ELSEVIER

Journal of Hepatology 44 (2006) S14–S18

Journal of Hepatology

www.elsevier.com/locate/jhep

Influence of HIV co-infection on hepatitis C immunopathogenesis

Margaret James Koziel*

Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine, Rm 223a, 330 Brookline Ave., Boston, MA 02215-5321, USA

The role of $CD4^+$ or $CD8^+$ T cells in chronic hepatitis C virus (HCV) infection is unclear. People with chronic infection have weak responses against HCV in the blood, but HCV-specific responses are present within liver. The prevailing hypothesis of liver injury in HCV is that $CD4^+$ and $CD8^+$ T cell responses mediate HCV-related liver damage but are ineffectual at clearing the chronic infection. However, we recently reported that vigorous $CD4^+$ responses that produce interferon gamma (IFNγ) early in infection are correlated with slower rates of disease progression, and compartmentalize to the liver. People with chronic HIV and HCV co-infection, particularly those with $CD4^+$ <200 cells/mm^3, have a higher rate of fibrosis development and severe liver disease. Co-infected people have variable degrees of immunosuppression that may provide insight into the relationship between cellular immune functions and the degree of liver damage as assessed by liver biopsy. People with co-infection may have quantitative or qualitative differences in the immune responses. We recently found a relationship between $CD4^+$ immune responses and liver histology. There are qualitative differences in the $CD4^+$ responses found in the liver in co-infected people compared to those with HCV alone, whereas no such differences are found when $CD8^+$ responses are measured. Neither $CD4^+$ nor $CD8^+$ responses correlate with the peripheral CD4 count.

Keywords: **Hepatitis C; HIV; T cell response; Liver fibrosis**

1. Immunity in chronic hepatitis C

The immune response against the hepatitis C virus (HCV) plays a major role in disease pathogenesis [1]. There is accumulating evidence that a broadly directed $CD4^+$ and $CD8^+$ T cell response is associated with spontaneous clearance of acute HCV [2]. However, there is considerable confusion regarding the role of cellular immune responses in chronic HCV, and which aspects of the immune response promote liver fibrosis and which aspects protect against it. Certainly, murine models of HCV expression support a pathogenic role of virus-specific $CD8^+$ cytotoxic T lymphocyte (CTL) in liver injury [3–5]. Animals who only express HCV under the control of an inducible promoter develop inflammation of the liver, whereas those animals who are constitutively tolerant to HCV proteins do not develop inflammation [3,4,6]. It was recently shown that adoptive transfer of HCV-specific CTL to transgenic animals bearing HCV structural proteins developed liver injury [5], further supporting the pathogenic role of CTL. Reconstitution of the immune system after a period of depressed cellular immune responses, such as occurs after successful engraftment of bone marrow following transplantation, can be associated with dramatic increases in inflammatory activity in the liver, presumably on the basis of enhanced HCV-specific immune responses [7].

Alternatively, the cellular immune response may exert a protective effect against disease progression. Patients with depressed cellular immunity, whether because of HIV or pharmacological suppression following organ transplantation [8], have more rapid disease progression, suggesting that some aspects of the cellular immune response, while clearly ineffective at clearing virus, serve to limit liver damage in the presence of viral replication.

2. CD4 responses

$CD4^+$ responses are critical to both the generation and maintenance of antiviral immune responses, because they

* Tel.: +1 617 667 0038; fax: +1 617 975 5235.
E-mail address: mkoziel@bidmc.harvard.edu (M.J. Koziel).

0168-8278/$30.00
doi:10.1016/j.jhep.2005.11.006

secrete cytokines that augment antibody production by B cells and prime $CD8^+$ cells specific for virus-infected cells. Without $CD4^+$ cells, induction of new immune responses is impaired and CTL memory cannot be maintained in vivo [9]. The importance of vigorous $CD4^+$ T cell responses in clearance of HCV is found in several lines of evidence. Firstly, individuals who mount a polyclonal HCV-specific $CD4^+$ response are more likely to clear HCV, whereas individuals who do not are more likely to become persistently infected [10–13]. Secondly, loss of HCV-specific $CD4^+$ T cells during the initial months of infection is associated with relapse of viraemia [14]. Thirdly, HCV-specific $CD4^+$ T cells are associated with an increase in HCV-specific proliferative responses [15]. The kinetics of this response appear to be important, as individuals who clear HCV infection have a more rapid and sustained induction of $CD4^+$ responses than those who develop persistent disease [16]. A vigorous CD4 response, therefore, appears to be essential to initial clearance, although it remains unclear why some individuals have such a protective response and others do not.

We have recently shown that HCV-specific $CD4^+$ responses early in the course of chronic hepatitis C are associated with the rate of subsequent fibrosis progression [17,18], but the role of other cellular immune responses is unknown. Recent studies by our group utilized the model of *Schistosoma mansoni* co-infection, in which there is rapid evolution to cirrhosis compared to those with HCV infection alone and a Th2 bias in co-infected people. The rate of fibrosis progression was associated with the magnitude of the peripheral and intrahepatic immune response, although the former waned over time, in that subjects who had a vigorous type 1 response in the peripheral blood mononuclear cells (PBMCs) and liver had slower fibrosis progression rates [17,18] (Fig. 1).

3. HCV-specific $CD8^+$ responses

It is generally believed that eradication of viruses replicating intracellularly is the function of $CD8^+$ CTLs. Highly activated viral-specific $CD8^+$ T cells are capable of controlling viral infection by killing infected host cells. In addition, they can also inhibit viral replication non-cytolytically via secreted antiviral cytokines such as interferon (IFN)γ, IFNαβ and tumour necrosis factor (TNF)α without lysing infected cells [19]. The importance of these non-cytolytic effector mechanisms has been shown for HIV and HBV [20–22], and HCV-specific CTL clones can produce IFNγ that inhibits HCV replication in the replicon system [23]. In chimpanzees and humans with acute spontaneous clearance of HCV, vigorous polyclonal and multispecific CTL responses develop early in infection [16,24,25]; such responses may be maintained for years after resolution of disease [26]. As with the HCV-specific CD4 response, it is not clear why the majority of exposed individuals fail to mount an effective CTL response. Responses can be detected in the PBMC of people with acute infection, but either these fail to be sustained for a sufficient period of time [16,27] or do not produce sufficient amounts of IFNγ necessary to inhibit viral replication [28].

Although it is often stated that HCV-specific immune responses are absent in chronic infection, this is not the case. Instead, responses in chronic infection appear to be preferentially localized to liver tissue. Both $CD4^+$ and $CD8^+$ responses are relatively enriched in liver tissue compared to those observed in peripheral blood [2,29–36]. Indeed, HCV-specific CTL can be readily expanded from liver tissue without exogenous antigenic stimulation in both humans and chimpanzees [29–31,37] and during chronic infection are detected at higher frequencies in liver than blood using tetramers [32,36]. Much less is known about the function of these T cells in the liver compared to their counterparts in the peripheral blood. In humans, reconstitution of the immune system after a period of depressed cellular immune responses, such as occurs after successful engraftment of bone marrow following transplantation, can be associated with dramatic increases in inflammatory activity in the liver, presumably on the basis of enhanced HCV-specific immune responses [7]. Additional supportive evidence for a role of CTL in liver injury comes from a

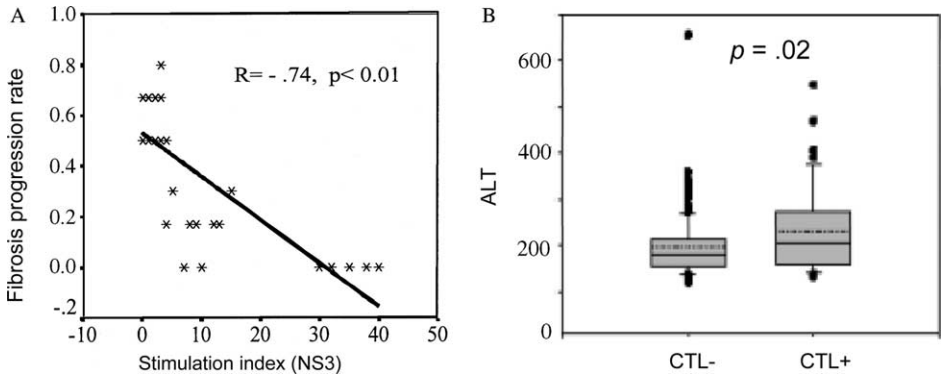

Fig. 1. Relationship of immune responses to histology in chronic HCV. (A) HCV-specific $CD4^+$ responses against NS3, measured using proliferation, early in chronic infection are inversely related to the fibrosis progression rate. From Ref. [17]. (B) The presence of an HCV-specific CTL response against any viral protein, measured by chromium release, is inversely associated with serum transaminases. From Ref. [44]. Reproduced with permission.