

CONTINUING MEDICAL EDUCATION

Alzheimer's disease: a molecular mechanism, new hypotheses, and therapeutic strategies

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Summary. Human diseases involving protein misfolding and aggregation have received increasing attention in recent years. Alzheimer's disease and other diseases associated with aging are sweeping the developed countries whose populations are rapidly aging. Recent progress has improved our knowledge about molecular and cellular pathogenesis of these diseases. For more than 20 years, multiple diseases such as Alzheimer's and Parkinson's diseases have been associated with accumulation of abnormal protein fibrils. These self-assembling fibrils, referred as "amyloid," have been considered the pathogenic molecules that cause cellular degeneration. Accumulation of fibrillar A β in plaques underlies the theory for Alzheimer's disease. Recent experiments have provided evidence that fibrils are not the only neurotoxins. Soluble oligomers and protofibrils play a crucial role in causing cellular dysfunction and death. These oligomers, the missing links in the original amyloid cascade hypothesis, have been incorporated into an updated amyloid cascade. Despite new information gained, there is no disease-modifying treatment. New insights into disease mechanisms and new therapeutic strategies give hope for change.

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia in elderly affecting 10% of individuals older than 65 and more than 25 million individuals worldwide (1).

At its onset, AD is a disease that manifests as deterioration in memory and inability to form new memories and to retrieve the stored ones (1, 2). Alois Alzheimer, a Bavarian psychiatrist, treated a middle-aged woman, Auguste D., a century ago. Once he asked Auguste D. to write her name. She was unable to do so and said, "I lost myself..." (1, 2). Over time, symptoms get worse with a progressive loss of cognitive and functional abilities. The disease accelerates the end of life, and AD with its complications represents the fourth leading cause of death (1). It is likely that Auguste D. case was familial AD as she died in her mid-fifties. Life span of patients with sporadic AD is variable – Ronald Reagan, the President of the United States of America, lived 20 years following the diagnosis (1).

Protein misfolding and aggregation

Misfolding and aggregation of proteins is one of the major threats for the cell function and viability.

Protein structures are not very stable entities. By changing temperature (shift from 37°C to 42°C), in the presence of oxygen free radicals, heavy metals, pH change, or toxic substances (e.g. certain antibiotics), the cell proteins will spontaneously unfold or will be chemically modified (oxidation, isomerization, glycation). The process of protein folding may be prone to errors due to genetic mutations that generate misfolding and prevent the association of the protein with other subunits and cofactors (3, 4).

Because an accumulation of unfolded proteins has a deleterious effect on cell function, the cells elaborated a range of mechanisms and quality control systems responsible for accurate synthesis of polypeptide chains, their proper folding, and targeting to the correct compartment. If native conformation of the protein is lost, the cell employs the mechanisms to prevent the aggregation of the unfolded proteins, refold them, and to cleave the misfolded proteins to amino acids. Proteins called molecular chaperones are one of the cell protective mechanisms (4, 5). Most of the chaperones present at high levels under normal cell conditions and prevent inappropriate folding within and be-

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tween nonnative polypeptides, promote the efficiency of de novo protein folding and intracellular localization of newly synthesized polypeptides. Under stress conditions, the synthesis of chaperones increases rapidly, and that ensures the viability of cells under high temperature or other harmful conditions. The cell also elaborated enzymatic mechanism (ubiquitin-proteasome system, UPS) to ensure the degradation of misfolded proteins to amino acids. These two main protective mechanisms are normally sufficient to prevent the accumulation of misfolded proteins (4, 5). However, during aging and under certain pathological conditions (genetic mutations), the capacity of this protein quality control mechanism is exceeded, and unfolded proteins accumulate inside the cell or in the extracellular space to dangerous levels (Fig. 1).

In a wide variety of systemic diseases, including many neurodegenerative disorders, unfolded polypeptides accumulate in cells as insoluble inclusions and appear to play a critical role in disease pathogenesis (2, 4–6). The genetic mutation that prevents normal protein folding is a cause of many hereditary diseases ranging from cystic fibrosis to many hemoglobinopathies and thalassemia where the excess globin chains accumulate and distort red blood cell shape (4, 7). Many neurological diseases (e.g. Alzheimer's

disease, Huntington's disease, Jacob-Creutzfeldt's disease) originate from the intracellular or extracellular deposition of abnormal proteins. Many reports give strong support that these various types of depositions arise from common mechanisms and elicit similar host response, as these depositions contain molecular chaperones and the components of UPS pathway (4, 6).

The nature of A β peptide

AD is a neurodegenerative disease with complex neuropathology and includes brain inflammation, shrinkage of hippocampus, degeneration of specific neuronal populations (1, 2). AD pathology is linked to two types of insoluble protein deposits: a) extracellular polymers of amyloid beta peptide (A β), which constitute "plaques"; b) intraneuronal polymers of hyperphosphorylated protein *tau*, which constitute "tangles" (1). The identification of plaques and tangles in the brain regions of the patient is the reason for AD diagnosis (1, 2).

A β peptide was recognized as the subunit of the amyloid plaque by Glenner and Wong in 1984 (8). A β is approximately 4-kDa peptide, derived from its precursor protein (amyloid precursor protein, APP) by proteolytic cleavages. Three major isoforms of 695, 751, and 770 amino acids are detected, occurring after an alternative splicing of APP. Moreover, the isoforms undergo the posttranslational modifications (glycation, sulfation, and phosphorylation). APP isoforms containing 751 and 770 amino acids are the most abundant isoforms in nonneuronal tissues. Neurons synthesize the isoform of 695 amino acids in more abundant amounts (2, 9).

APP is a transmembrane polypeptide cotranslationally translocated into the endoplasmic reticulum with the help of its signal peptide. APP is posttranslationally modified – N- and O-linked sugars are attached after biosynthesis – and the half-life of modified APP is 45–60 min (2, 10). During the secretory pathway, APP undergoes proteolytic cleavages (Fig. 2). The target of α -secretase is distant by 12 amino acids from N-terminal of the APP transmembrane domain. This cleavage results in the release of large soluble fragment (α -APP) into the extracellular space and retention of an 83-residue C-terminal fragment in the membrane (C83). The APP molecules not subjected to α -secretase cleavage can be cleaved by β -secretase, the cleavage site of which is distant by 16 amino acids, and a smaller domain (β -APP) is released retaining 99 residues (C99) in

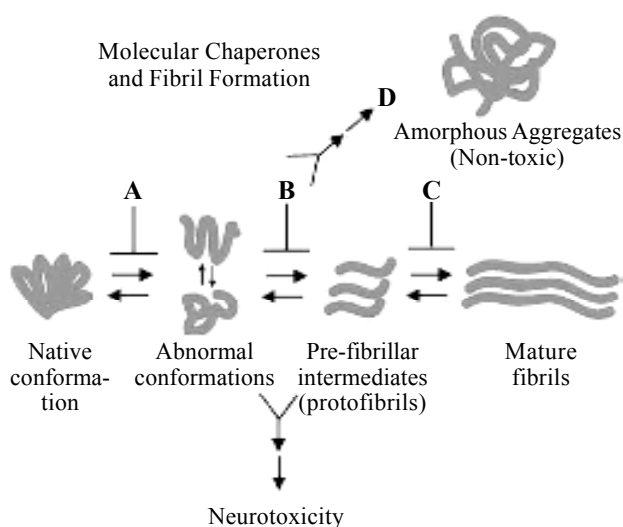


Fig. 1. A model for molecular chaperone suppression of neurotoxicity

(Muchovski PJ. Protein misfolding, amyloid formation and neurodegeneration: a critical role for molecular chaperone. *Neuron* 2002;35:9-12). Molecular chaperones may suppress amyloid formation by participation in the pathways A, B, and C. Chaperones may also facilitated conversion of toxic intermediates into nontoxic amorphous aggregates (pathway D).

the membrane. APP can be subjected to α -secretase (Fig. 2). The sequential cleavage by α -secretase and γ -secretase generates p3 fragment, meanwhile cleavage by β -secretase and γ -secretase produces A β fragment. γ -Secretase has two alternative cleavage sites (Fig. 2); therefore, A β fragment can consist of 40 amino acids (A β 40) or 42 amino acids (A β 42) (2, 11).

Genetics of Alzheimer's disease

It has been known that AD can be inherited in an autosomal dominant pattern. Inherited forms of AD account for 5% to 10% of cases. It is complicated to say how frequently genetic factors cause AD because of the late onset of disorder (2). The phenotypic analyzes revealed that APP-linked familial AD is indistinguishable from sporadic AD, the most common form of the disease. Sporadic AD is also identical to that caused by mutations in the APP and presenilin genes, which underlie more frequent familial AD (1, 2).

The mutations in APP gene are the first genetic cause of AD. The discovery of such mutations, the determination of their localization in the APP and genotype-to-phenotype relationships shed more light into the mechanism of AD (2). The mutations are located before β -secretase cleavage site, after α -secretase site, or immediately after γ -secretase cleavage site (Fig. 3). No other mutations in the APP

gene having an influence on AD development have been discovered. It is assumed that these mutations cause altered APP cleavage by three secretases (12). Currently, the increased A β production is associated with the nine mutations in APP gene. Mutation of two amino acids preceding β -secretase cleavage site results in an increased production of A β 40 and A β 42 due to increased cleavage by β -secretase (10, 11). Mutations of five amino acids just after γ -secretase cleavage site selectively increase production of A β 42 (10).

In 1995, researchers identified genetic mutations within presenilin 1 gene (PSEN1, 14 chromosome) and presenilin 2 gene (PSEN2, 1 chromosome) in several early-onset familial AD (13). So far, nearly 160 mutations (more than 258 families) in PSEN1 and 10 mutations (15 families) in PSEN2 genes are associated with familial AD (14, 15).

PSEN1 and PSEN2 encode 467- (presenilin 1) and 448-amino acid (presenilin 2) transmembrane proteins, respectively. Both presenilins (PS) are expressed in the brain and many tissue cells of the human body (15). It was shown that PS1 and PS2 are subunits of γ -secretase, which cleaves APP within its transmembrane domain and γ -secretase generates a spectrum of peptides (varies in length, \geq A β 42 and \leq A β 40), termed Ab, which accumulates in the brains of AD patients (15, 16). It was suggested that PS mutations selectively elevate the levels of highly

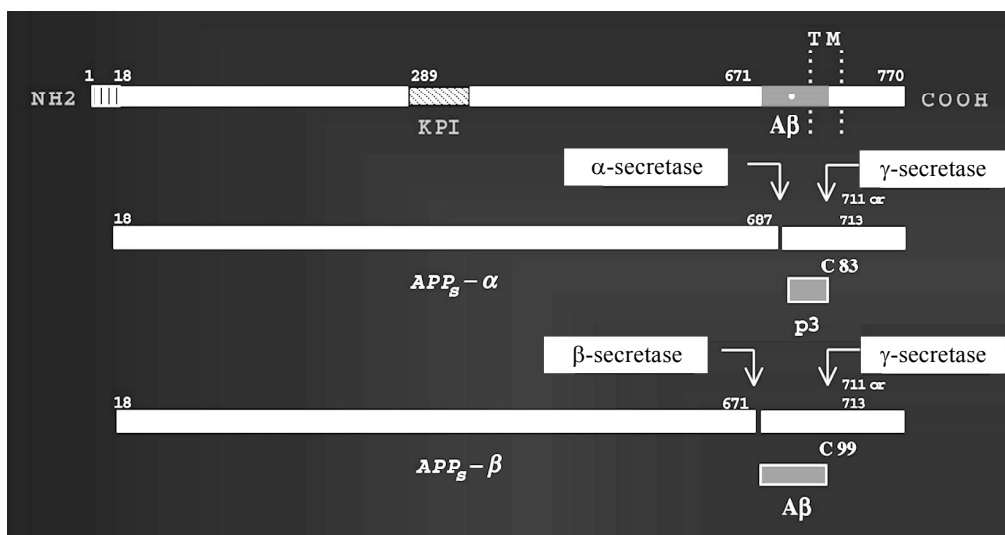


Fig. 2. APP protein and its principal metabolites

(Sekoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 2001;81:741-66)

Top diagram shows the largest APP alternate splicing form comprising of 770 amino acids. TM is a single membrane-spanning domain. The cleavage sites of α -, β -, and γ -secretase are indicated by arrows. A β fragment has 28 amino acid residues, located outside the membrane, and the first 12-14 amino acids of the transmembrane domain.

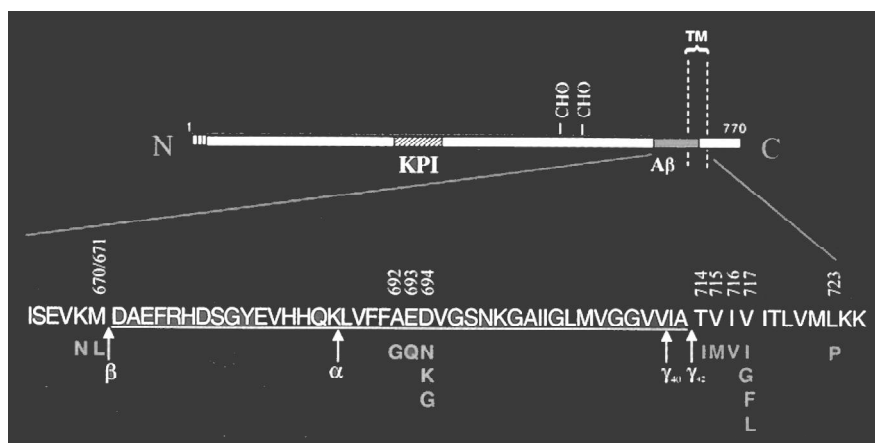


Fig. 3. APP mutations associated with familial AD

(Sekoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 2001;81:741-66)

The underlined residues represent A β peptide. TM, transmembrane domain; the bold letters indicate known missense mutations.

amyloidogenic A42 peptides by likely shifting the cleavage site in APP (15).

A β oligomers – the new neurotoxins

Genetic, biochemical, and animal modeling data strongly suggest that the amyloid beta-protein (A β) plays a central role in AD. Three principal forms of A β (38, 40, and 42 amino acids) are produced in respect to the cleavage site of APP by γ -secretase (16). The particular peptide form is relevant because A β 42 readily makes fibrils, especially in comparison to the less hydrophobic and much more abundant A β 40.

A β is a natural protein present in the brains and cerebrospinal fluid of healthy humans (17). The mere presence of A β does not cause neurodegeneration. The A β becomes a pathogenic substance when an ordered self-association of A β molecules into insoluble fibrils of 6–10 nm in diameter occurs (18). The synthetic A β in vitro can form amyloid fibrils similar to those present in human brain (19).

Accumulation of fibrillar A β in plaques underlies the dominant theory for AD, named the “amyloid cascade hypothesis,” generated in 1992 by Hardy and Higgins (20). However, neuropathologists have long raised concern about poor correlation between the severity of dementia and the density of fibrillar amyloid plaques in human brain (21, 22). The later studies have shown a clear relationship between soluble A β levels and the extent of synaptic loss and severity of cognitive impairment. The experimental study on transgenic mice by Dodart and colleagues (23) presented further evidence supporting the idea about the significance of soluble A β forms. Monoclonal an-

tibodies against A β peptide were administered to transgenic mice carrying the hAPP gene. Based on the results of Dodart's study, two significant conclusions were drawn. First, vaccinated mice exhibited reversal of their memory loss, with recovery evident in 24 hours. Reversibility cannot be reconciled if memory is lost due to nerve cell death. Second, the therapeutic benefits were obvious although the amyloid plaques were not destroyed (1, 23). Kotilinek and colleagues (24) confirmed that amyloid fibrils were not the single pathogenic agent in studies with different mice and different A β antibodies.

Immunological assays coupled with mass spectrometry indicate that biochemically measured levels of soluble A β , including soluble oligomers, correlate much better with the degree of cognitive impairment than plaque counts do (25). It was determined that the brains of AD patients contain elevated levels of soluble ligands – up to 70-fold more than in healthy persons (26). These increases occur in the frontal cortex, but not cerebellum, and this confirms the impact of oligomers on memory and recognition (1).

The striking amount of data published in the literature describes many types of in vitro assembly forms of synthetic A β including protofibrils (PFs), amyloid β -derived diffusible ligands (ADDLs), annular structures (doughnut-like structures of A β), globulomers, paranuclei and amyloid fibrils (27). Two groups of researchers (28, 29) established the existence of fibrillar intermediates called protofibrils (PFs). PFs are the structural intermediates to full-fledged fibrils and they are neurologically active (29). ADDL-like oligomeric assemblies have been isolated

from brains of AD patients, and their presence correlated with memory loss (26). It is suggested that not only PFs and ADDLs are neurologically active, but small oligomeric forms (dimeric and trimeric oligomers) occurring in vivo (APP transgenic mouse brain) have also been detected in human brain (30). These monomeric and oligomeric A β , and ADDLs target synapses and induce their degeneration (31, 32). Synapse loss is the most robust correlate of AD associated with cognitive deficits (33).

Unfortunately, the list of unanswered or partially answered questions is still long (1). Why is oligomer accumulation age dependent? Are there chaperones present to prevent oligomer formation? Do these chaperones become less active in AD?

Disease-modifying treatment – new insights

Genetic, biochemical, pathological, and pharmacological studies support the hypothesis that brain accumulation of oligomeric species of beta-amyloid peptides may cause Alzheimer's disease. These findings have raised the approach to target the oligomeric forms of A β . This new strategy is an immunotherapy through either A β peptide vaccination or infusion of monoclonal antibodies against A β (27, 34, 35). Vaccine trials in AD patients were terminated because of the development of T cell-mediated autoimmune meningoencephalitis in 6% of patients (27, 36). Despite its failure, the AD vaccine trial provided a promising result: in responders grouped based on their antibody titer, the progression of AD over a 12-month period was stopped (37). It was demonstrated that antibodies against A β could inhibit in vitro A β fibrillogenesis and disrupt pre-existing fibrils that resulted in reduced neurotoxicity in culture (38, 39). It has already been described that antibodies neutralize oligomers without binding to A β monomers or fibrils (40). The most advanced of these immunological approaches is bapineuzumab (is currently being co-developed by the pharmaceutical Elan's and Wyeth's companies), composed of humanized anti-A β monoclonal antibodies, that is being tested in two large late-stage trials (41).

The metabolism of the APP and the aggregation of its fragment A β are the focus of current studies. The proteases, γ -secretase and β -secretase, are the targets for development of disease-modifying treatment. A β peptides are produced by the enzymes β - and γ -secretase. Certain drugs inhibit γ -secretase activity and reduce oligomer formation. Several inhibitors of γ -secretase have been identified, and the most advanced is LY-450139 (semagacestat) that is being studied in one large long-term Phase III clinical study (41). However, γ -secretase activity is also involved in the differentiation and proliferation of embryonic cells, T cells, splenic B cells. Involvement of γ -secretase in cell differentiation may preclude a complete blockade of γ -secretase for prolonged times in vivo (42).

The compounds that stimulate α -secretase are also being developed. One of them, EHT-0202, has recently started a Phase II study (41). However, targeting β -secretase is impeded by the lack of suitable inhibitors to date.

Tarenflurbil is a selective agent reducing A β 42 formation, and it is the first drug of a novel class for mild AD treatment. Tarenflurbil modulates γ -secretase, shifting production to shorter, less toxic A β fragment. This selective agent, unlike other γ -secretase inhibitors, does not interfere with the function of β -secretase substrates (43, 44).

Nonsteroidal anti-inflammatory drugs (NSAIDs) may be suitable for modulation of both A β production and inflammatory activation. It was shown that NSAIDs indirectly reduce oligomer formation by shifting γ -secretase cleavage site in APP molecule by four amino acids to produce smaller, non-aggregating A β 38 fragment (27, 44).

Statins, tocopherol (vitamin E), estrogen, memantine produce limited clinical benefits (41, 43, 44). Unfortunately, drugs licensed for AD have moderate symptomatic benefits. Currently, there are no disease-modifying therapies available for the treatment of Alzheimer's disease (43, 44). The development of the drug targets along with the diagnostic tools – genetics, biomarkers, and neuroimaging techniques – is an active field of research.

Alzheimerio liga: molekulinis mechanizmas, naujos hipotezės, gydymo perspektyvos

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Raktažodžiai: Alzheimerio liga, baltymo susilankstymas, amiloidas, fibrilės, oligomerai.

Santrauka. Pastaraisiais metais ypač susidomėta ligomis, susijusiomis su netaisyklingu baltymų susilankstymu ir jų agregacija. Literatūroje pateikiama naujausia informacija apie molekulinę ir ląstelinę šių ligų patogenezę. Be to, poreikis kuo išsamesnės informacijos apie šių ligų mechanizmus kilo dėl didėjančio sergamumo Alzheimerio liga bei kitomis senatvinėmis ligomis, būdingomis ekonomiškai išsivysčiusioms šalims. Daugiau kaip 20 metų daugelis sisteminių ligų, įskaitant neurologines Alzheimerio ir Parkinsono ligas, siejamos su anomalių fibrilinių baltymų susikaupimu. Šios fibrilės, vadinamos amiloidu, laikomos patogeninėmis molekulėmis, sukeliančiomis ląstelių degeneraciją. Vyraujančios Alzheimerio ligos teorijos pagrindas yra plokštelių, sudarytų iš baltymo A β fibrilių, susiformavimas. Pasirodė, jog fibrilės nėra vienintelis toksinas, atsirandantis baltymų susijungimo procese. Šiandien žinoma, jog egzistuoja ikifibriliniai dariniai – tirpūs oligomerai ir protofibrilės, kurie yra neurologiškai aktyvūs. Šių darinių vaidmens įvertinimas Alzheimerio ligos patogenezei davė impulsą amiloido kaskados hipotezės korekcijai. Kol kas nėra veiksmingų Alzheimerio ligos gydymo priemonių. Tačiau naujas požiūris į ligos mechanizmą ir imunoterapinių priemonių, tokių kaip monokloniniai antikūnai ir vakcinos sukūrimas, teikia vilčių, jog situacija gerės.

References

- Klein WL. Cytotoxic intermediates in the fibrillation pathway: A β oligomers in Alzheimer's disease as a case study. In: Uvertsky VN, Fink AL, editors. Protein misfolding, aggregation, and conformational diseases. Part A: Protein aggregation and conformational diseases. New York: Springer; 2006. p. 61-75.
- Sekoe DJ. Alzheimer's disease: genes, proteins, and therapy. *Physiol Rev* 2001;81:741-66.
- Hartl FU, Hayer-Hartl M. Converging concepts of protein folding *in vitro* and *in vivo*. *Nat Struct Mol Biol* 2009;16:574-81.
- Sherman MY, Goldberg AL. Cellular defenses against unfolded proteins: a cell biologist thinks about neurodegenerative diseases. *Neuron* 2001;29:15-32.
- Macario AJ, Conway de Macario E. Sick chaperones, cellular stress, and disease. *N Engl J Med* 2005;353:1489-501.
- Muchowski PJ. Protein misfolding, amyloid formation, and neurodegeneration: a critical role for molecular chaperone. *Neuron* 2002;35:9-12.
- Amrani M, Allen NJ, O'Shea J, Corbett J, Dunn MJ, Tadjkarimi S, et al. Role of catalase and heat shock protein on recovery of cardiac endothelial and mechanical function after ischemia. *Cardioscience* 1993;4:193-8.
- Glener GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* 1984;120:885-90.
- Henriques AG, Vieira SI, Rebelo S, Domingues SC, da Cruz e Silva EF, da Cruz e Silva OA. Isoform specific amyloid-beta protein precursor metabolism. *J Alzheimers Dis* 2007; 11:85-95.
- da Cruz e Silva EF, da Cruz e Silva OA. Protein phosphorylation and APP metabolism. *Neurochem Res* 2003;28:1553-61.
- Walsh DM, Minogue AM, Sala Frigerio C, Fadeeva JV, Wasco W, Selkoe DJ. The APP family of proteins: similarities and differences. *Biochem Soc Trans* 2007;35:416-20.
- Chartie-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, et al. Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature* 1991;353:844-6.
- Rogaev EI, Sherrington R, Rogaeva EA, Levesque G, Ikeda M, Liang Y, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 1995;376: 775-8.
- Hardy J. The Alzheimer family of diseases: many etiologies, one pathogenesis? *Proc Natl Acad Sci USA* 1997;94:2095-7.
- Vetrivel KS, Zhang YW, Xu H, Thinakaran G. Pathological and physiological functions of presenilins. *Mol Neurodegener* 2006;1:4.
- Wakabayashi T, De Strooper B. Presenilins: members of the γ -secretase quartets, but part-time soloists too. *Physiology* 2009;23:194-204.
- Walsh DM, Selkoe DJ. A β oligomers – a decade of discovery. *J Neurochem* 2007;101:1172-2284.
- Busciglio J, Lorenzo A, Yankner B. Methodological variables in the assessment of beta-amyloid neurotoxicity. *Neurobiol Aging* 1992;13:609-12.
- Kirschner DA, Inouye H, Duffy LK, Sinclair A, Lind M, Selkoe DJ. Synthetic peptide homologous to beta protein from Alzheimer disease forms amyloid-like fibrils *in vitro*. *Proc Natl Acad Sci USA* 1987;84(19):6953-7.
- Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science* 1992;256:184-5.
- Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* 1988;23:138-44.
- Terry RD. Neuropathological changes in Alzheimer's disease. *Prog Brain Res* 1994;101:383-90.
- Dodart JC, Bales KR, Gannon KS, Greene SJ, DeMattos RB, Mathis C, et al. Immunization reverses memory deficits without reducing brain A β burden in Alzheimer's disease model. *Nat Neurosci* 2002;5:452-7.
- Kotilinek LA, Basckai B, Westerman M, Kawarabayashi T, Younkin L, Hyman BT, et al. Reversible memory loss in mouse transgenic model of Alzheimer's disease. *J Neurosci* 2002;22:6331-5.
- Naslund J, Haroutunian V, Mohs R, Davis KL, Davies P, Greengard P, et al. Correlation between elevated levels of amyloid β -peptide in the brain and cognitive decline. *JAMA* 2000;283:1571-7.
- Gong Y, Chang I, Viola KL, Lacor PN, Lambert MP, Finch CE, et al. Alzheimer's disease-affected brain; presence of oligomeric A β ligands (ADDLs) suggests a molecular basis for reversible memory loss. *Proc Natl Acad Sci USA* 2003; 100:10417-22.
- Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β -peptide. *Nat Rev Mol Cell Biol* 2007;8:101-12.

28. Harper JD, Wong SS, Lieber CM, Lansbury PT Jr. Observation of metastable A β amyloid protofibrils by atomic force microscopy. *Chem Biol* 1997;4:119-25.
29. Walsh DM, Lomakin A, Benedek GB, Condrom MM, Teplow DB. Amyloid beta-protein fibrillogenesis. Detection of a protofibrillar intermediate. *J Biol Chem* 1997;272:22364-72.
30. Lesné S, Koh MT, Kotilinek L, Kaye R, Glabe CG, Yang A, et al. A specific amyloid- β protein assembly in the brain impairs memory. *Nature* 2006;440(7082):352-7.
31. Coleman P, Federoff H, Kurlan R. A focus on the synapse for neuroprotection in Alzheimer disease and other dementias. *Neurology* 2004;63:1155-62.
32. Lacor PN, Buniel MC, Chang L, Fernandez S, Gong Y, Viola KL, et al. Synaptic targeting by Alzheimer's-related amyloid beta oligomers. *J Neurosci* 2004;24:10191-200.
33. Lambert MP, Velasco PT, Chang L, Viola KL, Fernandez S, Lacor PN, et al. Monoclonal antibodies that target pathological assemblies of A β . *J Neurochem* 2007;100:23-35.
34. Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, et al. Immunization with amyloid- β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 1999;400:173-7.
35. Bard F, Cannon C, Barbour R, Burke RL, Games D, Grajeda H, et al. Peripherally administered antibodies against amyloid β -peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease. *Nature Med* 2000;6:916-919.
36. Ferrer I, Boada RM, Sanchez Guerra ML, Rey MJ, Costa-Jussa F. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. *Brain Pathol* 2004;14:11-20.
37. Hock C, Konietzko U, Streffer JR, Tracy J, Signorell A, Muller-Tillmanns B, et al. Antibodies against beta-amyloid slow cognitive decline in Alzheimer's disease. *Neuron* 2003;38:547-54.
38. Solomon B, Koppel R, Hana E, Katzav T. Monoclonal antibodies inhibit in vitro fibrillar aggregation of the Alzheimer β -amyloid peptide. *Proc Natl Acad Sci USA* 1996;93:452-5.
39. McLaurin J, Cecal R, Kierstead ME, Tian X, Phinney AL, Manea M, et al. Therapeutically effective antibodies against amyloid- β peptide target amyloid- β residues 4-10 and inhibit cytotoxicity and fibrillogenesis. *Nature Med* 2002;8:1263-9.
40. Chromy BA, Nowak RJ, Lambert MP, Viola KL, Chang L, Velasco PT, et al. Self-assembly of A β (1-42) into globular neurotoxins. *Biochemistry* 2003;42:12749-60.
41. Frisardi V, Solfrizzi V, Imbimbo BP, Capurso C, D'Introno A, Colacicco AM, et al. Towards disease-modifying treatment of Alzheimer's disease: drugs targeting beta-amyloid. *Curr Alzheimer Res* 2009;7:40-55.
42. Imbimbo BP. Therapeutic potential of gamma-secretase inhibitors and modulators. *Curr Top Med Chem* 2008;8:54-61.
43. Hüll M, Berger M, Heneka M. Disease-modifying therapies in Alzheimer's disease: how far have we come? *Drugs* 2006;66:2075-93.
44. Christensen DD. Alzheimer's disease: progress in the development of anti-amyloid disease-modifying therapies. *CNS Spectr* 2007;12:113-23.

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