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A current view of Alzheimer's disease

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Abstract

Several genes that influence susceptibility to Alzheimer's disease (AD) have been known for over two decades. Recent advances have elucidated novel candidate genes and the pathogenetic mechanisms underlying neurodegeneration in AD. Here, we summarize what we have learned from studies of the known AD genes with regard to the causes of AD and emerging therapies. We also review key recent discoveries that have enhanced our understanding of the etiology and pathogenesis of this devastating disease, based on new investigations into the genes and molecular mechanisms underlying AD.

Introduction and context

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia in the elderly. As the incidence and prevalence of AD rise steadily with increasing longevity, AD threatens to become a catastrophic burden on health care, particularly in developed countries [1]. AD patients typically present with symptoms of global cognitive decline and loss of memory. Pathologically, the disease is characterized by excessive deposition of amyloid deposits (senile plaques), neurofibrillary tangles, synapse and neuronal loss, and inflammation in the brain. Among the major risk factors for AD, the strongest is increasing age followed by family history [2], gender (females at greater risk than males), and stroke/head trauma.

Genetics of AD

To date, more than 200 rare and fully penetrant autosomal-dominant mutations in three genes, the amyloid precursor protein (*APP*) and presenilin genes (*PSEN1* and *PSEN2*), have been shown to cause the early-onset (<60 years) familial form of AD (EO-FAD), which accounts for <10% of AD cases [3]. On the other hand, a common variant, ε4, in the gene encoding apolipoprotein E (*APOE*) is the only confirmed genetic risk factor for the late-onset form of AD (LOAD) (>90% of AD cases). Overall, these four genes together account for <50% of the genetic variance in AD, and the quest to identify the remaining genes has been challenging due to the complex and heterogeneous nature of the disease [4]. Several genes besides *APOE* have yielded significant evidence (based on meta-analyses) for association with LOAD, but with only modest effects [2].

Molecular pathology of AD

Arguably, the genetic discoveries mentioned above have driven our current understanding of the underlying molecular basis of AD more than any other findings. The proteolytic processing of APP and production of the major component of β-amyloid, Aβ peptide, by two proteases known as β- and γ-secretase are key events in the pathogenesis of disease. The Aβ peptide has two major forms, $A\beta_{40}$, which makes up approximately 90% of Aβ in the brain, and $A\beta_{42}$, which comprises approximately 10%. In addition, the hyperphosphorylation and aggregation of the microtubule-associated tau protein drive neurofibrillary tangle formation within neurons. Most of the mutations in the EO-FAD genes increase the ratio of $A\beta_{42}/A\beta_{40}$. The longer form of the peptide, $A\beta_{42}$, is considered to be the more neurotoxic species as it enhances the aggregation of Aβ into neurotoxic oligomers and senile plaques. Recent studies indicate that $A\beta_{42}$ oligomers and

neurofibrillary tangles lead to the disruption of synaptic neurotransmission, neuronal cell death, and inflammation in the hippocampus and cerebral cortex, thereby causing loss of memory and global cognition dysfunction.

Therapeutics in AD

Currently available drugs for AD, such as cholinesterase inhibitors (for example, Aricept®) and the glutamate antagonist Namenda®, treat mainly the symptoms, with no known effects on disease progress. Another drug, dimebolin, which is currently in clinical trials, is a retired antihistamine that is purported to be neuroprotective based on stabilizing mitochondria. Given that all four of the established AD genes lead to enhanced accumulation of $A\beta_{42}$ in the brain (EO-FAD genes via increased production of the peptide and APOE via decreased clearance), most of the current AD therapies in development are aimed at either curbing $A\beta_{42}$ production/aggregation or potentiating its degradation/clearance. This is being attempted with inhibitors and modulators of the β- and γ-secretases, compounds that attenuate Aβ aggregation (for example, by preventing interaction of the peptide with copper and zinc), and anti-Aβ immunotherapy aimed at stimulating the degradation of the peptide [5].

Major recent advances

Genetics

Given the strong genetic predisposition of AD, there have been a huge number of studies testing for genetic association with AD, including over 1,500 polymorphisms in over 500 candidate genes. As with most complex genetic disorders, the AD genetics field is rife with replications and refutations for hundreds of candidate genes. Recently, an online database known as 'AlzGene' has revolutionized our ability to follow and interpret these findings. AlzGene [6] is a publicly available database that provides up-to-date results of all genetic association reports since 1978 [2]. More importantly, it provides systematic meta-analyses for all polymorphisms (>200) tested in at least four independent study samples. After *APOE*, the gene with the strongest genetic effect on AlzGene was *CHRNB2*, which encodes the beta-2 subunit of the nicotinic cholinergic receptor. This is particularly interesting given that several drugs currently in clinical trials for AD target the nicotinic receptor. The advent of high-throughput genotyping arrays has also enabled 'unbiased' genome-wide screening to identify novel AD genes. To date, six novel LOAD genes have been reported with genome-wide significance [7-10]. One of these, *ATXN1* (ataxin 1), is the gene responsible for another neurodegenerative disorder, spinal cerebellar ataxia 1, and another is *CD33*, a lectin involved in the innate immune system [10].

Beta-amyloid toxicity

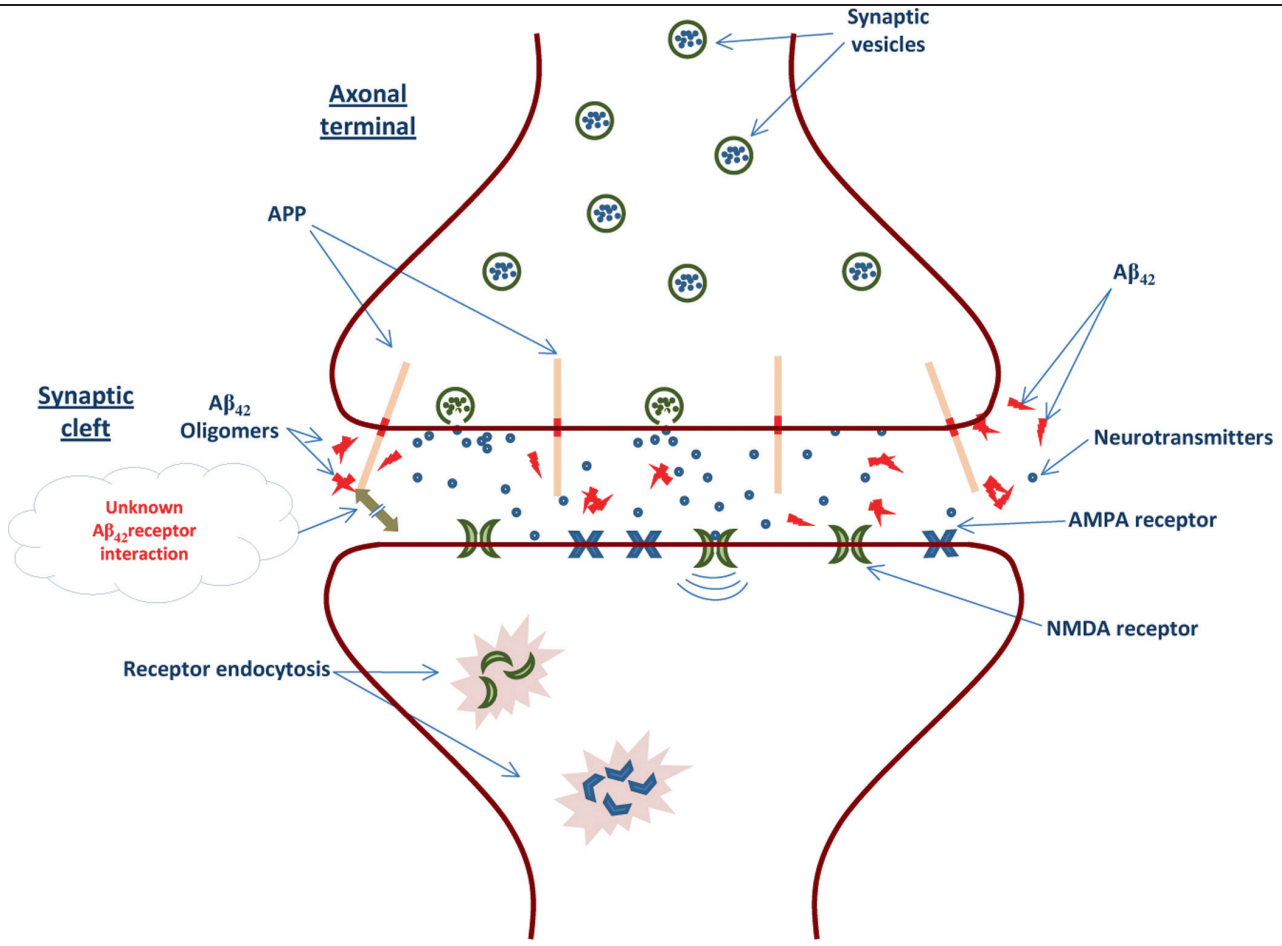
It is widely accepted that excessive β-amyloid deposition in the brain is a key factor in the pathophysiology of AD [4]. Valuable clues concerning the mechanism by which Aβ aggregates lead to cognitive dysfunction have emerged over the last several years. The original amyloid cascade hypothesis maintained that all AD neuropathology, including neuronal cell loss, generation of neurofibrillary tangles, and inflammation, occur downstream of senile plaque formation. However, the amyloid cascade hypothesis fails to explain the weak correlation between amyloid deposition and the clinical degree of dementia in AD [11]. Moreover, the decline in cognition correlates best with synaptic loss and not plaque counts, implying that synaptic perturbations cause AD and precede amyloid plaque deposition [12,13].

A spate of recent studies has initiated a paradigm shift regarding the molecular mechanism by which Aβ deposition leads to cognitive dysfunction. Over the past several years, it has become increasingly apparent that Aβ oligomers (for example, dimers) exert detrimental effects on synaptic function. More specifically, soluble Aβ oligomers have been shown to specifically impair long-term potentiation (LTP) and promote synaptotoxicity. This has led to the synaptic Aβ hypothesis [14], which maintains that free and soluble Aβ oligomers, either produced within the synapse or entering from outside, impair LTP. Furthermore, several reports indicate that Aβ oligomers trigger the internalization of post-synaptic AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)- and NMDA (*N*-methyl-D-aspartic acid)-type glutamate receptors [15,16], leading to loss of spines and inhibition of LTP (Figure 1a,b) [14,17-20]. More recently, high-affinity binding between Aβ and the cellular prion protein PrP^c has been reported, suggesting that PrP^c could be an important mediator in Aβ oligomer-induced synaptic dysfunction [21]. Understanding the interaction between Aβ and other cellular factors could provide new therapeutic potential in restoring the synaptic plasticity and possibly reversing AD symptoms.

Future directions

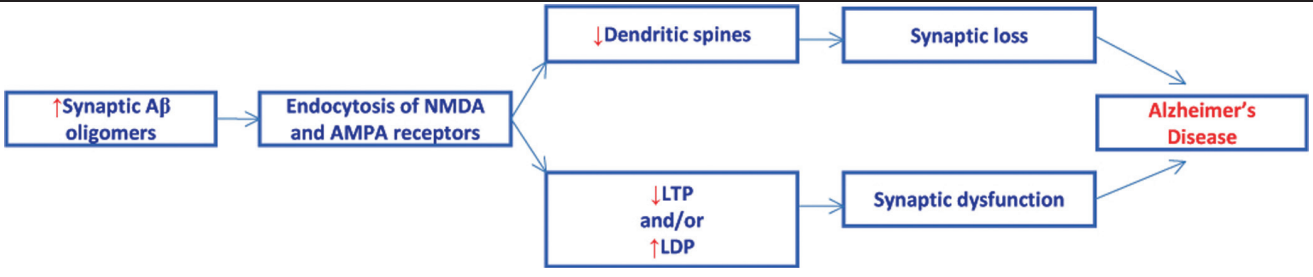
Recent advances have enabled the identification of novel AD genes as well as new insights into the causes of memory and cognitive dysfunction in AD. Genome-wide association studies are gradually elucidating the genetic basis of AD, similar to the case for schizophrenia and autism [22,23], by revealing gene defects and affected biological pathways. Meanwhile, advances in understanding how Aβ impairs cognition at the synaptic level could provide new therapeutic modalities for treating and preventing AD based on restoring the synaptic plasticity.

Figure 1a. Aβ-induced internalization of synaptic NMDA and AMPA receptors



Soluble Aβ oligomers promote receptor endocytosis, reducing the density of the receptors at the synapses. Aβ is secreted into the synaptic cleft via sequential cleavage of presynaptic amyloid precursor protein (APP) (internally or at the cell surface) by β-secretase and γ-secretase or gains entry from outside the synapse. The accumulation of Aβ oligomers in the synaptic cleft leads to reduced NMDA and AMPA receptor density in synapses, leading to attenuated long-term potentiation (LTP) and neurotransmission. While Aβ oligomers may play a normal role in controlling LTP, accelerated synaptic accumulation of Aβ oligomers (for example, due to familial Alzheimer's disease [AD] gene mutations) may lead to a toxic gain of function and cognitive decline. $A\beta_{42}$, amyloid-β-protein 42-mer; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartic acid.

Figure 1b. Synaptic Aβ hypothesis



Increased accumulation of synaptic Aβ oligomers promotes endocytosis of NMDA and AMPA receptors, leading to a reduction in dendritic spines and reduced long-term potentiation (LTP). Acceleration of this process could lead to a toxic gain of function in the form of an imbalance in the LTP/long-term depression (LTD) ratio. This, in turn, causes synaptic dysfunction, spine loss, and (potentially) synaptic loss, leading to cognitive decline and AD. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartic acid.

Abbreviations

$A\beta_{40}$, amyloid-β-protein 40-mer; $A\beta_{42}$, amyloid-β-protein 42-mer; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APOE, apolipoprotein E; APP, amyloid precursor protein; ATXN1, ataxin 1; CHRNB2, cholinergic receptor, nicotinic, beta 2 (neuronal); EO-FAD, early-onset familial form of Alzheimer's disease; LOAD, late-onset form of Alzheimer's disease; LTP, long-term potentiationl; NMDA, *N*-methyl-D-aspartic acid; PrP^c, cellular prion protein.

Competing interests

RET is a consultant for Eisai Incorporated (Woodcliff Lake, NJ, USA) and a consultant/shareholder for Prana Biotechnology Limited (Parkville, VIC, Australia). BVH declares that he has no competing interests.

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