

# In This Issue

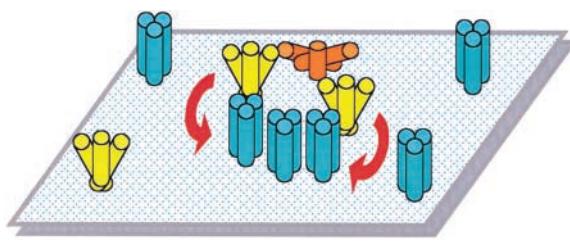
## Ready...set...fuse

The fusion of two lipid membranes underlies a huge range of biological phenomena, from infection by enveloped viruses to the secretion of cellular proteins, but a central aspect of membrane fusion has remained mysterious: do the proteins that mediate fusion act cooperatively or independently?

On page 833, Markovic et al. argue that teamwork is the order of the day in the widely studied model of influenza virus hemagglutinin (HA)-mediated fusion, and suggest that similar cooperative mechanisms may be a general feature of membrane fusion.

At low pH, trimers of HA undergo a conformational transition to mediate fusion between the viral envelope membrane and the membrane of a lysosome, allowing the virus to enter the cytoplasm. Using several approaches in different systems, the authors varied the density of HA trimers on membrane

surfaces and measured the speed and efficiency of the conformational transition. Although HA from two different viral strains exhibited different rates of activation, an increase in HA density always correlated with an



Fusion-competence is infectious.

increase in the percentage of activated HA, indicating positive cooperativity between HA trimers during activation.

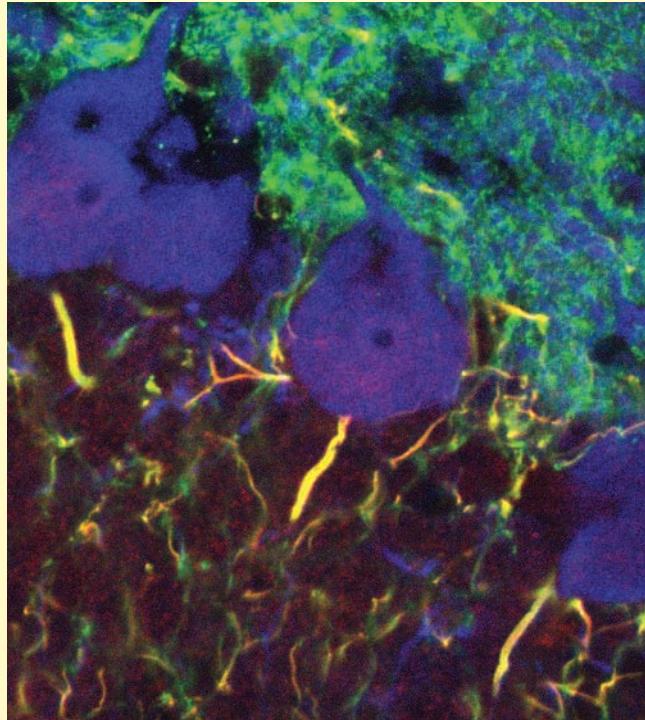
Markovic et al. propose that individual HA trimers establish a transient early state, which then promotes the transition

of neighboring trimers, causing activation to spread cooperatively. HA becomes concentrated in the contact zone because of its tendency to attach to the target membrane. At these higher HA densities in the contact zone, the

probability of activation would increase because each complex would be closer to neighbors that could promote the transition to fusion-competence through lateral contact. This mechanism would reduce the probability of premature HA activation, and would also allow the trimers to coordinate the release of energy that accompanies their conformational change, bringing about membrane fusion.

Besides providing a general model for membrane fusion, cooperative activation might also help explain the behavior of immune complexes and other multi-meric assemblies operating in the plane of a membrane. ■

## Ankyrin recruits a fleet



Ankyrin-G (green) helps cluster  $\beta$ IV spectrin (red) and others.

Axon initial segments are specialized microdomains that integrate neuronal inputs and initiate action potentials. On page 739, Jenkins and Bennett demonstrate that the ankyrin-G adaptor protein is required to coordinate the assembly of the initial segment during early development, and suggest that related mechanisms may regulate the assembly of other microdomains in a variety of cell types.

Concentrated in axon initial segments are both voltage-gated sodium channels and several proteins that have been hypothesized to direct the assembly of the microdomain. In the new work, the authors examined protein localization in Purkinje neuron initial segments during development in wild-type and ankyrin-G mutant mice. Ankyrin-G and  $\beta$ IV spectrin appear at axon initial segments by postnatal day 2, but the sodium channels and adhesion molecules are not fully assembled in the microdomain until seven days later. In mice lacking cerebellar ankyrin-G,  $\beta$ IV spectrin and other components of the microdomain fail to cluster in the axon initial segments.

The results imply that ankyrin-G directs the assembly of voltage-gated sodium channels,  $\beta$ IV spectrin, and adhesion molecules in the axon initial segment to form this critical microdomain. The presence of ankyrin-G in other microdomains, such as neuromuscular junctions and the basolateral domains of epithelial cells, suggests that it may function similarly elsewhere. ■