

Solving the Puzzle of the Resilient Embryo

Two types of regulatory proteins working in seesaw fashion ensure normal embryonic formation—even if the embryo is split in half.

Facing off below, identical tadpole twins—generated by cutting an embryo in two equal halves—are indistinguishable from the typical tadpole above.



IT WAS IN 1903 THAT BIOLOGIST HANS SPEMANN—USING A LOOP OF HIS BABY daughter’s hair and a newt egg—revealed the startling embryological mystery that would persist for more than a century. Testing the adaptability of an embryo, Spemann deftly lassoed the egg with the hair and constricted it so that all nuclear divisions occurred only on one side. Eventually, a nucleus would escape through the constriction to the other side and nuclear divisions would begin there as well. At this point, he would tighten the lasso to completely separate the two sides. To his amaze-

ment, both halves developed into identical, perfectly normal, half-sized embryos. This embryonic fail-safe machinery doesn’t only reside in amphibians, though. Identical twins often result when such egg splitting occurs in humans.

Now, HHMI investigator Edward M. De Robertis and graduate student Bruno Reversade have made an important advance in revealing the molecular mechanism underlying this remarkable resilience—namely, the “morphogenetic fields” that govern embryonic development. Such fields are gradients of regulatory proteins that guide differentiation of embryonic cells and organize the embryo’s overall shape. Although researchers have long known that such fields exist, little was known about the molecular basis of their function.

De Robertis and Reversade, both at University of California, Los Angeles, sought to understand the possible role of the regulatory molecules called bone morphogenetic proteins (BMPs). Other studies have shown BMPs to be key regulators in the dorsoventral (back-to-belly) patterning of embryos whereby dorsal cells differentiate into neural cells, and ventral cells become epidermal cells. Yet no one had been able to demonstrate their role by shutting down the system and eliminating such embryonic “self-regulation.”

In their experiments with embryos of the African frog *Xenopus*, the researchers split the embryos into dorsal and ventral halves and used sophisticated molecular techniques to selectively inhibit BMP signaling in each half. They then observed the effects of their manipulations on embryonic development.

The experiments, published in the December 16, 2005, issue of *Cell*, revealed

that while the ventral half of the embryo requires specific BMPs for normal development, “It was rather shocking to us that the dorsal part of the embryo developed fairly normally,” says De Robertis. Indeed, further experiments revealed that normal dorsal development instead requires a different member of the BMP family, called anti-dorsalizing morphogenetic protein (ADMP).

Importantly, De Robertis and Reversade discovered that the two kinds of proteins in embryo halves are regulated in a seesaw fashion. When the researchers decreased BMP signaling levels, they found that ADMP levels would rise, and vice versa. This compensatory ability is a key to self-regulation in the embryo, according to De Robertis.

Another surprise came when the researchers shut down all the relevant BMP proteins,

including ADMP, in *Xenopus* embryos. The entire surface of the embryo became neural tissue. “This is a major transformation of a type you almost never see in embryos,” says De Robertis. “It told us that BMPs play a crucial role in the establishment of a self-regulating morphogenetic field for dorsoventral patterning.” In fact, when the scientists grafted material from either dorsal or ventral BMP sources into embryos depleted of all BMPs, either of the grafts could restore normal embryo formation.

“We think this finding is important in showing that the embryo is probably patterned by two gradients of BMP—one from the dorsal side and one from the ventral,” says De Robertis. “The key to making a perfect baby every time, these experiments tell us, lies in the ability to have a double gradient that will ensure a robust developmental system.”

This discovery could also have important implications for efforts to use stem cells to rejuvenate tissues lost to disease or trauma. When cultured in vitro, stem cells tend to differentiate into multiple cell types, as their self-regulatory systems work to produce an embryo. De Robertis suggests it might be necessary to shut down such self-regulation in stem cells to induce them to produce specific tissues. —Dennis Meredith ■

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EDWARD DE ROBERTIS



Edward De Robertis (right)
and Bruno Reversade