Cholesterol and Alzheimer’s

Alzheimer’s disease (AD) presents in early- and late-onset forms that share the same neuronal pathology but have different genetic causes. A new study by Qiang Liu, Guojun Bu (Washington University, St. Louis, MO), and colleagues now suggests that both AD forms are linked to a cholesterol pathway.

Cholesterol was already linked to late-onset AD. The best-known risk factor for this disease is a specific form of apolipoprotein E (apoE), which delivers lipids such as cholesterol to neurons. But early-onset AD stems from mutations in genes encoding amyloid precursor protein (APP) or its cleaving enzymes, which result in the accumulation of disease-associated Aβ amyloids. How these disparate pathways both lead to AD was not known.

In addition to Aβ, APP cleavage also produces the APP intracellular domain (AICD) peptide. Liu et al. now show that AICD blocks the apoE pathway, thereby lowering cholesterol levels in the brain. AICD blocked the lipid’s import into neurons by reducing the expression of the apoE receptor, LRP1.

In AD, APP processing goes awry might cause AICD to accumulate, thus depriving neurons of cholesterol. Both early and late forms of AD may therefore stem at least in part from faulty, cholesterol-deprived neurons.

“We now have a better idea of APP’s function in the brain,” says Bu. “It could be linked to disease through both Aβ-dependent and -independent mechanisms.” JCB

Reference: Liu, Q., et al. 2007. Neuron. 56:66–78.

Structure of the meiotic spindle

The meiotic spindle is made up of shorter microtubules than previously believed, suggest results from Ge Yang, Gaudenz Danuser (Scripps Research Institute, La Jolla, CA), Ben Houghtaling, Tarun Kapoor (Rockefeller University, New York, NY), and colleagues. Current models of the spindle, as a bipolar array of overlapping filaments extending from opposite spindle poles, will require revision.

To get a closer look at the architecture of the meiotic spindle, Yang et al. incorporated labeled tubulin subunits into the spindle in a cell-free system. By refining their fluorescent speckle microscopy techniques, the authors were able for the first time to track individual tubulin subunits (seen as speckles) in a single tubulin polymer.

The authors identified pairs of speckles representing subunits on the same filament. Speckle separation supplied them with the minimum length of that filament. They then fitted a mathematical model to these observed lengths to predict overall filament lengths: most filaments were only ~40% of the total spindle length. The short filaments were also scattered throughout the spindle. The researchers now propose that the spindle is a tiled array of overlapping short filaments.

The group next examined how spindle-associated proteins might control filament and spindle size. By inhibiting microtubule motor proteins, they found that dynein–dynactin limited individual fiber lengths and thus overall spindle length. Kinesin 5 activity limited the overlap between fibers by sliding them apart. “Our work suggests the spindle is a self-organizing system, whose stability and functional characteristics are built on these kind of local interactions,” says Kapoor. JCB

Reference: Yang, G., et al. 2007. Nat. Cell Biol. doi:10.1038/ncb1643.

Localized mRNA is the norm

location, location, location. It’s critical for real estate, proteins, and—according to work by Eric Lécuyer, Henry Krause, and colleagues (University of Toronto, Canada)—mRNAs, too.

Several localized mRNAs have been previously studied, but just how many transcripts are localized in the cell, and in what patterns, is unknown. Lécuyer et al. approached this problem by optimizing fluorescence in situ hybridization (FISH) in a global analysis of developmentally expressed mRNAs. They found that 71% of the mRNAs in early fly embryos showed specific patterns of subcellular localization.

In several cases, they found new examples of mRNAs that colocalized with their protein products. Less energy is probably required to transport a few copies of an mRNA than to move around many more copies of the protein. And the proteins will be created where they are needed and possibly prevented from straying where they are not wanted.

“We need to revise the textbook image of proteins being made in a centralized location near the nucleus, then trafficking to their ultimate locations,” says Krause. “Our work shows that the mRNAs are an intelligent actor, not just a dumb vehicle for creating proteins.” With their new database, the group can now further investigate how and why mRNAs are localized. JCB

Reference: Lécuyer, E., et al. 2007. Cell. 131:174–187.