Human induced pluripotent stem cells (iPSCs) represent promising cell resource for disease modeling, drug screening and regenerative medicine. Since iPSCs are originally derived from somatic cells, tissue-specific epigenetic memory has been observed in early passage iPSCs, which may interfere with the directed differentiation towards target lineages. For example, blood-derived iPSCs have greater differentiation efficiency towards hematopoietic lineage than fibroblast-derived iPSCs, whereas beta cell-derived iPSCs have increased ability to differentiate into insulin-producing cells when compared to the isogenic non-beta iPSCs or ESCs. The somatic epigenetic memory of tissue-of-origin may be somewhat diluted with extensive passaging. However, extensive culture doesn’t significantly improve the epigenetic resemblance of iPSCs to authentic embryonic stem cells. Here we derived human iPSC from three types of somatic cells from the same individuals: fibroblast (FB-iPSCs), endothelial (EC-iPSCs) and cardiac progenitor cells (CPC-iPSCs). We then differentiated these iPSCs into endothelial cells and compared their molecular characteristics and functional behaviors in vivo and in vitro.

**Methods & Materials**

Donor cell isolation: human fibroblast, endothelial cells and cardiac progenitor cells were derived from the skin, aorta and heart of two aborted fetuses, respectively. The CPCs were enriched by using Sca1 coupled magnetic beads.

Human iPSC generation: human FBs, ECs and CPCs were reprogrammed by lentiviral infection with a vector carrying OCT4, SOX2, KLF4 and C-MYC transgenes.

EC differentiation: hiPSCs were first induced to embryoid bodies (EBs) by depletion of bFGF and then differentiated into EC lineage by sequential activation of Activin, BMP4, bFGF and VEGF. EBs were harvested on day 14 and sorted by FACS using CD31/CD144 double monoclonal antibodies.

Hindlimb ischemia model: hiPSCs were tagged with a triple fusion construct carrying Fluc, RFP and HSVtk. One million cells were intramuscularly injected around ischemic area and monitored by optical bioluminescence.

Single-cell qPCR: single cells were captured by using C1 single cell auto-prep arrays and then single-cell qPCRs were conducted on Biomark 48.48 Dynamic Array chips using the Biomark HD system (Fluidigm).

**Conclusions**

- Early-passage EC-iPSCs have higher differentiation propensity toward CD31+ endothelial cell lineage than FB-iPSCs and CPC-iPSCs. However, the biased differentiation propensity diminishes with extensive passaging.
- EC-iPSCs show higher EC-specific marker gene expression and EC identity maintenance with extensive culture than FB-iPSCs and CPC-iPSCs.
- Upon transplantation, EC-iPSCs exhibit greater revascularization capacity than those of FB-iPSCs and CPC-iPSCs in a mouse ischemic hindlimb model.
- In vivo transplanted EC-iPSCs maintain higher percentage of CD31+ population and stronger EC marker gene expression.

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