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“Obesity is a major risk factor in the development of adult-onset diabetes, which is characterized by the inability of cells in the body to respond to insulin. By studying key genetic switches that control food intake and metabolism, we hope to identify molecules that will be amenable to drug therapy for insulin-resistant individuals.”

Obesity, which is probably the most important factor in the development of insulin resistance—promotes insulin resistance through the inappropriate inactivation of a process called gluconeogenesis, where the liver creates glucose for fuel and which ordinarily occurs only in times of fasting. Yet, not all obese people become insulin resistant, and insulin resistance occurs in non-obese individuals, leading Montminy and his team to suspect that fasting-induced glucose production was only half the story.

It had been known that a condition known as ER (endoplasmic reticulum) stress is abnormally active in livers of obese individuals, where it contributes to the development of hyperglycemia, or high blood glucose levels. Glucose production is turned on by a transcriptional switch called CRTC2, which normally sits outside the nucleus waiting for the signal that allows it to slip inside and do its work. Once in the nucleus, it teams up with a protein called CREB, and together they switch on the genes necessary to increase glucose output. In insulin-resistant mice, however, the CRTC2 switch seems to get stuck in the “on” position, and the cells start churning out glucose like sugar factories in overdrive.

Surprisingly, when the researchers mimicked the conditions of ER stress in lean mice, CRTC2 moved to the nucleus but failed to activate gluconeogenesis. Instead, it switched on genes important for combating stress and returning cells to health. On closer inspection, they found that in this scenario CRTC2 did not bind to CREB but instead joined forces with another factor, called ATF6a. What's more, like jealous lovers CREB and ATF6a are competing for CRTC2's affection—the more ATF6a is bound to CRTC2, the less there is for CREB to bind to. This clever mechanism ensures that a cell in survival mode automatically shuts down glucose production, thus saving energy. Under the kind of persistent stress presented by obesity, however, levels of ATF6a go down, triggering aberrant glucose production in the liver, and explaining how obesity sets the stage for diabetes and why thin people can become insulin-resistant.

For more information, please visit
salk.edu/faculty/montminy.html



Left to right:

Standing: Sam Van de Velde, Jose Paz, Kim Ravnskjaer, Biao Wang, Youngsup Song, Jeong Ho Kim, Marc Montminy, Bing Luan, Hongbo Wang, Pankaj Singh, Naomi Goebel, Nina Miller, Jason Goode, Noel Moya

Seated: Motoyuki Igata, Yi Liu, Yiguo Wang, Liliana Vera, Susie Hedrick, Kristin Viste, Meghan Hogan