Insulin sends SEC16A packing
Study reveals that a protein known for its role in ER–Golgi transport also controls GLUT4 trafficking in adipocytes.

After a meal, insulin lowers blood glucose levels by stimulating the sugar’s uptake into muscle and fat cells via the glucose transporter GLUT4. Insulin promotes GLUT4’s translocation to the cell surface, a process that goes awry in patients with type II diabetes and which depends, in part, on the small GTPase RAB10. Bruno and Brumfield et al. reveal that RAB10 works with SEC16A—a protein involved in COPII vesicle biogenesis—to form the specialized transport vesicles that ferry GLUT4 to the plasma membrane (1).

Under basal conditions, only a small amount of GLUT4 is present at the surface of adipocytes, whereas the majority of the protein localizes to a perinuclear recycling endosome/trans-Golgi network compartment. Insulin both slows GLUT4’s internalization from the plasma membrane and enhances the transporter’s delivery to the cell surface in GLUT4-specialized vesicles (GSVs), thereby increasing GLUT4 surface levels and glucose uptake (2). GLUT4’s delivery to the plasma membrane is partially inhibited in the absence of RAB10 (3), but exactly how this small GTPase promotes the transporter’s translocation remains unclear. Timothy McGraw and colleagues at Weill Cornell Medical College in New York wanted to identify the proteins that act downstream of RAB10. “Identifying RAB10’s effectors would bring us one step closer to a molecular description of the pathway,” McGraw explains.

McGraw and colleagues, led by Joanne Bruno and Alexandria Brumfeld, took a biochemical approach to the problem, using mass spectrometry to identify proteins from insulin-stimulated adipocytes that bound to the active, GTP-bound form of RAB10 (1). One such interacting protein was SEC16A, and depleting this protein inhibited insulin-stimulated GLUT4 translocation to the same extent as knocking down RAB10.

In addition, knocking down SEC16A prevented active RAB10 from stimulating GLUT4 translocation, indicating that the protein acts downstream of the GTPase. SEC16A nucleates the formation of COPII vesicles at ER exit sites (4), raising the possibility that RAB10 and SEC16A regulate GLUT4 translocation by controlling ER-to-Golgi transport. However, though knocking down the COPII coat protein SEC23A also impaired GLUT4 translocation, depleting other COPII components had no effect on the transporter’s exocytosis. Moreover, RAB10 depletion had no effect on ER-to-Golgi trafficking. “So it seems that there are two pools of SEC16A,” McGraw says. “One involved in ER exit and one—regulated by RAB10—that controls GLUT4 trafficking.”

Accordingly, a portion of SEC16A localized next to GLUT4 in the perinuclear region of adipocytes. Proximity ligation assays revealed that this pool of SEC16A interacted with RAB10 in vivo, and insulin stimulation enhanced this association. Consistent with SEC16A’s role in ER exit, this second pool appears to promote GLUT4’s exit from the perinuclear compartment in GSVs. Knocking down SEC16A appeared to reduce the number of GSVs in insulin-stimulated adipocytes, and slowed the translocation of a reporter protein from the perinuclear compartment to the plasma membrane. “So it seems that, in fat cells, evolution has harnessed some of the machinery that makes COPII vesicles at ER exit sites, and uses it to form these specialized vesicles that ferry GLUT4 to the plasma membrane,” McGraw explains. The formation of these vesicles is enhanced in the presence of insulin, promoting GLUT4’s translocation to the cell surface.

McGraw and colleagues now want to investigate how RAB10 and SEC16A promote GSV biogenesis. They also want to determine whether RAB10 regulates other steps of GLUT4’s transport to the cell surface; the GTPase has, for example, been implicated in GSV docking at the plasma membrane (2, 5–6). SEC16A doesn’t localize to GSVs or the plasma membrane, however, suggesting that other RAB10 effectors may be involved at this stage of GLUT4 translocation.

1. Bruno, J., et al. 2016. J. Cell Biol. http://dx.doi.org/10.1083/jcb.201509052
2. Stöckl, J., et al. 2011. J. Cell Sci. 124:4147–4159.
3. Sano, H., et al. 2007. Cell Metab. 5:293–303.
4. Miller, E.A., and C. Barlowe. 2010. Curr. Opin. Cell Biol. 22:447–453.
5. Bai, L., et al. 2007. Cell Metab. 5:47–57.
6. Sadacca, L.A., et al. 2013. Mol. Biol. Cell. 24:2544–2557.