Editorial

Alzheimer's Disease

By

A. El-Sheshai

History

Alzheimer, a psychiatrist, looked in the brain and created a paradigm shift, at that time, by saying that a mental disorder, in his patient who was a 51-year-old woman with dementia in the asylum, was due to physical lesions in the brain. This did not go over well, the idea that physical lesions were causing this disease. And for decades we looked at these lesions, wondered about them, and asked questions about them. It wasn't until 1984 that Glenner, who studied amyloids (abnormal deposits of protein that misfolded and are conformationally abnormal), was able to take the amyloid from the senile plaques and also the amyloid around blood vessels in patients, and using a variety of chemical methods (at the time they were pretty revolutionary), he was able to dissolve the amyloid and come up with this amino acid sequence. He called the sequence of the small protein in the amyloid-beta peptide, A-beta, and when this sequence was published in 1984, it wasn't really a great revelation at the time. He predicted that the gene for A-beta making up the amyloid would be on chromosome 21 because he took the amyloid from Down syndrome patients (Bertram L,et al.2004). It turns out that Down syndrome patients who have an extra copy of chromosome 21 inevitably get AD-type pathology in the brain by middle age. So Glenner published the sequence, and predicted a gene on chromosome 21. In 1987; we found that the amyloid peptide precursor (APP) gene was indeed on chromosome 21. Glenner was right and APP would then be identified as the first AD gene. We finally had a target, something tangible to look at and ask, "How does this cause the disease?".This is what we learned. The APP gene is sticking out of a membrane so it looks like a stick, and the A-beta peptide can form amyloid. Normally, this protein, which plays multiple roles in the membrane, has to be clipped. You have to have different clips to release the A-beta peptide. Normally, along with the age, we produce some of this small peptide in the brain (Tanzi RE, et al.2000).The problem is: why do you produce more of itn AD? There are 2 ways. You can produce more or you can clear it away less. This has become really important now in the disease; we have to think both about the production of this peptide in the brain and also how the brain deals with it. Can it be cleared away? Some genes affect production, some genes affect clearance, and all of these genes are suggesting ways to treat this disease at its very roots, by either curbing production of A-beta or clearing it away. In 1990 the first mutations were found. Actually, the first mutation was found in a vascular AD case, and subsequently early-onset AD families were found. Warwick Daw, et al.Then we realized that only a handful of families could be explained by the APP gene, that most of the early-onset dominant AD in families was still unexplained. It wasn't until 1995 that we found 2 other genes called the presenilin genes, and we found that the presenilin genes worked at the level of the clips. In order to get the A-beta peptide released, 2 enzymes have to work, beta-secretase and gamma-secretase sequentially. The presenilins, we realized, are needed for the clip at the bottom of the A-beta peptide. Instantly we saw how this might play a role in the production of the peptide. In the end we would find that there are 150 different mutations in presenilin and APP, and they all lead to the same common culprit, A-beta 42. What is A-beta 42? It's a peptide that has 2 extra amino acids on the end making it extra prone to amyloid formulation and extra toxic to nerve cells. It's the A-beta 42 that is really the minor fraction of A-beta in the brain, but 150 different mutations in these genes increase that particular peptide(Mah Al,et al.2000).

The Molecular Genetics of Alzheimer's Disease

Over the last 2 decades, the discovery of the genes underlying AD has done more than anything else to guide the development of novel