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**gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis**

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**ABSTRACT**

**Objective** In patients with hepatitis C virus (HCV)/HIV co-infection, a faster progression of liver fibrosis to cirrhosis has been reported. In this study, an investigation was carried out to determine whether gp120, an HIV envelope protein, modulates the biology of human hepatic stellate cells (HSCs), a key cell type in the pathogenesis of fibrosis.

**Methods** Myofibroblastic HSCs were isolated from normal human liver tissue. Gene expression was measured by real-time PCR. Cell migration was assessed in Boyden chambers. Intracellular signalling pathways were evaluated using phosphorylation-specific antibodies or by transfection of a reporter plasmid.

**Results** Transcripts for the chemokine receptors CCR5 and CXCR4, which bind gp120, were detectable in human HSCs. Upon exposure to M-tropic recombinant gp120, which binds CCR5, a significant increase in HSC chemotaxis was observed (1.6±0.3-fold, p<0.03). The effects of gp120 were prevented by protein inactivation. gp120 also resulted in a significant increase in secretion (1.5±0.3-fold, p=0.03) and gene expression (1.47±0.13-fold, p=0.02) of the proinflammatory chemokine monocyte chemoattractant protein-1, and in increased gene expression of tissue inhibitor of metalloprotease-1 and interleukin-6 (2.03±0.57-fold, p=0.02). gp120-induced migration required Akt activation. gp120 also induced activation of nuclear factor-κB (NF-κB) and p38MAPK. Preincubation of HSCs with TAK779, a CCR5 receptor antagonist, prevented gp120-mediated chemotaxis and monocyte chemoattractant protein-1 secretion. Expression of CCR5 was detectable in areas of inflammation and fibrogenesis in liver biopsies of patients with HCV/HIV co-infection.

**Conclusions** This study shows that HIV gp120 modulates different aspects of HSC biology, including directional cell movement and expression of proinflammatory cytokines. These results identify a direct pathway possibly linking HIV infection with liver fibrogenesis via envelope proteins.

Hepatitis C virus (HCV) and/or hepatitis B virus (HBV) co-infection is a common finding in HIV-infected individuals.¹ In recent years, a better management of HIV infection with the use of highly active antiretroviral therapy (HAART) has led to a much longer survival of these patients, and to the emergence of different causes of death, including end-stage liver disease.² Evolution of chronic hepatitis to cirrhosis and its complications is dependent on progression of liver fibrosis, which leads to tissue scarring and contributes to hepatocellular dysfunction and appearance of portal hypertension.³ Accumulating evidence indicates that patients with HIV co-infected with hepatotropic viruses, and particularly HCV, have a much faster progression of hepatic fibrosis, leading to the earlier appearance of liver-related complications.¹ Thus, defining the mechanisms responsible for accelerated fibrogenesis is of clear relevance for a better management of this group of patients.

Recently, the molecular and cellular mechanisms underlying the development of liver fibrosis have been elucidated. A pivotal step in the understanding of the fibrogenic process has been the identification of the role of hepatic stellate cells (HSCs), non-parenchymal cells that in conditions of hepatic injury undergo “activation”; that is, phenotypic transition to myofibroblast-like cells.⁴ Upon activation, HSCs proliferate and migrate to areas of tissue remodelling, such as the portal–lobule interface in patients with viral hepatitis, and actively produce extracellular matrix. In addition, HSCs secrete a large number of cytokines and chemokines that amplify and maintain the inflammatory response.⁵ Isolation and culture of HSCs represents a well-established model system for the investigation of the basic mechanisms of liver fibrogenesis in different conditions, including viral hepatitis.⁶,⁷ We and others have recently found that the biology of activated HSCs is modulated by HCV-derived proteins in a profibrogenic fashion.⁸-⁹ During HIV infection, target cells are exposed to viral gene products expressed at the surface of infected cells, or released in the microenvironment. In particular, the HIV-1 envelope protein gp120 is present in tissues and circulates in the blood on the surface of virions or as a free protein.⁹ Although the accelerated course of fibrosis in HIV-co-infected individuals, in the present study we investigated whether gp120 could modulate the phenotype of cultured human HSCs.

**MATERIALS AND METHODS**

**Reagents**

Recombinant gp120 from different HIV strains (CN54, SF162 and IIIB) and the CCR5 receptor antagonist, TAK779, were obtained from www.aidsreagent.org. Phosphorylation-specific, polyclonal
antibodies against extracellular signal-regulated kinase (ERK), Akt, p38MAPK and p65NF-kB were from Cell Signalling Technology (Beverly, Massachusetts, USA). Monoclonal antibodies against β-actin and the nuclear factor-kB (NF-kB) inhibitor, N-p-tosyl-l-phenylalanine chloromethyl ketone (TPCK), were from Sigma (St Louis, Missouri, USA). The phosphatidylinositol 3-kinase (PI3K)/Akt inhibitor,LY294002, and the p38MAPK inhibitor,SB203580, were from Merck Chemicals (Nottingham, UK). Human recombinant platelet-derived growth factor (PDGF)-BB and recombinant human Rantes (regulated on activation normal T cell expressed and secreted; CCL5) were from Peprotech (Rock Hill, New Jersey, USA). Unless otherwise indicated, all other agents were of analytical grade and were purchased from Sigma. The luciferase reporter plasmid under the control of NF-kB (NF-kB-luc) was kindly provided by Dr Gianluca Tell (University of Udine, Italy).

Isolation and culture of human HSCs

Procedures for cell isolation and characterisation have been extensively described elsewhere. Cells were cultured on uncoated plastic dishes and used after complete transition towards a myofibroblast-like phenotype.12

RNA isolation and quantitative real-time PCR

Isolation of total RNA from cultured HSCs, and procedures used for real-time PCR were described in detail elsewhere. All probes were purchased as “erase activity (relative light units) was normalised by the protein

Chemotactic assay

Cell migration was measured in modified Boyden chambers equipped with 8 μm porosity polyvinylpyrrolidone-free polycarbonate filters, precoated with collagen (20 μg/ml of human type I collagen for 50 min at 37°C), as previously described.14

Measurement of monocyte chemoattractant protein-1 (MCP-1 or CCL2) and procollagen type I secretion

Confluent HSCs in 24-well plates were deprived of serum for 24 h. After replacement with 500 μl of fresh serum-free medium, cells were treated with recombinant gp120 at the indicated concentrations and time points. ELISAs were carried out as described elsewhere.15

NF-kB reporter assay

HSCs in complete medium were transfected with 7 μg of the luciferase reporter plasmid using nucleofection technology (Amaxa, Koln, Germany) as previously described. After 24 h, the cells were serum starved and the culture was continued for an additional 24 h before stimulation with recombinant gp120. After a 24 h incubation, the cells were lysed using 1× reporter lysis buffer (Promega, Milan, Italy) and luciferase activity was assayed using a commercial assay (Promega) according to the manufacturer’s protocol, and as previously described. Luciferase activity (relative light units) was normalised by the protein concentration in each sample.

Western blot analysis

Procedures for preparation of cell lysates, and subsequent analysis have been extensively described elsewhere.13

Flow cytometry

Subconfluent HSCs grown in complete medium were washed in Ca2+- and Mg2+-free phosphate-buffered saline (PBS), and then detached from the dish by incubation with 20 mM EDTA. Flow cytometry was performed using a monoclonal antibody against CCR5 (clone 45531, R&D Systems, Minneapolis, Minnesota, USA) or an isotype-specific control, as previously described. In selected experiments, the highly sensitive technique of fluorescence amplification by sequential employment of reagents (FASER) was utilised.16

Liver biopsies

Fragments of percutaneous liver biopsies carried out for diagnostic purposes were snap-frozen in liquid nitrogen and stored at −80°C or less until used. Three patients chronically infected with HCV and four patients with HCV/HIV co-infection were analysed. All patients had not previously received antiviral treatment against HCV, while all co-infected patients were receiving HAART.

Immunohistochemistry

These experiments were performed on frozen sections (6 μm thickness), as previously described in detail. Monoclonal anti-CCR5 antibodies (clone 45549, R&D Systems) were used as primary antibodies at a concentration of 5–10 μg/ml.

Ethical considerations

Any necessary ethics committee approval and/or informed consent were secured for patient material used in the present study.

Data analysis

Data presented as bar graphs are the mean of at least three independent experiments. Autoluminograms are representative of replicate experiments with similar results. Statistical analysis was performed by Student t test. p values ≤0.05 were considered significant.

RESULTS

Expression of the chemokine receptors CCR5 and CXCR4, which function as gp120-binding HIV co-receptors, has been previously reported in human activated HSCs. Thus, we first evaluated whether transcripts for these receptors were expressed in the culture conditions used in our studies. In two independent HSC lines, mRNA for CXCR4 and CCR5 was detectable by real-time PCR (figure 1A,B), although their expression levels were several fold lower than in RNA isolated from the bone marrow, used as a positive control. To support these observations further, we analysed the human immortalised HSC line, LX-2, which was also found to express both chemokine receptors (figure 1). To establish whether gp120 exerts some of the biological actions mediated by chemokine receptors, serum-deprived HSCs were exposed to different concentrations of recombinant gp120, and directional movement was measured in a chemotactic assay (figure 2). PDGF, used as a positive control, resulted in a significant, twofold induction of HSC migration, as previously reported by our group and by others. Exposure of HSCs to increasing concentrations of an M-tropic gp120 (CN54) increased cell migration, in a dose-dependent fashion (figure 2A). The effects were significant at all concentrations tested, although a peak increase in chemotaxis was observed at 500 ng/ml, with a 1.5-fold induction. When SF162, a gp120 derived from a different M-tropic HIV strain, was used (figure 2B), a significant induction of cell migration was also observed, with a peak at 500 ng/ml of similar magnitude to the one observed with CN54. In contrast, IIB gp120, a protein derived from a T-tropic HIV strain, induced HSC migration less effectively than the M-tropic gp120 proteins,
predominantly at concentrations $\geq 1000$ ng/ml (figure 2C). In order to exclude that the effects of gp120 on cell migration were non-specifically dependent on exposure of HSCs to high protein concentrations, or that they were related to the presence of endotoxin, we inactivated gp120 by boiling the protein for 30 min. This procedure is known to abolish gp120-induced biological effects without affecting lipopolysaccharide (LPS) activity. Protein inactivation abolished the chemotactic effects of gp120 (figure 2D). gp120, at concentrations as high as 1 mg/ml, did not induce any changes in HSC proliferation, as assessed by thymidine incorporation (data not shown).

We next evaluated the possible modulatory effects of gp120 on other characteristics of the activated phenotype of HSCs. Expression of proinflammatory chemokines contributes to the recruitment of leukocytes in several liver diseases, and is a feature of the activated HSC phenotype. In particular, MCP-1 is the major chemoattractant for mononuclear cells expressed by activated HSCs, and its expression is induced by numerous soluble mediators. Upon incubation with 500 ng/ml gp120 (CN54), secretion of MCP-1 in HSC-conditioned medium was significantly higher, with a >50% increase over basal levels (figure 3A). To provide further evidence for this action, and to explore the mechanisms of MCP-1 induction, we tested whether increased secretion of this chemokine was accompanied by upregulated gene expression. Indeed, incubation with HIV gp120 was found to increase MCP-1 mRNA levels significantly, as assessed by real-time PCR (figure 3B), confirming that gp120 elicits proinflammatory actions in HSCs. We also assessed the effects of gp120 on collagen secretion in the conditioned medium (figure 3C). We observed a statistically significant increase in collagen secretion in HSCs exposed to gp120, although the overall effect was very modest, leading to an induction of ~10% over basal levels.

To characterise further the modulation of the HSC phenotype by gp120, we analysed possible changes in the expression of $\alpha$-smooth muscle actin, a well-established marker of activation. Exposure to gp120 for prolonged periods of time did not result in any changes in $\alpha$-smooth muscle actin expression, at the level of both protein (figure 3D) and gene expression (data not shown). In contrast, gp120 significantly increased gene expression of tissue inhibitor of metalloprotease-1 (TIMP-1; figure 4A), which limits matrix degradation, and of interleukin-6 (IL-6), which contributes to generate proinflammatory signals (figure 4B). Taken together, these data indicate that gp120 induces proinflammatory cytokines and, to a lesser extent, direct profibrogenic effects in HSCs. In contrast, no significant effects of gp120 were
found on expression of IL-1 or transforming growth factor β (data not shown).

We next explored the molecular mechanisms responsible for the biological effects of gp120 in human HSCs, focusing on cell migration and MCP-1 secretion. Activation of PI3K and of its downstream effector, Akt, is required for cell migration induced by different agonists, including cytokines and chemokines.14-20 We analysed the ability of gp120 to activate Akt, measuring protein phosphorylation on activation-specific Ser473 residues (figure 5A). Exposure to 500 ng/ml gp120 (CN54) resulted in a rapid and marked increase in Akt activation, indicating that this HIV envelope protein efficiently activates motogenic pathways in HSCs. To confirm the functional relevance of Akt, we measured gp120-induced migration before and after preincubation of HSCs with LY294002, a specific inhibitor of the PI3K/Akt pathway (figure 5B). Inhibition of Akt activation markedly and significantly blocked gp120-induced migration, indicating that this pathway is required to generate chemotactic signals.

We next examined the possible mechanisms underlying the proinflammatory action of gp120, resulting in increased expression of MCP-1 and IL-6. In HSCs, expression of these cytokines is regulated by several pathways, including activation of NF-κB and p38MAPK.15-26 Activation of NF-κB is associated with phosphorylation of the p65 subunit on activation-specific residues (Ser536). gp120, at concentrations similar to those that induce MCP-1 expression, markedly upregulated p65NF-κB phosphorylation (figure 6A). To confirm the activation of NF-κB in response to gp120, HSCs were transfected with a luciferase reporter plasmid controlled by NF-κB. Exposure to gp120 resulted in a significant increase in NF-κB-dependent transcription, confirming that this pathway is activated following interaction of the HIV envelope protein with HSCs (figure 6B). In

![Figure 3](image1.jpg)  
**Figure 3** Upregulation of monocyte chemoattractant protein-1 (MCP-1) and collagen secretion by gp120. (A, C) Serum-starved primary hepatic stellate cells (HSCs) were incubated with 500 ng/ml gp120 (CN54) for 48 h. At the end of the incubation, conditioned medium was assayed for MCP-1 (A) or type I procollagen (C). (B) Primary HSCs were incubated with 500 ng/ml gp120 (CN54) for 8 h. Total RNA was isolated and analysed for MCP-1 expression by real-time PCR as described in the Materials and methods section. *p<0.05 vs gp120. (D) Primary HSCs were incubated with 500 ng/ml gp120 (CN54) for the indicated times. Total protein lysates were sequentially analysed for α-smooth muscle actin (α-SMA) expression and for extracellular signal-regulated kinase (ERK) (loading control) by western blot, as described in the Materials and methods section.

![Figure 4](image2.jpg)  
**Figure 4** gp120 upregulates expression of tissue inhibitor of metalloprotease-1 (TIMP-1) and interleukin-6 (IL-6). Primary hepatic stellate cells (HSCs) were incubated with 500 ng/ml gp120 (CN54) for 24 h. Total RNA was isolated and analysed for expression of (A) TIMP-1 or (B) IL-6 by real-time PCR as described in the Materials and methods section. *p<0.05 vs control.
To recruit TAK779, a specific receptor antagonist of CCR5, also induced cell migration, and its effects were reverted by the receptor antagonist, further confirming the expression of functional CCR5 by HSCs (figure 7E). Furthermore, TAK779 blocked the stimulatory effects of gp120 on MCP-1 secretion, indicating that CCR5 is also implicated in the proinflammatory effects of gp120 in HSCs (figure 7F). We next set out to provide an in vivo counterpart of the data obtained in the present study, analysing the expression of CCR5 in liver tissue of patients with HCV/HIV co-infection (figure 8). In both the presence and absence of HIV co-infection, a specific signal for CCR5 was detectable at the sinusoidal level, throughout the lobule. In addition, CCR5 was expressed by clusters of inflammatory cells in enlarged portal tracts, and by spindle-shaped cells localised in the context of the active fibrous septa, possibly representing activated HSCs or other fibrogenic cells (figure 8B,D). In negative controls, only a slight non-specific background was present, corresponding to lipofuscin accumulation in hepatocytes (figure 8A,C). Taken together, these data indicate that CCR5 is expressed in the liver during HCV/HIV co-infection.

**DISCUSSION**

This is the first demonstration that an envelope protein of HIV is capable of modulating the phenotype of HSCs in a profibrogenic fashion. Recombinant gp120 effectively induced a significant increase in HSC migration, and augmented secretion of MCP-1, a proinflammatory chemokine, and expression of IL-6. Secretion of type I procollagen and gene expression of TIMP-1 were also increased, although the effects on these latter factors were more modest. All these biological actions have a clear relevance for the fibrogenic process. During the progression of chronic viral hepatitis, fibrogenic cells, such as activated HSCs, accumulate at the interface with the expanded portal tract, where infiltration of inflammatory cells is maximal. Recruitment of activated HSCs via chemotaxis leads to accumulation of myofibroblasts in the areas of active tissue remodelling. Because an increased necroinflammatory activity is a characteristic of HCV/HIV co-infection, it may be speculated that gp120 exposed by infected mononuclear cells leads to active recruitment of HSCs, thus accelerating fibrogenesis. Further support for this scenario is provided by the observation, obtained in the present study, that gp120 induces MCP-1 secretion by HSCs. In the inflamed liver, HSCs are major contributors to the expression of MCP-1, leading to local amplification and maintenance of chronic inflammation. Furthermore, chemokines, including MCP-1, are chemoattractants for HSCs, and we have previously demonstrated that gp120 also induces MCP-1 secretion by human macrophages. Thus, gp120 may induce HSC accumulation both via direct chemotaxis and via secretion of MCP-1 by HSCs themselves and by activated macrophages, finally resulting in increased inflammation and fibrogenesis.

The actions of gp120 on target cells are mediated by interaction with at least two chemokine receptors, CCR5 and CXCR4, that transduce intracellular signals independently of CD4 engagement. Both of these receptors are expressed by human HSCs, as shown in this study and in those from other groups. gp120 from both M-tropic and T-tropic strains were found to be biologically active on human HSCs, although M-tropic proteins, acting on CCR5, exerted their biological actions at lower concentrations. Therefore, we focused on the possible role of CCR5, also based on previous observations that this receptor mediates profibrogenic actions in HSCs. Using TAK779, a specific CCR5 receptor antagonist, we show that the effects of gp120 on HSC migration and chemokine secretion were abolished. In addition, the ability of Rantes to induce HSC proliferation. These data demonstrate that gp120 effectively activates proinflammatory signalling pathways in human HSCs.

We next evaluated in further detail the role of the chemokine receptor CCR5 in mediating the actions of gp120 on HSCs. We focused on this receptor in the light of the effects of CN54, derived from an M-tropic strain, and because previous data have indicated a clear role for CCR5 in the biology of HSCs. To demonstrate that the CCR5 protein is expressed at the surface of HSCs, derived from an M-tropic strain, and because previous data have indicated a clear role for CCR5 in mediating the actions of gp120 on HSCs. We next evaluated in further detail the role of the chemokine receptor CCR5 in mediating the actions of gp120 on HSCs. We focused on this receptor in the light of the effects of CN54, derived from an M-tropic strain, and because previous data have indicated a clear role for CCR5 in the biology of HSCs. To demonstrate that the CCR5 protein is expressed at the surface of HSCs, derived from an M-tropic strain, and because previous data have indicated a clear role for CCR5 in mediating the actions of gp120 on HSCs. We next evaluated in further detail the role of the chemokine receptor CCR5 in mediating the actions of gp120 on HSCs. We focused on this receptor in the light of the effects of CN54, derived from an M-tropic strain, and because previous data have indicated a clear role for CCR5 in mediating the actions of gp120 on HSCs. We next evaluated in further detail the role of the chemokine receptor CCR5 in mediating the actions of gp120 on HSCs. We focused on this receptor in the light of the effects of CN54, derived from an M-tropic strain, and because previous data have indicated a clear role for CCR5 in mediating the actions of gp120 on HSCs.
chemotaxis was prevented by TAK779, providing further evidence for the expression of functional CCR5 by HSCs. In contrast, we were able to detect membrane expression of CCR5 only using a highly sensitive flow cytometry technique and in a small proportion of cells. Several hypotheses may be proposed to explain this finding. It is possible that culture of HSCs in the presence of serum alters the expression of CCR5, as has been shown for other chemokine receptors that are expressed in a cell cycle-dependent fashion. An alternative, and not mutually exclusive, hypothesis is that detachment of cells with EDTA, a procedure that requires considerable time and results in cell damage, alters the expression dynamics of CCR5. Therefore, to provide additional support for the possible role of CCR5 in this context and to translate these data partially to the clinical setting, we analysed CCR5 expression in liver tissue from patients with HCV/HIV co-infection. CCR5 was clearly expressed at the sinusoidal level, by inflammatory cells, and in cells of the fibrotic septum, demonstrating that a target of gp120 is indeed present in this context in vivo. Further studies are needed to establish better the contribution of CXCR4 and to identify definitely the receptor predominantly mediating the effects of gp120 on HSCs.

The experiments reported herein also demonstrate that the downstream signalling pathways activated upon exposure to gp120 are in line with the observed biological effects. In particular, activation of p38MAPK or NF-κB in HSCs has been previously shown to be necessary for agonist-induced chemokine secretion. Similarly, activation of the PI3K/Akt pathway regulates cell motility in response to a wide range of factors, and is required for HSC chemotaxis.

In the past 15 years, a large number of soluble factors, including cytokines, have been found to mediate fibrogenesis by acting on HSCs. In this study, we used the gp120 HIV envelope protein at concentrations similar to those used for studies in other cell types, such as mononuclear cells or hepatocytes. Not surprisingly, the concentrations required to achieve biological effects using recombinant viral proteins are higher than those used when working with cytokines. While cytokines interact with their receptors in a soluble form, envelope proteins are embedded in the cellular lipid monolayer, with a three-dimensional structure that may not be perfectly reproduced by a soluble recombinant protein. In addition, the local concentrations of gp120 may be even higher than those used in vitro, due to the hepatic accumulation of infected inflammatory cells expressing gp120 on their surface, although co-infected patients have lower CD4 mRNA levels than HCV-monoinfected patients.

Recently, the different constituents of HCV, including envelope, core and non-structural proteins, have been shown to be active as profibrogenic factors. Although interesting from a pathophysiological standpoint, it should be considered that, so far, no studies have convincingly demonstrated a correlation

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**Figure 6** gp120 activates nuclear factor-κB (NF-κB) and p38MAPK. (A) The experiment was conducted as described in figure 5A, analysing phosphorylation of p65NF-κB. (B) Hepatic stellate cells (HSCs) were transfected by nucleofection with a reporter plasmid under the control of the NF-κB promoter, as described. Then, serum-starved primary HSCs were incubated with 500 ng/ml gp120 CN54 for 24 h. Luciferase activity was measured as described in the Materials and methods section. *p<0.05 vs gp120. (C) The experiment was conducted as described for A, analysing phosphorylation of p38MAPK. (D) Primary HSCs were incubated in the presence or absence of the NF-κB inhibitor TPCK (10 μM) or with the p38MAPK inhibitor SB203580 (25 μM), and then incubated with gp120 CN54 (500 ng/ml) for 24 h, as indicated. At the end of the incubation, conditioned medium was assayed for monocyte chemoattractant protein-1 (MCP-1). **p=0.07 vs control; *p<0.05 vs gp120. ERK, extracellular signal-regulated kinase.
between HCV viral load and the severity of progression during chronic hepatitis. In contrast, in HCV/HIV-co-infected individuals, HIV RNA levels predict the fibrogenic progression of chronic hepatitis, and, in some series, reducing the HIV burden has been found to ameliorate the outcome of hepatitis. HIV infection may also alter the cytokine pattern and exacerbate the inflammatory response in the liver of patients chronically infected with HCV, as demonstrated by the observation that intrahepatic levels of proinflammatory cytokines were lower in patients treated with antiretroviral therapy.

On the other hand, patients monoinfected with HIV do not show significant liver fibrosis, indicating that HIV infection is not profibrogenic per se, but rather accelerates the fibrogenic process in the presence of hepatic damage such as that induced by hepatotropic viruses. The observation of a possible direct fibrogenic action of an HIV envelope protein reported herein indicates an additional mechanism providing a novel molecular basis for the strong clinical evidence linking HIV/HCV co-infection with accelerated fibrogenesis. Nonetheless, the relative weight of these actions in the overall fibrogenic process will require further evaluation. Along these lines, drugs that interfere with the binding of HIV with its chemokine co-receptors, which recently became available in clinical practice, should be tested for their possible action in the context of a HCV/HIV co-infection.

In conclusion, we have demonstrated that gp120 exerts profibrogenic action on human HSCs in culture, identifying a direct pathway possibly linking HIV infection with liver fibrogenesis via envelope proteins. These data open up new perspectives for the management of liver diseases in HCV/HIV-co-infected patients.

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