
Animal Asymmetries: Evolution and Mechanisms

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Asymmetry is a feature of animal body plans, which often reveals itself only upon closer inspection. While asymmetric coiling of snail shells is obvious even to the untrained eye, sea stars and sea urchins don't even seem to qualify as bilaterians at first glance, and vertebrate asymmetry is restricted to the asymmetric placement of many of the inner organs of the chest and abdomen.

In my talk I will present asymmetries of animal body plans in protostomians and deuterostomians and discuss their origin and functional relevance. As to the underlying molecular mechanisms, the asymmetric Nodal signaling cascade is a conserved prerequisite for asymmetric body plan specification in all cases. I will present evidence that symmetry breakage by cilia-driven leftward flow presents an ancestral character of vertebrates, likely the chordate phylum and maybe all deuterostomes. In vertebrates, leftward flow occurs in a transient structure, a monociliated epithelium, which is derived from superficial mesoderm and localizes to the

archenteron roof during gastrulation. The chick as an example for the highly derived birds lacks superficial mesoderm and flow. This loss should be secondary, as flow is present from fish and amphibians to mammals.

As well established as leftward flow is as a mechanism of symmetry breakage, as little understood are the exact events around flow, i.e. whether a morphogen is asymmetrically transported across the ciliary field, or whether flow is sensed on the left side, and a cascade of events set into action downstream of flow.

We have recently performed a number of experiments in the South African clawed frog *Xenopus laevis*, which is a particularly accessible model organism for laterality studies, to get insight into these questions. To that end we have performed gain- and loss-of-function studies in which particular components have been knocked down or misexpressed in defined tissues of the frog gastrula and neurula embryo. Our results show that asymmetric transport of a morphogen from right to left via flow

cannot account for symmetry breakage, as flow on the right side is dispensable for symmetry breakage. Rather, flow down-regulates an inhibitor of Nodal, which in frog is called Coco (cer12 in mouse, charon in zebrafish) specifically on the left side of the ciliated epithelium. Thus, symmetry breakage occurs by release of repression of the Nodal signaling cascade.

Earlier components, which have been described to be asymmetrically localized in early *Xenopus* embryos, could not be confirmed in our experiments. Rather we could show that these so-called early determinants (such as serotonin and the ion pump H-K-ATPase) are involved in the morphogenesis of the ciliated epithelium, most likely by acting upon non-canonical Wnt signaling.

Finally, we have studied the mechanisms by which the first asymmetric cue is transported to the left side, where the Nodal cascade is activated and asymmetric heart looping is induced. We find gap junctional communications to be at the center of this transfer. I will present a comprehensive model of symmetry breakage in the frog *Xenopus*, which should serve as a reference point to investigate symmetry breakage in other deuterostomians as well.

The insights gained in recent years into evolution and mechanisms of animal asymmetry have been made possi-

ble because of international collaborations of scientists from different backgrounds and working on different model organisms. What nowadays is considered standard for scientific research was uncommon in Alexander von Humboldt's days. Humboldt himself can be considered a pioneer of globalized research, as well as of research across discipline boundaries. It is therefore with particular delight to be able to present this lecture to an international audience at the Symposium "200 años of Humboldt" in Quito, the capital of Ecuador, where Humboldt has travelled and worked extensively, and to conduct research in collaboration with Ecuadorian scientists on Ecuadorian frog species.