Transgenic and Infectious Animal Models of HIV-Associated Nephropathy

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ABSTRACT
HIV-associated nephropathy (HIVAN) is a major cause of HIV-related morbidity and mortality. Transgenic and infectious models of HIVAN faithfully recapitulate the human disease and are important tools in advancing our understanding of disease pathogenesis, genetic susceptibility, and therapeutic intervention beyond the inhibition of viral replication. This review discusses the available transgenic murine models and infectious models of HIVAN in mice, rats, nonhuman primates, and felines. Particular emphasis is given to cell type–specific HIV expression as well as partial HIV genome expression used to map HIV-1 Nef and Vpr as pathologic determinants.


HIV-associated nephropathy (HIVAN) was first reported in 1984, when a small group of Haitian and African American patients with HIV presented with kidney disease without other risk factors.1 During the subsequent 24 years, HIVAN became the leading cause of ESRD in HIV-1–seropositive individuals and the third leading cause of ESRD in patients of African descent, the population comprising the vast majority of HIVAN cases. HIVAN prevalence in HIV-infected patients of African descent is estimated to be between 3 and 12%, putting global projections as high as 3 million prevalent cases. The results of a large number of studies that addressed HIVAN pathogenesis have led to a better understanding of the disease and improvements in clinical practice. Expert guidelines have now changed to recommend highly active antiretroviral therapy for patients with renal disease.4,5 Much of our knowledge of disease pathogenesis has derived from transgenic mouse models that express all or parts of the HIV genome. These animal models have been able to recapitulate many aspects of human HIVAN.

Clinically, HIVAN is characterized by proteinuria, often nephrotic range, and decreased renal function.6,7 Peripheral edema and hypertension are seen less often in HIVAN compared with other forms of renal disease, suggesting salt wasting perhaps as a result of tubulointerstitial disease.8 Renal ultrasound shows large echogenic kidneys, and urinalysis usually shows only elevated protein excretion and occasional hyaline casts.9,10 Although this kind of clinical data and diagnostic workup suggests the presence of HIVAN, the diagnosis can be made only by biopsy.

In HIVAN, the kidneys are often grossly enlarged, and biopsies demonstrate a number of distinct histopathologic changes. Glomerular disease is classically characterized by the presence of collapsing FSGS with retraction of the glomerular basement membrane.11 Focal microcystic dilation (three times the normal diameter of the renal tubules) are also present and accompanied by epithelial flattening of the cyst-lining cells.12 In addition, interstitial infiltration of lymphocytes and macrophages as well as interstitial fibrosis are often present.13 Ultrastructural changes include podocyte dedifferentiation and loss of foot process architecture as well as aberrant proliferation.14 Parietal epithelial cell proliferation, atrophy, apoptosis, and loss of polarization have also been reported.14 Immunohistochemical analysis reveals a loss of differentiation markers in podocytes (WT-1 synaptopodin, GLEPP-1, and podocalyxin) and an increase in the proliferation marker Ki-67.14–17 Renal tubular epithelial cells show similar loss of differentiation and inappropriate localization of the Na-K-ATPase to the apical and lateral membrane.18

This review describes the available murine and nonhuman primate models of HIVAN that have been useful in advancing our knowledge of the pathogenesis of HIVAN. A summary of the HIVAN animal models discussed is shown in Table 1.

TRANSGENIC MOUSE MODELS

Tg26 HIVAN Mouse Model
In 1991, the first HIVAN transgenic mouse model, termed “transgenic 26”
Death from uremia typically occurs 2 wk after the onset of edema. Histologically, Tg26 kidneys develop diffuse segmental and global glomerulosclerosis of the collapsing variant, microcystic tubular changes, and mononuclear interstitial infiltrate. Ultrastructurally, the podocytes show foot process effacement also characteristic of the human disease. At the time the mice were first generated, it was unclear whether renal expression of HIV genes was responsible for the HIVAN phenotype; however, renal transgene levels correlate with disease severity between different transgenic lines and also temporally with disease progression in the Tg26 line. Heterozygous Tg26 mice do not develop CD4+ T cell depletion, so it was thought to be unlikely that the renal disease observed was a result of immune dysregulation. Follow-up studies using reciprocal renal transplantation confirmed the hypothesis that renal expression of the HIV genome was responsible for disease phenotype. Nontransgenic mice receiving a Tg26 kidney developed HIVAN-like disease, whereas Tg26 mice receiving a nontransgenic kidney remained healthy. This result demonstrates that HIV gene expression in the kidney is both necessary and sufficient in the FVB background to cause disease in the mouse model.

This hypothesis was corroborated in human HIVAN biopsies, in which HIV mRNA and proviral DNA were found in both podocytes and tubular epithelial cells. The murine model of the microcystic epithelium also provides a unique insight to its pathogenesis. These flattened epithelial cells no longer express the HIV transgene despite its ubiquitous presence in all murine cells. This suggests that microcysts may result when the differentiated tubular epithelium transforms or is replaced by a primitive cell type, perhaps with little transcriptional capacity to support HIV gene expression.

Because the Tg26 mouse line faithfully reproduces characteristic HIVAN, it has been a valuable tool to probe the pathogenesis of disease. In vitro data demonstrating that HIV induces cell hypertrophy and cell-cycle dysregulation that is mediated by the viral protein Vpr were confirmed in vivo using the Tg26 model. Fas-FasL–mediated apoptosis in tubular epithelial cell lines was also subsequently characterized in the Tg26 model. The upregulation of several novel host factors, including FAT10 and Podocan, has been confirmed by immunohistochemistry in the Tg26 mouse model. The reproducibility of results in the murine model has spurred investigation of HIVAN cell biology in murine cell lines. Advantages of this approach include the generation of knockout cell lines or easily maintained cell lines of specific cell types such as podocytes by conditional immortalization.

The Tg26 mouse has also been a tool to investigate the genetic predilection for HIVAN. The initial Tg26 mouse line was generated on the FVB/N inbred mouse strain. Whereas this strain is susceptible to disease, Tg26 mice bred onto the mixed FVB/CAST background mouse strain and others do not develop disease. Using genome-wide linkage analysis, the genetic loci and genes responsible for disease penetrance can be determined providing candidates and pathways to examine in the human disease. Notably, mouse chromosome 3A1 to 3, a region syntenic to human chromosome 3q25 to 27, has been identified as a HIVAN-susceptibility locus (see Gharavi et al. 2003 in Table 1); however, when the FVB/N allele in this locus is selectively replaced with the CAST allele, the HIV transgenic mice show accelerated disease progression. Taken together, these studies suggest that HIVAN is a multifactorial disease and that variation in susceptibility likely results from the combined effect of protective and permissive nephropathy alleles (see Chan 2008 in Table 1). In addition, the nondiabetic ESRD African American major effect risk gene MYH9 that was identified in two large independent genetic screens was subsequently identified in murine genetic studies as well.

**Tissue- and Cell Type–Specific HIV Expression**

HIV transgenic mouse models can determine how different cell types and renal compartments contribute to the overall...
Table 1. Summary of 32 transgenic murine HIVAN models that are discussed in this reviewa

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal Line</th>
<th>Transgene</th>
<th>Promoter</th>
<th>Expression</th>
<th>Animal Strain</th>
<th>Disease Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dickie19 (1991)</td>
<td>Tg22c, Tg25</td>
<td>HIVΔgag/pol</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>Severe HIVAN-like disease; did not survive to breeding age</td>
</tr>
<tr>
<td></td>
<td>Tg26 (homozygous)</td>
<td>HIVΔgag/pol</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>Runted; severe HIVAN-like disease; death in &lt;40 d</td>
</tr>
<tr>
<td></td>
<td>Tg26 (heterozygous)</td>
<td>HIVΔgag/pol</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>HIVAN-like disease; death between 70 and 260 d</td>
</tr>
<tr>
<td>Gharavi et al.30 (2004)</td>
<td>Tg26</td>
<td>HIVΔgag/pol</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N × CAST</td>
<td>None</td>
</tr>
<tr>
<td>Chan et al.31 (2008)</td>
<td>Tg26</td>
<td>HIVΔgag/pol</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N (3A1-3 CAST)</td>
<td>Accelerated HIVAN-like disease</td>
</tr>
<tr>
<td>Hanna et al.34 (1998)</td>
<td>CD4/HIV</td>
<td>HIV(pNL43)</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>None</td>
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<tr>
<td>Hanna et al.37 (1998)</td>
<td>CD4/HIVΔNef</td>
<td>HIVΔNef</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CD4/HIV-1 Nef</td>
<td>Nef Only</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>HIVAN-like tubulointerstitial disease; no glomerular disease</td>
</tr>
<tr>
<td>Hanna et al.35 (2001)</td>
<td>CD4/HIV-1 Nef (AxxAxxQ)</td>
<td>Nef(A72.xxAxxQ78)</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>None</td>
</tr>
<tr>
<td>Hanna et al.36 (2004)</td>
<td>CD4/HIV-1 Nef (G2A)</td>
<td>Nef(G2A)</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CD4/HIV-1 Nef (Δ8–17)</td>
<td>Nef(Δ8–17)</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>HIVAN-like tubulointerstitial and glomerular disease</td>
</tr>
<tr>
<td></td>
<td>CD4/HIV-1 Nef (Δ25–35)</td>
<td>Nef(Δ25–35)</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>CD4/HIV-1 Nef (Δ57–66)</td>
<td>Nef(Δ57–66)</td>
<td>CD4C</td>
<td>Immune and glomerular cells</td>
<td>C57BL/6 × (C3H or CD1)</td>
<td>None</td>
</tr>
<tr>
<td>Kajiyama et al.42 (2000)</td>
<td>Tg26ΔNef (X5)</td>
<td>HIVΔgag/pol/nef</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>FSGS and tubulointerstitial disease</td>
</tr>
<tr>
<td>Dickie44 (1993)</td>
<td>HIV-1 LTR-Nef</td>
<td>HIV-1 Nef</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kajiyama et al.45 (2000)</td>
<td>Tg26ΔNef × HIV-1 LTR-Nef</td>
<td>HIVΔgag/pol/nef AND Nef</td>
<td>Podocyte</td>
<td>FVB/N</td>
<td>Podocyte dedifferentiation and proliferation</td>
<td></td>
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</table>

aSee text for details.
disease process. In natural infection, HIV infects podocytes, tubular epithelial cells throughout the nephron, and infiltrating lymphocytes and macrophages. In the Tg26 model, HIV expression is ubiquitous; therefore, tissue-specific expression models have been designed to study each compartment individually.

Transgenic mice expressing the full HIV genome expressed under a CD4 promoter were designed to restrict expression to immune cells (see Hanna et al.34 in Table 1); however, CD4 expression is promiscuous, and HIV was also produced in other kidney compartments, including glomerular cells. Nonetheless, this model shows characteristics of HIVAN. Specifically, transgenic mice with HIV under the control of the CD4 promoter develop severe tubular atrophy, tubulointerstitial nephritis, and fibrosis. FSGS was not originally reported in the CD4/HIV mice, although transgene expression was abundant in the glomerulus. In subsequent studies, however, using the same transgenic line, FSGS was observed.35,36 Extensive tubular dilation is also seen, although the kidneys are grossly smaller than those of control litters. This is in contrast to the Tg26 model and human HIVAN, in which the kidneys are enlarged up to 25%. The cause for this difference is unclear. Further studies showed that HIV-1 Nef was the major determinant of this phenotype when compared with the other HIV genes under the control of the CD4 promoter (see Hanna et al.37 in Table 1). The Nef PxxPxxP (amino acids 72 through 78) motif (an SH3-binding domain), the myristoylation site G2, and sequences amino acids 25 through 35 and amino acids 57 through 66 all are required for disease pathogenesis in the CD4 model (see Hanna et al.35,36 in Table 1). Subsequent studies suggested that Nef mediates podocyte proliferation and dediffer-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal Line</th>
<th>Transgene</th>
<th>Promoter</th>
<th>Expression</th>
<th>Animal Strain</th>
<th>Disease Phenotype</th>
</tr>
</thead>
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<tr>
<td>Dickie45 (2004)</td>
<td>Tg26ΔVpr (V13)</td>
<td>HIVΔgag/pol/Vpr</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>None</td>
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<td></td>
<td>Tg26ΔNef/Vpr (VN15)</td>
<td>HIVΔgag/pol/Nef/Vpr</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>None</td>
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<td>Vpr/Tat only (TV2)</td>
<td>Vpr-tat</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>FSIGS and tubulointerstitial disease, particularly in nursing mothers</td>
</tr>
<tr>
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<td>Vpr/Tat only (MeRV)</td>
<td>Vpr-tat</td>
<td>c-fms</td>
<td>Monocyte/macrophage</td>
<td>FVB/N</td>
<td>FGS without tubulointerstitial disease, particularly in nursing mothers</td>
</tr>
<tr>
<td></td>
<td>TV2 × V13</td>
<td>Vpr-tat AND HIVΔgag/pol/vpr</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>FVB/N</td>
<td>Severe early-onset HIVAN-like disease</td>
</tr>
<tr>
<td>Zuo et al.46 (2006)</td>
<td>Nephrin-Vpr</td>
<td>Vpr</td>
<td>Nephrin</td>
<td>Podocyte</td>
<td>FVB/N</td>
<td>FSGS and tubulointerstitial disease</td>
</tr>
<tr>
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<td>Nephrin-Nef</td>
<td>Nef</td>
<td>Nephrin</td>
<td>Podocyte</td>
<td>FVB/N</td>
<td>FSGS and tubulointerstitial disease</td>
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<td>Nephrin-Rev</td>
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<td>None</td>
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<td>Nephrin-Vif</td>
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<td>Nephrin</td>
<td>Podocyte</td>
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<td>None</td>
</tr>
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<td>Nephrin-Vpu</td>
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<td>Podocyte</td>
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<td>Nephrin-Vpr × Nephrin-Nef</td>
<td>Vpr AND Nef</td>
<td>Nephrin</td>
<td>Podocyte</td>
<td>FVB/N</td>
<td>Severe early-onset HIVAN-like disease</td>
</tr>
<tr>
<td>Ray et al.53 (2003)</td>
<td>Rat HIVAN model</td>
<td>HIVΔgag/pol</td>
<td>HIV-1 LTR</td>
<td>Ubiquitous</td>
<td>Sprague-Dawley</td>
<td>HIVAN-like disease with mesangial hyperplasia</td>
</tr>
</tbody>
</table>

*Δ denotes deletion of specific HIV gene(s) or HIV gene motifs within the transgene. "AND" denotes two separate transgenes expressed through crossbreeding as in phenotype rescue models.
entiation through its interaction with Src kinase and activation of the Stat3 and mitogen-activated protein kinases 1 and 2 pathways.38–40 Podocyte-specific expression of a HIVΔgag/pol/env construct in transgenic mice shows extensive HIVAN pathology. In these mice, the HIV LTR promoter was replaced by the podocyte-specific nephrin promoter Nphs1 (see Zhong et al.41 in Table 1). These mice exhibit proteinuria at 3 wk and have increased mortality compared with wild-type littermates. Collapsing FSGS with mesangial expansion is seen, and podocytes show diminished foot processes, an immature cuboid shape, and lack of the marker genes WT-1 and synaptopodin typical of differentiated podocytes. In addition to the glomerular phenotype, these mice also develop interstitial fibrosis, tubular microcystic dilation, and tubule cell proliferation as determined by Ki-67 staining. Glomerular cell proliferation is also observed, but it is unclear whether the cells invading Bowman’s space are podocytes or parietal cells that may even be podocyte precursors.42

Both the podocyte-specific and CD4-driven HIV transgenic models show tubular microcystic dilation despite the lack of transgene expression in the renal tubule itself. In addition, the renal tubule phenotype can occur independent of both an HIV-expressing lymphocytic infiltrate (not seen in this podocyte model) and FSGS (not seen in early reports of the CD4/HIV model44). A possible explanation is that podocyte expression generates HIV viral proteins in the glomerulus that are released into the circulation or into the urinary space with subsequent exposure to the tubules, but this remains unproved.

Single HIV Gene and Gene Deletion HIVAN Models

Several transgenic models, including the aforementioned CD4/HIV<sub>net</sub> only model, have attempted to determine the role of specific HIV genes in the pathogenesis of HIVAN. The results have been consistent, implicating both HIV-1 Nef and Vpr as the major contributors. Expression of an HIVΔgag/pol/nef transgene in mice causes FSGS and microcystic tubular dilation but not podocyte proliferation (see Kajiyama et al.43 in Table 1); however, the FSGS is exacerbated when this mouse line is backcrossed to a Nef-only transgenic line (see Dickie et al.44 in Table 1), implicating a role for both Nef and another HIV gene in HIVAN pathogenesis. A separate study examined a modified Tg26 model whereby vpr, nef, or both were additionally deleted (see Dickie et al.45 in Table 1). In this study, only mice carrying an intact Vpr gene developed proteinuria, and FSGS with tubular dilation was observed even in the Nef-deleted model. Furthermore, a Vpr-tat–only transgenic model developed a HIVAN-like phenotype that included both glomerular and tubular diseases, particularly in nursing female mice.45 Crosses between the Vpr-tat mouse and the Vpr-deleted mouse restored HIVAN pathology in its entirety. Interestingly, when Vpr was preferentially expressed in monocytes/macrophages using the c-fms promoter, renal disease was confined to the glomerular compartment.46 Possible explanations include expression of Vpr in glomerular macrophages, “off-target” expression of Vpr in glomerular mesangial cells, and an effect of circulating Vpr on the downstream glomerulus. Nonetheless, because Vpr is capable of causing glomerular pathology either alone or in conjunction with tubular pathology depending on the model system, Vpr is likely a direct contributor to disease in both compartments. Vpr-expressing constructs in mice, however, have not shown the podocyte proliferation that is observed in human HIVAN.

Nef and Vpr have also been independently expressed in podocytes specifically using the nephrin promoter (see Zuo et al.46 in Table 1). Podocyte-specific expression of either Nef or Vpr alone causes proteinuria by 10 wk and glomerulosclerosis and tubular injury between 4 and 6 mo in transgenic mice. When these mouse lines were crossed with each other to create a podocyte-specific Vpr/Nef transgenic line, the effect on disease was synergistic. Severe glomerulosclerosis and tubulointerstitial injury was seen in all Vpr/Nef mice by just 3 wk of age. Podocyte-specific expression of the single HIV genes Vif, Tat, Vpu, and Rev resulted in no renal injury.46
A doxycycline-inducible podocyte-specific Vpr transgenic model that used the podocin promoter also showed HIVAN pathology 16 wk after induction (see Hiramatsu et al.47 in Table 1). This system more accurately reflects a natural HIV infection because Vpr expression is restricted until adulthood and further validates the results from noninducible models.

**Therapeutic Testing in the HIVAN Mouse Model**

HIVAN mouse models have been used to investigate the potential efficacy of renoprotective therapeutic strategies in managing HIVAN. The angiotensin-converting enzyme inhibitor captopril reduces glomerular and tubulointerstitial pathology when administered to Tg26 (HIVΔgag/pol) mice.48 This result was consistent with the results of two small clinical trials that also showed angiotensin-converting enzyme inhibitor therapy is beneficial in HIVAN.49,50 More recently, the angiotensin II type 1 receptor blocker olmesartan also reduced disease in the inducible podocyte-specific Vpr murine HIVAN model.47 Conversely, administration of angiotensin II in this same model exacerbated progression of the disease.51 This effect was independent of angiotensin II or olmesartan’s effect on systemic BP because other vasoactive agents (norepinephrine, hydralazine, and azelnidipine) did not have an effect on renal pathology. Taken together, these studies suggest that the murine model seems to be an effective tool in further defining both mechanisms of disease and potential therapeutic interventions.

**RAT HIVAN MODEL**

Although the mouse model has been the primary small animal model of HIVAN, a Sprague-Dawley rat model also exists (see Ray et al.52 in Table 1).52,53 The same HIVΔgag/pol transgene driven by the viral LTR promoter in the Tg26 mouse model has been used to create a rat HIVAN model. Renal manifestations in these rats range from mild to severe and show the characteristic aspects of HIVAN pathology. The kidneys are grossly enlarged and diffusely pale and have a pitted appearance. Microcystic change, glomerular sclerosis, tubular cell proliferation, and visceral epithelial cell enlargement all are observed. In addition, the rat HIVAN model shows prominent mesangial hyperplasia with an increase in both glomerular and tubular basic fibroblast growth factor staining.53 One potential advantage of the rat model is that the HIV transgene seems to be more widely and efficiently expressed in rats than mice, perhaps indicating a improved functionality of HIV-1 tat, the viral transactivator.

**SIMIAN IMMUNODEFICIENCY VIRUS AND FELINE IMMUNODEFICIENCY VIRUS: NATURAL MODELS OF LENTIVIRUS-INDUCED RENAL DISEASE**

Simian immunodeficiency virus (SIV) and feline immunodeficiency virus (FIV) are lentiviruses closely related to HIV. In both instances, host infection can result in nephropathy.

Primates infected with SIV or a chimeric SHIV also develop renal insufficiency resembling aspects of both HIVAN and hemolytic uremic syndrome. In an early study, one of three rhesus macaques and one of three pig-tailed macaques each intravenously infected with the SIV isolate SIV/Mne developed renal disease including FSGS, tubular necrosis, and interstitial inflammation (see Benveniste et al.54 in Table 2). Another study followed rhesus and pig-tailed macaques infected with different SHIV strains (SHIV KU-1, SHIV KU-2, and SHIV KU-MC4) that were derived from passaging the nonpathogenic SHIV-4 clone in vivo. Here, varying degrees of renal disease severity were also observed (see Stephens et al.55 in Table 2). Subsequent characterization of the most pathogenic clone, SHIV KU2-MC4, found that it had a newly acquired tropism to macrophages compared to the parent strain.56 Two other studies have examined the role of viral tropism in renal disease development. Five of seven rhesus macaques intravenously inoculated with a macrophage-tropic form of SIV (SIVmacR71/17E) developed FSGS and also showed mild microcystic dilation and lymphocyte infiltration (see Stephens et al.57 in Table 2). In another study, six rhesus macaques were inoculated with a lymphocyte-tropic form of SIV (SIVmac239; see Gattone et al.58 in Table 2). Glomerulosclerosis (two of six

Table 2. Summary of nine infectious HIVAN models that are discussed in this review*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Animal</th>
<th>Viral Infection</th>
<th>Disease Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benveniste et al.54 (1988)</td>
<td>Rhesus macaque</td>
<td>SIV/Mne</td>
<td>1 of 3 developed mixed HIVAN/HUS pathology</td>
</tr>
<tr>
<td>Stephens et al.55 (2000)</td>
<td>Pig-tailed macaque</td>
<td>SIV/Mne</td>
<td>1 of 3 developed mixed HIVAN/HUS pathology</td>
</tr>
<tr>
<td>Stephens et al.55 (2000)</td>
<td>Rhesus macaque</td>
<td>SHIV-4 (HIV-1 HXB2</td>
<td>Non-pathogenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for tat, rev, vpu, env in SIVmac239)</td>
<td></td>
</tr>
<tr>
<td>Stephens et al.55 (2000)</td>
<td>Pig-tailed macaque</td>
<td>SHIV KU-1</td>
<td>1 of 3 developed FSGS</td>
</tr>
<tr>
<td>Stephens et al.55 (2000)</td>
<td>Rhesus macaque</td>
<td>SHIV KU-2</td>
<td>3 of 4 developed FSGS in &lt;10% of glomeruli</td>
</tr>
<tr>
<td>Stephens et al.55 (2000)</td>
<td>Rhesus macaque</td>
<td>SHIV KU2-MC4</td>
<td>2 of 2 developed FSGS in &gt;60% of glomeruli</td>
</tr>
<tr>
<td>Stephens et al.57 (1998)</td>
<td>Rhesus macaque</td>
<td>SIVmacR71/17E</td>
<td>5 of 7 developed mixed HIVAN/HUS pathology</td>
</tr>
<tr>
<td>Gattone et al.58 (1998)</td>
<td>Rhesus macaque</td>
<td>SIVmac239</td>
<td>5 of 6 developed at least one aspect of HIVAN pathology</td>
</tr>
<tr>
<td>Poli et al.59 (1993)</td>
<td>House cat (Felis catus)</td>
<td>FIV of unknown origin</td>
<td>12 of 15 developed renal disease</td>
</tr>
</tbody>
</table>

*HUS, hemolytic uremic syndrome.
primates), mesangial hyperplasia (three of six), and tubulointerstitial inflammation (five of six) all were observed. When SIV env gp120 sequences were recovered from the glomeruli of diseased primates, they had evolved to a macrophage-tropic phenotype. These results indicated that selective pressure is exerted in the glomerulus. Studying viral tropism and evolution is a major advantage of the primate model over the transgenic murine models that are incapable of probing this aspect of HIVAN.

FIV infects both domestic and feralelines, causing an AIDS-like illness. In addition, FIV-related renal disease has been reported. In one study, glomerulosclerosis, tubulointerstitial disease, and/or mesangial widening with IgM, C3, and mild IgG deposition was observed in 12 of 15 FIV+ felines (see Poli et al.59 in Table 2). A subsequent study demonstrated direct FIV infection of the tubular epithelium by p24 immunostaining and PCR suggesting a similar pathogenesis as HIVAN60; however, because FIV has no functional homolog to HIV-1 Vpr and Nef, the primary culprits in HIVAN, the mechanism is likely different. A possible explanation is that the FIV Vif gene may be fulfilling HIV-1 Vpr’s role of impairing cell division. Recent studies of HIV have shown that gene deletions of both Vpr and Vif are required to completely prevent G2 “stalling” (a process in between complete G2 arrest and normal cell-cycle progression), but the mechanism is unknown.61,62

CONCLUSIONS

The pathogenesis of HIVAN is a multifactorial process whereby genetic susceptibility, host response, and viral factors are important contributors. Animal models have provided a valuable research tool to study each aspect of pathogenesis. They have shown that intracellular renal expression of HIV is both sufficient and required to cause HIVAN in a genetically susceptible host. Tissue-specific models have further defined the role of HIV infection of individual renal compartments. Single HIV gene or gene deletion transgenic models have defined HIV-1 Nef and Vpr as the major disease contributors. In addition, small animal models have been used to test therapeutic efficacy. Last, whereas murine transgenic models are nonreproductive and applicable only to post–HIV entry events, primate models of SIV-associated nephropathy provide some insight into the role of viral evolution.

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DISCLOSURES

None.

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