Topic: Arrhythmia (Basic), Electrophysiology**Cell-specific Mathematical Modelling of hiPSC-CMs and Its Potential for Prediction of Drug Testing**

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Background

Human induced pluripotent stem cells-derived cardiomyocytes (hiPSC-CMs) are expected tool for preclinical evaluation of the safety and efficacy of compounds on the heart. Its action potential (AP) parameters were measured in order to estimate pro-arrhythmic effects of new drugs, mutation of ion-channels, and so on. But, hiPSC-CMs exhibit varying AP morphologies, and even exhibit paradoxical reaction for some compounds.

Hypothesis

Variations of APs of hiPSC-CMs express their total balance of ion-currents, and might affect the result of drug-testing. So, in order to interpret the results of drug-testing using hiPSC-CMs platform accurately, cell-specific precise mathematical modelling of hiPSC-CMs may be useful.

Methods

We developed novel hiPSC-CMs mathematical models based on HuVEC model (Asakura et al, 2014), adopting experimental data of

ionic channels. We recorded APs from 40 hiPSC-CMs, and reproduced all AP morphologies simulationally by changing conductance of each ion current. After that, *in silico* IKr-blocking test was performed.

Results

All 40 AP morphologies were successfully recapitulated within 5 % error range. In simulational IKr-blocking test, AP duration (APD) prolongation was observed in 15 cells (37.5%). In 21 cells, APD prolongation and rising of maximum diastolic potential (MDP) was observed. In 4 cells, APD shortening and rising of MDP was observed. All APD shortening cell has morphological character of MDP > -68.0 mV.

Conclusion

Our new mathematical models can reproduce experimental AP morphology precisely. To interpret the results of hiPSC-CMs drug testing appropriately, cell-specific computer simulation is very useful. ■