Active balance between two proteins ensures that embryos develop with the proper proportions

August 2 2013

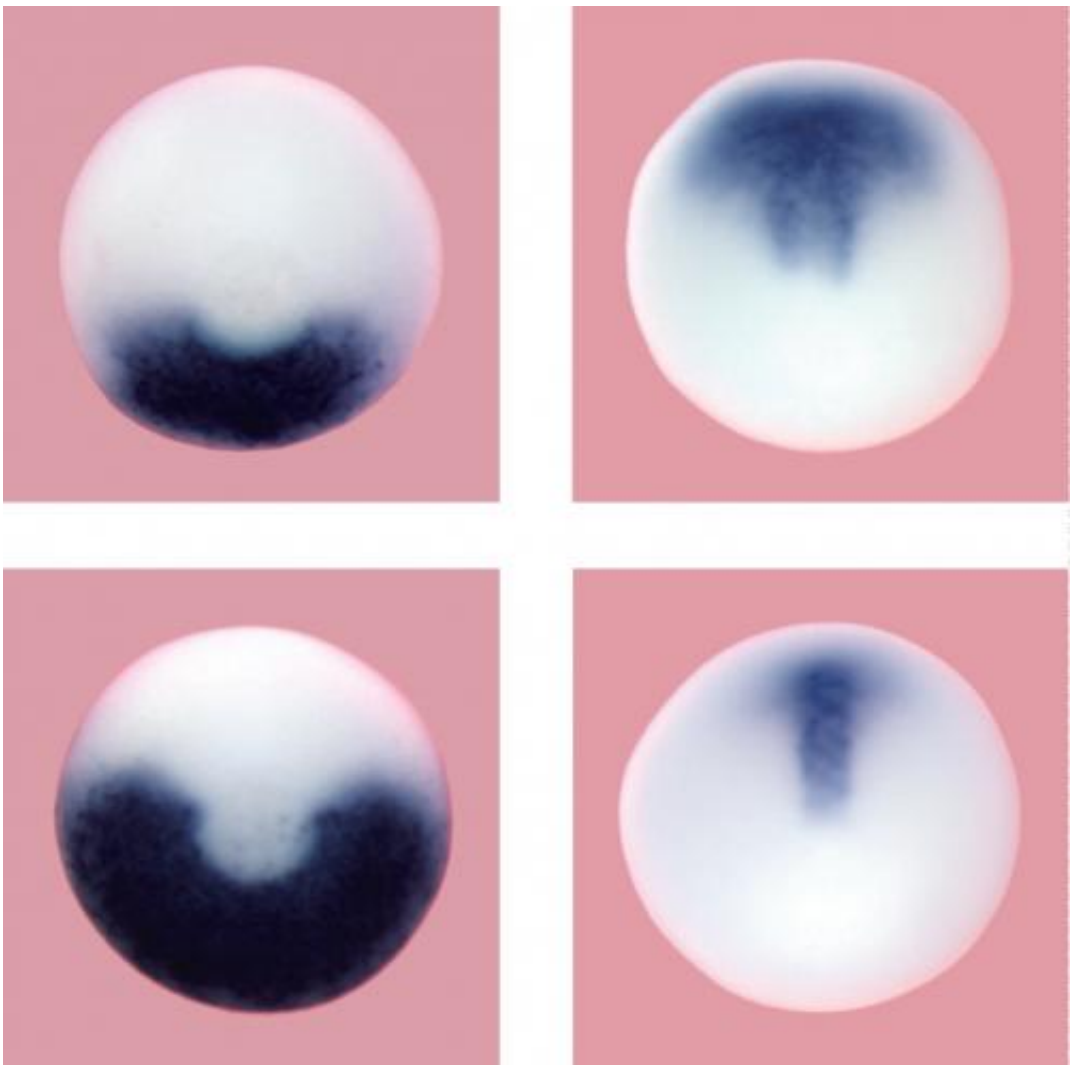

Figure 1: The ventral and dorsal ‘ends’ of a Xenopus embryo (top) are respectively defined by cells with high levels of Sizzled (top left) and Chordin

(top right). This dorsal-ventral boundary can be shifted (bottom) by reducing levels of Chordin, leading to overproduction of Sizzled (bottom left), or reduced levels of Sizzled, which in turn leads to increased Chordin degradation (bottom right). Credit: 2013 Elsevier

Early in development, the embryo establishes the various axes that determine the symmetry of the mature animal. For example, the patterning of dorsal and ventral surfaces governs formation of the organism's back and belly. There are developmental mechanisms that regulate this patterning to ensure that the various body parts develop in proportion to each other but exactly how these mechanisms function remains uncertain. Yoshiki Sasai, Hidehiko Inomata and colleagues from the RIKEN Center for Developmental Biology have now clarified how dorsal-ventral (DV) scaling is maintained in the African clawed frog, Xenopus laevis.

A cluster of cells known as Spemann's organizer establishes the 'dorsality' of the embryo by secreting the protein Chordin, which inhibits signals that would otherwise initiate development of ventral tissues. The effect of Chordin is known to be tightly constrained to the dorsal region. "If a Xenopus embryo is bisected into a dorsal and ventral half, the dorsal half will still give rise to a well-proportioned, half-size embryo," explains Inomata. However, the mechanism responsible for localizing the effect of Chordin was previously unknown.

The researchers conducted a series of experiments to understand how Xenopus establishes this DV boundary. Chordin is naturally degraded by protease enzymes distributed throughout the early embryo. These proteases are selectively inhibited by another protein called Sizzled, and the researchers found that Chordin's reach is determined by the range at which Sizzled can block protease activity.

Sizzled is primarily produced at the ventral pole of the embryo via the same 'ventralizing' signal that gets switched off by Chordin. This creates a critical feedback loop: Chordin only acts in cells where Sizzled is present, but Sizzled is only produced in cells where Chordin levels are low. The DV boundary is thus established in those cells where Chordin prevents continued production of Sizzled and where low levels of Sizzled prevent further diffusion of Chordin (Fig. 1). Regardless of embryo size, this boundary reliably scales with the distance of the organizer from the ventral pole. "Our results indicate that the dynamic state of Sizzled protein accumulation conveys body size information for scaling," says Inomata.

While these findings resolve an important developmental puzzle, the frog embryo lacks important elements of complexity found in other vertebrate species. "During early Xenopus development, the size of the embryo is nearly unchanged, but in many animals the embryo becomes larger and dynamically changes size," says Inomata. "We'd like to examine whether our scaling model is applicable to this type of growing developmental field."

More information: Inomata, H., Shibata, T., Haraguchi, T. & Sasai, Y. Scaling of dorsal-ventral patterning by embryo size-dependent degradation of Spemann's organizer signals. *Cell* 153, 1296–1311 (2013). dx.doi.org/10.1016/j.cell.2013.05.004

Provided by RIKEN