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 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 multimeric assemblies operating in the plane of a membrane.

Ankyrin recruits a fleet

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 βIV 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, βIV 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, βIV 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.
Heparan sulfate gets specific

Proteoglycans on the cell surface can exhibit a baffling diversity of structures, but the relative importance of that diversity in controlling the specificity of interactions between proteins is not known. On page 845, Allen et al. demonstrate that heparan sulfate serves as a tissue-specific regulator of interactions between FGF family members and FGF receptors. Besides providing important insight into the mechanism of FGF signaling, the work suggests that specific heparan sulfate sequences on a cell’s surface can determine the cell’s ability to respond to exogenous signals.

The formation of an FGF signaling complex requires that both an FGF-family protein and its receptor interact with a heparan sulfate proteoglycan, but little was known about the function of heparan sulfate in this complex. The authors probed frozen tissue sections of mouse embryos with FGF-2 and FGF-4 to detect heparan sulfate expression patterns, and also examined the ability of two FGF receptor constructs to promote FGF signaling complex formation.

FGF-2 and FGF-4 bind to many of the same tissues, but FGF-4 does not recognize heparan sulfate in the heart or major blood vessels. One of the two FGF receptor constructs also demonstrated much less promiscuous complex-forming activity than the other. The results suggest that FGF-2, FGF-4, and FGF receptors recognize different forms of heparan sulfate that are expressed in a tissue-specific manner.

The authors have now expanded their analysis to include five different FGFs and four different receptors, and have determined that both FGFs and FGF receptors seek specific binding sites on heparan sulfate, displaying a binding pattern that changes during the course of development. Because heparan sulfate is also a ligand for a variety of growth factors and viruses, the findings imply a wide range of specific functions for proteoglycans.

Another Notch in CD44

Although the cellular adhesion molecule CD44 is involved in processes ranging from lymphocyte homing to tumor metastasis, it has remained unclear how CD44 transduces the intracellular signals required for such a broad range of activities. On page 755, Okamoto et al. propose a surprising mechanism for CD44 signal transduction: a cytoplasmic domain is cleaved from the protein, after which it translocates to the nucleus and acts directly as a transcriptional regulator.

Previous work demonstrated that the extracellular domain of CD44 can be cleaved by membrane-associated proteases, regulating the interaction between CD44 and the extracellular matrix. Okamoto et al. identified a subsequent proteolytic cleavage that releases a fragment of the CD44 intracellular domain (CD44ICD). This fragment translocates to the nucleus, where it activates transcription from the TPA-responsive transcriptional regulation elements found in front of a variety of cellular genes. CD44ICD overexpression also induces CD44 mRNA expression, suggesting a feedback mechanism to regulate CD44 levels. In addition to illuminating the mechanism of CD44 signaling, the new work provides the first example of an adhesion molecule using a type of signal transduction first described for Notch, in which a cleavage fragment of a membrane receptor serves as a transcriptional activator.

The leg bone’s connected to the...cerebellum?

In a result that bodes well for medical applications of stem cells, Priller et al. report on page 733 that bone marrow-derived stem cells can differentiate into apparently normal Purkinje neurons in an adult mouse brain. Although previous work demonstrated that bone marrow transferred into an irradiated mouse could give rise to cells expressing neuronal markers, the authors are the first to identify donor-derived neurons that appear to be morphologically normal and functional, and to determine that the donor-derived cells survive as the mouse ages.

The authors transferred the green fluorescent protein (GFP) gene into donor bone marrow cells, and then identified GFP-expressing cells in the brains of mice that received the transplanted bone marrow. Donor-derived Purkinje cells were not seen four months after transplantation, but had appeared by 12 months posttransplantation and persisted at least three months beyond that, observations that encompassed most of the lifespan of the mice. Priller et al. speculate that the delayed colonization of the cerebellum by the donor cells may be due to the death of the recipient’s original Purkinje cells during aging. If true, this model suggests that bone marrow-derived stem cells might be able to preferentially regenerate neurons lost to aging or disease.