HIV hepatotropism and pathogenesis: new challenges

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“...the mechanisms of HIV-associated liver pathology remains inconclusive.”

Ample recent evidence shows that HIV can productively and persistently infect liver in a CD4-independent manner, and modulate liver biology.

“In HIV-infected patients, CD4-independent nonlymphoid tissue tropism, including liver infection and its impact on liver pathobiology, is well known today.”

HIV-1 is inherently nonhepatotropic, but in some cases can establish cytopathic liver infections. HIV is a retrovirus, having a dimeric, single-stranded, sense RNA genome that consists of nine genes (*gag*, *pol*, *env*, *tat*, *rev*, *nef*, *vif*, *vpr* and *vpu*) [1]. The *env* gene codes for the viral envelope protein gp160, which is further cleaved by the viral protease to produce gp120 and gp41. HIV enters the lymphoid cells through ligating gp120 to cell surface receptor CD4 and a chemokine coreceptor [2]. In HIV-infected patients, CD4-independent nonlymphoid tissue tropism, including liver infection and its impact on liver pathobiology, is well known today. The spectrum of HIV-induced liver diseases includes hepatitis, alcohol-associated steatohepatitis, nonalcoholic steatohepatitis, endothelialitis, necrosis and granulomatosis [3,4]. Though liver fibrogenesis and hepatotoxicity are associated with continued antiretroviral drug administration, these continue to be prescribed owing to the necessity of balancing potential toxic effects with the need to increase patient CD4⁺ T-lymphocyte count and control retroviral replication [5]. Despite the availability of extensive clinical data on the subject, the mechanisms of HIV-associated liver pathology remains inconclusive. The viral hepatotropism and the complexity of clinical manifestations,

therefore, offer challenging opportunities to study the underlying molecular mechanisms and to formulate effective therapeutic strategies.

Tissue tropism of HIV

Entry of HIV into target cells requires interaction of the viral gp120 with the cell surface receptor CD4, aided by chemokine coreceptors [2,5]. Macrophage-tropic HIV primarily uses the chemokine (C-C motif) coreceptor CCR5 (R5-tropism), whereas T lymphocyte-tropic HIV utilizes the chemokine (C-X-C motif) coreceptor, CXCR4 (X4-tropism). Dual-tropic HIV strains (R5-X4-tropism) also exist that require both of the coreceptors. Also, a few rare HIV isolates have been demonstrated to use alternative chemokine coreceptors, such as CCR1, CCR2b, CCR8, CXCR6 and G protein-coupled receptors (GPR1 or GPR15/Bob) in cultured CD4⁺ cell lines [6]. Several reports have also shown that HIV is capable of cross-tissue tropism by infecting certain nonlymphoid tissues, including colon, rectum, duodenum, cervix, retina and the brain, as well as megakaryocytes *in vivo* [7]. Moreover, HIV RNA, proviral DNA and capsid antigen (p24) have been detected in liver sinusoidal endothelial cells (LSECs), Kupffer cells, portal mononuclear inflammatory cells, and hepatocytes in clinical subjects [8].

Permissiveness of CD4⁺ cells to HIV infection

Although, many human HIV-2 and nonhuman SIV isolates can infect cells without the need for a CD4 receptor [9], CD4-independent HIV has only rarely been isolated. A variety of human cell lines (e.g., colorectal carcinoma, rhabdomyosarcoma, bone marrow CD34⁺ precursor, glioma and neuroblastoma) known for not expressing CD4, have been found susceptible to

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HIV infection *in vitro* [7]. In a recent study, a quasispecies of a CD4-independent HIV isolate (SDA-1) has been shown to utilize coreceptor CXCR4 or CCR5 in the absence of CD4 [10]. Moreover, the SDA-1 efficiently entered and replicated in human hepatoma cells as well as primary hepatocytes, through CXCR4 ligation, without any sign of apoptosis. Nevertheless, the limited sensitivity of the techniques employed, as well as the subdetectable levels of CD4 after several passages of cultured cells, cannot rule out the possibility of CD4 expression on these cells.

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Hepatotropism & liver pathology

Currently, there is convincing evidence for the infectivity of HIV in various human liver cells, as well as SIV infection in monkey liver [8,9,11]. In line with this, productive infection of feline immunodeficiency virus in primary cultures of cat LSECs has also been reported [12]. An earlier report on *in vitro* productive infection of HIV in human primary liver cells (LSECs and Kupffer cells), including hepatic cell lines (e.g., HepG2, HuH7 and Hep3B), further support these *in vivo* observations [7]. By contrast, recently, Iser and colleagues have shown the indispensability of CCR5 and CXCR4 in HIV entry into multiple liver cell lines, using antagonist agents that block these coreceptors [13]. However, they could not detect the expression of CD4, CCR5 or CXCR4 on the surfaces of these cells. There is convincing evidence of a direct cytopathic effect of HIV on liver tissue, independent of retroviral drug toxicity or hepatitis virus coinfection. The CCR5 and CXCR4 coreceptors of hepatocytes, as well as stellate cells, are reported to be involved in fibrogenic developments [14]. The viral gp120 binding of hepatic CXCR4 is reported to upregulate TNF-related TRAIL-R2 expression, causing TRAIL-mediated apoptosis of hepatocytes [15]. Furthermore, HIV protein R has been shown to modulate the activity of host transcription factors, such as PPAR- γ , which are crucial in lipid metabolism, insulin sensitivity, inflammatory processes and fibrogenesis [16,17]. An HIV-related liver portal obliteration with nodular regenerative hyperplasia, responsible for noncirrhotic portal hypertension, has also been reported [18]. Recently, gp120 has been demonstrated to modulate hepatic chemokine receptors as well as

stellate cell biology, and has been linked to liver fibrogenesis [19–21].

Treatment options & complications

Currently, there are nearly 25 approved drugs (eight nucleos(t)ide-based and four non-nucleos(t)ide-based viral reverse-transcriptase inhibitors, nine viral protease inhibitors, one viral integrase inhibitor, one membrane fusion inhibitor, and one CCR5 receptor inhibitor) available for HIV treatment. Though liver fibrogenesis and hepatotoxicity is associated with continued antiretroviral drugs, including HAART administration, it is prescribed for the necessity of balancing potential cytotoxic effects with the need for increasing the CD4⁺ cell count as well as controlling viral replication [22]. The emergence of viral genetic (polymerase/reverse-transcriptase gene) mutants against nucleos(t)ide analogs has been very challenging in the management of HIV infection. This situation becomes clinically more complicated in patients with coinfection with hepatitis viruses, like HBV that shares the same nucleos(t)ide analogs. Since analogs such as lamivudine and entecavir, used in long-term monotherapy, generally lead to the emergence of drug-resistant HIV strains, their use in clinical settings is restricted [23]. Furthermore, combinatorial therapy with interferon, pegIFN- α -2b plus another potential analog adefovir (preferred over lamivudine resistance) has not led to any significant success [24]. Although a few studies have examined emergence of tenofovir resistance in HIV, tenofovir in combination with another highly potential analog, emtricitabine, is being used as a preferred regimen to treat HIV patients [25].

Conclusion

It is now accepted that HIV can also infect hepatocytes, including LSECs, PMICs and Kupffer cells. Since no matching preventive or therapeutic breakthrough has been achieved in the field so far, the molecular aspects of the retroviral infection of liver and its consequences remain challenging.

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