Cell Death and Differentiation (2003) 10, S25–S26

www.nature.com/cdd

News and Commentary

HIV/HCV co-infection: putting the pieces of the puzzle together

G Antonucci*[,1], D Goletti[1], S Lanini[1], E Girardi[1] and O Loiacono[2]

[1] Istituto Nazionale per le Malattie Infettive; IRCCS L. Spallanzani, Rome, Italy
[2] Cattedra di Gastroenterologia Universita di Palermo, Italy
* Corresponding Author: Dr G Antonucci, Istituto Nazionale per le Malattie Infettive; IRCCS L. Spallanzani, Via Portuense, 292 00191 Rome, Italy. Tel: 3906 55170485; Fax: 3906 5594224; E-mail: antonucci@inmi.it

Cell Death and Differentiation (2003) **10,** S25–S26. doi:10.1038/sj.cdd.4401164

The most relevant consequence of human immunodeficiency virus (HIV) infection is the exposure of the patient to opportunistic agents. In addition, HIV may also modify the natural history of some non-opportunistic pathogens, which in turn may alter the course of HIV infection.

A well described example of the effect of a co-infection with HIV and a non-opportunistic pathogen is given by *Mycobacterium tuberculosis* (MTB). HIV-induced immunosuppression may increase the risk of progression from latent infection to active tuberculosis by 100–300 times, and may also alter the clinical expression of tuberculosis. Thus, the recent spread of the HIV pandemic has significantly contributed to the resurgence of tuberculosis in many areas of the world that have a high prevalence of HIV–MTB co-infection. On the other hand, it has also been suggested that active tuberculosis may accelerate the clinical progression of HIV disease, although less convincing evidence exists in favor of this hypothesis.[1]

With the sharp increase in life-expectancy in persons with HIV infection related to the introduction of highly active antiretroviral therapy (HAART),[2] another co-infection with a non-opportunistic pathogen, involving HIV and hepatitis C virus (HCV), is emerging as a potentially relevant public health issue. In fact, at least 30% of individuals infected with HIV are estimated to be co-infected with HCV, rising to 70–90% in special groups of HIV-infected persons, such as intravenous drug users (IVDUs).[3] HCV, which shares common routes of transmission with HIV, has the potential to cause death by liver fibrosis that may further progress to cirrhosis.

To date, there is accumulating evidence that HCV liver-disease progression is accelerated by HIV infection, appearing to be related to the progression of HIV disease.[4] Moreover, a possible detrimental effect of HCV-infection on HIV-infected patients has also been suggested.[5]

Although evidences of the increasing risk of morbidity and mortality due to HCV in HIV co-infected patients has recently been reported,[6] the precise mechanisms by which HIV may favor HCV-induced fibrogenesis in the liver remain largely unclear.

Liver fibrosis is a dynamic process involving complex cellular and molecular mechanisms initiated by chronic inflammation due to liver-tissue damage, led by the activation of quiescent hepatic stellate cells (HSC), and resulting in the re-modeling and deposition of the extracellular matrix (ECM). Studies of hepatic fibrogenesis in experimental models, as well as in human liver diseases, clearly indicate that a shift from production of Thelper (h)-1 cytokines to Thelper (h)-2 cytokines occurring mainly in the Kuppfer cells and in other local cellular populations inside the chronic inflammatory-milieu, are crucial to induce the activation of HSC.[7]

HCV infects and damages hepatocytes, thus initiating the process that may eventually lead to liver-fibrosis and cirrhosis. On the other hand, HIV is involved in a wide range of hepatic complications, but it is not known to induce liver fibrosis *per se*. How might a non-fibrogenic virus influence liver fibrogenesis driven by HCV?

A shift of the host immune response to the Th-2 cytokines during the late stages of HIV disease has been clearly demonstrated.[8] Nevertheless, a more direct involvement of HIV in the process of liver-fibrogenesis may also be hypothesized. Kupffer cells, which play a main role in the liver fibrogenesis, are the primary hepatic target cell population for HIV infection *in vivo*.[9]

Unlike the HIV-infected residential macrophages of the lung and the brain, which respectively lead to interstitial pneumonia in children and encephalopathy, the infection of Kupffer cells in the liver does not lead to any known syndromes. Thus, the pathogenesis of liver injury in the course of retrovirus infection has been investigated in simian immunodeficiency (SIV)-infected macaques, which has been proven to be the animal model most similar to human infection, and which develops an immunodeficiency disease resembling AIDS. In this model, the number of Kupffer cells infected, as well as their content in viral proteins and their histological lesions, increased with the progression of SIV disease. Moreover, infected Kupffer cells clearly produced Th-2 citokines, and inflammatory infiltrates around the portal triads were also observed. Interestingly, in this model an increase in the content of ECM was not observed.[10]

Given the inherent difficulty of HCV in infecting primates, to our knowledge experimental models with animals co-infected with a retrovirus and HCV have not yet been carried out. Buch *et al*.[11] inoculated $SHIV_{KU}$-infected macaques with eggs of Schistosoma mansoni, a pathogen inducing a strong inflammatory response in the liver, a prominent Th-2 cytokine production, and fibrosis. Under these conditions, macrophages of the hepatic inflammatory milieu supported high viral replication. These findings were

not observed in livers of macaques tested with complete Freund's adjuvant, a Th-1/Th-2 inducer.

Overall, these studies suggest a very intriguing interplay between a virus closely related to HIV and a fibrogenic pathogen, in enhancing Kupffer cell activation, Th-2 cytokine production, inflammatory infiltrates production, and virus replication in the setting of an infection-induced liver-fibrotic process. Similarly, it may be hypothesized that in co-infected patients HIV directly contributes in accelerating the rate of HCV-driven fibrosis, especially during the more advanced stage of immunosuppression.

Aside from this immune-mediated mechanism, very recent findings suggest that the altered balance between the metalloproteinases (MMPs), molecules devoted to degrading ECM, and their inhibitors (TIMPs) may also play an important role in the enhancement of liver-fibrosis progression observed in co-infected patients. A striking unbalance between MMP-9 levels and TIMP-1 levels has been reported in co-infected patients, significantly higher than that observed among HIV and HCV-mono-infected patients.[12]

Interestingly, HCV infection in turn seems to affect HIV disease.[5] To explain this effect a negative influence of HCV on the kinetics of T cells, especially on CD4+ T cells, has been suggested.[13] Recently, Laskus *et al.*[14] provided evidence that in co-infected patients HCV infects CD4+ cells, strongly suggesting the possibility that HCV may replicate in the same T-cells as HIV. Moreover, Taya *et al.*[15] reported a close relationship between HCV infection of peripheral blood mononuclear cells and cell-surface Fas expression, suggesting the possibility of HCV infection to trigger CD4+ cells apoptosis. It could be plausible that in immune-deficient, co-infected patients, these alterations may lead to either a more rapid progression of HIV-infection or an impaired immune-reconstitution after starting HAART, although in HCV mono-infected patients they are clinically inactive.

If both HIV and HCV infections affect the disease progression of each other, the practical result is that co-infected patients should be promptly and aggressively treated for both infections. Given that HCV disease is a treatable one, and that current optimum therapies may be toxic, particularly for those patients taking HAART, new and better therapeutic options are needed. A better understanding of cellular and molecular mechanisms of HIV/HCV co-infection could be useful when addressing this issue.

1. Havlir DV, Barnes PF (1999) N. Engl. J. Med. 340: 367–373
2. Palella Jr FJ *et al.* (1998) N. Engl. J. Med. Mar. 338: 853–860
3. Lauer G *et al.* (2001) N. Engl. J. Med. 345: 41–52
4. Benhamou Y *et al.* (2001) Hepatology 34: 283–287
5. Greub G *et al.* (2000) Lancet 356: 1800–1805
6. Bica I *et al.* (2001) Clin. Infect. Dis. 32: 492–497
7. Olaso E *et al.* (1998) J. Hepatol. 29: 836–847
8. Navikas V *et al.* (1994) Clin. Exp. Immunol. 96: 59–63
9. Lefkowitch JH (1997) Semin. Liver Dis. 17: 335–343
10. Persidsky Y *et al.* (1995) Hepatology 21: 1215–1225
11. Buch S *et al.* (2001) Cytokine 13: 295–304
12. Mastroianni CM *et al.* (2002) HIV Clin. Trials 3: 310–315
13. Graham CS *et al.* (2000) Lancet 356: 1865–1866
14. Laskus T *et al.* (2000) Clin. Infect. Dis. 181: 442–448
15. Taya N *et al.* (2000) Br. J. Haematol. 110: 89–97