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Commentary

Liver disease as a result of chronic hepatitis C virus (HCV) infection is a global problem. While some HCV infections resolve spontaneously, viral persistence associates with compromised T cell immunity. In this issue of the *JCI*, Chen et al. and Coss et al. explored virus-specific CD4+ T cell response during HCV infection. Both studies evaluated the HCV-specific T cells of patients with different courses of infection. Chen et al. revealed that initial CD4+ T cell responses are similar during early infection and that T cell failure resulted from loss of the virus-specific T cells themselves. Coss et al. showed that HCV-specific CD4+ T cells temporarily recovered in some women following childbirth. These studies contribute to our understanding of CD4+ T cell functionality during different natural courses of infection, with the notable implication that restoring CD4+ T cell immunity might contribute to controlling HCV infection.

CD4+ T cell responses in human viral infection: lessons from hepatitis C

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Liver disease as a result of chronic hepatitis C virus (HCV) infection is a global problem. While some HCV infections resolve spontaneously, viral persistence associates with compromised T cell immunity. In this issue of the *JCI*, Chen et al. and Coss et al. explored virus-specific CD4+ T cell response during HCV infection. Both studies evaluated the HCV-specific T cells of patients with different courses of infection. Chen et al. revealed that initial CD4+ T cell responses are similar during early infection and that T cell failure resulted from loss of the virus-specific T cells themselves. Coss et al. showed that HCV-specific CD4+ T cells temporarily recovered in some women following childbirth. These studies contribute to our understanding of CD4+ T cell functionality during different natural courses of infection, with the notable implication that restoring CD4+ T cell immunity might contribute to controlling HCV infection.

Introduction

Hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease, liver cirrhosis, and death worldwide. It is also an excellent model to study the role of virus-specific T cell responses in human viral infection with a dichotomous outcome: viral clearance versus persistence. Indeed, studies in acutely and chronically infected patients have shown that the presence of highly functional and multi-specific CD4+ T cell responses is associated with viral clearance, whereas chronic infection is characterized by only weak and functionally impaired CD4+ T cell responses (1–9). The central role of CD4+ T cells has been further underlined in the chimpanzee model, where antibody-mediated depletion of CD4+ T cells in two immune chimpanzees resulted in persistent, low-level viremia following reinfection (10). However, despite these associations, several important questions have remained open. For example, little is known about the phenotype and fate of the virus-specific CD4+ T cells that are present during acute versus chronic infection. It is also currently unclear whether the weak and impaired CD4+ T cells present during chronic infection can recover when infection is controlled. With the usage of MHC class II tetramers that allow a reliable analysis of virus-specific CD4+ T cells, and with access to unique and longitudinal patient samples, Chen et al. and Coss et al. provide important information regarding these open questions in this issue of the *JCI* (11, 12).

Shaping CD4+ T cell immunity in resolving versus persisting infection

Chen et al. analyzed the phenotype and function of HCV-specific CD4+ T cells in acutely infected patients who either spontaneously cleared the virus or progressed to chronic infection (11). Interestingly, they found that the virus-specific CD4+ T cells did not differ between the patient groups during the acute infection phase, irrespective of the infection outcome. Indeed, no differences in the frequency, phenotype (including inhibitory molecules), and functionality of virus-specific CD4+ T cell responses were observed. Most cells expressed the inhibitory and activating molecules programmed death 1 (PD-1), cytotoxic T lymphocyte–associated protein 4 (CTLA-4), and CD38, indicating activation (Figure 1A). In agreement with previous studies (13–15), the frequency of the virus-specific CD4+ T cells diminished rapidly in patients who progressed to chronic infection. Accordingly, HCV-specific CD4+ T cell responses were hardly detectable during chronic infection. These results clearly indicate that the absence of vigorous CD4+ T cell responses during chronic infection is not caused by deficient priming, but rather by rapid disappearance of the CD4+ T cells themselves. In subjects who resolved the infection, the frequency of HCV-specific CD4+ T cells remained rather stable. These cells downregulated PD-1, CTLA-4, and CD38, and upregulated the memory marker CD127, thus resembling memory cells (Figure 1A). In contrast, virus-specific CD4+ T cells in patients with ongoing viral replication displayed a higher expression of PD-1 and CTLA-4 but also CD38, indicating continuous activation. These results align with previous studies showing upregulated inhibitory molecules in the chronic phase of infection (16, 17).

Pregnancy-associated viral control is linked to CD4+ T cell function

Coss et al. addressed the important question of whether the immune system can functionally restore these scarce and impaired CD4+ T cells in chronically infected subjects when the virus is controlled (12). One exceptional period of viral control has been previously reported by the Honegger group in some chronically HCV-infected women after child-

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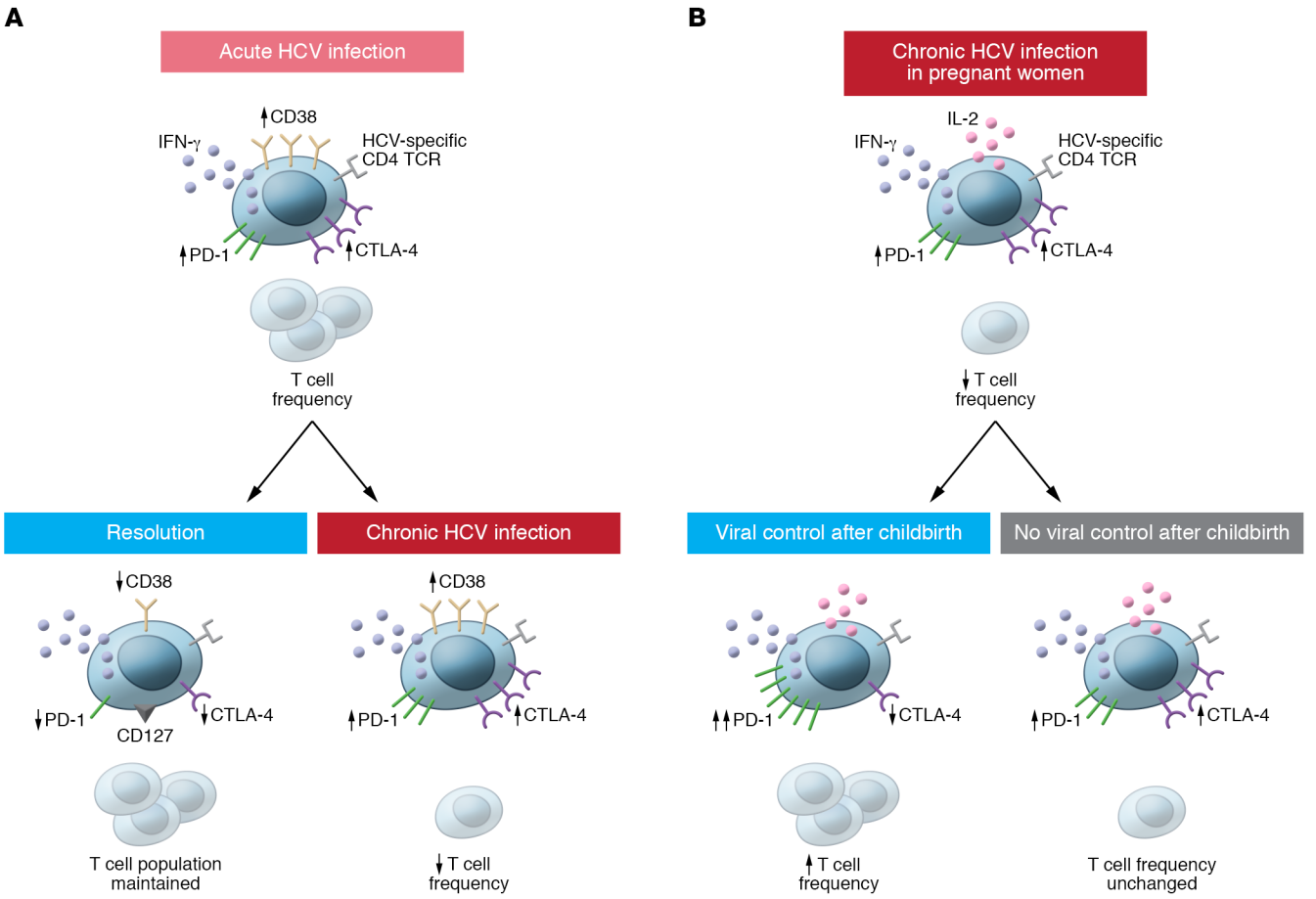

Figure 1. Virus-specific CD4⁺ T cell response during HCV infection. Characterization of virus-specific CD4⁺ T cells in acute resolving versus persisting HCV infection as displayed by (**A**) Chen et al. and (**B**) Coss et al. in the setting of pregnancy-associated viral control.

birth (18, 19). Importantly, by analyzing the virus-specific CD4⁺ T cell response in this unique cohort, Coss et al. observed a higher frequency of circulating virus-specific CD4⁺ T cells in women who were 3 months postpartum and had achieved viral control (defined by at least 1 $\log_{10}$ viral load reduction) compared with the same patients in their last trimester and with women with no viral control. The higher number of CD4⁺ T cells was also reflected by higher frequencies of interferon γ–producing (IFN-γ–producing) and interleukin 2–producing (IL-2–producing) virus-specific cells (Figure 1B). Noteworthy, both correlated with the extent of reduction of viral load. These results indicate a direct role of virus-specific CD4⁺ T cells in viral control, although the underlying mechanisms have not been addressed (12). However, based on the previous finding by the same group that the drop in viremia after childbirth is accompanied by renewed selection pressure on class I epitopes (18), it is tempting to speculate that CD4⁺ T cells primarily mediate their antiviral effects by providing help for CD8⁺ T cell responses.

Implications for immunotherapy and therapy-mediated viral elimination

Importantly, both studies explored the dynamic expression of inhibitory receptors on virus-specific CD4⁺ T cells (11, 12). First, during acute infection, a high expression of inhibitory receptors such as PD-1 and CTLA-4 is observed irrespective of the outcome of infection, further supporting the concept that these markers not only indicate exhaustion, but also activation. It is noteworthy, however, that an upregulation of PD-1 and CTLA-4 on virus-specific CD4⁺ T cells was linked to impaired proliferative capacity. Second, the coexpression of inhibitory receptors on CD4⁺ T cells was significantly less pronounced compared with CD8⁺ T cell responses (20), indicating a differential regulation of CD4⁺ versus CD8⁺ T cells. Thus, restoring these different T cell subsets will likely require different checkpoint inhibitors. Third, in periods of viral control, recovered HCV-specific CD4⁺ T cells still highly expressed PD-1, but not CTLA-4. These results again suggest that PD-1 is a marker of activation. However, they also agree with previous findings that PD-1 is maintained on virus-specific CD8⁺ T cells after direct-acting antiviral–mediated (DAA-mediated) HCV elimination (21), indicating a possible chronic signature on T cells that is not simply reversed by antigen reduction. Clearly, further studies are required to address the transcriptional, phenotypical, and functional recovery of virus-specific CD4⁺ T cells in clinical settings of viral control. One such obvious situation is DAA-mediated elimination, where early immunological studies have failed to show significant changes within the CD4⁺ compartment (22). In line with this, clinical studies showed a lack of protective immu-

nity from reinfection in subjects who had successfully cleared HCV infection by DAA therapy (23). These results suggest that loss of antigen alone may be insufficient to fully restore $CD4^+$ T cell–mediated immunity, as has also been shown for the $CD8^+$ T cell compartment (24).

Taken together, the two elegant studies by the groups of Honegger and Lauer give several important insights into the central role, fate, and recovery potential of virus-specific $CD4^+$ T cells in the control of HCV infection (11, 12). They also point out the importance of HCV as a unique model to study virus-specific $CD4^+$ T cells in a relevant human infection with a dichotomous outcome and with spontaneous and therapy-mediated episodes of viral control.

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