Fueling the body on fat

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Researchers have found what appears to be a critical tuning dial for controlling whole body energy, according to a new report in the January issue of *Cell Metabolism*. When energy levels within cells drop, it sets off a series of events designed to increase the amount of calorie-rich dietary fat that the body will absorb.

This energy reset mechanism is surely critical for survival under natural conditions of scarcity to ensure a steady supply of fuel, the researchers say. Today, many of us who enjoy a Western diet loaded with fat might do better if we could find a way to turn the activity of the so-called AMPK-SRC-2 pathway down.

"Thousands of years ago, this would have been crucial," said Bert O'Malley of Baylor College of Medicine. "Now it's trouble because we eat so much fatty food."

Earlier studies had shown the enzyme AMPK to be an ancient energy sensor. The enzyme causes cells to consume less energy in the form of ATP and to produce more. AMPK also drives appetite.

The new work shows that AMPK also allows for the optimal absorption of the most energy-rich fuel from the diet: fat. That effect of AMPK depends on its activation of SRC-2, a master control gene whose job is to switch other genes on.

When SRC-2 springs into action, it controls genes that lead to the secretion of bile from the gall bladder into the intestine. "You need bile

to emulsify and absorb fat," O'Malley explained.

Mice lacking SRC-2 fail to absorb fat normally, they report. Those deficiencies can be corrected by restoring bile acids to the gut.

Together with earlier work, the findings present a "pretty picture" in which SRC-2 is involved in absorbing and storing fat. SRC-2 is also known to play a role in releasing stored glucose from the liver. "It's all about energy accretion, storage and delivery," O'Malley says.

This process takes place on a daily basis even when there is already plenty of fat stored in the body. "It's designed to get in more fat," he says. "Over evolutionary time, when you didn't know when the next meal would be, you really couldn't get enough fat. Now, our next meal is at the corner McDonald's."

The discovery reveals a key mechanism linking the cellular energy state with the whole-body energy state and may ultimately have important clinical implications, the researchers say.

"Obesity is all about fat absorption and storage," O'Malley said. "If you could turn that down, you could have a major effect on a disease that is slowly killing the population." He says his team is now conducting studies in search of SRC-2 inhibitors that might do exactly that.

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