HIV-1 *vpr* causes G2/M Arrest and Apoptosis in Human Renal Proximal Tubule Cells
Implications for HIV Associated Nephropathy (HIVAN) Pathogenesis

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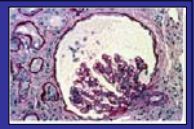
BACKGROUND – HIV Associated Nephropathy

HIV Associated Nephropathy



- Affects almost exclusively blacks
- The prevalence in blacks with HIV-1 is 3.5-12%
- Estimated 1-3 million cases worldwide
- Leading cause of End Stage Renal Disease (ESRD) in HIV-1 seropositives
- 3rd Leading cause of ESRD in U.S. Blacks
- **HIVAN is caused by HIV-1 infection and subsequent viral protein production in glomerular and tubular kidney epithelial cells**

HIV-1 Genome

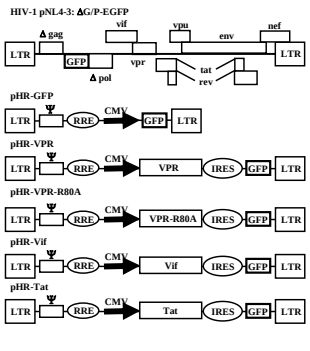
Role in HIVAN	Dispensible	Dispensible	SUSPECTED (based on transgenic mouse models)	Dispensible	Glomerular Proliferation

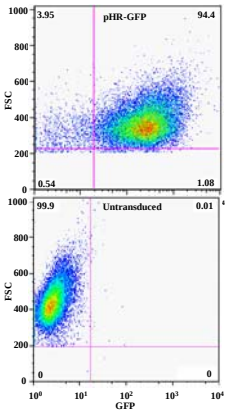
STUDY AIM

To determine the effect of HIV-1 vpr expression in an in vitro model of the human renal proximal tubule.

METHODS

Methods: A psuedotyped lentivirus delivery system was used to transduce a human renal proximal tubule cell line (HK2). Using the VZV.G envelope efficient transduction was achieved as measured by GFP reporter expression.





RESULTS

Fig 1. HIV-1 vpr inhibits the growth of human renal proximal tubule cells *in vitro*.

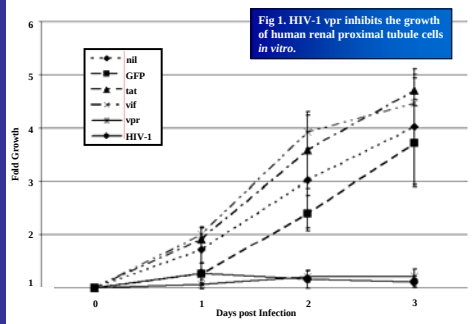
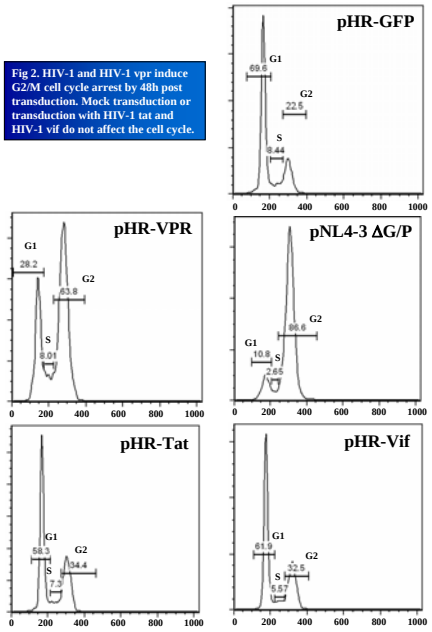


Fig 2. HIV-1 and HIV-1 vpr induce G2/M cell cycle arrest by 48h post transduction. Mock transduction or transduction with HIV-1 tat and HIV-1 vif do not affect the cell cycle.



RESULTS Cont.

Fig 3. HIV-1 vpr induces apoptosis following G2/M cell cycle arrest. Apoptosis was measured by Annexin-V staining (Fig. 3) and sub-G1 cell cycle PI staining (Fig. 4).

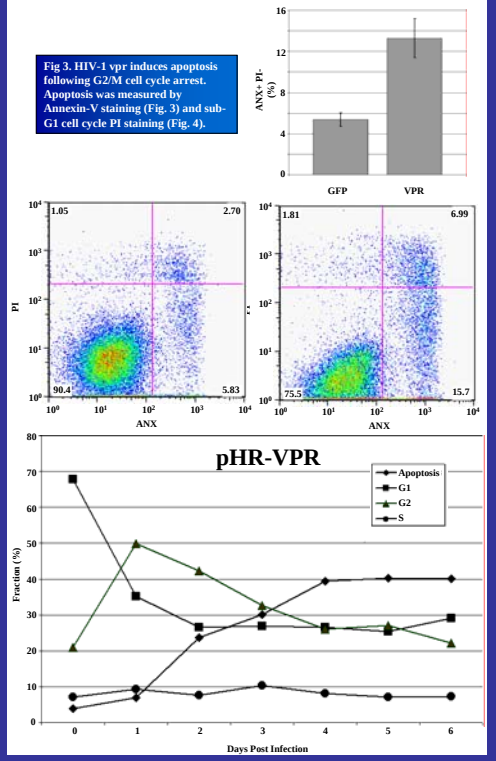
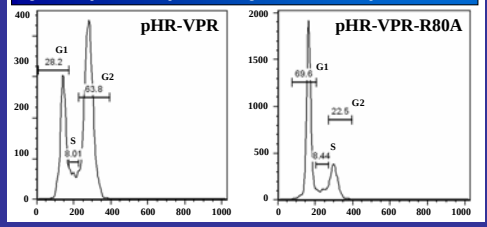


Fig 5. HIV-1 vpr R80A is incapable of inducing G2 arrest in the renal proximal tubule



SUMMARY

The proximal tubule epithelium is directly infected by HIV-1 and undergoes distinct pathologic change including microcystic dilitation and apoptosis. The protein HIV-1 vpr is important for HIVAN pathogenesis in the murine disease model. Transgenic mice expressing HIV-1 vpr show mild pathology and those expressing an HIV-1 genome without vpr show a much less severe pathology. These results demonstrate that HIV-1 vpr is capable of causing G2 arrest and apoptosis and may be a key contributing pathogenic factor.

Defining the specifics of HIV associated nephropathy will not only provide therapeutic targets, but potentially predictive host susceptibility alleles, as well as predictive viral polymorphisms.

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