of apoptotic cells (Torre et al., 2002). *In vitro* HIV-1 impeded with phagocytosis via CR3 or FcR and also impaired internalization of *Candida albicans* and *Toxoplasma gondii* (Crowe et al., 1994; Kedzierska et al., 2002; Azzam et al., 2006; Leeansyah et al., 2007). As recently shown, Nef was a crucial factor in disrupting phagocytosis in HIV-1-infected cells (Mazzolini et al., 2010).

HIV and its accessory genes alter macrophage immune responses, macrophage cell cycle and enhance their own viral replication in macrophages (Margottin et al, 1998; Hassaïne et al, 2001; Federico et al, 2001; Coberley et al, 2004; Olivetta et al, 2005). HIV mediated a pro-inflammatory gene expression pattern in macrophages as demonstrated by microarray analyses, and this pro-inflammatory cytokine profile is suggested to enhance virus replication and persistence of chronically activated macrophages *in vivo*. In addition to up-regulation of pro-inflammatory cytokines, IFN- and NFκB-responsive cyto- and chemokines were increased upon HIV-1 infection. Up-regulation of these IFN- and NFκB-responsive cyto- and chemokines may promote recruitment of CD4<sup>+</sup> T cells and macrophages to sites of infection, which would promote the viral spread (Cicala et al, 2002; Izmailova et al, 2003; Woelk et al, 2004). Only low expression levels of CD4 are detected on the surface of macrophages; in contrast high levels of heparan sulfate proteoglycans (such as syndecan), macrophage mannose receptor (MR), and elastase are expressed (Nguyen and Hildreth, 2003; Bristow et al, 2003; De Parseval et al, 2005). HIV can attach and internalize into macrophages via these receptors. Expression of both chemokine co-receptors, CCR5 and CXCR4, was verified on primary human macrophages, and they can be infected with R5-, dual- and X4-tropic virus isolates *in vitro* and *in vivo* (Verani et al, 1998; Liu et al, 1996; Samson et al, 1998; Clapham and McKnight, 2002). Once ingested by macrophages, HIV accumulates in endocytic compartments similar to multivesicular bodies, which facilitate HIV assembly and escape immune surveillance (Kramer et al, 2005). This accumulation of HIV in the cytoplasmic vesicles of macrophages results in persistent storage of infectious virions and a delayed rapid infection of CD4<sup>+</sup> T cells (Sharova et al, 2005). When a virological synapse is formed between a macrophage and a T cell, the virus is efficiently

transmitted. Therefore tissue macrophages were claimed to act as 'Trojan horse', that hide the virus from the immune system and disseminate the virus even after months.

### 3.4 Monocytes in acute HIV infection

Similar to DCs, LCs and macrophages, monocytes provide a first line of defense against invading pathogens and act as key mediators of innate immune mechanisms. On the other hand, they are also targets for monocyte-tropic pathogens, such as *Listeria*, cytomegalovirus and HIV (Drevets and Leenen, 2000). Monocytes express CD4, CCR5 and CXCR4 and are in particular susceptible to macrophage-tropic HIV strains. Similar to macrophages, monocytes are resistant to the cytopathic effects of HIV, they represent a key virus reservoir and may also disseminate HIV in different locations such as the brain (Kedzierska and Crowe, 2002; Crow et al., 2003). Early in acute infection, HIV and SIV enter the central nervous system (CNS) and macrophages and monocytes seem to play a crucial role in the neuropathogenesis of HIV-infection and to contribute to HIV-mediated dementia due to production of pro-inflammatory cytokines and neurotoxins (Chakrabarti et al., 1991; Kedzierska and Crowe, 2002). The induction of pro-inflammatory cytokines is thought to facilitate the entry of monocytes into the brain by disrupting the blood-brain and blood-cerebrospinal fluid barrier (Persidsky et al., 2000; Eugenin and Berman, 2003). In particular, CCL2 was associated with inflammation of the CNS (Mahad and Ransohoff, 2003). This cytokine is mainly secreted by monocytes and macrophages and initiates migration of T cells and other monocytes into the CNS and promotion of neuronal cell-death during HIV and SIV infection (Gartner and Liu, 2002; Fantuzzi et al., 2003). HIV-1 Tat activates microglial and perivascular cells to produce pro-inflammatory proteins, thereby leading to monocyte infiltration into the brain (Pu et al., 2003). Other features promoted by Tat following infection with HIV were chemotaxis of monocytes, their adhesion to the endothelium, and their recruitment into extra-vascular tissues. This modulation of the chemotactic activity seems to be mediated by the Tat cysteine-rich domain (Albini et al., 1998).

Thus, monocytes represent a principal reservoir for HIV persistence due to the long storage period of infectious viral particles and infectious HIV was shown to be recovered from patients obtaining ART. HIV thus affects multiple immune functions of monocytes/macrophages (chemotaxis, phagocytosis, intracellular killing, APC function, cytokine production) and thereof allows establishment as well as re-activation of other opportunistic infections (Kedzierska and Crowe, 2002).

### 3.5 $\gamma\delta$ T cells in acute HIV infection

$\gamma\delta$ T cells are primarily situated in the gastrointestinal mucosa and play an important role in the first line of defense against viral, bacterial, and fungal pathogens.  $\gamma\delta$ T cells make up 50% of all lymphocytes in the intraepithelial compartment and about 10% of lymphocytes in the lamina propria (James et al., 1986; Targan et al., 1995).  $\gamma\delta$ T cells recognize soluble protein and non-protein Ags, but the mechanism of recognition remains elusive.  $\gamma\delta$ T cells participate in the immune response to various viruses, including herpes simplex virus, Epstein-Barr virus, and HIV-1 (Maccario et al., 1995). Co-culture of  $\gamma\delta$ T cells with HIV-1 infected lymphocytes resulted in increased cytotoxicity and production of HIV-1-suppressive mediators against the infected cells (Wallace et al., 1996; Poccia et al., 1999; Cipriani et al., 2000). HIV-1 infection is accompanied by significant changes in the blood and mucosal  $\gamma\delta$ T



cells during acute infection and, despite HAART, persist into the chronic phase, but the factors involved in these changes remain to be investigated.

#### 4. Conclusions

In summary, innate immune responses contribute significantly to the first line of defense against invading HIV-1 particles on the one hand, but the virus has evolved different strategies to escape from the innate immune system on the other hand. While Langerhans Cells and plasmacytoid dendritic cells exert efficient antiviral actions by degrading the virus via Birbeck granules (LCs) or secreting high amounts of type I interferons (especially IFN $\alpha$ ), interstitial dermal dendritic cells are suggested to contribute in viral transport and dissemination. The antiviral functions of LCs are also reversed upon co-infection with other STIs or microbes due to the competition of the pathogens for Langerin. The competition for Langerin allows attachment of HIV-1 to its main receptors, CD4 and the chemokine-co-receptor CCR5, on LCs and thus facilitates infection of LCs and subsequent transfer to CD4<sup>+</sup> T cells in the lymph nodes. This process of 'cis'-infection of DCs, migration to the lymphatic tissues and transmission to CD4<sup>+</sup> T cells is also thought to be contrived by dermal DCs. The virus is furthermore efficiently protected against complement-mediated lysis due to acquisition of regulators of complement activation during the budding process from the host cell (CD55, CD59) and additionally in fluid-phase (fH). Thus, most of the virus is opsonized with C3-fragments *in vivo*, which allows interaction with complement-receptor expressing cells at mucosal surfaces. Therefore the host immune system itself has to reverse the protection of the virus against complement-mediated lysis. As recently demonstrated (Banki/Posch et al., 2010), complement-opsonization acts as endogenous adjuvant for the dendritic cell-mediated induction of retrovirus-specific CTLs *in vitro* and *in vivo*, which was the first evidence that specific CTLs are efficiently stimulated in a complement- and DC-dependent manner. This enhanced and efficient CTL-stimulatory capacity of DCs upon complement-opsonization of HIV may provide a host-cell protecting mechanism at the beginning of infection and understanding the exact interplay between differentially opsonized retroviral particles and APCs is of prime importance for DC-based vaccination strategies against retroviral infections. Not only benefits result from the complement opsonization of HIV- such complement-opsonized particles can also be ingested by CR3-expressing macrophages and monocytes, the major reservoirs of long-term HIV-persistence beside latently infected CD4<sup>+</sup> T cells. These cells facilitate HIV assembly and escape immune surveillance by hiding the particles from the immune system and by allowing efficient transfer of the particles to target cells in a delayed manner and another compartment. Instead of destroying the virus at the initial phases of infection, macrophages and monocytes seem to act as 'Trojan horse' by actively contributing to the spread of HIV over long time periods. Beside LCs and pDCs,  $\gamma\delta$ T cells, primarily located in the gastrointestinal mucosa, NK and NK T cells, that are activated by IFN $\alpha$ -secreted pDCs, build an important first line of defense against viral, bacterial, and fungal pathogens. HIV-1 counteracts this innate immune barrier by changing their functions and decreasing their numbers by yet mainly undefined mechanisms. The HIV-mediated loss in numbers of important innate immune cells, such as pDCs, NK and NK T cells or  $\gamma\delta$ T cells, is associated with a modified cytokine microenvironment, which may additionally account for the chronic establishment of HIV-infection in the host. Because it is difficult identifying infected individuals very soon after exposure, little is known respecting the earliest events of HIV transmission in the

genital tract or rectal mucosa. Most of the findings are deriving from *in vivo* models of SIV infection (rev. in Haase, 2005) and from *ex vivo* models aimed to identify cells and factors affecting the transmission of HIV (rev. in Hladik and McElrath, 2008). Even when using animal models the exact process how the virus infiltrates mucosal barriers to establish a productive infection in the host is extremely complex to evaluate. There are multiple innate soluble and cellular factors acting together upon entry of HIV into the host – yet, the innate mechanisms and even the specific adaptive immune responses fail to restrict the replication of HIV in most infected individuals indicating the selection of viral mutants that are able to efficiently escape these early and late cellular and humoral immune responses. In the last years, increasing evidence suggests that especially immunologic and virologic events occurring during primary infection irreversibly weaken the immune system, which is not able to restore and gradually fails to resist viral and opportunistic infections.

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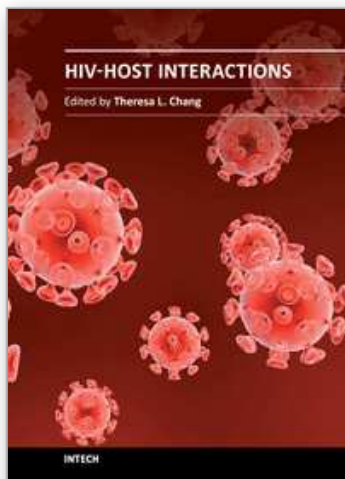
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### **HIV-Host Interactions**

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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and *Trichomonas vaginalis* on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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