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, for example in 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 'the node', with hundreds of cilia moving in a clockwise rotational manner (Figure 1; Nonaka *et al.*, Cell *95*, 829-837,1998). The sum of the vortical motions of the cilia, however, generates a leftward flow of the surrounding fluid rather than a vortex. Because of the posteriorly tilted rotation axis, the node cilia can generate leftward force without pre-existing left-right asymmetry. (Figure 2; Nonaka *et al.*, PLoS Biology *3*, e268, 2005).

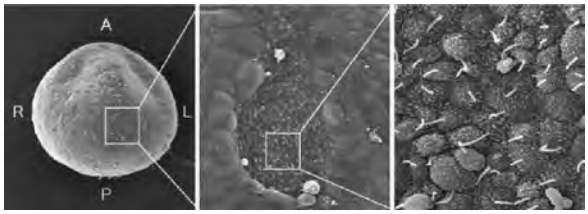

Figure 1. Left, ventral view of a 7.5-day mouse embryo. Middle, the node. Right, node cilia.

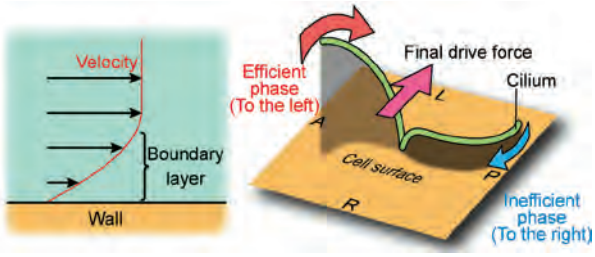

Figure 2. Mechanism to generate leftward flow by a rotating cilium. Left, fluid very close to the wall is generally reluctant to move (surface effect). Right, this constraint negatively affects water-dragging efficiency by the cilium. Given that the cilium rotates clockwise with a posteriorly tilted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

The leftward flow, known as nodal flow, determines subsequent L-R development. This idea has been confirmed by two experiments. Firstly, mutations without motile cilia in the node result in randomized L-R asymmetry. Secondly, and more importantly, embryos raised in a rightward artificial flow of culture medium develop reversed L-R asymmetry (Figure 3; Nonaka *et al.*, Nature *418*, 96-99, 2002).

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

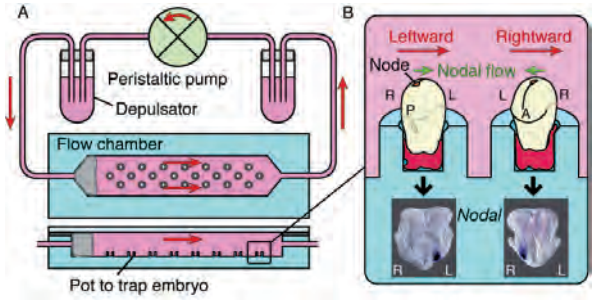

Figure 3. Flow culture experiment. A, A peristaltic pump and depulsators supply constant fluid flow in the chanber (red arrows). B, Embryos held in the pots receive the pump-driven flow on their surface. If the pump-driven flow reverse intrinsic nodal flow (green arrows), expression of nodal, a master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

Ⅱ. New microscopy

Long-term live imaging techniques of early mouse embryos promise to be extremely useful for our analyses of L-R development as well as for broader research interests. For this purpose, we are working to introduce a digital scanned light-sheet microscope (DSLM, Figure 4) that has been developed by Dr. Ernst Stelzer in European Molecular Biology Laboratory (EMBL).

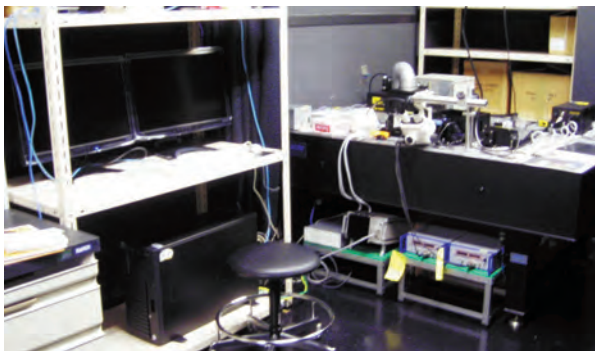

Figure 4. DSLM in construction