TMEM100: A Novel Intracellular Transmembrane Protein Essential for Vascular Development and Cardiac Morphogenesis

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TMEM100 • BMP • ALK1 • Cardiovascular development

Among members of the TGFβ superfamily, bone morphogenetic protein (BMP) 9 and BMP10 regulate vascular endothelium differentiation and morphogenesis by activating the specific receptor complex, which consists of ALK1 (or ACVRL1), BMPR2, and endoglin. Mutations in *ACVRL1*, *BMPR2*, or *ENG* are associated with hereditary hemorrhagic telangiectasia and pulmonary arterial hypertension in humans [1, 2]. We previously identified *TMEM100* as a downstream target gene of BMP9/BMP10-ALK1 signaling pathway [3]. TMEM100 is a novel intracellular protein with two putative transmembrane domains, and its amino acid sequence is highly conserved from fish to humans.

To clarify the physiological significance of TMEM100, we generated *Tmem100*-deficient mice and found that all mutant embryos died in utero around embryonic day 10.5 (E10.5). LacZ reporter driven by the *Tmem100* locus was predominantly expressed in endothelial cells of developing arteries and endocardium. *Tmem100* null embryos showed severe vascular dysmorphogenesis and cardiac enlargement at E9.5 and massive pericardial effusion and growth retardation at E10.5 (Fig. 21.1). These phenotypic abnormalities were virtually identical to those observed in *Alk1*/*Acvrl1*-deficient mice, suggesting that *Tmem100* is an important downstream gene of BMP9/BMP10-ALK1 signaling during cardiovascular

Note: This Chapter is also related to Part VI.

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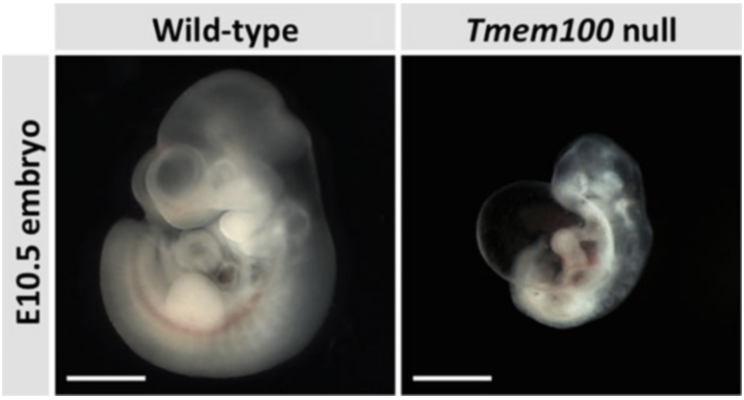

Fig. 21.1 *Tmem100* null embryos at E10.5 show severe cardiovascular dysmorphogenesis, massive pericardial effusion, and growth retardation (*scale bar*, 1 mm)

development. We also demonstrated that *Tmem100* null embryos showed atrioventricular canal cushion formation defect, indicating Tmem100 works also as an important factor for valve and septum morphogenesis.

Taken together, our studies indicate that TMEM100 is a novel endothelial-specific protein for cardiovascular morphogenesis downstream of BMP9/BMP10-ALK1 signaling. Clarifying the function of TMEM100 will lead to a better understanding of the mechanisms of cardiovascular morphogenesis and the etiologies of human congenital diseases.

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