**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 endothelial 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 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 progressiva [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].
Declaraton of interest
The authors declare that there is no conflict of interest.

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