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Editorial

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Human induced pluripotent stem cell–derived endothelial cells for modelling of endothelial dysfunction

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Abstract

Human induced pluripotent stem cells (hiPSCs) cells are a type of cells derived from human somatic cells that are reprogrammed to an embryonic stem cell (ESC)–like pluripotent state. hiPSCs are being explored as disease modelling and drug discovery for diabetes mellitus. Modelling endothelial dysfunction using endothelail cells (ECs) derived from diabetic hiPSCs has the potential for evaluating the therapeutic effect of drugs or chemicals on endothelial dysfunction and for understanding the cross-talk between ECs and inflammatory cells or cytokines which will benefit the development of new therapeutic strategies for treatment of cardiovascular diseases.

Editorial

Human induced pluripotent stem cells (hiPSCs), a type of cells derived from human somatic cells, are reprogrammed to an embryonic stem cell (ESC)-like pluripotent state [1]. hiPSCs not only hold potential to provide immunologically compatible autologous cells for "personalized" cell transfer therapy, they also offer an opportunity for modelling human disease in cell culture dish to screen and identify drugs for treatment of inherited and acquired diseases. The differentiated cells from disease specific hiPSCs retain disease-related phenotypes which can be served as an in vitro model of pathogenesis. This provides an provides an innovative way to explore the molecular mechanisms of diseases [2].

Disease-specific hiPSC-ECs have been generated to study disease mechanisms or to screen drugs. Various disease-specific hiPSC lines have been generated and reported, including Moyamoya disease [3], fibrodysplasia ossificans progressive [4], the bone morphogenetic protein receptor type II (BMPR2) mutation [5], type 1 diabetes mellitus [6], type 2 diabetes mellitus [6], Huntington's disease [7], Kawasaki disease [8], atrial or ventricular septal defects, pulmonary valve stenosis, cardiomyopathy [9], calcified aortic valve disease [10], and hemophilia A [11]. They provide a unique opportunity to study underlying mechanisms of disease pathophysiology and establish a platform for high-throughput drug screening and toxicity testing.

Human iPSCs have been successfully differentiated into vascular cells, including endothelial cells (iECs) [12,13] and smooth muscle cells (iSMCs) [14]. Earlier iEC differentiation protocol involved co-culture of hiPSCs with OP9 cells [15]. More recently, efficient iEC differentiation protocols, either 2-or 3-dimensional system, with defined factors have been developed [12,13,16,17]. iECs have typical EC characterizations: they express a panel of EC cell surface markers, such as CD31, CD144 and vWF-VIII, are able to uptake low-density lipoprotein and form tubular structure *in vitro* [12,13]. A large number of iECs can be obtained from hiPSCs and be used for treatment of peripheral artery disease, acute and chronic heart failure, stroke and certain forms of retinopathy associated with endothelial dysfunction to promote the repair of injured tissue.

The vascular ECs play an important role in cardiovascular homeostasis through paracrine factors that regulate vascular tone, fibrinolysis, cell adhesion, and blood flow [18,19]. It is known that endothelial dysfunction is a risk factor for cardiovascular disease (CVD). The iECs differentiated from iPSCs, which were reprogrammed from fibroblasts of mouse with diet-induced obesity, exhibited signs of endothelial dysfunction and had poor treatment efficacy following transplantation in a hind limb ischaemia model [20]. iPSCs from db/db mouse had impaired differentiation into CD34/Tie2 expressing endothelial progenitor-like cells and reduced angiogenic potential [21].

Modelling endothelial dysfunction using human diabetic iECs can be used to evaluate the therapeutic effect of drugs or chemicals on endothelial function and to understand the cross-talk between ECs and inflammatory cells or cytokines which will benefit the development of new therapeutic strategies for treatment of cardiovascular diseases.

Although much progress has been achieved recently, challenges remain in variability of generating different subtypes of iECs, stability of iEC expansion in vitro, and improving iEC function for treatment of ischemic disease, especially iECs differentiated from disease-specific hiPSCs [22].

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Declaration of interest

The authors declare that there is no conflict of interest.

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References

1. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, et al. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 131: 861-872.

2. Kawser Hossain M, Abdal Dayem A, Han J, Kumar Saha S, Yang GM, et al. (2016) Recent Advances in Disease Modeling and Drug Discovery for Diabetes Mellitus Using Induced Pluripotent Stem Cells. *Int J Mol Sci* 17: 256.

3. Hamauchi S, Shichinohe H, Uchino H, Yamaguchi S, Nakayama N, et al. (2016) Cellular Functions and Gene and Protein Expression Profiles in Endothelial Cells Derived from Moyamoya Disease-Specific iPS Cells. *PloS one* 11: e0163561.

4. Barruet E, Morales BM, Lwin W, White MP, Theodoris CV, et al. (2016) The ACVR1 R206H mutation found in fibrodysplasia ossificans progressiva increases human induced pluripotent stem cell-derived endothelial cell formation and collagen production through BMP-mediated SMAD1/5/8 signaling. *Stem Cell Res Ther* 7: 115.

5. Gu M, Shao NY, Sa S, Li D, Termglinchan V, et al. (2017) Patient-Specific iPSC-Derived Endothelial Cells Uncover Pathways that Protect against Pulmonary Hypertension in BMPR2 Mutation Carriers. *Cell stem cell* 20: 490-504.

6. Teo AK, Gupta MK, Doria A, Kulkarni RN (2015) Dissecting diabetes/metabolic disease mechanisms using pluripotent stem cells and genome editing tools. *Mol Metab* 4: 593-604.

7. Lim RG, Quan C, Reyes-Ortiz AM, Lutz SE, Kedaigle AJ, et al. (2017) Huntington's Disease iPSC-Derived Brain Microvascular Endothelial Cells Reveal WNT-Mediated Angiogenic and Blood-Brain Barrier Deficits. *Cell Rep* 19:1365-1377.

8. Ikeda K, Mizoro Y, Ameku T, Nomiya Y, Mae SI, et al. (2016) Transcriptional Analysis of Intravenous Immunoglobulin Resistance in Kawasaki Disease Using an Induced Pluripotent Stem Cell Disease Model. *Circulation journal: official journal of the Japanese Circulation Society* 81: 110-118.

9. Ang YS, Rivas RN, Ribeiro AJS, Srivas R, Rivera J, et al. (2016) Disease Model of GATA4 Mutation Reveals Transcription Factor Cooperativity in Human Cardiogenesis. *Cell* 167: 1734-1749.

10. Theodoris CV, Li M, White MP, Liu L, He D, et al. (2015) Human disease modeling reveals integrated transcriptional and epigenetic mechanisms of NOTCH1 haploinsufficiency. *Cell* 160: 1072-1086.

11. Wu Y, Hu Z, Li Z, Pang J, Feng M, et al. (2016) In situ genetic correction of F8 intron 22 inversion in hemophilia A patient-specific iPSCs. *Sci Rep* 6: 18865.

12. Su L, Kong X, Lim S, Loo S, Tan S, et al. (2018) The prostaglandin H2 analog U-46619 improves the differentiation efficiency of human induced pluripotent stem cells into endothelial cells by activating both p38MAPK and ERK1/2 signaling pathways. *Stem Cell Res Ther* 9: 313.

13. Zhang S, Dutton JR, Su L, Zhang J and Ye L (2014) The influence of a spatiotemporal 3D environment on endothelial cell differentiation of human induced pluripotent stem cells. *Biomaterials* 35: 3786-3793

14. Maguire EM, Xiao Q, Xu Q (2017) Differentiation and Application of Induced Pluripotent Stem Cell-Derived Vascular Smooth Muscle Cells. *Arterioscler Thromb Vasc Biol* 37: 2026-2037.

15. Choi KD, Yu J, Smuga-Otto K, Salvagiotto G, Rehrauer W, et al. (2009) Hematopoietic and endothelial differentiation of human induced pluripotent stem cells. *Stem Cells* 27: 559-567

16. Lee SJ, Sohn YD, Andukuri A, Kim S, Byun J, et al. (2017) Enhanced Therapeutic and Long-Term Dynamic Vascularization Effects of Human Pluripotent Stem Cell-Derived Endothelial Cells Encapsulated in a Nanomatrix Gel. *Circulation* 136: 1939-1954.

17. Liu X, Qi J, Xu X, Zeisberg M, Guan K, et al. (2016) Differentiation of functional endothelial cells from human induced pluripotent stem cells: A novel, highly efficient and cost-effective method. *Differentiation: research in biological diversity* 92: 225-236.

18. Messner B and Bernhard D (2014) Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol* 34: 509-515.

19. Lee WH, Ong SG, Zhou Y, Tian L, Bae HR, et al. (2019) Modeling Cardiovascular Risks of E-Cigarettes with Human-Induced Pluripotent Stem Cell-Derived Endothelial Cells. *Journal of the American College of Cardiology* 73: 2722-2737.

20. Gu M, Mordwinkin NM, Kooreman NG, Lee J, Wu H, et al. (2015) Pravastatin reverses obesity-induced dysfunction of induced pluripotent stem cell-derived endothelial cells via a nitric oxide-dependent mechanism. *Eur Heart J* 36: 806-816.

21. Stepniewski J, Kachamakova-Trojanowska N, Ogrocki D, Szopa M, Matlok M, et al. (2015) Induced pluripotent stem cells as a model for diabetes investigation. *Sci Rep* 5: 8597.

22. Carcamo-Orive I, Huang NF, Quertermous T and Knowles JW (2017) Induced Pluripotent Stem Cell-Derived Endothelial Cells in Insulin Resistance and Metabolic Syndrome. *Arterioscler Thromb Vasc Biol* 37: 2038-2042.