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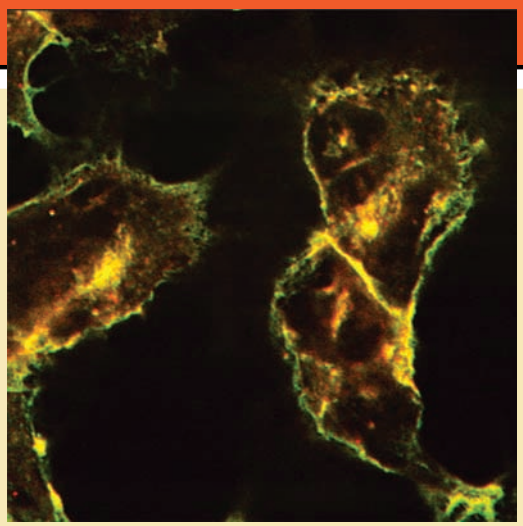
In This Issue

Heparin sustains the brain



Cleavage of APP by BACE1 (red) is prevented by specific HS (green) structures.

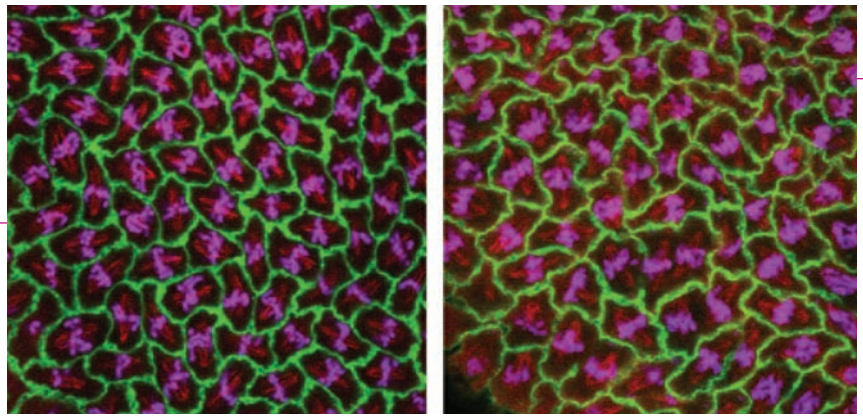
Amyloid plaque formation can be inhibited by an unlikely culprit, according to work by Scholefield et al. on page 97. The group finds that heparan sulfate (HS)—normally a part of the cell surface and extracellular matrix—functions in cells to slow the production of the plaque components of Alzheimer's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



Furrows (green) are not fully formed if recycling endosomes are disturbed (right).

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.

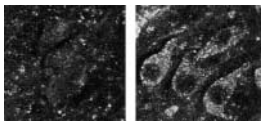
The group had previously found that a centrosome-associated protein called Nuf is necessary for actin remodeling during the cytokinetic-like furrow formation of multinucleated fly embryos—a process that prevents individual dividing nuclei from bumping into each other. Centrosomes organize microtubules 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. ■

Text By Nicole LeBrasseur
lebrasn@rockefeller.edu

To kill a brain cell

The consequences of amyloid formation by the amyloid precursor protein (APP) in Alzheimer's disease (AD) have been the focus of many studies, yet little is known about the nonpathogenic function of APP. On page 27, some progress is made in this direction by Chen et al., who show that APP induces a suicide pathway in neurons.



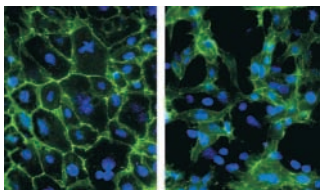
High levels of APP-BP1 (white), as found in Alzheimer's patients (right), kills neurons.

APP initiates this death-inducing cascade when it encounters the binding protein APP-BP1. High levels of APP in neurons, or the APP mutant version associated with AD, promoted the recruitment of APP-BP1 to lipid rafts and activated its death-inducing activity. Past in vitro work has shown that APP-BP1 activates the ubiquitin-like protein NEDD8. NEDD8 conjugation of proteins such as Cullin (part of the SCF complex) drives entry into the cell cycle. In neurons, this push into mitosis somehow causes cell death rather than division. Chen et al. show that the APP-induced death also requires NEDD8 activation, as well as interaction of APP-BP1 with an intracellular domain of APP.

Unusually high levels of APP-BP1 and active NEDD8 were found in brain tissue from AD patients. Thus, constitutive activation of APP-BP1–mediated cell death may contribute to AD. The authors speculate that, under normal conditions, APP-BP1 remains inactive unless APP is bound by some as-yet unidentified extracellular ligand. The physiological relevance of this neuronal death program is unknown, but cloning of the APP ligand may offer some insight. ■

Integrin is on uPAR to unleash cells

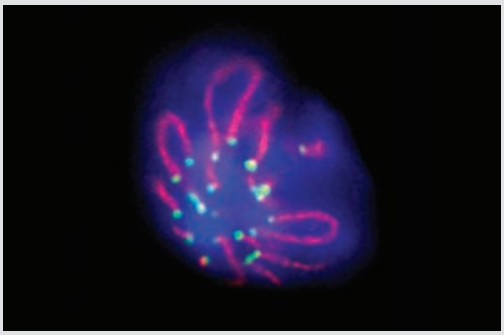
On page 177, Zhang et al. show that the extracellular domain of the α3β1 integrin can hijack a glycolipid-anchored receptor and thus trigger movement of an epithelial cell by inhibiting E-cadherin–mediated cell contacts.



E-cadherin (green) contacts dissolve when uPAR and α3β1 interact (right).

Integrins on epithelial cells are well known to tether the cells to matrix components—laminin-5 in the case of α3β1—but are not usually associated with cell–cell contacts. Zhang et al. show that α3β1 can inhibit cell–cell contacts when α3 binds to the urokinase receptor, uPAR, a known inducer of cell migration in response to certain cytokines. Expression of both uPAR and α3β1 mobilized cells by reducing E-cadherin and γ-catenin levels at cell junctions, thus dissociating the cells. Other uPAR-induced changes included expression of several genes that are associated with the epithelial–mesenchymal transition, such as the transcription factor SLUG.

The mesenchymal phenotype is a result of localized Src kinase activation induced by the uPAR–α3β1 complex. Disruption of Src signaling by overexpression of its protein interaction domains inhibited uPAR-induced cell motility. High uPAR levels are associated with tumor metastasis and a poor prognosis. Since mutations in the α3 extracellular domain that abolish uPAR binding also block motility, mice expressing these mutants may have a better prognosis. ■



Telomeres (green) cluster for too long in spermatocytes lacking H2AX.

Choreographing telomeres

A histone variant involved in DNA repair and phosphorylated in response to critically short telomeres is nonetheless not involved in most aspects of telomere maintenance, according to Fernandez-Capetillo et al. (page 15). Their results suggest that this histone, H2AX, instead choreographs meiotic telomere movements.

Telomeres at the ends of DNA strands are protected by proteins that prevent chromosome fusions. If these proteins are perturbed or if telomeres are severely shortened, the DNA damage response is triggered, repair factors are recruited to telomeres, H2AX is phosphorylated, and chromosome fusions and cell senescence often ensue. H2AX is a target of the ATM kinase, which itself helps to protect shortened telomeres from fusion events.

Given this background, the authors expected that H2AX might also function in telomere maintenance. Instead they found that H2AX mutant cells had telomeres of normal length and had normal chromosome fusion responses to shortened or deprotected telomeres. Telomeres were affected by H2AX loss, however, during a unique organizational stage in which telomeres cluster to form a bouquet-like structure that is associated with the onset of meiotic recombination.

Meiotic H2AX mutant cells were often unable to resolve the bouquet structure, and spermatocyte development frequently stalled at this stage. The group found that the H2AX phosphorylation that occurs in response to recombination-induced double-stranded DNA breaks is reduced in ATM mutants. Dephosphorylation of H2AX might signal that break repair has reached an advanced stage, recombination is near completion, and the bouquet structure can be resolved. This model would explain why development of ATM mutant spermatocytes also stalls in the bouquet stage. ■