ENDOTHELIN-1 IS A KEY CANDIDATE TO EXERT PATHOPHYSIOLOGICAL EFFECTS ON CARDIOMYOCYTES DERIVED FROM HYPERTROPHIC CARDIOMYOPATHY-INDUCED PLURIPOTENT STEM CELL

Oral Contributions
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Background: Despite the accumulating genetic and molecular research into hypertrophic cardiomyopathy (HCM), it remains unclear how this condition develops and worsens pathologically and clinically in terms of the genetic-environmental interactions. Establishing human disease models for HCM would help us to clarify the disease mechanisms. Patient-specific induced pluripotent stem cells (iPSC) thus hold much promise for this task.

Methods: We generated iPSCs from three patients with HCM and three healthy-control subjects. To identify candidate disease-promoting environmental factors, the cardiomyocytes differentiated from each iPSC line were stimulated by several cardiomyocyte hypertrophy-promoting factors. The HCM pathological phenotypes were examined based on the morphological properties, such as cell size and intracellular myofilament structures, in randomly chosen cardiac troponin-T-positive single cardiomyocytes. Moreover, high-speed video imaging with motion vector prediction algorithm revealed physiological contractile dynamics in the iPSC-derived single cardiomyocytes.

Results: Control- and HCM-iPSC-derived cardiomyocytes were similar under the basal condition in pathological features and contractile dynamics. However, only the HCM-iPSC-derived cardiomyocytes showed pathological phenotypes such as cardiomyocyte hypertrophy and increased intracellular myofilament disorganization in the presence of endothelin-1 (ET-1) induction with a dose-dependent manner. Physiological analyses revealed that self-beating HCM-iPSC-derived cardiomyocytes stimulated by ET-1 showed variable contractile directions. Finally, inhibiting the endothelin type-A receptor rescued these deleterious effects.

Conclusions: Interactions between genetic backgrounds and the environmental factor, ET-1, promote the HCM pathological phenotypes and contractile variability in iPSC-derived cardiomyocytes. Our results may push ahead with the developments of novel therapeutic strategy focused on the underlying pathogenesis of HCM.