HIV-1 Infection of Renal Cells in HIV-Associated Nephropathy

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"If there is one thing the history of evolution has taught us it's that life will not be contained. Life breaks free, it expands to new territories and crashes through barriers." (Dr. Ian Malcolm in *Jurassic Park*)

Some of the deadliest infectious agents to humanity arose by host range expansion, jumping species barriers, whereas others engage in an evolutionary arms race with the human immune system to survive. Two of these, HIV-1 and trypanosomes, have converged to define the etiology of HIV-associated nephropathy (HIVAN), a rapidly progressive CKD that occurs in the setting of HIV-1 infection but only in individuals of recent African ancestry. Early in the United States HIV/AIDS epidemic and before effective antiretroviral treatment, approximately 10% of the HIV-seropositive black population developed HIVAN. At the same time in the epidemic, the HIV-seropositive white population did not develop HIVAN.

In the current paradigm, HIVAN is caused by direct HIV-1 infection of renal epithelial cells. This is made on the basis of several corroborating observations: viral nucleic acids are present in podocytes and tubular epithelial cells in human biopsies, HIVAN can be recapitulated in transgenic mouse models expressing the viral DNA in renal cells, and antiretroviral therapy has reduced the incidence of HIVAN and improved renal function and pathology in patients with HIVAN.[1] However, renal epithelial cells lack the receptor (CD4) and coreceptors (CCR5 or CXCR4) that are required for HIV-1 infection in T cells and macrophages, a conundrum that has left some in the HIV/AIDS research community skeptical that HIVAN results from direct renal cell infection. Fueling the controversy are the inconsistent and contradictory reports on whether cultured renal epithelial cells can be infected by HIV-1 *in vitro*, and whether the infection is productive (capable of producing new infectious virus) or abortive.[2]

Although the canonical CD4 receptor-mediated entry mechanism *via* interaction with the viral coat protein gp120 is highly efficient, additional (albeit less efficient) mechanisms of HIV infection have been described for other immune cell types and have been examined in renal cells.[3] These alternative mechanisms include the use of other receptors, such as c-type lectins or cell surface heparan sulfate proteoglycans, which bind the heavily glycosylated gp120 by nonspecific electrostatic interactions, and the adherent virus is subsequently engulfed by endocytosis, phagocytosis, or pinocytosis. Within the cell, whether this engulfed virus can escape the endocytic vacuole and proceed through the viral lifecycle is unclear. The engulfed virus can be trafficked to lysosomes and degraded, or enter recycling endosomes and return to the extracellular environment unchanged, neither of which would result in a chronically infected cell or a productive infection. Cell-mediated mechanisms of infection have also been described that require a direct cell contact with an infected immune cell. Shed virus from the immune cell is confined and protected within the cell–cell junction composed of lipid raft microdomains (termed virologic synapse), which also supports endocytic uptake. Although the cell–cell transmission of virus has been documented *in vitro*, how this occurs *in vivo* is unclear, and it would be considerably more challenging for a functional virologic synapse to form in the complex tissue anatomy of the kidney.

In the report by Li *et al.*,[4] a new piece to the kidney infection puzzle has been added: the role of inflammation to prime renal cells for infection. Using a clever unbiased screening method, Li *et al.* identified membrane bound TNF (tm-TNF) as a host protein that facilitated more efficient *in vitro* infection of cell-free virus entering by a dynamin-dependent endocytic mechanism. TNF expression is inducible in most renal cells, is initially synthesized as a transmembrane protein, and soluble TNF (sTNF) can be produced by ectodomain shedding. The functions of sTNF in the inflammatory response are well described; however, the functional roles of tm-TNF are not well understood but may involve novel outside-in or inside-out signaling events related to its roles as both a ligand and a receptor.[5] Some of these signaling events, including robust NF-κB activation, are well known to enhance viral replication. However, Li *et al.* determined NF-κB activation was not the tm-TNF–dependent event that enhanced infection in podocytes. Infection could be blocked with either the addition of a TNF neutralizing antibody or expression of an inactive TNF mutant, but activation of NF-κB by sTNF treatment did not recreate the enhanced infectivity initiated by tm-TNF expression. Although the actual mechanism of entry through tm-TNF was not defined in this study, on the basis of the methods used, the results suggest some aspect of tm-TNF trimerization, integration or organization into lipid rafts, or potentially oligomerization with other receptors may be important events in the enhanced viral entry.

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Another well established concept in the HIVAN paradigm is that HIVAN occurs only in populations of recent African ancestry worldwide. This includes current sub-Saharan African populations where HIVAN is a significant complication of HIV infection. In the United States, Blacks and Dominican, Cuban, and Puerto Rican Hispanics, who trace ancestry to these same African populations, are similarly susceptible to HIVAN and are at greater risk for other forms of CKD.[6] The recent identification of polymorphisms in *APOL1* that are common in black ancestry but absent in white ancestry explains this genetic susceptibility.[1] APOL1 is a unique molecule in the primate innate immune armamentarium with efficient trypanosome killing activity. Polymorphisms in *APOL1* arose and were selected for in recent African populations to restore killing activity against a *Trypanosoma brucei* subspecies that itself evolved as a counter-mechanism to evade wild-type APOL1 killing. Individuals homozygous for these *APOL1* polymorphisms (referred to as risk alleles), for reasons yet to be established, have a substantially increased risk for HIVAN in the setting of uncontrolled HIV-1 infection with a 29-fold higher odds ratio compared with whites.[7] Approximately 12%–15% of the United States black population are homozygous for *APOL1* risk alleles, and this percentage closely matches the prevalence of HIVAN (10%) in the HIV-infected United States black population early in the epidemic. Recent studies, however, have discounted the role of the abundant APOL1 plasma protein as causing kidney disease,[8,9] and thus attention is now focused on the role of APOL1 protein expressed in kidney cells as the key player in the APOL1-dependent pathogenic mechanism.[10,11]

Interestingly, Li *et al.* did examine HIV-1 infection in podocyte cell lines that were either homozygous for wild-type *APOL1* (G0/G0) or homozygous for *APOL1* risk alleles (G1/G1). No difference was found in the infection of these cell lines. Considering the converging evidence of both HIV-1 infection and *APOL1* expression in podocytes as fundamental events in HIVAN pathogenesis, it seems logical there must be a functional interaction between APOL1 and some aspect of the HIV-1 lifecycle that is different with the *APOL1* risk alleles. Identifying this intracellular connection is our best opportunity to define the intracellular role of APOL1 in podocytes, which may explain the genetic predisposition not only to HIVAN but also other kidney diseases associated with *APOL1* risk alleles. Two recent studies have identified a role for wild-type APOL1 in suppressing HIV-1 replication.[12,13] These studies suggest APOL1 is a new host restriction factor for HIV-1 (and possibly other viruses) that could be exploited for future antiviral therapy development. Whether the *APOL1* risk alleles have lost these virus restriction functions has not been tested.

HIV-1 has found a way into renal cells, but the key question is why does this cause kidney disease only in the host with *APOL1* risk alleles? APOL1 evolved as part of our immune system, and it is tempting to speculate APOL1 may have an additional immune role against viruses. Understanding the HIVAN pathogenic mechanism remains incomplete until we understand the normal function of APOL1 in the kidney and what is lost or gained with the *APOL1* risk alleles.

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DISCLOSURES

None.

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