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# Factors Contributing to HIV-1 Induced Pathogenesis in the Human Thymus

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## 1. Introduction

HIV infection is associated with a progressive loss of CD4<sup>+</sup> T cells, leading to an acquired immunodeficiency syndrome (AIDS). The CD4<sup>+</sup> T-cell depletion is due to the direct destruction of infected CD4<sup>+</sup> T cells, as well as to an impaired production of T cells in the thymus. Our understanding of the exact role of the thymus in HIV-1 infection and HIV-1 pathogenesis remains incomplete, although substantial progress has been made over the last decade. *De Novo* generation of naïve human T cells occurs in the thymus, seeded with CD34<sup>+</sup> progenitor cells, migrating from the bone marrow. These progenitor cells sequentially undergo a process of tightly controlled differentiation, including the rearrangement of T cell receptor genes, ultimately leading to the generation of functionally mature CD4<sup>+</sup> and CD8<sup>+</sup> single-positive (SP) T cells. Much has been learned of the types of cells in the thymus that are targets for CXCR4-tropic and CCR5-tropic HIV-1 isolates. Several groups provided evidence that HIV can infect thymocytes at various developmental stages. In addition, HIV activates the natural type-I-interferon (IFN)-producing plasmacytoid dendritic cells (pDC) that may induce bystander effects resulting in chronic immune activation. Evidence is also mounting that HIV induces abnormal development of regulatory T (Treg) cells in the thymus, either by direct infection or by enhancement of their survival and function, mediated by host-derived pro-inflammatory molecules. Collectively, these events compromise thymic function resulting in a decreased thymic output and a general decline in peripheral CD4<sup>+</sup> T-cell numbers. Here we aim to discuss the cellular targets for CCR5-tropic and CXCR4-tropic HIV-1 isolates in the thymus, and how virus tropism relates to architectural differences observed in the HIV-infected thymus. In addition, we will discuss the role of pDC and Treg in HIV pathogenicity, and the impact of type I IFN on T cell regeneration. Finally, we will review the present status on the use of humanized mouse and non-human primate models to study HIV-1 infection of the thymus.

## 2. Thymic seeding progenitor cells

T cells uniquely complete their development in the specialized environment of the thymus, which in addition to TCRαβ T cells also supports development of functionally different

types of T cells, including TCR $\gamma\delta$  T cells, NKT cells, and regulatory T cells. The human thymus is seeded by hematopoietic progenitor cells that arrive via the blood and initially originate from the fetal liver (between week 6-20 of gestation) and later from the fetal bone marrow (from week 20 of gestation) and adult bone marrow. Our current understanding is that the thymus remains active through an advanced age, suggesting that thymic seeding progenitor cells (TSPs) should be present in adult blood. It is well established that all hematopoietic precursors in humans are present within a population of cells that express CD34 (Payne & Crooks, 2002), and this marker is useful in elucidating pathways in the development of particular hematopoietic lineages. In umbilical cord blood (UCB), CD34<sup>+</sup>CD45RA<sup>+</sup>CD7<sup>+</sup> cells are found to have T, B, and NK and some granulocyte-macrophage (GM) precursor activities (Haddad et al., 2004; Hao et al., 2001). Phenotypically these cells resemble the CD34<sup>+</sup>CD38<sup>low</sup> Early Thymic Progenitor cells (ETP), which are present within the thymus and have T cell, NK cell, and Dendritic Cell (DC) precursor activities (Res et al., 1996). The ETP have not yet undergone T cell receptor (TCR) gene rearrangements confirming that they form the most immature population in the thymus (Dik et al., 2005). This, together with the observation that ETP co-express CD10, makes it tempting to speculate that they are the direct progeny of the CD34<sup>+</sup>CD45RA<sup>+</sup>CD7<sup>+</sup>CD10<sup>+</sup>CD38<sup>low</sup> UCB cells (Hao et al., 2001). In addition, the notion that the human thymus harbors multipotential precursors indicates that T cell commitment takes place within this organ (Bhandoola et al., 2003). While these results are in line with data obtained in the mouse, more recent studies suggested that the murine thymus can be seeded not only by multipotent precursors, but also by precursor cells that are lineage restricted (Petrie & Kincade, 2005; Porritt et al., 2004). If that would be the case in humans, such lineage restricted cells should be present in UCB, but conflicting results were reported on this issue. One study failed to find evidence for the presence of TCR rearrangements in UCB CD34<sup>+</sup> cells (Blom et al., 1997), but another study reported the presence of complete TCR $\delta$  and partial TCR $\beta$  (D $\beta$ -J $\beta$ ) rearrangements in CD34<sup>+</sup>CD7<sup>+</sup> cord blood precursors (Ktorza et al., 1996). It is obvious that re-analysis preferentially by single-cell PCR analysis of the recently identified rare CD34<sup>+</sup>CD45RA<sup>+</sup>CD7<sup>+</sup> UCB population is required to solve this issue (Haddad et al., 2004; Hao et al., 2001). T cell-restricted precursors were convincingly identified in human bone marrow (Klein et al., 2003a), but whether these cells can migrate to the thymus is unclear. In the mouse it was demonstrated that for the proper seeding of progenitor cells into the thymus the collective action of the chemokine receptors CCR7 and CCR9 is required (Zlotoff et al., 2010). The role of these chemokine receptors to direct human progenitor cells into the thymus has not been established. In summary, at least a proportion of the precursors that seed the human thymus are multipotent. It remains elusive whether or not some of the precursors that migrate into the thymus are lineage restricted before entrance, and which signals control their thymic seeding.

### 3. Cellular stages in the development of early thymic progenitor cells into mature T Cells

In the thymus different regions can be distinguished, including the cortex and the medulla (Figure 1). The early steps in T cell development are induced in the cortex, which is characterized by a high cell density resulting from a high degree of proliferating immature

thymocytes. In addition, an area of low cell density can be observed, which is known as the medulla. Based on phenotype and status of the TCR gene rearrangements we have gained significant insight in the various transitional stages of T cell development in the human thymus (Figure 2) (Spits et al., 1998; Spits, 2002). The ETP, lacking TCR rearrangements, are enclosed within a population of cells that express CD34, but lack CD1a expression. The downstream CD34<sup>+</sup>CD1a<sup>+</sup> population is committed to the T cell lineage because they are unable to develop into non-T cells (Dalloul et al., 1999; Galy et al., 1993; Res & Spits, 1999; Spits et al., 1998). The cells that subsequently upregulate CD4 and downregulate CD34 are generally referred to as CD4 immature single-positive (CD4 ISP) (Hori et al., 1991). Downstream of the CD4 ISP subset are CD4<sup>+</sup>CD8 $\alpha$ <sup>+</sup> $\beta$ <sup>-</sup> (early double-positive) and CD4<sup>+</sup>CD8 $\alpha$ <sup>+</sup> $\beta$ <sup>+</sup> populations (Galy et al., 1993; Hori et al., 1991), which are the precursors of double-positive (DP) TCR $\alpha$  $\beta$ <sup>+</sup> cells. During the early stages in T cell development, the TCR loci undergo sequential rearrangements in the order of TCR $\delta$  >  $\gamma$  >  $\beta$  >  $\alpha$  (Blom et al., 1999; Dik et al., 2005; Verschuren et al., 1998). Depending on differences in the sensitivity of the assay used to measure TCR $\beta$  rearrangements productive TCR $\beta$  V-DJ rearrangements were either found in the CD34<sup>+</sup>CD1a<sup>+</sup> cells (Dik et al., 2005) or in the CD4 ISP cells (Blom et al., 1999). It cannot be excluded, however, that a small contamination in the sorted CD34<sup>+</sup>CD1a<sup>+</sup> cells in combination with a highly sensitive PCR detection assay was responsible for the positive signal (Dik et al., 2005). Only productive, in-frame TCR $\beta$  rearrangements result in the production of a TCR $\beta$  protein, which together with the CD3 subunits and the invariable pre-TCR- $\alpha$  (pT $\alpha$ ) chain ensures cell surface expression of a pre-TCR. At this stage a process referred to as  $\beta$ -selection occurs in distinct populations of cells that differ in CD4 and CD8 expression. Both CD4 ISP and CD4<sup>+</sup>CD8 $\alpha$ <sup>+</sup> $\beta$ <sup>-</sup> early double-positive subsets were found to contain intracytoplasmic (ic) TCR $\beta$ <sup>-</sup> and icTCR $\beta$ <sup>+</sup> cells (Blom et al., 1999; Carrasco et al., 1999). Ten to twenty percent of the CD4 ISP are icTCR $\beta$ <sup>+</sup>, and in contrast to the TCR $\beta$ <sup>-</sup> CD4 ISP, these icTCR $\beta$ <sup>+</sup> CD4 ISP are larger and express elevated levels of CD28 and CD71 (Taghon et al., 2009). A larger proportion is  $\beta$ -selected after upregulation of CD8 $\beta$  (Carrasco et al., 1999; Trigueros et al., 1998). Hence, these findings suggest that expression of a TCR $\beta$  protein and the ensuing  $\beta$ -selection occur within a certain developmental window and are not tightly coupled to regulation of CD4, CD8 $\alpha$ , and CD8 $\beta$  expression.

Activation of the pre-TCR on the cell surface induces TCR $\beta$ -selection, which is a collective process leading to survival and proliferation of the cells, allelic exclusion, and induction of TCR $\alpha$  rearrangements (Spits, 2002). Subsequently, CD4<sup>+</sup>CD8<sup>+</sup> DP T cells express a mature TCR $\alpha$  $\beta$  complex on their cell surface, which is followed by positive and negative selection (Klein et al., 2009; Siggs et al., 2006). Positive selection mediated by the cortical thymic epithelial cells secures the survival of T cells that recognize self-major histocompatibility (MHC) antigens complexed with self-peptides with low/intermediate affinity. Conversely, high affinity self-peptide MHC complexes expressed by thymic dendritic cells (DC) in the medulla are pivotal for deletion of auto-reactive T cells, which is called negative selection. In the majority of cases when no interaction of TCR and MHC complexes can be established, the cells are unable to survive and die as a result of death by neglect. Positively selected thymocytes differentiate into T cells that express CD27 and CD45RA and high levels of CD3/TCR (CD3<sup>hi</sup>) similar to naive T cells present in cord blood. Finally, lineage determination signals enforce the differentiation into either the helper CD4<sup>+</sup> T cell or cytotoxic CD8<sup>+</sup> T cells lineages.



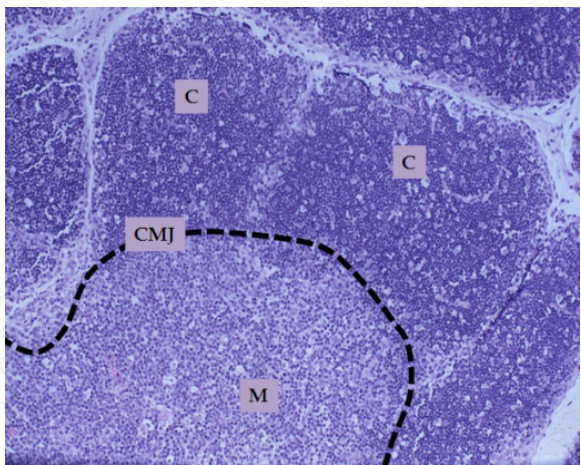


Fig. 1. Photomicrograph of the thymus. This section of human thymus (original magnification x10, courtesy of Dr. B. Jamieson, UCLA, Los Angeles, USA) was stained with hematoxylin/eosin and shows the cortex (C), which is a dense area of proliferating lymphocytes (thymocytes), and the medulla (M), where fewer cells localize and negative selection takes place. It is believed that progenitor cells enter the thymus at the cortico-medullary junction (CMJ) before migration into the cortex and commitment into the T cell lineage.

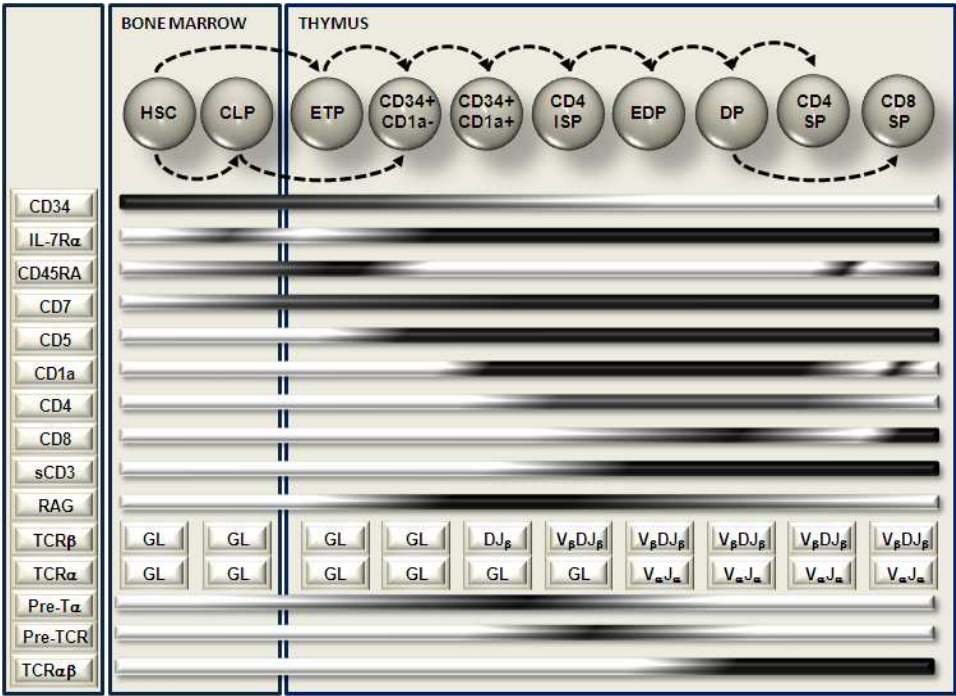


Fig. 2. Schematic model of human T cell development. Shown is the expression of cell surface markers on thymic progenitor cells and during the different stages of human T cell development in the thymus (black indicates expression, white indicates no expression). In addition, the status of T cell receptor (TCR)  $\alpha$  and  $\beta$  gene rearrangements is shown. Hematopoietic stem cell (HSC), common lymphoid progenitor (CLP), early thymic progenitor (ETP), immature single positive (ISP), early double positive (EDP), single positive (SP), germline (GL), Diversity-Joining TCR $\beta$  (D-J $\beta$ ), Variable-DJ TCR $\beta$  (V $\beta$ DJ $\beta$ ), Variable-Joining TCR $\alpha$  (V $\alpha$ J $\alpha$ ).

#### 4. Role of cytokines in T cell development

A role for interleukin (IL)-7 in the development of T cells in the thymus has been highlighted by many groups. The IL-7 receptor consists of two chains, IL-7R $\alpha$  and gamma common ( $\gamma$ c), which is also part of the receptors for IL-2, IL-4, IL-9, IL-15, and IL-21. Genetic defects in the genes encoding for  $\gamma$ c (Noguchi et al., 1993; Russell et al., 1993), IL-7R $\alpha$  (Giliani et al., 2005; Puel et al., 1998), or the Janus kinase Jak3, a component of the IL-7-induced signal transduction pathway (Macchi et al., 1995; Russell et al., 1995), account for the majority of severe combined immune deficiencies (SCID). This disease is characterized by strongly reduced numbers of T cells. The most frequent form of SCID is caused by mutations in the  $\gamma$ c-encoding gene (reviewed in (Fischer et al., 2005)). In these patients, T and NK cells are absent, but in contrast to what is observed in  $\gamma$ c-deficient mice, B cell development is normal (Noguchi et al., 1993; Russell et al., 1993). While IL-7R $\alpha$ -deficient patients also display a profound T cell deficiency, they have near normal NK and B cell numbers (Giliani et al., 2005; Puel et al., 1998). This indicates that human T cell development, but not survival and proliferation of lymphoid precursors, specifically and critically depends on IL-7. The precise function of IL-7, which is produced by thymic epithelial cells, in human T cell development remains incompletely understood. Expansion and differentiation of developing T cells in a FTOC is inhibited by blocking the IL-7R signaling pathway using anti-IL-7 and anti-IL-7R antibodies (Pallard et al., 1999; Plum et al., 1996). This indicates that IL-7 has a crucial role in mediating survival and proliferation of human T cell precursors. It has been reported that this is likely mediated by IL-7-induced Phosphoinositide Kinase-3 (PI3K) activation through one tyrosine residue at position 449 in the cytoplasmic tail of the IL-7R $\alpha$  chain (Pallard et al., 1999). Based on the notion that the distribution of subsets in the thymuses of IL-7R $\alpha$ -deficient mice was near normal, it was argued that IL-7 does not appear to be critical for differentiation of mouse TCR $\alpha\beta$  T cells in the thymus (Peschon et al., 1994). In humans, however, there is evidence that IL-7 is important for differentiation of human T cells. First, differentiation of CD34<sup>+</sup> precursors in a FTOC in the presence of anti-IL-7R antibody is almost completely blocked at the transition of CD34<sup>+</sup>CD1a<sup>+</sup> cells into CD4 ISP (Plum et al., 1996). Second, according to one report, thymocytes from  $\gamma$ c-deficient infants possess TCR $\beta$  D-J but lack V-DJ $\beta$  rearrangements (Sleasman et al., 1994). Although a function of IL-7 in TCR $\beta$  rearrangements in human pre-T cells has yet to be confirmed, it may reflect the complete lack of T cells in many  $\gamma$ c- and IL-7R $\alpha$ -deficient patients (Giliani et al., 2005; Pesu et al., 2005). Conversely, IL-7 is required for peripheral T cell homeostasis in humans (Napolitano et al., 2001), which raises the alternative possibility that the combined defects in early T cell development and in T cell homeostasis are causal to the absolute T cell deficiency in  $\gamma$ c-deficient patients. Collectively, these results indicate that IL-7 is indispensable for human T cell development, and moreover suggests that IL-7 is more critical for human than for mouse T cell development.

#### 5. HIV tropism vs. thymic architecture

HIV can enter the cell through two major co-receptors, CXCR4 and CCR5, which are chemokine G-protein coupled receptors. Under physiological conditions CXCR4 ligates the chemokine CXCL12/SDF-1 $\alpha$ , while CCR5 can be engaged by several chemokines, including RANTES (CCL5) or the macrophage inflammatory proteins MIP-1 $\alpha$  (CCL3) and MIP-1 $\beta$  (CCL4) (Rossi & Zlotnik, 2000). Based on the expression pattern of these chemokine

receptors on leukocytes a clear distinction can be made between CXCR4 (X4)-tropic and CCR5 (R5)-tropic viruses (Deng et al., 1996; Dragic et al., 1996; Feng et al., 1996). In bone marrow, on average 40% of the CD34<sup>+</sup> progenitor cells express the chemokine receptor CXCR4 (Ishii et al., 1999). This subset was shown to have restricted lymphoid precursor activities, and resemble the CD34<sup>+</sup>CXCR4<sup>+</sup> cells in neonatal UCB, which are likely the precursors of human CLPs (Haddad et al., 2004; Hao et al., 2001). CCR5 is expressed on the cell surface of only a minority of freshly isolated CD34<sup>+</sup> CB cells (1–21%), although at the intracellular level more than 80% of the CD34<sup>+</sup>CB cells expressed abundant CCR5 receptors (Basu & Broxmeyer, 2009). While chemotaxis of CD34<sup>+</sup>CB cells was not induced by the CCR5 ligands CCL3, CCL4 and CCL5, they transiently enhanced chemotaxis mediated by CXCL12, the ligand for CXCR4 (Basu & Broxmeyer, 2009). Whether CD34<sup>+</sup> cells can be infected by HIV has been the subject of great discussion through the years. Recently, Carter et al. (Carter et al., 2010) demonstrated that CD34<sup>+</sup> cells can be infected by both X4 and R5-tropic viruses *in vitro* as well as *in vivo*, thus potentially becoming a significant reservoir of HIV. In the thymus, both CXCR4 and CCR5 are expressed as well (Figure 3) (Berkowitz et al., 1998b; Gurney & Uittenbogaart, 2006; Kitchen & Zack, 1997; Kitchen & Zack, 1999; Pedroza-Martins et al., 1998; Zaitseva et al., 1998; Zamarchi et al., 2002; Zhang et al., 1998). Several studies have shown that expression of CXCR4 and CCR5 are modulated during thymocyte development (Berkowitz et al., 1998b; Gurney & Uittenbogaart, 2006; Zaitseva et al., 1998). CXCR4 is expressed on the majority of thymocytes at all stages of differentiation with the highest level of CXCR4 expression on the CD34<sup>+</sup> and CD4 ISP subsets (Berkowitz et al., 1998b; Hernandez-Lopez et al., 2002; Zaitseva et al., 1998). It was observed that CXCL12, in synergy with IL-7, mediates survival of these thymic progenitor subsets (Hernandez-Lopez et al., 2002). In accord with its co-receptor profile, CD4 ISP cells are infected with X4-tropic HIV-1, which has a cytopathic effect in the thymus resulting in a major depletion of cells (Gurney & Uittenbogaart, 2006; Kitchen & Zack, 1997). On more mature stages of T cell development CXCR4 is downregulated (Berkowitz et al., 1998b; Gurney & Uittenbogaart, 2006; Zaitseva et al., 1998). Notably, however, infected CD8<sup>+</sup> T cells are detected in the HIV-1 infected thymus, which can be explained by the observation that immature thymocytes, before they have differentiated into single positive thymocytes, can be infected by X4-tropic HIV-1 (Gurney & Uittenbogaart, 2006; Kitchen & Zack, 1997; Lee et al., 1997). Just prior to emigration from the thymus CXCR4 is again upregulated (Gurney & Uittenbogaart, 2006). Taken together, X4-tropic viruses can infect cells that are present in both the cortex and the medulla (Jamieson et al., 1995; Uittenbogaart et al., 1996). It is important to keep in mind that most of this work has been done with HIV laboratory strains that are highly cytopathic and may not be representative of what is happening *in vivo* in humans. This is enforced by the finding that HIV pediatric isolates from newborn children are not as cytopathic as the laboratory strains in infecting thymocytes at least *in vitro* (Pedroza-Martins et al., 1998). Unlike CXCR4, the expression of CCR5 is much less widespread (Berkowitz et al., 1998a). CCR5 is detected on a relatively small proportion of thymocytes, including mature CD4 and CD8 single positive T cells which express CD27 but lack CD45RA (Berkowitz et al., 1998b; Gurney & Uittenbogaart, 2006), and is downregulated just prior to exiting the thymus (Berkowitz et al., 1998a; Gurney & Uittenbogaart, 2006). R5-tropic viruses are less cytopathic, which may at least in part be explained by the restricted co-receptor expression on a small subset, resulting in a much slower depletion of thymocytes (Jamieson et al., 1995). Moreover, the CCR5 expressing thymocytes are confined in the medullary area, which constrains prevalent replication of R5 viruses throughout the thymus (Berkowitz et al.,



1998a). Notably, like X4-tropic viruses, R5 strains are capable of depleting thymocytes leading to reduced cellularity in the thymus. One explanation can be that in addition to  $\text{TCR}\alpha\beta^+$  T cells, other  $\text{CCR5}^+$  cells are found in the thymus, including conventional DC (cDC), plasmacytoid DC (pDC), macrophages,  $\text{CD161}^+$  T cells and  $\gamma\delta$  T cells (Gurney et al., 2002; Gurney et al., 2004; Keir et al., 2002; Rozmyslowicz et al., 2010; Schmitt et al., 2006). Another explanation can be that pDC (see paragraph below) in response to the virus produce large amounts of type I IFNs (Gurney et al., 2004), which contributes to immune activation followed by cell death and T cell depletion. The pDC are likely more susceptible to R5-tropic HIV infection as they express CCR5 at higher levels compared to single positive thymocytes (Gurney et al., 2004). It was recently reported that IFN- $\alpha$  induced expression of CCR5 on CD4 ISP thymocytes, which consequently expands the tropism for R5-tropic viruses (Stoddart et al., 2010). This, together with the observation that thymi from HIV-infected individuals present with higher CCR5 expression on mature thymocytes as compared with thymocytes from uninfected individuals (Bandera et al., 2010), enforces the notion that immune activation has a detrimental role in thymic depletion.

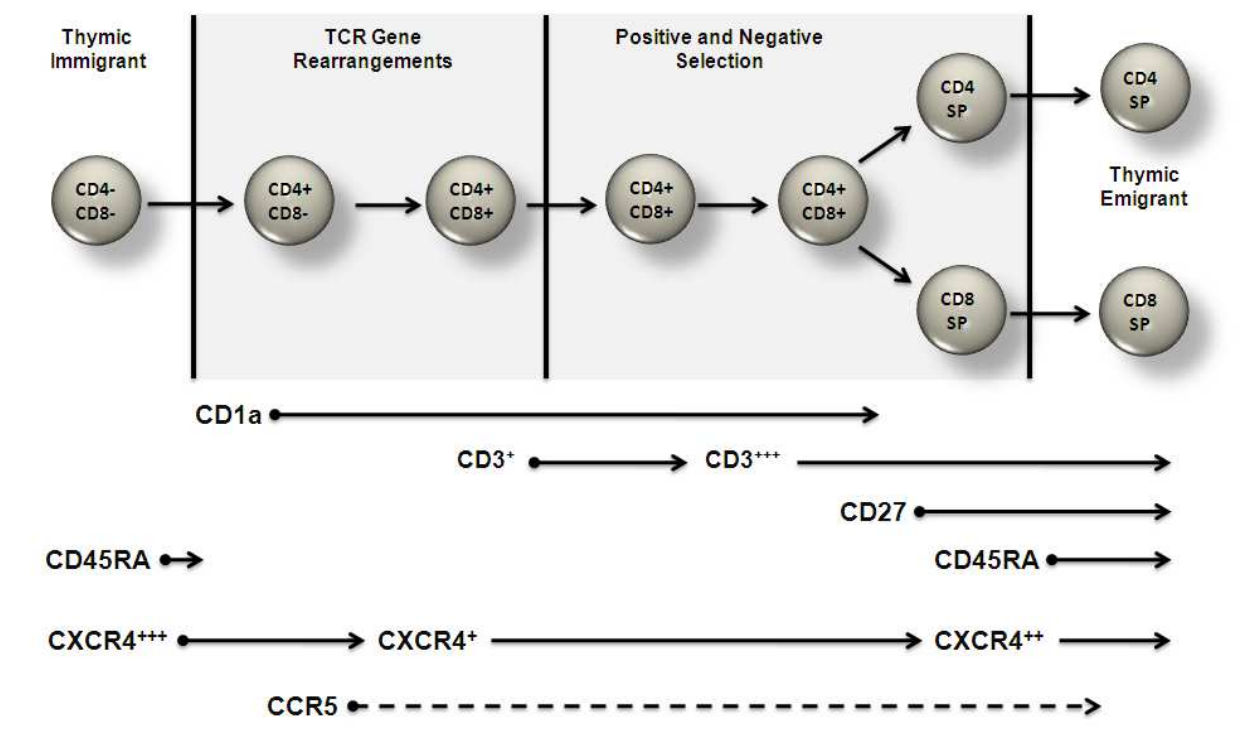


Fig. 3. Expression of chemokine receptors CXCR4 and CCR5 on cells at different stages during T cell development in the human thymus. The solid line arrows indicate high expression of the different cell surface markers, while the dotted line arrow indicates low expression. T cell receptor (TCR), single positive (SP).

6. Role of pDC in HIV pathogenesis in the thymus

Rare immune subsets like DC, play significant roles in the regulation of the immune system (Banchereau et al., 2000a; Banchereau et al., 2000b; Cella et al., 1999; Cella et al., 2000; Grouard et al., 1997; Kadowaki et al., 2000). Among the different types of DC subsets are pDC, which are present in cord and peripheral blood, T cell areas of the lymph nodes and in the medullary area of the thymus, and have the capacity to produce high levels of type I



IFN, i.e. IFN $\alpha$  and IFN $\beta$ , in response to viruses and other stimuli (Bendriss-Vermare et al., 2001; Cella et al., 1999; Foster et al., 2000; Kadowaki et al., 2000; Olweus et al., 1997; Res et al., 1999; Siegal et al., 1999; Vandenabeele et al., 2001). Type I IFNs are survival factors for pDC, while maturation of pDC depends on IL-3 (Grouard et al., 1997). Exposure of peripheral blood pDC to virus, or alternatively IFN- $\alpha$  or IL-3 either in combination with CD40L or TNF- $\alpha$ , leads to the appearance of pDC with a mature phenotype illustrated by the finding that they express increased levels of HLA Class II and costimulatory molecules (Kadowaki et al., 2000; Kohrgruber et al., 1999). pDC can differentiate *in vitro* into mature DC capable of stimulating CD4<sup>+</sup> naïve T cells to proliferate and differentiate, and depending on the environmental signals polarize T cells into T helper 2 (Th2) (Rissoan et al., 1999) or Th1 cells (Cella et al., 2000). Also, pDC have the ability to shape CD8<sup>+</sup> T cell responses either directly (Gilliet & Liu, 2002) or via crosspresentation (Hoeffel et al., 2007), and NKT cell responses (Kadowaki et al., 2001a). However, the central role of pDC *in vivo* is likely that of an IFN- $\alpha/\beta$  producing cell, and not an antigen presenting cell (Haeryfar, 2005).

In response to enveloped RNA and DNA viruses (Milone & Fitzgerald-Bocarsly, 1998), including live and inactivated HIV-1 (Beignon et al., 2005; Ferbas et al., 1994; Fong et al., 2002; Hardy et al., 2007; Yonezawa et al., 2003), human pDC are the main producers of IFN- $\alpha$  (Ferbas et al., 1994; Ishikawa et al., 2005; Milone & Fitzgerald-Bocarsly, 1998; Siegal et al., 1999). In contrast to conventional cDC, pDC do not produce interleukin-12 (IL-12) (Ito et al., 2006). The capacity of IFN- $\alpha$  production in response to virus is already present at the pro-pDC stage (Blom et al., 2000) and can be sustained during activation and maturation (Cella et al., 1999). IFN- $\alpha$  produced by pDC induces maturation of conventional cDC and thereby provides a link between innate and adaptive immunity (Ito et al., 2001). Several viral infections induce IFN- $\alpha$ , but the pathways that lead to IFN- $\alpha$  production are likely different. Recent reports suggest that in HIV-1 infection IFN- $\alpha$  production by pDC is stimulated through interaction of HIV-1 RNA with Toll like receptor (TLR)7 (Beignon et al., 2005; Hardy et al., 2007; O'Brien et al., 2011). Although it has been shown that pDC can be productively infected by R5-tropic and X4-tropic HIV-1 (Gurney et al., 2004; Keir et al., 2002), IFN- $\alpha$  production by pDC does not depend on productive HIV-1 infection (Beignon et al., 2005; Hardy et al., 2007). Furthermore, pDC express TLR9, which after engagement by oligodeoxynucleotides (ODNs) containing unmethylated CpG motifs mimicking bacterial DNA, activate the cells to secrete high levels of type I IFNs (Kadowaki et al., 2001b).

Development of pDC both in human and mouse depends on FLT3L (Blom et al., 2000; Gilliet et al., 2002). Furthermore, the Ets transcription factor Spi-B and the basic helix-loop-helix factor E2-2 are essential for the development of human pDC *in vitro* as well as *in vivo* (Cisse et al., 2008; Nagasawa et al., 2008; Schotte et al., 2003; Schotte et al., 2004). In the human thymus a cell type very similar to peripheral pDC was identified. These CD3<sup>-</sup> cells express CD4, CD45RA and high levels of CD123 and are localized at the cortico-medullary junction and in the medulla (Bendriss-Vermare et al., 2001; Olweus et al., 1997; Res et al., 1999; Schmitt et al., 2000; Vandenabeele et al., 2001). There are similarities but also differences between thymic and peripheral pDC. Both thymic and peripheral pDC respond, in addition to IL-3, also to GM-CSF (Ghirelli et al., 2010; Vandenabeele et al., 2001). Like the peripheral pDC, the thymic pDC have the capacity to develop into mature DC, but some differences were observed in the expression of certain cell surface antigens (Res et al., 1999). Thymic pDC consistently express CD2, CD5 and CD7, while peripheral pDC do not express CD7 and are heterogeneous with respect to the expression of CD2 and CD5 (Bendriss-Vermare et al., 2001; Res et al., 1999; Schmitt et al., 2006). Interestingly, thymic pDC constitutively

express low levels of IFN- $\alpha$ , which is upregulated by HIV-1 infection *in vivo* (Gurney et al., 2004). Moreover, thymic pDC produce less IFN- $\alpha$  upon infection with virus (Schmitt et al., 2006). These differences may imply either that thymic and peripheral pDC are different subsets, or that these alterations are enforced by the thymic microenvironment.

The role of pDC in controlling HIV-1 replication is still incompletely resolved. Several reports describe a decrease in frequency and function of peripheral blood pDC in HIV-1-infected patients (Chehimi et al., 2002; Donaghy et al., 2001; Feldman et al., 2001; Pacanowski et al., 2001; Soumelis et al., 2001). A decrease in pDC has been correlated with an increase in HIV-1 RNA virus load and opportunistic infections, suggesting that a loss of these cells may contribute to disease progression in HIV-1-infected patients (Donaghy et al., 2001; Siegal et al., 2001). This decrease in peripheral blood pDC may be due to HIV-1 induced cell death or migration of pDC from the peripheral blood to lymphoid tissues. In accord with the latter option, it was reported that HIV-1 infection induces pDC maturation resulting in expression of CCR7 and migration to lymph nodes (Schmidt et al., 2005), which is a major site of HIV-1 pathogenesis (Herbeuval et al., 2006). While pDC can suppress HIV-1 replication *in vitro* (Gurney et al., 2004; Yonezawa et al., 2003) and *ex vivo* (Meyers et al., 2007), pDC through their production of IFN- $\alpha$  have also been found to contribute to HIV pathogenesis by TRAIL-mediated apoptosis of uninfected CD4<sup>+</sup> T cells (Herbeuval et al., 2006). Recent data suggest that despite a decrease in pDC numbers in peripheral blood of HIV infected individuals, their production of TLR7/8 agonist induced cytokine/chemokine is even higher than that of pDC of non-infected individuals thereby contributing to chronic immune activation (Sabado et al., 2010). With respect to thymic pDC, these are also targets for CXCR4- and CCR5-tropic HIV as they express CD4 in addition to both CXCR4 and CCR5. Notably, the expression level of CCR5 on pDC is higher than on thymocytes, suggesting that pDC are more susceptible to CCR5-tropic HIV infection than thymocytes (Gurney et al., 2004; Ho Tsong Fang et al., 2008; Schmitt et al., 2000). Studies in the SCID-hu Thy/Liv mouse model (see paragraph on “Humanized mouse models to study HIV-1 immuno-pathogenesis”) show that pDC are productively infected by HIV and that HIV infection induces IFN- $\alpha$  production resulting in upregulation of MHC-I and the interferon stimulated gene (ISG), MxA (Gurney et al., 2004; Keir et al., 2002; Schmitt et al., 2006). Recently, the suggestion was raised that as a consequence of upregulated MHC-I expression levels in the thymus, the generation of dysfunctional CD8<sup>+</sup> T cells with low expression of CD8 was induced resulting from altered negative selection (Favre et al., 2011). While no conclusive evidence was presented, when true this may have detrimental effects on thymopoiesis in the HIV-1-infected thymus, and contribute to the immunodeficiency of HIV disease.

## 7. Impact of IFN-alpha on T cell regeneration

Type I IFNs, including IFN- $\alpha$  and - $\beta$ , are important cytokines that have been classically described to have an immunoregulatory function with central roles as antiviral mediators (Brassard et al., 2002; Grandvaux et al., 2002). However, type I IFNs have additional effects besides their well-known antiviral function. It has been shown that high concentrations of IFN- $\alpha$  interfered with T and B cell development in mice (Lin et al., 1998). In the thymus, an 80% decrease in the overall cellularity and a 50% reduction of the CD4<sup>+</sup>CD8<sup>+</sup> DP population was observed (Lin et al., 1998). Considering the key role of IL-7 during T cell development (see paragraph above “Role of cytokines in T cell development”) it was speculated that type

I IFNs might interfere with IL-7 signaling. Consistent with this it was shown that type I IFNs inhibited IL-7-driven expansion of CD4-CD8-CD44<sup>+</sup>CD25<sup>+</sup> (also known as double negative (DN)2) cells in murine fetal thymus organ cultures (Su et al., 1997).

The main producers of type I IFNs are pDC, which express TLR7 and TLR9 enabling them to sense nucleic acids derived from viruses or bacteria (Kadowaki et al., 2001b; Cella et al., 1999; Kadowaki et al., 2000). In addition to secondary lymphoid organs and peripheral blood, pDC are present in the thymus, where they locate in the medulla and at the cortico-medullary junction (Bendriss-Vermare et al., 2001; Res et al., 1999; Vandenabeele et al., 2001). As this latter location is where TSP cells enter the thymus, it is conceivable that thymic pDC affect T cell development. In line with this it was demonstrated that IFN- $\alpha$ , when exogenously added as recombinant protein, impaired early human T cell development by interfering with the IL-7 signaling pathway (Schmidlin et al., 2006). Moreover, similar findings were observed when pDC were activated either by HIV-1 or the TLR9 agonist CpG-ODN in a co-culture setup in which thymic progenitor cells were induced to differentiate into both T cells and pDC (Schmidlin et al., 2006). Addition of neutralizing antibodies against type I IFNs in this system relieved the block in T cell development illustrating that type I IFNs produced by activated pDC have a detrimental effect on early T cell progenitor cells (Schmidlin et al., 2006). It remains largely elusive whether type I IFNs affect later stages of T cell development. This is not unlikely, however, given the architectural localization of pDC in the medulla, and the finding that the majority of thymocytes express the type I IFN receptor (CD118) on their surface (Keir et al., 2002). In fact, IFN- $\alpha$  was reported to interfere with IL-7-induced maturation at the transition of human CD3<sup>+</sup>CD1a<sup>+</sup> to CD3<sup>+</sup>/hiCD1a<sup>-</sup> thymocytes (Schmidlin et al., 2006). In addition, IFN- $\alpha$  induced the up-regulation of MHC class I expression in the thymus (Keir et al., 2002). This may cause adverse T cell selection in the thymus by changing the avidity of the TCR for MHC potentially depleting part of the mature CD8<sup>+</sup> T cell repertoire.

## 8. Role of regulatory T cells in HIV pathogenesis in the thymus

CD4<sup>+</sup>CD25<sup>+</sup> regulatory T (Treg) cells are a distinct subset of CD4<sup>+</sup> T cells, which play a significant role in the generation and maintenance of peripheral tolerance (Maloy & Powrie, 2001; Sakaguchi, 2000; Sakaguchi, 2005). Although in humans Treg cells in the periphery constitute a small subset of the total T-cells (1%-2%) (Baecher-Allan et al., 2001), there is accumulating evidence that they play a significant role in the negative control of a broad spectrum of immune responses to antigens, such as in tumor immunity, organ transplantation, allergy, and microbial immunity (reviewed in (Sakaguchi, 2005)). Treg cells are identified by their constitutive expression of the alpha chain of the interleukin 2 (IL-2) receptor (CD25) and the presence of the forkhead/winged-helix transcription repressor FoxP3 (scurfin) (Baecher-Allan et al., 2001; Fontenot et al., 2003; Hori et al., 2003; Khattri et al., 2003; Yagi et al., 2004). There is mounting evidence that FoxP3 plays a crucial role in the development and function of human (Walker et al., 2003; Yagi et al., 2004) and murine (Fontenot et al., 2005) CD4<sup>+</sup>CD25<sup>+</sup> Treg cells (reviewed in (Fontenot & Rudensky, 2005)). In addition to FoxP3, the cytokine IL-2 is essential for the development of Treg cells in the thymus and their maintenance in the periphery (reviewed in (Sakaguchi, 2005)). Although Treg cells show low levels of proliferation *in vitro* (Baecher-Allan et al., 2001), peripheral expansion of thymus-derived natural Treg (nTreg) cells ensures maintenance of the peripheral Treg pool in the adult mouse (Hori et al., 2002). In addition, antigen-dependent

proliferation of Treg cells has been shown *in vivo* (Klein et al., 2003b; von Boehmer, 2005). The mechanism of T cell suppression by Treg cells is dependent on direct cell-cell contact (reviewed in (von Boehmer, 2005)). However, in addition to the direct effects of Treg cells, bystander effects include the production of cytokines (IL-10 and TGF- $\beta$ ) that have suppressive effects on immune responses (reviewed in (von Boehmer, 2005)).

In mice and rats as well as humans, nTreg cells develop intrathymically (Jordan et al., 2001; Kasow et al., 2004) and acquire their regulatory function while still in the thymus (Itoh et al., 1999; Saoudi et al., 1996; Stephens et al., 2001). Treg cells are continuously produced in the thymus as a distinct lineage contiguous with peripheral blood Treg cells (reviewed in (Fontenot et al., 2005; Sakaguchi, 2005)). There is recent evidence that thymic pDC play a role in the development of nTreg (Hanabuchi et al., 2010; Martin-Gayo et al., 2010). Both pDC and Treg cells are located closely together in the thymic medulla, which may suggest interactions between them (Martin-Gayo et al., 2010; Res et al., 1999; Watanabe et al., 2005). In addition to the induction of Treg cells by cDC activated with the IL-7 like cytokine thymic stromal lymphopoietin (TSLP) (Watanabe et al., 2005), FoxP3<sup>+</sup> Treg cells can also be induced in the thymus by pDC after these have been stimulated with TSLP (Hanabuchi et al., 2010). The role of TSLP activation of pDC in the development of thymic Treg is however still unclear as Martin-Gayo *et al.* found that thymic pDC were unresponsive to TSLP, but responsive to CD40L and IL-3 (Martin-Gayo et al., 2010). It is interesting to note that nTreg cells generated in the presence of cDC have opposite IL-10/TGF- $\beta$  cytokine profiles from those generated with pDC (Martin-Gayo et al., 2010). Thus, the interaction of pDC and cDC with Treg cells may play an important role in the development of tolerance in the thymus.

In contrast to adult peripheral blood, Treg cells in the human fetal and postnatal thymus (Annunziato et al., 2002; Cupedo et al., 2005; Kasow et al., 2004) and in cord blood (Takahata et al., 2004; Thornton et al., 2004) have a naïve phenotype, although they suppress the proliferation of CD25-negative T cells, similar to Treg cells in the periphery. Treg cells identified by high expression of CD25 and FoxP3 are already present in the human fetal thymus and secondary lymphoid organs (Cupedo et al., 2005; Darrasse-Jeze et al., 2005). T cells expressing GITR, CTLA-4 and CD122 and high levels of CD25, corresponding to the phenotype of Treg cells, develop in the human thymus at the CD4<sup>+</sup>CD8<sup>+</sup> stage during transition of CD27<sup>-</sup> to CD27<sup>+</sup> stage (Cupedo et al., 2005). When Treg cells leave the thymus and enter fetal secondary lymphoid tissues, lymph nodes and spleen, they acquire a memory/activated phenotype (Cupedo et al., 2005). In the normal functioning immune system there is a balance between the interactions of Treg cells and effector T cells, whereas deficiency of functional Treg cells leads to inappropriate immune responses to microbial infections and autoimmunity as exemplified in humans who suffer from the X-linked immunodeficiency syndrome (IPEX) with a mutation in FoxP3 (reviewed in (Fontenot et al., 2005; Sakaguchi, 2005)). In addition to CD4<sup>+</sup> Treg cells, CD8<sup>+</sup>CD25<sup>+</sup> Treg cells have been identified in the thymus (Cosmi et al., 2003). The CD8<sup>+</sup>CD25<sup>+</sup> Treg cells express FoxP3 mRNA, but lower levels of CD25 than the CD4<sup>+</sup> Treg cells (Cosmi et al., 2003).

There is ample evidence that Treg cells play a significant role in infectious diseases including viral infections (reviewed in (Belkaid & Rouse, 2005; Mills & McGuirk, 2004)). In humans, circulating peripheral Treg cells suppress CD4<sup>+</sup> and CD8<sup>+</sup> antiviral immune responses in chronic viral infections, such as HCV (Cabrera et al., 2004), CMV and HIV (Aandahl et al., 2004; Andersson et al., 2005; Eggena et al., 2005; Kinter et al., 2004; Oswald-Richter et al., 2004; Weiss et al., 2004). There is a clear measurable restoration of antiviral immune responses to CMV and HIV *in vitro* when CD4<sup>+</sup>CD25<sup>+</sup> T cells are completely



removed (Aandahl et al., 2004; Weiss et al., 2004). Although Treg cells produce immunosuppressive cytokines, IL-10 and TGF- $\beta_1$  in response to p24 antigen stimulation, the down modulation seen by CD4<sup>+</sup>CD25<sup>+</sup> T cells is cell-cell contact dependent and independent of IL-10 and TGF- $\beta_1$  (Kinter et al., 2004; Weiss et al., 2004). The impact of Treg cells on HIV-1 infection is still unclear and may depend on the stage of infection. Early in viral infection, the proportion of Treg cells is unaltered as compared to normal controls (Aandahl et al., 2004). Elevated levels of circulating HIV specific CD25<sup>hi</sup>CD4<sup>+</sup> T cells were observed in a majority of healthy, yet chronically, HIV infected individuals (Kinter et al., 2004). However, Treg cell numbers declined proportionately with the loss of CD4<sup>+</sup> T cells and disease progression (Kinter et al., 2004; Oswald-Richter et al., 2004). Treg cells were increased in tonsils, but decreased in the peripheral blood of untreated chronically HIV infected individuals, indicating that viral antigenic stimulation may have increased Treg cells in the lymphoid tissue and may have a detrimental effect on local immune responses (Andersson et al., 2005). A recent study in HIV infected individuals undergoing cardiac surgery showed that Treg cells were increased in the thymus of HIV-infected individuals as compared to uninfected individuals (Bandera et al., 2010). In a study of treatment naïve, chronically HIV infected individuals in Uganda, depletion of Treg cells was associated with immune activation (Eggena et al., 2005). The underlying mechanism suggests a complex balance between Treg cells and effector T cells. In summary, it will be of significant clinical value to determine at which stages of disease and in which tissues Treg cells have detrimental or protective effects on the immunopathology observed in HIV infection.

## 9. SIV pathogenic and non-pathogenic models

The use of animal models has been of great importance to study the thymus in HIV infection. In this regard the non-human primate models, and the SCID-hu and humanized mouse models, as discussed in the next section, are providing a great deal of knowledge on the role of the thymus in HIV infection. Studies in pathogenic and non-pathogenic models of simian immunodeficiency virus (SIV) infected non-human primates have further increased our understanding on the role of the thymus in HIV infection. In the non-pathogenic model SIV infection of its natural hosts (chimpanzees, sooty mangabeys, African green monkeys, and others) does not lead to depletion of CD4<sup>+</sup> T lymphocytes and AIDS, in contrast to the pathogenic model in which SIV infects its non-natural host (rhesus macaques) (reviewed in (Silvestri, 2008)). Effective innate immune responses including IFN- $\alpha$  and ISG are induced, but rapidly controlled in acute SIV infection of sooty mangabeys (SM) (Bosinger et al., 2009) and African Green monkeys (Diop et al., 2008; Jacquelin et al., 2009). However, acute SIV infection of rhesus macaques (RM) induces chronic immune activation and continuous expression of ISG (Bosinger et al., 2009). An increase in the ISG, MxA mRNA was found in lymphoid tissues, including the thymus, in SIV infected rhesus macaques. However, the elevated MxA levels did not correlate with control of viral infection in the animals (Abel et al., 2002) and are likely a sign of immune activation. Non-responsiveness to TGF- $\beta_1$  was found to play a role in the lack of resolution of immune activation in rhesus macaques (Ploquin et al., 2006). Chronic immune activation was recognized many years ago as a major player in poor prognosis HIV infected individuals (Giorgi et al., 1999). Thus interference with immune activation was explored by administration of an antibody to the IFN- $\alpha$  receptor in SIV infected macaques, which reduced the loss of CD4<sup>+</sup> T cells in these animals (Tovey et al., 1994).

Studies of lymphoid tissues in SIV infected macaques have shed light on the differences between changes in T lymphocytes in peripheral blood and primary (thymus) and secondary lymphoid organs. In the thymus and secondary lymphoid organs proliferation of T lymphocytes and absolute CD4<sup>+</sup> T lymphocytes were increased in acute SIV infection, but decreased in peripheral blood (Sopper et al., 2003). However in animals with first indication of AIDS, thymocytes were severely decreased (Sopper et al., 2003). Increased levels of thymocyte proliferation were also observed by Wykrzykowska *et al.* (Wykrzykowska et al., 1998) after an initial increase in apoptosis and depletion of thymic progenitors. Apoptosis in SIV infected macaques correlated with peak viremia and disruption of the apoptotic pathway (Rosenzweig et al., 2000). Pathogenicity of the virus on the level of apoptosis in the thymus was observed in macaques infected with a pathogenic and non-pathogenic HIV/SIV hybrid virus (SHIV) (Iida et al., 2000). Recent thymic emigrants can be determined by measuring T cell receptor excision circles (TRECs) in peripheral blood and provide a mirror of thymic function. Increased or stable levels of TRECs were found early after infection, but TREC levels decreased later when depletion of CD4<sup>+</sup> thymocytes and apoptosis were observed in one of the animals (Sodora et al., 2002). Elevated TREC levels as compared to non-infected controls were observed in macaques infected with a less pathogenic SIV $\Delta$ nef virus indicating that the thymus can maintain its function in the presence of low viral loads (Ho Tsong Fang et al., 2005). However the thymus as the major player in maintaining naïve peripheral CD4<sup>+</sup> T cells has been disputed. Proliferation of peripheral T lymphocytes does also play a role in maintaining peripheral T cell homeostasis. Thymectomies of juvenile SIV infected macaques showed that TRECs in peripheral blood decreased after thymectomies. However, thymectomy in the SIV infected animals did not impact their clinical course or the ratio of CD45RA<sup>+</sup> to CD45RA-CD4<sup>+</sup> T cells (Arron et al., 2005).

## 10. Humanized mouse models to study HIV-1 immuno-pathogenesis

A small, easy-to-handle animal model that would facilitate the study of the pathophysiology of acute HIV-1 infection has been warranted after we were confronted with the HIV pandemic in the 1980s. Normal mice cannot be studied due to the limited species tropism of HIV, and therefore humanized mouse models have been instrumental to study HIV infections. Over the last decades significant progress has been made in the generation of humanized mouse models (Figure 4) with a functional human immune system, which has not only added to our insight into the development of human stem cells and the reconstitution of a human immune system in an *in vivo* setting, but also initiated studies on the preclinical testing of novel antiviral compounds, and the evaluation of vaccines.

Initially, humanized mice were generated using mice with the *scid* mutation in the C.B-17 mouse strain (Bosma et al., 1983). Such mice lack mature T and B cells due to a mutation in the *prkdc* gene, which is involved in rearrangement of TCR and Ig genes (Kirchgessner et al., 1995). Adoptive transfer of human peripheral blood lymphocytes (PBL) in C.B-17 SCID mice, which is commonly referred to as the human (hu) PBL-SCID model, resulted in the reconstitution of mature human T and B cells (Mosier et al., 1988). Although these transferred human lymphocytes only survived for a short period of time limiting long-term studies, hu-PBL-SCID mice have been used to study certain aspects of HIV-1 infection, including the importance of the state of activation of human CD4<sup>+</sup> T cells at the time of primary infection in determining HIV-1 pathogenicity (Fais et al., 1999; Rizza et al., 1996). Resolutions to bypass the limited survival time of human lymphocytes were obtained by the

transfer of human pluripotent progenitor cells ensuring development of multiple hematopoietic lineages. In such an optimized setting, human fetal thymic (FT) lobes and pieces of fetal liver (FL) were transplanted under the kidney capsule in C.B-17 SCID mice (McCune et al., 1988). In this hu-thymus (Thy)/liver (Liv) SCID mouse model almost exclusively T cells developed, which transiently migrated from the human thymus graft to the periphery. When compared to the first model, also this latter model suffers from the disadvantage that human T cell survival is reduced, although this is more apparent later after transplantation. This hu-Thy/Liv-SCID model has been extensively used for the analysis of human hematopoiesis, especially T cells, and as an animal model of HIV infection (McCune, 1997). HIV-1 injection in the thymic implant of hu-Thy/Liv-SCID mice resulted in significant HIV-1 infection not only in the Thy/Liv implant, but also in the spleen and peripheral blood, which indicated that HIV-1 infection could spread from the thymus to the peripheral lymphoid compartment (Kollmann et al., 1994). The effect of HIV-1 infection on thymocyte maturation and depletion depended upon the strain of HIV-1 infecting the thymus (Kollmann et al., 1995).

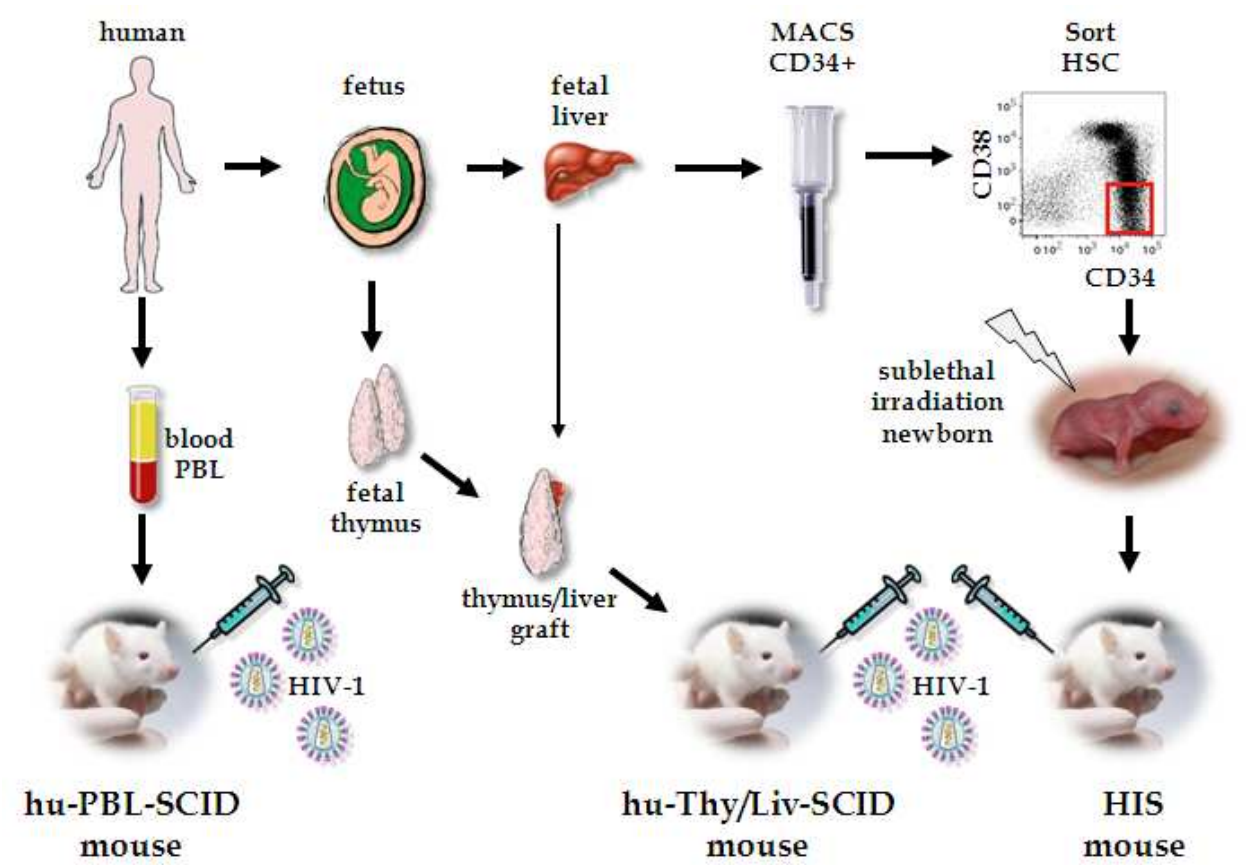


Fig. 4. Humanized mouse models to study HIV-1 infection *in vivo*. Several ways to generate humanized mouse models have been established (see text for further details). Human peripheral blood lymphocytes (hu-PBL) are injected in severe combined immunodeficient (SCID) mice to generate hu-PBL-SCID mice. Pieces of fetal liver (Liv) and thymus (Thy) can be grafted in SCID mice to generate the hu-Thy/Liv-SCID mouse. To create a human immune system (HIS) mouse, newborn immunodeficient mice are injected intrahepatically with CD34<sup>+</sup>CD38<sup>-</sup> human stem cells (HSC) after cell sorting from the fetal liver (or alternatively cord blood, bone marrow, mobilized peripheral blood, not shown).

To further optimize the humanized mouse model approaches were established to repopulate sublethally irradiated C.B-17 SCID mice with progenitor cells from human bone marrow or umbilical cord blood (Lapidot et al., 1992; Vormoor et al., 1994). In addition to development of T cells these mice also developed B cells and myeloid cells, which presented the potential to establish a humanized mouse model with a functional human immune system. Ablation of mouse NK cells further increased the frequency of thymopoiesis in animals reconstituted with human umbilical cord blood cells. This was not only demonstrated when using antibodies to deplete mouse NK cells (Kerre et al., 2002), but also when using recipient mice with a NK cell deficient genetic background (Greiner et al., 1998). Reconstitution of mice that are either defective in NK cell activity (non-obese diabetic (NOD)/SCID mice (Ogasawara et al., 2003) or NOD/SCID/ $\beta 2m^{-/-}$  mice (Kollet et al., 2000) or have impaired NK cell development (NOD/SCID/ $\gamma_c^{-/-}$  mice (Hiramatsu et al., 2003) were shown to have improved human T cell development. Despite their promise, however, repopulation of human T cells in the periphery of these mice are suboptimal (Hiramatsu et al., 2003; Kerre et al., 2002; Kollet et al., 2000). In addition to the genetic background, also the age of the mice upon reconstitution of HSC appears crucially important. Several groups observed that injection of human HSC to sublethally irradiated newborn BALB/c Rag2 $^{-/-}$   $\gamma_c^{-/-}$  (BALB-Rag/ $\gamma$ ) mice improved the reconstitution success rate (Gimeno et al., 2004; Traggiai et al., 2004). More than 80% of these humanized mice, either referred to as "human adaptive immune system Rag2 $^{-/-}$   $\gamma_c^{-/-}$  mice" (huAIS-RG) (Traggiai et al., 2004) or "human immune system BALB-Rag2 $^{-/-}$   $\gamma_c^{-/-}$ " (HIS BALB-Rag/ $\gamma$ ) (Gimeno et al., 2004), exhibited at least 10% or more human CD45 $^{+}$  cells in peripheral blood and other lymphoid organs. Similar improvements were observed in newborn NOD/SCID/ $\gamma_c^{-/-}$  (NOG) mice (Ishikawa et al., 2003; Ishikawa et al., 2005; Ito et al., 2002; Shultz et al., 2005) and to a lesser extent in newborn NOD/SCID/ $\beta 2m^{-/-}$  mice when used as recipient of HSC (Kollet et al., 2000).

Part of the human CD4 $^{+}$ T cells in the spleen and peripheral blood of NOG mice express the co-receptors CXCR4 and CCR5 (Watanabe et al., 2007). In the thymus, CXCR4 is expressed on the majority of CD4 $^{+}$ CD8 $^{+}$  thymocytes as well as on small numbers of CD4 $^{+}$ CD8 $^{-}$  cells and CD4 $^{-}$ CD8 $^{+}$  cells, while CCR5 was only expressed on a minor proportion of the thymocytes (Watanabe et al., 2007). Notably, early after HIV-1 infection of huNOG mice no viremia could be detected, and a detectable viral load was only observed late after infection using high doses of R5-tropic or X4-tropic HIV-1. No significant decline in the CD4/CD8 ratio was observed after R5-tropic virus infection of huNOG mice (Watanabe et al., 2007). Conversely, the HIS BALB-Rag/ $\gamma$  mice infected with a high dose R5-tropic HIV-1 did develop an inversion of the CD4/CD8 T-cell ratio in peripheral blood (Berges et al., 2006; Gorantla et al., 2007). After X4-tropic virus infection of huNOG mice a CD4 $^{+}$  cell decline was detected at later time points (Watanabe et al., 2007). These findings suggest that humanized mice are less susceptible to low dose infection and undergo a slow course of CD4 T-cell depletion as compared to HIV-1 infected individuals. In addition, immune responses to HIV-1 infection in HIS mice generated from newborns are suboptimal resulting in only poor development of virus-specific antibodies and absence of HIV-specific T cell responses (An et al., 2007; Baenziger et al., 2006; Gorantla et al., 2007; Sato et al., 2010).

A more sophisticated HIS mouse model has been generated using NOD/SCID mice that were co-transplanted with human fetal Thy/Liv and CD34 $^{+}$  HSC either from fetal liver (Lan et al., 2006; Tonomura et al., 2008) or bone marrow (BLT mice) (Melkus et al., 2006). BLT mice mounted stronger antigen-specific T-cell responses and T cell-dependent IgG production after in vivo antigen immunization (Melkus et al., 2006; Tonomura et al., 2008). Notably, a detectable viral load was observed in BLT mice after low dose infection with R5-



tropic virus, which was associated with the depletion of human CD4<sup>+</sup> T cells in the blood (Brainard et al., 2009). Also, it was demonstrated that B cells in BLT mice were able to mount robust virus-specific antibody responses, although these responses were delayed as compared to adult human HIV infection (Brainard et al., 2009). Besides the intravenous route of HIV infection, HIS mice can be infected with HIV by relevant intravaginal and intrarectal routes (Berges et al., 2008; Denton et al., 2008; Sun et al., 2007). Taken together, this advanced humanized BLT mouse model shows great potential as a model to study HIV infection *in vivo* and holds promise for prospective studies to test the efficacy of candidate HIV vaccines and to validate the activity of antimicrobial agents acting at mucosal surfaces.

## 11. Summary and conclusion

Our knowledge of HIV infection of the thymus is primarily derived from animal models except for incidental reports of HIV infection *in vivo* in infants, children and adults (Bandera et al., 2010; Brunner et al., 2011; Calabro et al., 1995; Gaulton et al., 1997; Haynes et al., 1999; Rosenzweig et al., 1994). Indirect evidence of the impact of antiretroviral therapy on recovery of the thymus has been obtained through imaging studies and measurements of TRECs (Dion et al., 2007; Halnon et al., 2005; Lee et al., 2006; McCune et al., 1998 and reviewed in (Ho Tsong Fang et al., 2005)). It is clear that the thymus plays an important role in HIV infection and in the regeneration of naïve CD4<sup>+</sup> T cells. Thymocytes, but also minor thymocyte subsets are targets for CCR5- and CXCR4-tropic HIV. These subsets include CD4<sup>+</sup> TCRα/β, TCRγ/δ and CD161<sup>+</sup> cells resembling NK-T cells (Gurney et al., 2002), Treg, cDC and pDC. Furthermore, pDC stimulated with HIV produce high levels of IFN-α, and thereby contribute to immune activation in particular when IFN-α levels are not controlled. Notably, insufficient T cell regeneration may not only be at the level of the thymus, but also at the level of hematopoietic stem cells. This is illustrated by the recent finding that the function and numbers of CD34<sup>+</sup> hematopoietic stem cells in peripheral blood of HIV infected individuals are impaired despite control of viral replication (Sauce et al., 2011). Also, impaired progenitor cell function of umbilical cord blood CD34<sup>+</sup> cells, including decreased cloning efficiency and generation of CD4<sup>+</sup> T lymphocytes in fetal thymic organ culture, was observed in HIV-negative infants born to HIV-positive mothers (Nielsen et al., 2001). Consistent with these results, failure of hematopoiesis leading to impaired T cell regeneration was observed in SIV infected macaques and found to be unrelated to viral loads (Thiebot et al., 2005). Finally, a recent observation suggests that CD34<sup>+</sup> cells can also be infected with HIV (Carter et al., 2010). Collectively, these results imply that HIV in addition to thymic destruction can also adversely affect thymic progenitor cells, likely caused by immune activation, and thereby contribute to T cell depletion in HIV infected individuals.

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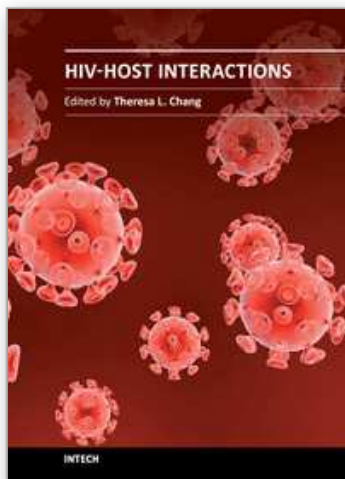


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### **HIV-Host Interactions**

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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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