Dissecting the Left Heart Hypoplasia by Pluripotent Stem Cells

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Keywords
Hypoplastic left heart syndrome • Pluripotent stem cells • Disease modeling

The genetic background of hypoplastic left heart syndrome (HLHS) is still unknown. Cardiac differentiation from pluripotent stem cells (PSCs) can recapitulate the cardiogenesis in vitro, and PSC technology could be useful to dissect the diseases with the complex mechanisms. In the past few years, some researches were reported to seek the pathogenesis of HLHS by using PSCs. This paper reports the achievements.

1. Gaber N et al. showed that human embryonic stem cells (hESCs) during cardiovascular lineage with hypoxia recapitulated the phenotype of the HLHS heart, which was characterized by increased expression of the oncogenes and TGF-ß1, damaged DNA, and senescence with cell cycle arrest [1]. The phenotypes were rescued by TGF-ß1 inhibition.
2. Jiang Y et al. generated disease-specific induced pluripotent stem cells (iPSCs) from a patient with HLHS [2]. HLHS-iPS-derived cardiomyocytes demonstrated repression of MESP1, TNNT2, and delayed expression of GATA4 compared with hESCs and control-iPSCs. HLHS-iPS-derived cardiomyocyte showed calcium oscillation under caffeine and inositol trisphosphate receptor upregulation, presumably as a result of ryanodine receptor dysfunction.

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T. Nakanishi et al. (eds.), *Etiology and Morphogenesis of Congenital Heart Disease*,
DOI 10.1007/978-4-431-54628-3_47

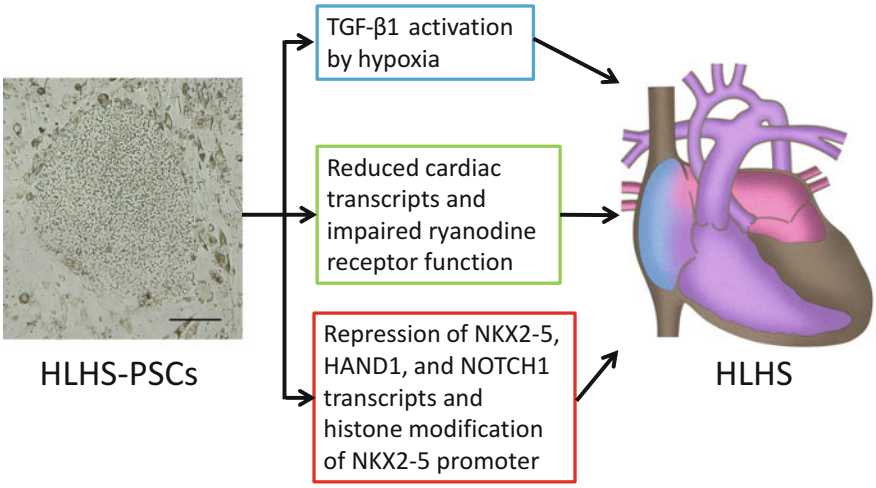

Fig. 47.1 PSC technology models HLHS. Three possible mechanisms of HLHS were unveiled by PSCs. Bar, 200 μm

3. Kobayashi J et al. generated five HLHS-iPSC lines and found repression of the transcripts such as NKX2-5, HAND1, HAND2, NOTCH1, HEY1, HEY2, and TBX2 in HLHS-iPS-derived cardiomyocytes [3]. The promoter activities of SRE, TNNT2, and NPPA were suppressed in HLHS-derived cardiac progenitor cells and iPSCs compared with those from bi-ventricle (BV). All promoter activities of both cell types could be fully restored by co-transfection of NKX2-5, HAND1, and NOTCH1, and co-transfection of the shRNAs into BV-derived cells reduced the promoter activation. HLHS-derived cardiomyocytes demonstrated repressed H3K4me2 and acH3 and increased H3K27me3 in NKX2-5 promoter, implying suppressed NKX2-5 promoter activity.

Taken together, the PSC technology can be useful to dissect the complex heart diseases. Further investigation using this technique is necessary to determine the pathogenesis of HLHS (Fig. 47.1).

References

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