Insulin May Guide Gene Expression

Eating a piece of cake launches a flurry of chemical processes. As the body digests the cake, sugars and fats entering the bloodstream signal the pancreas to release insulin, a hormone that spreads far and wide, binding to receptor proteins on cells. This starts an intracellular chain reaction that provides the sweet-eater with a jolt of energy.

Like other signaling molecules, insulin sets in motion a bucket brigade of enzymes inside the cell, with each enzyme doing its bit in a process that regulates how the body uses fuel. Instead of dousing a fire, however, this brigade stokes one. Some sugars and fats are promptly stored; others drive cell reproduction and growth.

Research now suggests that, in addition to controlling immediate fuel processing, insulin may also direct the activity of some of the genes that guide energy production. Scientists at Harvard Medical School in Boston studying a gene called *daf-16* in the nematode *Caenorhabditis elegans* have found that when insulin is scarce or absent, proteins encoded by the gene run amok—disrupting the bucket brigade and creating a worm version of diabetes. In worms with a normal supply of insulin, proteins encoded by *daf-16* remain under control.

Surprisingly, however, the researchers also found that nematodes with a mutated *daf-16* gene function normally—even when insulin is missing. If the *daf-16* gene in *C. elegans* has an equivalent in humans, it may become a linchpin in the study of diabetes, they report in the Oct. 30 NATURE.

"Worms without *daf-16* can live without insulin. We're proposing that, in humans, maybe the same is true," says study coauthor and geneticist Gary Ruvkun. "Or, maybe we can turn down the amount of *daf-16* activity in people and mimic what we see in the worm." Ruvkun places the chances of humans having a gene that is functionally equivalent to *daf-16* at "about 90 percent."

The researchers also found that *C. elegans* with mutated genes for insulin receptor proteins were able to grow and reproduce without insulin, provided their *daf-16* gene was inactivated.

The *daf-16* gene is one of several that encode proteins which govern cellular metabolism by guiding the manufacture of the fuel-processing enzymes. Ruvkun and his colleagues have also identified the related *daf-7* and *daf-3* genes and the proteins they encode. The proteins encoded by *daf-16* and *daf-3* resemble frog proteins known to interact with each other, although not as part of the frog's metabolism. This leads the researchers to speculate that the worm proteins also interact on the biochemical level—like "gears in a machine," Ruvkun says.

Human versions of *daf-3* and *daf-16* may also interact to regulate metabolism, Ruvkun predicts. People and worms diverged 800 million years ago on the evolutionary time line, but Ruvkun contends that the hormones and binding proteins that regulate metabolism—all the gears and levers—were present at that point in our common ancestry.

He likens this molecular machinery to durable software. "This is an ancient program," he says. "It makes sense that metabolism would be ancient," because it is basic and essential. The body needs to know when its energy should be stored and made ready for use and when it can relax and use this fuel to rebuild itself.

The cause of diabetes remains elusive, but as this research suggests, the interplay of genes seems to have a role, says biochemist Joan T. Harmon of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md. "We must leave open all pathways for finding the cause. Using models such as nematodes [can have] great advantages. . . . This will be a very interesting story to follow."

Molecular biologist Graeme I. Bell, a Howard Hughes Medical Institute researcher at the University of Chicago, says the research "is setting the stage for what we're going to be able to do in humans" in the future. "What's true in frogs, worms, and mice is often true in man." The researchers, he says, are "generating very interesting clues into a possible defect in man that now we have to pursue."

Ideally, if a drug can be devised to "turn down" or even "turn off" expression of the protein encoded by *daf-16,* "it may replace insulin therapy," Ruvkun says. "That's pointing to an entirely novel way of thinking about treating diabetes. We usually try to mimic insulin."

The new strategy may even be simpler to carry out, he says. Rather than struggle to make drugs that behave like insulin, the preferred course may be to disable *daf-16.* —*N. Seppa*

Melting driven by particle size

When a solid melts, its regular arrangement of particles breaks down into a disordered assemblage. Such an abrupt shift from order to disorder isn't limited to heat-driven melting, however. In a layer with particles of two sizes, a similar change occurs when the ratio of their radii exceeds a certain threshold. Now, researchers have used computer simulations to study that size-driven transition in a mixture containing equal numbers of disks with two different radii.

When one type of particle is 8 percent larger than the other (top left), nearly all of the particles are surrounded by six neighbors, although a few have either five (red) or seven (blue). When the size disparity increases to 10 percent (top right), more such defects appear. Raising the disparity slightly, to 10.2 percent (bottom right), produces a highly disordered, liquidlike state, that is also evident at 12 percent (bottom left), which may include other types of defects (yellow and green).

M. Reza Sadr-Lahijany and H. Eugene Stanley of Boston University and Purusattam Ray of the Institute of Mathematical Sciences in Madras, India, report their results in the Oct. 27 PHYSICAL REVIEW LETTERS. —I. Peterson