PKCs pick through $\text{Ca}^{2+}$

Calcium signals destined for mitochondria are first screened by protein kinase C (PKC) isoforms, according to Pinton et al., on page 223. Different PKCs then adjust the organelles’ responses to their liking. PKC is a $\text{Ca}^{2+}$-activated kinase that comes in many flavors. Pinton et al. analyzed the contribution of several of these flavors to $\text{Ca}^{2+}$ signaling by overexpressing or inhibiting individual isoforms in cells. Their effects were assessed by stimulating cells with an extracellular agonist to elicit $\text{Ca}^{2+}$ stores from the ER into the cytoplasm.

One flavor, PKC$\alpha$, limited all $\text{Ca}^{2+}$ signaling by dampening this ER release. Others, however, worked specifically at the mitochondria. PKC$\xi$ increased mitochondrial $\text{Ca}^{2+}$ uptake, whereas PKC$\beta$ and $\delta$ reduced it. Thus, activation of PKC upon initial stimulation may alter the effect of subsequent $\text{Ca}^{2+}$ spikes. Mitochondria are known to respond less to the second of two consecutive stimuli. The authors now show that PKC$\beta$ is needed for this dampening. This function might make cells less sensitive to apoptotic signals, for example, which induce mitochondrial $\text{Ca}^{2+}$ influx.

The PKC isoforms that decrease $\text{Ca}^{2+}$ uptake also decrease mitochondrial membrane potential. There may be a causal link, but mitochondrial $\text{Ca}^{2+}$ transporters have not been cloned, so identifying the relevant PKC substrates will require the purification of mitochondrial proteins that are phosphorylated in response to $\text{Ca}^{2+}$.

Next vesicle SNAP’d up

Secretory vesicles wishing to play follow-the-leader use a particular SNARE to show them where the leader went, as shown by Takahashi et al. on page 255. Vesicles heading to the plasma membrane sometimes selectively bind to another that has already fused there. This process, called sequential exocytosis, is efficient at large-scale secretion because vesicles in the cytosol can be mobilized without being transported all the way to the plasma membrane. Using 2-photon imaging, the authors show that sequential exocytosis is directed by a plasma membrane SNARE called SNAP25.

Sequential exocytosis was examined in insulin-secreting pancreatic $\beta$ cells, in which SNAP25 diffused into the bulge where the leading exiting vesicle had fused with the plasma membrane. SNAP25 rarely diffused into spots where only one vesicle exited, but was seen at the majority of sequential exocytosis sites.

Although sequential exocytosis is common in many exocrine or endocrine cell types (which contain SNAP25), it accounted for only a small fraction of $\beta$ cell exocytosis. Cholesterol depletion freed SNAP25 for easier diffusion and increased sequential exocytosis seven fold. Restricting SNAP25 to lipid rafts might thus be one way to prevent exhausting insulin reserves, which are doled out steadily in small quantities.