T Regulatory Cells
Sentinels Against Autoimmune Heart Disease
Madeleine W. Cunningham

Myocarditis is an acute inflammatory disease of the heart and a precursor of dilated cardiomyopathy.1–8 Dilated cardiomyopathy is a more chronic disease which is characterized by ventricular hypertrophy and which may be a direct result of myocarditis and lead to heart failure.1–3,9 Myocarditis is often characterized by a cellular infiltrate, and if inflammation of the myocardium does not resolve during the acute stage, the heart may be compromised because of necrosis and direct loss of myocytes,10 scarring from granulomatous inflammation,11,12 or fibrosis because of proliferation of fibroblasts and collagen deposition.13,14 Although TH1 or TH2 cell mediated immunity is blamed for disease, myocarditis has been reported to develop independently of TH1 and TH2 mechanisms.15 In some cases of myocarditis, antibody deposition and antibody-mediated cell signaling of the β-adrenergic receptor or the calcium channel may affect cardiomyocyte function and lead to cardiomyopathy or apoptosis in the myocardium.16–18 Whichever type of disease occurs, the myocardium may deteriorate from relapsing and remitting disease and become enlarged and functionally weakened because of the immune attack on the heart.

In this issue of Circulation Research, Huber and colleagues report that a coxsackievirus variant can affect the outcome of myocarditis by inducing regulatory T cells which abrogate disease in the tumor necrosis factor (TNF) transgenic mouse model of myocarditis as discussed below.19 Viral infection has long been associated with the development of myocarditis, of which the coxsackieviruses are reported frequently to react with toll-like receptor (TLR) 4 in the heart and develop inflammation because IL-1β, IL-6, and TGFβ in granulomatous myocarditis functions in disease protection, and decreased γ IFN results in disease production. IL-4 and histamine release drive fibrosis in the heart as seen in asthmatic conditions.32 Fortunately, T cell mediated disease-producing mechanisms are under the control of regulatory T cells.33–36 Huber and colleagues describe a transgenic model of myocarditis and cardiomyopathy where transgenic mice express TNF-α in the heart and develop inflammation because of the expression of TNF-α.19 The new model demonstrated development of TH1 inflammatory responses with induction of γ IFN and IgG3 antibodies. IgG3 antibodies have been linked before to pathogenic responses in rodent models.16,37 The most interesting part of the study was the observation that myocarditis could be overcome by a coxsackievirus variant which maintained and induced T regulatory cell function. The study of 2 different coxsackieviruses led to 2 inflammatory heart disease. Viral replication in cardiomyocytes leads to induction of cytokines including α and β-interferons which are important antiviral cytokines which inhibit viral replication.23,24 In the early acute phase of myocarditis, the virus reacts with toll-like receptor (TLR) 4 which signals danger in the heart.25,26 The response to TLR4 signaling includes the induction of inflammatory cytokines. Innate and adaptive host responses including α and β-interferon production may be sufficient to contain the virus and limit cellular infiltration. In most cases, myocarditis resolves and the host will not develop chronic disease and heart failure. However, in some patients the disease becomes autoimmune and inflammatory and the innate and adaptive immune responses are primed by the viral infection to respond against heart tissue epitopes. Most importantly, the cardiomyocytes release cardiac myosin during lytic viral infections, and the host recognizes myosin as a foreign antigen and responds by an adaptive immune response against the heart.27,28 Once the myocardium is scarred or fibrotic, there is loss of function. The fact that Huber and colleagues report in this issue of Circulation Research that a coxsackievirus can control myocarditis and induce regulatory T cell function is remarkable.19

The many facets of immune attack in myocarditis are reflected in the heterogeneous nature of the disease in humans making the decision about diagnosis and treatment uncertain.22 Immune attack may include cytolytic CD8+ T cells with necrosis,10 CD4+ T cells and γ IFN in granulomatous myocarditis,20,30 or macrophages and mast cells secreting profibrotic mediators including histamine, IL-4, TGFβ, and IL-1β in chronic myocarditis with fibrosis of the myocardium.13,14,31 It is tricky immunity, because in granulomatous myocarditis, γ interferon (IFN) drives a scarring TH1 T cell mediated disease, whereas in the fibrotic form of myocarditis, γ IFN functions in disease protection, and decreased γ IFN results in disease production. IL-4 and histamine release drive fibrosis in the heart as seen in asthmatic conditions.32 Fortunately, T cell mediated disease-producing mechanisms are under the control of regulatory T cells.33–36

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entirely different outcomes. One of the 2 viruses protected against viral myocarditis by activating CD4+ CD25+ FoxP3+ T cells with a regulatory phenotype, whereas the other virus maintained disease by upregulating TNF-α expression in the TNF-α transgenic mice. The viruses differed only in one amino acid in the nonconserved region of the VP2 capsid protein. The protective variant virus induced regulatory T cells which abolished autoimmunity in the TNF-α myotropic transgenic mice.

The study by Huber and colleagues demonstrates that not only the state of the host but the virulence properties of the virus may induce proinflammatory cytokines such as TNF-α which led to myocarditis in the heart. The mechanism by which TNF may downregulate T regulatory cells has been recently described as related to a decrease in transcription factor FoxP3 by T regulatory cells. FoxP3, transcription factor forkhead box p3, is currently one of the most specific markers for natural CD4+ regulatory T cells. Recent studies have shown that autoimmune myocarditis and multiorgan inflammation are controlled by FoxP3+ T cells highly expressing the glucocorticoid-induced TNF receptor family-related protein (GITR). Depletion of the GITR+ T regulatory cells allowed activation of autoimmune heart disease. Other studies suggest that regulatory T cell expansion and function can be downregulated by TLR2 ligation.

In summary, regulatory T cells play a major role in protection against inflammation in the heart, and their alteration by viral infection may contribute substantially to the outcome of myocarditis.

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References


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