Roles of Endothelial Hrt Genes for Vascular Development

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Masahide Sakabe, Takashi Morioka, Hiroshi Kimura, and Osamu Nakagawa

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Notch signaling • Vascular development • Endothelial cells

Various cellular signaling pathways play essential roles in regulating embryonic vascular development. Among them, Notch signaling is implicated in arterial endothelium differentiation and vascular morphogenesis. Mice that lack Notch receptors or other signaling components die in utero due to severe vascular abnormalities. We previously identified the Hairy-related transcription (Hrt) factor family, also called Hey, Hesr, CHF, Herp, and Gridlock, as downstream mediators of Notch signaling in the developing vasculature [1]. The Hrt family proteins, Hrt1/Hey1, Hrt2/Hey2, and Hrt3/HeyL, mainly act as transcriptional repressors, by binding to consensus DNA elements or by associating with other DNA-binding transcription factors. The mice deficient for *Hrt2* showed perinatal lethality due to ventricular septal defects and mitral valve insufficiency, and cardiomyocyte-specific deletion of *Hrt2* caused abnormal expression of atrial-specific genes in the ventricle and cardiac dysfunction in adulthood [2].

M. Sakabe • O. Nakagawa (✉)
Laboratory for Cardiovascular System Research, Nara Medical University Advanced Medical Research Center, 840 Shijo-cho, Kashihara, Nara 634-8521, Japan
e-mail: osamu.nakagawa@ncvc.go.jp

T. Morioka
Laboratory for Cardiovascular System Research, Nara Medical University Advanced Medical Research Center, 840 Shijo-cho, Kashihara, Nara 634-8521, Japan

Second Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

H. Kimura
Second Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

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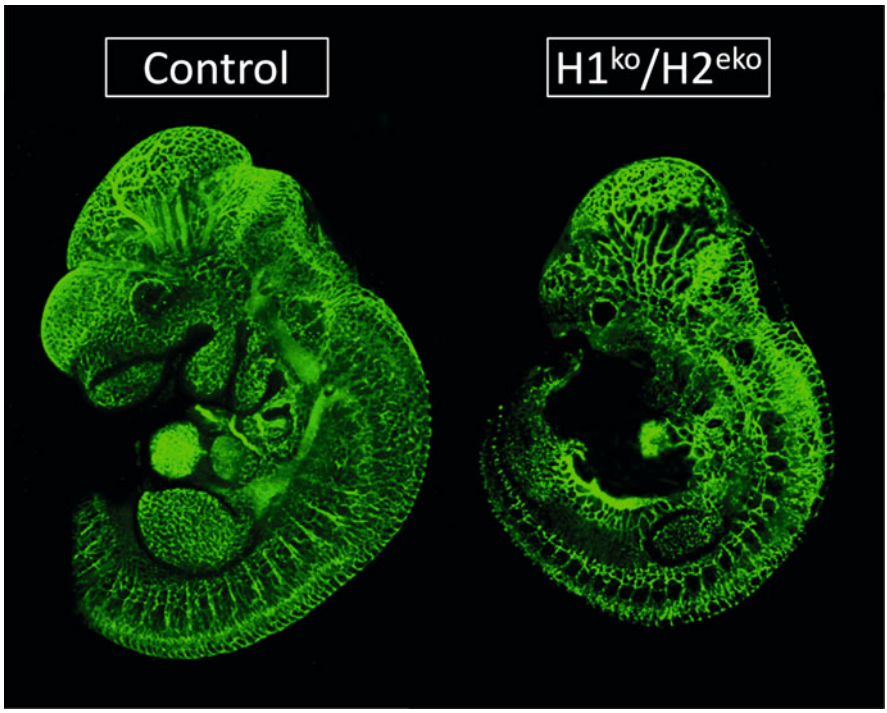

Fig. 31.1 The mice in which *Hrt2* was deleted specifically in endothelial cells with the global *Hrt1* null background ($H1^{ko}/H2^{eko}$) show embryonic lethality with severe defects of vascular morphogenesis. Whole mount PECAM1 immunostaining demonstrated impairment of vascular network formation in $H1^{ko}/H2^{eko}$ embryos

It was also reported that combined loss of *Hrt1* and *Hrt2* resulted in early embryonic lethality due to vascular demise similar to that observed in Notch signal-deficient embryos. While *Hrt1* and *Hrt2* are expressed in endothelial cells as well as smooth muscle cells of embryonic vasculature, it remained unclear which vascular cell type requires *Hrt1*/*Hrt2* functions. In the present study, we generated the mice with endothelial-cell-specific deletion of *Hrt2* combined with global *Hrt1* null mutation and analyzed their vascular phenotypes during embryonic development. The loss of endothelial *Hrt1*/*Hrt2* caused early vascular abnormalities virtually identical to those observed in the global *Hrt1*/*Hrt2* knockout mouse embryos (Fig. 31.1), suggesting that *Hrt* functions in endothelial cells are indispensable for normal vascular development.

References

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