In This Issue

Heparin sustains the brain

Amyloid plaque formation can be inhibited by an unlikely culprit, according to work by Scholefield et al. on page 97. The group finds that heparan sulfate (HS)—normally a part of the cell surface and extracellular matrix—functions in cells to slow the production of the plaque components of Alzheimer’s disease.

Amyloid plaques are aggregates of the amyloid β-peptide (Aβ). Aβ is produced upon intracellular cleavage of the amyloid precursor protein (APP) by the BACE1 β-secretase and subsequent processing of one of the resulting fragments by γ-secretase. Plaque aggregation in the extracellular matrix is promoted by HS. Scholefield et al. now show that HS also has an anti-plaque activity: it inhibits BACE1.

The group finds that HS and BACE1 colocalize at the cell surface and in the Golgi—both regions that have been suggested as sites of APP cleavage. HS binding to BACE1 inhibited the protease’s ability to cleave APP by blocking APP’s access to the active site.

The level of inhibition of BACE1 was dependent on various aspects of HS structure, including saccharide length and degree of sulfation. Since HS is widely expressed, basal BACE1 activity may be low unless regulated alteration of HS structural motifs relieves the inhibition. The structural specificity of HS inhibition of BACE1 is also consistent with the fact that HS structures are known to change with age and in Alzheimer’s disease–affected individuals.

In another article in this issue that addresses BACE1 regulation, Lee et al. (page 83) show that BACE1 cleavage is promoted by phosphorylation of APP. These insights into BACE1 regulation should benefit those trying to design drugs that target its activity. Novel heparan-based drugs could even prevent Alzheimer’s in two ways—they might be designed both to inhibit BACE1 production of Aβ and to interfere with HS promotion of Aβ aggregation.

Recycling endosomes: good for the furrow environment

Cytokinesis requires dramatic actin remodeling to produce the wall of actin and myosin that pinches apart the two daughters. Loads of membrane also have to be added to accommodate the increased surface area at the point of separation. On page 143, Riggs et al. show that these two processes may be coordinately accomplished by recycling endosomes (REs)—vesicles that take in and then return plasma membrane components via a centrosome-targeted pathway.

The group had previously found that a centrosome-associated protein called Nuf is necessary for actin remodeling during the cytokinetic-like furrow formation of multinucleated fly embryos—a process that prevents individual dividing nuclei from bumping into each other. Centrosomes organize microtubules but are not known to coordinate actin polymerization. So when Nuf turned out to be a homologue of Arfophilin, a mammalian GTPase effector found on REs, the authors guessed that this vesicle association, rather than centrosome association, was relevant to organizing furrows. Riggs et al. now show that indeed Nuf is part of the RE pathway.

Nuf influences REs by binding to the small GTPase Rab11 and localizing it to REs. Mutation of either Rab11 or Nuf inhibits both membrane recruitment and actin remodeling at early stages of furrow formation. The group suggests two models to explain RE involvement in furrow formation and, by extension, cytokinesis. Vesicles budding from the plasma membrane might grab hold of pieces of actin at the cortex, thus bringing both membrane and actin to the furrow. Alternatively, REs might harbor actin-organizing or -polymerizing activities such as Rac1. If so, REs could be involved in actin remodeling in other processes, including phagocytosis. The results also suggest that other unexplained functions attributed to centrosomes may instead be related to REs.