DEVELOPMENTAL BIOLOGY

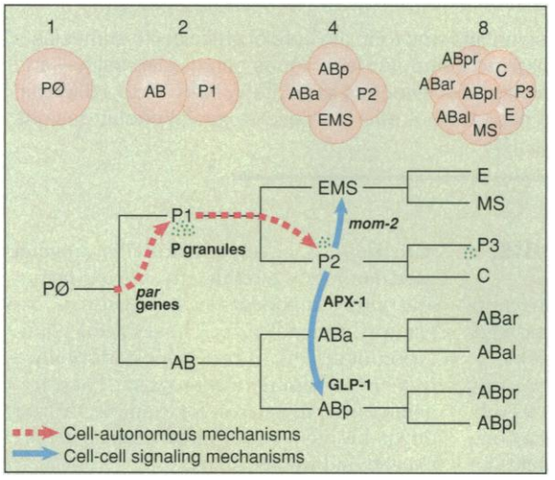
Divide and Confer: How Worm Embryo Cells Specialize

NASHVILLE, TENNESSEE—The one-cell animal embryo, or zygote, faces a daunting engineering task: implementing the architectural plans inscribed in its DNA for building a complex, multicelled body. So, like any sensible construction supervisor, the zygote swiftly divides the project into manageable chunks, assigning some of its progeny to build only gut, for example, and others to make only muscle or skin. Just how each early embryonic cell gets its orders is understood only for the fruit fly *Drosophila melanogaster*—an achievement that helped win 1995's Nobel Prize in medicine for three developmental biologists. Now, however, the communication lines governing embryonic development are emerging in another animal beloved of developmental researchers: the tiny worm known as *Caenorhabditis elegans*.

At the national meeting of the Society for Developmental Biology held 3 weeks ago in Nashville, one research team described the identification of a protein that plays a key role in the first step of the worm's embryonic development: the division of the zygote into two unequal daughter cells. Two other teams described new genes responsible for a round of signaling among the zygote's granddaughters, which tells them what kind of cells they should eventually produce. While a few other early developmental control genes had previously been found for *C. elegans*, researchers welcome the results as signaling the beginning of a new era in understanding the worm's development. Says Susan Strome, a developmental geneticist at Indiana University: "*C. elegans* is entering the heyday that *Drosophila* entered years ago."

The first stage of worm differentiation takes place within the single-celled zygote, when some intracellular materials, including P granules and developmental factors, shift to one side, ensuring that its two daughters—the smaller, posterior cell called P1 and the larger cell designated AB—will differ from each other. And the job of conveying those factors, Cornell University developmental geneticist Kenneth Kemphues reported in Nashville, falls to the protein myosin. Myosin is a muscle contractile protein that in nonmuscle cells can "walk" along the network of microfilaments that makes up the cell's cytoskeleton, dragging other materials with it or changing the cytoskeleton's shape.

Hints of the cytoskeleton's involvement in the zygote's unequal division had come in 1987 when Kemphues and developmental geneticist Jim Priess, now at the Fred Hutchinson Cancer Research Center in Seattle, studied mutants in which the developmental factors fail to collect on one side of the zygote. Dividing mutant embryos also looked as if they had been exposed to a chemical that inhibits microfilaments, leading the researchers to speculate that the affected genes—which they named *par-1* through *par*-6 (for *par*titioning defective)—encode proteins that somehow regulate the cytoskeleton during cell division, making sure that it sends materials to the right daughter.



Family tree. A shift of developmental determinants within the *C. elegans* zygote helps make one daughter cell different from the other *(dotted arrows)*. In the four-cell embryo, signaling between cells *(solid arrows)* further narrows some cells' missions.

Now researcher Su Guo in Kemphues's lab has found evidence of direct interaction between the PAR proteins and the cytoskeleton. She exposed filters laden with many different *C. elegans* protein fragments to radioactive PAR-1 protein and found that PAR-1 specifically binds to myosin. The Kemphues team also found that in zygotes depleted of myosin, the PAR proteins don't take up their usual positions on the cell wall, proving that myosin is required to localize them.

As soon as AB and P1, the original daughters of the zygote, divide, the embryo begins making use of a second differentiation mechanism: molecular signaling between cells. Two other presentations at Nashville have identified key signaling molecules for two of these interactions. In both of these, the signal is sent by one of P1's daughters, the P2 cell, but the recipients differ.

One of P2's interactions is with the ABp cell, a daughter of AB. Initially, ABp and its sister ABa look identical, but they later give rise to very different sets of skin, muscle, neural, and other cells. And 2 years ago, several groups of researchers reported a hint that ABp receives its differentiation signal from P2. They showed that removing P2 from its normal position adjacent to ABp causes ABp's descendants to develop identically to those of ABa.

Researchers suspected that the signal is sent by a surface protein called APX-1, whose structure resembles that of the *Drosophila* Delta signaling protein, for they knew that it is received by GLP-1, a *C. elegans* equivalent of a *Drosophila* protein called Notch, which responds to Delta signals. In Nashville, University of Massachusetts developmental geneticist Craig Mello reported evidence for this suspicion. Antibody staining carried out by Mello, Priess, Hutchinson researcher Katherine Mickey, and others showed that APX-1 appears only on the surface of P2, where it contacts GLP-1 on ABp.

ABp isn't the only cell that receives counsel from P2. So does P2's own sister cell, EMS. It has been known for several years, for example, that an EMS cell separated from the neighboring P2 divides not into its usual daughters, E (which produces only the endoderm or gut) and MS (which builds mesodermal tissues such as muscle), but into two MS-like cells—indicating that P2 provides a signal that "polarizes" EMS, ensuring that endoderm-specific genes will be activated only in daughter E. Mutational studies implicated a gene called *mom-2* as part of this polarizing signal. The next question was whether the *mom-2* protein product is the sender or the recipient of P2's signals. And at the meeting, developmental geneticist Bruce Bowerman of the University of Oregon said that Chris Thorpe, a researcher in his lab, had found the answer.

When Thorpe assembled "chimeric" embryos from isolated cells in which *mom-2* was inactivated in either EMS or P2 cells, he found that mutant EMS cells joined to normal P2 cells divided into normal E and MS cells. But when normal EMS cells were joined to mutant P2 cells, the embryos produced no endoderm. "That nailed down that the gene is required in P2 for sending the signal," Bowerman says.

As the advances reported in Nashville demonstrate, the task of understanding *C. elegans* embryogenesis is gradually yielding to researchers' own division of labor. "We're gaining the ability to find the factors setting cell fates and to see how cell-autonomous mechanisms and cell-cell signaling mechanisms work together," says Kemphues. "That's very exciting."

—Wade Roush