Cardiac Sodium Channel Disease Modeling Using Patient-Derived Induced Pluripotent Stem Cells

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Human induced pluripotent stem cells (hiPSCs) were first established more than 10 years ago, and have now been applied in regenerative medicine, drug development, and disease modeling. Human cardiac cells are ideal for cardiovascular disease (CVD) modeling; however, obtaining cardiac tissue from patients is highly invasive and in vitro maintenance of adult cardiomyocytes (CMs) is difficult. In contrast, hiPSCs can be developed from any individual, so it is possible to miniaturize the disease in a dish, thus obtaining the disease-causing cells by differentiation of patient-derived hiPSCs. In the cardio-
vascular field, the use of patient-derived hiPSCs has been reported in several diseases such as arrhythmias and cardiomyopathies as well as metabolic disorders. Furthermore, because of the dramatic advances in gene-editing technology, we can now investigate the precise disease-causing mechanisms by correcting the disease-causing mutations. Thus, hiPSC technology is a new tool for understanding disease mechanisms, investigating genotype-phenotype correlations, and developing novel therapeutic strategies (Figure).

Cardiac voltage-gated sodium channel Nav1.5, encoded by SCN5A, carries the inward sodium current, which is responsible for the rapid upstroke of the action potential in CMs and consequently for proper cardiac excitability and impulse propagation. Mutations in SCN5A have been reported to cause various cardiac arrhythmias with or without dilated cardiomyopathies. In this issue of the Journal, Hayano et al report on the generation of iPSCs from the cells of a patient with SCN5A missense mutation D1275N, which did not result in major differences in the biophysical properties of the channel, compared with the wild-type channels in vitro. The clinical manifestations of this mutation were sinus node dysfunction and atrioventricular block. The authors report that SCN5A-D1275N hiPSC-derived CMs showed reduced sodium channel protein expression and maximum sodium conductance. Furthermore, the authors show that treatment with the proteasome inhibitor MG132 rescued the membrane Nav1.5 protein levels, suggesting ubiquitin-dependent proteolysis as the underlying mechanism for the loss of Nav1.5 function in cells with the D1275N mutation. This report clearly shows the advantage of an hiPSC system over human embryonic kidney (HEK) 293 cell-based heterologous expression system. The same group recently reported that hiPSC-CMs derived from patients with long QT syndrome 15 recapitulated the disease phenotype, and ablation of the mutant allele rescued the electrophysiological abnormalities. As shown by these reports, the hiPSC system is a powerful tool to investigate disease mechanisms.

Although patient-derived hiPSC-CMs have recapitulated the phenotypes of CVDs, there are several limitations to the use of these cells. First, hiPSC-CMs are immature compared with adult CMs. Furthermore, the biophysical properties of the ion currents of hiPSC-CMs and human adult CMs are different. Therefore, hiPSC-CMs can be used for early-onset diseases such as inherited channelopathies but not for late-onset diseases. Second, per the current differentiation protocols, hiPSC-CMs are a mixture of nodal, atrial, and ventricular cells. We can distinguish them by their electrophysiological characteristics, but we need to purify the specific subtype of the disease-causing cells; for example, nodal cells for cardiac conduction diseases. Third, the heart is a complex organ comprised of CMs and non-CMs such as fibroblasts, smooth muscle cells, and epicardial cells; therefore, we need to use multicellular or 3-dimensional systems to recapitulate diseases with diverse phenotypes. Thus, although hiPSC technology has provided a great opportunity to investigate CVDs, further studies are necessary to overcome these limitations.

References