Lack in Treatment Options for Virus-Induced Inflammatory Cardiomyopathy
Can iPSC-Derived Cardiomyocytes Close the Gap?

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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. In this regard, to confirm the value of iPSC-CM as a tool to study CVB3 infection and drug screening, some considerations have to be made. It would be of interest to verify whether there are patient-specific differences between iPSC-CM in the susceptibility of CVB3 infection and drug responsiveness. In this regard, to confirm the value of iPSC-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. 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, 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. 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. 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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