"HIV-Associated Nephropathy" and "Focal Segmental Glomerulosclerosis"

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Patients with HIV-1 infection are at risk for several renal syndromes, including proliferative glomerulonephritis and focal segmental glomerulosclerosis(FSGS).

The pathogenesis of HIV-associated FSGS has been particularly enigmatic. Our laboratory has been interested in several questions.

1) Is there HIV-1 RNA and DNA in kidney, and is it localized to lymphoid cells and/or to renal parenchymal cells? Recent in situ hybridization studies suggest that occasional cells, most likely infiltrating mononuclear cells, express HIV-1 RNAs. Attempts to infect isolated renal parenchymal cells have met with varied success, with the most consistent infections being in renal tubular epithelial cells. Nevertheless, we have found that cultured renal tubular epithelial cells have a block to productive infection with HIV-1, whereby the virus enters the cell, full-length retro-transcripts are produced, but integration into the host genome does not occur. Further, HIV-1 infection of normal renal tissue maintained in explant culture is confined to lymphocytes and macrophages. Taken together, these findings suggest that the major pathway of HIV-1 injury may be the localization of virally infected lymphoid cells to kidney.

2) How does HIV-1 injure the kidney? If HIV-1 infects renal parenchymal cells, then direct cytotoxic effect remains a possibility. At present, we believe that a major route of injury may be localization of infected lymphoid cells to kidney, with release of cytokines(including TGF-beta) and viral proteins.

Alternatively, circulating cytokines or viral products released from infected cells in lymph nodes may mediate injury. Work from several laboratories using HIV-transgenic mice suggest that particular viral accessory genes play an essential role in inducing renal injury, and when these proteins are expressed in renal cells they result in toxicity and FSGS.

3) Why are some patients, in particular those of African descent, at particular risk for FSGS when infected with HIV-1? Idiopathic FSGS is more common among African Americans than among Americans of other races, and HIV-1 associated FSGS is largely a disease of African Americans. On the other hand,

most patients with FSGS lack family members with the disease. These observations suggest that FSGS may be the result of a genetic risk factor interacting with one of a number of environmental factors, including HIV-1. Many laboratories are actively pursuing the search for FSGS-susceptibility genes using a variety of genetic approaches.

HIV-associated Renal Disease

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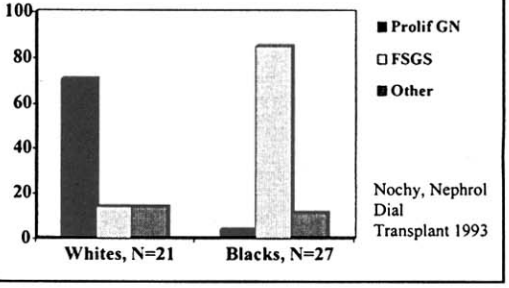
HIV-associated Renal Disease

- Clinical problem in countries with HIV infection
- Elucidating the mechanisms of renal injury may provide insight into how other viruses induce renal disease

HIV-associated Nephropathies

- Common
  - Focal segmental glomerulosclerosis ("HIVAN")
  - Immune complex renal disease
  - IgA nephropathy
- Uncommon
  - HUS/TTP
  - MPGN (HCV)
  - Membranous nephropathy
  - Amyloid

HIV-associated nephropathies



HIV-associated FSGS : Presentation

- Affects predominantly patients of African ancestry
- Can present early in HIV-1 infection but typically presents when CD4 below 200
- Edema and hypertension typically absent
- Large, echogenic kidneys by ultrasound

Lentiviruses and Kidney Disease

Virus	Host	Disease
HIV-1	Human	FSGS
HIV-2	Human	-
SIV	Monkey	FSGS
FIV	Cat	FSGS
EIAV	Horses	-
CAEV	Goat	-

HIV-associated FSGS

1. Is there HIV-1 in kidney?
   - Lymphocytes and macrophages
   - Parenchymal renal cells
2. How does the virus injure the kidney?
3. Why do only some patients develop kidney disease?

Localizing HIV-1 in Kidney

- Immunohistochemistry
  - Tubular epithelial cells (p24) — Cohen, 1989
  - Negative — Barbiano, 1990
  - Nonspecific — Nadasdy, 1992
- PCR for viral DNA
  - Glomeruli, tubules, interstitium — Kimmel, 1993
- In situ hybridization for viral RNA
  - DNA probes: GEC, TEC — Cohen, 1989
  - RNA probes: negative — Pardo, 1991

HIV Localization in Kidney : Summary

- Remains controversial
- HIV-1 likely infects lymphocytes and/or macrophages which enter kidney
- Definitive evidence of HIV-1 infection of renal parenchymal cells has not been developed - although low level productive infection has not been excluded

HIV-associated FSGS

1. Is there HIV-1 in kidney?
2. How does the virus injure the kidney?
   - Cytopathic effect
   - Immune response
   - Viral protein toxicity
3. Why do only some patients develop kidney disease?

Nephrotic Syndrome in HIV-Transgenic Mice

	WT	Transgenic
Edema	-	+
Proteinuria	-	+
Serum albumin	3.5±0.5 g/dl	2.4±0.4 g/dl *
Serum cholesterol	143±26 mg/dl	387±148 mg/dl **

HIV-transgenic Mouse Summary

- HIV-transgenic mice develop FSGS and ESRD
- Replicating virus, immunodeficiency, and opportunistic infection not required in mouse
- Athymic mouse experiments suggest cell mediated immunity not required
- Direct effect of viral proteins on renal cells
- Accessory genes *vif, vpr, vpu* may be critical

HIV-associated FSGS

1. Is there HIV-1 in kidney?
2. How does the virus injure the kidney?
3. Why do only some patients develop kidney disease?
   - Opportunistic infection
   - Viral strain: nephrotoxic or renotropic
   - Host genetic factors

Genetics of HIV-associated FSGS

- Human genetic variability
  - >95% variation not racially based
  - <5% variation between races
- African Americans: admixed population
  - 70% African genes
  - 30% Caucasian, Native American
- Gene or genes present in African population predisposes to renal disease

FSGS Genetic Study

- AA > W: idiopathic/collapsing/HIV FSGS (less clear for secondary FSGS)
- Most patients lack a family history of FSGS
- Genetic basis + environmental factor
- Therefore unaffected sibs cannot serve as control
- AA FSGS (N=139)
- AA control group: HIV+ 8 yr, no renal disease (N=205)

FSGS Genetic Study: Candidate Gene Approach

Hemodynamic	CK, other	CKR
• ANG	• SDF1	• CCR2
• Renin	• MDC	• CCR3
• ACE	• IFNG	• CCR5
• ATR1A	• IL2	• CCR8
• KLK1		• STRL33
		• APJ

ACE Polymorphisms

- ACE gene contains an polymorphism in intron 16 with insertion or deletion of 287 bp
- DD genotype associated with renal disease progression (diabetes, IgA)
- DD genotype associated with FSGS in Koreans (Lee, Nephron 1997)
- DD polymorphism associated with higher serum ACE levels in Caucasians but not African Americans

ACE Polymorphisms in African Americans with FSGS

- II polymorphism is over-represented in FSGS patients (29%) compared to control patients (14%, $P<0.007$)
- Findings suggest that an unidentified polymorphism in the ACE gene may contribute to the risk for FSGS in African Americans

Summary

- Black patients: FSGS
- Other racial groups: immune complex disease
- Localization of replicating HIV-1 in kidney remains controversial
- Expression of viral proteins induces FSGS in transgenic mice
- Host genetic factors likely contribute to FSGS