Spatiotemporally Restricted Developmental Alterations in the Anterior and Secondary Heart Fields Cause Distinct Conotruncal Heart Defects

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Mayu Narematsum and Yuji Nakajima

Abstract

During the early heart development, heart outflow tract elongates by the addition of cardiomyocytes from the anterior heart field (AHF)/secondary heart field (SHF). Dye-marking experiments in early chick embryos clarified that each AHF/SHF migrates to distinct conotruncal regions. Local administration of retinoic acid to the AHF/SHF causes distinct conotruncal heart defects in a region and stage dependent manner. For example, impaired development of AHF at HH stage 12 (corresponding to Carnegie stages 10–11 in human embryos) causes dextroposed aorta including transposition of the great arteries (TGA), while SHF at HH stage 12 persistent truncus arteriosus (PTA). Our results indicated that the abnormal development of certain AHF/SHF at certain stages causes specific spectrum of conotruncal heart defects.

Keywords

Second heart field · Heart outflow tract · Transposition of great arteries · Congenital heart defects · Retinoic acid

Developmental alterations of the heart outflow tract (OFT) cause conotruncal heart defects (CTHDs), which are often diagnosed in infants with congenital heart defects. During the early heart development, the OFT elongates by the addition of

M. Narematsum · Y. Nakajima (✉)

Department of Anatomy and Cell Biology, Graduate School of Medicine,
Osaka City University, Osaka, Japan

e-mail: narematsum@med.osaka-cu.ac.jp; yuji@med.osaka-cu.ac.jp

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Table 59.1 Conotruncal heart defects produced by local administration of RA to the AHF or SHF at early looped-heart stage in chick embryonic hearts

RA addition	At stage 12 ^a	At stage 14 ^b
To AHF	TGA, DORV	PTA
To SHF	PTA	PTA, DORV

^aCorresponding to embryonic day (ED) 8.5 in mouse and Carnegie stage 10 in human

^bED 9.0 in mouse and Carnegie stage 11 in human

cardiomyocytes from the second lineage of heart-forming regions, which reside in the first and second pharyngeal arches (anterior heart field [AHF]) as well as in the splanchnic mesoderm of the pericardial coelom in the posterior pharyngeal arches (secondary heart field [SHF]) [1]. As the arterial pole moves in the anterior-to-posterior (cranial-to-caudal) direction, the AHF is first added to the OFT followed by the SHF. Therefore, abnormal development of certain parts of the AHF or SHF at certain stages may cause specific CTHDs.

Dye-marking experiments in chick embryos at the early looped-heart stage showed that the right and left AHFs migrate ipsilaterally to form the proximal OFT, whereas SHFs migrate rotationally to form the distal OFT beneath the semilunar valves [2]. The results indicated that each AHF/SHF migrates to generate distinct conotruncal regions.

Retinoic acid (RA) is a potent teratogen to induce CTHDs. Local administration of RA to the AHF in chick embryos at early looped-heart stage (stage 12) caused a truncated OFT, thereby resulting in transposition of the great arteries (TGA) and double outlet right ventricle (DORV) (Table 59.1) [3]. The left AHF was more sensitive to RA in the development of TGA. Accordingly, the proximal OFT, especially the subpulmonic region, may play a role in conotruncal rotation to establish the left ventricle-to-aortic connection [4]. Persistent truncus arteriosus (PTA) occurred when RA was added to the SHF at stage 12 as well as to the AHF/SHF at stage 14 (Table 59.1). Accordingly, normal development of the distal OFT is necessary for conotruncal septation involving the aortico-pulmonary septum, a derivative of the cardiac neural crest. In conclusion, AHF at the early looped-heart stage, corresponding to Carnegie Stages 10–11 in human embryos, is the region responsible, and impediment of which causes a dextroposed aorta including TGA.

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