BDR SEMINAR in Kobe

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14:00-15:30, 1F Auditorium, DB Building C

Left-right asymmetry: forming the right cardiac loop

Summary

Left-right partitioning of the mammalian heart underlies the double blood circulation. Impairment of left-right patterning leads to heterotaxy, including complex cardiac malformations. However, the pathological mechanisms of these diverse cardiac malformations remain unclear. Asymmetric heart morphogenesis is initiated in the embryo, when the cardiac tube acquires a rightward helical shape during the process of heart looping. Whereas the molecular cascade breaking the symmetry has been well characterised, how Nodal signalling is sensed by cells to generate asymmetric organogenesis remains unknown, as well as the contribution of other factors.

Heart looping has been previously analysed simply as a binary decision of direction. We work on the hypothesis that asymmetric morphogenesis has more parameters, so that it is the fine 3D shape of the heart loop that is key for the alignment of cardiac chambers. We have reconstructed and quantified the 3D shape changes during heart looping in the mouse. In combination with cell labelling and computer simulations, we have proposed a model of heart looping, centred on the buckling of the tube growing between fixed poles, which functions as a random asymmetry generator. We have identified sequential and opposed left-right asymmetries at the tube poles, which bias the buckling, thus leading to a helical shape. By manipulating Nodal signalling in time and space, we show that it is not involved in the buckling or in the initiation of asymmetry. Instead, Nodal is required transiently in heart precursors, to amplify and coordinate asymmetries at the heart tube poles. Thus, it functions as a bias to generate a robust helical shape. Taken together, our tools and model provide a novel framework for asymmetric morphogenesis, which is relevant to complex congenital heart defects.

1. Le Garrec, Domínguez Macías et al., A predictive model of asymmetric morphogenesis from 3D reconstructions of mouse heart looping dynamics. *eLife*, 6:e28951 (2017)

2. Desgrange, Le Garrec and Meilhac, Left-right asymmetry in heart development and disease : forming the right loop. *Development* 145(22):dev162776 (2018)

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