Contrasts in neuronal aggregates

The protein aggregates of various neurodegenerative diseases are not created equal. So say Matsumoto et al. (page 75), who find that the aggregates of familial amyotrophic lateral sclerosis (fALS) are unusually porous compared to those of Huntington’s disease (HD).

Both diseases are associated with the neuronal aggregation of a mutant protein in affected individuals. For fALS, the mutant protein is the free radical scavenger SOD1. The authors found that, unlike mutant htt, which forms a solid, impenetrable aggregate in HD, mutant SOD1 formed a honeycomb-like structure. YFP and other globular proteins were able to diffuse freely through cells containing SOD1 aggregates.

Certain proteins were not as free to come and go, however. These proteins might thus be the basis for cellular toxicity. The proteasome, a known interacting partner for many neurodegenerative disease–associated proteins, was trapped by the SOD1 aggregates, as it is by htt aggregates. Proteasomal activity was thus stymied.

Possibly due to this degradation impairment, SOD1 aggregates are generally thought to cause neuronal cell death. Some reports, however, have shown no correlation between the two. Matsumoto et al. believe that the contradictory findings stem from studying populations of cells, only a small percentage of which contain aggregates. Using live cell imaging, the authors were able to follow specifically those cells that formed aggregates. They found that 90% of them died soon after aggregate formation.

If neuronal death in fALS indeed stems from the aggregates’ sequestration of the proteasome, restoring proteasome activity to neurons might be a useful therapeutic strategy. But as different mutant proteins form unique aggregates, researchers should not assume that all aggregate-associated diseases can be treated the same. Aggregates of mutant ataxin-1, for instance, do not sequester the proteasome, suggesting that the same strategy might not counter spinocerebellar ataxia.

Breaking cell bonds

Cell–cell junctions are pulled apart by cytoskeletal traction forces during epithelial cell scattering. The results from De Rooij et al. (page 153) suggest that down-regulation of the cell–cell glue, E-cadherin, is not required in this process.

During cell scattering induced by hepatocyte growth factor (HGF), cell contacts must necessarily be disrupted. The down-regulation of E-cadherin expression or function by HGF has thus been the focus of attention for researchers interested in how epithelial cells acquire migratory abilities. Now, the new findings indicate that cadherins remain functional but are forcibly ripped apart.

HGF-treated cells that did not migrate away from their neighbors maintained functional E-cadherin adhesions. New adhesions were also built as scattering cells made new encounters. Though working properly, E-cadherin adhesions were rapidly lost just as cells started migrating.

According to the authors, the cell–cell junctions are pulled apart by forces stemming from cell–matrix adhesions. Thick actin bundles were seen between matrix-attached focal adhesions in distant parts of the cell and those adjacent to cadherin-based junctions. Active myosin, which contracts actin fibers, localized along these bundles upon HGF treatment.

Strong integrin-based adhesions to collagen and fibronectin supported fast, efficient scattering. The weaker bonds of laminin were less efficient in inducing scattering, even though laminin supported the fastest migration velocity.

Some tension is required to maintain cell–cell adhesions, but clearly too much can be their downfall. The authors are thus curious to know how adhesions measure tension levels and how E-cadherin junctions are pulled apart. Only thin actin filaments were seen linking the cytoskeleton to a cell–cell junction under tension. As thin filaments are probably not strong enough to break cadherin bonds, perhaps a stiff membrane helps out.

As scattering is a model for metastasis, the results are supported by recent findings from others that increased stiffness promotes malignant behavior (Paszek et al. 2005. Cancer Cell. 8:241–254). De Rooij believes that contraction forces are also likely to control the transient lapses in endothelial cell–cell adhesions that allow immune cells to leave the vasculature.
New route to Aβ

On page 87, Yu et al. reveal that autophagic vesicles (AVs) are a breeding ground for the toxic β-amyloid peptide (Aβ). Prevention of abnormal AV accumulation might thus ward off Alzheimer’s disease (AD).

Aβ had previously been localized to nebulous endocytic compartments. Based on evidence that AVs in liver contain the Aβ precursor, Yu et al. wondered whether autophagocytosis also creates Aβ. They found that isolated neuronal AVs contained Aβ and were highly enriched for the enzymes that create it. AVs were a major source of intracellular Aβ, which is increasingly thought to be more toxic than the secreted form.

Healthy brain tissue rarely contained AVs and thus accumulated little Aβ. But the authors found that neurons of brains in the early stages of AD, before neurodegeneration was apparent, contained unusually high numbers of AVs. These compartments normally fuse with degradative lysosomes, which might get rid of any Aβ, but this fusion apparently failed in the diseased neurons.

High levels of Aβ, as in AD neurons, were seen in cells in which the authors used nutrient starvation to induce autophagy. Suppressing autophagy, in contrast, decreased Aβ production. If Aβ oligomers create holes in membranes, as has been proposed, caustic or partially degraded AV proteins might escape into the cytoplasm. Along with Aβ, these troublemakers might be dealt with by therapeutic treatments that promote their digestion, such as AV acidification. JCB

Docked to prevent secretion

Docking state at the plasma membrane is not a prerequisite for vesicle secretion, according to findings on page 99. Gomi et al. find that docking actually impedes vesicle release during regulated secretion.

The secretion of vesicles such as insulin granules must be tightly regulated to prevent unwanted insulin escape. A pool of granules that can be seen attached (or docked) at the plasma membrane seem to be poised for this regulated release, e.g., upon glucose sensing. But the new findings show that glucose-stimulated insulin secretion is even stronger when these docked vesicles are missing.

Gomi et al. first identified the molecule that docks granules as a Rab GTPase effector called granuphilin. In mice lacking granuphilin, the pool of docked granules was missing from pancreatic β-cells. Yet even more insulin was secreted in response to glucose stimulation than from wild-type β-cells.

Granuphilin might restrict secretion by interfering with the membrane fusion machinery. The restoration of docking in knock-out β-cells required the ability of granuphilin to bind, with the help of active Rabs, to a plasma membrane SNARE called syntaxin. The authors found that granuphilin stabilized a fusion-incompetent syntaxin complex. Syntaxin activation, and thus regulated secretion, might be promoted by signals downstream of glucose that inactivate the Rab and release granuphilin. JCB

ER for tiny calcium domains

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iny microdomains of mitosis-driving calcium signals are created by the ER, as shown by Parry et al. on page 47.

Although these calcium spikes were suspected to exist—based on findings that blocking calcium signals prevents mitosis in sea urchins—they have often eluded visualization. Parry et al. were able to detect the calcium spikes by using fly embryos, in which the space between the ER and the mitotic spindle is wider than in other systems.

The group identified two sets of mitotic calcium signals that were shaped by the ER—one large spike between the embryo cortex and the ER, and two smaller spikes between the ER and the spindle. Cortical calcium spiked during interphase. At the cortex, calcium might be inducing the actin rearrangements that separate the nuclei of early fly embryos, as recent findings showed that calcium spikes are needed for cytokinesis.

The two spindle-adjacent spikes occurred just before mitosis and at anaphase. These spikes probably activate calmodulin and its kinase, but their downstream targets are not yet known. As inhibitors of calcium release prevented anaphase chromatin separation, securin and separase are possible targets. Higher concentrations of inhibitors even prevented nuclear envelope breakdown. The authors suspect that cyclins and Cdk5 are other downstream targets, as well as possible initiators, of the calcium signals. JCB