Direct-acting antivirals trump interferon-alpha in their capacity to rescue exhausted T cells upon HCV clearance

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The treatment of HCV has been transformed by the capacity of direct acting antivirals (DAAs) to eliminate the infection by attacking the virus effectively. In this issue Martin et al. reveal that these drugs can also harness the immune system by releasing it from the burden of chronic antigen load [1]. Their important findings underscore a detrimental immunoregulatory component to the effects of interferon-alpha (IFN-α), which was not able to boost antiviral T cells in the manner now demonstrated with DAAs, even when it achieved viral clearance [2].

CD8 T cells are well-recognised to be critical for the control of viruses such as HCV but to be depleted and dysfunctional (exhausted) in chronic infection [2–5]. There are clear demonstrations of the inverse relationship between duration and level of viraemia and T cell responses in murine and human persistent viral infections [2,3,6]. However it has been difficult to determine to what extent the persistent, high antigen load in these settings contributes to the failure of the T cell response [7] or is rather a result of it. A vital issue in the attempt to cure persistent viral infection is whether removal of antigen will be sufficient to allow recovery of T cells with antiviral efficacy. Alternatively, T cells may be permanently scarred by, for example, stable imprinting of PD-1 [8], or subject to other ongoing tolerising mechanisms, which are particularly prevalent in the liver environment [9].

Previous data from the HCV field had suggested that whilst T cells show variable recovery following spontaneous or therapeutically removal of antigen in acute infection, they might no longer be amenable to rescue in chronic infection [4,10,11]. Thus patients with IFN-α induced clearance of chronic HCV had no consistent recovery of virus-specific T cells [10–12]. Now the Thimme group demonstrate that when the antigen load is reduced by IFN-free therapy, there is a striking recovery of the capacity of HCV-specific T cells to expand in culture. Responders to DAAs had a significant increase in the number of detectable HCV-specific responses, and in their frequencies after in vitro expansion, whereas non-responders did not. Three of the 25 responders had no detectable HCV-specific T cells and a further three showed no increase on therapy, but this could reflect the fact that the study was focused on 4 immunodominant epitopes, thereby under-estimating the full extent of reconstitution [1]. This focused approach did, however, allow the vital distinction between T cells directed against consensus vs. mutated viral sequences. HCV clearance had less impact on the expansion of responses to mutated epitopes [1], in line with the concept that these T cells have already escaped from the effects of continuous MHC/peptide stimulation [13]. Importantly, T cell responses directed against CMV and flu epitopes within HCV-infected patients were not augmented by therapy, arguing against a direct capacity of DAAs to boost T cells generally. Taken together, their findings support a role for viral clearance in driving a recovery of HCV-specific T cells.

So why does IFN-α not have analogous effects on T cells even when it eliminates the virus? In addition to its direct antiviral effects, IFN-α has diverse effects on innate and adaptive immunity, with the dual potential to either enhance immune cell activation or to exert negative immunoregulatory effects [14]. The effects of interferon on T cells are particularly pleiotropic, varying from beneficial (promoting their expansion) to detrimental (inhibiting their proliferation and driving apoptosis), depending on timing, T cell phenotype and prior antigen experience [15]. However a number of studies have pointed to IFN-α signalling exerting a predominantly negative effect on T cells in persistent viral infections [14]. These unexpected findings have been reinforced by the recent discovery that IFN-α blockade in vivo enhances T cell-dependent resolution of LCMV by reducing excessive immune activation and accompanying immune suppressive mechanisms [14]. The emerging concept that IFN-α predominantly suppresses antiviral T cells in persistent viral infection is congruent with their lack of convincing reconstitution following IFN-α (in comparison to DAA)-mediated viral clearance in HCV [1,10–12] and HBV [16,17]. In fact in both these infections, IFN-α therapy can profoundly decrease global and virus-specific T cells [12,18]. In contrast, IFN-α therapy potently expands activated, TRAIL-expressing NK cells [5,18] that have the potential to delete virus-specific T cells [19], providing one putative mechanism for the lack of antiviral T cell reconstitution. In addition, T cells in IFN-treated patients continue to be inhibited by PD-1...
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Fig. 1. Differential effect on T cells of IFN-α vs. DAA-induced HCV clearance. The high antigen load in persistent HCV infection results in constant T cell triggering by MHC/HCV peptide complexes (shown on infected hepatocytes, centre). The contribution of this antigen load to T cell exhaustion is revealed by the expansion of T cells achieved when it is removed by DAA-induced HCV clearance (right). When HCV clearance was induced by IFN-α therapy (also resulting in loss of MHC presentation of HCV peptides, left), equivalent T cell recovery was not observed, pointing to an immunosuppressive effect of IFN-α.

[11,16,18], whereas initial data from Martin et al. suggest that expression of this co-inhibitory receptor is reduced by IFN-free viral clearance. The contrasting T cell reconstitution seen with these two different approaches underscores the need to modulate the immunosuppressive effects of IFN-α in order to capitalize on its potential benefits in the therapy of HBV.

The data presented by Martin et al. raise a number of interesting questions. As the Thimme group has previously shown, it is not just the number of virus-specific T cells but also their functional profile that determine antiviral efficacy [9,20]. In the present study they had sufficient cells from one patient to elegantly demonstrate an increase in their antiviral efficacy against a hepatoma cell line with an HCV reporter replicon [1]. It will be interesting in future studies to see whether a full functional restoration and reversal of exhausted phenotype is achieved in most DAA responders. It is tempting to speculate that the recovery of T cells achieved using IFN-free regimens may contribute to the high sustained cure rates and lack of off-treatment relapses seen with these drugs. This would imply that the extent of T cell reconstitution might be able to be used as a guide to personalize DAA therapy. Could a lack of induction of T cells signal the need for therapy intensification and conversely, could good T cell recovery allow shorter treatment duration in some patients, with the expectation that any residual virus will be cleared by T cells? The authors suggest that induced T cells may even be able to provide some protection against reinfection with a new strain of HCV, although this might be limited by virus variability and the possibility that recovered T cells will lack the capacity of memory cells to survive long-term in the absence of antigen [2].

In conclusion, Martin et al. make the rather ironic observation that drugs designed purely to target the hepatitis C virion have turned out to have better potential to indirectly boost antiviral T cell immunity than the standard “immunomodulatory” therapy with interferon. Their study highlights how vital ongoing antigenic stimulation is in driving T cell exhaustion and suggests an encouraging degree of reversibility to this process. It will stimulate efforts to move towards a functional cure in other persistent infections such as HBV and HIV by finding ways to further reduce antigen load, thereby potentially unleashing effective antiviral T cells.

Conflict of interest

MKM has carried out consultancy for Roche, Gilead, BMS, Transgene and ITS and received an unrestricted educational grant from BMS.

References


