Studies have shown that Notch-mediated signals inhibit the capacity of ectodermal cells to become neurons, but they don't affect all ectodermal cells the same way. "If we take away the activity of one gene in the Notch pathway, instead of getting one neuron in the sensory bristle, we get four neurons," says Posakony, who is studying the pathway. That is, the Notch-mediated signal prohibits three of the cells from becoming neurons, but not the fourth. Exactly why the cells respond differently is unclear, but Yuh Nung Jan of UC San Francisco has evidence that it might be because some cells have previously acquired more of a membrane-associated protein called Numb than others. Numb may be a negative regulator of the Notch pathway, Posakony says, in which case those cells that have greater amounts of the protein may fail to respond to Notch signals and go on to become neurons, while the others become accessory cells.

Although researchers have some clues to how similar signaling pathways can cause different responses, no one expects that getting the full picture will be easy. The problem is complicated by the fact that cells are rarely exposed to one signal at a time, but are usually under a barrage of signals, some positive, some negative. "The real challenge will be to find out how a cell getting signals from, say, five different receptors integrates them and makes the right decision," says Rubin.

While that may be difficult, fully understanding development will require that researchers accomplish the arduous task of fitting the various signal transduction pathways into a complex model showing their overlapping relationships with each other and with additional regulatory molecules. Says Igor Dawid, a developmental biologist at the National Institute of Child Health and Human Development in Bethesda, Maryland: "There's no way around knowing all the players and their interactions. Eventually some people may throw up their hands and say it's too complicated, but you have to know who talks to whom and how it works, or else you don't understand it." Indeed, the cross-talk and intense peer pressure directed at a cell during development could easily rival the loud taunts, competition, and coercion seen on a busy playground.

–Karen Schmidt

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Additional Reading

H. Maruta and A. W. Burgess, "Regulation of the Ras signalling network," *BioEssays* **16**, 489 (1994).

W. S. Katz and P. W. Sternberg, "A plethora of intercellular signals during *Caenorhabditis elegans* development," *Current Opinion in Cell Biology* **4**, 939 (1992).

MEDICAL APPLICATIONS

Moving Developmental Research Into the Clinic

George Bernard Shaw thought youth was wasted on the young. In the same way, some clinicians think embryogenesis is wasted on the embryo. Starting from a few unspecialized cells, the embryo can spawn all the new cells and tissues needed to provide an organism with its correct complement of organs. Unfortunately, the adult doesn't possess that full range of biological skills. But if similar capacities could be bestowed at will on the adult human, many diseases could be cured simply by growing new tissues to replace damaged ones. "A very important medical goal," says developmental biologist Randal Johnston of the University of Calgary, "is to be able to emulate embryonic conditions and trigger cell proliferation in adults where these abilities are diminished."

With that goal in mind, industrial and academic developmental and cell biologists are exploring a variety of approaches to harnessing the embryo's generative powers to provide new therapies for disorders as diverse as diabetes, blindness, heart failure, neurodegenerative diseases such as Alzheimer's and Parkinson's, hard-to-heal wounds, and broken bones. Some researchers, for example, are testing the prospect of transplanting embryonic cells into the adult as a means of regenerating worn-out tissue. But that approach suffers from more than the practical obstacles that plague any new therapeutic strategy; it has the drawback that any use of fetal tissue is ethically controversial.

The approach that's the most advanced clinically doesn't suffer from that problem, however. It takes advantage of the fact that many of the protein "factors" known to trigger growth and cell differentiation during organ formation in the embryo do not become obsolete in the adult. In the embryo, these proteins impinge on every aspect of the developmental process, from the first laying down of the embryo's head-to-tail and dorsal-ventral axes to the formation of specific organs like the kidney, brain, and bone (see Article by Kessler and Melton on p. 596). And while their organ-building capabilities may not be so versatile later in life, they do help maintain and repair tissues and regulate their responses to the external environment.

Some of these proteins are already in clinical use: for example, erythropoietin, which triggers red blood cell production from stem cells in the embryo's yolk sac, liver, and spleen and in the adult's bone marrow, is used to treat the anemia that can be caused by kidney disease and by cancer and AIDS therapies. Over the next few years, clinical applications of growth and differentiation factors can be expected to explode as more are unearthed and more uses are found for those already discovered.

One of the new "embryonic" therapies that is closest to clinical application uses the proteins to restore damaged tissues. This therapeutic strategy is based on "a very nice rationale," says the National Cancer Institute's (NCI's) Michael Sporn, namely, that "the repair of soft and hard tissue in the adult is nothing but a recapitulation of what goes on in the embryo."

As an example, Sporn cites a protein called transforming growth factor β (TGF-β), which he and NCI colleague Anita Roberts helped identify back in 1983. TGF-β was named because in a culture medium it causes some cells, such as the fibroblasts that form connective tissue, to divide uncontrollably, much as if they have undergone a cancerous transformation. But TGF-β and certain related proteins also play a role in normal de-

SOME GROWTH OR DIFFERENTIATION FACTORS IN CLINICAL TESTING

Factor	Application	Status
Erythropoietin	Anemia due to kidney failure	FDA approved
Nerve growth factor	Peripheral neuropathies	Early trials
Insulin-like growth factor	Diabetes	Midphase trials
Brain-derived neurotrophic factor	Lou Gehrig's disease	Early trials
Transforming growth factor β	Macular holes (retinal wounds)	Late trials
Platelet-derived growth factor	Diabetic skin ulcers	Late trials
Osteogenic protein	Bone healing	Midphase trials
Granulocyte colony stimulating factor	Stimulating white blood cells after marrow transplant	FDA approved

velopment where they help to regulate the growth of embryonic connective tissues.

In the adult, TGF-β assists in healing wounds by luring immune cells to injury sites to destroy invading pathogens and remove dead tissue. TGF-β also triggers production of new connective tissue proteins, such as collagen and fibronectin, that help to close wounds. Buoyed by these observations, plus the results of numerous animal studies that have shown that a single topical dose of TGF-β enhances wound healing, the biotechnology industry has started testing the efficacy of TGF-β to aid wound healing in humans.

TGF-β has already shown promise in preliminary trials in patients suffering from a type of retinal deterioration called a macular hole. This condition, in which a hole appears in the macula, the central portion of the retina, costs some 20,000 elderly Americans their sight each year. Macular holes can be treated with surgery to reattach the retina to the underlying epithelium, but the operation fails to seal the macular holes nearly half of the time. Judging by the small clinical trials completed so far, this result can be improved upon by administering TGF-β into the eye at the time the surgery is performed, says John Thompson of St. Joseph Hospital in Baltimore, who helped develop the technique. "We can close about 95% of holes using TGF-β, compared to about 53% without it," he says.

Celtrix Pharmaceuticals, a biotech firm in Santa Clara that makes TGF-β, is now running a much larger trial, including 120 patients, to see if these promising early results will be borne out. Celtrix is also one of several biotech companies testing the ability of TGF-β and other growth factors, such as platelet-derived growth factor, to heal the skin ulcers that plague people with diabetes and circulatory diseases.

Tissue repair in the adult "is nothing but a recapitulation of what goes on in the embryo."

—Michael Sporn

All these trials involve giving growth factors to speed healing, but paradoxically, in some circumstances it may actually be better to inhibit TGF-β's activity. And those circumstances again demonstrate the advantages of being able to mimic embryonic processes.

A wound to the fetus in the womb heals without a scar. The reason may be, says Sporn, that fetal wounds contain little TGF-β, which can contribute to scar formation by stimulating the growth of connective tissue. That observation leads to the possibility that antibodies to TGF-β might one day be used to mop up excessive amounts of the protein in conditions where scarring is disfiguring or debilitating—for example, following severe burns, or for people suffering from glomerulonephritis, a condition in which the membranes of the kidneys may become so scarred that the kidneys fail.

TGF-β isn't the only type of growth factor that the biotech industry is concentrating on in an effort to mimic what happens to the developing embryo. The others include the bone-growth–promoting factors—called either osteogenic or bone morphogenic proteins—which help model the embryonic skeleton and allow adult bone to remold itself in response to changing stresses; these might be used for healing bone fractures (*Science*, 21 January, p. 324). For example, Creative BioMolecules in Hopkinton, Massachusetts, in partnership with a biotech subsidiary of the orthopedic product company Stryker Corporation of Kalamazoo, Michigan, is in the final stages of clinical trials testing the ability of osteogenic proteins to mend difficult-to-heal fractures of the tibia, the major weight-bearing bone of the lower leg. "Each year in the United States about 40 to 50 thousand people suffer complicated fractures that, because of infections or other problems, fail to heal," says Marc Charette, senior director of research and development at Creative BioMolecules. Usually, the only option is a bone graft from the patient's own hip or a bone transplant from a cadaver, which is risky because it can trigger a rejection response or carry infections. "A nice alternative would be to be able to go to the shelf and take a bottle of [osteogenic proteins] and apply it as paste to the fracture," says Charette.

Other possibilities being explored for clinical use include the neurotrophic factors—proteins such as nerve growth factor, insulin-like growth factor, and ciliary neurotrophic factor (CNTF)—that help neurons grow in the developing embryo and ensure their survival in the adult. Now, a battery of biotech companies is intent on developing them as drugs to treat neurodegenerative diseases, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, and peripheral nerve degeneration. Successful clinical development of these factors may not be easy, however. One indication comes from a trial testing CNTF in ALS patients, which was canceled by Regeneron Pharmaceuticals, the company conducting it, after the factor failed to help the patients (*Science*, 6 May, p. 772). Still, given that the diseases for which the new therapies are wanted are for the most part untreatable, efforts to find out whether these or as-yet-undiscovered growth and differentiation factors can help the patients will continue.

–Rachel Nowak

AXON GUIDANCE

Wiring the Nervous System

Navigating the interstates from New York to San Francisco is a tough job for a driver—but it's easy compared to what the neurons of the developing nervous system must do to reach their goals. During embryogenesis, more than a hundred billion fledgling neurons shoot out slender fibers known as axons that ultimately form an estimated hundred trillion links with their target cells. And not only do these axons often have to travel a long way—from the muscles of the foot or hand all the way to the brain, for example—they must also find precisely the right cells to hook up with at their destinations. "How are axons able to grow through the embryonic environment with unerring precision?" wonders Marc Tessier-Lavigne, a Howard Hughes Medical Institute (HHMI) investigator at the University of California (UC), San Francisco.

Though that question has intrigued developmental biologists for more than a century, only recently have they begun to get a handle on the road signs that guide the roving axons to their journey's end. They have found that an axon is steered by an array of guidance molecules in different locations: fixed on the surfaces of cells, within the extracellular matrix (a meshlike structure that fills in the space between cells), or secreted by the axon's targets.

The swiftness with which these discoveries are being made has accelerated in recent months. The first class of diffusible axon chemoattractant molecules was reported in August in *Cell*, when Tessier-Lavigne and his colleagues announced the discovery in chick brains of proteins called netrins, which are thought to steer axons around developing spinal cords. And to the delight of those in the field, efforts in vertebrates are dovetailing with work on the simpler nervous systems of worms and fruit flies.

"The pace has picked up quickly. The molecules that are being found are just the tip of the iceberg," says Corey Goodman, an HHMI investigator at UC Berkeley. Some researchers are even tantalized by the prospect that guidance molecules might help damaged or severed nerves regrow correctly, although they caution that much more work will be needed to establish that. "Everyone thinks there's going to be interesting clinical applications, but that won't happen for a number of years," says Goodman.