HIV-1 and Kidney Cells: Better Understanding of Viral Interaction

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Key Words

HIV-associated nephropathy (HIVAN) • HIV-associated immune complex kidney disease (HIVICK) • Tubular cells • Podocytes • DEC-205

Abstract

HIV-associated nephropathy (HIVAN) is the most common disease affecting untreated seropositive patients of African descent. Besides genetic (African descent) and HIV-1 infection (environmental), specific host factors such as activation of renin-angiotensin-aldosterone system (RAAS) have also been demonstrated to play a role in the manifestation of HIVAN. The recent identification of *MYH9* as susceptible allele is a key step forward in our understanding for the pathogenesis of focal glomerulosclerosis in people of African-American descent. HIV-1 transgenic models have significantly advanced our knowledge base in terms of role of HIV-1 genes in general and individual gene in particular in the development of renal lesions mimicking HIVAN. These studies suggest that viral replication is not needed for the development of renal lesions. Renal biopsy data from HIVAN patients suggest that renal epithelial cells express HIV-1 genes and thus it may be sufficient to invoke HIVAN phenotype in the presence of specific host and genetic factors. On the other hand, immune response to infection may be required to induce HIV-1 associated immune complex kidney disease (HIVICK). Since renal cells lack conventional HIV-1 receptors, HIV-1 entry into renal cells has been a mystery. Recently, non-

conventional pathways have been demonstrated to facilitate HIV-1 entry into renal cells in in vitro studies. These include presence of DEC-205 receptors in renal tubular cells and lipid rafts in podocytes. However, HIV-1 entry through these pathways only allows non-productive infection. It appears that the presence of specific genetic and host factors in in vivo conditions may be facilitating the development of the productive HIV-1 infection in kidney cells.

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Introduction

HIV-associated nephropathy (HIVAN) is the most common cause of renal disease in untreated HIV-1 seropositive patients and represents approximately 50% of biopsy-proven cases of HIV-1-related renal disease [1]. It is characterized by focal glomerular sclerosis (FGS) often of the collapsing variant and microcystic dilatation of tubules. HIVAN occurs predominantly in patients of African descent and is considered to be caused by a combination of genetic, environmental and host factors [2]. HIV-1 infection is also associated with other immune-mediated renal diseases and is known as HIV immune complex kidney disease (HIVICK). Manifestation of HIVAN phenotype requires presence of multiple factors including genetic, environmental and host factors; therefore, to have insight into the HIVAN pathogenesis, one has to understand the involved basic science concepts. The present re-

Fig. 1. Confluence of factors contributing to the pathogenesis of HIVAN.

view has been designed to simplify the understanding of basic science concepts associated with the pathogenesis of HIVAN. Moreover, data pertaining to HIV-1 entry into renal cell has been reported only in in vitro studies and that too in cell culture system; therefore, at present we have only limited knowledge pertaining to in vivo HIV-1 entry into kidney cells.

Genetic Factors Contributing to the Pathogenesis of HIVAN

The recent reports have identified *MYH9*, a nonmuscle myosin, as an associated gene for the development of idiopathic and HIV-1-related focal segmental glomerulosclerosis in people of African descent [3]. In one of the studies, Papeta et al. [4] used combination of a gene profiling and linkage analysis to identify three genomic loci that regulate a network of podocyte genes and found that two of these loci confer disease susceptibility in a transgenic model of HIVAN. In another study, Kopp et al. [3] found the E-1 haplotype of *MYH9* had a large frequency difference between African-Americans (60%) versus European-Americans (4%) and was strongly associated with renal disease. *MYH9* is highly expressed in podocytes; however, the mechanism by which this non-coding polymorphism enhances disease susceptibility is not clear.

Environmental Factors Contributing to the Pathogenesis of HIVAN

There is enough evidence that indicate that kidney cells are infected in patients with HIVAN [1, 5]. The presence of HIV-1 mRNA has been detected in epithelia in

renal biopsy studies [1]. That highly active antiretroviral therapy (HAART) has been shown to slow down the progression of renal failure in HIVAN patients suggests direct viral effects on the kidney in HIVAN pathogenesis [6]. Moreover, relapse of HIVAN has been reported after cessation of HAART [7].

Host Factors Contributing to the Pathogenesis of HIVAN

Activation of the renin-angiotensin-aldosterone system (RAAS) in general, and Ang II in particular, have been implicated in the development of HIVAN [8–10]. Blockade of the production of Ang II as well as blocking the effect of Ang II has been demonstrated to slow down the progression of HIVAN in humans as well as in experimental animal models of the HIVAN [8–10]. Along the same lines, infusion of Ang II in HIVAN mice has been demonstrated to accelerate the development of renal lesions [11]. Since the presence of host factors such as activation of the RAAS and or African descent in other disease models are associated with classical FGS only (but not the collapsing variant), it appears that renal cell HIV-1 gene expression is a prerequisite for the development of HIVAN. As proposed in figure 1, HIVAN pathogenesis requires a confluence of host (RAAS activation), genetic (African descent) and environmental (HIV-1 gene expression) factors to develop the overt HIVAN phenotype.

Route of HIV-1 Entry into Renal Cells Is Controversial

HIV-1 enters susceptible cells by fusion of its envelope with the plasma membrane after binding to the CD4 molecule and interaction with the chemokine coreceptors CCR5 or CXCR4. However, HIV-1 entry into CD4-negative human cells has also been widely reported [12]. In the majority of instances, the HIV-1 entry into CD4-negative cells occurred through the endocytic pathways.

In the past, expression of HIV-1 receptors by renal cell has been a controversial issue [1]. However, the present consensus indicates that renal cells do not express classical HIV-1 receptors such as CD4, CXCR4, and CCR5 [1, 13]. Since renal cells do not express conventional HIV-1 receptors but have been shown to harbor HIV-1, the role of nonconventional receptors was suspected by many investigators [1]. The role of C-type lectins in HIV-1 pathogenesis has been highlighted by studies demonstrating

their capability to bind HIV-1 in a CD4-independent manner [14]. This large group of proteins such as dendritic cell-specific ICAM-3-grabbing nonintegrin (DC-SIGN), macrophages mannose receptor (MMR), and DEC-205 are specialized in the recognition of carbohydrate structures present on cellular and viral proteins and are implicated in several processes, including cell adhesion and antigen presentation. DC-SIGN is highly expressed in dendritic cells and was originally cloned for its ability to bind and internalize heavily glycosylated HIV-1 glycoprotein (gp) 120 protein [14]. DEC-205 is an endocytic receptor that plays an important role in antigen presentation [14]. Recently, DEC-205 has been demonstrated to serve as a receptor for HIV-1 entry into tubular cells [15].

Lipid rafts are membrane microdomains enriched with cholesterol and glycosphingolipids (GSLs). Many viruses including HIV-1 utilize a lipid raft-mediated endocytosis for their entry [16]. HIV-1 entry into T cells takes place through lipid rafts by using the raft-colocalized CD4 and chemokine receptors. Depletion of cholesterol from the target cell membrane has been associated with significant inhibition of productive infection in T cells. Recently, HIV-1 has been reported to utilize lipid rafts for its entry into human podocytes [17].

Role of HIV-1 Transgenic Models in the Understanding of HIVAN

In the beginning of the HIV era, there was no ideal model of HIVAN [1]. Rodents cannot be infected with HIV-1, and transgenic techniques allow only for the study of the post-integration phase of the HIV-1 cycle. Moreover, all HIV-1 transgenics use replication defective proviral DNA, eliminating the possibility of the formation of a new virus. Therefore, these transgenics are unlikely to have immune response typical of viral infection. Nevertheless, viral proteins often hijack the host cellular machinery to support viral replication, altering normal cellular function and thus mimicking the clinical manifestation of AIDS. However, many HIV-Tg mice that express HIV-1 genes in renal epithelial cells do not develop renal disease [18]. Moreover, specific host/genetic factors are needed for the development of the full HIVAN phenotype. These findings further confirm that expression of viral genes alone (not replicative infection) in the presence of specific genetic and host factors can induce HIVAN. On the other hand, viral replication or immune response to infection may be required

to induce HIVICK. Although at present these hypotheses are still debated, this is the prevailing view for the wide spectrum of renal lesions in patients with HIV-1 infection.

Tubular Cells Serve as a Reservoir for HIV-1

Infection of renal tubular cells both in *in vivo* and *in vitro* studies has been reported [5]. Tubular epithelial cells collected from children with HIVAN have been demonstrated to undergo HIV-1 infection in *in vitro* studies [5]. Interestingly, in an isolated case report, Winston et al. [19], demonstrated that HIV-1 gene expression by renal tubular cells persisted despite there was no viral load in the circulating blood. This group of investigators suggested that renal tubular cells have potential to serve as a reservoir for HIV-1 infection.

HIV-1 Enters into Tubular Cells via DEC-205 Receptor

Both human proximal tubular cell line (HK2 cells) and primary renal tubular cells have been recently demonstrated to express DEC-205 receptors [15]. Renal tubular cells also expressed DEC-205 *in vivo* [15]. In *in vitro* studies, interaction of HIV-1 with DEC-205 results in the internalization of the virus and the establishment of a nonproductive persistent infection of HK2 cells. The virus can be rescued by cocultivation of HIV-1-harboring HK2 cells with primary macrophages as well as T cells [15]. HIV-1 infection is blocked by pretreatment with specific anti-DEC-205 antibody. Moreover, expression of DEC-205 in 293T cells lacking the DEC-205 receptor renders them susceptible to HIV-1 infection. These findings suggest that DEC-205 acts as an HIV-1 binding receptor mediating internalization of the virus into cells expressing DEC-205, thereby allowing them to serve as a viral reservoir from which the virus can be rescued and disseminated through encounters with immune cells. These findings were further confirmed in primary renal tubular cells [15].

Proposed Role of GSLs in Tubular Cell HIV-1 Entry

Recently Khan et al. [20] demonstrated presence of globotriaosyl ceramide (Gb₃, it is the functional receptor for Shiga or Vero toxin on the cell surface) in both glomerular and tubular cell. Interestingly, HIV-1gp120

Table 1. Role of HIV-1 genes in the induction of kidney cell injury

HIV-1 genes	Findings indicating the role in kidney cell injury
<i>vpr</i>	Mice transgenic for Vpr alone develop FGS [24]. Vpr expression in podocyte alone has been demonstrated to cause FGS [24].
<i>nef</i>	Podocyte expression of <i>nef</i> alone can cause podocyte proliferation and dedifferentiation [25]. Its expression with other HIV-1 genes in podocytes alone can cause FGS [24]. Podocyte expression of <i>nef</i> alone is also associated with mesangial cell proliferation [35].
<i>env</i>	gp160 and gp120 modulate proliferation and apoptosis in mesangial cells [24, 32, 33]
<i>tat</i>	Mice transgenic for <i>tat</i> and <i>vpr</i> genes develop FGS [24]. Podocyte expression of <i>tat</i> along with other HIV-1 genes can cause FGS [14].
<i>rev</i>	Its expression in podocytes alone along with other HIV-1 genes can result in FGS [24].
<i>vif</i>	Its expression in podocytes alone along with other HIV-1 genes can result in FGS [24].
<i>gag</i> , <i>pol</i> , and <i>vpu</i>	No reported role in kidney cell injury [24].

could bind to Gb₃ in tubular cells only (VT-1-dependent and detergent-sensitive manner). Since the binding of VT-1 to Gb₃ in renal cells contributed to the pathogenesis of renal lesions in hemolytic uremic syndrome in children, these investigators speculated that interaction between gp120 and Gb₃ might be playing a role in the entry of HIV-1 into tubular cells. However, this hypothesis needs to be tested.

HIV-1 Induces Apoptosis in Tubular Cells

Renal tubular cells infected with HIV-1 as well as transduced with HIV-1 transgene (NL4-3, an HIV construct carrying all HIV-1 genes except *gag* and *pol*) have been reported to undergo apoptosis [21]. Moreover, HIV-1 proteins such as HIV-1 envelope gp120 (it constitutes the envelope surface unit of the HIV-1 virus) [22] have been reported directly to induce apoptosis of human tubular by activation of TGF (transforming growth factor)- β and smads (small/mothers against decapentaplegic ho-

mologues, downstream signaling genes of TGF- β) [22]. Additionally, human tubular cells expressing either Vpr or gp120 proteins have been demonstrated to undergo apoptosis [21, 23]. Human tubular cells expressing the HIV-1 transgene have also been demonstrated to undergo cell cycle arrest in G2/M phase [21]. Although it appears that at present we have limited knowledge of tubular cell entry of HIV-1, there is plenty of data indicating the direct effect of HIV-1 on tubular cells in general and HIV-1 proteins in particular contributing to the pathogenesis of HIVAN.

HIV-1 and Endothelial Cells

Although presence of endoplasmic reticular bodies in endothelial cells is a frequently encountered finding in patients of HIVAN, the role of endothelial cell HIV-1 infection in the pathogenesis is poorly understood. Cultured primary human glomerular endothelial cells express CXCR4, and cells can fuse with HIV-1 gp120 by a CD4 independent mechanism [24]. However, to have a clear understanding of the pathogenesis of HIVAN, it will be important to delineate the involved mechanism of HIV-1 passage across endothelial cells to reach podocytes and tubular cells.

Role of Podocytes in HIVAN

Podocytes are considered to be the key cell contributing to the HIVAN phenotype [1]. Renal biopsy data from HIVAN patients indicate that podocytes are infected with HIV-1 [1]. Moreover, in situ hybridization as well as polymerase chain reaction indicated that podocytes contained viral RNA and proviral DNA in HIVAN patients [25]. In HIVAN, podocyte dysfunction appears to be the result of the combination of the direct effect of viral gene products expression, host, and genetic factors [26–28] (table 1).

Problems Encountered in Carrying in vitro Studies in Podocytes

The study of podocytes in culture had been controversial because of its terminally differentiated phenotype. However, this problem was taken care of by the development of a conditionally immortalized human podocyte cell line by transfection with the temperature-sensitive

SV40-T gene [28]. These cells provide an accurate phenotype for studying proteins and pathways involved in human renal disorders including HIVAN.

HIV-1 Entry into Podocytes

A single study demonstrated the presence of CXCR4 in human podocytes [30]. However, the presence of conventional HIV-1 receptors in podocytes remains controversial [13]. Recently, HIV-1 entry into human podocytes has been reported in *in vitro* studies [17]. In these studies, podocyte viral entry was inhibited by disruption of lipid rafts [17]. On the other hand, cholesterol repletion to cholesterol depleted cells normalized the viral entry into podocytes [17]. These findings are consistent with the reported observations on dendritic cells (DCs)-HIV-1 binding and uptakes in immature DCs occur through a cholesterol-dependent pathway [31].

HIV-1 Induces Podocyte Apoptosis through the Induction of Oxidative Stress

Podocytes expressing HIV-1 have been demonstrated to display enhanced levels of oxidative stress [32]. In HIV-1-infected podocytes, HIV-1 activated the p66ShcA pathway, which was associated with deactivation of FOXO3A-mediated stress response program [32]. Consequently, HIV-1 transduced podocytes showed enhanced DNA damage and a compromised DNA repair program [32]. These effects of HIV-1 promoted apoptosis in human podocytes. On the other hand, podocytes lacking either p66ShcA or FOXO3A were resistant to the oxidative as well as pro-apoptotic effect of HIV-1 [28]. Interestingly, the HIV-1 protein Tat has been reported to stimulate proliferation of human podocytes in *in vitro* studies [33]; whereas, the HIV-1 protein Nef stimulated proliferation of mouse podocytes [34] but not of human podocytes [unpubl. obs.]. These *in vitro* findings are consistent with some of the characteristic *in vivo* podocyte phenotypes in HIVAN patients [1].

HIV-1 Proteins Have a Bimodal Growth Effect on Mesangial Cells

Human mesangial cells do not express conventional HIV-1 receptors. However, occurrence of HIV-1 infection in mesangial cells through orphan G protein coupled re-

ceptors has been reported in *in vitro* studies [35]. Moreover, both gp160 and gp120 have been demonstrated to have a bimodal effect on mesangial cell growth [36]. At lower concentrations, these HIV-1 proteins stimulated mesangial cell proliferation, whereas at higher concentrations these HIV-1 proteins induced mesangial cell apoptosis. Gp120-induced mesangial cell proliferation was mediated through the activation of the Akt pathway [37]. Interestingly, mesangial cells harvested from HIV-1 transgenic mice showed both accelerated rate of proliferation as well as of apoptosis [38]. Since antioxidants were able to inhibit these growth characteristics of mesangial cells, these pro-mitogenic and pro-apoptotic effects of the HIV-1 transgene were attributed to the levels of ongoing oxidative stress [38].

Role of ApoE in HIV-1-Induced Mesangial Cell Proliferation

Recently, podocyte HIV-1 expression has been reported to attenuate podocyte apoE expression in both *in vitro* and *in vivo* studies [39]. ApoE stimulates production of perlecan (proteoglycan) by podocytes [40]. *In vivo* mesangial cells are quiescent because of the sustained production of perlecan (an inhibitor of mesangial cell proliferation). However, if the production of perlecan decreases as a result of podocyte injury, it would promote mesangial cell proliferation. On that account, apoE null mice have been demonstrated to develop mesangial cell proliferation followed by glomerulosclerosis [40]. Since podocyte HIV-1 infection also attenuated podocyte expression of apoE, it appeared that mesangial cell proliferation seen in HIVAN might have occurred in the absence of mesangial cell HIV-1 infection. Interestingly, mesangial expansion has been considered a precursor of conventional focal glomerulosclerosis; therefore, patients with HIV-1 infection manifesting in the form classical focal glomerulosclerosis would also be considered as a variant of HIVAN.

Conclusions

HIVAN is the manifestation of viral infection, genetic predisposition and the presence of specific host factors (fig. 1). Clinical data not only suggest the role of direct viral infection but kidney cells also seem to serve as a reservoir for HIV-1. However, renal cells do not express conventional HIV-1 receptors. *In vitro* data suggest that HIV-

1 can enter into kidney cells through nonconventional receptors and has the potential to transmit the virus to the target cells. Thus, both in vitro and in vivo data indicate the role of kidney cells as a reservoir; however, the involved mechanism for the development of kidney cell HIV-1 infection (productive) is not clear.

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