Mycarditis classically refers to inflammation of the heart muscle. The mechanisms include host immune dysregulation and viral triggers such as coxsackievirus (CVB), adenovirus, parvovirus, and hepatitis C virus. The pathophysiology is initiated by viral proliferation in a susceptible host, inducing host immune response. The latter, when exuberant, leads to myocyte destruction and dilated cardiomyopathy. Clinically, patients with viral myocarditis will spontaneously recover in one third of cases, persist with the disease in one third, and deteriorate in another third of the cases.

**Recent biopsy series in patients with dilated cardiomyopathy have revealed an interesting situation in which patients with symptoms of heart failure may show the presence of the viral genome alone, without any evidence of an overt inflammatory process.** This raises the question of whether the virus can be directly responsible for the cardiomyopathy or whether it is merely an incidental bystander.

Viruses are exquisitely designed nanoparticles packaged with just the critical amount of genetic material to allow them to adapt to changing host and environmental conditions and to pass on genetic material to progeny. CVBs are single-stranded RNA viruses that have natural tropism for gut epithelial cells, immune cells, neurons, and cardiomyocytes. All strains of CVBs use the coxsackie–adenoviral receptor molecule to gain entry into host cells (Figure). The coxsackie–adenoviral receptor is a critical tight-junction protein important for cell–cell communication and for maintenance of cell membrane integrity. Interestingly, viruses such as CVB must use host signaling mechanisms, including tyrosine kinases such as Abl, fyn, or p56lck, to rearrange host actin and cytoskeleton and thus gain entry into the host cell and release viral RNA into the cytoplasm.

To facilitate entry into cells, it is not surprising that CVBs also produce proteases that can lyse the cell–cell or cell–matrix connections. CVB3 produces protease 2A, a cysteine endopeptidase that can specifically cleave the dystrophin–sarcoglycans complex, which is responsible for the linkage of myocyte cytoskeleton to the extracellular matrix. This cleavage leads to dystrophin dysfunction and to loss of sarcolemmal integrity, likely aiding viral entry. This action resembles that of the naturally occurring human mutations in the dystrophin–glycoprotein complex such as X-linked muscular dystrophies, which are often associated with dilated cardiomyopathy.

Following up on initial in vitro observations, in this issue of the *Circulation*, Xiong et al have gone on to show that the conditional expression of this protein is alone sufficient to lead to dilated cardiomyopathy in vivo. The presence of protease 2A coincided with the compromise of sarcolemmal integrity and the loss of intact dystrophin by immunostaining. These findings suggest that viral endopeptidases, when present in adequate concentrations or expressed for a sufficient duration, can produce myocyte cytoskeletal and sarcolemmal disruptions, leading to dilated cardiomyopathy. These findings indirectly show that the naturally occurring mutations, as seen in the X-linked dystrophies at the sarcoglycans complex, are critically related to the phenotype of cardiomyopathy. The viral myocarditis model, therefore, is a mimic of the genetically induced cardiomyopathy, disrupting the same cytoskeletal target in an acquired manner.

The advantage of the conditional heart-targeted model used by Xiong et al is that the protein is only expressed in the heart, and the transgene is only produced when the mice are adults. This strategy avoids the complications of having a protease 2A presence in utero, which can lead to unintended effects during development. On the other hand, the transgenic model forces the protease to be produced in relatively high quantities for a prolonged period, which probably does not occur with a natural viral infection. In the latter setting, the protease likely will be produced only for a brief few days when the virus is actively proliferating. Nevertheless, this study provides significant proof that the production of this cytoskeletal-modifying protease is sufficient to produce dilated cardiomyopathy.

What role does the host immune response play in this setting? How does the host deal with the presence of foreign viral particles in the heart and elsewhere and successfully
clear the viruses from the heart in the majority of the cases? On the other hand, how do we reconcile the presence of the inflammatory cell infiltrates that are seen on many biopsy sections and that can ultimately contribute to the evolution of dilated cardiomyopathy?

The original Dallas criteria for the diagnosis of myocarditis on myocardial biopsies stipulated the presence of lymphocytic infiltrates concurrent with evidence of myocyte necrosis. Most experts would agree that in real practice, the Dallas criteria are overly strict, leading to underdiagnosis of the condition. Nevertheless, these criteria underscore that the host inflammatory response is an integral part of the disease process—but how does the viral infection lead to mobilization of lymphocytes to the myocardium?

The presence of viruses or other foreign particles can trigger the activation of innate immune responses in the host tissue through a family of toll-like receptors. In contrast to the T- and B-cells of acquired immunity, which require perfect matching of specific antigenic peptide sequences for activation, the toll-like receptors require only very general triggers or pathogen-associated molecular patterns. Engagement of the toll-like receptors produces rapid signal transduction in the host, leading to activation of adaptor proteins such as MyD88, IRAK-4, and TRAF-6. This activation triggers translocation of interferon regulator factor transcription factors to the nucleus to produce interferons, and this activation also triggers translocation of nuclear factor-κB to produce cytokines. We have shown previously that excessive activation of the MyD-88/nuclear factor-κB axis leads to increased inflammation and higher mortality rates, whereas activation of interferon regulator factor-3 and interferons are protective and antiinflammatory for the host, with a reduced mortality rate.
In addition to the toll-like receptor family, there are other means by which the host cells, and particularly myocytes, can direct innate immunity to enhance host survival, attenuate the virus, or both. In addition to these positive regulators of host-defense responses outlined above, there are also systems of negative modulators that will counteract the cytokine activation. One system is the intracellular suppressors of cytokine signaling (SOCS) system of signaling pathways that negatively regulate innate immune response. The SOCS system particularly downregulates cytokine signals going through the gp130 receptor on the myocytes. The gp130 receptor engages cytokine ligands such as interleukin-6 and cardiotropin-1, which are cardiac myocyte growth and survival factors. Deficiency of gp130 signaling leads to increased apoptosis and susceptibility to other insults and injury such as ischemia or viral infection.

Yajima et al have previously found that SOCS1 and SOCS3 signaling can downregulate the JAK/STAT signal-transduction pathways and significantly increase the host’s susceptibility to CVB infection, but SOCS2 did not. However, SOCS1 also interferes with interferon signaling, making it difficult to dissociate the interferon-dependent and -independent contributions on host susceptibility. On the other hand, SOCS3 downregulates the JAK/STAT pathway but does not alter interferon signaling. SOCS3 transgenic mice-induced loss of STAT3 led to increased susceptibility to viral injury. This effect is mimicked by ablation of gp130-receptor signaling. The gp130-mediated protective effect seems to be mediated by STAT3 phosphorylation, leading intriguingly to a more robust dystrophin–sarcoglycan complex in the membrane, increasing the sarcolemmal integrity. This is compatible with the overall concept that viral infections engage host growth and replication machinery but also disrupt the membrane apparatus to gain efficient access to the intracellular compartment. If the cytoskeleton is maintained intact and the membrane remains robust, the viral infection is more attenuated, and the host survives better. The converse has been observed in dystrophin-deficient mdx mice, which have increased susceptibility to viral infection.

What are the implications of these findings for the clinician? First, viral infection can directly remodel the myocardium, leading to dilated cardiomyopathy. One example, discussed here, is that the production of viral protease 2A by CVB can directly cleave the dystrophin–sarcoglycan complex, leading to sarcolemmal disruption and dilated cardiomyopathy. On the other hand, the virus can also trigger innate immunity, which can strengthen the host to fight against the infection—for example, through activation of STAT3 and gp130 signaling for survival, and interferon regulator factor-3 triggering interferon production for systemic clearance of the virus. Unfortunately, activation of innate immunity can also have the adverse consequences of production of cytokines and costimulation of T-cells, leading to clonal expansion and inflammatory infiltrate. Excessive inflammation leads to paradoxical destruction of the host myocardium, leaving the patient worse off than he or she would have been with no inflammation at all.

In a perfect world, one would like to see a host capable of recognizing the viral presence at the earliest opportunity and clearing the virus before it could have the chance to proliferate, elaborating proteases, and remodeling the matrix–cytoskeleton connections in the heart. The most effective approaches to date are either vaccination to induce immunologic memory or the administration of type I interferons to enhance viral clearance. Results of ongoing clinical trials evaluating the potential of interferons in rapidly mediating viral clearance and, possibly, improving clinical outcome, are eagerly anticipated. However, other intriguing treatment targets may also be important, including a means to inhibit SOCS3 or promote STAT3 signaling to strengthen the host; such a means could be useful for broad cases of cardiac injury. In addition, the ability to inhibit dystrophin–sarcoglycans breakdown, possibly through blockers of peptidases such as protease 2A, may also prevent cardiomyopathy of diverse origin.

Ultimately, nature may produce the best tools to understand many of our biological enigmas. Indeed, viruses may be the best-designed nanoparticles for unraveling the mysteries of dilated cardiomyopathy, offering novel avenues for treatment of this most challenging condition.

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References


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Yuichiro Maekawa, Maral Ouzounian, M. Anne Opavsky and Peter P. Liu

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