fruit flies to sort out the signaling pathway used by a protein called Notch, which plays a key role in determining cell fates in animals ranging from nematodes to humans.

How cells learn their future

One common function for signaling pathways is in determining the fate of cells. Activation of Notch in particular cells in a fruit fly, for example, makes those cells become skin cells rather than nervous system cells. The question of how cells learn their fates ranked equal to signal transduction in our survey. But a signal passed from cell to cell is not the only way cells' futures are fixed. "There is a whole separate issue, which is barely just scratched," says Chris Doe of the HHMI at the University of Illinois, Urbana-Champaign, "and that is that you can also [determine] cell fate by putting something in the cell asymmetrically."

One example cited by Doe is a protein called Numb, which is made in a particular type of cell that forms a sensory organ in fruit flies. Yuh Nung Jan and his colleagues at the HHMI at UC San Francisco recently showed that, during cell division, the Numb protein segregates at one end of the cell. As a result, one daughter cell receives all of the Numb protein; the other receives none. The daughter that gets the Numb becomes a sensory neuron, and the other becomes a support cell. "Something has to set up that first asymmetry" that sends two sibling cells to different fates, says Doe. Numb itself is a good candidate, although no one yet knows its biochemical function. As more labs focus on the nature of such cellular decisions, says Doe, a more complete picture of the role of protein partitioning is bound to emerge.

And as the respondents to our survey told us, cell fate is just one of the many topics that are ripe for the plucking as developmental biology basks in its productive prime of life. Indeed, as it moves into its eleventh decade, the field will clearly continue to rush headlong toward the answers to some of its most fundamental questions concerning how a single cell becomes a full-fledged organism.

–Marcia Barinaga

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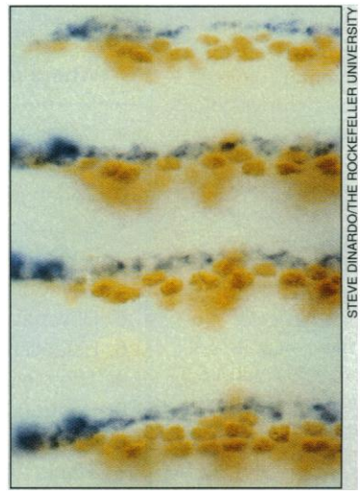
MORPHOGENESIS

Finding Clues About How Embryo Structures Form

When Michelangelo created his masterpiece, David, he probably used a large hammer and chisel to hew the figure's overall shape and progressively smaller tools to refine David's anatomical features from the ringlets in his mane of hair down to the cuticles of his fingers and toes. But his array of tools wasn't enormous: As the artist moved from one part of the sculpture to another, he no doubt relied on a select array of a few tools, using them over and over again to shape quite different features. Now, researchers are beginning to recognize that nature displays a comparable economy in choosing the molecular tools that shape the developing embryo.

Just how the seemingly homogeneous blob of cells that forms the early embryo is molded into the tissues and organs that form a complete living organism is a mystery that has long intrigued scientists. Even now, researchers do not yet have a complete picture of that process. One area that remains perplexing comes later in development, when organs and tissues are formed as part of the process called morphogenesis. Researchers consider understanding that process to be of the highest importance: It ranked first in *Science*'s survey of key unanswered questions in the field (see story on p. 561).



STEVE DINARDO/THE ROCKEFELLER UNIVERSITY

Together. In these four segments of a fruit fly embryo the genes *wingless* (*blue stain*) and engrailed (*brown*) are expressed in close-by cells.

Although morphogenesis is far from understood, developmental biologists are beginning to pile up clues. What they are finding is that, just as Michelangelo used and reused some of the same tools, the same families of molecules that guide the earliest stages of embryogenesis—setting up such basic elements of body pattern as the head-to-tail and dorsal-ventral axes—also help out in morphogenesis.

What is more, these molecules have been heavily conserved over the course of evolution, playing similar developmental roles in species ranging from the fruit fly to fish to mice to human beings. "Once a primordial multicellular organism figured out how to direct certain cells to become head, others to become tail, and which cells should become dorsal and which ventral, it was probably easier in evolutionary terms to elaborate on these early signaling events than to change the nature of the signals altogether," says developmental biologist Brigid Hogan of Vanderbilt University Medical School in Nashville, Tennessee.

Although there are many illustrations of this repeated reuse of developmental signals (see Article by Kessler and Melton on p. 596), one of the clearest and best understood examples comes from a family of structurally related genes that includes *wingless* (*wg*) in the fruit fly *Drosophila melanogaster* and the *Wnt* genes in vertebrates. *Wg*, the prototype of this family, was first identified by R. P. Sharma and V. L. Chopra of the Indian Agricultural Research Institute in New Delhi as the gene at fault in certain fruit fly mutants with defective wing development. Other researchers, including Nick Baker of the Medical Research Council in Cambridge, England, subsequently showed that forming wings isn't *wg*'s first appearance on the developmental stage. Far from it: Expression of *wg* also helps specify the position or organization of the 14 segments that ultimately form the major components of the adult fruit fly's body, and later helps establish the dorsal-ventral axis of the imaginal discs. "This is a prime example of a single gene being used and reused during the course of development," says Philip Ingham of the Imperial Cancer Research Fund in London, who studies development in the fruit fly and the zebrafish.

The *Wnt* genes, the vertebrate relatives of *wg*, are proving just as versatile. Roel Nusse, then a postdoc in Harold Varmus's lab at the University of California, San Francisco, identified the first *Wnt* gene, *Wnt-1*, in the early 1980s. Since then, researchers have identified at least 14 other *Wnt*s, which act both early and late in embryogenesis.

Take *Wnt-3a*. Andrew McMahon's group at Harvard University has evidence from mice that this *Wnt* family member is needed for formation of the mesoderm during gastrulation, which is the complex series of cell movements that leads to formation of the three primordial tissue types in the embryo

(the others are ectoderm and endoderm). McMahon's group, as well as that of Mario Capecchi at the University of Utah in Salt Lake City, has also implicated *Wnt-1* in a much later event, formation of the vertebrate brain. And in as-yet-unpublished work, McMahon and his colleagues find that still another *wg* relative, *Wnt-4*, is needed for formation of the kidney.

In Michelangelo's case it is clear how so few tools could be used to exert so many different, remarkable effects: the missing ingredient was genius. But just how *wg* and its relatives bring about such a diverse array of developmental effects is still mysterious. Researchers know that the proteins encoded by these genes are secreted by the cells that make them and can diffuse to neighboring cells, where they presumably bind to specific receptors or other molecules on the surfaces of their target cells. Although no receptors for *Wnt* proteins have been identified, researchers believe that the binding transmits a signal to the interior of the target cell that somehow leads to the regulation of other genes or proteins.

During specification of the segments of the embryonic fruit fly, for example, the expression of *wg* is required for expression of a gene called *engrailed* (*en*). And though formation of the mouse brain might seem to have little in common with the patterning of the fruit fly body, recent work by Alexandra Joyner's group at New York University and that of McMahon suggests that part of *Wnt-1*'s action in the embryonic brain may be due to its ability to regulate a mammalian equivalent of *en*.

Although researchers have established that such interactions are important for morphogenesis, many questions remain. For one, researchers want to know what *en* or other genes that are turned on in response to *wg* signals actually do. One thing that is known is that the *en* gene encodes a transcription factor, a protein that helps turn genes on or off; its action as a gene regulator presumably contributes to its developmental effects. For the most part, however, the genes turned on or off by *en* haven't been identified yet.

There is also the question of how *wg* turns on *en*. Several researchers, including Eric Wieschaus of Princeton University, Nusse, now at Stanford, and Norbert Perrimon of Harvard Medical School, have been making progress in identifying the components of the *wg* signaling pathway in *Drosophila*. Among these is the protein encoded by a gene called *armadillo*. The researchers' findings indicate that *wg* acts through *armadillo* and another gene, called *dishevelled*, to bring about expression of *en*.

One interesting facet of *armadillo* could shed light on how *wg* and its relatives contribute to morphogenesis: The protein it encodes is structurally related to proteins called *beta*-catenin and plakoglobin. These are vertebrate proteins that facilitate cell adhesion by helping cells attach to each other or to the extracellular matrix, the material between cells. The resemblance suggests that Armadillo might be an adhesion protein. That idea has received support from experiments in which Weischaus showed that Armadillo is localized at adhesive junctions in *Drosophila* ovary cells and that mutations in the gene disrupt cell adhesion.

The possibility that Armadillo is involved in cell adhesion makes intuitive sense, as many aspects of morphogenesis involve carefully controlled changes in cells' ability to adhere to one another. To form the embryo correctly, for example, cells must migrate, which requires that they lose contact with cells in one area and establish contact with cells in their new residence.

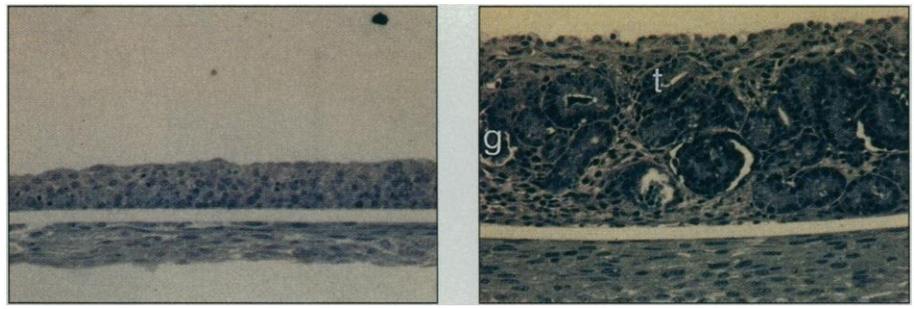
Some of the *wg* family members' effects on morphogenesis might therefore be due to their ability to alter the distribution or concentration of Armadillo or other adhesion proteins in the embryo. Researchers working with the vertebrate *Wnts* are beginning to accumulate circumstantial evidence for this hypothesis, although they do not yet have direct proof. Anthony Brown and his colleagues at Cornell University Medical College in New York City have shown that *Wnt-1* expression increases the concentration of the adhesive proteins plakoglobin and E-cadherin by a line of cultured neuronal cells; the cells consequently show increased adhesive abilities, which Brown attributes to the action of *Wnt*. Noting that cadherin is a membrane-spanning protein that binds plakoglobin, an intracellular protein, at adhesive junctions, he says: "We believe that a member of the *Wnt* family increases the stability of this plakoglobin-cadherin complex and facilitates cellular adhesion."

McMahon and the groups of Doris Herzlinger and Brown at Cornell have further evidence that adhesion might have functional consequences in kidney development. During the formation of the organ, a mass of mesenchymal cells, derived from the mesoderm, condenses around the tip of the embryonic ureter. The condensed mesenchymal cells then differentiate into epithelial cells that eventually become the nephron, which contains the kidney's filtering unit.

The induction of mesenchyme to epithelium and the aggregation of the cells into tubules is partly dependent on cell adhesion, and McMahon's group finds that the processes are disrupted by knocking out *Wnt-4*. In addition, Herzlinger and Brown have shown that *Wnt-1* can induce embryonic mesenchymal cells to aggregate and differentiate into kidney epithelial cells in culture. The researchers haven't yet put all the pieces of the puzzle together, however, and shown that *Wnts* are causing these effects by stimulating production of adhesion molecules.

That's just one of the daunting tasks researchers face as they try to determine how molecular signals bring about morphogenesis. Still, they are hopeful that answers will be forthcoming. "We're on the verge of enormous progress," says Harvard developmental biologist Cliff Tabin. "A lot of the key players have been identified, and the tools have just recently been developed to begin asking how patterning occurs during morphogenesis. We don't understand anything well enough to draw any sweeping generalizations, but it's clear that the field is moving quickly." But even when all of nature's techniques have been identified, a residue of amazement will remain, just as it does when we view Michelangelo's David.

–Nancy Touchette



DORIS HERZLINGER/CORNELL UNIV. MEDICAL COLLEGE

Kidney induction. Mesenchymal cells co-cultured with cells producing *Wnt-1* protein *(right)* differentiate into kidney structures, including nephron tubules (t) and glomerular (g) tissue, an effect not seen with control cells *(left)*.

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