Hypertrophic cardiomyopathy (HCM) is a heterogeneous monogenic heart disease and is characterized by abnormal thickening of the myocardium due to cardiomyocyte enlargement. HCM is a frequent cause of sudden death in young people and leads to heart failure due mainly to diastolic dysfunction. Although the mortality rate for non-obstructive HCM patients is approximately 10% in 10 years, a small subset of patients with non-obstructive HCM patients progresses to end-stage HCM whose mortality rate is 11% per year. As the known predictor of end-stage HCM is a familial history of end-stage HCM, some genetic backgrounds might affect the disease progression of HCM. On the other hand, the prognosis in infantile HCM (diagnoses before 1 year old) is poor compared with that in adults/adolescents. Although there are some common causes of HCM other than genetic disorders such as inborn errors of metabolism, muscular dystrophy, and malformation syndromes in HCM in children, especially in infants, the 1-year survival rate in idiopathic HCM patients who were diagnosed before 1 year old is lower than that in idiopathic HCM patients who were diagnosed after 1 year old. Therefore, understanding the pathophysiology and underlying mechanisms of infantile HCM might also lead to an understanding of a malignant subset of HCM in adults and the development of novel therapeutic strategies for HCM.

Recent advancements in reprogramming technologies have enabled the development of iPSC cells from patients for disease research and drug development. Several reports have already shown the disease specific phenotypes of HCM using familial adult HCM patient-derived iPSC cells including cardiomyocyte hypertrophy accompanied by the upregulation of ANF and MYH7, disorganized sarcomeres, and abnormal calcium handling and arrhythmia. However, since iPSC cell-derived cardiomyocytes are immature, it remains an open question whether the disease specific phenotype of adult onset diseases can be recapitulated using iPSC cell-derived cardiomyocytes and infantile onset diseases might be more promising for iPSC cell-based research.

In this issue of International Heart Journal, Sakai, et al. examined the phenotype of infantile HCM using patient-derived iPSC cells. They established iPSC cells from 2 patients with idiopathic HCM and Noonan syndrome and both patients were diagnosed as HCM before birth. The large cell area and higher diastolic intracellular calcium concentration in iPSC cell-derived cardiomyocytes were identified as the phenotypes. Interestingly, they also screened drugs to attenuate these phenotypes and identified Pyr3, an inhibitor of transient receptor potential channel 3 (TRPC3), and found it decreased both the size and diastolic intracellular calcium concentration in iPSC cell-derived cardiomyocytes from both Noonan syndrome and idiopathic infantile HCM patients (Figure).

There are still some issues with respect to the development of a novel therapeutic strategy for HCM. Pyr3 attenuated the enlargement of cell size of HCM iPSC cell-derived cardiomyocytes with unknown mechanisms. Cardiomyocyte hypertrophy is the promising phenotype of HCM and massive left-ventricular hypertrophy is one of the risk factors for sudden cardiac death in HCM patients. However, it remains unclear whether cardiomyocyte hypertrophy in HCM is the main cause of the disease or the result of the adaptive responses for some conditions including genetic disorders. It has been reported that treatment with MYK-461, a novel compound that reduces contractility by decreasing the adenosine triphosphatase activity of the cardiac myosin heavy chain, attenuated hypertrophy and inhibited fibrosis in a human HCM mouse model, indicating that hyperdynamic contraction is essential for HCM pathophysiology and that the inhibition of sarcomere contraction attenuates cardiomyocyte hypertrophy, which leads to fibrosis prevention. If Pyr3-mediated attenuation of cardiomyocyte hypertrophy inhibits apoptosis of cardiomyocytes, treatment with Pyr3 may inhibit the progression to end-stage HCM.

Diastolic dysfunction is the leading cause of heart failure in HCM and a recent report has indicated that the diastolic function parameter might be the predictor of out-...
The phenotypes of infantile HCM iPS cell-derived cardiomyocytes and the efficacy of Pyr3. Infantile HCM iPS cell-derived cardiomyocytes showed a large cell area and increased diastolic intracellular calcium concentrations compared with control iPS cell-derived cardiomyocytes. Isoproterenol further increased the cell area and the diastolic intracellular calcium concentration in infantile HCM iPS cell-derived cardiomyocytes. Treatment with Pyr3 normalized such morphological and physiological disease-specific phenotypes through TRPC3 dependent or unknown mechanisms.

Figure

come in HCM patients. Although Pyr3 also attenuated the higher diastolic intracellular calcium concentration in HCM iPS cell-derived cardiomyocytes, it also remains unclear whether Pyr3 can attenuate diastolic dysfunction in HCM. Recent advancements in tissue engineering technology provide the functional evaluation platform of human cardiac tissues containing cardiomyocytes and fibroblasts. As bioengineered cardiac tissues can be used for direct contractile force measurement, it will be necessary to assess the effects of Pyr3 on the diastolic function of iPS cell-derived cardiac tissues from healthy volunteers and HCM patients. Several groups have reported increased contraction rates in bioengineered cardiac tissues using iPS cell-derived cardiomyocytes from HCM patients with the BRAF mutation and PRKAG2 mutation, while an increased relaxation rate has also been reported in iPS cell-derived cardiac tissues from patients with the BRAF mutation. Therefore, diastolic dysfunction might not be recapitulated in iPS cell-derived cardiac tissues from some genetic disorders. Diastolic function is not only regulated by the cardiomyocyte relaxation speed but also myocardium stiffness. Native T1 mapping and extracellular volume fraction in cardiac MRI study have been reported to be significantly higher in HCM compared with patients with hypertensive heart disease, suggesting that diastolic dysfunction might be enhanced by fibrosis in HCM. Since fibroblasts were reported to be converted to fibrotic phenotypes in pathological conditions, a fibrotic cardiac tissue model will be useful for evaluating diastolic dysfunction of HCM.

Unfortunately, the precise mechanisms of Pyr3 on HCM iPS cell-derived cardiomyocytes remain elusive. Since Btp2, another TRPC3 inhibitor that also has an inhibitory effect on store operated calcium entry, did not show any effect on HCM iPS cell-derived cardiomyocytes, the effects of Pyr3 might be regulated by TRPC3 independent mechanisms. However, the findings in the current study have provided the key target compound to attenuate cardiomyocyte hypertrophy and impaired diastolic calcium homeostasis in infantile HCM iPS cell-derived cardiomyocytes. Understanding the Pyr3-mediated downstream signaling pathway in HCM iPS cell-derived cardiomyocytes will hopefully lead to the identification of the factor responsible for cardiomyocyte hypertrophy and diastolic dysfunction in HCM and the subsequent development of novel therapies.

Disclosures

Conflicts of interest: None.

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