Modification of Cardiac Phenotype in Tbx1 Hypomorphic Mice

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Tbx1 • Truncus arteriosus • Environmental modification

Congenital heart disease is still the leading cause of death within the first year of life. Our lab forces on understanding the morphology of congenital heart disease. Outflow tract anomalies, including abnormal alignment or septation, account for 30 % of all congenital heart disease. To solve the developmental problem of these defects, we are interested in the role of the second heart field (SHF) that gives rise to the outflow tract structure.

TBX1, a member of the T-box family of transcription factors, is a major genetic determinant of 22q11 deletion syndrome (22q11DS) in human. 22q11DS is the most frequent chromosomal microdeletion syndrome in human and characterized by abnormal development of the cardiac outflow tract, such as persistent truncus arteriosus (PTA), tetralogy of Fallot, interrupted aortic arch, and ventricular septal defects.

In the developing murine heart, Tbx1 is expressed in the SHF, but not in the cardiac neural crest cells (NCCs). Our past experiments suggested that sonic hedgehog signal was necessary for maintenance of the *Tbx1* expression in the pharyngeal mesoderm including the SHF [1]. *Tbx1* null ($Tbx1^{-/-}$) mice demonstrated PTA reminiscent of the 22q11DS heart phenotype. We generated

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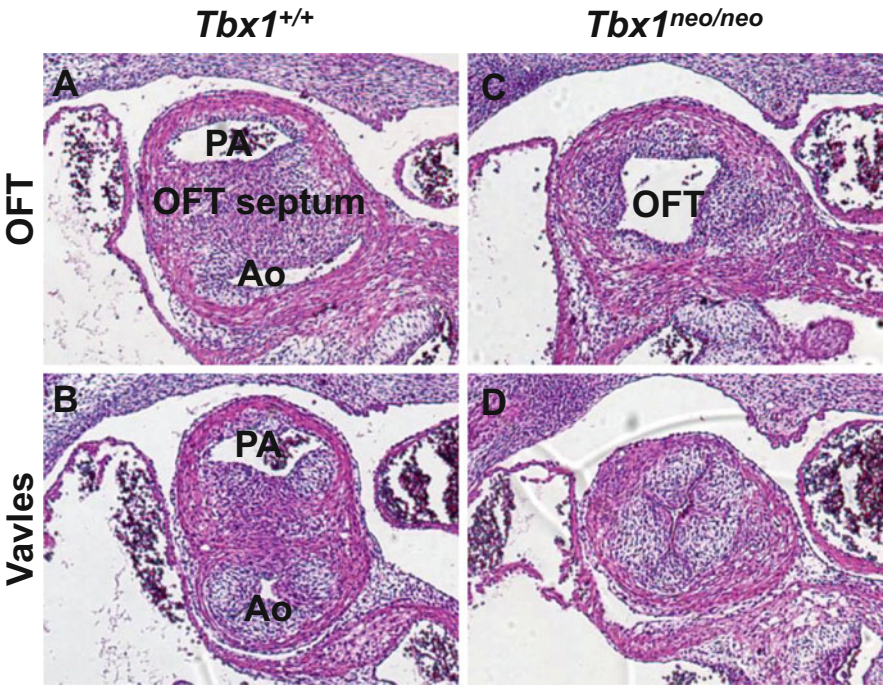

Fig. 28.1 Coronal sections of $Tbx1^{+/+}$ (**a**, **b**) and $Tbx1^{neo/neo}$ (**c**, **d**) embryos at E13.5. $Tbx1^{+/+}$ showed the normal outflow tract (OFT) septation, whereas $Tbx1^{neo/neo}$ demonstrated PTA. *Ao* Aorta, *PA* pulmonary artery

Tbx1 hypomorphic allele ($Tbx1^{neo/+}$) [2] for attempting to recapitulate the human genotype and phenotype correlation. Mice homozygous for this hypomorphic allele expressed around 25 % of Tbx1 mRNA compared to wild-type mice. We demonstrated that Tbx1 is a dosage-dependent gene and believe that the Tbx1 dosage can be affected by genetic and/or environmental modifiers because of highly variable phenotype of 22q11DS instead of the relatively uniform chromosomal microdeletion. We are trying to create the phenotype variability of PTA in this hypomorphic model (Fig. 28.1) by application of environmental modifiers. Through this study, we would better understand the interaction between the gene dosage and environmental factors during the development of outflow tract defects.

References

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