Significance of Transcription Factors in the Mechanisms of Great Artery Malformations

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Keywords

Congenital cardiovascular disease · Great arteries · Notch signaling

Members of the Hey transcriptional factor family are Notch target genes [1], and they have unique and redundant functions in cardiovascular development. Among them, we recently reported that Hey1 had an indispensable role for the great artery formation (Fig. 60.1) [2].

Dysfunction of several transcription factors is correlated with anomalies of the great arteries. Human *TBX1* is the gene responsible for 22q11.2 deletion syndrome, and mutant mice for *Tbx1* recapitulate the phenotypes such as interruption of aortic arch type B and right-sided aortic arch. These defects are originated from the impaired development of the fourth pharyngeal arch arteries (PAAs) at early embryonic stages, and migration, proliferation and survival of the neural crest cells are affected in *Tbx1* mutant mice [3]. Similarly, the deficiency of upstream and downstream transcription factors of Tbx1, such as Foxc2, Gbx2 and Hes1, results in abnormal great arteries.

The malformation of great arteries in *Hey1* knockout mice is also associated with the fourth PAA defect although the expression of Tbx1 and target genes as well as the behavior of neural crest cells are normal [2]. Interestingly, the tubular endothelial structure is disturbed, and the expression of a Notch ligand, Jagged1, in endothelial cells is markedly reduced in the defective fourth PAAs of *Hey1* knockout embryos (Fig. 60.1) [2], suggesting that Hey1 is necessary for the endothelial organization of the fourth PAA. Elucidating the mechanism of Hey actions, especially

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Fig. 60.1 Defects of great artery morphogenesis and pharyngeal arch artery development in *Hey1* knockout mice

tissue specificity and direct target genes, and relationship with Tbx1 pathway will provide further understanding of the fourth PAA development and related human congenital cardiovascular diseases.

References

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