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A Century of Alzheimer's Disease

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One hundred years ago a small group of psychiatrists described the abnormal protein deposits in the brain that define the most common neurodegenerative diseases. Over the past 25 years, it has become clear that the proteins forming the deposits are central to the disease process. Amyloid-β and tau make up the plaques and tangles of Alzheimer's disease, where these normally soluble proteins assemble into amyloid-like filaments. Tau inclusions are also found in a number of related disorders. Genetic studies have shown that dysfunction of amyloid-β or tau is sufficient to cause dementia. The ongoing molecular dissection of the neurodegenerative pathways is expected to lead to a true understanding of disease pathogenesis.

On 3 November 1906, at the 37th meeting of the Society of Southwest German Psychiatrists in Tübingen, Germany, Alois Alzheimer presented the clinical and neuropathological characteristics of the disease (*1*, *2*) that Emil Kraepelin subsequently named after him (*3*). Alzheimer's disease (AD) is now the most common neurodegenerative disease, with more than 20 million cases worldwide. At the time of his lecture, Alzheimer was head of the Anatomical Laboratory at the Royal Psychiatric Clinic of the University of Munich. He had moved there in 1903 after having spent 14 years at the Municipal Institution for the Mentally Ill and Epileptics in Frankfurt, where Franz Nissl had introduced him to brain histopathology. In November 1901, Alzheimer admitted Auguste D., a 51-year-old patient, to the Frankfurt hospital because of progressive memory loss, focal symptoms, delusions, and hallucinations. After the death of Auguste D. in April 1906, her brain was sent to Munich for analysis. Alzheimer's use of the silver staining method developed by Max Bielschowsky 4 years earlier (*4*) was crucial for the identification of neuritic plaques and neurofibrillary tangles, the defining neuropathological characteristics of the disease. Whereas plaques had been reported before, first by Blocq and Marinesco in an elderly patient with epilepsy (*5*), Alzheimer was the first to describe the tangle pathology. In 1911, he found a different type of nerve cell inclusion in two cases with focal degeneration of the cerebral cortex (*2*). This is now known as the Pick body (even though it was first described by Alzheimer) and the clinicopathological entity is known as Pick's disease, after Arnold Pick, who first described it in 1892 (*6*). Pick's disease belongs to the spectrum of frontotemporal lobar degeneration (FTLD).

The presence of abnormal deposits helped greatly with disease classification (*7*). However, their molecular composition and role in the pathological process remained unknown. Over the past 25 years, a basic understanding has emerged from the coming together of two independent lines of research. First, the molecular study of the deposits led to the identification of their major components. Second, the study of rare, inherited forms of disease resulted in the discovery of the causative gene defects. In most cases, the defective genes encode the major components of the pathological lesions or factors that change their levels. It follows that a toxic property of the proteins that make up the filamentous lesions underlies the inherited disease cases. A similar toxic property may also cause the much more common sporadic forms of disease. Here we review the evidence implicating amyloid-β and tau in neurodegeneration.

Abnormal Filaments

In the electron microscope, plaques and tangles contain abnormal filaments (*8*, *9*). Plaque filaments are extracellular and have the molecular fine structure of amyloid. This term refers to filaments with a diameter of around 10 nm that have a cross-β structure and characteristic dye-binding properties. Most tangle filaments have a paired helical morphology and are also amyloid-like. Paired helical filaments are present in nerve cell bodies, as well as in neurites in the neuropil and at the periphery of neuritic plaques. After the identification of filaments (*8*, *9*), it took another 20 years before their major components were known. The identification of amyloid-β as the major plaque component and tau as the major tangle component ushered in the modern era of research on AD (Fig. 1A). Filamentous tau deposits are also present in a number of other neurodegenerative disorders, including Pick's disease (Fig. 1B).

Amyloid-β

Amyloid-β is 40 to 42 amino acids in length and is generated by proteolytic cleavage of the much larger amyloid precursor protein (APP), a transmembrane protein of unknown function with a single membrane-spanning domain (*10*–*13*) (Fig. 2A). The N terminus of amyloid-β is located in the extracellular domain of APP, 28 amino acids from the transmembrane region, and its C terminus is in the transmembrane region. The enzymes whose activity gives rise to the N and C termini are called β-secretase and γ-secretase, respectively. A third enzyme, α-secretase, cleaves between residues 16 and 17, precluding amyloid-β formation. The major species of amyloid-β are 40 or 42 amino acids long, and it is the more amyloidogenic 42–amino acid form (with its two additional hydrophobic amino acids) that is deposited first (*14*). In the three-dimensional structure of the amyloid-β fibril, residues 1 to 17 are disordered, with residues 18 to 42 forming a β-strand–turn–β-strand motif that contains two parallel β sheets formed by residues 18 to 26 and 31 to 42 (*15*).

Mapping of the *APP* gene to chromosome 21, together with observation of plaques and tangles in most elderly individuals with Down's syndrome (trisomy of chromosome 21), suggested an important role for amyloid-β. However, direct genetic evidence was lacking. It came from work on hereditary cerebral hemorrhage with amyloidosis–Dutch type (HCHWA-D), a rare condition characterized by recurrent hemorrhages resulting from the deposition of amyloid-β in cerebral blood vessel walls. HCHWA-D is caused by a missense mutation in the amyloid-β portion of APP (*16*). Six years after the purification of amyloid-β from meningeal blood vessels of AD brains (*10*), this was the second time that cerebral blood vessels were found to play a crucial role in advancing the understanding of AD. Although HCHWA-D is characterized by amyloid-β deposits in the walls of cerebral microvessels, it differs from AD in several respects. Thus, when present, dementia is vascular in origin. Furthermore, plaques are sparse and tangles absent.

In the late 1980s, it was speculated that mutations in the *APP* gene would also be found in familial AD, some cases of which had been linked to chromosome 21 (*17*, *18*). The first such mutations were soon identified (*19*–*21*) (Fig. 2, B and C). Amyloid-β is a normal, secreted product (*22*–*24*), which suggests that it has a (still unknown) physiological function. *APP* mutations increase amyloid-β production or lead to an increased proportion of amyloid-β ending at residue 42 (*25*, *26*). Most mutations flank the amyloid-β region, with the secreted peptide being the wild type. However, several mutations are within amyloid-β itself. Like the HCHWA-D mutation, some of these mutations have little effect on APP processing but increase the propensity of amyloid-β to form fibrils (*27*). Missense mutations in amyloid-β lead to vascular deposits, parenchymal plaques, or both. Twenty missense mutations in the *APP* gene have been described (Fig. 2C). Recently, increased gene dosage was identified as another cause of disease (Fig. 2B). Duplication of the *APP* gene gives rise to amyloid-β deposition in brain neuropil, cerebral blood vessels, or both locations, with clinical pictures of AD or recurrent brain hemorrhages (*28*, *29*). These findings are remi-

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niscent of Down's syndrome, although brain hemorrhages are only rarely observed. They underscore the need to understand more about the factors that determine whether amyloid-β is deposited in brain or vasculature. Neuronally derived amyloid-β is transported to the vasculature, where it is cleared via transport into the blood or via the perivascular fluid drainage pathway (*30*). These findings have been replicated to some extent in transgenic mice. Expression of mutant human APP in nerve cells leads to amyloid plaque and blood vessel wall deposits (*31*, *32*). However, tangles and extensive nerve cell loss have not been observed in these mouse lines.

Mutations in the *APP* gene account for only a minority of familial AD cases. Linkage studies established the presence of a major disease locus on chromosome 14 (*33*), and positional cloning led to the identification of mutations in the *presenilin-1* gene, which encodes a polytopic membrane protein (*34*). Mutations in *presenilin-1* are the most common cause of familial AD. Mutations in the related *presenilin-2* gene also give rise to AD (*35*, *36*). More than 160 mutations in the *presenilin* genes have been identified. Presenilins are central components of the atypical aspartyl protease complexes responsible for the γ-secretase cleavage of APP (*37*, *38*), but other transmembrane proteins are also γ-secretase substrates. *Presenilin* gene mutations increase the ratio of amyloid-β 42 to amyloid-β 40, and this appears to result from a change in function (*39*) that manifests itself in reduced γ-secretase activity. In preclinical cases with *presenilin-1* mutations, deposition of amyloid-β 42 is an early event (*40*, *41*). The phenotypic spectrum associated with *presenilin* gene mutations may extend beyond AD to encompass cases of FTLD with tau deposits (*42*). If confirmed, this would indicate that these mutations can cause disease through amyloid-β–independent effects. Support for this notion comes from transgenic animal models, which have suggested that a reduction in γ-secretase activity can lead to the hyperphosphorylation of tau in the absence of amyloid-β deposits (*43*). Unlike the presenilins, no disease-causing mutations have been identified in the aspartyl protease BACE1, which is identical with β-secretase (*44*).

Taken as a whole, the work on familial AD forms the bedrock of the amyloid cascade hypothesis (*45*), which holds that an increase in amyloid-β 42 triggers all cases of AD, with tangle formation, nerve cell degeneration, and dementia being downstream events.

Tau

It took several years of work before it was clear that the paired helical filaments are made of full-length, hyperphosphorylated tau, a protein involved in microtubule assembly and stabilization (*46*–*53*). In the human brain, six tau isoforms are produced from a single gene through alternative mRNA splicing (*54*) (Fig. 3A). They fall into two groups on the basis of numbers of microtubule-binding repeats, with three isoforms having three repeats each and three isoforms having four repeats each. The presence or absence of N-terminal inserts distinguishes the three isoforms in each group. In the normal human brain, similar levels of three- and four-repeat isoforms are expressed. In tau filaments from AD brains, all six isoforms are present in proportions similar to those in normal brains. Filamentous tau deposits are also found in a number of other neurodegenerative diseases, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), Pick's disease, argyrophilic grain disease (AGD), and the Parkinson-dementia complex of Guam (*55*). In PSP, CBD, and AGD, the deposits are present in nerve cells and glial cells, whereas in AD, Pick's disease, and the Parkinsonism-dementia complex of Guam they are largely confined to nerve cells. Unlike AD, these diseases all lack amyloid-β pathology. Besides AD, several other neurodegenerative diseases are associated with extracellular protein deposits, such as the Abri peptide in familial British dementia and the prion protein (PrP) in Gerstmann-Sträussler-Scheinker (GSS) disease. As in AD, abundant deposits of tau form in nerve cell bodies and around plaques in familial British dementia and in GSS disease caused by certain *PrP* gene mutations (*56*, *57*).

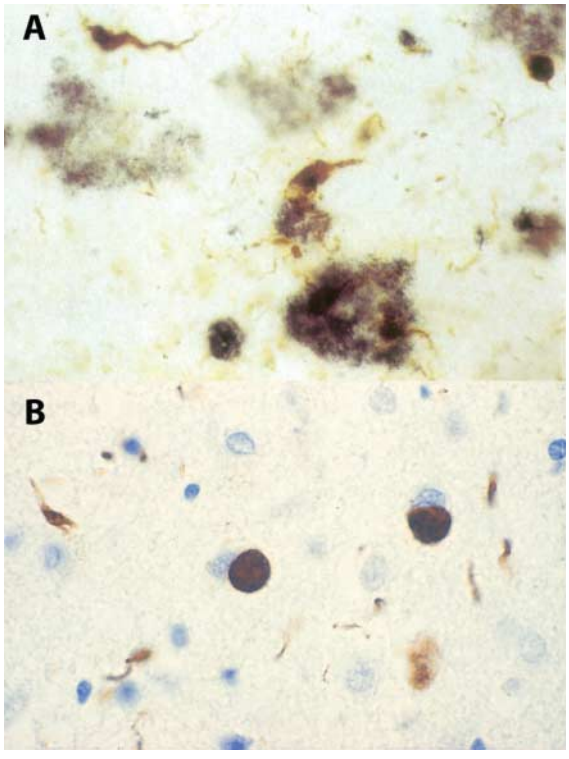

Fig. 1. The abnormal deposits that Alzheimer described. (**A**) Neuritic plaques made of amyloid-β (blue) and neurofibrillary tangles made of tau (brown) in Alzheimer's disease. (**B**) Pick bodies and neurites made of tau (brown) in Pick's disease.

Hyperphosphorylation of tau is common to all diseases with tau filaments and may be required for toxicity. Much is known about phosphorylation sites and candidate protein kinases and phosphatases, auguring well for the development of preventive strategies aimed at reducing tau phosphorylation (*58*). Whereas the phosphorylated sites in tau are similar in the different diseases, the isoform composition of tau filaments differs. In PSP, CBD, and AGD, four-repeat tau isoforms are present, whereas tau isoforms with three repeats are found in Pick's disease. All six isoforms are present in Parkinsonism-dementia complex of Guam, familial British dementia, and cases of GSS disease with tau deposits. The molecular dissection of tau filaments gave a complete description of their composition and provided clues about the mechanisms underlying their formation. However, the relevance of tau dysfunction for the etiology and pathogenesis of AD and related disorders had remained unclear. Such a connection had been suspected because the distribution and abundance of tau pathology correlated well with nerve cell degeneration and clinical symptoms (*59*). However, the identification of mutations in the genes encoding APP and presenilin, and the presence of tau deposits in a number of apparently unrelated disorders, cast doubt on the importance of tau.

The finding that mutations in the *Tau* gene cause the inherited frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) removed this doubt (*60*–*62*). To date, 39 such mutations have been described (Fig. 3B). FTDP-17, which belongs to the FTLD spectrum of diseases, is quite varied. It can present predominantly as a dementing disorder, a parkinsonian disease, or a condition with motor neuron disease–like symptoms. Neurological syndromes similar to PSP, CBD, and Pick's disease have also been described. Filamentous tau inclusions are invariably present in the absence of amyloid-β deposits. Depending on the mutations, the inclusions are present in nerve cells or in nerve cells and glia, and consist of three-repeat tau, four-repeat tau, or all six isoforms. The different isoform compositions are reflected in varied filament morphologies. *Tau* mutations are located in the coding region or the intron flanking alternatively spliced exon 10. The latter encodes the microtubule-binding repeat included in four-repeat tau. Functionally, mutations fall into two largely nonoverlapping categories: those that influence the alternative splicing of tau pre-mRNA, and those whose

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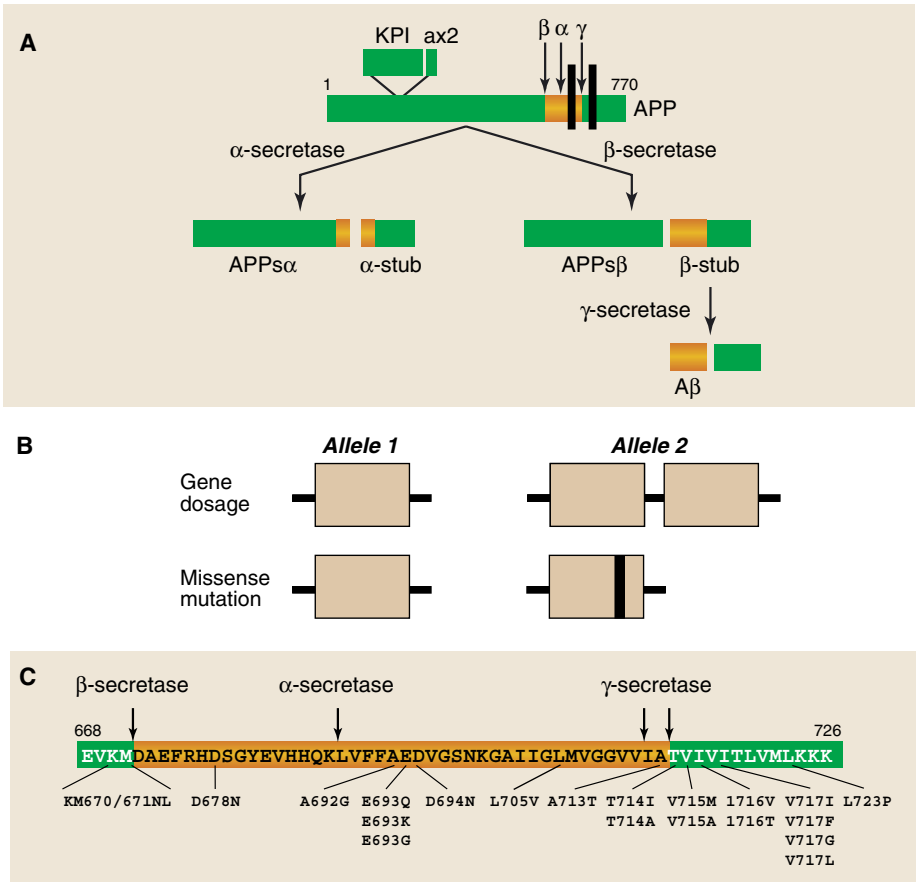

Fig. 2. Amyloid-β. (**A**) Generation of amyloid-β (Aβ) from the amyloid precursor protein (APP). Cleavage by β-secretase generates the N terminus and intramembranous cleavage by γ-secretase gives rise to the C terminus of amyloid-β. Cleavage by α-secretase precludes Aβ formation. (**B**) Duplication of the *APP* gene and missense mutations (black box) in the *APP* gene cause inherited forms of Alzheimer's disease and cerebral amyloid angiopathy. (**C**) Twenty missense mutations in *APP* are shown. Single-letter abbreviations for amino acid residues: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; Y, Tyr.

primary effect is at the protein level. In accordance with their location in the microtubule-binding region, most missense mutations reduce the ability of tau to interact with microtubules (*63*). Some mutations also promote aggregation into filaments. Intronic mutations and most coding region mutations in exon 10 increase the splicing of exon 10, leading to the relative overproduction of four-repeat tau (*61*, *62*, *64*). In the normal brain, a correct ratio of three-repeat to four-repeat tau isoforms is essential for preventing neurodegeneration and dementia. Multiplications of *Tau* have so far not been reported. Although the pathway leading from a mutation in *Tau* to neurodegeneration is only incompletely known, it appears likely that a reduced ability to interact with microtubules is necessary for setting in motion the gain of toxic function that will cause neurodegeneration. This work is relevant beyond FTDP-17, because it shows that whenever filamentous tau inclusions form in the brain, abnormalities in tau are directly involved in the ensuing neurodegeneration.

FTLD itself is genetically heterogeneous, with a substantial number of cases exhibiting tau-negative, ubiquitin-positive nerve cell inclusions. Mutations in the genes encoding the apparently unconnected p97 (*65*), CHMP2B (charged multivesicular body protein 2B) (*66*), and, in particular, progranulin (*67*, *68*) cause these forms of FTLD. In contrast to *Tau* mutations, they all appear to lead to disease through loss of function of the mutant allele.

Haplotypes H1 and H2 characterize the *Tau* gene in populations of European descent (*69*). They are the result of a 900-kb genomic inversion polymorphism that encompasses *Tau* (*70*). Heterozygous microdeletions in this region give rise to a form of mental retardation (*71*–*73*). These findings point to a possible role for tau in brain development and are consistent with the notion that FTDP-17 is caused by a gain of toxic function of tau. Inheritance of H1 is a risk factor for PSP and CBD (*69*, *74*, *75*). An association has also been described between H1 and idiopathic Parkinson's disease (*76*), a disease without tau pathology. H1 has been shown to be more effective than H2 at driving the expression of a reporter gene, which suggests that higher levels of tau are expressed from H1 (*77*). However, it remains unclear how this could explain the preferential deposition of four-repeat tau in PSP and CBD.

The work on FTDP-17 has led to the development of robust transgenic mouse models that replicate the essential molecular and cellular features of the human tauopathies, including tau hyperphosphorylation, filament formation, and extensive nerve cell loss (*78*, *79*). The crossing of lines expressing mutant tau with lines expressing mutant APP results in enhanced tau pathology (*80*).

Sporadic Alzheimer's Disease

Most cases of AD are sporadic, with dominantly inherited forms accounting for less than 1% of the total. Inheritance of the ε4 allele of apolipoprotein E (*APOE*) is the only well-established genetic risk factor for sporadic AD (*81*), but its mode of action is unknown. Amyloid-β deposits are more abundant in ε4-positive than in ε4-negative cases (*82*). In addition, apoE4 is associated with a number of other factors that may contribute to AD pathology, including low glucose usage, mitochondrial abnormalities, and cytoskeletal dysfunction (*83*).

Age is a major risk factor for AD, and small numbers of plaques and tangles form in most individuals as they grow older (*59*). Tau pathology appears first in the transentorhinal region, from where it spreads to the hippocampus and amygdala, followed by neocortical areas. Amyloid-β deposits tend to appear first in the neocortex. Both types of inclusion seem to form independently, with tangles appearing first. At later stages, extensive amyloid-β deposition in the neocortex has been reported to precede severe tangle pathology (*84*), leading to the suggestion that amyloid-β deposition may exacerbate age-related tau pathology. This would be consistent with what is known from cases with *APP* gene mutations and duplications, where overproduction of amyloid-β 42 is upstream of tau dysfunction. Mutations in *Tau*, on the other hand, lead to filament formation, neurodegeneration, and dementia but do not give rise to amyloid-β deposits. An outstanding question relates to the molecular nature of the neurotoxic species. In recent years, evidence has accumulated that suggests that oligomeric species of amyloid-β and tau may be major culprits (*85*). For tau, it appears likely that the mere presence of abnormal filaments in nerve cell processes is also detrimental to the parent cell, if only because they are space-occupying lesions that are bound to interfere with axonal transport.

In AD, neurodegeneration is estimated to start 20 to 30 years before the appearance of the first clinical symptoms. The early clinical phase

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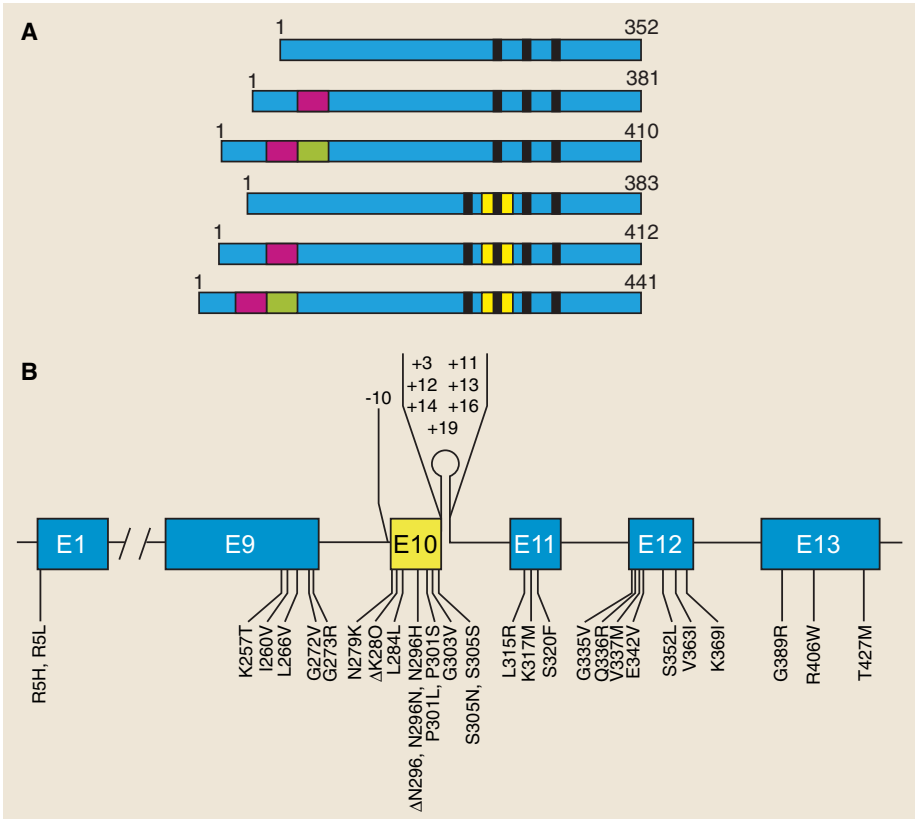

Fig. 3. Tau. (**A**) The six tau isoforms expressed in adult human brain. Alternatively spliced exons are shown in red, green, and yellow, respectively, and the microtubule-binding repeats are indicated by black bars. (**B**) Mutations in the *Tau* gene in frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Thirty-one coding region mutations in exons (E) 1, 9, 10, 11, 12, and 13 and eight intronic mutations flanking E10 are shown.

is often called amnestic mild cognitive impairment (aMCI) (*86*). The neuropathological features of aMCI are intermediate between those of normal aging and AD, in that tau deposits are abundant in the entorhinal cortex and hippocampus and some amyloid-β deposits are present in the neocortex (*87*). For aMCI, the regional distribution of tau deposits correlates better with the degree of cognitive impairment than does the amyloid-β load. It has been suggested that the transition from aMCI to AD occurs when tau pathology spreads beyond the medial temporal lobe. Work has so far concentrated on the presence of deposits. In the future, it will be important to measure levels of amyloid-β and tau oligomers in aMCI.

The long presymptomatic phase of AD augurs well for the development of preventive strategies. To test their effectiveness, it will be necessary to identify neuropathological abnormalities before the development of cognitive changes. Use of Pittsburgh compound B (PIB), a thioflavin T derivative, has already resulted in the visualization of amyloid-β deposits in patients with AD and in some nondemented elderly individuals (*88*), which suggests that imaging with PIB can detect clinical and preclinical disease. In the future, it may also become possible to image tau deposits in the living human brain.

Closing Remarks

The protein deposits described by Alzheimer are at the center of current work. Although much has been learned, major questions remain. Perhaps the greatest unknown relates to the links between amyloid-β and tau. Another important question concerns the mechanisms that determine the selective vulnerability of defined neuronal and glial populations. A related issue has to do with the molecular species that cause nerve cell degeneration. During his lifetime, Alzheimer was best known for his clinicopathological studies of neurosyphilis, then a pressing problem in psychiatry and the prime example of an organic brain disorder. It receded after advances in microbiology and the advent of chemotherapeutics and antibiotics. The hope is that in the not too distant future, on the basis of the knowledge gained, safe and effective treatments will also become available for AD and related disorders.

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100 Years and Counting: Prospects for Defeating Alzheimer's Disease

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This week marks a century since the first description of Alzheimer's disease (AD). Despite approval of several drugs for AD, the disease continues to rob millions of their memories and their lives. Fortunately, many new therapies directly targeting the mechanisms underlying AD are now in the pipeline. Among the investigative AD therapies in clinical trials are several strategies to block pathogenic amyloid-β peptides and to rescue vulnerable neurons from degeneration. Complementary but less mature strategies aim to prevent the copathogenic effects of apolipoprotein E and the microtubule-associated protein tau. New insights into selective neuronal vulnerability and the link between aging and AD may provide additional entry points for therapeutic interventions. The predicted increase in AD cases over the next few decades makes the development of better treatments a matter of utmost importance and urgency.

It used to be said that neurologic diseases were easy to diagnose but impossible to treat. Today, effective treatments are available for many neurologic conditions, but for the 4.6 million new patients worldwide who will be affected by AD this year (*1*), the old mantra still rings too true. Although multiple drugs have now been approved, their expected benefits are modest. One hundred years after the discovery of AD, the lack of treatments with a major impact might be discouraging. Fortunately, basic research is identifying many of the pathways that contribute to this devastating disease (Fig. 1), providing unprecedented opportunities for the development of new treatments aimed at the root causes of AD. Here, we review several of these efforts and consider both shorter- and longer-term prospects for effectively treating AD.

Current Standard of Care

Five drugs are approved in the United States for the treatment of AD (*2*, *3*), although tacrine is now rarely used because of hepatotoxicity (Table 1). Cholinesterase inhibitors are designed to combat impairment of cholinergic neurons by slowing degradation of acetylcholine after its release at synapses. Memantine prevents overstimulation of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, which may contribute to the pathogenesis of AD and other neurodegenerative conditions by causing excitotoxicity (*4*). In clinical trials, both cholinesterase inhibitors and memantine have shown beneficial but modest effects on cognitive test scores, behavioral measures, and functional outcomes (*5*–*9*). However, because the benefits of cholinesterase inhibitors are small and may be seen in only a subset of patients, their cost effectiveness has been questioned (*10*). Because memantine is beneficial in patients already taking cholinesterase inhibitors and may even reduce their side effects, the two are often used together (*9*). Many AD patients also receive antipsychotics or antidepressants to manage neuropsychiatric and behavioral symptoms or take over-the-counter preparations whose therapeutic value is uncertain, including ginkgo biloba and vitamins C and E (*2*, *11*–*14*).

In the Pipeline: Targeting Aβ

The marginal benefits of current therapies emphasize the need for more potent AD drugs. Several new compounds are now being tested for safety (phase I and IIA) and efficacy (phase IIB and III) in clinical trials (Table 2) (*15*). To date, emphasis has been on strategies to reduce the pathogenicity of amyloid-β (Aβ) peptides (*16*), widely believed to play a key role in AD.

Reducing Aβ production is one goal. Aβ is generated from the amyloid precursor protein, APP, via sequential cleavage by β- and γ-secretase (Fig. 2). γ-Secretase inhibitors have reached clinical trials, but published results are limited. One compound, LY450139, was well tolerated and reduced the amount of Aβ in the plasma, but not in the cerebrospinal fluid (CSF) (*17*). The potential for dose escalation is limited, because γ-secretase also cleaves other substrates, including Notch, and nonselective γ-secretase inhibitors have deleterious effects on embryogenesis in zebrafish and on lymphoid and gastrointestinal tissues in mammals (*18*, *19*).

Thus, several approaches are being pursued to design next-generation γ-secretase drugs that selectively reduce APP cleavage (Fig. 2). As opposed to the standard strategy of inhibiting proteases by blocking their active sites, one approach targets the substrate-docking site of γ-secretase to selectively interfere with APP binding (*20*). Another idea capitalizes on the observation that γ-secretase has an adenosine triphosphate (ATP)–binding site that selectively modulates APP processing (*21*). Blocking this site inhibits APP, but not Notch, cleavage (*22*). Yet another approach is to modulate, rather than inhibit, γ-secretase activity. Besides the γ site, γ-secretase also cleaves at a more C-terminal ε site critical for proper Notch signaling. The TMP21 accessory component of γ-secretase suppresses γ-cleavage without affecting ε-cleavage of APP or Notch, suggesting a means to inhibit Aβ production without Notch-dependent adverse effects (*23*). Lastly, even at the γ site, APP can be cleaved at different positions, creating 40– or 42–amino acid forms; the $Aβ_{42}$ peptide appears to be the most pathogenic. Certain nonsteroidal anti-inflammatory drugs (NSAIDs) allosterically modulate γ-secretase to favor production of $Aβ_{40}$ over $Aβ_{42}$ (*24*, *25*) and are now in phase III trials.

β-Secretase, whose cleavage of APP precedes that of γ-secretase (Fig. 2), is another prime target to inhibit Aβ production. It has fewer known substrates than γ-secretase and a more benign gene-knockout phenotype in mice (*26*), suggesting that β-secretase inhibitors may be safer than γ-secretase inhibitors. Genetic elimination of β-secretase prevented memory deficits in human APP transgenic mice (*27*). For structural reasons, it has been more difficult to design small-molecule inhibitors for β-secretase than for γ-secretase, but this problem appears to be surmountable (*26*). Other APP-cleaving enzymes might also be good targets. Stimulating α-secretase can reduce Aβ because the enzyme cleaves APP within Aβ (*28*–*30*). Preventing caspase cleavage of the APP intracellular domain may also be beneficial (*31*).

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