Diabetes as a stress response

The origin of adult-onset diabetes may be a counterproductive stress reaction in the endoplasmic reticulum (ER), according to Umut Özcan, Gökhan Hotamisligil (Harvard School of Public Health, Boston, MA), and colleagues.

Type II or adult-onset diabetes has remained a mystery because the body seemingly acts against its own interests. As caloric intake and obesity rise, the body does not increase insulin responses to pack away the excess energy but instead becomes resistant to insulin’s energy-storing signal. This just makes the situation worse. "You develop a little bit of obesity and then everything starts going crazy," says Hotamisligil.

The Boston team now suggests that the body sees the stress of dealing with excess calories as analogous to an environmental or infectious stress, and responds appropriately. "Insulin is the most powerful signal opposing the mobilization of energy," says Hotamisligil. "You turn it off to mobilize energy against the pathogen or other stress."

The ER appears to be the site of this regulatory action. The Boston team found that indicators of ER stress such as the unfolded protein response were elevated in liver and adipose tissue but not muscle of diabetic mice. Drugs and genetic conditions that exacerbated ER stress, both in cultured cells and diabetic mice, resulted in increased insulin resistance. In cultured cells the converse was also true: an overdose of a stress-fighting protein reduced markers of insulin resistance.

ER stress may arise because extra calories have to be processed by the ER as they get turned into either extra proteins or more lipids. "Under the best conditions the [fat] cell uses all its capacity," says Hotamisligil. The stress signaling goes from the ER to the insulin receptor complex via the immune-activating JNK kinase, which may explain why the immune response is also turned on during type II diabetes.

Muscle is not a secretory cell type and thus may escape the original insult, but other studies suggest that it succumbs to a signal from fat cells that promotes insulin resistance. This signal may have been helpful during evolution but is now less useful, when the greater threat is not bugs but burgers. JCB

Reference: Özcan, U., et al. 2004. Science. 306:457–461.

A SNARE for fast endocytosis

A fusion-promoting exocytic protein is also required for fast endocytosis, based on results from Ferenc Deák, Thomas Südhof, Ege Kavalali (UTSW, Dallas, TX), and colleagues. The requirement may give hints about how neurons recycle synaptic vesicles back into the cell so rapidly, and how exocytosis prepares the way for such a fast process.

Exocytosis is greatly reduced but not eliminated at synapses lacking the SNARE fusion-promoting protein synaptobrevin/VAMP. The group found that endocytosis was delayed in these neurons even if amounts of exocytosis were first equalized at wild-type and mutant synapses by using different stimulation protocols. Dyes provided a further suggestion that mutant synapses had selectively lost fast endocytosis, as mutant synapses released both fast- and slow-diffusing styryl dyes and wild-type synapses released only the fast-diffusing dye.

Hints of an endocytic SNARE role have been seen previously in yeast and flies. But in neither has the link been made to the special case of fast endocytosis. This process is essential for neurons, but the responsible molecules, unlike the clathrin used during slow endocytosis, remain obscure. Fast endocytosis may involve partial retention of vesicle structure (“kiss and run”) between fusion and endocytosis.

What synaptobrevin is actually doing to promote endocytosis remains unclear. It may either act as a nucleator of endocytic proteins or, the authors suggest, be required to take the exocytic vesicle into a pathway that is primed for fast endocytosis. For example, synaptobrevin on the vesicle might attach to plasma membrane SNAREs to set up a hemi-fusion state, but then release the plasma membrane SNAREs before full fusion. Thus disengaged, the hemi-fusion structure could, when the pro-fusion calcium signal arrived, move into full fusion mode and back out to endocytosis without having to wait for SNARE disentanglement. JCB

Reference: Deák, F., et al. 2004. Nat. Cell Biol. doi: 10.1038/ncb1185.