NEURODEGENERATIVE DISEASES

Possible New Cause of Alzheimer's Disease Found

Scientists usually blame errors in protein structure on mistakes in the DNA—the genes that are passed on from one generation to the next and provide the blueprints for proteins. But as any manufacturer knows, mistakes can arise not only in the blueprint, but also on the production line. A team of Dutch scientists reports on page 242 that aging cells seem to be plagued by mistakes in protein assembly, possibly contributing to the brain degeneration characteristic of Alzheimer's disease (AD).

Fred van Leeuwen and his colleagues at the Netherlands Institute for Brain Research in Amsterdam have found a new kind of faulty protein in the abnormal plaques and tangles that are hallmarks of Alzheimer's brain pathology. While 40% of Alzheimer's cases apparently arise from specific gene mutations, there seems to be nothing wrong with the DNA blueprints for these proteins. The scientists theorize that the mistakes arose during protein synthesis—and that such mistakes may help cause Alzheimer's in the majority of patients.

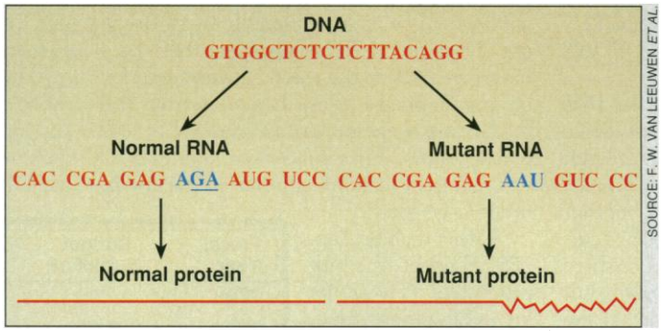
Some researchers caution that the results are preliminary and are based on tests that could be misleading. But others, including Zaven Khachaturian, who is a scientific adviser for the Alzheimer's Association, say that if it is right, the work could help explain why age is the greatest risk factor for developing AD—because the protein errors would presumably increase with time.

And the findings may have even wider importance. Similar mistakes could take place in thousands of proteins, says Rudolph Tanzi of Harvard University, contributing not only to other age-associated diseases, but also to aging in general. If so, he says, the finding would have "profound implications beyond the genes that they're looking at."

The team first found evidence for such protein-synthesis mistakes more than 10 years ago in an unusual breed of rat, which carries a mutation in a gene that helps regulate urine production. As expected, those rats produced none of the normal protein at birth, but surprisingly, as the animals aged, more and more of the normal protein showed up in their brain cells.

A closer look at both the DNA of the gene and the messenger RNA (mRNA) transcribed from it, which tells the cell to make the corresponding protein, provided an explanation. The scientists found that the mutation itself—a loss of a single base pair that shifts the genetic code by one, totally garbling the instructions for making the protein—was still present. But some of the mRNA had acquired a compensating mistake: In decoding the RNA, the cell had misread a "GAGAG" sequence, shortening it by two bases to "GAG." Because three bases code for one amino acid—the actual building blocks of proteins—the loss of two more bases restored the proper reading frame and produced a functioning protein.

In subsequent work, the team found evidence for the same type of GA deletions in mRNAs in the brains of normal aging rats and humans. Because GAGAG, the sequence that is prone to being misread, shows up in mRNAs coding for hundreds of different proteins, van Leeuwen and his colleagues decided to search for other proteins affected by frameshift errors. They looked at two proteins involved in Alzheimer's disease: β amyloid precursor protein (βAPP) and ubiquitin. No one knows exactly what the βAPP does normally, but it can be cleaved to produce a smaller protein—β amyloid—that is abundant in Alzheimer's plaques. Ubiquitin is a garbage-disposal protein, marking faulty proteins for degradation and disposal in the cell. It, too, is common in Alzheimer's plaques and also in tangles.



Assembly-line slippage. Loss of two bases (GA) in the mRNA for the β amyloid precursor protein garbles the rest of the sequence.

To see if mutant proteins were present in AD brains, the scientists synthesized the theoretical proteins that would result from GA deletions and injected them separately into rabbits, which produced antibodies to the proteins. The scientists then applied the antibodies to brain samples from Alzheimer's patients and people with Down syndrome, who develop early symptoms of AD. The antibodies reacted with their target proteins in almost all the Alzheimer's and Down samples, and in elderly nondemented controls with early signs of plaques and tangles. Samples from young controls showed no reactivity.

The researchers then took a closer look at the proteins stained by the antibodies. In mixtures of proteins from Down and AD patients' brains, the team's antibody stained a 38-kilodalton protein—the size expected of the βAPP mutant, because the frameshift produces an early stop signal that makes the mutant roughly half as big as the normal protein. In addition, analysis of mRNAs turned up examples of GA deletions in all of the AD and Down syndrome patients studied.

The scientists speculate that as cells age, the protein assembly line becomes more error-prone, causing mutated proteins to build up and somehow damage cells. For example, the loss of normal ubiquitin could allow the cell to choke on faulty or unneeded proteins. "It's like when the garbage can is not emptied," says van Leeuwen. "It causes big problems for the cell."

How a shortened βAPP could contribute to the disease is harder to explain. Indeed, a shortened protein might even interfere with a mechanism most Alzheimer's researchers favor: They believe that abnormal cleavage of βAPP produces a longer than normal form of β amyloid, which tends to form toxic deposits that eventually kill brain cells. But the shortened version of βAPP might not be able to produce β amyloid at all, says John Hardy of the Mayo Clinic in Jacksonville, Florida.

Indeed, Hardy isn't convinced that altered βAPP and ubiquitin are present in diseased brains. The brain cells affected by Alzheimer's are so damaged, he says, that the antibodies could be staining many things besides the mutant βAPP and ubiquitin. And even if the mutant proteins are present, he says, "they are much more likely to be an effect than a cause" of AD brain damage. While van Leeuwen concedes that it's unclear how the GA deletion in βAPP might lead to AD, he says there are several possibilities. For example, the mutant protein might disrupt the processing of the normal protein so that it produces the longer form of β amyloid.

The current evidence is already enough to intrigue Khachaturian. The work "puts [AD] in a different frame of reference." he says, and provides a plausible connection between AD and aging. Caleb Finch of the University of Southern California in Los Angeles adds that he, for one, will pay close attention to errors in protein synthesis. The finding raises "many perplexing mysteries," he says, "but their resolution will be the basis for a whole new set of hypotheses" about how the disease causes its devastation.

—Gretchen Vogel