Abstractions

LAST AUTHOR

In mammals, blood sugar levels must be carefully balanced: too low, and the brain and other organs are starved; too high, and nerves, blood vessels and organs may be damaged. Thus, when mammals fast, even for brief periods such as during sleep, the pancreas releases glucagon, a hormone that stimulates the liver to produce glucose. Conversely, when mammals eat, an increase in pancreatic insulin instructs the liver to halt this activity. In obesity, this regulation tends to be lost, leading to insulin resistance — in which the liver becomes deaf to insulin's signals — and elevated blood sugar levels, or hyperglycaemia. Marc Montminy and his colleagues at the Salk Institute for Biological Studies in La Jolla, California, have now discovered a mechanism by which the protein CRTC2 (also known as TORC2) contributes to this problem (see page 534). Montminy tells *Nature* more.

What does CRTC2 do?

The CRTC2 protein functions as a genetic switch that triggers glucose production by the liver during fasting. We discovered that, in addition to responding to glucagon, CRTC2 can sense increases in stress in the endoplasmic reticulum (ER) — the cellular site that processes and folds newly synthesized proteins. Normally, ER stress acts as a brake on liver cells' production of glucose. But in obesity, the ER-stress pathway is chronically activated, so CRTC2's ability to cut glucose production is compromised. A component of the ER-stress brake, the protein ATF6, is also reduced, allowing the CRTC2 switch to boost glucose production, leading to hyperglycaemia and insulin resistance.

Can you fix this defect?

We were able to partly restore normal glucose regulation in obese mice by increasing the liver's production of ATF6. We inserted the ATF6 gene into an engineered adenovirus and injected this into obese mice. The virus then travelled to the liver, where it boosted the production of ATF6, restoring it to roughly normal levels. As a result, blood glucose levels stabilized.

How did you get the mice to become obese?

We fed them a Western-style diet in which 60% of the calories were provided by fat. After eight to ten weeks, the mice became obese and displayed physiological changes consistent with insulin resistance.

Does this work have implications for humans?

Developing drugs that modulate the ER-stress pathway in the liver could be of therapeutic benefit to obese individuals who are insulin resistant. ■

MAKING THE PAPER

Taylor Perron

Erosion theory explains uniform patterning of landscapes.

For more than a century, geologists have been aware that some landscapes bear seemingly uniform patterns, such as evenly spaced ridges and valleys. Taylor Perron, a geologist at the Massachusetts Institute of Technology in Cambridge, became intrigued by this ridge–valley 'wavelength' as he observed Earth's topography from aeroplanes, particularly over the central California Coast Ranges between San Francisco and Los Angeles. "Geologists," he says, "have a marked preference for window seats."

Perron and his colleagues, Jim Kirchner and Bill Dietrich at the University of California, Berkeley, decided to examine how erosional processes create these patterns by comparing a computational model with precise measurements of various landscapes. "We agreed that if we were going to try to explain how landscapes form, we'd have to be able to explain these patterns," says Perron.

The first step was to scout for sites — which they did with satellite images and Kirchner's Cessna aircraft — where they would be able to gain access on foot. "If you want to write the equations that describe how the topography evolves, it's important to stand there and see what's happening," says Perron. But accessing such sites required delicate negotiations with landowners, especially on agricultural and ranching lands, where soil erosion is a sensitive topic.

In the Salinas Valley of central California, where rows of lettuce, artichoke and other crops stretch as far as the eye can see, Perron and his team found a ranching family that granted them access to a section of Gabilan Mesa. This is a swath of land with relatively uniform valley spacing that covers thousands of square kilometres.

There, Perron and colleagues took a close-up look at the physical processes sculpting the landscape, including gully erosion, which slowly deepens valleys by scouring soil, and 'bioturbation', such as ground-squirrel burrowing, which gradually smooths the landscape by stirring the soil and moving it downslope. "The basic mechanism is a competition between one process that incises valleys and another process that tends to smooth them out," says Perron.

This mechanism was also found to occur at four other sites the team examined, with differences in climate and rock type accounting for variations in wavelength from site to site.

Next, the authors turned to laser altimetry, a technique that relies on the Global Positioning System and aircraft-mounted lasers to produce precise digital topographic maps, even in landscapes covered by dense vegetation. Using this, the team precisely measured the ridge–valley wavelengths at the five field sites, and tested whether the measured wavelengths matched the predictions of a computational model built from their field observations. To Perron's excitement, they did (see page 502).

Having developed a computational model that accurately predicts the natural patterns in landscapes, geologists can learn more about how factors such as climate have shaped Earth's topography. And the model could potentially be applied farther afield — on Mars, for example, where evenly spaced ridges and valleys have formed on steep slopes such as those within impact craters. Knowing that similar topographical patterns occur on other planets, says Perron, "can tell us many things about those landscapes, even if we can't get there on the ground." ■

FROM THE BLOGOSPHERE

Neil Armstrong's "one small step" to the surface of the Moon has reverberated for the past 40 years. Freelance reporter Lucas Laursen looks back at the Apollo 11 mission, twittering events in 'real time' as they happened in 1969 (http://twitter.com/ApolloPlus40).

In the accompanying blog series, @ApolloPlus40 (http://tinyurl.com/lxp6vu), Laursen has gathered stories of public and political reactions to the missions, as well as the medical and technological doors it opened.

In one post, he covers a 14 July editorial that responded to then NASA administrator Thomas Paine's view that the mission was "a triumph of the squares" (a synonym for nerd) by promoting the astronauts' clean-cut image. Another post tells of the plea of a reverend to Paine to direct agency technology toward the plights of hunger and poverty. Paine is said to have sagely noted: "It will be a lot harder to solve [these problems] than it is to send men to the Moon."

The series continues through the anniversary of the launch, on 16 July, and will cover the duration of the mission, up until 13 August, when the returning astronauts left quarantine. ■

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