Human heart-on-a-chip microphysiological system comprising endothelial cells, fibroblasts, and iPSC-derived cardiomyocytes

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Abstract

In recent years, research on organ-on-a-chip technology has been flourishing, particularly for drug screening and disease model development. Fibroblasts and vascular endothelial cells engage in crosstalk through paracrine signaling and direct cell-cell contact, which is essential for the normal development and function of the heart. Therefore, to faithfully recapitulate cardiac function, it is imperative to incorporate fibroblasts and vascular endothelial cells into a heart-on-a-chip model. Here, we report the development of a human heart-on-a-chip composed of induced pluripotent stem cell (iPSC)-derived cardiomyocytes, fibroblasts, and vascular endothelial cells. Vascular endothelial cells cultured on microfluidic channels responded to the flow of culture medium mimicking blood flow by orienting themselves parallel to the flow direction, akin to *in vivo* vascular alignment in response to blood flow. Furthermore, the flow of culture medium promoted integrity among vascular endothelial cells, as evidenced by CD31 staining and lower apparent permeability. The tri-culture condition of iPSC-derived cardiomyocytes, fibroblasts, and vascular endothelial cells resulted in higher expression of the ventricular cardiomyocyte marker IRX4 and increased contractility compared to the bi-culture condition with iPSC-derived cardiomyocytes and fibroblasts alone. Such tri-culture-derived cardiac tissues exhibited cardiac responses similar to *in vivo* hearts, including an increase in heart rate upon noradrenaline administration. In summary, we have achieved the development of a heart-on-a-chip composed of cardiomyocytes, fibroblasts, and vascular endothelial cells that mimics *in vivo* cardiac behavior.

Keywords: induced pluripotent stem cells, fibroblasts, endothelial cells, heart, heart-on-a-chip, organ-on-a-chip