Interferon Alfa Partially Inhibits HIV Replication in Hepatocytes In Vitro

TO THE EDITOR—Interferons are potent antiviral agents that activate expression of numerous interferon-stimulated genes (ISGs) that also have antiviral properties. Interferon alfa is commonly used to treat chronic hepatitis C virus (HCV) infection, although several viral proteins have been implicated in the inhibition of ISGs and/or key components of interferon signaling pathways [1].

In a recent Journal article, Azzoni et al investigated the antiviral effects of pegylated (Peg) interferon alfa-2a on human immunodeficiency virus (HIV) suppression [2]. Twelve weeks of Peg–interferon alfa-2a monotherapy resulted in sustained suppression of HIV in 45% of patients despite interruption of antiretroviral therapy (ART). Other clinical trials also support an approximately 0.5 log reduction in plasma HIV RNA in patients treated with Peg–interferon alfa-2a in the absence of ART [3–6].

We recently reported that HIV infects hepatocyte-derived cell lines, as well as primary human hepatocytes [7]. Integrated HIV proviral DNA was detected in hepatocytes and was inhibited by the integrase inhibitor raltegravir in a dose-dependent manner. HIV p24 protein was also detected in cell culture supernatants and was inhibited by zidovudine. Levels of HIV were modest, compared with those in a lymphocyte cell line, suggesting that low-level viral replication occurs in hepatocytes.

Given the in vivo data from Azzoni et al and our in vitro findings, we evaluated whether HIV replication in hepatocytes was limited by interferon and/or ribavirin (RBV). The Huh7.5JFH1 cell line, which produces infectious HCV virions [8], was infected with the NL4–3 isolate of HIV as described previously [7]. Incubation with 0.1, 1.0, or 1000 ng/mL consensus interferon (Infergen, Three Rivers Pharmaceuticals [Cranberry Township, PA]) and/or 0.1, 1.0, or 10 μg/mL ribavirin (Roche Laboratories [Nutley, NJ]) was performed 1 day before and during HIV infection. At day 3, HIV p24 and HCV core proteins were quantified in cell culture supernatants by enzyme-linked immunosorbent assays with lower limits of detection of 4.3 pg/mL (PerkinElmer [Boston, MA]) and 1 ng/mL (Cell Biolabs [San Diego, CA]).

As shown in Figure 1, there was a modest dose-response effect of RBV on HIV replication in hepatocytes, resulting in 10.4%, 25.3%, and 37.5% inhibition at RBV doses of 0.1, 1.0, and 10 μg/mL, respectively. Interferon treatment at doses of 0.1, 10, and 1000 ng/mL inhibited HIV replication by 3.7%, 38.5%, and 45.2%, respectively. The combination of RBV plus interferon inhibited HIV replication in

Figure 1. Cell culture supernatant levels of human immunodeficiency virus (HIV) p24 protein (pg/mL) in HIV-infected Huh7.5JFH1 cells in the presence of consensus interferon (0, 0.1, 1.0, or 1000 ng/mL) and/or ribavirin (RBV; 0, 0.1, 1.0, and 10 μg/mL). Numbers in italics denote the percentage inhibition of HIV replication, compared with the HIVNL4–3–only condition.
hepatocytes by 12.6%, 59.8%, and 96.9%. By comparison, RBV plus interferon inhibited HCV replication in HIV-infected hepatocytes by 8.4%, 31.7%, and 47.1% (data not shown).

The liver is an understudied reservoir of HIV replication [9]; thus, the effects of antiviral agents on inhibition of viral infection and replication are not well characterized. However, HIV is associated with accelerated liver disease and lower HCV treatment response rates in vivo [10]. Thus, antiviral agents, such as interferon, that have activity against both HIV and HCV may prove important in the clinical management of HIV pathogenesis, HCV pathogenesis, and HIV-mediated liver damage. Our in vitro findings demonstrate a suppressive effect of interferon on HIV replication in hepatocytes that support and extend the previous conclusions by Azzoni et al that interferon may contribute to HIV control in vivo. This suppressive effect on HIV replication may also ameliorate the deleterious effects of HIV on the liver. Interferon may limit both HIV and HCV replication in difficult-to-treat populations, such as individuals with HIV/HCV coinfection, and requires additional investigation in vivo.

Notes

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Ling Kong and Jason T. Blackard
Division of Digestive Diseases, University of Cincinnati College of Medicine, Ohio

References


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Correspondence: Jason Blackard, PhD, Division of Digestive Diseases, University of Cincinnati College of Medicine, ML 0595, 231 Albert Sabin Way, Cincinnati, OH 45267 (jason.blackard@uc.edu).

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