Part II
Left-Right Axis and Heterotaxy Syndrome

Perspective

Bradley B. Keller

The generation of a unique left-right patterning is essential to higher organisms with complex multicellular organs, and errors in patterning represent the origins of some of the most complex forms of congenital heart disease (CHD). Our understanding of these heterotaxy-related syndromes has evolved from initial clinicopathologic correlates over a century ago to the generation and investigation of model organisms (fly, frog, mouse) and the subsequent identification and validation of patterning-related genes and pathways critical for normal human development and responsible for disease states.

Dr. Shiraishi reviews human heterotaxy syndromes associated with CHD, providing a broad overview of the role of cilia, molecular mechanisms involved in left-right patterning, and associated clinical features. Early asymmetric expression of critical morphogens in left-right patterning (Nodal, Lefty2, Pitx2) is required for normal development, and errors in the expression of these morphogens result in patterning errors. Heterotaxy-related CHD is often associated with unbalanced development of the ventricles, resulting in variations of “single ventricle” physiology and requiring staged surgical palliation to separate the venous and systemic circulations. Children and adults with palliated single ventricle physiology, including heterotaxy patients, face a range of medical complications related to cardiac dysfunction and the consequences of increased central venous pressure and reduced cardiac performance. As highlighted by Dr. Shiraishi, large gaps in our

B.B. Keller, M.D. (*)
Division of Pediatric Heart Research, Cardiovascular Innovation Institute, Louisville, KY, USA
Department of Pediatrics, University of Louisville, 302 East Muhammad Ali Blvd, Louisville 40202, KY, USA
e-mail: Brad.Keller@louisville.edu
understanding of the pathogenesis of heterotaxy syndromes and their optimal medical and surgical management still exist. Hopefully, readers of these chapters will be intrigued and encouraged to pursue solutions.

Dr. Hamada provides an update on the investigation of cilia-mediated flow patterns during early embryogenesis. Motile cilia generate unique extraembryonic flow patterns that mechanically condition non-motile cilia in the ventral node, impact subsequent morphogenesis, and can be explored in fly and mouse model systems. Several key morphoregulatory pathways including agonists and antagonists of noncanonical Wnt signaling and stretch-sensitive Pkd Ca^{2+} channels are clearly involved.

Dr. Shibata and colleagues share some interesting findings on the association of heterotaxy/polysplenia syndrome, single gene mutations in several patterning genes, including BMPR2, and pulmonary artery hypertension. These associations require further investigation in model systems where the consequences of CHD including heterotaxy syndrome can be explored in aging animals and in adults with congenital heart diseases.

Thus, the clinical presentation of CHD associated with heterotaxy represents a spectrum of common final pathways and a range of early errors in embryo patterning and morphogenesis, modified during fetal life and then palliated using our current medical and surgical therapies. Investigation of the mechanisms responsible for normal and aberrant patterning and morphogenesis will continue to reveal important genes and pathways that can be used to identify the origins of CHD and may also be important for future targeted therapies, for example, related to pulmonary artery vascular remodeling and hypertension.