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Role of heme-oxygenase-1 and ferroportin in HIV-1 infection

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Abstract

HIV-1 transcription is activated by HIV-1 Tat protein, which recruits CDK9/cyclin T1 and other host transcriptional co-activators to the HIV-1 promoter. Tat itself is phosphorylated by cell cycle kinase 2 (CDK2) and inhibition of CDK2 by small interfering RNA or iron chelators inhibits HIV-1 transcription. HIV-1 transcription is also activated by NF-kB that binds to HIV-1 LTR independent to Tat but can also be recruited Tat-dependently by CDK9/cyclin T1. Previously induction of heme oxygenase-1 (HO-1) by hemin was shown to inhibit HIV-1 in vitro and *in vivo*. We also showed previously that expression of ferroportin inhibits HIV-1 transcription. We show here that treatment with hemin induces both HO-1 and ferroportin expression and potently inhibits HIV-1. We also show that hemin induces expression of IkBα, an inhibitor of NF-kB, and p21, a CDK2 inhibitor. These effects were replicated with novel iron chelators, PpY-eT and PpY-aT, which both efficiently inhibited HIV-1 and induced the expression of IkBα and p21. Ferroportin Q248H mutation has an allele frequency of 2.2-13.4% in African populations and is associated with a mild tendency to increased serum ferritin in the general population. Ferroportin Q248H mutation associates with lower hepcidin levels in HIV-1 infected Rwandese. We also recently showed that ferroportin Q248H mutant has reduced sensitivity to physiologic hepcidin concentrations. In the absence of hepcidin, both WT ferroportin and Q248H ferroportin efficiently inhibited HIV-1 transcription and replication. Hepcidin treatment induced HIV-1 transcription and replication inhibited by WT ferroportin but not Q248H mutant ferroportin. Also, HIV-1 replication was reduced in primary monocytes from ferroportin Q248H subjects as compared to controls. In conclusion, HIV-1 can be inhibited through the induction and HO-1 and ferroportin likely through the upregulation of IkBα and 21. An expression of ferroportin Q248H that has a decreased sensitivity to hepcidin may offer an additional protection from HIV-1.

Biography

Sergei Nekhai has a Ph.D. degree in Biophysics from St. Petersburg Nuclear Physics Institute, Russia. He obtained his postdoctoral training at the George Washington University. He serves as co-Director for Howard University's Center for Sickle Cell Disease and Director of Proteomics. He studies HIV-1 transcription, pulmonary hypertension in sickle cell disease and iron metabolism with the focus on ferroportin mutations that might pose a risk for iron overload and worsen HIV-1 infection in African-Americans. He has more than 60 publications in basic virology and hematology journals and serves as a PI and co-PI on several NIH-funded grants.