MEETING AMERICAN CHEMICAL SOCIETY

Chemists Search for Solutions

BOSTON, MASSACHUSETTS—From 18 to 22 August, nearly 15,000 chemists gathered here to discuss work on problems ranging from health to energy sources. Among the highlights: tailored immunosuppressants, a new understanding of the molecular miscues that trigger diabetes, and a novel way of storing hydrogen gas for fuel-cell vehicles.

Sugar Chain Promotes Tolerance

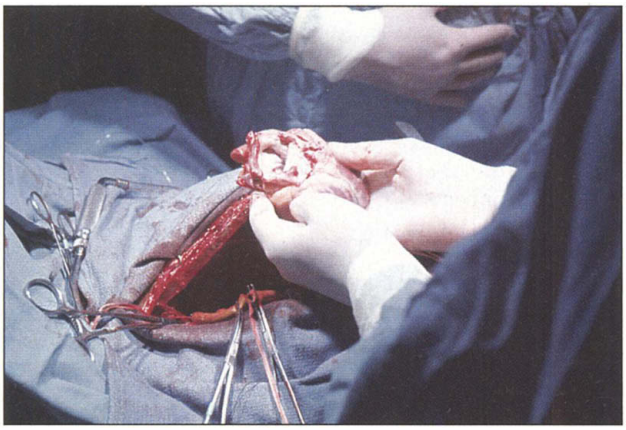
Each year nearly 6000 patients in the United States alone die while waiting for a lifesaving organ donation that never comes. Using organs from animals such as pigs might help relieve the shortage. Unfortunately, the surfaces of pig cells express a sugary coating not found in humans, which prompts the human immune system to mount a violent attack that kills the transplanted organ within hours. Researchers have made progress in engineering pig tissues that don't express the sugar. But at the meeting, chemist Laura Kiessling of the University of Wisconsin, Madison, offered hope for a simpler route: teaching the human immune system to tolerate the alien sugar.

Kiessling reported that she and her colleagues and students synthesized polymers of varying lengths and tested them on animals and cell cultures. Long-chain polymers, they found, provoked strong immune reactions, but short ones—including those made by linking molecules of the death-baiting sugar—induced tolerance.

"It's beautiful work," says Peng G. Wang, a chemist at Wayne State University in Detroit, Michigan, who specializes in making similar complex sugar chains, called carbohydrates. The new work, Wang says, helps explain the fundamental process by which immune cells decide either to mount an immune reaction or to promote tolerance. It should also provide researchers with a systematic way of triggering different types of immune responses—a tool that could prove useful in coming up with drugs to promote tolerance. Such drugs will still likely be years in the making, Wang predicts, "but this is an important first step in that direction."

Using carbohydrate chains to control the immune system is not a new approach. In recent years Samuel Danishefsky of Memorial Sloan-Kettering Cancer Center in New York City and others have made important progress in showing that sugar chains can serve as vaccines by coaxing the immune system to generate antibodies against the sugars—which also abound on the surfaces of cancer cells. Danishefsky's group and others have shown that long chains of the sugars bind to numerous receptors on antibody-generating cells called B cells. If enough of the B-cell receptors are activated, they set off a signaling cascade inside the cell that spurs it to mass-produce antibodies to the sugars, which are then released into the body.

B cells, however, don't launch an immune attack on everything they encounter. In particular, when they run up against smaller amounts of an antigen, they typically ignore it. So Kiessling and her team reasoned that if they made carbohydrate compounds that triggered fewer B-cell receptors, they might generate immune tolerance instead of an antibody attack.



CREDIT: BETTMANN/CORBIS

Hold your fire. A trick with sugars might help the body accept transplants without the need for all-out immunosuppressants.

To find out, Kiessling's students first conducted a test tube test to see if they could induce tolerance to an antigen called dinitrophenyl. They synthesized a series of polymer chains that displayed roughly 25, 50, 100, and 200 dinitrophenyl groups. They then fed the polymers to separate dishes of B cells sporting dinitrophenyl receptors. As expected, the long polymers containing 100 and 200 copies of the dinitrophenyl prompted a strong immune reaction in the B cells, whereas the shorter chains did not.

Encouraged, the researchers turned to galactosyl-α1-3-galactose, the sugar that prompts human immune cells to reject pig organs. Galα1-3Gal, as it is called, is a small sugar, not a polymer. The cells of pig tissue are spangled with copies of the molecule, attached to much larger proteins. In the body of a transplant patient, the sugars bind to clusters of receptors on each B cell, sounding the call to arms that dooms the transplanted cells—just as long dinitrophenyl polymers do. Without this clustering, however, the sugar molecules wouldn't set off the alarm.

To make Galα1-3Gal induce a mild clustering effect, Kiessling's team strung together sugar molecules to build two different polymers, containing 25 and 50 sugar groups. They hoped that the polymers, like the short dinitrophenyl chains, would bind to fewer receptors and thus promote tolerance without setting off the cellular tripwire.

Teaming up with researchers at BioTransplant, a biotech company in Boston, Kiessling's group tested the sugar compounds in mice genetically engineered not to express Galα1-3Gal. Because the mice's immune systems weren't trained to recognize the sugar, they should have launched powerful immune responses when they encountered it. But when the mice were injected with the 25- and 50-sugar polymers, their B cells stopped producing antibodies, presumably because they had become tolerant of them.

The result shows that "we can control whether compounds produce an immunity response or a tolerance response," Kiessling says. And that might lead to a new generation of tailored immunosuppressants designed not to wipe out the entire immune system but rather to lower the body's defenses to just the antigens of choice.

A Master Key to Diabetes?

If Stuart Schreiber is right, researchers might need to rethink their understanding of the molecular misfires that trigger adult-onset diabetes. Schreiber, a chemical biologist at Harvard University across the Charles River from the meeting, described a raft of recent published and unpublished experiments that suggests that diabetes might result from a single nutrient-sensing pathway gone awry rather than from a combination of separate molecular missteps as is commonly thought today. What's more, his team discovered a small, druglike molecule that in test tube studies seems to correct the error and return the cells to normal.

John Schwab, a chemist in the division of pharmacology, physiology, and biological

chemistry at the National Institute of General Medical Sciences in Bethesda, Maryland, calls the new studies "incredibly interesting." Schwab says the work could lead to a new molecular understanding of how diabetes occurs and might eventually pave the way to novel treatments.

Schreiber's group has long been picking up hints that a problem with the way cells sense glucose and other nutrients could play a role in diabetes. In the late 1980s, he and his team started studying the molecular workings of an immunosuppressant drug called rapamycin. They discovered that in mammalian cells rapamycin binds to a protein known as FKBP12 and that the rapamycin-FKBP12 complex, in turn, binds to another protein called FRAP. Later, they found that this molecular trio tricks yeast cells into behaving as if they are starving. It turns off dozens of genes involved in glucose metabolism and cell growth and division, and it turns on a suite of genes that allow the cells to burn proline, a metabolic pathway that is less efficient but valuable when food is scarce.

Such insensitivity to glucose is a hallmark of diabetes. But Schreiber's team didn't know whether the condition in yeast had anything to do with nutrient sensing in humans, who, like other mammals, have a far more complex energy-sensing system than yeast does. The system comes into play when molecular receptors on islet cells in the pancreas detect glucose, a signal that triggers them to release the hormone insulin. The insulin then binds to cells throughout the body and spurs them to metabolize glucose.

In type II (adult-onset) diabetes, however, it is thought that islet cells lose their sensitivity to glucose and that insulin-responsive cells lose their sensitivity to insulin. The prevailing wisdom is that both pathways must go awry for a person to develop diabetes. But Schreiber and colleagues suspected that the story might be simpler than that. Could the FKBP12-rapamycin-FRAP complex, they wondered, override the entire nutrient-metabolism apparatus in otherwise normal mammalian cells, just as it does in yeast? If so, a single molecular monkey wrench might knock out both pathways at once.

The researchers already knew that the complex hit the insulin pathway. Earlier studies had shown that normally insulin-responsive cells treated with rapamycin seemed oblivious to insulin even when they were swimming in it. To find out about the glucose pathway, Schreiber and colleagues bathed rat islet cells in either a high-glucose or a low-glucose nutrient solution. They then added rapamycin to some of the cells and analyzed the effects with gene chips, which tracked the activity level of 8800 different genes in the cells. The glucose-rich cells treated with rapamycin showed essentially the same genetic profile as glucose-poor cells grown without rapamycin. The similarity suggests that rapamycin was somehow interfering with cells' ability to process glucose, thus coaxing mammalian cells into behaving as if they were starving—just as it did in yeast cells. In his talk, Schreiber also noted that drug company data show that as many as 20% of patients who take rapamycin as a drug also develop diabetes.

Still, few diabetics are ever exposed to rapamycin. So how do they develop the disease? Schreiber suspects that either genetic or environmental factors interfere with the same nutrient-sensing pathway that rapamycin strikes.

If so, there might be hope for reversing the damage. In a final set of experiments Schreiber described at the meeting, he and his team created a library of small, druglike molecules and screened for a compound that would block rapamycin's cell-starvation activity. They found one, dubbed SMIR-4, that when added to yeast cells in a glucose-rich medium that was spiked with rapamycin blocked the cells' starvation response and returned their gene expression patterns to normal. Just how SMIR-4 manages the trick is still unclear, Schreiber says. But down the road, either this compound or others like it will likely be tested in animals to see if they can reverse the nutrient-sensing deficiencies that appear to play a role in diabetes. If successful, the compounds could then become candidates for treating diabetes, a disease for which patients at best can only try to minimize their symptoms.

Conducting Plastics Pack the Hydrogen

Hydrogen gas is a tantalizing fuel source, because it generates only water when burned. But the so-called fuel of the future has its drawbacks. Among other things, the gas is so lightweight that it's tough to store enough of it in a vehicle's gas tank. To solve that problem, chemists have sought solid materials that trap hydrogen much as a sponge soaks up water. At the meeting, Sung June Cho, a chemist at the Korea Institute of Energy Research in Taejon, reported a potential breakthrough in the search: cheap polymers that can store about twice as much of the gas as another leading material. If the polymers can release that hydrogen on demand—a feat not yet demonstrated—they could lead to plastic gas tanks that carry cars hundreds of kilometers between fill-ups.

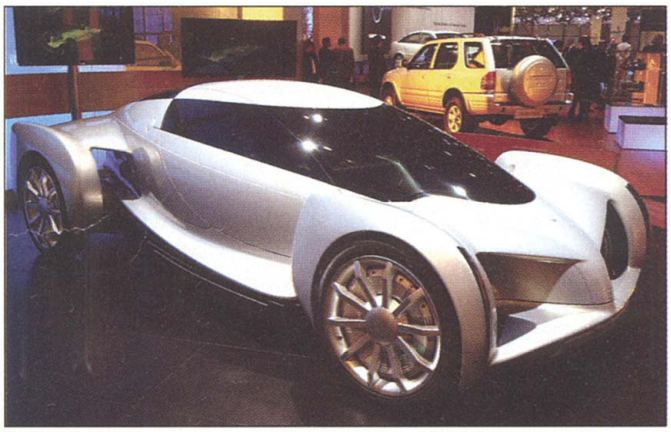
Researchers say they've heard such promises before. In 1999, a team of physicists from Singapore reported that nanotubes spiked with metals could absorb up to 20% of their own weight in hydrogen. That result has never been reproduced. Still, other teams have shown that the tiny tubes can hold about 4% or so, close to the magic figure of 6.5% needed for a viable hydrogen-storage material.

Cho and colleagues suspected that the storage capabilities of nanotubes result in part from their ability to conduct electrical charges, which might help hydrogen molecules adhere. But nanotubes can cost hundreds of dollars a gram, making them impractical for real-world use. So Cho and his colleagues decided to see whether cheaper conducting plastics are equally good at capturing hydrogen.

They got a pleasant surprise. When the researchers made films of polyaniline and polypyrrole—two common conducting plastics—and added pressurized hydrogen, they found that the polymers could hold up to 6% of their weight in hydrogen at room temperature. When they then treated the films with hydrochloric acid, which perforated the film, storage capacity jumped up to 8%.

The result "kind of surprised a lot of people," says Kurt Rothenberger, a chemist at the National Energy Technology Laboratory in Pittsburgh. "This is something that other groups will be very interested in," he says. But Rothenberger and others at the meeting stressed that a practical hydrogen-storage material would have to give up the gas when it is needed. Cho says his team is testing his plastics for that ability right now.

–ROBERT F. SERVICE



CREDIT: LAURENT GILLIERON/KEYSTONE/AP

Gas guzzler. Hydrogen "sponge" might put H-powered vehicles on the road at last.