Coxackievirus was first discovered as a filterable agent associated with a paralytic syndrome, so named for its identification in Coxsackie, New York (coxsackievirus type A).1 Coxackievirus type B (CVB) was isolated the following year from patients with aseptic meningitis,2 and by the mid-1950s, an association with acute myocarditis in humans was becoming clear.3–6 Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in humans was becoming clear. Many other viruses have since been shown to have an association with acute myocarditis in human...
Shi et al. describe the protective role that T-regs play in immune infiltration of the heart during viral myocarditis, suggesting that there is a balance to be struck between clearance of infection and immune-associated damage to the myocardium. In fact, the authors observed decreased viral loads consonant with a decrease in immune infiltration due to reduced tumor necrosis factor α release and lower CAR expression; such findings suggest a more intimate link between inflammation and virus replication than previously posited. Thus, moderating the immune response may be critical for prevention of chronic virus replication. This issue should receive attention given the fact that dilated cardiomyopathy is thought to result from repeated rounds of injury and repair that ultimately weaken the heart muscle.

Although the dominant factor in virus suppression during T-reg treatment was most likely downregulation of CAR expression, we propose that the alteration in signaling evoked by T-regs also plays a significant role in modulating virus replication. The basis of our argument is that CAR expression was suppressed 3-fold in vivo and 5-fold in a dividing cardiomyocyte cell line in vitro, but the suppression of viral load in the T-reg group was almost 2-logarithms reduced as compared with the control group. Although the correlation between cell receptor expression and virus infection may not be linear, the decreased levels of CAR may not explain the entire antiviral and protective effect of T-regs in the myocardium during virus infection. It is entirely possible that the signaling environment altered by the adoptive transfer of T-regs may have also contributed to a less favorable environment for virus replication. The authors reported the altered, prosurvival activation of Akt in the T-reg–treated groups,7 which suggests that the activation of other signaling proteins may have been altered by T-reg transfer. We have reported that Akt activation is required for successful CVB3 replication,16 a prosurvival protein required by the virus to optimize the longevity of the infected cell to promote optimal progeny virus production. On the other hand, the Akt activation reported by Shi et al. may merely be a reflection of a virus-protective environment created by allografted T-regs in the myocardium. It is quite clear that an unbraked immuno-logically active environment supports enhanced cellular signaling driven by viruses for successful replication.10,16,17 For example, we have previously reported that the powerful immune-stimulating protein p38 is required for effective virus replication in a similar CVB3 myocarditis mouse model.10 The activation of p38 mitogen-activated protein (MAP) kinase was not investigated by Shi et al.7 but we would predict less net activation of p38 in the presence of allogeneic T-regs and thus an environment that is less conducive to virus replication. Although p38 MAP kinase activation is required for suppressor (T-reg) T-cell activity and function,18 we propose that adoptive transfer of T-regs may have decreased the immune infiltrate in the myocardium with less activation of p38 MAP kinase.

Our laboratory has reported that inhibition of p38 MAP kinase is an effective antiviral strategy in vitro19 and in vivo.10 Thus the intimate link of this molecule to the immune response is perhaps not surprising; one might expect that Akt activation, p38 inhibition, and T-reg immune control lead to improved outcome and result in lower viral load and immune infiltration. With regard to new treatment strategies, this does not necessarily mean that we should be injecting allogeneic T-regs into patients with myocarditis, but methods should be pursued that mediate the immune response to swing the pendulum in favor of viral clearance and repair and away from immune infiltration of the myocardium that favors higher viral loads. The work of Shi and several other recent studies have demonstrated the evolved ability of the virus to bias immune activation and associated signaling queues for the benefit of virus replication. Given the results presented by Shi et al.7 one might initially conclude that immune suppression would be a sound therapeutic strategy. However, the Myocarditis Treatment Trial, wherein patients were treated with immunosuppressive agents,20 showed that such administration had no significant benefit for outcome of human myocarditis. As such, pan-immune suppression is not the way forward, and better targeted methods of immune modulation are needed. Shi et al. demonstrate that transforming growth factor β secreted by T-regs may have been responsible for the decreased CAR expression and enhanced Akt activation.
(Figure). This suggests that we need not inhibit the immune response entirely, but rather target, modulate, and encourage the arm of the immune system that promotes virus clearance. The way forward may not be adoptive transfer of T-regs, but administration of an as yet undiscovered drug that can promote T-reg differentiation and function. These findings may even translate to approaches for lessening immune rejection of allografts through induction of immune senescence after transplantation; cotransplantation of T-regs might induce tolerance of grafted tissue.

In conclusion, the novel studies of Shi and colleagues help us to reconcile the complex relationships between the degree of immune infiltration and viral load. With more support for a model wherein virus replication is driven by the signaling queues provided by the immune response, we may move toward treatments that modulate the immune response in favor of resolution of infection and earlier repair of the damaged tissue.

Disclosures

None.

References


Key WORDS: Editorials ■ infection ■ inflammation ■ myocarditis ■ signal transduction
Regulating Viral Myocarditis: Allografted Regulatory T Cells Decrease Immune Infiltration and Viral Load
David J. Marchant and Bruce M. McManus

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