HIV-1 Entry into Renal Epithelia

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Presence of HIV-1 nucleic acid in both glomerular and tubular cells indicates that the kidney may serve as a reservoir for HIV-1.1,2 Moreover, HIV-1 genes express in tubular epithelial cells in the absence of detectable viral load in HIV-associated nephropathy (HIVAN).3 Although these studies offered strong evidence for renal epithelial cell infection, the mechanism of HIV-1 entry is not clear.

Recently, several investigators attempted to identify the route of HIV entry into renal epithelia.4–6 DEC-205, an endocytic receptor abundantly present on dendritic cell surfaces, is present in renal tubular epithelial cells and may facilitate HIV-1 entry.4 Upon co-culture with T cells, a small fraction of internalized virus is also rescued by T cells, raising a possibility of productive infection within tubular epithelia.4 Another cell surface molecule, globotriaosyl ceramide (Gb3), which acts as a receptor for Shiga or Vero toxins, is also present on glomerular and tubular epithelial cells.6 The Gb3 interaction with gp120 promotes a CD4-, CXCR4-, and/or CCR5-dependent fusion process; however, the exact role played by Gb3 in HIV-1 entry into tubular cells is not clear.

Recent studies strongly suggested that cell-to-cell transmission is much more efficient than cell-free transmission.7,8 Cell-to-cell transmission is described mostly between infected T cells or virus-laden antigen-presenting cells and uninfected T cells. This interaction at the site of cell-to-cell contact is called a virologic synapse with polarized T cells forming a protrusion called uropod, which mediates contact with the other cell.9,10 Chen et al.,11 in this issue of JASN, describe similar interactions between infected T cells and renal tubular epithelia. These investigators in their in vitro experimental model found viral transmission from infected T cells to renal tubular epithelial cells through cell-to-cell interaction, which they argue occurs through the formation of a virologic synapse.11 They used replication competent green fluorescence protein (GFP)-tagged HIV to infect primary CD4+ T cells or a T cell line. During co-culture, T cells efficiently transmitted this laboratory-manipulated virus to renal tubular cells. Transmission was not limited to renal tubular epithelial cells alone but also took place in other epithelia, suggesting that transmission specificity may depend on epithelial cell type. Furthermore, efficient transfer happened only with viral particles contained within T cells, whereas transmission of cell-free virus was minimal. The viral transmission was CD4 independent and did not require envelope protein (Env). Rather, heparan sulfate proteoglycans (HSPGs), specifically syndecan 1 and agrin, seemed important in this transmission, although their functional role without the engagement of Env was not clarified.

HIV-1 entry into epithelial cells, independent of CD4, has been reported by several investigators.4,12,13 Renal epithelial cell expression of conventional receptors such as CD4, CXCR4, and CCR5, which are commonly used by HIV-1 for entry into T cells, remained controversial.4,12,13 Interestingly, tubular cell expression of other transmembrane family receptors such as STL33, GPR1, and APJ along with low levels of viral expression has been reported in isolated cases13–15; however, confirmation of their presence and studies pertaining to their functional role are still awaited.

Besides conventional receptors and co-receptors used by HIV-1, several other cell surface molecules may be used by HIV-1 to enter the cell.16–19 The most studied among them have been dendritic cell-specific ICAM-3–grabbing non-integrin (DC-SIGN), but macrophage mannose receptor, galactosylceramide, and HSPGs may also facilitate viral entry. These nonconventional pathways of HIV-1 entry may facilitate viral compartmentalization in various organs, and, thus, the repertoire of HIV-1 reservoirs may be much more varied than previously thought.

Role of HSPGs in HIV-1 transmission from T cells to intestinal epithelial cells (HT29) is known20 and suggests nonconventional cell surface HIV-1 entry through a virologic synapse.20,21 In the studies carried out by Chen et al.,11 the punctate expression of GFP in renal tubular cells is indicative of viral transfer because the GFP is part of Gag moiety. In addition, further confirmation of viral transfer to renal tubular cells was shown by quantification of unspliced forms of viral RNA; however, the efficiency of virus replication was not evaluated.

Glomerular visceral epithelial cells (podocytes) are also infected by HIV-1 in patients with HIVAN.1 Dysregulated podocyte growth displayed in HIVAN is attributed to HIV-1 gene expression. Although direct evidence demonstrating HIV-1 transmission into podocytes has never been shown, recent in vitro studies suggested the possibility of nonproduc-
tive infection in podocytes.22–24 Mikulak et al.22,23 demonstrated that both DC-SIGN and lipid rafts facilitate HIV-1 entry into cultured human podocytes through endocytic pathways. Khatau et al.24 further confirmed the role of endocytic pathways in podocyte HIV-1 entry. It has been suggested that for HIV-1 entry into podocytes, other genetic or host factors are needed for productive infection.

Not too long ago, the notion of HIV cell fusion was the dominant mechanism for entry, whereas internalization of virus by other routes would result in viral degradation.25 This earlier notion was supported by observations that HIV mediates fusion between adjacent target cells, whereas cortical actin imposes restriction on HIV infection in resting T cells.26 Nevertheless, pseudotyping the HIV core with the low pH-dependent G glycoprotein of vesicular stomatitis virus suggests an alternative route for viral entry,27 and electron microscopic studies reveal HIV fusion with endosomes and microsomes.28 Furthermore, pH-modulating agents increase HIV accumulation by avoiding viral degradation in lysosomes,29 and inhibition of clathrin-mediated endocytosis reduces infection in HeLa-derived cells.30 All these observations indicate now that endocytic pathways not only play an important role for HIV-1 entry but also provide an opportunity for HIV-1 to fuse with cell membranes in endosomes. These endocytic pathways also operate for HIV-1 entry into kidney cells.4,22

Better and more effective therapies may be formulated if the mechanisms leading to HIV-1 entry and its replication into renal epithelia are fully understood. In vitro studies by Chen et al.11 showing HIV-1 entry by formation of virologic synapses between infected T cell and tubular cells and similar studies by others4,22–24 describing use of nonconventional receptors may facilitate understanding of the mechanisms involved in HIV-1 entry into renal epithelia. Further studies are now needed to delineate the mechanism of intracellular membrane trafficking used by HIV-1 for its replication.

ACKNOWLEDGMENT

This work was supported by grants RO1 DK084910 and RO1 DK083931 (P.C.S.) from National Institutes of Health (Bethesda, MD).

M.H. is a visiting professor from Jamia Milia Islamia Central University (New Delhi, India).

DISCLOSURES

None.

REFERENCES


mediates HIV-1 infection of T-cell lines. AIDS Res Hum Retroviruses 9: 167–174, 1993

See related article, “Virological Synapses Allow HIV-1 Uptake and Gene Expression in Renal Tubular Epithelial Cells,” on pages 496–507.