

## Diabetic mice cast suspicion on protein

When scientists arrive in the laboratory on a Monday morning and discover that some of their prized mice died over the weekend, the misfortune tends to get their attention. One such incident has now thrown a spotlight on a protein that may lie at the heart of type 2 diabetes, which strikes as much as 6 percent of the U.S. population.

Unlike type 1 diabetes, an autoimmune disorder in which the body destroys cells that make the hormone insulin, type 2 diabetes involves both decreased production of insulin and a diminished ability on the part of many tissues to respond to the hormone. Scientists have long found this combination difficult to explain with a single gene mutation, and it is one of many factors pointing to the involvement of several genes in the development of type 2 diabetes.

Yet investigators who have engineered mice to lack a single gene—the one that encodes a protein called insulin receptor substrate 2 (IRS-2)—have found to their surprise that the animals display both of the main characteristics of type 2 diabetes. Many of the mice ultimately fall into a coma and die if untreated.

This discovery “brings together the two arms of the disease in a common molecular pathway,” says Morris F. White of the Howard Hughes Medical Institute (HHMI)

at Harvard Medical School in Boston.

White and his colleagues study how cells respond to insulin, which regulates the concentration of the sugar glucose in blood. Years ago, they discovered IRS-1 and realized that it helps transfer insulin's signal into cells.

When an insulin molecule arrives at a cell, it latches onto a surface protein known as the insulin receptor. That interaction causes a chemical modification of proteins in the cell, such as IRS-1, which then disperse and activate other proteins, explains White.

Mice made to lack IRS-1 don't develop diabetes, however. They are smaller than normal and some tissues don't respond efficiently to insulin, but the mice compensate with insulin-making beta cells that enlarge and proliferate.

Although discouraged by that finding, White went on to create mice without IRS-2, a closely related protein his group had also discovered. When some of those mice died of dehydration at around 8 to 10 weeks, investigators found that the animals' urine was flooded with glucose.

Further studies revealed that the animals' skeletal muscle and liver had developed a significant resistance to insulin. The animals were also unable to boost insulin production. Mice without IRS-2 start life with fewer beta cells than

normal mice, the researchers found. Moreover, instead of making more beta cells as their resistance to insulin developed, these mice continued to lose the insulin producers over time.

It's not clear what role IRS-2 plays in beta cells or even if it acts there only in response to insulin. Whatever the trigger, the protein may help the cells enlarge, proliferate when needed, or avoid death from various stresses, such as high concentrations of sugar in the blood.

Other diabetes researchers remain skeptical that IRS-2 plays a major role in the human illness, noting that White and his colleagues have so far failed to unearth people with diabetes who have flaws in the gene for IRS-2.

“Time will tell how relevant IRS-2 is to the human condition,” says Graeme I. Bell, an HHMI investigator at the University of Chicago. “Mutations in it don't seem very important in man.”

Preliminary investigations have hinted that some people with type 2 diabetes have altered IRS-2 activity, White counters. In those people, mutations in other genes or environmental factors such as body weight may regulate the protein and any role it may play in diabetes.

White suggests that stimulating IRS-2 activity could offer a treatment for either type of diabetes. “If we can figure out what's triggering IRS-2 in beta cells, we have a potential drug target to keep beta cells alive,” he says. —J. Travis

## Cowbirds get head start with egg tricks

Even before breaking out of the egg, the brown-headed cowbird sabotages the nestmates whose home it has usurped.

Several tricks enable the cowbird to win or tie the race to be the first egg to hatch, report D. Glen McMaster of Saskatchewan Wetland Conservation Corp. in Regina and Spencer G. Sealy of the University of Manitoba in Winnipeg. In the February *CONDOR*, they analyze cowbird eggs laid in the nests of yellow warblers, who tend baby cowbirds even if in doing so their own young starve.

By hatching first, the cowbird gets a head start on feeding and becomes the biggest, grabbiest nestling. It overwhelms the young of its host not by pushing them overboard, but by stealing dinner.

Researchers have speculated that cowbirds get their head start by prolonging the incubation needed by eggs of smaller birds. McMaster and Sealy tested the idea by comparing the amount of time yellow warbler eggs took to hatch in more than 41 nests with a cowbird egg and 26 without. The cowbird egg added about a day and a half to the normal 11-day incubation of yellow warblers, the researchers report. Tests in incubators supported the conclusion.

Eric K. Bollinger of Eastern Illinois University in Charleston, who has also studied cowbirds, welcomes McMaster and Sealy's robust demonstration of the prolonged incubation. “They were the first to show it well,” he says.

“It's simply a heat-shielding phenomenon,” Bollinger speculates. Because the cowbird egg is roughly twice the size of the warbler eggs, it keeps the incubating parent from making optimal contact with those eggs.

The new study also suggests that brown-headed cowbirds' eggs develop unusually quickly for their volume. After testing the eggs in incubators, McMaster and Sealy calculate that the cowbird's development indeed outpaces the warbler's.

Cowbirds might even be able to accelerate their hatching after picking up clues that nestmates are ready to break out, the researchers suggest. One hint might be the tiny clicking sounds an embryo makes as it nears hatching and starts to breathe. That clicking seems to help ducks hatch in unison.

McMaster and Sealy checked to see whether cowbird eggs in incubators hatched faster when nestled against warbler eggs. The difference didn't reach statistical significance. “I don't think it completely kills the idea,” McMaster says, noting that incubation failures shaved his sample to just a few eggs. Bollinger isn't ready to dismiss the notion either. “The data are suggestive,” he says. “It's certainly a clever idea.”

Cowbirds are blamed for decreasing the populations of cherished species and threatening the survival of such rarities



*Cowbirds, shown here in a flock of more than 10,000, leave their eggs in the nests of many other species. Although some birds reject the intrusion, at least 140 species will raise cowbird young.*

as the willow flycatcher. Yet the declines are hardly all the cowbirds' fault, McMaster observes. The willow flycatcher has only 10 percent of its original habitat, whereas the cowbird's habitat has expanded as a certain other species has cut down forests. “Is the cowbird really the villain?” he asks. —S. Milius