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HIV- Associated Nephropathy: Pathogenesis

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Abstract

Purpose of review—HIV-associated nephropathy (HIVAN) is characterized histologically by a collapsing form of FSGS, microcystic tubular dilation, interstitial inflammation and fibrosis. In this review, we provide a summary of the current state of knowledge about the mechanisms involved in the pathogenesis of HIVAN.

Recent Findings—Two variants in the ApoL1 gene have been identified as the susceptibility alleles that account for a majority of the increased risk of FSGS and non-diabetic ESRD in Blacks. HIVAN1 and HIVAN 2 are the other host susceptibility genes that have been identified in animal models for HIVAN. HIV infects renal tubular epithelial cells likely through direct cell-cell transmission. Both in vivo and in vitro evidence suggests that nef and vpr are the key viral genes mediating HIVAN. Nef induces podocyte dysfunction whereas Vpr induces RTEC apoptosis.

Summary—HIVAN results from direct infection by HIV-1 and expression of viral genes, especially nef and vpr, in renal epithelial cells in a genetically susceptible host. The infected renal epithelium acts as a separate viral compartment from the blood and facilitates evolution of strains distant from blood. Dysregulation of several host cellular pathways, including those involved in cell cycle and apoptosis, ultimately results in the unique histopathological syndrome of HIVAN.

Keywords

HIVAN; Glomerulosclerosis; Podocyte; ApoL1

Introduction

HIVAN is one of the leading causes of end-stage renal disease (ESRD) in HIV-1 seropositive patients. Clinically, it presents with progressive azotemia, significant proteinuria and little or no peripheral edema in patients with advanced HIV disease. Renal parenchymal injury is characterized by epithelial cell proliferation, dedifferentiation and apoptosis along the entire nephron. Histologically, it is distinguished by finding collapsing glomerulopathy, microcystic tubular dilation, interstitial inflammation and fibrosis. In this review, we provide a summary of the current state of knowledge about the mechanisms involved in the pathogenesis of HIVAN.

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Mechanism of HIV infection of the kidney

The development of the first HIV transgenic mouse model in 1991, using a replication deficient HIV-1 proviral construct, was a key advancement that helped researchers to probe the pathogenesis of HIVAN (1).

1. Expression of HIV-1 gene in the kidney required for development of HIVAN

Reciprocal transplantation studies using these HIV-transgenic mice demonstrated that viral gene expression within the kidney itself played a role in the pathogenesis of HIVAN (2). HIV-1 transgenic kidneys transplanted into normal littermates developed HIVAN, whereas normal kidneys remained disease free when transplanted into HIV-1 transgenic littermates. Subsequent studies have confirmed the presence of HIV nucleic acid in podocytes, parietal epithelial cells, tubular epithelial cells, T-cells and macrophages in human HIVAN renal biopsy specimens (3, 4).

2. HIV infected renal epithelium constitutes a distinct viral compartment

Bruggeman et al detected HIV-1 proviral DNA in renal epithelial cells (REC) even in patients with undetectable levels of viral RNA in the peripheral blood (3). This phenomenon was also emphasized in a case report of a patient who developed HIVAN in the setting of acute HIV-1 seroconversion (5). Despite achieving rapid resolution of clinical renal disease after initiation of combined anti-retroviral therapy (cART), HIV-1 mRNA was still detectable in the renal tissue. Marras et al further explored this concept by performing phylogenetic comparative analysis of the viral sequences obtained from RECs and peripheral blood mononuclear cells (PBMC) in patients with HIVAN by laser-capture microdissection and found evidence for kidney-specific viral evolution (6). Together, these findings suggest that the kidney acts as a compartment that is separate from the blood and that HIV-1 can actively replicate in the kidney even in patients who achieve serological viral suppression with treatment.

3. Mechanism of HIV-1 renal infection

The mechanism by which HIV-1 enters RECs remains an enigma since these cells do not express the classic HIV surface receptor (CD4) or co-receptors (CXCR4 or CCR5)(6, 7). HIV-1 infection of RECs was possible using isolates from PBMCs of children with HIVAN, but not with common laboratory HIV-1 isolates, suggesting again that there may be renal tropic strains of HIV (8). Zerhouni-Layachi et al derived viruses from kidney and PBMCs of patients with HIVAN and attempted to infect primary CD4⁺ T cells, cells expressing either CXCR4 or CCR5 and a renal epithelial cell line (HPT-1). They found that while the kidney-derived viruses were dual tropic (utilized both CXCR4 and CCR5) and successfully infected all four cell lines, the blood-derived variants could infect only CCR5-expressing cells (9). Mikulak et al found that HIV-1 viral entry into conditionally immortalized human podocytes (CIHPs) was reduced significantly when treated with Methyl- β -cyclodextrin, which extracts cholesterol from cell membranes resulting in the disruption of lipid rafts within the membranes (10). However, results from other studies examining the role of lipid rafts have been conflicting (11–14).

Recently, Ping et al using live confocal imaging followed interactions between renal tubular epithelial cells (RTECs) and co-cultured CD4⁺ T-cells that were infected with a fluorescently tagged HIV virus (15). They found that viral RNA was directly transferred from the infected CD4⁺ T-cells into RTECs. The virus transfer required stable cell-cell adhesion and cell surface heparin sulfate proteoglycans (which serve as attachment receptors for HIV-1 on macrophages and dendritic cells) but was independent of HIV Env expression. They also demonstrated that virus transfer lead to de novo synthesis of viral proteins in the

infected RTECs. Furthermore, the quantity of viral RNA transferred through cell-cell contact was much greater than that achieved by exposure of RTECs to large amount of cell-free virus. And, interestingly, reverse transcriptase, protease or integrase inhibitors blocked de novo synthesis of viral proteins in the RTECs that acquired the infection from cell-free virus but not in RTECs that acquired the virus via cell-cell contact. Thus, it seems that direct transfer of virus from infected T-cells to RTECs is possible in vitro on cell-cell contact via a highly efficient and CD4 and Env independent mechanism. The extent to which this happens in vivo and contributes to the pathogenesis of HIVAN has not been established yet.

Host genetic factors that play a role in the pathogenesis of HIVAN

There were 4208 cases of incident ESRD in the US in HIV patients from 2000 to 2007 and 88% of these patients were African-American (16). This strong predilection for the black race underscores the key role that host genetic factors play in the pathogenesis of HIVAN.

1. HIVAN1 and HIVAN2

Gharavi et al assessed the influence of genetic background on the development of HIVAN by making F1 hybrids of HIV-1 transgenic mice on FVB/N background (TgFVB mice) with five other inbred strains (CBA, DBA/2, CAST/Ei, C3H/He, BALB/c) and found striking variation in disease phenotype ranging from no renal disease to severe renal disease (17). And, when they performed genome-wide linkage analysis using heterozygous offspring resulting from a backcross between FVB/CAST F1 and TgFVB F1 mice, they identified a 30-cM interval on chromosome 3 that was strongly associated with renal disease. This locus, which was named HIVAN1, correlated with human chromosome 3q25-27, which has been previously linked to diabetic (18, 19) and hypertensive nephropathy (20). Furthermore, when the HIVAN 1 locus from the CAST mice (CAST alleles were associated with greater risk of disease) was introduced into the genome of TgFVB mice, the cogenic mice developed accelerated and more severe nephropathy than the TgFVB mice, further adding to the evidence that the HIVAN1 locus increases susceptibility to HIVAN (21). Using expression quantitative trait locus analysis, Papeta et al found that there was significant variation in the expression of the heritable podocyte gene nephrosis 2 homolog (Nphs2; which encodes podocin) in HIV-1 transgenic mice of different genetic background (22). Nphs2 expression was regulated by HIVAN1 and also another susceptibility locus on Chromosome 13 which was named HIVAN2. It was also observed that variation in expression of podocin resulted in reactive changes in other podocyte genes and the HIV-1 transgene interfered with this transregulation. Together, these findings suggest that podocyte genes are regulated by an interconnected network which is altered by HIV-1 infection in the presence of host susceptibility alleles (Figure 1).

2. MYH9 and APOL1

In 2008, two publications reported a strong association between non-muscle myosin heavy chain-9 (MYH9) gene on chromosome 22 and susceptibility to HIVAN, idiopathic FSGS and hypertensive ESRD in blacks (23, 24). Intriguingly, mutations in MYH9 gene were previously associated with Epstein and Fechtner syndromes which are characterized by macrothrombocytopenia, deafness, and rarely nephritis (25). To further define the causal mutations in MYH9, Genovese et al performed genome-wide association analysis using more than one million single-nucleotide polymorphisms in African American and European American patients with FSGS and compared the results to unselected controls (26). They found that variants in a 60 kb region of chromosome 22 containing MYH9 and Apolipoprotein L1 (ApoL1) genes were strongly associated with increased risk of FSGS in African Americans. No associations were detected in European Americans. Furthermore, when they studied polymorphisms in this region using DNA sequence data in a larger

worldwide cohort they were able to identify that it was actually two ApoL1 variants (named G1 and G2), which were inherited in an autosomal recessive pattern, and not variants in the MYH9 gene that were associated with FSGS and hypertension related ESRD (27). The G1 and G2 variants were common in African chromosomes, absent from European chromosomes and were located on haplotypes that showed statistical evidence of natural selection. ApoL1 encodes a serum factor that lyses *Trypanosoma brucei* and confers resistance to *T. brucei*. However, *T. brucei* evolved over the years into two additional subspecies *T. b. rhodesiense* and *T. b. gambiense* and both these subspecies can infect human beings because they produce an ApoL1 inhibitor. The authors found that the G1 and G2 ApoL1 mutations, which are associated with renal disease, confer resistance to *T. b. rhodesiense* infection as the inhibitor cannot bind to the variant protein. Thus, it seems that positive selection of these mutations in Africans to counter an endemic parasitic disease may have contributed to higher rates of FSGS, hypertensive ESRD and potentially HIVAN in these individuals.

Dysregulated podocyte phenotype in HIVAN

Podocytes are highly differentiated and quiescent cells in the normal glomerulus. In HIVAN, they exhibit a dysregulated phenotype characterized by increased proliferation, apoptosis and dedifferentiation.

1. Podocyte dedifferentiation and proliferation

Podocytes in HIVAN have reduced expression of typical markers such as synaptopodin and Wilms' tumor-1 and increased expression of desmin, a component of intermediate filaments (28). They also demonstrate increased expression of proliferation markers such as Ki-67 and cyclins (A, D1) and decreased expression of cyclin-dependent kinase inhibitors (p27, p57), indicating that these cells have re-entered the cell cycle (29). These findings were corroborated by immunostaining renal tissue from TgFVB mice (30). Furthermore, podocytes derived from TgFVB mice demonstrate increased spontaneous proliferation and loss of contact inhibition when compared to non-transgenic podocytes (31). And, infection of the non-transgenic podocytes with HIV-1 induces similar behavior, further substantiating that HIV-1 gene expression is responsible for these changes (31).

2. Role of specific viral proteins in podocyte dysfunction

To identify the specific viral proteins responsible for podocyte dysfunction, Hussain et al engineered mutated lenti virus constructs, each of which lacked a single HIV gene (*env*, *vif*, *vpr*, *vpu*, *nef*, or *rev* genes) and infected cultured murine podocytes with these constructs (32). They found that presence of *nef* alone was required and sufficient to induce aberrant proliferation and de-differentiation (32, 33). The importance of the *nef* gene has also been demonstrated in vivo. Zuo et al generated transgenic mice that expressed individual HIV-1 genes in podocytes and found that expression of *nef* or *vpr* was sufficient to induce podocyte de-differentiation and glomerulosclerosis. Furthermore, *nef* and *vpr* double-transgenic mice develop more severe nephropathy than *vpr* or *nef* single-transgenic mice, indicating that *vpr* and *nef* may have a synergistic role in inducing podocyte dysfunction.

3. Host cellular pathways involved in podocyte dysfunction

He et al found that in cultured podocytes *nef* activates Src kinase by interacting with its SH3 domain, which in turn leads to activation of Stat3 and Ras-c-Raf-MAPK 1, 2 pathways leading to podocyte proliferation and de-differentiation (34). Also, staining for phosphor-MAPK 1,2 and Stat3 was enhanced in the podocytes of kidneys from HIVAN patients when compared with HIV patients with non-HIVAN kidney diseases or non-HIV patients with FSGS or minimal-change disease. In addition, they confirmed in vivo that reduction of Stat3

activity ameliorates proteinuria, podocyte injury, and glomerulosclerosis in HIV-1 transgenic mice (35). They also reported that Nef reduces activity of RhoA and increases activity of Rac1 through direct interaction with diaphanous interaction protein (36). The alteration of RhoA/Rac1 balance leads to reduction of stress fiber in podocytes and foot process effacement (Figure 2).

Recent studies suggest that all-trans-retinoic acid (atRA) can reverse these nef-induced signaling pathway alterations in podocytes. atRA is able to reverse HIV-1 induced podocyte injury by activating cyclic AMP/protein kinase A pathway. atRA also inhibits extracellular signal-regulated kinase (ERK) phosphorylation through CREB-mediated activation of MAPK phosphatase-1 (34, 37). In vivo, atRA reduces proteinuria and glomerulosclerosis in HIV-1 transgenic mice. These results suggest a potential role for atRA in the treatment of patients with HIVAN.

Several studies suggest roles of NF- κ B and oxidant stress in HIV-induced podocyte injury. In HIV-1 infected podocytes there is persistent activation of NF- κ B due to increased phosphorylation and degradation of I κ B (the NF- κ B inhibitor) leading to activation of transcription of HIV-1 and increased podocyte proliferation (38). In cultured podocytes derived from TgFVB mice, NF- κ B regulates apoptosis by controlling the expression of the Fas ligand (39). A recent study also showed that when p66ShcA (a key regulator of apoptosis in the setting of oxidative stress) was down regulated, there was reduction in HIV induced apoptosis (40).

There is also evidence of activation of other signaling pathways such as mTOR pathway (41) and Notch signaling pathway (42) in the renal tissues of TgFVB mice.

4. Host response genes involved in podocyte dysfunction

Kaufman et al reported that expression of homophilic adhesion molecule sidekick-1 (sdk-1) is dramatically increased in podocytes of TgFVB mice and in HIVAN biopsy specimens (43). Subsequently, they found that sdk-1 is an important mediator of cellular adhesion in HIV-infected podocytes and may contribute to podocyte clustering that is characteristic of pseudocrescent formation in HIVAN (44). More recently, they demonstrated that sdk-1 is also upregulated in podocytes derived from idiopathic FSGS patients (45). They also showed that transgenic mice with podocyte specific overexpression of sdk-1 developed severe FSGS and proteinuria. Their data suggests that the underlying mechanism involves disruption of the actin cytoskeleton possibly via alterations in the function of slit diaphragm linker protein MAGI-1.

Tubulointerstitial inflammation is a prominent feature of HIVAN

Several case reports and retrospective studies show improved renal outcomes with corticosteroids in patients with HIVAN, suggesting a key role for tubular inflammation in the pathogenesis of HIVAN (46, 47).

Ross et al found that after HIV-1 infection of human RTECs, the most prominent response was upregulation of pro-inflammatory mediators (48). Most of these genes were also found to be up regulated in kidneys of TgFVB mice. The mean renal interstitial (and glomerular) levels of several chemokines were also higher in HIV-infected patients than normal subjects (49).

HIVAN is also characterized by marked increase in apoptosis of RTECs, which is much higher than what is seen in HIV-seronegative patients with FSGS (50). HIV-1 vpr gene expression in cultured RTECs induces dysregulation of cytokinesis and apoptosis (51). Vpr

also induces increased expression of FAT10 (an ubiquitin-like protein that co-localizes with vpr in the mitochondria) in human and murine RTECs and inhibition of FAT10 expression prevents vpr-induced apoptosis (52). Recent studies suggest that vpr causes sustained ERK activation, resulting in caspase 8-mediated cleavage of BID (BH3 interacting domain death agonist) to truncated BID, which in turn facilitates Bax-mediated mitochondrial injury and apoptosis (53).

Conclusions

Several important advances have been made in understanding the pathogenesis of HIVAN as summarized in this review. The recent identification of ApoL1 as a key susceptibility allele represents a critical milestone in our understanding of increased susceptibility of blacks to HIVAN and other renal diseases. The discovery that HIV-1 can infect RTECs through direct cell-cell transmission is also an important breakthrough. Both in vitro and in vivo studies suggest that nef and vpr are the key HIV genes responsible for development of HIVAN. Several host cellular responses that are activated in the kidney as a result of HIV-1 infection have also been elucidated and they involve key pathways in cell cycle and apoptosis. However, additional research is needed to understand the complex interaction between genetic susceptibility, viral factors and host response factors that result in the unique phenotype of HIVAN. Findings from HIVAN will almost certainly provide insight into the susceptibility of Blacks to renal diseases in general.

Key points

- HIVAN is a leading cause of ESRD in HIV-1 seropositive patients and is characterized histologically by a collapsing form of FSGS, microcystic tubular dilation, interstitial inflammation and fibrosis.
- Two variants in the ApoL1 gene have been identified as the susceptibility alleles that account for a majority of the increased risk of FSGS and non-diabetic ESRD in Blacks.
- HIV infects renal tubular epithelial cells likely through direct cell-cell transmission.
- Nef induced podocyte dysfunction and Vpr induced apoptosis of renal tubular epithelial cells play a key role in the pathogenesis of HIVAN.
- Several host cellular responses that are activated in the kidney as a result of HIV-1 infection have been elucidated and they involve key pathways in cell cycle and apoptosis.

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Abbreviations

apoE	Apolipoprotein E
ApoL1	Apolipoprotein L1
atRA	all-trans-retinoic acid
BID	BH3 interacting domain death agonist

cART	Combined anti-retro-viral therapy
CIHPs	Conditionally immortalized human podocytes
ERK	Extracellular signal-regulated kinase
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
HIVAN	HIV associated nephropathy
MHY9	Non-muscle myosin heavy chain 9
PBMCs	Peripheral blood mononuclear cells
RECs	Renal epithelial cells
RTECs	Renal tubular epithelial cells
TgFVB	HIV-1 transgenic mice on FVB/N background

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Figure 1. Schema for the pathogenesis of HIVAN

HIVAN results from direct infection by HIV-1 and expression of viral genes, especially Nef and Vpr, in renal epithelial cells in a genetically susceptible host. HIV likely infects RTECs through direct cell-cell transmission and the infected renal epithelium acts as a separate viral compartment from the blood and facilitates evolution strains distant from blood. HIVAN1 and HIVAN 2 are the host susceptibility genes that have been identified in animal models for HIVAN. Two variants in the ApoL1 gene were recently identified as the susceptibility alleles that account for a large proportion of the excess risk of FSGS in African Americans (which was previously attributed to MYH9). Viral infection results in dysregulation of several host cellular pathways, including those involved in cell cycle and apoptosis. This leads to podocyte proliferation and differentiation, RTEC apoptosis, tubulo-interstitial inflammation and ultimately results in the unique histopathological syndrome of HIVAN.

Figure 2. Nef-induced signaling pathways in podocytes

The proline rich PxxP domain of Nef interacts with SH3 domain of SRC family kinases. This leads to inhibition of RhoA and activation of Rac1 pathways via direct interaction with diaphanous interaction protein (DIP). MAPK1,2 and Stat3 pathways are also activated. Alterations in these host signaling pathways results in cytoskeletal disorganization, podocyte dedifferentiation and proliferation and ultimately in collapsing FSGS and HIVAN. Abbreviations: SH3, Src homology 3; RhoA, Ras homolog gene family member A; Rac1, Ras-related C3 botulinum toxin substrate 1; MAPK 1,2 Mitogen-activated protein kinase 1,2; STAT3, signal transducer and activator of transcription 3.