

Spiraling Back in Time

AGING A GENE THAT DISTINGUISHES LEFT FROM RIGHT DURING DEVELOPMENT.

The same gene that places a human's heart on the correct side of the body also controls whether a snail's shell twists left or right, scientists have found. The discovery suggests that this mechanism is far more ancient than researchers had thought.

All vertebrates express a gene called *nodal* on the left side of the embryo during early development. *Nodal* activates another gene, *Pitx*, leading to the body's normal asymmetry—some organs develop on one side, where there are high concentrations of *nodal*'s protein



The left shell from *Amphidromus preverus*, an Indonesian snail, is sinistral (left-coiling) while the right one is dextral (right coiling).

product, while others develop where there are low levels. Though *nodal* is ubiquitous in vertebrates, researchers had been unable to find this gene in fruit flies (*Drosophila*) and the roundworm *Caenorhabditis elegans*, important model organisms.

These animals have left/right asymmetries but control them with a different system, says Nipam Patel, an HHMI investigator at the University of

California, Berkeley. So, "the thought was that *nodal* hadn't been there in the common ancestor of flies, *C. elegans*, and people," he says.

To see how other non-vertebrate organisms control asymmetry, Patel and Cristina Grande, a postdoctoral researcher in his lab, searched for *nodal* in a left-spiraling freshwater snail, commonly known as the bloodfluke planorb, and the owl limpet, a marine snail whose organs have the opposite orientation. Not only did they find *nodal* and *Pitx*, they also showed that, in concert with their asymmetries, the limpet expressed both these genes on the right side of the body, and the freshwater snail expressed both on the left.

The researchers went on to inhibit *nodal* signal in snails. "Most died," says Patel, "but a fraction of those that survived had a straight shell." The findings appeared February 19, 2009, in the journal *Nature*.

The study suggests that a common ancestor of snails and vertebrates used the *nodal* pathway to establish left-right asymmetry, explains Patel. The next step, he says, is to determine what activates *nodal*. Researchers partially understand the process in vertebrates, but "in snails classic genetic studies tell us that the mother puts something into the egg that initially establishes asymmetry, but we have no idea what this is." ■ —BENJAMIN LESTER

IN BRIEF

shows that, to display one kind of antigen at a time, *Giardia* parasites don't simply transcribe one gene—they transcribe all 200 antigen genes and then destroy all but one antigen's messenger RNA. To show that was the case, Luján and coworkers silenced the RNA interference machinery of *Giardia*, shutting down a process that helps destroy the unneeded RNA.

To Luján's surprise, the mutant parasites came out wearing a "Technicolor Dreamcoat" of all 200 antigens. Moreover, gerbils infected with this "Dreamcoat" *Giardia* became immune to the normal parasites; their immune systems could recognize all of *Giardia*'s disguises.

Many pathogens, including those that cause malaria, have developed ways to vary their surface antigens. "The idea of blocking antigenic variation opens a lot of new doors to developing vaccines," says Luján. The research appears in the December 11, 2008, issue of *Nature*.

VOLCANOES IN THE GENOME

Ten million years ago, the genome of a common ancestor of humans, gorillas, and chimpanzees underwent drastic changes, HHMI researchers have found. Segments of DNA began to duplicate faster than ever, and the quick pace of duplication in some areas of the genome created

unstable hotspots, which can still be found in humans today.

To determine just when these unstable regions first appeared, HHMI investigator Evan Eichler and colleagues at the University of Washington compared the genomes of chimpanzees and humans with those of macaques and orangutans—which branched off from the same lineage earlier in evolution. Macaques and orangutans, the team found, lack most of the gene duplications that humans and chimpanzees have. The findings appear in the February 12, 2009, issue of *Nature*.

In humans, unstable regions of the genome have been associated with disorders including autism and schizophrenia. However, Eichler points out, the fact that these regions have remained in the human genome for 10 million years, and that they carry rapidly evolving genes, implies that some of the rearrangements created a reproductive edge.

"I believe that the negative selection of having these duplications is being outweighed by the selective advantage of having these newly minted genes, but that's still unproven," says Eichler. The ancient gene duplication, he hypothesizes, could be responsible for the genetic flexibility that has resulted in uniquely human characteristics.

HOW ANTIBIOTICS KILL BACTERIA

The rise of antibiotic-resistant infections has spurred research into how the most effective antibiotics work. While it's known that they disrupt bacteria's ability to build proteins, DNA, or cell walls, these effects don't always have deadly consequences. James J. Collins wanted to know how some antibiotics—called bactericidal—are able to kill bacteria with these methods, while other antibiotics use the steps to simply halt the bacteria's growth.

Collins, an HHMI investigator at Boston University, worked with colleagues to trace what happens at the molecular level to *Escherichia coli* bacteria after treatment with gentamicin, a bactericidal antibiotic. Gentamicin interferes with the *E. coli* ribosome and causes it to build defective proteins, which nevertheless travel to their designated places inside the cells. Faulty proteins in the cell membrane trigger something like a bacterial panic attack—an overblown response to stress—eventually producing free radicals that destroy the cell. Gentamicin became even more effective when the researchers weakened *E. coli*'s protein quality control, potentially pointing out new ways to combine drugs and to lower doses.

Although other types of bactericidal antibiotics have different cellular targets,