JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 6, NO. 7, 2021

EDITORIAL COMMENT

Do Genes Influence Susceptibility to Myocarditis?*

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Myocarditis most often results from an autoimmune response to viral infection, with the variability in clinical severity and likelihood of recovery partly explained by differences in viral genetics and the effects of age, sex, and host comorbidities (1). Because these factors provide an incomplete explanation for the variable risk of myocarditis after exposure to the same injury, clinical and experimental studies have sought to define the role of host genetic susceptibility. Toll-like receptor 3 mutations increase susceptibility to enteroviral myocarditis and cardiomyopathy (2). Genetic variation within interferon-induced transmembrane protein 3 (*IFITM3)* is associated with influenza infection severity (3). Spontaneous autoimmune myocarditis develops in mice expressing the human major histocompatibility complex molecule HLA-DQ8 (4). Other, nonimmune mechanisms, including efficient cleavage of host proteins by viral proteases and deficiency of cytoskeletal proteins such as dystrophin, contribute to the risk of cardiomyopathy due to myocarditis (5).

Previously silent recessive defects in nonimmunity genes increase the risk or severity of viral myocarditis. For example, mutations in dystrophin increase susceptibility to myocardial CVB3 infection (5). In children with acute myocarditis, the frequency of potentially pathogenic variants in the genes *DSP*, *PKP2*, and *TNNI3* (encoding, respectively, desmoplakin, plakophilin-2, and troponin I type 3) is increased (1). In peripartum cardiomyopathy, a disorder previously thought to be purely environmental, the prevalence of truncating variants in genes associated with dilated cardiomyopathy is increased and associated with a lower rate of left ventricular recovery (6).

In this issue of *JACC: Basic to Translational Science*, Kontorovich et al (7) report the rates of damaging genetic variants (DVs) in 117 patients with biopsy-proven acute myocarditis derived from 3 cohorts and in 468 control subjects from the Icahn School of Medicine BioMe Biobank who had no history of cardiomyopathy or neuromuscular disease. The cohort was 88.9% adult and mostly European/Caucasian. They found that the rates of DV were significantly higher (16.2%) in the pooled cohort compared with the matched controls (7.2%). Subgroup analysis revealed a 23% rate of DVs in the 13 pediatric cases, which was higher than the 15.4% rate in adults. Two of the children had multiallelic DVs compared with none in adults. A *TTN* DV was present in 6% of myocarditis versus none in control cohorts. Finally, the rate of DV was higher in subjects with lymphocytic myocarditis (LM) compared with those with non-LM (including giant cell myocarditis, eosinophilic myocarditis, and cardiac sarcoidosis). However, there was no significant difference in DV rate between men and women (18.4% vs 15%) or between those with and without myocardial viral genomes.

These data are unique as the only reported clinical dataset of biopsy-proven myocarditis with comprehensive histology, viral genome analysis, and cardiomyopathy genetics. The novel observations in a primarily adult population demonstrate that silent recessive defects partly explain the variability in susceptibility to myocarditis. However, these findings also raise a host of new questions about the cellular mechanisms involved in pathogenesis. The genes in

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2021.06.003

this report encode proteins with a variety of roles in membrane and cytoskeletal function. How do the alterations in protein quantity or function lead to greater risk of arrhythmia or cardiomyopathy? If myocarditis requires an autoreactive immune response, do these cytoskeletal changes provide an unusually strong immunogenic stimulus or overcome homeostatic regulation by different means? If the paradigm of pathogenesis remains a simple "two-hit" injury consisting of a genetic predisposition and an acute viral infection, why was the rate of DVs in viral gene-positive versus -negative subjects similar?

During Coxsackievirus myocarditis, the virus protease cleaves dystrophin and affects the function of cardiomyocyte sarcolemma. Knockout mice for dystrophin had increased susceptibility to viral myocarditis. Mice with a mutation in the dystrophin site for virus protease cleavage showed higher susceptibility to Coxsackievirus myocarditis (8). These findings suggest that certain cytoskeletal protein DVs lower the cardiac protection to withstand virus infection and might even affect disease severity. In addition, cardiomyocytes with cytoskeletal protein DVs are more fragile (5). More cardiomyocyte death could present cryptic epitopes to immune cells, causing subclinical noninfectious inflammation that could induce cardiac specific memory T cells. Cardiac inflammation is, for example, frequently observed in autopsies of patients with arrhythmogenic right ventricular cardiomyopathy. The tissue memory T cells can contribute to more severe inflammation during viral myocarditis with an added autoimmune component. It remains to be investigated how the predisposition to autoimmune myocarditis could be affected by cytoskeletal protein DVs.

Perhaps the link between host cytoskeletal protein DVs and cardiomyopathy is even more complex. In patients with *HLADQA1*/B1** alleles, cross-reactive $CD4^+$ T cells primed in the intestine can enter the heart and exacerbate cardiotropic virus myocarditis. In genetically susceptible individuals, elevated *Bacteroides*-specific $CD4^+$ T-cell and B-cell responses contributed to myocarditis (1). The pathogenesis of cardiomyopathy in that model involved a novel pathway in which peptides from commensal bacteria promoted inflammatory cardiomyopathy. One direction for clinical research from Kontorovich et al's findings would be to examine the influence of the DVs on variable penetrance and inflammation in subjects with permissive HLA alleles.

The findings of the Kontorovich et al (7) study are limited by the relatively homogenous subject population with western European ancestry. Similar genetic studies in African populations are actively being pursued. Future studies should integrate gene-environment interactions, including nutritional factors, that affect susceptibility to infectious and noninfectious myocarditis. These findings should also stimulate studies to define the role for DV genetic testing in unaffected relatives. The findings of Kontorovich et al (7) will hopefully lead to studies that dissect the effects of DVs on types of immune response, their severity, and outcomes, including the likelihood of recovery of left ventricular function and the risk of recurrent myocarditis.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by National Institutes of Health/National Heart, Lung, and Blood Institute grants R01HL135165-03 to Dr Cooper and 2R01HL118183 and R01HL136586 to Dr Čiháková and American Heart Association 2019 and 2020 Transformational Project Awards 19TPA34910007 to Dr Čiháková. Dr Cooper has received funds from BMS, Cantargia, and Cardiol for consulting.

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KEY WORDS cardiomyopathy, giant cell myocarditis, myocarditis, viral myocarditis