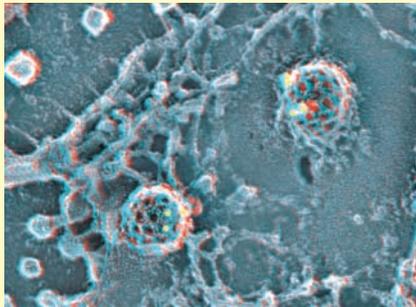


Joined at the Hip

A direct link between clathrin cages and actin is described on page 1209 by Engqvist-Goldstein et al.

The protein that forms the link is huntingtin interacting protein 1 related (Hip1R), which was characterized previously as an actin-binding protein that associates with clathrin-coated pits and vesicles. The related protein Hip1 has been implicated in Huntington's disease, where loss of an



Hip1R (gold) bridges actin and clathrin.

interaction between normal huntingtin protein and Hip1 may cause problems with membrane-cytoskeletal integrity in the brain.

Engqvist-Goldstein et al. now show that Hip1R tightly associates with clathrin during endocytosis

and that purified Hip1R both binds to purified clathrin cages and stimulates cage assembly *in vitro*. They also show that clathrin cages assembled *in vitro* with Hip1R copellet with F-actin at low speed.

Other workers have induced the formation of clathrin coated pits using only clathrin, two coat proteins, and membranes. Actin and Hip1R may be needed, however, for the pits to mature into vesicles. The importance of the actin interaction can now be tested in cell culture systems. ■



Mice lacking two adhesion molecules (right) have smaller cerebellums.

Cooperation in the cerebellum

By crossing knockout mice deficient for two cell adhesion molecules, Sakurai et al. have obtained the first genetic evidence for the molecules' functional overlap, and have explained why earlier tissue culture results were not replicated in single knockout mice (page 1259).

Sakurai and colleagues started by engineering mice deficient for NrCAM, which had only mild (~11%) growth defects in two cerebellar lobes. When the authors crossed the NrCAM-deficient mice with existing mice that are deficient for the related cell adhesion molecule L1, the cerebellum of the double knockout was drastically reduced in size, and the mice were small and never survived later than eight days after birth. The mice probably die because their lack of coordination does not allow them to compete successfully for food.

The cerebellar defect may be largely a result of reduced migration or decreased survival of granule cells. In the double knockout, these interneurons initially differentiate and start migrating correctly, but they reach their final destination in vastly reduced numbers. There is no accumulation of these cells in other areas of the cerebellum, suggesting a survival problem.

The survival hypothesis would be consistent with tissue culture experiments, in which Sakurai et al. added L1 antibodies to cells isolated from NrCAM-deficient mice, and observed a dramatic reduction in viability at around day 14 of culture. More experiments along these lines should reveal the specific functions of L1, NrCAM, and the two other related CAMs (neurofascin and CHL1) in processes such as cell migration, axon bundling, and synaptogenesis. ■

Sticky utrophin messages

On page 1173, Gramolini et al. report that utrophin mRNA is immobilized by binding to an actin-dependent structure. Manipulation of this system may be important for the therapy of Duchenne muscular dystrophy (DMD).

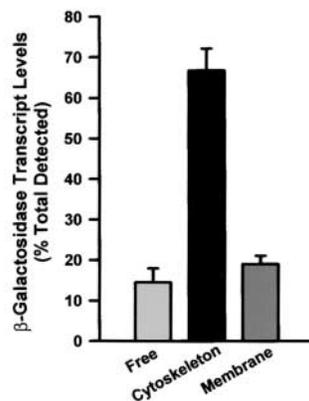
DMD is characterized by a weakened linkage from muscle cells to the extracellular matrix because of a compromised dystrophin complex. Utrophin may be able to substitute for dystrophin, but utrophin's expression is normally limited to the areas near where nerves contact muscle cells. This is due, at least in part, to the concentration of utrophin mRNA to these regions.

In multinucleated muscle cells, the utrophin gene is preferentially expressed

from nuclei that are close to the sites of nerve contact. Gramolini et al. now find that this high localized concentration of mRNA is then maintained by the

binding of utrophin polysomes, via the utrophin 3' untranslated region, to actin-dependent structures.

The possible relevance of these results to DMD therapy arises because individuals with DMD may mount an immune response to dystrophin introduced by gene therapy, given that the individual's body has never seen the protein before. Although increased expression of utrophin should not cause such an autoimmune reaction, the localization of utrophin translation may limit utrophin's usefulness. If, however, the tethering system described by Gramolini et al. can be manipulated with small molecules, the dispersed expression of utrophin may act as one element of a DMD therapy. ■



Utrophin mRNAs bind to actin.