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INVITED REVIEW

Genetic Knockouts Suggest a Critical Role for HIV Co-Receptors in Models of HIV gp120-Induced Brain Injury

Ricky Maung · Kathryn E. Medders · Natalia E. Sejbuk · Maya K. Desai · Rossella Russo · Marcus Kaul

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Abstract Infection with HIV-1 frequently affects the brain and causes NeuroAIDS prior to the development of overt AIDS. The HIV-1 envelope protein gp120 interacts with host CD4 and chemokine co-receptors to initiate infection of macrophages and lymphocytes. In addition, the virus or fragments of it, such as gp120, cause macrophages to produce neurotoxins and trigger neuronal injury and apoptosis. Moreover, the two major HIV co-receptors, the chemokine receptors CCR5 and CXCR4, serve numerous physiological functions and are widely expressed beyond immune cells, including cells in the brain. Therefore, HIV co-receptors are poised to play a direct and indirect part in the development of NeuroAIDS. Although rodents are not permissive to infection with wild type HIV-1, viral co-receptors - more than CD4 - are highly conserved between species, suggesting the animals can be suitable models for mechanistic studies addressing effects of receptor-ligand interaction other than infection. Of note, transgenic mice expressing HIV gp120 in the brain share several pathological hallmarks with NeuroAIDS brains. Against this background, we will discuss recently completed or initiated, ongoing studies that utilize HIV co-receptor knockout and viral gp120-transgenic mice as models for in vitro and in vivo experimentation in order to address the potential roles of HIV gp120 and its co-receptors in the development of NeuroAIDS.

Keywords HIV-1 · Infection · AIDS · NeuroAIDS · HAND · Chemokine receptor · Neurodegeneration · Transgenic · Knockout · Animal model

R. Maung · K. E. Medders · N. E. Sejbuk · M. Kaul (✉)
Infectious and Inflammatory Disease Center,
Sanford-Burnham Medical Research Institute,
10901 North Torrey Pines Road,
La Jolla, CA 92037, USA
e-mail: mkaul@sanfordburnham.org

M. K. Desai · R. Russo · M. Kaul
Neuroscience, Aging and Stem Cell Research Center,
Sanford-Burnham Medical Research Institute,
10901 North Torrey Pines Road,
La Jolla, CA 92037, USA

R. Russo
Department of Pharmacobiology,
University of Calabria,
87036 Arcavacata di Rende, Italy

M. Kaul
Department of Psychiatry,
University of California,
San Diego, 9500 Gilman Drive,
La Jolla, CA 92093, USA

Introduction

Infection with the human immunodeficiency virus-1 (HIV-1) and acquired immunodeficiency syndrome (AIDS) remain 30 years into the epidemic a persistent public health problem worldwide. In addition to a progressive destruction of the immune system, HIV-1 also initiates a spectrum of neurological problems and neurocognitive impairments that historically have been described as NeuroAIDS but are now also comprehensively categorized under the term HIV-associated neurocognitive disorders (HAND) (Antinori et al. 2007). While much information has been gained over the years regarding HIV-1 infection of the periphery and the central nervous system (CNS) in general, the pathological, cellular and molecular mechanisms leading to HAND, NeuroAIDS and AIDS remain incompletely understood.

An important step in AIDS and NeuroAIDS research occurred in the mid 1990s, when it was discovered by

several groups that HIV-1 infection required, in addition to CD4, one or two chemokine receptors as co-receptors. The most prominent HIV co-receptors are CCR5 (CD195) (Alkhatib et al. 1996; Dragic et al. 1996; Choe et al. 1996; Doranz et al. 1996) and CXCR4 (CD184) (Bleul et al. 1996), and together with CD4 they provide the preferred binding site for the HIV-1 envelope protein gp120 on the virus' target cells.

Furthermore, several lines of evidence based on work of numerous investigators over many years strongly suggest that NeuroAIDS, HIV-1 associated neurodegeneration and consequent HAND may occur via at least two major mechanisms (reviewed in (Kaul 2008)). The first is neurotoxicity as a consequence of either direct exposure to HIV-1 and its fragments or indirect injury through neurotoxins released by infected or immune-stimulated, inflammatory microglia and macrophages (MΦ) in the brain (Giulian et al. 1990; Kaul et al. 2001; Gonzalez-Scarano and Martin-Garcia 2005; Lindl et al. 2010). The second assault of HIV on the brain comprises the impairment of neurogenesis (Krathwohl and Kaiser 2004; Tran et al. 2005; Poluektova et al. 2005; Okamoto et al. 2007).

Since HIV-1 was discovered and linked to the development of AIDS (Barre-Sinoussi et al. 1983; Hahn et al. 1984), multiple approaches have been taken to generate suitable animal models for studying HIV disease, including NeuroAIDS (Gardner and Luciw 1989; Klotman and Notkins 1996; Toggas and Mucke 1996; Ambrose et al. 2007; Nath et al. 2000; Van Duyne et al. 2009).

Animal models in AIDS and neuroAIDS research

The variety of model systems employed in AIDS research includes chimpanzees and other non-human primates, cats and rodents (rats and mice) (Nath et al. 2000; Ambrose et al. 2007; Gardner and Luciw 1989; Reid et al. 2001; Keppler et al. 2002; Klotman and Notkins 1996; Toggas and Mucke 1996; Van Duyne et al. 2009). Chimpanzees can be infected with some HIV-1 groups but rarely develop AIDS and are primarily employed in vaccine research (Nath et al. 2000). Other non-human primates, cats and rodents are not permissive to wild type HIV-1. However, several non-human primate species are susceptible to Simian Immunodeficiency virus (SIV) and cats can be infected by Feline Immunodeficiency virus (FIV) (Ambrose et al. 2007; Clements et al. 1994; Olmsted et al. 1989). Both viruses can cause in a species-specific fashion an AIDS-like disease and neuropathological changes or even encephalitis, and macaques and cats are therefore used for studies of the pathogenesis of AIDS and NeuroAIDS (Ambrose et al. 2007; Clements et al. 1994; Olmsted et al. 1989; Meeker et al. 1997; Jacobson et al. 1997; Clements et al. 2008). While SIV is considered to be the animal virus most closely related to HIV-1, significant differences exist between the viruses. Therefore, several SIV-HIV hybrid viruses have been generated in order to better adapt the SIV model for HIV research (Ambrose et al. 2007).

Among the various model systems, rodents have turned out to be useful in spite of the fact that they cannot be productively infected with wild type HIV-1. Interestingly however, two recently generated chimeric HIV mutants in which the envelope protein gp120 was replaced by the gp80 of ecotropic murine leukemia virus (EcoHIV) allowed for the first time to establish in mice a lasting lentiviral infection that also triggered an immune response (Potash et al. 2005). Furthermore, one of the chimeric viruses was shown to be neuroinvasive, suggesting its potential suitability for NeuroAIDS research.

Other approaches to generate small animal models for AIDS and NeuroAIDS research took advantage of the fact that certain mouse strains can be reconstituted with a human hematopoietic system which is permissive to HIV infection (Van Duyne et al. 2009; Dash et al. 2011). Numerous other studies have employed the intracranial injection of HIV-infected human monocyte-derived macrophages into the brains of mice with severe combined immunodeficiency (SCID). This model demonstrated that HIV-infected macrophages can cause a neuropathology that shares key features with post mortem brains from NeuroAIDS patients (Persidsky et al. 1996; Limoges et al. 2000; Poluektova et al. 2002; Sas et al. 2007). Furthermore, these studies indicated that HIV-infected cells in the brain can trigger a peripheral immune response.

Another important advantage of rodents, both mice and rats, is that they can be genetically modified (Klotman and Notkins 1996; Toggas and Mucke 1996; Van Duyne et al. 2009; Reid et al. 2001). Several transgenic mice and a rat have been generated that express an entire HIV genome and develop AIDS-like diseases (Leonard et al. 1988; Iwakura et al. 1992; Hanna et al. 1998a; Hanna et al. 1998b; Reid et al. 2001). Furthermore, transgenic mouse microglia carrying the provirus of a macrophage-tropic HIV-1 were shown to release infectious virus (Wang et al. 2003). Transgenic mice expressing the entire HIV genome or distinct components of the virus, such as gp120, Tat or Vpr, in the brain show various degrees of neuropathology, including pruning of neuronal dendrites, loss of synapses and neurons as well as glial activation, and also behavioral alterations that recapitulate several features observed in NeuroAIDS patients (Thomas et al. 1994; Toggas et al. 1994; Berrada et al. 1995; Toneatto et al. 1999; Kim et al. 2003; Bruce-Keller et al. 2008; Jones et al. 2007; D'hooge et al. 1999). Overall, the exact spectrum of pathological features with resemblance to AIDS and NeuroAIDS depends on the specific animal model and ranges from

depletion of CD4+ T-cells to immunodeficiency to wasting disease to failure-to-thrive to neuronal injury and loss to behavioral impairment to shortened life span. Of note, studies employing injection of HIV-infected macrophages in the brain or HIV-infected humanized mice or transgenic expression of entire viral genomes are useful to investigate the sum of the pathological effects of all viral components, but do not allow to discern the potential contribution of a single viral factor. Therefore, approaches that use injection or transgenic expression of one viral component at a time appear very useful as well. A number of such studies have addressed the pathological potential of HIV-1 gp120, Tat and Vpr, and indeed suggested that isolated viral factors can produce some of the pathological characteristics of HIV disease and NeuroAIDS (Toggas et al. 1994; Berrada et al. 1995; Toneatto et al. 1999; Kim et al. 2003; Bruce-Keller et al. 2008; Jones et al. 2007; Bachis et al. 2006; Hauser et al. 2009). Mice have in comparison to all other animal models one additional advantage, the availability of many specific genetic knockout mutants. Thus, transgenic and genetic knockout mice allow studying the effect of viral and host factors in a way that is not possible in any other model.

The remainder of this article will discuss recent studies in the field of NeuroAIDS research that employed transgenic mice expressing HIV-1 gp120 in the brain and mouse strains deficient in the major HIV coreceptors CCR5 and CXCR4. As such this review will primarily focus on a selection from a variety of model systems that are available to investigate aspects of NeuroAIDS and in particular the potential role of viral gp120. Several other animal models for NeuroAIDS research will be presented in more detail elsewhere in this journal, and we encourage the reader to consider the here discussed findings in the context of data obtained in other models. Like all investigations using animal models, our studies served at least one of two purposes: either improving our understanding of the neuropathological mechanism(s) of HIV infection, or suggesting potential future therapies for NeuroAIDS.

Chemokine receptors, HIV-1 infection and neuroAIDS

Several excellent reviews extensively discuss the currently recognized 20 chemokine receptors and over 50 chemokines (Locati and Murphy 1999; Zlotnik and Yoshie 2000; Rot and von Andrian 2004; Cartier et al. 2005; Biber et al. 2006; Domanska et al. 2011). Chemokines are mostly small, ~7 to 14 kD, proteins that have been categorized into four subfamilies based on different cysteine-containing sequence motifs near their N-terminus, α or CXC, β or CC, γ or XC and δ or CX3C ligands (L). Chemokine receptors have been named in analogy, such as α or CXCR and β or CCR, and belong to the large family of seven transmembrane domain G protein-coupled receptors (Zlotnik and Yoshie 2000). Interestingly, chemokine receptors and their ligands are expressed in a wide variety of cell types in both the periphery as well as the central nervous system (CNS) (Locati and Murphy 1999; Rot and von Andrian 2004; Bajetto et al. 2001; Cartier et al. 2005; Biber et al. 2006; Miller et al. 2008; Domanska et al. 2011; Gorry and Ancuta 2011). Chemokines and their receptors were historically described as a biological system that controls cell migration, mostly as part of the immune defense system. However, it has become clear over time that this complex receptor-ligand network contributes to many more biological processes, including organ development, vascularization, cell proliferation and apoptosis, in both health and disease. Chemokine receptors play well recognized pathological roles in diseases such as asthma, cancer and, most prominently, HIV infection (Locati and Murphy 1999; Bisset and Schmid-Grendelmeier 2005; Durig et al. 2001; Domanska et al. 2011; Gorry and Ancuta 2011).

In HIV-1 infection, CD4 and the chemokine receptors CCR5 (CD195) and CXCR4 (CD184) likely provide the first sites of host-virus interaction. The virus binds via its envelope protein gp120 first to CD4 receptors, which are only located on cells of immune lineage, in order to then efficiently engage chemokine co-receptors and eventually infect its primary target cells, macrophages/microglia and $CD4^+$ T-lymphocytes (Bleul et al. 1996; Alkhatib et al. 1996; Dragic et al. 1996; Kaul et al. 2001; Gonzalez-Scarano and Martin-Garcia 2005). Besides CCR5, CCR3 possibly also facilitates HIV infection of microglia in the brain (He et al. 1997). While most macrophage/microglia-tropic (M-tropic) HIV are CCR5-preferring (R5) and most CD4+ T-lymphocyte-infecting HIV (T-tropic) are CXCR4-preferring virus strains (X4), many R5 viruses can readily infect CCR5-expressing T cell populations and several X4 viruses can spread among macrophages(Alkhatib et al. 1996; Dragic et al. 1996; Choe et al. 1996; Bleul et al. 1996). In addition, numerous HIV-1 strains exist that can use both CCR5 and CXCR4 (R5X4) and can propagate in macrophages and T cells (dual tropic) (Doranz et al. 1996). Therefore HIV tropism seems to be determined by more factors than co-receptor usage (Gorry and Ancuta 2011). CCR5, however, plays a crucial role in HIV-1 infection and disease. In fact, most sexually transmitted viral strains prefer CCR5, and a congenital deletion mutation, named CCR5Δ32, causes the absence of this chemokine receptor from the cell surface and offers significant protection from infection (Dean et al. 1996). Most interestingly, a recent transplantation of CCR5Δ32 hematopoietic stem cells into a HIV patient with acute myeloid leukemia allowed survival for already more than 20 month without detectable viral titer in the absence of anti-retroviral therapy (Hutter et al. 2009). In the presence of CCR5, its endogenous ligands,

namely 'macrophage inflammatory protein' (MIP)-1α (CCL3), MIP-1β (CCL4) and 'regulated-and-normal-T cell-expressed-and-secreted' (RANTES, CCL5), can slow progression to AIDS (Cocchi et al. 1995). However, once HIV infection is established, dual tropic and X4-preferring viruses can evolve, and these viruses usually herald progression to AIDS (Michael and Moore 1999). Interestingly, $CD4^+$ T-lymphocytes seem to be more efficient propagators of HIV-1 than macrophages, but also rapidly die from apoptosis, except for a certain number of memory cells that constitute a quiescent, latent reservoir (Pantaleo and Fauci 1995; Chun and Fauci 1999; Alexaki et al. 2008). Macrophages infected with HIV-1, on the other hand, appear to produce less virus but constitute a long-lived reservoir and are the primary suspects for trafficking HIV into the brain where the virus may then spread to local macrophages and microglia (Koenig et al. 1986; Kaul et al. 2001; Gonzalez-Scarano and Martin-Garcia 2005; Kraft-Terry et al. 2009).

Interestingly, expression of CCR5 and CXCR4 is not restricted to cells of immune lineages, such as macrophages and microglia. Neurons and astrocytes, which lack CD4, readily express the two major HIV co-receptors (Lavi et al. 1997; Halks-Miller et al. 1997; Rottman et al. 1997; Kaul et al. 2007). Of note, interaction between HIV-1 gp120 and CXCR4, independent of CD4, has been reported to trigger intracellular Ca^{2+} accumulation and signaling (Hesselgesser et al. 1997). Furthermore, the virus seems to be able to enter astrocytes via a process that requires a mannose receptor and leads to a non-productive infection (Liu et al. 2004). While neurons appear to resist HIV infection, direct interaction of gp120 with neuronal chemokine receptors may nevertheless contribute to neuronal injury (Hesselgesser et al. 1997; Hesselgesser et al. 1998; Wang et al. 2009). In any case, several lines of evidence suggest that activation of HIV co-receptors on $CD4^+$ macrophages, with or without resultant HIV infection, and subsequent release of neurotoxins, including excitotoxins, chemokines and pro-inflammatory cytokines, provide the predominant trigger for neuronal injury and death (Giulian et al. 1990; Giulian et al. 1993; Kaul and Lipton 1999; Porcheray et al. 2006; O'Donnell et al. 2006; Cheung et al. 2008; Eggert et al. 2010; Medders et al. 2010; Kaul et al. 2001; Gonzalez-Scarano and Martin-Garcia 2005; Kraft-Terry et al. 2009). In line with this hypothesis two recent studies observed that the amount of pro-viral HIV DNA in peripherally circulating monocytes and macrophages correlates well with HAND (Shiramizu et al. 2005; Shiramizu et al. 2006).

Development of NeuroAIDS in patients during life time is believed to underlie the neurological and neurocognitive complications subsumed under the term HAND. HIV-associated dementia (HAD) represents the most severe manifestation of HAND (Antinori et al. 2007) and has been correlated to a range of *post mortem* diagnosed neuropathological features that are often referred to as HIV encephalitis (HIVE). The neuropathological hallmarks include infiltration predominantly by monocytes and macrophages entering from the blood stream, activated resident microglia, microglial nodules, multinucleated giant cells, widespread reactive astrocytosis, myelin pallor, and decreased synaptic and dendritic density, combined with selective neuronal loss (Petito et al. 1986; Masliah et al. 1997a). Interestingly, cognitive dysfunction and HAND during life seem to correlate with evidence of excitatory neurotoxins in cerebrospinal fluid (CSF) and serum (Heyes et al. 1991) and the amount of pro-viral HIV DNA in peripherally circulating monocytes and macrophages (Shiramizu et al. 2005; Shiramizu et al. 2006). In contrast, HAND is not necessarily reflected by the numbers of HIV-positive cells, multinucleated giant cells or the abundance of viral antigens in brain tissue found at autopsy (Glass et al. 1995; Achim et al. 1994; Wiley et al. 1994; Masliah et al. 1997a). Instead, clinical signs of HAND coincide best with *post mortem* findings of decreased synaptic and dendritic density, selective neuronal loss (Masliah et al. 1997a; Achim et al. 1994; Wiley et al. 1994), increased counts of microglia (Glass et al. 1995), and elevated tumor necrosis factor (TNF)-α mRNA in microglia and astrocytes (Wesselingh et al. 1997).

The genome of HIV-1 encodes nine proteins with structural, regulatory or accessory functions (reviewed in (Ellis et al. 2007)). Most of these viral factors have been implicated in the process of infection and in the HIV life cycle; six of the proteins have been reported to directly or indirectly affect neurons and glia (Ellis et al. 2007). Beyond establishing the first virus-host interaction and initiating infection, the envelope protein gp120 seems to be a major inducer of apoptosis in infected and uninfected bystander lymphocytes (Perfettini et al. 2005a; Perfettini et al. 2005b) and has been implicated in brain injury underlying HAND (Brenneman et al. 1988; Giulian et al. 1993; Meucci and Miller 1996; Kaul and Lipton 1999; Liu et al. 2000; Kaul et al. 2001; Mattson et al. 2005). In fact, the envelope glycoprotein gp120s of various HIV-1 strains produce in vitro and in vivo injury and apoptosis in both primary human and rodent neurons (Brenneman et al. 1988; Lannuzel et al. 1995; Meucci and Miller 1996; Singh et al. 2005; Giulian et al. 1993; Toggas et al. 1994; Meucci et al. 1998; Kaul and Lipton 1999; Kaul et al. 2007; Hesselgesser et al. 1998). These observations may not be completely surprising considering the high degree of conservation between human, mouse and rat for the two major HIV-co-receptors and CD4. Homology in percent at the level of protein sequence between the various species is: hu CXCR4: 91% with rat CXCR4, 89% with mouse; 96% between mouse and rat; hu CCR5: 82% each with rat and mouse CCR5; 92% between mouse and rat CCR5; hu CD4: 56% with mouse CD4

(L3T4), 53% with rat CD4; 74% between mouse and rat (Maung et al. 2011).

Chemokine receptor knockout-mice in neuroAIDS research

In order to investigate the role of CCR5 and CXCR4 in neuronal injury and death as it can be induced by HIV-1 gp120, we employed mice deficient in either one or both of the viral co-receptors (Kaul et al. 2007). Mice expressing both alleles of both chemokine receptors served as wild type controls. Of note, embryos derived from murine chemokine receptor wild type between days E14.5 and E16 and rat embryos at days E16 to E17 give rise to cerebrocortical cell cultures that respond in an almost identical fashion to recombinant HIV gp120s from R5-, X4- and R5X4 viral strains in neurotoxicity experiments (Kaul et al. 2007). Mixed cerebrocortical cell cultures, containing neurons, astrocytes and microglia were prepared from mouse embryos of all four genotypes between days E14.5 and E16 and allowed to differentiate in vitro for 17 days before neurotoxicity studies. Interestingly, based on immunostaining with cell type-specific markers for neurons, astrocytes and microglia and with regard to the percentage of the different cell types, wild type and chemokine receptor-deficient cerebrocortical cell cultures appeared indistinguishable (Kaul et al. 2007). However, while the in vitro approach appears helpful by leveling the field for survival, growth and development of cerebrocortical cells with and without HIV co-receptors, a look at the in vivo situation reveals important peripheral and central differences between the genotypes.

CXCR4 knockout (KO) mice have been generated by three different groups (Ma et al. 1998; Zou et al. 1998; Tachibana et al. 1998). Mice heterozygous for CXCR4 gene deficiency are viable, fertile and appear indistinguishable from wild type littermates. In contrast, homozygous CXCR4-deficient animals die *in utero* or at the first day after birth (Ma et al. 1998). Although it has been estimated that about one third of CXCR4 KO embryos are dead at day E18.5, we found that they seem to stay alive throughout E14.5 to E16 (Kaul et al. 2007). The most prominent pathology of CXCR4-deficient mice revealed by histological analysis presented itself as severe alterations in bone marrow and cerebellum (Ma et al. 1998; Zou et al. 1998; Tachibana et al. 1998). All other organs appeared grossly and microscopically normal, although the lungs were collapsed, the kidneys showed vascular congestion and pronounced interstitial hemorrhage, and intestinal vascularization seemed to be abnormal (Tachibana et al. 1998). Interestingly, contrary to other CXCR4 mutant mouse strains generated in two different laboratories (Zou et al. 1998; Tachibana et al. 1998), no septal defects were observed in the CXCR4 mutant strains described by a third group (Ma et al. 1998).

Hematopoiesis in CXCR4-deficient mice is also affected. At E15.5, the bone marrow is hypocellular with remarkably reduced hematopoiesis compared to wild type littermates, and comprises primarily stromal cells and osteoclasts with severe reduction in all hematopoietic lineages. While surviving E18.5 KO embryos show cellularity comparable with wild type and normal numbers of maturing erythrocytes and megakaryocytes, hematopoiesis remains underdeveloped (Ma et al. 1998; Zou et al. 1998; Tachibana et al. 1998).

While B-lymphopoiesis in CXCR4-KO liver at E18.5 is strongly reduced compared to wild type and heterozygotes, T-lymphopoiesis appears undisturbed in CXCR4-deficient thymus. Myelopoiesis, however, is also defect in CXCR4 deficiency, with virtual absence of myeloid forms at day E18.5 (Ma et al. 1998; Zou et al. 1998; Tachibana et al. 1998).

Regarding the central nervous system, the cerebellum of CXCR4-deficient (and SDF-1 KO) mice displays a highly abnormal structure while cerebrum, basal ganglia, midbrain, and spinal cord appear normal. In the cerebellum, the external granular layer (EGL) seems diminished and chromophilic cell clumps are visible after H&E staining. Furthermore, the EGL is irregular, the overall shape of cerebellum is altered, and foliation is absent. Purkinje cells which are normally located immediately underneath the EGL, are located ectopically in the absence of CXCR4 (Ma et al. 1998; Zou et al. 1998). In addition, CXCR4 KO mice display significant defects in the formation of the hippocampus, in particular the dentate gyrus (Lu et al. 2002). A reduction in the number of neural precursors and cells in the rostral migratory stream indicate a severe disturbance of hippocampal neurogenesis. CXCR4 also plays a crucial role in the correct placement of interneurons in the neocortex during brain development (Stumm et al. 2003).

CCR5 KO mice have been generated independently by two groups (Zhou et al. 1998; Huffnagle et al. 1999). CCR5-deficient mice are viable, fertile and at birth indistinguishable from wild type or heterozygous littermates. Histopathological analysis of major organs does not indicate any abnormalities in gross morphology. No differences between CCR5 KO and wild type mice were found in cells from thymus, spleen, lymph nodes, and bone marrow using markers for T-, B-, granulocyte, and monocyte/macrophage type cell populations. Also, there was no significant change observed in macrophage recruitment in a disease model of glucan-induced granuloma. However, CCR5-deficient macrophages display reduced cytokine production compared to their wild type counterparts (GM-CSF, IL-1ß, IL-6=50%), although production of TNF-α and IL-10 appear to be normal. In the T cell compartment,

the lack of CCR5 goes along with enhanced cytokine production (IFNy: 5-fold, GM-CSF: 2.5-fold, IL-4: 2-fold). Interestingly, peripheral production of chemokines, namely CCR5 ligands CCL5/RANTES, CCL3/MIP-1α, or CCL4/MIP-1ß, seems to be not different between CCR5-expressing and deficient mice. On the other hand, depending on the antigen trigger CCR5 KO show enhanced cell-mediated or humoral immune responses compared to wild type controls (Zhou et al. 1998).

Over time, several studies have revealed that with regard to infections and inflammation, CCR5 plays important roles in the resolution of some diseases but exerts an aggravating effect in other pathological circumstances. As such, CCR5 KO mice present with more severe disease outcome in the case of infection with *L. monocytogenes* (Zhou et al. 1998), *Cryptococcus neoformans* (Huffnagle et al. 1999), *Toxoplasma gondii* (Luangsay et al. 2003; Khan et al. 2006), *Trypanosoma cruzi* (Machado et al. 2005), Influenza A virus (Dawson et al. 2000), Herpes Simplex Virus (HSV)-2 (Thapa et al. 2007), HSV-1 (Teixeira et al. 2010), and lethality in West Nile virus (WNV) infection (Glass et al. 2005).

In contrast, CCR5 KO mice show less severe disease or protection during Lipopolysaccharide (LPS)-induced endotoxemia (Zhou et al. 1998), IFNγ-induced pulmonary emphysema (Ma et al. 2005; Bracke et al. 2007), atherosclerosis due to high fat diet (Potteaux et al. 2006; Zernecke et al. 2006; Braunersreuther et al. 2007), inflammation-associated hepatic fibrosis (Seki et al. 2009) and in a model of cerebral malaria triggered by infection with *Plasmodium berghei* (Belnoue et al. 2003; Nitcheu et al. 2003)

Overall, the above reports suggest that differences due to the absence of the β-chemokine receptor emerge primarily with a challenge of the immune response. Still, a recent study of 12 to 18 month old CCR5 KO mice found in comparison to age-matched controls memory impairment, astrocytosis and increased β-amyloid deposition in the brain (Lee et al. 2009). As a note of caution, the controls in this study did not completely match the genetic background of the CCR5 KO animals. In contrast, our group has been studying the consequences of CCR5-deficiency for the CNS in a different mixed genetic background using a breeding strategy that allows for production of CCR5-expressing and –lacking animals as littermates. Thus, the animals in our investigations share a common genetic background. Interestingly, we found in a genome-wide gene expression analysis using RNA from whole brain tissue significant differential regulation between CCR5 KO and wild type mice for more than 250 genes (Maung et al. 2011).

CCR5-CXCR4 Double KO (DKO) mice were generated by our group through cross-breeding of animals first described by Ma and colleagues (CXCR4KO) and Huffnagle and collaborators (CCR5KO) (Ma et al. 1998; Huffnagle et al. 1999; Kaul et al. 2007). The new mouse line is maintained using viable CXCR4$^{+/-}$CCR5$^{+/-}$ and CXCR4$^{+/-}$CCR5$^{-/-}$ animals which allow for production of homozygous, single and double chemokine receptor KO embryos as well as wild type controls.

Cerebrocortical cultures with the various chemokine receptor deficiencies (CCR5 KO, CXCR4 KO, CCR5-CXCR4 double KO and wild type as control) enabled us to show that both CCR5 and CXCR4 can separately mediate the neurotoxic effect of gp120 depending on the co-receptor usage of the virus strain from which the envelope protein was originally isolated (Kaul et al. 2007). The fact that the absence of CCR5 or CXCR4 in mixed neuronal-glial cerebrocortical cells from mouse abrogates or significantly decreases neurotoxicity by CCR5- or CXCR4-preferring gp120s, respectively, resembles the specificity of HIV co-receptor usage in human cells. Thus, the murine system provides a suitable model for these functional studies of the two major HIV co-receptors. Moreover, only cerebrocortical cells of CCR5-CXCR4 DKOs were resistant to the neurotoxicity of any tested viral gp120. Interestingly, however, when we replaced microglia in CCR5-CXCR4 DKO cerebrocortical cell cultures with human monocytic THP-1 cells, which express both HIV co-receptors, neurotoxicity of gp120 was restored (Medders et al. 2010). This finding indicates that activation by HIV gp120 of viral co-receptors in macrophages and microglia may suffice to indirectly produce neuronal injury and death, and that CXCR4$^{-/-}$CCR5$^{-/-}$ neurons are still susceptible to macrophage toxins induced by HIV-1 envelope protein.

HIV-1 gp120-transgenic mice as animal model in neuroAIDS research

Three different genetically engineered mouse lines have been reported so far that express either HIV-1 gp120 or its precursor gp160 as transgene in the absence of other viral proteins. Of note, two of these transgenic mice have been specifically generated for NeuroAIDS research (Toggas et al. 1994; Berrada et al. 1995) while a third line was designed to study the effect of the viral envelope on CD4^{+} T lymphocytes (Finco et al. 1997).

The HIV gp120-transgenic mouse aimed at investigating the demise of T-cells in AIDS is a viral gp120-human CD4-doubly transgenic animal expressing both proteins in lymphocytes (Finco et al. 1997). The viral gp120 is derived from HIV-1 SF2 and is expressed under the control of a modified Thy1.2 promotor containing an immunoglobulin heavy chain enhancer (Thy-1Eμ) which leads to transgene expression in most peripheral T-cells and thymocytes, but

also the central nervous system. Therefore, it may not seem surprising that these animals develop besides antibody-dependent T-cell depletion also pathological changes in the blood–brain-barrier (BBB) (Toneatto et al. 1999). However, it remains unknown whether or not these animals display any additional neuropathological changes.

A transgenic mouse that expresses viral gp160 of the HIV-1 strain IIIB under the control of the human neurofilament light chain promotor in neurons shows expression of viral envelope in brain stem and anterior horns of the spinal cord and dendritic swellings in motor neurons and other fibers of the spinal cord (Berrada et al. 1995). Surprisingly, however, no expression is detected in cerebral cortex.

The first HIV gp120-transgenic mouse reported is apparently so far also the most studied model and expresses a soluble viral envelope gp120 of HIV-1 LAV in the brain in astrocytes under the control of the promoter of glial fibrillary acidic protein (GFAP-gp120-transgenic mouse) (Toggas et al. 1994). The expression of transgene is the highest in neocortex, olfactory bulb, hippocampus, tectum, selected white matter tracts, and along the glia limitans. Although this transgenic mouse only expresses viral gp120, it develops a neuropathology that is strikingly similar to human AIDS brains, including decreased synaptic and dendritic density, frank neuronal loss, increased numbers of activated microglia and pronounced astrocytosis (Toggas et al. 1994). The potential relevance of this model is supported by a comparable neuropathology that results when HIV-infected human macrophages are intracerebrally administered into SCID mice, an experimental approach that also closely recapitulates the above mentioned features of the neuropathology in human AIDS brains (Persidsky et al. 1996). The founder lines described in the first study of GFAP-gp120-transgenic mice also suggested that neuropathology required a sufficiently high expression of gp120 RNA while unfortunately at the time, due to a lack of suitable antibodies, the protein itself was not detected. However, a peripheral immune challenge with recombinant gp160 triggered a strong lymphocyte-mediated immune response and infiltration of the brain only in gp120-transgenic animals, but not non-transgenic littermate controls or in GFAP-LacZ transgenic mice, thus providing indirect evidence for the presence of envelope protein in the CNS of gp120-transgenic mice (Toggas and Mucke 1998). Several subsequent studies included an additional GFAP-gp120-transgenic founder line that expresses more easily detectable envelope protein levels and therefore is called gp120-transgenic *H*igh *P*rotein *E*xpressor, (HPX) line (Toggas and Mucke 1996; Garden et al. 2002; Lee et al. 2011; Maung et al. 2011).

The neuropathological features that have so far been described for the GFAP-gp120-transgenic mouse comprise: 1) Loss of neuronal dendrites at 3, 6, 10 and 12 months of age (Toggas et al. 1994), (Garden et al. 2002; Kang et al. 2010; Maung et al. 2011), (see Fig. 1 for immunofluorescence staining of neocortex of 6 months-old mice); 2) loss of synapses at 3 and 6 months (Toggas et al. 1994; Maung et al. 2011); 3) activated microglia at 3, 6, 10 months (Toggas et al. 1994; Kang et al. 2010; Maung et al. 2011); 4) astrocytosis at 3 and 6 months (Toggas et al. 1994; Maung et al. 2011), and 5) compromised neurogenesis at 2 and 4 to 5 months (Okamoto et al. 2007; Lee et al. 2011).

In addition, GFAP-gp120-transgenic mice display in comparison to non-transgenic littermate controls behavioral changes or impairment at 12 months, such as reduced escape latency, swimming velocity, and spatial retention (D'hooge et al. 1999) as well as reduced contextual but not cued fear conditioning at 9 to 13 months (Maung et al. 2011). In line with these findings, electrophysiological studies detect abnormalities in short- and long-term potentiation in the CA1 region of the hippocampus in gp120-transgenic mice (~53 day and 10.5 month-old mice) (Krucker et al. 1998), (Piña-Crespo et al, unpublished observations). Moreover, gp120-transgenic mice present with an altered acute response to Methamphetamine that manifests as changes in stereotypic behavior (Roberts et al. 2009).

Several studies have aimed at unraveling the potential pathological mechanisms underlying the neuropathological and behavioral features of GFAP-gp120-transgenic mice. Compared to non-transgenic controls, only young but not 6 months-old gp120-transgenic animals were found to have increased plasma corticosterone, and plasma and pituitary adreno-corticotropic hormone (ACTH) levels, indicating activation of the hypothalamic-pituitary axis (HPA) (Raber et al. 1996). This endocrine activation depended on activation of *N*-methyl-*D*-asparate-type glutamate receptors (NMDAR), neuronal nitric oxide synthase (nNOS) and reactive oxygen species (ROS) as it was inhibited by the non-competitive NMDAR inhibitor memantine, the nNOS blocker N^{G}-methyl-*L*-arginine (LNMA) and a superoxide dismutase (SOD)-transgene (Raber et al. 1996). Hence, excitotoxic and oxidative stress are suspected as major contributors to the development of gp120-induced brain injury and possibly NeuroAIDS.

On the other hand, activation of protein kinase C (PKC) may contribute to astrocytosis and potentially HIV gp120-associated neuronal injury (Wyss-Coray et al. 1996). Also, compared to non-transgenic littermate controls, gp120-transgenic animals show increased expression of matrix metalloproteinase (MMP)-2 (Marshall et al. 1998) and accumulation of phosphorylated protein Tau (pTau) (Kang et al. 2010), but it remains to be elucidated if these factors are contributing causes or mere consequences of gp120-initiated CNS insult. However, increased immunostaining

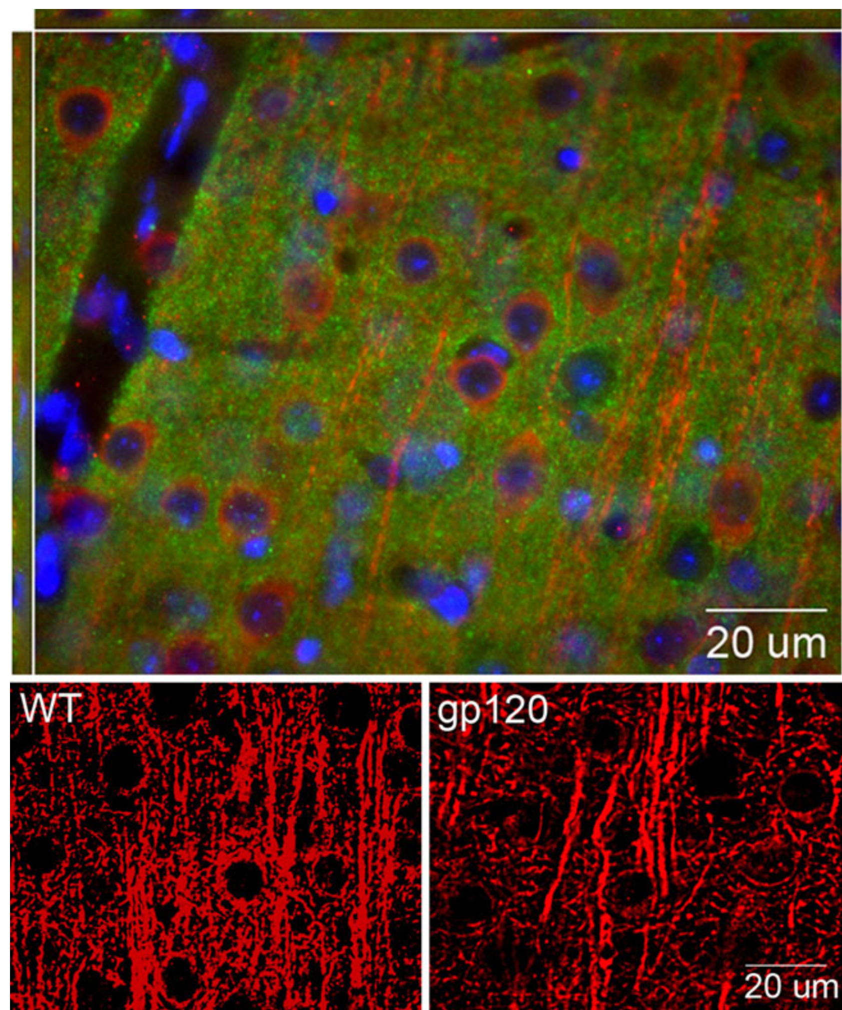

Fig. 1 Immunofluorescence staining of MAP-2-positive neuronal dendrites in cerebral cortex of HIV gp120-transgenic and non-transgenic, wild type control mice. Sagittal brain sections of 6 months-old gp120-transgenic and WT littermate controls were immunostained for neuronal MAP-2 (*red*). In the upper panel Synaptophysin (*green*) and DNA (*blue*) is shown in addition to indicate pre-synaptic terminals and nuclei, respectively. Fluorescence-labeled sections were analyzed using a Zeiss Axiovert 100 M inverted microscope and Slidebook software (Intelligent Imaging Innovations, Denver, CO) to record Z-stacks for 3D reconstruction (*upper panel*, 3 color fluorescence of WT brain) and deconvolution (*lower panels*, MAP-2 only). Representative images of mid-frontal cortex, layer 3, are shown. Note the blood vessel on the left side of the upper panel and the diminished MAP-2-positive structural features of gp120-transgenic in comparison to WT brain in the lower panel

for pTau was also found in brain specimen of NeuroAIDS patients in comparison to age-matched healthy controls, thus revealing another pathological feature of HIV-infected brains that is present in the transgenic mouse model (Kang et al. 2010).

Besides the investigation of putative mechanisms contributing to the development of NeuroAIDS, GFAP-gp120-transgenic mice have been used to explore potential strategies for protection of the CNS against damage associated with the expression of gp120 or HIV infection. Memantine, which acts as a non-competitive inhibitor of NMDARs and thus ameliorates excitotoxicity protected 1 to 6 weeks-old gp120-transgenic mice from loss of neuronal dendrites and pre-synaptic terminals (Toggas et al. 1996). Interestingly, human amyloid precursor protein expressed as transgene also protected neurons of gp120-transgenic and control mice at ~5 months of age against acute or chronic excitotoxic injury (Mucke et al. 1995; Masliah et al. 1997b). Another recent study found that voluntary exercise or a selective serotonin re-uptake inhibitor (Paroxetine) rescued hippocampal neurogenesis in gp120-transgenic mice (Lee et al. 2011), but it remained unclear if the protective effects extended into the cerebral cortex. On the other hand, we found in a collaborative study that erythropoietin (EPO) in combination with insulin-like growth factor-1 (IGF-1) abrogated neuronal injury and pTau accumulation, but not astrocytosis, in both cerebral cortex and hippocampus of gp120-transgenic mice (Kang et al. 2010).

Ongoing and future neuroAIDS-related studies utilizing chemokine receptor deficient and HIV gp120-transgenic mouse models

In order to extent our above mentioned in vitro studies on the potential role of HIV envelope gp120 and chemokine receptors in the development of NeuroAIDS into an in vivo model, we have crossed HIV gp120-transgenic with CCR5 KO mice (Maung et al. 2011). Investigating the role of CCR5 in gp120-transgenic mice seems most interesting because this chemokine receptor and its physiological

ligands influence HIV disease beyond a role in the initial HIV-target interaction leading to viral entry (Dolan et al. 2007; Ahuja et al. 2008). In fact, we previously found that CCR5-ligands, such as CCL4/MIP-1β and CCL5/RANTES prevent neurotoxicity of gp120 from R5-, X4-, and R5X4-viruses (Kaul et al. 2007). Thus, a clear rationale exists to hypothesize that CCR5 can affect the neuropathology of gp120-transgenic mice, even though the viral envelope in this model is derived from HIV-1 LAV (Toggas et al. 1994), a virus generally considered to be of the less frequent CXCR4-preferring variety that can infect macrophages (Valentin et al. 2000).

Cross-breeding of HIV gp120-transgenic with CCR5 KO mice produces viable and fertile offspring with all expected genotypes. Following an established approach, we first estimated the percentage of MAP-2 or Synaptophysin-positive neuropil by quantitative fluorescence and deconvolution microscopy in sagittal brain sections of 6 months-old gp120transgenic mice both expressing and lacking CCR5, using CCR5KO and wild type (wt)/non-transgenic animals as control. Interestingly, only CCR5wt/gp120-transgenic mice displayed a significant reduction in the percentage of MAP-2 positive neuropil and Synaptophysin immunoreactivity in comparison to all of the other three genotypes. Surprisingly, quantification of GFAP immunofluorescence revealed that astrocytosis occurred in brains of gp120-transgenic animals regardless of CCR5-deficiency. Thus, CCR5 is necessary to produce neuronal injury but not astrocytosis (Maung et al. 2011).

Microarray analysis of brain tissue from 6 months-old mice revealed that HIV-1 gp120 caused differential expression of about 800 genes in the presence of CCR5 but of only about 50 genes in the absence of the HIV co-receptor. Differentially expressed genes in CCR5wt/gp120tg mice suggested alterations in the function of the nervous system, immune response, cell trafficking, endocrine system, metabolism and cell death pathways compared to non-transgenic controls. Gene expression between CCR5KO/gp120tg and non-transgenic CCR5KO control mice differed mostly for GFAP and factors of the innate immune system. Interestingly, a database analysis showed that numerous genes differentially expressed in CCR5wt/gp120tg mice have also been reported for the brains of neurocognitively impaired AIDS patients and SIV-infected non-human primates, including the chemokines CCL2/MCP-1 and CXCL10/IP-10 (Maung et al. manuscript in preparation).

Ongoing and future studies will expand the characterization of the combined chemokine receptor knockout and transgenic mouse model and address questions regarding the mechanism of CCR5 function under in vivo conditions. Altogether, we propose that an in depth analysis of existing models for HIV disease of the CNS, including the one described here, will generate invaluable information. Because only if we learn what the currently existing models do or do not provide can we design the next generation of new and better animal models. Given the apparent limitations of all current animal models, new and improved in vivo models will be necessary for a better understanding and future treatment of NeuroAIDS.

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Conflict of interest disclosure The authors state that they have no conflict of interest.

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