LABORATORY FOR SPATIOTEMPORAL REGULATIONS

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In spite of superficially bilateral symmetry, our bodies are highly asymmetric along the left-right (L-R) axis, such as the placement of internal organs. Our main aim is to clarify the mechanism by which mammalian embryos generate and establish the L-R asymmetry.

I. Initial step for the left-right asymmetry

The first L-R asymmetry in mammalian development arises on the embryonic surface. A gastrulating mouse embryo has a shallow hollow on its ventral surface, called as ëthe nodeí, with hundreds of cilia moving in a clockwise rotational manner (Figure 1; Nonaka et al., 1998). Sum of the vortical motions of the cilia however generates leftward flow of the surrounding fluid rather than a vortex. Because of posteriorly tilted rotation axis, the node cilia can generate leftward force without pre-existing left-right asymmetry. (Figure2; Nonaka et al., 2005).

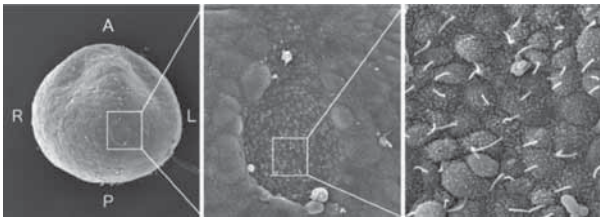

Figure 1. Left, ventral view of a 7.5-day mouse embryo. Middle, the node. Right, node cilia.

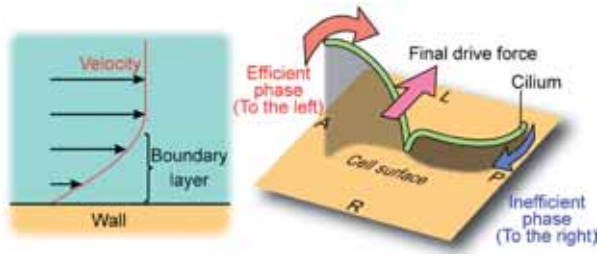

Figure 2. Mechanism to generate leftward flow by a rotating cilium. Left, fluid very close to the wall is generally reluctant to move (surface effect). Right, this constraint negatively affects water-dragging efficiency by the cilium. Given that the cilium rotates clockwise with a posteriorly tilted axis, fluid dragged to the right is less than that to the left, resulting leftward force production.

The leftward flow, called nodal flow, determines subsequent L-R development. This idea has been confirmed by several evidences: First, mutations without motile cilia in the node result in randomized L-R asymmetry. Second and more important, embryos raised in a rightward artificial flow of culture medium develop reversed L-R asymmetry (Figure3; Nonaka et al., 2002).

While it is clear that nodal flow conveys asymmetric information, the entity of the information remains unclear. We are now working to clarify the mechanism how the direction of nodal flow is converted to the subsequent step, asymmetric gene expression.

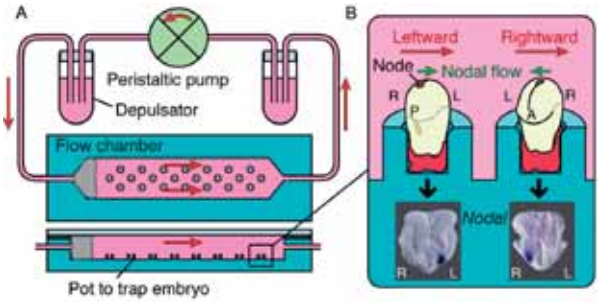

Figure 3. Flow culture exiperiment. A, A peristaltic pump and depulsators supply constant fluid flow in the chanber (red arrowheads). B, Embryos held in the pots receive the pump-driven flow on their surface. If the pump-driven flow reverse intrinsic nodal flow, expression of nodal, a master gene for the leftness, is reversed (Right).

II. New microscopy

Long-term live imaging techniques of early mouse embryos should be extremely useful for our analyses of L-R development and broader research interests. For this purpose, we are working to introduce Single Plain Illumination Microscope (SPIM) that has been developed by Dr. Ernst Stelzer in EMBL.

Publication List:

Review article

Marshall, W.F., and Nonaka, S. (2006). Cilia: tuning in to the cell's antenna. Curr. Biol. *16*, R604-614.