

Untangling a deadly conspiracy

King et al. reveal on page 541 how tau and β -amyloid might collaborate to spark the cellular devastation of Alzheimer's disease (AD). The findings suggest that the two rogue proteins team up to break down the microtubules that enable neurons to deliver necessities to their axons.

AD's hallmarks are β -amyloid plaques that pile up outside of neurons and tangles of tau that amass inside. How the two proteins interact remains mysterious, but previous work indicates that β -amyloid lies upstream of tau in the cell damage pathway.

To clarify the connection, King et al. engineered kidney cells to pump out tau. In neurons from AD patients, microtubules collapse. The researchers saw the same effect when they dosed their engineered kidney cells with A β 42, a particularly destructive version of β -amyloid.

Individual β -amyloid molecules can link together into long, tough fibrils that are prevalent in plaques. The cells were impervious to this fibrous form of β -amyloid, however, supporting the hypothesis that fibrils represent the brain's attempt to incarcerate ruinous β -amyloid.

A β 42 also triggered microtubule breakdown in neurons, but not if the researchers first blocked tau with RNAi. The scientists now want to decipher how β -amyloid prods tau to do its bidding to cause microtubule collapse. Breaking down microtubules might harm neurons by interfering with the transport of essential cargo into axons and delivery of patches to fill gaps in the cell membrane. **JCB**

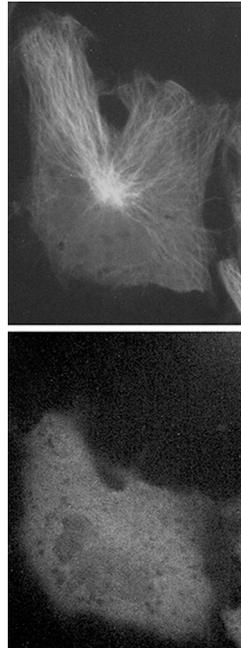
Lining up microtubules

Like a deaf bat, a kidney cell without a cilium is cut off from its surroundings. It can't tell up from down or sense fluid movements and concentration gradients. By aligning microtubules within the cell, a protein implicated in the development of kidney cysts is vital for building cilia, as Schermer et al. show on page 547.

Patients lacking the von Hippel-Lindau tumor suppressor protein (pVHL) suffer from a profusion of cancers and kidney cysts. Several other cyst-promoting kidney diseases involve cilia defects, and previous work suggested that pVHL was essential for making cilia.

Schermer et al. probed pVHL's influence on microtubules, which form the core of the cilium. Contradicting a prior study, the researchers found that loss of pVHL didn't speed the breakdown of microtubules within kidney cells. However, removing the protein did seem to alter the direction in which microtubules grow. In cells lacking pVHL, microtubules point every which way. But in cells that manufacture the protein, the tubes are oriented in roughly the same direction, toward the cell's boundary.

How pVHL exerts its effects remains a mystery, but the team found that it gloms onto a protein complex that helps direct cell polarity. The researchers now want to determine how pVHL collaborates with this protein complex to chart the right path for microtubules. **JCB**



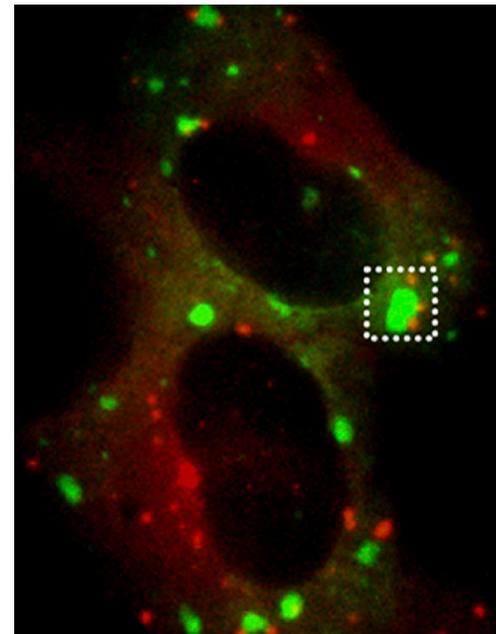
With tau's aid, β -amyloid spurs the cells' microtubule network (white) to crumble (bottom).

Molecular mothballs for RNA

Stressed-out cells pack away all but their crucial messenger RNAs for better times. The zipcode binding protein (ZBP1) functions as a preservative for the stored RNA, as Stöhr et al. report on page 527. By sheltering some cached molecules, the protein might help cells to recover quickly once conditions improve.

Heat, reactive oxygen species, and other harsh stimuli shut down production of proteins not needed for dealing with the stress. Cells switch off the nonessential proteins by diverting their mRNAs into stress granules. These structures can hold onto the strands or pass them to processing bodies for digestion. Researchers don't know why some mRNAs escape break-down.

ZBP1 stabilizes several RNAs in the cytoplasm, prompting Stöhr et al. to investigate whether it does the same in the stress granules. The protein doesn't dictate which mRNAs gather in the organelles, the researchers found,



Stress granules (green) pass mRNAs not protected by ZBP1 to processing bodies (red) for destruction.

but it does influence what happens to them. Knocking down ZBP1 increases the deterioration of four RNAs that ZBP1 binds but does not affect the decay of non-ZBP1 targets.

Depleting ZBP1 also reduces the amount of mRNA that remains in the storage granules. The missing strands presumably depart for processing bodies or other sites where they are chopped up. **JCB**