DEMENTIA IN 2012

Further insights into Alzheimer disease pathogenesis

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In 2012, studies of autosomal dominant Alzheimer disease (AD), late-onset AD, and a rare genetic mutation of amyloid precursor protein provided support for the critical role of amyloid in AD pathogenesis. Increasing evidence implicated cell-to-cell transmission in the spread of tau and amyloid, highlighting novel targets for therapeutic intervention.

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2012 witnessed the failure of two amyloid-β (Aβ)-targeted drugs, bapineuzumab and solanezumab, in phase III trials for Alzheimer disease (AD)-related dementia. Such disappointing results have raised concerns about whether the treatments were initiated too late in the disease, whether Aβ levels were sufficiently reduced, and/or the validity of the 'amyloid cascade hypothesis', which places Aβ at the heart of AD pathology.

> "... the AD process begins more than 20 years prior to onset of dementia..."

Until now, much of the causal evidence for this hypothesis has come from studies of families with autosomal dominant AD, who have genetic mutations that lead to overproduction of Aβ. A recent paper by Bateman *et al.*[1] from the Dominantly Inherited Alzheimer's Network (DIAN) study is noteworthy, therefore, as it provides a comprehensive description of the sequence of clinical and biomarker changes that occur in autosomal dominant AD, enabling comparison with such changes in late-onset AD (LOAD)—the sporadic form that accounts for most AD patients. Bateman *et al.*[1] evaluated 88 carriers of mutations that cause autosomal dominant AD, and 40 healthy noncarriers. Clinical and cognitive parameters were assessed, as well as various brain scans and cerebrospinal fluid (CSF) levels of Aβ, tau and/or phosphorylated tau. Expected year of dementia onset (EYO) for each individual was estimated on the basis of the age of disease onset in their affected parent.

Differences in Mini-Mental State Examination score between mutation carriers and noncarriers were detected 5 years before EYO, and differences in memory function were detected 10 years before EYO. Decreased glucose metabolism in the precuneus in mutation carriers was detected 10 years before EYO, and hippocampal atrophy was detected 15 years before EYO. In addition, mutation carriers had substantial Aβ deposition in the precuneus and caudate nucleus 15 years before EYO—a pattern different to that seen in LOAD. Similar to studies of patients with LOAD, CSF tau was elevated 15 years before EYO, and CSF Aβ reached low levels 10 years before EYO, with concentrations seeming to decline as early as 25 years before EYO. Together, the findings of this study[1] suggest that the AD process begins more than 20 years prior to onset of dementia.

A limitation of the study by Bateman *et al.*[1] is that it used cross-sectional data to infer the longitudinal progression of events. Nevertheless, the finding that gene mutations that lead to overproduction of amyloid cause a sequence of biochemical and clinical changes similar to those seen in LOAD is consistent with the amyloid cascade hypothesis for LOAD.

Further evidence that the AD process begins several years prior to onset of dementia was provided by Buchhave *et al.*,[2] who found that CSF $A\beta_{1-42}$, but not tau, had reached disease-associated levels up to 10 years before onset of LOAD.

A landmark publication in 2012 by Jonsson *et al.*[3] added strong support to the amyloid cascade hypothesis through identification of a rare variant of the amyloid precursor protein (*APP*) gene that seems to protect carriers from AD. The investigators searched whole-genome sequence data from a large Icelandic cohort, including those aged at least 85 years without a diagnosis of AD, for *APP* mutations that affect AD risk. They found the single nucleotide polymorphism rs63750847—which results in an Ala673Thr substitution in APP—was significantly more common in elderly controls without AD than in the AD group (1/OR = 5.29), indicating strong protection against AD. In individuals aged 85, rs63750847 was enriched in those who were cognitively intact compared with those who had dementia (1/OR = 7.52). Furthermore, age-adjusted cognition was significantly better in carriers of rs63750847 than in noncarriers.

The Ala673Thr substitution on APP is located close to the target site of β-site APP cleaving enzyme 1 (BACE1)—the enzyme that generates Aβ, suggesting that the variant might impair BACE1 cleavage. Jonsson *et al.*[3] found that production of Aβ was reduced in cells transfected with Ala673Thr APP versus Aβ production in wild-type cells, and the mutant peptide was processed 50% less efficiently than wild-type peptide in a BACE1 cleavage assay. This study is the first example of a sequence variant conferring strong protection against AD, and indicates that reducing BACE1 cleavage of APP (that is, reducing production of Aβ) could protect against AD.

Despite considerable evidence for a causative role for Aβ in AD, focal neurodegeneration and symptomatology correlate most strongly with extent and amount of tau and/or phosphorylated tau deposition in the brain. Furthermore, memory impairment correlates with the level of tau-containing neurofibrillary tangles in the entorhinal cortex (ERC) and hippocampus.

The mechanism by which tau spreads from the ERC (possibly originating in the brainstem[4]) to the hippocampus and cortex has been a topic of great interest. The 2012 reports by Liu *et al.*[5] and deCalignon *et al.*[6] shed important new light on this issue. Both groups created a transgenic mouse model in which a mutant form of tau (linked to neurofibrillary tangle formation in frontotemporal dementia) was selectively expressed in a fraction of layer II neurons in the medial ERC (mERC). Using various staining techniques to detect misfolded tau pathology, they found production of misfolded tau in the mERC at

Key advances

- Studies of autosomal dominant Alzheimer disease (AD) suggest that the disease process begins more than 20 years prior to onset of dementia[1]
- A mutation in the gene encoding amyloid precursor protein that prevents cleavage into amyloid-β (Aβ) protects against late-onset AD[3]
- Misfolded tau seems to be transferred from neuron to neuron[5,6]
- Inoculation of mouse brains with Aβ produced widespread cerebral amyloidosis[7]

> “...research highlights of 2012 provide new support for the central role of amyloid in AD pathogenesis”

3–6 months of age. Mutant tau pathology was found months later in the granular layer of the dentate gyrus, followed by its accumulation in hippocampal subfields, and then in the cortex. Given that the mutant tau was only expressed in the mERC and not in ‘downstream’ regions, the pattern of spread suggested that misfolded tau is transferred to new cell populations, recapitulating the tauopathy that defines early stages of AD. These results also highlight a potential approach to therapy that targets cell-to-cell transmission of tau.

Along similar lines, Stohr *et al.*[7] investigated cell-to-cell transmission of Aβ through inoculation of mouse brains with either purified Aβ from brain aggregates or with synthetic Aβ aggregates. The intervention was found to cause widespread cerebral amyloidosis, leading the authors to conclude that Aβ alone is sufficient for formation for a self-propagating protein assembly, and that “Aβ aggregates are prions.” Indeed, reviewing evidence for cell-to-cell spread of Aβ, tau, α-synuclein, superoxide dismutase, and huntingtin protein, Prusiner[8] proposed that “proteins causing neurodegeneration are all prions.”

Despite these advances, the mechanism by which Aβ and tau interact to cause AD remains poorly understood. Accumulation of Aβ in transgenic mice does not produce the characteristic tauopathy, and in human frontotemporal dementia and chronic traumatic encephalopathy, widespread deposition of misfolded tau occurs without accumulation of Aβ. Nevertheless, the important findings reported in 2012 concerning cell-to-cell transmission of tau and Aβ certainly suggest new targets for therapy.

In conclusion, despite disappointing results from clinical trials of anti-amyloid monoclonal antibodies, the research highlights of 2012 provide new support for the central role of amyloid in AD pathogenesis. In addition, the growing number of papers reporting cell-to-cell transmission of tau, amyloid and other misfolded proteins highlight an exciting area that will lead to improved understanding of the mechanisms by which these proteins cause neurodegeneration and lead to clinical symptoms, and could provide targets for development of new therapeutics.

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Competing interests
The author declares an association with the following company: Elan. See the article online for full details of the relationship.

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EPILEPSY IN 2012

Advances in epilepsy shed light on key questions

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Research on epilepsies in 2012 has substantially advanced our knowledge of these often devastating conditions. From important discoveries that revealed causative factors and the molecular basis of disease, to major implications for surgical decision-making, these studies set the scene for future advances in the field.

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A common and often devastating group of disorders, the epilepsies deserve an intense research focus to improve our understanding of their neurobiology and, thereby, improve the lives of affected individuals. In 2012, some studies in this field employed prospective large-cohort designs to answer key questions, whereas others yielded insights into the molecular determinants of both mild and severe epilepsies, as well as cortical malformations.

Therapeutic epilepsy surgery, although undeniably effective in lesional epilepsies, has been applied late and inconsistently in most patients. Publishing their results in 2012, the Early Randomized Surgical Epilepsy Trial (ERSET) study group compared surgical therapy with continued medical therapy in patients with refractory mesial temporal lobe epilepsy (MTLE)—an epilepsy in which surgery generally carries a good prognosis.[1] Participants had MTLE that was well-localized in terms of both imaging and EEG, and had failed two adequate trials of antiepileptic drugs. A unique feature of this trial is that participants were included within 2 years of failing their medication trial, which enabled comparison of surgery with medical therapy at the earliest point that patients could be deemed ‘refractory’. The researchers hypothesized that early, successful treatment would minimize both long-term comorbidities and risk of premature death.[2] Surgery early in the course of epilepsy, however, was still regarded as so radical that the trial was unable to recruit adequate numbers of participants and was stopped prematurely, with only 38 of the planned 200 participants included.

Despite recruitment difficulties, the trial was overwhelmingly positive: seizure freedom at 2 years was achieved in 73% of surgically treated patients ($n = 15$) compared with none of the medical therapy group ($n = 23$).[1] Disabling seizures were defined by the presence of objective features, impaired function or awareness, or convulsive attacks. Isolated auras were not included in the assessment. Drawing of conclusions with regard to the secondary outcomes, such as quality of life, was difficult owing to the small sample size, but a trend towards improved quality of life