Selective clusters

Adam Douglass and Ronald Vale (University of California, San Francisco, CA) find that interactions between proteins, not lipids, drive the formation of plasma membrane microdomains in signaling T cells.

In active T cells, signal transduction proteins cluster within the plasma membrane, probably to enhance signaling by concentrating the interacting proteins. Popular model mechanisms for clustering involve either lipid rafts or actin. But Douglass and Vale found that the signaling proteins themselves hold clusters together.

In their system, T cell clusters included the LAT adaptor protein, the Lck tyrosine kinase, and the CD2 costimulatory transmembrane protein. LAT and Lck are thought to be raft-localized proteins. But mutation of their raft-localizing regions did not alter LAT or Lck diffusion or clustering. By contrast, mutating LAT residues that are essential for protein–protein interactions prevented LAT clustering.

Clusters were also maintained in the absence of actin polymerization, although actin was needed for cluster formation. Douglass and Vale think that actin or actomyosin may be needed for the initial movement of proteins into clusters, but not for anchoring them together.

When tracking single molecules, the authors noticed that LAT and Lck diffused rapidly outside of clusters but became temporarily trapped, probably via protein–protein interactions, when encountering cluster sites. Nonclustering proteins were rarely trapped and were forced to navigate between clusters.

Vale notes that their findings do not rule out the existence of lipid rafts. Rather, the findings support the idea that “protein–protein interactions may be a more common mechanism for creating signaling microdomains,” he says. He hopes eventually to understand why microdomains need to be formed during T cell signaling. “Many people in the signaling field think about which molecules interact with one another,” he says, “but the issue of how the molecules are organized spatially and how this affects their function is often not addressed.” JCB

Reference: Douglass, A.D., and R.D. Vale. 2005. Cell. 121:937–950.

Axon size matters

Noise means an axon can be only so small before it fails, say Aldo Faisal, Simon Laughlin (University of Cambridge, UK), and John White (Boston University, Boston, MA).

Axons are inherently noisy due to the spontaneous openings and closings of ion channels that cause membrane potential fluctuations. When the noise becomes too great, a spontaneous action potential ensues, which can disrupt communication between axons. As the rate of this spontaneous firing increases exponentially as axon diameter decreases, Faisal wondered whether channel noise limits axon size.

To test this question, the team developed a mathematical model that tracks axon dynamics when single ion channels “behave badly,” or open and close at the maximum threshold observed experimentally. Using data from well-studied biological systems, such as specialized cortical rodent and squid axons, they found that axon diameter is the most significant factor affecting spontaneous action potentials; other factors such as channel density, channel conductance, and membrane properties had little effect.

Although the necessary molecular machinery can be packaged into an axon only 0.06 μm in diameter, the model predicted that axon size must be at least 0.10 μm. Below this size, spontaneous axon firing is so prevalent that effective communication between axons becomes garbled. Indeed, the smallest natural axons that they found were 0.10 μm in diameter, with a few unusual exceptions.

The mechanism driving action potentials is one of the best-studied cellular signaling systems, but “it is not well-appreciated that these biological systems are not perfectly reliable,” says Faisal. Recognizing that noise is inherent in biological signaling systems at the nanometer scale is important both for studying cells and for applying nanotechnology founded on similar biomolecular mechanisms. JCB

Reference: Faisal, A.A., et al. 2005. Curr. Biol. 15:1143–1149.