tion and promote the rational design of strategies for accelerating groundwater remediation.

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PERSPECTIVES: BIOMEDICINE

Tauists and βaptists United—Well Almost!

Virginia M.-Y. Lee

The brains of Alzheimer's disease (AD) patients contain two hallmark pathological features: neurofibrillary tangles composed of tau protein and senile plaques composed of deposits of amyloid-β peptide. A controversy still rages over whether tau tangles or amyloid-β plaques are the primary cause of neurodegeneration in AD, and each has its vocal advocates—the tauists and βaptists, respectively. Yet despite decades of intense research, the primacy of each pathology is still in dispute and the connection between them remains largely speculative. Work described by Lewis *et al.* (*1*) and Götz *et al.* (*2*) on pages 1487 and 1491 of this issue, respectively, provides convincing evidence that a causal connection exists between the two pathologies. Both groups independently demonstrate in transgenic mice that amyloid-β deposits influence the formation of tau tangles in brain areas that are known to be affected in AD.

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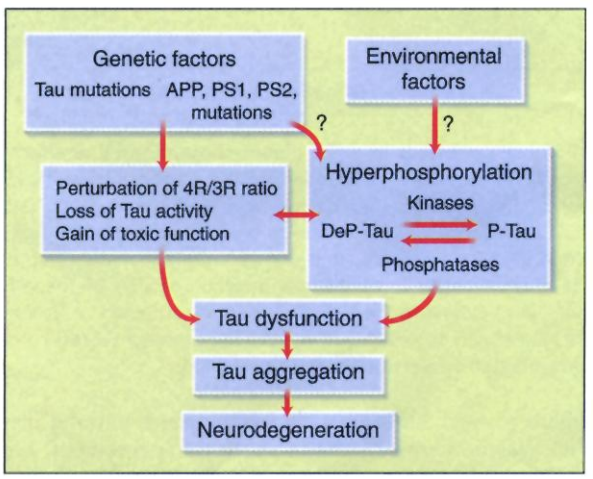
Patients with an early-onset familial form of AD carry mutations in genes encoding either amyloid-β precursor protein (APP) or one of the presenilin proteins (*3*–*5*). These mutations appear to cause AD by increasing the production of the stickier form of amyloid-β peptide ($A\beta_{1-42}$), thus implicating amyloid-β plaques in AD pathogenesis (*6*–*9*). Mutations in the gene encoding tau, a microtubule-binding protein, have been found in several neurodegenerative diseases linked to chromosome 17 (collectively called the tauopathies). The discovery of tau neurofibrillary tangles in the absence of amyloid deposits in these diseases provides unequivocal evidence that tau abnormalities alone are sufficient to cause neurodegeneration in the brain (*10*–*12*). The puzzle is that mouse models of AD do not accurately recapitulate the dual pathology of the disease. For example, transgenic mice that overexpress APP carrying a familial AD mutation do not develop tau tangles (*9*, *13*). Furthermore, bigenic mice—generated by crossing APP transgenic mice (with amyloid deposits) and wild-type tau transgenic mice (with tau inclusions)—do not show classic AD pathology in which amyloid plaques are surrounded by a corona of dystrophic neurites containing intracytoplasmic tau tangles (*14*).



Tau in the middle. The importance of tau in the pathogenesis of neurodegenerative diseases, including AD and the tauopathies. Patients with the early-onset familial form of AD carry mutations in APP, or presenilin 1 or 2 (PS1, PS2), which result in increased deposition of amyloid-β peptide. In the tauopathies, mutation of the tau protein results in several changes including an upset in the 4R/3R ratio (tau isoforms with either four or three microtubule-binding repeats), an altered ability of tau to bind to microtubules, and increased aggregation of tau into filaments. These changes lead to accumulation of abnormally hyperphosphorylated tau filaments in intracytoplasmic clumps called neurofibrillary tangles. Amyloid-β deposits have now been found to exacerbate tau tangle formation in brain regions of transgenic mice that are known to be involved in AD. (DeP-Tau and P-Tau, dephosphorylated and phosphorylated tau, respectively).

In the new work, Lewis *et al.* (*1*) and Götz *et al.* (*2*) independently demonstrate that amyloid-β influences the formation of tau tangles in transgenic mice. Lewis *et al.* detected many more tau tangles in the limbic system and the olfactory cortex of bigenic mice (Tau/APP) expressing both mutant tau (P301L) and mutant APP compared with transgenic animals expressing only mutant tau. This suggests that either APP or its product amyloid-β influences the formation of tau tangles. Taking a different approach, Götz *et al.* directly injected the fibrillar form of amyloid-β peptide, $A\beta_{1-42}$, into the hippocampus of tau mutant mice and observed a dramatic increase in tau tangles in the amygdala, one of the regions affected in AD. It is intriguing that tau tangles did not develop in the hippocampus—the site where $A\beta_{1-42}$ was injected—but rather appeared in the amygdala, a site to which hippocampal neurons project. A remarkably similar separation of tau and amyloid-β pathology is described by Lewis *et al.* (*1*) in their Tau/APP mice. Amyloid plaques did not comingle with tangle-bearing neurons, and the classic AD plaques with a corona of tau-positive dystrophic neurites were not found in these mice. Although neither of these two transgenic mouse models recapitulate all aspects of AD pathology, they both provide important insights into AD pathogenesis by showing that interactions between amyloid-β and tau lead to increased tau tangle formation

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in brain areas known to be involved in AD.

Multiple lines of transgenic animals engineered to develop AD-like amyloid-β plaque formation have been developed. Yet despite the presence of abundant senile plaques in these mice, there appears to be little or no neuronal cell loss (*15*, *16*). This suggests that amyloid deposits alone may be insufficient to cause neurodegeneration. In contrast, the formation of tau tangles accompanied by axonal and/or neuronal loss has been detected in several transgenic mouse models of tauopathies (*17*, *18*). Indeed, a recent study from Feany's group showed that transgenic flies overexpressing wild-type and mutant forms of human tau accumulate tau protein, resulting in progressive neurodegeneration and eventual neuronal loss in an age-dependent manner (*19*). Intriguingly, the wild-type and mutant fly models of tauopathy did not develop the neurofibrillary tangles characteristic of rodent and human AD, although aggregates of tau were detected. An earlier study in lamprey fish demonstrated that expression of wild-type tau in lamprey neurons resulted in tau-rich tangles and degeneration of the neurons containing them (*20*). Because the development of tau tangles is an invariant feature of both the rare familial form and the common sporadic form of AD, it is tempting to speculate that the formation of tau tangles or aggregates may be a necessary prerequisite for neurodegeneration in AD (see the figure). The identification of a number of neurodegenerative diseases characterized by tau tangles (either with or without other pathologies) suggests that tangle formation may initiate as well as contribute to the final step in the relentlessly progressive brain degeneration that characterizes AD. Future experiments with Lewis's Tau/APP mice could test this hypothesis by determining whether brain regions that have more tangles than plaques also have increased neuronal loss.

The discovery of possible interactions between amyloid-β deposits and tau tangles and the availability of transgenic mouse models containing both pathologies will facilitate efforts to develop more effective AD therapies. Indeed, the success of several emerging therapeutic approaches that target the production, aggregation, and clearance of amyloid-β peptide deposits is likely to depend on the severity or stage of AD brain degeneration and the extent of tangle formation. Thus, eliminating amyloid-β deposits by administering an amyloid-β vaccine may improve cognition in AD patients who have few tau tangles, but may have little or no effect on late-stage AD patients who have already developed significant tau pathology. It would be wise for future AD therapies to combine targeting of amyloid-β deposits with strategies for eliminating tau tangles.

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PERSPECTIVES: CELL BIOLOGY

Caveolae—Not Just Craters in the Cellular Landscape

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Caveolae—flask-shaped invaginations in the plasma membrane—are present on many types of mammalian cells, including endothelial cells, smooth muscle cells, and adipocytes. Like lipid rafts (their close relatives), caveolae are plasma membrane assemblies of glycosphingolipids and cholesterol that are associated with specific molecules including signaling proteins (*1*, *2*). Often they contain the protein caveolin and have proteins anchored to glycosylphosphatidylinositol (GPI), a plasma membrane phospholipid. But exactly why cells have caveolae or lipid rafts is puzzling. They are believed to be involved in cholesterol transport, the transport of solutes across endothelial cells, tumor suppression, and signal transduction through immune and growth factor receptors. In addition, it seems they have been commandeered by several species of viruses, parasites, and bacteria (and even bacterial toxins) to enable these pathogens to enter host cells (*3*–*13*). Classic endocytosis (uptake of extracellular agents) depends on clathrin-coated pits and involves an intracellular pathway in which lysosomes fuse with internalized vesicles, degrading their contents. In contrast, and clearly of benefit to pathogens, caveolae-dependent endocytosis does not feed into the lysosome pathway and does not result in the degradation of the contents of caveolar vesicles.

If taken up into host cells by classic endocytosis, intracellular pathogens must avoid degradation in the endosome-lysosome pathway, either by escaping from their endocytic vacuoles (phagosomes) into the cytoplasm (before lysosomes fuse with phagosomes) or by actively neutralizing the microbicidal agents inside the phagolysosome after fusion. Smart pathogens and bacterial toxins can avoid this problem by binding to caveolae and triggering endocytosis through a pathway that avoids lysosomes altogether. *Escherichia coli* bacteria that express the FimH antigen use caveolae to invade phagocytic cells such as macrophages (*3*, *4*). Under serum-free conditions in culture, FimH-expressing *E. coli* are internalized by phagocytes and, strikingly, remain viable within phagosomes, which fail to fuse with lysosomes (*3*). Known disrupters of caveolae formation block uptake of FimH-expressing *E. coli* but not of opsonized *E. coli* (bacteria coated in antibody) that are taken up into clathrin-coated pits and enter the classic endosome-lysosome pathway (*4*). Apparently, caveolae-dependent endocytosis is triggered when bacterial FimH binds to its GPI-anchored receptor CD48 in the caveolae of the host cell (*4*). Once bound to caveolae, the bacteria become encapsulated within caveolar vesicles characterized by specific markers (cholesterol, caveolin, and G_{M1}) (*4*).

A broad range of pathogens (or their products) prefer caveolae- or lipid raft–mediated endocytosis, including: mycobacteria (*5*), simian virus 40 (SV40) (*2*), *Toxoplasma gondii* and *Plasmodium falciparum* (malaria) parasites (*6*, *7*), and toxins of *Vibrio cholerae* and *Helicobacter pylori* bacteria (*8*, *9*). Caveolae are also important in pathogen trafficking within the cell after endocytosis, as exemplified by the fact that they shuttle SV40 virus to the endoplasmic reticulum (*2*) and cholera toxin to the Golgi apparatus (*8*). In some cases, the endocytosed microbial cargo is directly transported across the cell (transcytosed), as exemplified by human im-

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