STALLing for signaling

Extracellular receptors anchored in the plasma membrane outer leaflet somehow entice intracellular proteins to the cytosolic side of the membrane for activation. Companion studies by Suzuki et al. (pages 717 and 731) give a peek at these dynamics at the level of single molecules.

The team shows that liganded clusters of the GPI-anchored receptor (GPI-AR) CD59 undergo temporary immobilizations, called STALLs (stimulation-induced temporary arrest of lateral diffusion), which serve as fleeting platforms for activating a signaling cascade. How a signal gets from the outside in without a transmembrane stretch has been intensely investigated.

When GPI-ARs come together, a slew of events take place inside the cell: the cluster can associate with Go proteins, activate Src-family kinases (such as Lyn), and trigger the IP3/calcium signaling cascade. Previous studies based on large aggregates of GPI-ARs pointed to the involvement of raft microdomains for regulating the interactions.

To show how these events occur over space and time, the authors chose a single-molecule approach that used a more physiological clustering of just three to nine CD59 receptors. The CD59 clusters recruited both Lyn and Goi2 frequently and transiently (100–200 ms). The resulting meeting between Goi2 and Lyn activated Lyn and led to a CD59 STALL, which lasted for about half a second.

The STALL may be the result of Lyn’s phosphorylating an unknown protein that hooks the CD59 receptors to actin filaments. However it happens, the STALL created a temporary landing platform for PLCγ, which converts PIP2 to IP3 and thereby releases calcium from the ER. Treatments that interfered with STALLs also blocked the calcium signal.

Each PLCγ molecule hovered at the membrane for only ~0.25 s, but the total IP3 signal has been measured to last for ~15 min. The authors suggest that the bulk signal is produced by the summation of thousands of digital bursts from individual PLCγ molecules. A transmembrane mutant of CD59 also induced Lyn recruitment, albeit at lower levels, leading this group to conclude that both protein- and lipid raft–based interactions are at work. Exactly how a raft microdomain might draw this molecular crowd remains up for grabs.

Bim plays apoptosis offense

A revision of competing ideas about programmed cell death is in order, according to results from Weber et al. (page 625). The work gets a step closer to nailing down the controversial role of the BH3-only family of proteins as playing offense on the pro-death team of apoptotic proteins, rather than defense against the opposing protective agents.

Three groups of apoptosis proteins control a cell’s life-or-death fate: Bax/Bak (the executioners) and BH3-only proteins are pro-apoptotic, whereas a subset of Bcl-2 proteins are anti-apoptotic. But researchers have had a hard time deciding how the BH3-only proteins, a group that includes Bim, factor into the equation. One side argues that BH3-only proteins bind to Bax/Bak directly to turn on these killing machines. Another line of thinking has the BH3-only proteins running interference for the killers by soaking up and neutralizing the protective Bcl-2 members.

Here, Weber and colleagues introduce clues that suggest a bit of rethinking may be in order. An inducible version of Bim showed that high levels of Bim caused death without coming into contact with Bcl-2 protectors. In yeast that lacked any Bcl-2 proteins, Bim still enhanced the death action of Bax. This enhancement appeared to work by helping Bax insert into the mitochondrial membrane—but without a direct interaction.

The authors speculate that the translocation of Bim and other BH3-only proteins into the mitochondrial membrane sets up their pro-death teammate Bax to join them there. In any event, neither the direct-binding model or the displacement model appears to explain entirely how these proteins play the game.