iPSC-CM (Cardiomyocytes derived from iPS Cells) as A Platform for the Study of Inherited Arrhythmias
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How can we take advantage of iPSC-CMs from both healthy individuals and patients?

1. Elucidation of mechanism(s) underlying unknown diseases
2. Drug Development and Repositioning
3. Drug Sensitivity Testing
4. Drug Toxicity Testing
5. Regenerative Medicine
6. Gene Therapy (including new drugs and gene editing technique)
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**<hiPSC generation>**

- Human induced pluripotent stem cell lines were generated from healthy individuals or pts by retrovirally infected with OCT3/4, SOX2, Klf4 and c-Myc. (Takahashi K, Yamanaka S, et al. Cell. 2007)

**<Cardiomyocyte differentiation>**

- Cardiomyocyte differentiation was conducted through embryoid body (EB) formation as follows. (Dubois NC, et al. Nature. 2011)
iPS-derived CM
Endoderm  Mesoderm  Ectoderm

24 yo female, cardiac Na channelopathy
New Therapeutic Strategies:
iPSC-CM can be a platform of drug development

Hayano et al. Development of a Patient-Derived Induced Pluripotent Stem Cell Model for the Investigation of SCN5A-D1275N-Related Cardiac Sodium Channelopathy. Circ J 2017
A famous missense mutation associated with various phenotypes: DCM, cardiac conduction disease, atrial/ventricular tachyarrhythmias, and cerebral stroke. (Groenewegen et al., Circ Res 2003)
On our survey of 50 Japanese carriers of D1275N mutation, 40 (85%) had arrhythmias (both brady and tachy), and 6 presented both arrhythmias and DCM.

Early onset of arrhythmias (~80% by 35yo). 50% received PMI due to CCD. 50% had atrial tachycardia.

Stroke occurred in 12 (24%) at young age (31yo)
SCN5A-D1275N-Related Cardiac Sodium Channelopathy: family presentation

Family tree

AF
(+)

(−)

Cl

24 F

Filled symbols indicate PMI.
(+): SCN5A D1275N positive
Proband’s father had AF, and her younger brother had cerebral infarction.

Proband’s 12-lead ECG

Marked junctional bradycardia (HR 33 bpm)
Holter ECG: Sinus arrest >12 sec and AV block
iPS-derived CM

(Courtesy of Dr T. Makiyama)

Intracellular Ca signaling detected by a Ca-sensitive fluorescent dye
SCN5A-D1275N-Related Cardiac Sodium Channelopathy

Spontaneous beating rate of EBs

Western blotting of Nav1.5 Protein expression level

mRNA expression level of SCN5A transcripts

A

B

C

***P<0.001

*P<0.05
Patch-clamp data on single iPSC-CMs were consistent with results of Nav1.5 protein expression experiments.
Where can the disorder happen?

Promoter
Transcription factors

Nucleus

DNA

Splicing

Translation

Transport

Degradation: Ubiquitin-proteasome system

Cell Membrane

(Shimizu W and Horie M, Circ Res, 2011)
MG132, a proteasome inhibitor, restored NaV1.5 cell membrane expression up to those of the controls.
Summary of iPSC-CM as a study platform

Promoter
Transcription factors

Nucleus

(1) Splicing

(2) Transport

(3) Degradation: Ubiquitin-proteasome system

(4) Translation

DNA

(Shimizu W and Horie M, Circ Res, 2011)
Conclusions

1). Development of iPSC-derived CMs is now well advanced, offering a promising platform of human origin for better understanding of the functional significance of inherited diseases including inherited arrhythmias.

2). It also serves as a platform for the assessment of therapeutic agents.
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