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Pathogenesis of Liver Damage in HCV-HIV Patients

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Abstract

The coinfection of HIV and HCV has become a pathology with several distinctive characteristics. Pathogenesis of liver damage in patients with HIV and HCV coinfection is complex and multifactorial. It derives from a balance of factors which interact among themselves in a dynamic way. The reasons for the accelerated course of HIV/HCV coinfection are mainly related to two principal causes: the persistence of HCV, which depends upon alterations of cell-mediated immunity, and the activation of the immune system towards secretion of proinflammatory and profibrotic cytokines. This review will first focus on the characteristics of both these immune-mediated mechanisms, and then their implication on fibrogenesis as well as on other pathogenetic mechanisms, such as interactions between viruses and the deficit of protective mechanisms. A better knowledge of adaptive immune mechanisms, cytokine alteration, interference with host defense mechanisms, and the "cross-talk" among the viruses will improve the understanding of the pathogenetic mechanism and provide the opportunity to cure this disease. **(AIDS Rev. 2008;10:15-24)**

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Key words

HIV-HCV coinfection. Liver fibrosis. Pathogenesis. Liver damage.

Introduction

Progressive chronic liver disease associated with hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality in patients infected with HIV. Numerous studies have shown that infection with HIV exacerbates the natural history of chronic HCV infection. Increased rates of liver fibrosis and progression to end-stage liver disease have also been well documented in HIV-infected individuals coinfected with HCV. In prospective studies, HIV/HCV coinfection is associated with a higher cumulative incidence of end-stage liver disease and shorter survival times than is HCV monoinfection. A meta-analysis of studies involving HIV/HCV-coinfected patients reported a correlation between HIV coinfection and an increased risk for the progression of HCV-related liver disease[1].

The reasons for the accelerated course of HIV/HCV coinfection are mainly related to two principal causes: the persistence of HCV, which depends upon alterations of cell-mediated immunity, and the activation of the immune system towards secretion of proinflammatory and profibrotic cytokines.

This review will first focus on the characteristics of both these immune-mediated mechanisms and then on their implication on fibrogenesis. Other pathogenetic mechanisms, such as interactions between viruses and the deficit of protective mechanisms, are actually under investigation and will be discussed briefly.

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HCV persistence and alteration of cell-mediated immunity

The successful control of viral infections depends on the generation and maintenance of long-lasting spe-

cific memory CD4+ T-cells, which support the production of antibodies and the function of specific CD8+ T-cells[2-5].

In the case of HIV and HCV infection, early containment (HIV-1) or clearance (HCV) of infection is associated with induction of strong CD4 and CD8 T-cell responses. On the other hand, these same kinds of responses have been suggested to play a role in disease pathogenesis, due to the accelerated destruction of hepatocytes in the case of HCV and lymphocytes in the case of HIV-1[6-9]. Some evidences have also postulated that the increased rate of fibrosis in individuals coinfected with HCV and HIV-1 may be related to the loss or dysregulation of these immune responses[10].

Many findings indicate that CD4+ T-cell responses represent a critical component of a successful immune response against HCV[11]. During the acute phase of HCV infection, the breadth of this response correlates with early control[12,13]. After successful clearance, CD4+ T lymphocytes that proliferate in response to recognition of viral antigen are found in 64-79% of spontaneous controllers[14,15]. In humans, CD4+ T-cell depletion due to HIV is associated with declining levels of functional CD8+ T-cells specific for HCV[4].

A recent cross-sectional study of 103 persons infected with HCV demonstrated that the presence of HIV-1 antibodies alone is not sufficient to alter the breadth, magnitude, or specificity of the HCV-specific CD8 T-cell response. However, frequencies of these cells depend on the immune status of the individual as defined by absolute CD4 T-cell count, independent of whether or not HCV viremia is present or controlled. The same author demonstrated that HCV-specific CD8 T-cell responses decline with diminishing absolute CD4 counts, providing a possible explanation for the more rapid HCV disease progression in the setting of HIV-1 coinfection. These data suggest that the magnitude and breadth of HCV-specific CD8 cells are sensitive to the T helper (Th) lymphocyte environment[5].

The above evidence confirms a critical role of virus-specific CD4+ T-cells in HCV control. Previous studies have shown a complex effect of HIV infection on HCV-specific CD4+ T-cells in persons with chronic HCV viremia[16-18].

It is well known that subjects with chronic HIV-1 infection rarely demonstrate strong HIV-1-specific CD4 proliferative responses, with the exception of individuals with long-term nonprogressive disease[19,20]. The proliferative response by CD4 cells upon stimulation with HCV proteins is also weak in individuals with chronic HCV infection[21-24], but vigorous CD4 responses have been detected in individuals who spontaneously resolve the infection[24-26].

A study[19] carried out to evaluate the cellular immune response in peripheral blood against HIV-1 and HCV in 22 subjects with HIV-1 infection and HCV coinfection, demonstrated markedly weaker CD8 T-cell responses to HCV than to HIV-1 in coinfected persons, regardless of disease stage. The Th responses to HCV were entirely absent in this cohort with dual infection. Notably, HAART-associated control of HIV-1 plasma viremia was associated with the frequent detection of HIV-1-specific Th responses in dually infected persons, much higher than typically reported in persons with chronic HIV-1 monoinfection[26,27]. However, none of these persons had detectable HCV-specific Th responses.

A CD8 T-cell response against HIV-1 was readily detected in all 22 subjects, regardless of the stage or course of the HIV-1 or HCV infection and regardless of HIV-1 or HCV viral load. The CD8 T-cell response against HIV-1 was strong and broadly directed in the majority of individuals. In contrast, HCV-specific CD8 T-cell responses were absent in the majority of individuals, and in the few persons with detectable HCV-specific CD8 T lymphocytes, the response was generally weak and not explained by advanced HIV-1-induced immunodeficiency, as most subjects in the cohort were controlling HIV-1, either spontaneously or with HAART.

These authors also included in the study a matched cohort of persons with chronic or resolved HCV monoinfection. The results confirmed a difference in the HCV-specific CD4 T-cell response as, in the control cohort, a proliferative response was detected with statistically significantly higher frequency than in the coinfected group (47 vs. 0%; $p < 0.002$). Overall, the comparison of the intra-individual cellular immune response toward HIV-1 and HCV in coinfected persons shows that an individual having a strong cellular immune response against HIV-1 generally does not have a similar response against HCV. One explanation for the low frequency of HCV-specific T- cells in peripheral blood might be compartmentalization of these cells to the liver as the main site of infection[28] (Table 1).

Other interesting data on the pathogenesis of HIV/HCV coinfection come from a study designed to compare the T-cell responses to HCV and HIV in HIV-infected long-term nonprogressors and HIV-positive progressors coinfected with HCV, and in HIV-negative HCV-infected patients[20].

The authors demonstrated that long-term nonprogressors of HIV infection develop strong T-cell-mediated responses against both HIV and HCV. As ex-

Table 1. Mechanisms of persistence of HCV-related liver disease in HIV infection

- Adaptive immunity related
  - Reduced frequencies of CD8 HCV-specific responses
  - Reduced CD8 response to HCV
  - Reduced HCV-CD4 response
  - Stronger T-cell response to HIV-HCV in HIV long-term nonprogressors
- Compartmentalization on CD4 and intrahepatic immunologic alteration
  - Reduced secretion of intrahepatic IFNγ, TNFa and IL-10
  - Reduced portal CD4 cells
  - Increase of lobular apoptotic lymphocytes
  - Periportal hepatocyte proliferation correlates with degree of fibrosis

IFN: interferon; TNF: tumor necrosis factor; IL: interleukin.

pected, the Th1 cell responses observed in long-term nonprogressors are stronger than in HIV-positive progressors, but more interestingly, they are also stronger than in HIV-negative HCV-infected patients. These observations of stronger Th1 response to HCV in long-term nonprogressors even in comparison with HIV-negative patients despite lower CD4 counts suggest a better immune control of the HCV infection in those individuals.

The evidence that in long-term nonprogressors there is a positive correlation between the HCV-specific Th1 CD4 and CD8 T-cell responses, emphasizes the importance of Th1 responses in maintaining the immune control of such chronic HCV infection in this particular group of patients. Also, these findings strongly suggest a compartmentalization of the T-cells specific for HCV; they may be concentrated in the liver and circulate only poorly. To better understand the importance of compartmentalization of immune cells, many studies have focused on the breadth and characteristics of immune response in the liver.

The liver of HCV/HIV-coinfected individuals is depleted of total intrahepatic $CD4^+$ T-cells[29], correlating with the low levels of antigen-specific $CD4^+$ T-cell responsiveness within intrahepatic lymphocytes, even after long-term culture with interleukin-2 (IL-2)[21].

Because liver disease may be related to both the magnitude of $CD4^+$ responses as well as the nature of the cytokines produced by these cells, one paper examined differences in patterns of cytokine secretion, by HCV-specific intrahepatic enzyme-linked immunosorbent spot (EliSpot) assays, against multiple HCV antigens and with several cytokines to determine if HCV-specific responses are qualitatively different in individuals with HIV coinfection compared with individuals with HCV alone[21].

The CD4-enriched cells that are non-specifically expanded from liver biopsy tissue show no difference in secretion of interferon-γ (IFNγ) or tumor necrosis factor-α (TNFα) in response to HCV or recall antigens between these groups. Subjects with HCV monoinfection have significantly more IL-10 secretion by intrahepatic $CD4^+$ cells in response to HCV proteins. This response is HCV-specific because there was no difference in IL-10 secretion to either recall antigen tested. Subjects with HIV/HCV coinfection had significantly less intrahepatic $CD4^+$ T-cell HCV-specific IL-10 production.

Previous studies suggested that TNFα would play a proinflammatory role, given its known role in the pathogenesis of hepatocyte toxicity, and was associated with increased inflammation and fibrosis in both groups[30]. Instead, intrahepatic CD4-enriched T-cell secretion of TNFα in response to HCV antigens or Candida was inversely associated with grade and stage scores for the HIV/HCV group, but not the HCV-monoinfected group. This may be explained by the fact that TNFα is released by activated macrophages, not by virus-specific $CD4^+$ cells[31]. The TNFα may be a marker for other cytokines that are dysregulated in HIV and have some protective effect on liver histology, as TNFα has not been shown to control HCV replication[32-34].

The complex interplay existing between immune dysregulation and proliferation and apoptosis in patients with HIV/HCV coinfection has also been investigated.

A study by Canchis[35] phenotyped and enumerated proliferative and apoptotic intrahepatic T-cells and hepatocytes within the portal and lobular regions, areas of the liver with distinct micro-anatomic, immunologic, and functional characteristics. Portal CD4 cells were decreased in coinfected compared with monoinfected patients, while the number of lobular CD4 cells did not differ significantly. The number of apoptotic lymphocytes in the liver lobule was increased in HCV/HIV-coinfected patients compared with monoinfected patients. Moreover, the authors demonstrated an increased periportal hepatocyte proliferation in coinfected patients with detectable HIV-RNA levels, and an inverse association between periportal hepatocyte proliferation and elevated HCV-RNA levels. Hepatocyte proliferation was significantly increased in patients with HIV-RNA levels of > 400 copies/ml compared with patients with HIV-RNA levels of < 400 copies/ml. The same authors

demonstrated previously that hepatocyte proliferation increased with increasing severity of liver inflammation and fibrosis in HCV infection[36], a process that is evidently independent of the level of peripheral blood HCV-RNA. Consequently, both viruses, HIV and HCV, may contribute to periportal hepatocyte proliferation.

Analyses of peripheral blood in coinfected persons have confirmed a paucity of $CD4^+$ T-cell responses against HCV, when measuring IFNγ secretion[37].

A cross-sectional comparison among controls, patients with HCV infection, HCV/HIV-coinfected patients, coinfected patients receiving treatment for HIV, and untreated HIV-infected patients showed that the frequency of IFNγ-producing cells in response to two HCV proteins were very low in HCV-infected patients. Lymphocytes of HCV-infected patients show weak proliferative responses to HCV antigens, while responses to other antigens are preserved. Infection with HIV-1 potentiates this deficiency. Poor CD4 T-cell responses to HCV are associated with and may determine the failure to control HCV propagation[38].

Another study[39] tested the hypothesis that antigen-specific IFNγ responses are correlated with milder liver disease in subjects coinfected with HIV-1 and HCV. Cellular immune responses were studied in a cohort with HIV/HCV coinfection (n = 107) who underwent liver biopsy. Of note, there were too few subjects (11%) with severe immunosuppression, so the association of immune responses and severe fibrosis in those with CD4 cell counts < 200 x 106/l could not be evaluated[40].

The authors measured HCV-specific and recall responses in peripheral blood mononuclear cells (PBMC) using IFNγ and IL-10 EliSpot, and correlated these immune responses with liver histology. There were significant negative correlations between inflammatory scores and IFNγ production in response to the HCV protein core, NS5 and summed HCV responses. Lower fibrosis scores were also correlated with higher IFNγ production in response to NS5 and summed HCV proteins. Higher IFNγ production in response to Candida was significantly associated with lower inflammatory and fibrosis scores. In multivariate models, factors associated with severe fibrosis were lower IFNγ responses to Candida and summed HCV proteins. Factors associated with severe inflammation were detectable HIV viral load and lower HCV viral load, while predictors of mild inflammation included undetectable HIV viral load and higher IFNγ response to Candida.

Mouse models of liver injury demonstrate that excessive type 1 immune responses (including IFNγ and IL-12) are associated with inflammation but not fibrosis[41,42]. In contrast, type 2 responses (including IL-4, IL-5, and IL-13) are associated with an enhancement in hepatic fibrosis.

There were no associations between CD4 cell counts and any immune responses on univariate analysis, indicating that an ability to mount cellular immune responses is not purely a function of the degree of immunosuppression, but may be related to a qualitative defect.

Overall, higher levels of IFNγ secretion to recall and HCV proteins were associated with less severe inflammation and less fibrosis. In contrast, IL-10 showed minimal associations with severity of liver disease.

Finally, important data came from a paper which focused on coinfected patients who spontaneously controlled their HCV infection[43].

The authors show that CD4 T-cell depletion induced by HIV-1 is associated with loss of adaptive HCV-specific immune responses. Moreover, the findings of this paper indicate that the ability of HIV-infected subjects to control HCV infection depends on the maintenance of a vigorous immune response, and that additional episodes of HCV viremia occur frequently in HIV-1 subjects. Preservation of higher CD4 cell counts allows maintaining lower HCV-RNA levels after recurrence.

The HIV/HCV-coinfected individuals who demonstrated spontaneous control of HCV have CD4 lymphocytes targeting multiple proteins and specificities, as has been shown for the monoinfected population[44,45]. Maintenance of higher CD4 T-cell counts was the most important feature of these individuals. Patients with low nadir CD4 T-cell counts did not recover HCV-specific CD4 lymphocyte responses, despite significant immune reconstitution on antiretroviral therapy, suggesting that treatment of HIV infection before advanced immunosuppression may preserve memory T-cell responses against HCV[53].

In conclusion, the above-reported data suggest that maintaining or restoring immune function is the best way to slow the progression of the natural history of the liver disease. In clinical practice, this means considering an early onset of antiretroviral therapy to avoid the progression of immune-function damage, and to reduce the hepatocyte proliferation and apoptosis triggered by uncontrolled HIV-RNA replication.

Mechanisms of liver disease: alteration of the cytokine network

It is thought that the immune dysfunction is due not only to a loss of CD4 T-cells, but also to an imbalance of production of many cytokines that augment or sup-

Table 2. Mechanisms of liver damage in HIV-HCV patients

Predominant Th1 response:
– Increased levels of IFNγ and IL-10 → reduced inflammation and fibrosis.

Predominant Th2 response (CD30):
– Increase of type 2 cytokine pattern IL-4, IL-5, IL-6, IL-9, IL-13 after stimulation with HCV antigens → increase of inflammation and fibrosis.

Role of IFNγ controversial:
– Increase of intrahepatic IFNγ correlates to histopathologic grading scores.

Th: T helper cells; IFN: interferon; IL: interleukin.

press immunologic functions[46,47]. The alteration of the cytokine network has important implications, not only on the global immune regulation, but also on the immunologic alteration occurring in HIV/HCV coinfected subjects (Table 2).

The T helper cells comprise several subsets with distinct functions, which are affected differentially by HIV infection[48]. Among the cytokines, IL-12 is one of the most critical because it enhances natural killer (NK) and Th1 functions, and induces production of other cytokines, particularly IFNγ and IL-2, and the generation of cytotoxic lymphocytes[49]. It has been reported that IL-12 production is decreased in HIV-1-infected patients[50].

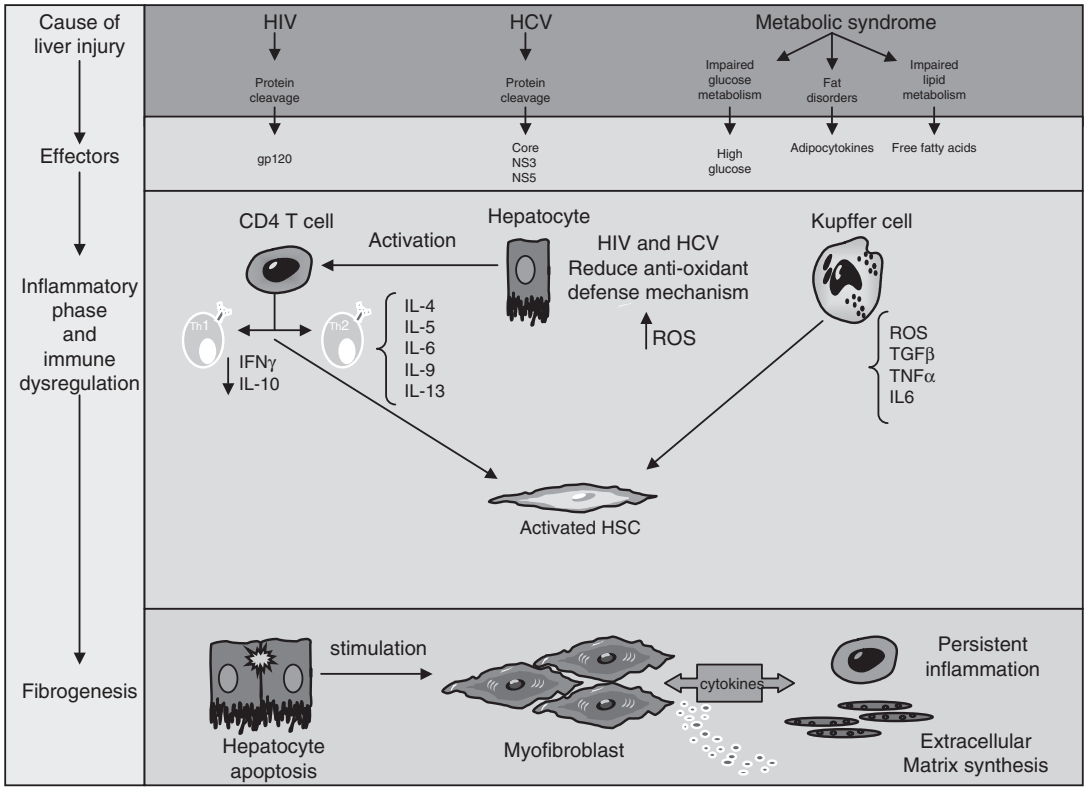
Type 1 helper cells produce IL-2, IFNγ and lymphotoxin and are important for an effective antiviral defense. Type 2 helper cells secrete IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and can act as counterparts, downregulating antiviral activity by inhibiting Th1 cytokine formation[51]. Therefore, the designation type 1 or type 2 cytokine pattern appears to be more appropriate.

In HIV infection, it has been suggested that a shift from type 1 towards type 2 cytokine production may be linked to an increased expression of CD30, a member of the TNF/nerve growth factor receptor superfamily, on T lymphocytes[52-56]. In subsequent studies on HIV infection[57-63,65,67], however, a shift in cytokine production was not reported by all groups. Moreover, CD30 T lymphocytes were not found to be associated with a strict type 2 cytokine profile in other experimental settings[64-67]. In immunocompetent patients with HCV monoinfection, antigen-specific expansion of CD30 T-cells and simultaneously a decrease in type 1 cytokine production has been noted[80].

The study of Woitas, et al.[68] showed that PBMC of HIV/HCV coinfected patients produce enhanced amounts of the proinflammatory cytokines IL-2 and IFNγ when stimulated with HCV core antigens *in vitro.* Next to quantitative changes, the authors observed an important qualitative difference in cytokine responses between HCV-monoinfected and HIV/HCV-coinfected patients. A similar degree of CD30 induction was noted on T-cells after stimulation with HCV antigens specifically in both groups of HCV-infected patients. Contrary to previous observations in HIV infection[65-67,70], HCV core antigens induced CD30 on lymphocytes, which had no distinct type 2 cytokine profiles.

In another study[69], the authors compared the expression of NKp46 (a natural killer cell marker), CD3 (a T-cell marker), IFNγ, TNFα (proinflammatory cytokines) and IL-10 (an anti-inflammatory cytokine) mRNA in the liver of naive HIV/HCV-coinfected patients, coinfected patients treated with antiretroviral therapy, and naive HCV-monoinfected patients. All three groups had comparable HCV viremia, with coinfected patients showing similar and relatively high $CD4^+$ T-cell counts and significantly different HIV viremia. Interestingly, when compared to the others, naive coinfected patients showed significantly higher intrahepatic mRNA levels for CD3, IFNγ and TNFα, whereas the expression of NKp46 and IL-10 were comparable in all three groups. Higher histopathologic grading scores within each group were independently associated with higher mRNA contents for CD3 and IFNγ and higher serum alanine aminotransferase levels at the time of liver biopsy. These results suggest that HIV infection may alter the pattern of cytokine release and exacerbate the immune-mediated inflammatory response in the liver of patients chronically infected with HCV, and antiretroviral therapy may prevent this effect[81].

The role played by HCV genotype on the cytokine network has been addressed by a study of patients with HIV/HCV coinfection and infection with HCV genotype 2 or 3 (2/3)[70]. They are compared with coinfected patients infected with genotype 1 and HCV-monoinfected patients matched for HCV genotype. The IFNγ, IL-10, IL-4 and IL-4d2 mRNA were quantified by real-time PCR in unstimulated PBMC and after *in vitro* stimulation with HCV core or nonstructural 3/4A antigen. In unstimulated PBMC, levels of IFNγ and IL-4 mRNA were lowest in HIV/HCV genotype 1 patients, intermediate in HIV/HCV genotype 2/3 patients and highest in HCV genotype 2/3 patients. Neither HCV genotype nor HIV affected levels of IL-10 mRNA in unstimulated PBMC, or IFNγ, IL-4 and IL-10 mRNA in PBMC stimulated with HCV antigens. Levels of IL-4 and IL-4d2 mRNA correlated in mitogen-stimulated PBMC from all patient groups, but both were low in HIV/HCV genotype 1 patients. Serum soluble



Th: T helper cells; IFN: interferon; IL: interleukin; ROS: reactive oxygen species;
TGF: transforming growth factor; TNF: tumor necrosis factor; HSC: hepatic stellate cell.

Figure 1. *Cellular mechanisms of liver fibrosis in HIV/HCV coinfected patients. HIV and HCV and metabolic syndrome produce mediators and impair antioxidant defense, inducing inflammatory actions in hepatic cells. A shift from Th1 to Th2 and CD4 depletion lead to a release of inflammatory cytokines that activate Kupffer cells. This inflammatory state stimulates the activation of resident HSC into fibrogenic myofibroblasts. Activated HSC also secrete cytokines that perpetuate their activated state. If the liver injury persists, accumulation of activated HSC and portal myofibroblasts occurs, synthesizing large amounts of extracellular matrix proteins and leading to tissue fibrosis.*

CD30 levels (a putative marker of a T2 cytokine environment) did not differ between patient groups. The data do not suggest a shift in the T1/T2 balance driven by HIV coinfection or HCV genotype, but either may affect IL-4 bioavailability.

The shift from T1 to T2 cytokine pattern means the "kick-off" of profibrotic state by an exaggerated immune-mediated inflammatory response in the liver. Also in this case, antiretroviral therapy may be useful in preventing this effect.

HIV/HCV coinfection: implications on liver fibrogenesis

Hepatic fibrosis is the result of the wound-healing response of the liver to repeated injury[71]. The cells mainly involved in this process are hepatic stellate cells (HSC) (Fig. 1)[72]. After an acute liver injury (e.g. viral hepatitis), parenchymal cells regenerate and replace the necrotic or apoptotic cells. This process is associated with an inflammatory response and a limited deposition of extracellular matrix (ECM). If the hepatic injury persists, then eventually the liver regeneration fails, and hepatocytes are substituted with abundant ECM, including fibrillar collagen. The distribution of this fibrous material depends on the origin of the liver injury. In chronic viral hepatitis and chronic cholestatic disorders, the fibrotic tissue is initially located around portal tracts, while in alcohol-induced liver disease, it locates in pericentral and perisinusoidal areas[73]. As fibrotic liver diseases advance, disease progression from collagen bands to bridging fibrosis to frank cirrhosis occurs.

Liver fibrosis is associated with major alterations in both the quantity and composition of ECM[74]. In advanced stages, the liver contains approximately six-times more ECM than normal, including collagens (I, III, and IV), fibronectin, undulin, elastin, laminin, hyaluronan, and proteoglycans. Accumulation of ECM results from both increased synthesis and decreased degradation. Interestingly, HSC express a number of neuroendocrine markers (e.g. reelin, nestin, neurotrophin, synaptophysin, and glial-fibrillary acidic protein) and bear receptors for neurotransmitters[75-77].

Quiescent HSC express markers that are characteristic of adipocytes (peroxisome proliferator-activated receptor, sterol regulatory element-binding protein-1c, and leptin), while activated HSC express myogenic markers (smooth muscle actin, c-myb, and myocyte enhancer factor-2).

Hepatic cell types other than HSC may also have fibrogenic potential. Myofibroblasts derived from small portal vessels proliferate around biliary tracts in cholestasis-induced liver fibrosis to initiate collagen deposition[78,79]. Hepatic stellate cells and portal myofibroblasts differ in specific cell markers and response to apoptotic stimuli[80]. Culture of $CD34^+CD38^+$ hematopoietic stem cells with various growth factors has been shown to generate HSC and myofibroblasts of bone marrow origin that infiltrate human livers undergoing tissue remodeling[81,82]. These data suggest that cells originating in bone marrow can be a source of fibrogenic cells in the injured liver.

The relative importance of each cell type in liver fibrogenesis may depend on the origin of the liver injury. While HSC are the main fibrogenic cell type in pericentral areas, portal myofibroblasts may predominate when liver injury occurs around portal tracts.

Both HIV[83] and HCV[84] may have a significant role by themselves in causing cellular damage by reducing antioxidant protective factors and triggering apoptosis. Redox mechanisms play important roles in cellular susceptibility to apoptosis signals. Pathologic states are preceded by: (i) depletion of intracellular antioxidants, glutathione and thioredoxin; (ii) increased reactive oxygen species production; and (iii) changes in mitochondrial transmembrane potential (delta psi m). Disruption of delta psi(m) appears to be the point of no return in the effector phase of apoptosis. Viral proteins Tat, Nef, Vpr, protease, and gp120 have been implicated in initiation and/or intensification of oxidative stress and disruption of delta psi(m). Redox-sensitive transcription factors, nuclear factor kappa B (NFκB), AP-1, and p53, support expression of viral genes and proinflammatory lymphokines. Reactive oxygen species regulate apoptosis signaling through Fas, TNF, and related cell death receptors, as well as the T-cell receptor. Oxidative stress in HIV-infected donors is accompanied by increased glucose utilization both on the cellular and organism levels. Generation of glutathione and thioredoxin from their corresponding oxidized forms is dependent on nicotinamide adenine dinucleotide phosphate provided through the pentose phosphate pathway of glucose metabolism.

A complex interplay among different hepatic cell types takes place during hepatic fibrogenesis (Fig. 1)[85]. Hepatocytes are targets for most hepatotoxic agents, including hepatitis viruses, alcohol metabolites, and bile acids[86]. Damaged hepatocytes release reactive oxygen species and fibrogenic mediators and induce the recruitment of white blood cells by inflammatory cells. Apoptosis of damaged hepatocytes stimulates the fibrogenic actions of liver myofibroblasts[87]. Inflammatory cells, either lymphocytes or polymorphonuclear cells, activate HSC to secrete collagen[88]. Activated HSC secrete inflammatory chemokines, express cell adhesion molecules, and modulate the activation of lymphocytes[89]. Therefore, a vicious circle in which inflammatory and fibrogenic cells stimulate each other is likely to occur[90]. Fibrosis is influenced by different T helper subsets, the Th2 response being associated with more active fibrogenesis[91]. Kupffer cells are resident macrophages that play a major role in liver inflammation by releasing reactive oxygen species and cytokines[92,93].

Nonalcoholic steatohepatitis (NASH) is another condition which can cause a fibrotic state. It is associated to other metabolic disturbances such as obesity, type 2 diabetes mellitus and dyslipidemia, which are also considered as comorbidities in HIV patients[94]. A two-hit model has been proposed for explaining the pathogenesis of NASH-associated liver fibrosis. Hyperglycemia and insulin resistance lead to elevated serum levels of free fatty acids, resulting in hepatic steatosis. In the second hit, oxidative stress and proinflammatory cytokines promote hepatocyte apoptosis and the recruitment of inflammatory cells, leading to progressive fibrosis.

The pathogenesis of HCV-induced liver fibrosis is poorly understood due to the lack of a rodent model of persistent HCV infection[95]. The HCV escapes surveillance of the human leukocyte antigen II (HLA-II)-directed immune response and infects hepatocytes, causing oxidative stress and inducing the recruitment of inflammatory cells.

The T-helper 2 response (secretion of IL-4, IL-5, IL-13) by CD4 T-cells, in conjunction with secretion of transforming growth factor (TGF)-3 may promote collagen deposition leading to fibrosis, whereas other inflammatory cytokines such as IFNγ and IL-10 attenuate fibrogenesis[96]. Also, the levels of plasma TGFβ/3, another profibrotic cytokine, are increased in HIV-1-seropositive hemophiliacs coinfected with HCV[97]. As discussed previously, HIV is associated with the dysregulation of various cytokines and chemokines, and changes in their relative balance within the liver may address towards a profibrotic state. The HIV may induce a loss of intrahepatic lymphocytes capable of secreting antifibrotic cytokines such as IL-10[98]. Probably, the shift from Th1 to Th2 cytokine network may account for increased fibrogenesis, also, if it is not a rule.

The observation that the lack of IFNγ secreting T lymphocytes is associated with accelerated fibrosis suggests that these cells may have a protective role against the fibrotic process. These cells, detectable by the circulation of lobular apoptotic lymphocytes and by increased levels of IFNγ, could possibly attenuate fibrosis in the liver. The IFNγ is also a proinflammatory molecule, which, although beneficial for its antiviral properties, may also trigger a damage to hepatocytes[99,100]. The balance of HCV-specific T-cells that secrete IFNγ, TNF-chemokines, and IL-10 may account for the faster rate of fibrogenesis observed in these subjects.

Finally, recent preliminary data shows that exposure to the gp120 envelope protein from CCR5-tropic HIV led to HSC activation and increased production of collagen and proinflammatory cytokine[101]. This intriguing mechanism suggests a direct role of HIV for inducing the fibrogenesis and may open an interesting option to stop this process by using chemokine receptor antagonists.

Fibrogenesis in HIV/HCV patients is a process probably more complex than in monoinfected patients because it depends upon an interplay of immunologic, viral and exogenous factors, many of them being difficult to control. Treating both infections and also managing oxidative stress are probably the best way to achieve the control of the diseases.

Conclusion

The coinfection of HIV and HCV has become a pathology with several distinctive characteristics. Pathogenesis of liver damage in patients with HIV and HCV coinfection is complex and multifactorial. It derives from a balance of factors which interact among themselves in a dynamic way. A better knowledge of the adaptive immune mechanism, cytokine alteration, interference with host defense mechanisms, and the "cross-talk" among the viruses will improve the understanding of the pathogenetic mechanism and provide the opportunity to cure this disease.

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