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“Humanized mice for HIV and AIDS research”

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Abstract

HIV has a very limited species tropism that prevents the use of most conventional small animal models for AIDS research. The *in vivo* analysis of HIV/AIDS has benefited extensively from novel chimeric animal models that accurately recapitulate key aspects of the human condition. Specifically, immunodeficient mice that are systemically repopulated with human hematolymphoid cells offer a viable alternative for the study of a multitude of highly relevant aspects of HIV replication, pathogenesis, therapy, transmission, prevention, and eradication. This article summarizes some of the multiple contributions that humanized mouse models of HIV infection have made to the field of AIDS research. These models have proven to be highly informative and hold great potential for accelerating multiple aspects of HIV research in the future.

Keywords

humanized mice; HIV; HIV latency; HIV persistence; BLT; NOD/SCID; MoM; ToM

HIV Tropism

HIV is a human-specific pathogen that does not cause disease in other species, although it can replicate in chimpanzees [1–5]. HIV cannot infect mice, rats, rabbits, or macaques [6–10]. The species-specificity of HIV is not limited to its interactions with its receptor CD4 and co-receptors CXCR4 or CCR5 on host cells. Mouse and rat cells that have been engineered to express human CD4 and either CCR5 or CXCR4 on their cell surface do not support HIV replication [7,10]. Additional viral restriction factors like TRIM5 α and APOBEC3 limit the ability of HIV to replicate in cells from other species [11–17]. The multiple barriers to HIV replication found in other species limit the availability of adequate animal models to study fundamental aspects of HIV biology and its interactions with the host.

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Human-mice chimeras

Human hematopoietic stem cells have the unique capacity of engrafting, greatly expanding, and repopulating immunodeficient mice with virtually all different types of human immune cells [18–27]. Humanized mouse models are produced *via* transplantation of CD34+ stem cells and/or implantation of human tissue into immunodeficient mice [27]. Depending on whether tissue or CD34+ cells are used and the strain of mouse, this results in systemic or local reconstitution with human hematopoietic cells. Different humanized mouse models are repopulated with different human immune cell populations that can include B cells, monocytes/macrophages, dendritic cells, NK cells and T cells. The types of human cells present in each model depends on the strain of immunodeficient mouse used. However, all animals generated with CD34+ cells first generate human myeloid and B cells. Only certain mouse strains human T cells are generated. These T cells are produced in the mouse thymus and presumed to be educated in the context of mouse major histocompatibility complex (MHC)[28–30]. In order to generate human T cells that are educated in the context of bona-fide human MHC (HLA molecules), human thymus tissue is implanted under the kidney capsule. Over time, the thymic tissue involutes and disappears. Co-implantation of thymus with a piece of autologous human liver results in the creation of a functional human thymus that persists for the life of the animal and continuously produces human thymocytes (SCID-hu thy/liv mice, T cell-only mice (ToM), and bone marrow/liver/thymus (BLT) mice). In this unique circumstance, T cells can develop in the presence of human thymic epithelium, resulting in HLA class I and II restriction [31,32]. BLT mice differ from SCID-hu thy/liv mice and ToM in that they also receive an autologous human bone marrow transplant after the implantation of human liver and thymus tissue, from which T cell progenitors and other human hematopoietic cells are derived. As a result, BLT mice are systemically reconstitution with virtually all other types of human hematopoietic cells [33,34]. Several new strains of immunodeficient mice have been recently used to generate humanized mice that have been extensively employed to study relevant aspects of HIV *in vivo* [35].

Current Humanized Mouse Models

Humanized mouse models currently available (Figure 1) are capable of replicating both HIV-1 and 2 exclusively in human immune cells that are present both in the periphery and in tissues. Human immune cells present in these different types of humanized mice are capable of inducing innate and adaptive immune responses, albeit with different efficiency [27,34,36–39]. The systemic distribution of human immune cells in all tissues examined, render humanized mice susceptible to HIV infection by the same natural routes in which humans acquire HIV. Specifically, humanized mice can be infected with HIV after a parenteral, rectal, vaginal, or oral HIV exposure. Infection can be readily monitored in peripheral blood plasma using conventional viral load assays and it results in progressive CD4+ T cell depletion in peripheral blood and tissues. Similar to what occurs in humans, early after infection, there is a dramatic and rapid depletion of CD4+ T cells in mucosal tissues like the gastrointestinal (GI) tract of humanized mice that is not reflected in peripheral blood. One important attribute of humanized mice is that HIV infection can be treated with the same antiretroviral drugs that are used in humans [40–46]. Also like in

humans, treatment of HIV infection in humanized mice results in systemic recovery of CD4 T cells.

As with any animal model, there are limitations to the use of humanized mice in HIV research. These include the relatively small volume of peripheral blood plasma that can be obtained longitudinally from the same animal for viral load analysis, the limited number of peripheral blood cells that can be used for *ex vivo* functional analysis, and their relatively short life-span. Therefore, humanized mice are an accelerated model to evaluate relevant aspects of HIV infection. Due to the fact that humanized mice are xenographs between humans and mice, the structure of their secondary lymphoid tissues do not always fully replicate what is observed in humans. In addition, wasting disease can develop over time in highly engrafted animals [28,47]. However, lymphoid structure can be improved by immunization with sheep red blood cells and recent data indicates that wasting disease may be eliminated in humanized mice generated in new immunodeficient mouse strains [34,48]. Humanized mouse models can mount adaptive immune responses. Presently, human IgG immune responses in most humanized mouse models are not optimal and improvements will be needed to extend their usefulness for vaccine studies [27,28,49,50]. Current models have served to test the effectiveness of immune approaches to control HIV replication and kill infected cells [45,51–53].

The GI tract of humanized mice, rectal transmission, HIV prevention and persistence

Robust reconstitution of the reproductive and GI tracts of humanized mice with human immune cells has allowed for in vivo experimentation to study important aspects of mucosal HIV transmission, and more importantly, the evaluation of possible prevention strategies. The presence of human immune cells in the GI tract of humanized mice was first described in BLT humanized mice by Melkus et al [34]. Human T cells, B cells, and myeloid cells were observed in aggregates resembling gut-associated lymphoid tissue (GALT) [34]. Sun et al. [39] performed a detail flow cytometric characterization of the different types of human cells present in the GI tract of BLT mice and showed the presence of human T and B cells, monocyte/macrophages, and dendritic cells in all of the segments of the gut. An important part of these studies was the demonstration of lamina propria (LP) and intraepithelial (IE) CD4+, CD8+ and CD4+CD8+ T cells in the small and large intestines [39]. Indicators of the faithful reconstitution of the GI tract in BLT mice were 1) the fact that the human intestinal T cells present in BLT mice display a memory phenotype, 2) the presence of double positive T cells, a feature that is characteristic in human tissue, and 3) the presence of CD8 single positive T cells in the lamina propria that expressed both the CD8 α and CD8 β chains which is in contrast with the exclusive expression of the CD8 α chain in CD4+CD8+ T cells also found in the lamina propria [39,54,55].

The existence of human immune cells in the GI tract of other humanized mouse models has also been described [56–58]. Denton et al. investigated the differences and similarities in the human immune reconstitution of the GI tract between multiple humanized mouse models [59] and noted that regardless of the mouse strain or the humanization protocol (i.e.

humanization by CD34+ transplantation alone or CD34+ transplantation of thy/liv implanted animals), human immune cells, including human T cells, were present in the peripheral blood. However, qualitative and quantitative differences have been observed between the different models in reconstitution of the GI tract with human immune cells [59,60]. Notably, immune aggregates are virtually absent in humanized mice generated using NOD/SCID/ $\gamma_c^{-/-}$ (NSG) immunodeficient mice due to the lack of a common gamma chain [61]. However, despite the absence of GALT structures in BLT mice constructed using NSG mice, their GI tract is well reconstituted with human T cells, monocyte/macrophages, and dendritic cells. Nevertheless, human B cells are almost completely absent in the gut of these animals. Consistent with these observations human IgA1+ and IgA2+ cells were extensively found in the lamina propria of NOD/SCID BLT mice but rarely found that of NSG BLT mice suggesting that the existence of human plasma cells in the intestinal lamina propria of BLT mice is dependent on the presence of GALT structures.

Humanized BLT mice were the first model ever used to study rectal HIV transmission. Sun et al. showed that BLT mice could be infected after rectal exposure to HIV and that infection resulted in significant destruction of the human T cells present throughout the GI tract [39]. BLT mice have been also used to investigate the *in vivo* efficacy of topical microbicides to prevent rectal HIV transmission [62]. Specifically, this model has been used to 1) demonstrate that systemic and topical tenofovir is highly effective at preventing rectal HIV transmission, 2) investigate the stability of drug resistance mutations *in vivo*, and 3) evaluate transmission of drug resistant viruses [41,62]. The availability of efficient drug regimens capable of effectively suppressing HIV replication in BLT mice have made this model useful for the study of HIV persistence [42,53,63,64]. Currently, BLT mice are being used to investigate HIV persistence in the GI tract. In the future, this will facilitate the evaluation of HIV eradication approaches targeting the HIV reservoir in the GI tract.

The female reproductive tract of humanized mice, vaginal transmission, HIV prevention and persistence

Repopulation of the female reproductive tract (FRT) of BLT mice with a full complement of human hematopoietic cells has made this model a good system for the evaluation of vaginal HIV transmission and prevention strategies [40,46,65–67]. Specifically, HIV is observed in the peripheral blood plasma of BLT mice exposed vaginally to HIV during acute infection and can be detected as early as one week after exposure [40,43,46,67]. Vaginal infection results in sustained levels of plasma viremia and the progressive systemic loss of CD4 T cells [40]. Vaginal HIV acquisition in BLT mice can be prevented by topical administration of microbicides or antiretrovirals which result in different levels of protection [65]. BLT mice have also been used to evaluate the efficacy of long acting formulations of antiretrovirals for HIV prevention after vaginal exposure [46,67].

Recently, Olesen et al performed a detailed and comprehensive phenotypic characterization of the human lymphocyte subsets present in the FRT and cervicovaginal secretions (CVS) of BLT mice [68]. HIV levels and cellular dynamics in CVS during HIV infection were also analyzed together with virological suppression and cellular dynamics in the FRT and CVS

during suppressive antiretroviral therapy (ART). These analyses demonstrated that HIV replication occurs in the FRT soon after exposure and continues during the course of infection. Soon after vaginal HIV exposure, an increase of CD4+ T cells was observed in CVS, providing additional target cells for infection. The CD4+ T cell increase was then followed by a delayed increase of CD8+ T cells in CVS. Surprisingly, despite the strong suppressive effect of ART on the viral load in CVS, HIV-RNA+ cells were still present in both the FRT and CVS. However, when analyzed *ex vivo*, cells isolated from the FRT and CVS of ART-suppressed BLT mice did not transmit HIV in a sensitive co-culture assay. These observations are consistent with the concept that HIV treatment can prevent transmission. However, the presence of infected cells despite ART in the FRT indicate that this is a possible tissue reservoir for HIV that can contribute to persistence in treated individuals.

Humanized mouse models for HIV persistence

SCID-hu thy/liv mice were first described by McCunne *et al.* as a model for the analysis of human hematolymphoid differentiation and function in a human thymic organ without systemic reconstitution [69]. Brooks *et al.* [70] used SCID-hu thy/liv mice to show that HIV latency could be generated during thymopoiesis and that this process could contribute to the systemic establishment of HIV latency in peripheral organs. The authors postulated that the transcriptional silencing that occurs during thymopoiesis silenced the HIV promoter, resulting in latently infected single-positive CD4 T cells. *Ex vivo* induction of cells with either anti-human CD3 antibodies or cytokines, resulted in the production of virus showing that HIV latency was readily established in thymocytes. In a subsequent analysis, the authors demonstrated that latent HIV could be reactivated *ex vivo* using prostratin and IL-7 [71,72] and that reactivated cells could be killed by immunotoxins *ex vivo* [73].

Implantation of thy/liv tissue into NSG mice results in the development of a thymic organoid similar to the one that develops in SCID-hu thy/liv mice [74]. However, NSG-hu thy/liv mice have human T cells systemically distributed in all tissues, including the peripheral blood, spleen, thymus, lymph nodes, bone marrow, liver, and lung [74]. Because of the lack of any antigen presenting cells in these mice, they have been designated as T cell-only mice or ToM. ToM do not develop signs of graft *versus* host disease, are susceptible to HIV infection, and support high levels of viral replication as determined by the analysis of plasma vRNA [74]. HIV-infected cells are found in all tissues examined. ART suppresses viremia in ToM and its interruption results in viral rebound [74]. In ToM, HIV can establish latency in the absence of any other human hematopoietic cell types [74]

HIV persistence BLT mice

BLT mice have been extensively used to study HIV persistence, induction, and killing strategies in an effort to eradicate HIV-infected cells [42,53]. Latently infected cells are present in HIV-infected ART suppressed BLT mice at approximately 8 IUPM (infectious units per million) resting CD4+ T cells [42]. Administration of a toxin conjugated to an antibody targeting the HIV Env protein to ART-treated and suppressed animals resulted in a dramatic decrease in the systemic levels of residual HIV-infected cells [53]. Recently Tsai *et*

al evaluated the effect of panobinostat on HIV persistence *in vitro* and in BLT mice [63]. *In vitro* administration of panobinostat resulted in modest increases in the levels of HIV-RNA in peripheral blood cells from HIV-infected and suppressed patients. Exposure of latently infected resting CD4⁺ T cells isolated from suppressed patients to panobinostat also resulted in a modest induction of replication competent HIV. Administration of panobinostat to BLT mice resulted in robust increases in the levels of histone acetylation in all tissues evaluated confirming its *in vivo* activity [63]. Despite clear systemic bioactivity of panobinostat, no increases in HIV-RNA were noted in cells isolated from tissues of suppressed BLT mice. Analysis of the levels of latently infected resting human CD4⁺ T cells demonstrated no difference between animals that received panobinostat and those that did not (controls). These results were interpreted as suggesting that single induction agents might not be sufficient for HIV reactivation in tissues *in vivo* and that combinations might be needed. Consistent with this hypothesis, Halper-Stromberg et al recently published results using a combination of three different inducers that resulted in a reduction in the number of animals that rebounded after analytical treatment interruption [51].

Humanized mouse models for the study of HIV infection in the CNS

Humanized mouse models have been used for almost three decades to study the effects of HIV infection in the CNS [75]. For the most part, two different strategies have been used for these studies: 1) direct injection models where human cells are introduced into the brain of mice or 2) hematopoietic stem cell transplant models in which human cells naturally migrate into the brain of mice. Direct injection of HIV-infected cells into the brains of mice results in neuropathology similar to humans with HIVE (HIV encephalitis), including encephalitis, astrogliosis, multinucleated giant cell formation, infiltration of mononuclear phagocytes, and decreased microtubule-associated protein-2 (MAP-2) expression [76,77]. In another model, mice previously reconstituted with human peripheral blood leukocytes (PBLs) were inoculated with HIV-infected autologous macrophages in the brain [78,79]. In these mice, human PBLs were found in the meninges, choroid plexus, and the ventricles which are regions patrolled by circulating immune cells [80]. In infected animals, CNS entry of lymphocytes (including CD8⁺ T cells) was highest at seven days post macrophage injection.

To avoid the traumatic nature of direct brain injection, investigators have used mice humanized by human CD34⁺ stem cell transplantation [81]. In these models, human HLA-DR expressing cells were found in the cortex, meninges, and brain stem of uninfected mice. Interestingly, the numbers of these cells increased during the course of HIV infection and infected cells were found in the perivascular spaces and the meninges of the brain where CD8⁺ T cells were present [82]. Human CD8⁺ T cell depletion has been used in these models to accelerate disease. CD8⁺ T cell depletion results in increased HIV Gag expression in the cerebellum and an increased inducible nitrous oxide synthase (iNOS) expression in both the cerebellum and cortex [82,83]. These models have been extensively used to evaluate novel therapeutic approaches aimed at suppressing viremia in the brain with the goal of ameliorating disease [84–87]. One of the important limitations of these models is the lack of HIV-infected microglia since these cells have been postulated to be an important source of HIV in the CNS [88–90].

HIV infection of macrophages

Since the early days of the AIDS epidemic macrophages have been considered to be potentially important targets for HIV infection and contributors to pathogenesis and disease progression [91]. However, their contribution to HIV persistence has not been fully established. The fact that most strains of HIV (particularly transmitted/founder viruses) do not infect macrophages and that for each infected macrophage there are many more infected T cells has greatly complicated this analysis. In an effort to circumvent these difficulties, investigators using non-human primates have used several approaches to minimize the contribution of T cells. CD4 depletion prior to infection was shown to lead to SIV infection of macrophages that maintain a constant level of viral production [92,93]. In order to facilitate the analysis of HIV infection of macrophages *in vivo*, Honeycutt et al developed a novel humanized mouse model (designated myeloid-only mice or MoM) in which the only targets for HIV infection are human myeloid cells [94]. Using this model, Honeycutt et al demonstrated that macrophages (in the complete absence of human T cells) can sustain robust levels of HIV replication in peripheral blood for the life of the animals [94]. However, even though all viruses used for these studies replicated efficiently in humanized mice containing T cells (BLT mice and ToM), MoM could only be infected with a group of viruses that are characterized by their ability to infect cells containing low levels of human CD4 receptor on their surface [95]. None of the so called “T cell-tropic” viruses replicated in MoM confirming their restricted tropism for T cells and their inability to replicate in macrophages.

Honeycutt et al used several experimental lines of evidence to confirm replication of HIV in macrophages *in vivo*. Specifically, the presence of HIV-RNA in plasma, the presence of HIV-RNA in cells in all tissues analyzed, the presence of HIV antigen in macrophages in tissues, and electron microscopy analysis of HIV particles budding from macrophages in bone marrow were all used as evidence of productive HIV replication in MoM. The fact that the brain of MoM is reconstituted with human macrophages allowed the analysis of HIV infection in the central nervous system (CNS) of MoM. Readily detectable levels of HIV-DNA and HIV-RNA in the brains of infected MoM confirmed the presence of HIV-infected cells in this organ. Immunohistochemical analysis for productively infected cells in the brains of MoM was used to demonstrate the presence of HIV p24 expressing human macrophages in the brain stem, cerebellum, cerebral cortex, caudate putamen, corpus callosum, midbrain, and ventral striatum [95]. Finally, in order to determine if infected macrophages from MoM could transfer HIV infection to a new host, macrophage cells isolated from the tissues of infected MoM were injected into uninfected animals. In all cases, infected macrophages isolated from MoM were able to establish a de novo infection in a different host. To confirm that this is also the case in the normal setting where both human T cells and macrophages are present, cells from infected BLT mice were used to isolate tissue macrophages that were then injected into naïve animals. This transfer of macrophages also resulted in the establishment of infection in the new host. These results demonstrate that HIV present in macrophages of BLT mice and MoM can efficiently transmit de novo infection into a new host and replicate *in vivo* in the presence or in the complete absence of human T cells.

These studies by Honeycutt et al establish tissue macrophages as true targets of productive HIV infection. Even though not directly demonstrated, these results also imply that tissue macrophages might serve as a reservoir for latent HIV infection. The fact that no infected monocytes are present (or are present at very low levels) in peripheral blood of patients and MoM strongly indicates that analysis of HIV latency in myeloid cells in humans or other animal models will need sampling of tissues to perform persistence, latency and induction analyses as recently described by Avalos et al [96]. One important consideration regarding the use of any type of humanized mouse model for the study of HIV infection of the CNS is the fact that it has not been demonstrated that human hematopoietic stem cells can differentiate into microglial cells in the brain. Recent evidence from mice suggests that microglia are derived from precursor cells present in the yolk sac during embryonic development. Therefore, it is not likely that adult hematopoietic stem cells transplanted to adult animals or even neonates can give rise to human microglia in the brain. In order to overcome this limitation, newer models where human microglia cells reconstitute the brain of mice will have to be implemented [97,98].

In summary, humanized mouse models have contributed extensively to the study of virtually all aspects of HIV/AIDS. They have been particularly useful for the study of HIV replication, pathogenesis, transmission, prevention and more recently cure. The potential of humanized mice for the *in vivo* analysis of HIV persistence has not been fully realized. But important insight has already been derived from multiple experiments performed by numerous laboratories using several different models. Humanized mice could provide significant advantages for the analysis of several important aspects of HIV persistence and eradication. The advent of improved strains of mice to be used for humanization experiments together with a better understanding of the human/mouse interphase will undoubtedly benefit the field of HIV research.

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Highlights

1. HIV the causative agent of AIDS has an extremely limited tropism and does not replicate in mice, rats or non-human primates.
2. Humanized mouse models contain different components of the human hematolymphoid system that permit HIV replication in a small animal model.
3. Humanized mouse models like the T cell only mouse or the myeloid only mouse permit the analysis of key aspects of HIV biology in individual cell types.
4. The systemic reconstitution of humanized mice with human cells permit the detail in vivo analysis of HIV persistence and possible eradication approaches.

Figure 1. Humanized mice for HIV research

Illustrated are five different humanized mouse models that have been extensively used for the study of HIV in vivo. Note that each model has a different type and/or distribution of cells. For example ToM have systemic repopulation with human T cells whereas MoM do not have any T cells but have a full complement of antigen presenting cells. BLT mice have both all different types of T cells in addition of a full complement of antigen presenting cells.