With Aβ, the danger lies within

The most obvious symptom is not always the most relevant. In Alzheimer’s disease (AD), for example, post-mortem brain analyses show large extracellular amyloid plaques of fibrillar Aβ protein. But the plaques arise late, whereas an intracellular version of the toxic protein fragment (Aβ1–42, a fragment of the amyloid precursor protein) is seen earlier, coincident with the first cognitive defects. Now Zhang et al. (page 519) show that minute amounts of this intracellular Aβ1–42 are toxic to primary neurons, even when injected directly into the cytoplasm.

The final concentration of injected Aβ1–42 is 1–100 pM, for a total of somewhere between 1,500 and 150,000 molecules per neuron. In contrast, the same neurons are not significantly affected by up to 10 μM extracellular Aβ1–42, nor by intracellular Aβ1–40. Perhaps because the Aβ1–40 cannot multimerize. Death requires transcription and translation, and the activities of p53, Bax, and caspase 6, probably in that order. The pathway from Aβ1–42 to p53 remains a mystery. Zhang et al. are now looking at kinases that are known to regulate p53 activity.

What goes wrong first in AD is also not clear. If Aβ1–42 exerts its activity in the cytoplasm it must first escape from the secretory pathway. Zhang et al. suggest this may happen by either reverse translocation from the ER or leakage from endosomes. As the details of these pathways are fleshed out, both the trafficking and apoptotic pathways may become excellent targets for AD drugs.

GRASP65 gets the chop

Early in apoptosis, caspase 3 chops up the Golgi stacking protein GRASP65 to fragment the Golgi, according to results presented by Lane et al. on page 495. The fragmentation may cut the Golgi into manageable pieces, and allow dispersion of the pieces so that they can be incorporated into apoptotic bodies near the disintegrating plasma membrane.

Lane et al. map the relevant cleavage sites on GRASP65 to the COOH terminus of the protein. A GRASP65 protein with these sites mutated is no longer cleaved, and the mutant protein preserves ~1/4 of the Golgi stacking after apoptosis induction. Given that GRASP65 is located only in the cis Golgi, it might be expected to protect at most half of the Golgi from a loss of stacking. Lane et al. suspect that other caspase substrates control degradation of the rest of the Golgi, although they show that a number of other known Golgi stacking proteins are not cleaved during apoptosis.

The results with mutant GRASP65 underscore the in vivo importance of GRASP65 in construction of the Golgi, which was previously only hinted at in in vitro assays. This function may be performed by the cleavable COOH terminus of the protein, whereas the vesicle tethering function of GRASP65 relies on the NH2 terminus. The mechanisms by which the COOH terminus carries out its job, including any protein partners, remain unknown.

Building a spindle pole

Castillo et al. (page 453) have identified what may be a key event in building the spindle pole body (SPB) of budding yeast. They found that the kinase Mps1p phosphorylates and thus helps organize Spc42p, an important component of the SPB central plaque. Mps1p has been a difficult protein to study, as it does double duty as a regulator of SPB structure, and as part of the spindle checkpoint signal cascade. Previous conditional mutants have knocked out both functions, perhaps because the mutations have been focused in the catalytic domain of Mps1p. But Castillo et al. aim their mutagenesis at the essential NH2 terminus of the protein. They use a strain lacking Cin8p protein, as this condition makes the checkpoint essential, and thus ensures that any surviving mutant retains Mps1p checkpoint function.

The resulting SPB-assembly mutant, mps1–8, can be suppressed by overexpressed Spc42p. Spc42p communoprecipitates with Mps1p, and is an in vitro substrate for its kinase activity. Finally, Mps1p is necessary for overexpressed Spc42p to form an extended super-plaque.

Mps1p is known to phosphorylate other SPB proteins at other times in SPB duplication. Thus Mps1p is one of several mitotic kinases that have multiple functions. The challenge now is to understand how these many functions are coordinated.