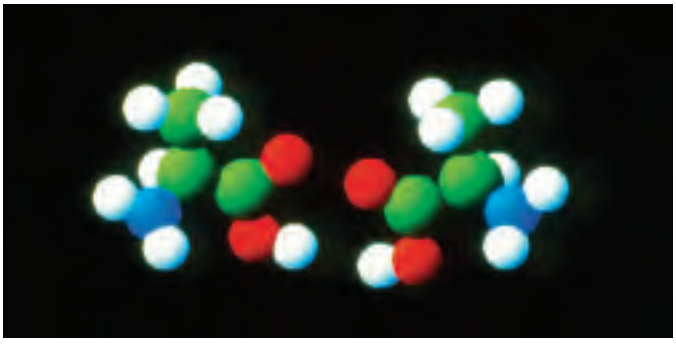
Righty, Lefty

AN UNUSUAL TYPE OF AMINO ACID ACTS AS A GROWTH SIGNAL IN BACTERIA.

Amino acids—the building blocks of proteins—are chiral molecules, which means they can exist in two mirror forms. While L-forms of amino acids are predominantly found in nature, the D-forms are less abundant and little is known about their biological function. But new research shows that the few D-amino acid outliers play a vital role in regulating cell wall growth in bacteria.

Matthew K. Waldor, an HHMI investigator at Brigham and Women's Hospital, was studying how *Vibrio cholerae*, the bacterium that causes cholera, gets its characteristic rod shape. His lab identified a mutant that became spherical when cultured overnight. Waldor's team suspected that something was accumulating in the culture that affected the mutant bacterium's shape. They analyzed the chemicals floating in the soup around the bacteria and found a plethora of right-handed, or D-amino acids.



*The amino acid alanine in its **L**- and **D**-forms, mirror images of one another.*

"This was really amazing," says Waldor. "No one even knew that bacteria make these types of D-amino acids, and not only were they there, they were there in high concentrations."

The cell wall of most bacteria, including *V. cholerae*, consists of a complex of molecules called peptidoglycans and is separated from the watery cytoplasm of the cell by an inner membrane. Scientists have puzzled over how the inside of the cell coordinates growth with the cell. Waldor's group found that D-amino acids are chemical signals that can downregulate cell wall metabolism when bacteria slow their growth.

His lab group pinpointed an enzyme, called a racemase, that *V. cholerae* uses to create certain D-amino acids and mutated it to test the effects. Without D-amino acids, the cell wall's growth was uncoordinated with the cell's inner growth. The team's findings were published in *Science* on September 18, 2009. ■

–SARAH C.P. WILLIAMS

IN BRIEF

when studying Hox proteins, DNA-binding proteins that help control an organism's development. Different Hox proteins must bind their various DNA targets with high specificity, and scientists didn't know how they did it.

Collaborating with an x-ray crystallographer and a developmental biologist, Honig's lab group previously analyzed images of two different DNA sequences bound to a Hox protein. One sequence was highly specific for that Hox protein; the other was able to bind other Hox proteins as well. They found that the more specific sequence had a narrower groove in its double helix than the other sequence, and this groove was targeted by the protein.

The team's newest findings, published in *Nature* on October 29, 2009, explain why: a narrower groove changes the electrostatic potential of the DNA molecule in that area, facilitating binding to certain proteins. Honig and his collaborators also scanned a database of other DNA-binding proteins to see which would bind to DNA with narrower grooves. They were able to establish some general rules on what protein parts tend to be attracted to narrow grooves. They next want to use this information to develop algorithms to predict how proteins use DNA shape to recognize binding sequences.

PREGNANCY PROBLEM'S LATE EFFECTS

Pre-eclampsia, a complication of pregnancy that leads to high blood pressure and impaired kidney function, seems to resolve itself as soon as the baby is delivered. But scientists have begun to link pre-eclampsia with health problems later in life, including high cholesterol, high blood pressure, heart disease, and stroke. Now, research by HHMI investigator S. Ananth Karumanchi, of Beth Israel Deaconess Medical Center, has also linked it to thyroid problems down the road.

Excess levels of a protein called sFLT-1 lead to pre-eclampsia by blocking VEGF, a protein needed for blood vessel growth and repair, according to Karumanchi's earlier studies. VEGF-blocking drugs are sometimes used to stop the growth of cancerous tumors but these drugs may lead to pre-eclampsia-like signs and symptoms. He noticed that some cancer patients taking VEGF-blocking drugs developed low thyroid function and wondered whether pre-eclampsia patients also had this risk.

Karumanchi combed through data from previous studies and found that women with a history of pre-eclampsia during pregnancy had a one in five risk of low thyroid function over the 20 years following a pregnancy—the normal rate is one in 15 women. The analysis, published online November 17, 2009, in the *British Medical Journal*, could encourage doctors to keep a closer eye on women's thyroid function tests after pre-eclampsia.

GENETIC DIAGNOSIS

For the first time, scientists have diagnosed a genetic disease by sequencing all of a patient's protein-encoding genes—not testing for just one suspected disease. A team led by HHMI investigator Richard P. Lifton used a novel technique to make the rapid diagnosis on an infant in Turkey who was constantly dehydrated and failing to gain weight.

Lifton's lab group, at Yale School of Medicine, started with a blood sample from the patient. Instead of searching the entire genome for a disease-causing mutation, they used a microarray chip that separated out only the protein-encoding DNA—about 1 percent of the genome. Mutations there can lead to proteins being