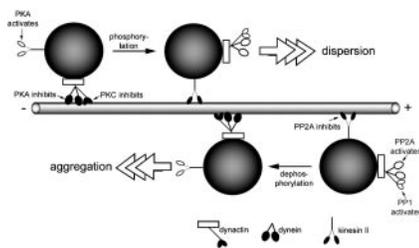


### Regulating Organelle Transport\*

Two major models have been proposed to explain how the direction of organelle transport along microtubules is controlled, and beginning on page 155, Reese and Haimo provide significant new support favoring one model over the other. Kinesin and dynein, the microtubule motor families responsible for transporting organelles in opposite directions, have been studied extensively, but it remained unclear how the overall direction of transport is controlled. In one model, motors cyclically bind to, and dissociate from, organelles, and the types of motors present on an organelle determine its direction of movement. In the other model, both types of motors remain on organelles, but their activity is differentially regulated.

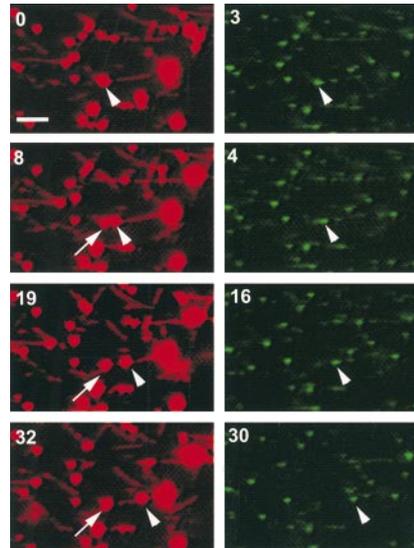


Using frog melanophores, the authors find that cytoplasmic dynein, dynactin, and kinesin II remain attached to pigment granules, whether the granules are being aggregated or dispersed. However, motors and dynactin from melanophores aggregating or dispersing their granules have differential microtubule binding activities that can be reversed by the same phosphatases and kinases that control transport direction *in vivo*. Based on their results, Reese and Haimo propose a model in which phosphorylation and dephosphorylation cyclically activate and inhibit motor–microtubule interactions to determine the direction of organelle transport.

### In Vitro Endocytic Vesicle Sorting System

Beginning on page 179, Bananis et al. describe the first *in vitro* system for studying the segregation of ligand and receptor in early endosomes. In addition

to providing important insights into the mechanisms driving endosome fission, the new work establishes a defined system in which additional factors involved in segregation can be identified and studied.

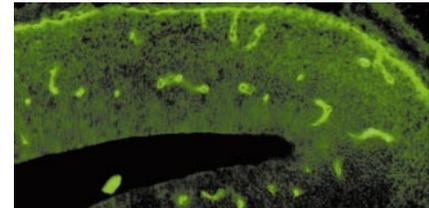


The mechanism by which endocytic vesicles sort ligand from receptor has been difficult to characterize, though previous work suggested that microtubules and molecular motors are involved in this process. Using an endocytic vesicle preparation derived from rat liver, the authors reconstituted the process *in vitro*. This system demonstrates that vesicles must bind to and move along microtubules to undergo fission, which produces two daughter vesicles, one enriched in receptor and one enriched in ligand. Motility and fission require ATP, and are prevented by inhibitors of kinesins, but not by inhibitors of dynein. The researchers conclude that endosome fission requires microtubules and kinesin-based motors, and suggest that efficient segregation of ligand and receptor could occur *in vivo* through multiple rounds of fission. The availability of the *in vitro* system should lead to a more detailed understanding of this process.

### Two Isoforms of Agrin

Burgess et al. (page 41) show that the proteoglycan agrin, which is critical in

organizing synaptic differentiation at the neuromuscular junction, exists in two isoforms with distinct NH<sub>2</sub>-terminal sequences. The two isoforms differ in both tissue distribution and subcellular localization, suggesting a mechanism by which agrin could play diverse roles in cell–cell interactions.



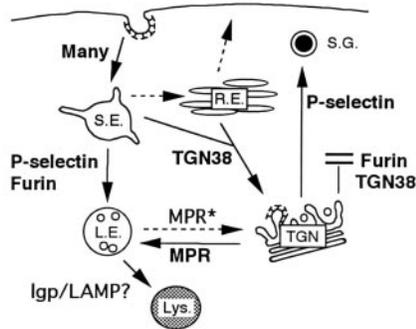
Though agrin is expressed in a variety of tissues, its roles at sites other than the neuromuscular junction have remained poorly understood. In the new work, the authors found that mice express two isoforms of agrin with distinct NH<sub>2</sub>-terminal peptides, dubbed the short NH<sub>2</sub>-terminal (SN) and long NH<sub>2</sub>-terminal (LN) forms. The presence of two isoforms *in vivo* explains the lack of homology between the NH<sub>2</sub> termini of agrins isolated from rats and chickens. Whereas SN-agrin is found primarily in the nervous system, LN-agrin is found in both neural and nonneural tissues. At the subcellular level, LN-agrin is matrix-associated, whereas SN-agrin is attached to the plasma membrane. When LN-agrin expression is abolished in mice, the animals show drastic defects in the formation of neuromuscular junctions. The data suggest that LN-agrin is a component of the basal lamina that plays a signaling role at the neuromuscular junction, whereas SN-agrin may be involved primarily in interactions between neurons.

### P-Selectin Sorting Pathway

In findings that provide important new insights into the mechanisms of receptor recycling, Straley and Green (page 107) show that the transmembrane protein P-selectin is recycled to the TGN through late endosomes, rather than sorting or recycling endosomes. Previous work had suggested that this pathway was used primarily by specialized proteins residing in the

\*The paper highlighted in "Regulating Organelle Transport" was retracted on January 15, 2003.

late endosomes and TGN, but the new results imply that it may be a more general sorting pathway used by a variety of proteins.

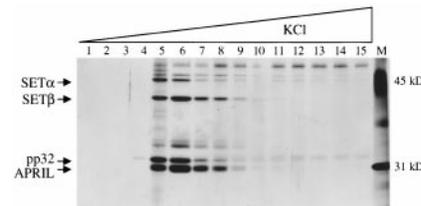


P-selectin, a cell adhesion protein involved in inflammation, is sorted from the recycling pathway used by the LDL receptor in endosomes, but it has remained unclear whether this sorting occurs in early or late endosomes, or a combination of the two. The authors studied the internalization of P-selectin in PC12 and CHO cells, and found that P-selectin is transported to the TGN six to seven times faster than the LDL receptor. P-selectin colocalizes with the LDL receptor for 20 min after internaliza-

tion, but a mutant deficient in endosomal sorting activity is rapidly separated from the LDL pathway, indicating that P-selectin is sorted from the LDL receptor in early endosomes. P-selectin is then selectively transported to late endosomes, resulting in rapid delivery to the TGN.

### Controlling mRNA Stability

Using affinity chromatography, Brennan et al. (page 1) identified four previously described proteins as factors that interact with HuR, a ubiquitously expressed protein that can bind and stabilize mRNAs containing AU-rich elements (AREs). The newly discovered ligands appear to modulate the binding of HuR to ARE-containing mRNAs, suggesting that the ligands could have an important role in regulating mRNA stability.



The stability of ARE-containing mRNAs, which include the mRNAs for protooncogenes, cytokines, and lymphokines, appears to be altered through a variety of cell signaling pathways, but the molecular details of this process have remained unknown. In the current work, the authors identified four protein ligands to HuR in HeLa cell extracts, three of which have been described previously as inhibitors of protein phosphatase 2A, a conserved serine/threonine phosphatase. Two of the ligands are also nucleocytoplasmic shuttling proteins that are exported through the CRM1 nuclear export factor. One model consistent with the data is that the HuR binding proteins modulate HuR activity directly, whereas protein phosphatase 2A acts upstream in regulating ARE-mediated mRNA stability. Since all four of the HuR ligands are associated with cellular growth and differentiation, the researchers suggest that the ligands may help stabilize ARE-containing mRNAs to promote cellular differentiation.

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