P-50

3D analysis of heterotaxy in the mouse model : from the embryonic heart loop to complex congenital heart diseases

Bernheim S., Desgrange A.(1), Le Garrec J.-F. (1), Lokmer J. (1), Houyel L.(2), Meilhac S. (1)*
1 Imagine - Institut Pasteur, Laboratory of Heart Morphogenesis, Paris, France
2 Unité de Cardiologie Pédiatrique et Congénitale, Hôpital Necker Enfants Malades, Paris, France

Introduction: The left-right asymmetric morphogenesis of the heart is initiated during the embryonic process of heart looping. The molecular cascade at the origin of the left-right asymmetry in the embryo has been well established in the mouse model and is affected in human cases of heterotaxy. Laterality defects such as heterotaxy are challenging to phenotype, because of partial penetrance, the number of organs affected and the complexity of the anatomical variations in the heart. Thus, laterality defects are currently incompletely phenotyped in the mouse model, hindering understanding of the pathophysiological mechanisms. Recent advances in imaging and computational analyses have opened the possibility to quantify morphogenetic processes in 3D and combine different modalities to detect different aspects of the phenotype.

Methods: We present a complete framework for imaging in 3D the shape and cellular architecture of the heart during embryogenesis and at birth, but also its relation to other visceral organs and the main vessels. This is validated in a model of heterotaxy.

Results: Using High Resolution Episcopic Microscopy (HREM), we have established a procedure to quantify the 3D shape of the embryonic heart loop. By lightsheet microscopy, we have addressed asymmetries in cell behaviour during heart looping. To correlate variations in embryonic shapes with specific configurations of heterotaxy at birth, we have established a multimodality-imaging pipeline combining echography, micro-computed tomography (micro-CT) and HREM. In the same individual, the embryonic shape is analysed by echography, whereas the situs of visceral organs is imaged by micro-CT. Finally, 3D reconstructions of the heart by HREM can identify complex cardiac malformations at birth, using the anatomical criteria of the segmental approach.

Conclusion: This strategy is applicable to analyse a variety of mouse mutants with laterality defects. From quantitative 3D analyses at multiple scales and multiple stages, it is expected to provide novel insight into the mechanism of congenital heart defects associated with heterotaxy.