Inflammatory cardiomyopathy (myocarditis) is defined as an inflammatory disease of the myocardium, associated with necrosis and degeneration of cardiomyocytes, which leads to cardiac dysfunction and can progress to dilated cardiomyopathy. Patients with dilated cardiomyopathy have only a 5-year survival rate of 55% under current heart failure treatment, indicating the need for target-specific strategies. Immunosuppressive therapies can exert beneficial effects in chronic, virus-negative inflammatory cardiomyopathy, whereas immunoadsorption might be effective in a subset of dilated cardiomyopathy patients with autoantibodies against heart tissue antigens. Furthermore, there is some evidence that immunomodulation with interferons can be cardioprotective, at least, in Coxsackievirus B3 (CVB3)– but not in Parvovirus B19–positive inflammatory cardiomyopathy. At present, these specific treatment options have not yet been proved in major trials or not yet approved by the Food and Drug Administration, leaving the search for new therapeutic options still open. Experimental studies evaluating the potential of T regulatory cells, mesenchymal stromal cells, or targeting B lymphocytes are further attempts to develop new therapeutic options for inflammatory cardiomyopathy via targeting immunocompetent cells.

Among the different causes of myocarditis, including infectious and noninfectious agents such as viruses, bacteria, fungi, drugs, and toxins, viruses have traditionally been considered the most common cause of myocarditis and dilated cardiomyopathy. The pathogenesis of CVB3 belonging to the enterovirus genus is well studied in mice and cellular models, including HEK293T and HeLa cells and immortalized mouse atrial tumor HL-1 cells, which are not reflective of adult human cardiomyocytes. Immunosuppressive therapies can exert beneficial effects in chronic, virus-negative inflammatory cardiomyopathy, whereas immunoadsorption might be effective in a subset of dilated cardiomyopathy patients with autoantibodies against heart tissue antigens. Furthermore, there is some evidence that immunomodulation with interferons can be cardioprotective, at least, in Coxsackievirus B3 (CVB3)– but not in Parvovirus B19–positive inflammatory cardiomyopathy. At present, these specific treatment options have not yet been proved in major trials or not yet approved by the Food and Drug Administration, leaving the search for new therapeutic options still open. Experimental studies evaluating the potential of T regulatory cells, mesenchymal stromal cells, or targeting B lymphocytes are further attempts to develop new therapeutic options for inflammatory cardiomyopathy via targeting immunocompetent cells.

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In this issue of Circulation Research, Sharma et al. used human induced pluripotent stem cell–derived cardiomyocytes (iPS-CM) as an in vitro model for CVB3–induced myocarditis and antiviral drug screening platform. Since the discovery of human iPS in 2007 by Takahashi and Yamanaka, the programming of human somatic skin fibroblasts to pluripotency via the ectopic expression of the transcription factors Oct4, Sox2 in combination with either Krüppel-like factor 4 and Myc or Nanog and Lin28, human iPS have been used as a source of cardiac regeneration and as a tool for modeling cardiac disease. IPS offer indeed an exceptional possibility to create disease-specific cellular models, to investigate underlying mechanisms, to optimize therapy, and to develop novel strategies for drug discovery and testing, because they can be derived from any patient, can self-renew, and differentiate into many cell types. With respect to disorders of the cardiovascular system, iPS-CM have been generated from patients with genetic cardiac disorders including LEOPARD syndrome, (type II) long-QT syndrome, familial dilated cardiomyopathy, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. The iPS-CM presented the disease signature, and for some disorders, pharmacological agents could be identified that abrogated the disease phenotype. iPS-CM are ideal cells for studying mechanisms of CVB3 infection of cardiomyocytes because they are nonimmortalized cells, which can be mass-produced and express ion channels and sarcomeric proteins present in adult human cardiomyocytes. Using the human iPS-CM technology, Sharma et al. found that iPS-CM, like primary cardiomyocytes, express the Coxsackie and adenovirus receptor needed for CVB3 internalization and are susceptible for CVB3 infection. Via a luciferase-expressing CVB3 strain (CVB3-Luc), the authors quantified viral replication on iPS-CM, a method they used for the first time to quantitatively assess the efficacy of antiviral compounds in reducing CVB3 proliferation in iPS-CM. The authors did not observe a difference in time of the cytopathic effect onset between 6 human iPS-CM lines, derived from healthy individuals and 2 different reprogramming protocols, at a CVB3-Luc multiplicity of infection 5.

Despite the merit of this study using iPS-CM as drug platform to test antiviral strategies against CVB3, some considerations have to be made. It would be of interest to verify whether there are patient-specific differences between iPS-CM in the susceptibility of CVB3 infection and drug responsiveness. In this regard, to confirm the value of iPS-CM as a tool to study CVB3 and antiviral therapies and to confirm its patient specificity, correlations between CVB3 susceptibility...
of human iPS-CM and CVB3 copy number in endomyocardial biopsies of corresponding patients are desired. As such, iPS-CM might have a prognostic value, only in relation to endomyocardial biopsies, the diagnostic gold standard.24 It should also be recognized that via using iPS-CM as antiviral drug platform, only 1 aspect of the viral pathogenesis, that is, the direct cytotoxic effect of CVB3 in cardiomyocytes, is taken into account and not the systemic immune effects,9 which are triggered by the virus. In addition, it should be addressed that concentrations of antiviral drugs tested on iPS-CM combining efficacy with absence of toxicity cannot necessarily be extrapolated to the human in vivo condition. Last, but most importantly, the prevalence of enteroviral-positive patients is relatively low today. Predominantly, patients with inflammatory cardiomyopathy have Parvovirus B19—positive endomyocardial biopsies.25 In contrast to enteroviruses for which immunomodulation with interferon might be a therapeutic option, there are no specific antiviral strategies for Parvovirus B19 identified so far. Hereby, it is important to take into account that Parvovirus B19 leads, in contrast to enteroviruses, to a predominant endothelial infection.26,27 Therefore, it will be a further challenge and need to set up iPS-derived endothelial cells and to screen for anti-Parvovirus B19 pharmaca in the near future, too.

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Disclosures

None.

References


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