In This Issue

Rafts and the evil amyloids

Lipid rafts are bad news for those with Alzheimer's disease (AD). On page 113, Ehehalt et al. show that formation of the β-amyloid peptide (Aβ), which is tightly linked to AD, depends on the raft association of one of its creators.

The creating enzyme is β-secretase, which cleaves the amyloid precursor protein (APP) to release a product that is then processed into Aβ. Several recent lines of evidence suggest that cholesterol is somehow linked to Aβ production. For instance, high cholesterol levels are correlated with an increased likelihood of developing AD.

As cholesterol is found in membrane lipid rafts, the authors investigated whether APP and β-secretase were linked with these compartments. They found that, indeed, both proteins were found in lipid rafts. Further increasing the fraction of APP and β-secretase in lipid rafts (by oligomerizing each protein) released more Aβ.

The small size of lipid rafts makes it unlikely that both proteins are found within the same raft. The group demonstrates, however, that endocytosis is necessary for Aβ formation. Thus, endocytosis may lead to a clustering of rafts that puts β-secretase within striking distance of APP. The regulation and mechanism of this clustering await further studies.

Decreasing cholesterol levels in cells limited Aβ secretion, but how cholesterol is involved is also not yet clear. Perhaps specific lipids are required to activate β-secretase. The authors plan to use purified secretase and APP to determine whether raft lipids are needed for processing.

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Caspases chew on electron transport

Caspases seem to have their hand in everything during apoptosis. They cleave and activate enzymes that degrade DNA, induce cell blebbing, and induce changes in the plasma membrane that make the dying cell attractive to phagocytes. Now, add another to the list—caspases disturb electron transport.

Ricci et al. (page 65) show that, in both isolated mitochondria and living cells, caspase-3 induces a loss of membrane potential in mitochondria that have been permeabilized by proapoptotic proteins. Inhibition of caspase activity prevented this loss in potential, which places membrane potential loss downstream of cytochrome c release and subsequent activation of caspases.

Mitochondria lost membrane potential because complexes I and II were injured. Caspase-treated permeabilized mitochondria did not consume oxygen in response to substrates used by complexes I and II, although the other complexes remained intact. The interference of the transfer of electrons by complexes I and II to complex III produced reactive oxygen species and is expected to limit ATP production and disturb mitochondrial metabolism. Together, these effects may be critical for dismantling the cell during death, although their importance has not been established. The authors are currently identifying caspase substrates within complexes I and II. They will then determine whether blocking cleavage of these substrates changes either mitochondrial responses to caspases or the pattern of cell death.

Even with fully functioning complexes I and II, apoptosis may still induce DNA damage and cytoskeletal and plasma membrane changes that lead to cell death. But life or death may not be the whole story when it comes to apoptosis. Given the widely conserved nature of various components of apoptosis, perhaps all the small effects are important because they add up to a dying cell that can be readily eaten and quickly discarded.