9 Pulmonary Arterial Hypertension in Patients with Heterotaxy/Polysplenia Syndrome

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Gene • TGF-β • BMPR2

Early progressive pulmonary arterial hypertension (PAH) is often observed in patients with heterotaxy/polysplenia especially who have an intracardiac systemic-to-pulmonary shunt. However, its etiology is uncertain and its management is not well established. There was only a Japanese report about PAH in consecutive patients with heterotaxy/polysplenia syndrome [1]. They seemed to develop pulmonary vascular obstructive disease earlier and more severe than expected, even in cases with only pre-tricuspid systemic-to-pulmonary shunt although more detailed analysis is required.

Improved understanding and studies about the molecular genetics of heterotaxy syndrome indicate that this disease can be caused by single gene mutations. Genes currently implicated in human heterotaxy syndrome include *ZIC3*, *LEFTYA*, *CRYPTIC*, and *ACVR2B* [2]. The establishment of left-right asymmetry is regulated by a number of developmental signaling pathways including the notch, which mediate nodal expression surrounding the node [3]. Nodal, a growth regulator produced by the node, is a signaling molecule belonging to the transforming growth factor (TGF)-β superfamily that plays a variety of roles in the early development [4]. Mouse nodal acts through type I (ALK-4, 5, and 7) and type II (ACVR2B) receptors of the TGF-β superfamily. Ligand activation of the receptors requires one or more co-receptors, Cryptic and Cripto. Lefty-1 (homologue of LEFTYA) is a nodal antagonist that is expressed in medial left lateral plate mesoderm [5].

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The mutation in *BMPR2*, which encodes type II receptor of the bone morphogenic protein (BMP), is a well-known genetic cause of PAH [6]. BMP is also belonging to the TGF-β superfamily. Although there has been no report that describes the association between PAH and mutation of genes implicated in heterotaxy syndrome, they might have some effect on the signaling pathway downstream of BMP and, consequently, be relevant to the pulmonary vascular pathogenesis in progressive PAH.

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