Alzheimer disease is a severe, progressive neurodegenerative brain disorder that accounts for as much as 80% of dementia cases. It is the seventh leading cause of death in the United States. Although Alzheimer disease was initially described more than a century ago, a clear understanding of its mechanisms still does not exist. More importantly, there is no cure for patients with this disorder. Treatments approved by the US Food and Drug Administration (FDA), including use of acetylcholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) receptor antagonists, only target symptoms and are mildly effective at best.

The lack of cure is not the result of a lack of research or efforts. A steady increase in worldwide efforts to fight this devastating disease has occurred following recognition of its immense socioeconomic impact and emotional toll on family members and caregivers. These worldwide efforts have led to substantial progress in understanding many aspects of Alzheimer disease and in providing the basis for new therapeutic approaches. The present article reviews the most recent developments in understanding the molecular and cellular mechanisms of Alzheimer disease pathogenesis. These mechanisms are summarized in the Figure.

Basic Pathologic Factors
The pathologic brain features described in 1907 by Dr Alois Alzheimer—namely senile plaques and neurofibrillary tangles—still serve as the hallmarks for final diagnosis of the disease. Landmark research since the 1980s has established that plaques are composed mainly of extracellular deposits of β-amyloid peptides, most of which contain 38 to 43 amino acids, and that neurofibrillary tangles contain hyperphosphorylated tau protein filaments inside affected neurons.

Sequencing of β-amyloid peptides has demonstrated that they are generated by the sequential proteolytic cleavage of a large protein, referred to as amyloid precursor protein (APP). Although the physiologic function of
APP remains undefined, immunohistochemical studies have localized APP activity to the plasma membrane, the trans-Golgi network, the endoplasmic reticulum, and the endosomal, lysosomal, and mitochondrial membranes. Tau is a microtubule-associated protein that can be phosphorylated on multiple sites by several kinases.8,9

Although the hallmark pathologic features (ie, plaques and tangles) have long been suspected to represent the cause of Alzheimer disease, recent findings have raised doubt about this assumption. Other pathologic factors for Alzheimer disease include synaptic degeneration; dystrophic neurites; accumulation of abnormal endosomes, lysosomes, and mitochondria; neuronal loss; and glia-mediated inflammation. Recent research has also implicated impairment of adult neurogenesis in the hippocampus of individuals with Alzheimer disease.10 Among all Alzheimer disease pathologic features, synaptic loss and selective neuronal death in the limbic system and neocortex are best correlated with cognitive impairment.11-14

Tau Dysfunction

Early biochemical studies revealed that neurofibrillary tangles contain highly phosphorylated tau proteins. However, after several decades of intensive research, it is still not clear whether tau phosphorylation is necessary and sufficient for the formation of tangles. Recent research has shown that truncated tau exhibits a higher tendency of aggregation than native tau, indicating that proteolytic modification may participate in tangle formation.15-17 The distribution and amount of neurofibrillary tangles are correlated with the severity of cognitive impairment in patients with Alzheimer disease.14,18

Although no direct evidence has firmly established a causal role for tau hyperphosphorylation and neurofibrillary tangles in Alzheimer disease, several mutations in the tau gene are known to lead to another type of dementia—the familial frontotemporal dementia with Parkinsonism linked to chromosome 17 (FTDP-17).19-21 A number of studies have shown that expression of tau with FTDP-17 mutations in mice results in neurodegeneration with obvious axonal injury.22,23 In addition, overexpression of tau caused exaggerated and facilitated pathogenesis in transgenic mice carrying mutant APP.24,25 Genetic removal of tau from these transgenic mice led to reduced Alzheimer disease–type pathologic features,26 suggesting that tau is essential for β-amyloid–induced neuronal toxicity (at least in transgenic mice).

A more recent study27 has shown that tau facilitates β-amyloid toxicity by directing the Src kinase Fyn to the NMDA receptors, increasing the interactions of Src kinase Fyn with the PSD95 proteins and resulting in excitotoxicity. Furthermore, suppression of tau phosphorylation in transgenic mice in which mutant tau was expressed led to abrogated neurofibrillary tangles as well as improved contextual memory and motor function.28 These recent advancements in knowledge of mechanisms suggest that tau and its interacting proteins may be potential targets for Alzheimer disease drug development.

Genetics and the Amyloid Cascade Hypothesis

Although most cases of Alzheimer disease are sporadic and idiopathic, mutations in three genes have been identified as being responsible for a small fraction of early-onset Alzheimer disease, also known as familial Alzheimer disease (FAD). This type of Alzheimer disease accounts for approximately 5% of all Alzheimer disease cases. These genes are those coding for APP,29 presenilin 1 (PS1, also known as PSEN1), and presenilin 2 (PS2, also known as PSEN2).30-33 Mutations in the PS1 and PS2 genes account for as much as 50% of all FAD cases.34 More than 30 mutations in the APP gene and more than 180 mutations in PS1 and PS2 genes have been identified.35

Other genetic factors leading to FAD include APP locus duplication36 and polymorphisms in the APP promoter region.37 Earlier research showed that insoluble fibrillar β-amyloid aggregates were neurotoxic in both in vitro and in vivo conditions, a finding that led to the amyloid cascade hypothesis of Alzheimer disease.38 Mutations in all three genes were shown to increase the production and aggregation of β-amyloid, an effect...
that was extensively used to support the amyloid cascade hypothesis.\(^{36}\)

Generation of \(\beta\)-amyloid from APP involves three proteases/secretases—\(\alpha\), \(\beta\), and \(\gamma\). Cleavage of APP by \(\beta\)-secretase and \(\gamma\)-secretase produces the \(\beta\)-amyloid peptide, the secreted ectodomain APP\(_{\text{ect}}\) and an intracellular fragment called APP intracellular domain. By contrast, cleavage of APP by \(\alpha\)-secretase and \(\gamma\)-secretase results in a p3 peptide, the homologue PS2 to function as \(\gamma\)-secretase, their association with three additional proteins—nicastrin, aph-1, and pen-2—is required. Together, these proteins form a tetrameric complex with PS1 and PS2 as the catalytic subunit.\(^{50-53}\) The reasons that PS1 and PS2 require the other three proteins to function as \(\gamma\)-secretase are not known. Some investigators have proposed that association of PS1 and PS2 with the three additional proteins may facilitate the correct protein assembly, subcellular targeting, and substrate recognition.

Taked together, compelling genetic and molecular evidence supports the amyloid cascade hypothesis for FAD. However, whether the amyloid cascade hypothesis also accounts for sporadic Alzheimer disease remains uncertain. Also unclear is how \(\beta\)-amyloid generation sets in motion the molecular cascade leading to the Alzheimer disease pathologic process.

Since it was first proposed, the amyloid cascade hypothesis has been challenged because of the poor correlation between the number of amyloid plaques that contain fibrillar \(\beta\)-amyloid and the severity of dementia. Furthermore, amyloid plaques have also been reported in individuals who show no cognitive impairment.\(^{34,55}\) Recent research has indicated that levels of soluble oligomeric \(\beta\)-amyloid exhibit a better correlation than number of amyloid plaques with synaptic loss and severity of cognitive impairment.\(^{55}\) Additional in vitro studies have shown that various soluble oligomeric species of \(\beta\)-amyloid are more toxic than the fibrillar species.\(^{56}\)

\(\beta\)-amyloid oligomers isolated from brains of individuals with Alzheimer disease show a wide range of molecular weight distribution (ie, from less than 10 kDa to more than 100 kDa). However, the identity of the isoforms responsible for the pathologic process in Alzheimer disease is still under debate. Also remaining unclear is how \(\beta\)-amyloid monomers are converted into oligomers and how oligomers induce neuronal injury. Lauren et al\(^{58}\) recently reported that \(\beta\)-amyloid oligomers could bind to the cellular prion protein (PrP\(^{C}\)) with nanomolar affinity, suggesting that PrP\(^{C}\) may function as a receptor for \(\beta\)-amyloid oligomers. Binding of \(\beta\)-amyloid oligomers to PrP\(^{C}\) blocked the formation of long-term potentiation, a widely recognized cellular mechanism for certain forms of learning and memory.\(^{59,60}\) This finding provided a potential mechanism for synaptic dysfunction in Alzheimer disease.

These oligomers have also been shown to disrupt many neuronal functions and to induce cell death by binding to the p75 nerve growth factor receptor,\(^{61-63}\) the NMDA receptor,\(^{64,65}\) the insulin receptor,\(^{66,67}\) and the frizzled receptor.\(^{68}\) Besides directly interacting with various receptors, \(\beta\)-amyloid oligomers could induce synaptic dysfunction by interacting with scaffold proteins in the postsynaptic density (PSD) region, such as PSD-95 and Shank.\(^{69-71}\) Furthermore, \(\beta\)-amyloid oligomers can induce cell injury via interaction with endocytic pathways. Still other possibilities that have been proposed for oligomer activity include effects on membrane properties, such as formation of channellike structures,\(^{72,73}\) and effects causing mitochondrial dysfunction.\(^{74}\)

**Brain Aging**

For sporadic Alzheimer disease cases, which account for the majority of Alzheimer disease cases, the most important risk factor is aging. Although environmental factors—ranging from aluminum, mercury, and viruses to education and mental stimulation—have been proposed to affect the onset of sporadic Alzheimer disease, results from studies of twins strongly suggest the involvement of genetic factors in this condition.\(^{75}\) However, some questions remain regarding these findings.

To date, polymorphism in the apolipoprotein E (ApoE) gene is the only...
confirmed genetic risk factor for sporadic Alzheimer disease. Apolipoprotein E is involved in lipid transport and exhibits three alleles (ε2, ε3, ε4). Many studies have demonstrated that the presence of the ε4 allele is a risk factor for sporadic Alzheimer disease and late-onset FAD. Compared to individuals who do not have an ApoE ε4 allele, individuals who have one ε4 allele are at a 2-fold to 3-fold increased risk for Alzheimer disease, and individuals who have two ε4 alleles are at a 12-fold increased risk for Alzheimer disease. The ApoE ε4 allele is also associated with an earlier age of Alzheimer disease onset. Individuals with one ε2 allele, individuals who have one ε4 allele are at a 2-fold to 3-fold increased risk for Alzheimer disease, and individuals who have two ε4 alleles are at a 12-fold increased risk for Alzheimer disease. The ApoE ε4 allele is also associated with an earlier age of Alzheimer disease onset. 

The manner in which ApoE polymorphism affects Alzheimer disease onset remains unknown. Several studies indicate that ApoE may affect β-amyloid aggregation and clearance. All cells of the body produce β-amyloid throughout life, though neurons produce the highest amounts of β-amyloid. The age-dependency of β-amyloid accumulation and Alzheimer disease onset suggests that intrinsic properties of aged brains precipitate the pathologic cascade.

**Lysosomal Dysfunction**

Early studies showed that lysosomal dysfunction is an early-onset phenomenon of brain aging in mammals. Lysosomes play a major role in the degradation of long-lived proteins and old or damaged organelles, with lysosome cargoes being delivered via the autophagic pathway and internalized materials being delivered to lysosomes. Likewise, cargoes in the autophagic pathway are transported by autophagosomes, which fuse with lysosomes to become autophagolysosomes.

As the two pathways converge at the late-endosome and lysosome level, function of both systems could be affected by interruption of these downstream organelles. Initial evidence that dysfunction of the endocytic pathway might contribute to Alzheimer disease pathogenesis came from postmortem studies showing that lysosomal hydrolases were increased in the vicinity of amyloid plaques in brains. This effect was found to be most evident in brain areas exhibiting early signs of neuronal damage. Subsequent research revealed a potential role of the endocytic pathway in secretase-mediated generation of β-amyloid.

Recently, several studies reported that autophagic activity was linked to amyloidogenesis in Alzheimer disease. Because γ-secretase complexes are enriched in endocytic and autophagic pathways, dysfunction in these pathways could conceivably lead to altered generation of β-amyloid, and thus to Alzheimer disease pathogenesis.

Interestingly, recent research has shown that PS1 has a secretase-independent function. Repetto et al. reported that PS1 deficiency in fibroblasts led to increased levels of epidermal growth factor receptor, which was rescued by the expression of wild-type PS1 or of its C-terminal fragment. Other findings have shown that PS1 deficiency in hippocampal neurons resulted in increased levels of telencephalin, a neuron-specific cell adhesion molecule involved in long-term potentiation. The increases in both epidermal growth factor receptor and telencephalin were assumed to be caused by impairment in endosomal-lysosomal trafficking.

A recent report indicated that PS1 deletion completely and selectively blocked autophagic-lysosomal proteolysis. Further experiments have revealed that PS1 is essential for lysosomal acidification, because it functions as an endoplasmic reticulum chaperone protein to facilitate the maturation and targeting of vacuolar-type H+-ATPase (v-ATPase), a proton pump essential for lysosomal pH setting. Of clinical significance, autophagic/lysosomal dysfunction has been associated with the nonlysosomal localization of v-ATPase in fibroblast cells, with PS1 mutations causing FAD.

These findings provide evidence that PS1 mutations could lead to Alzheimer disease through disruption of lysosomal function—individually or in concert with APP proteolytic activity. Disruption of endosomal-lysosomal function, such as by inhibition of cholesterol transport and by aging, could result in PS1 accumulation in late endosomes and lysosomes. This disruption also alters APP processing, with decreased β-secretase-mediated cleavage of full-length APP, increased γ-secretase-mediated cleavage of C-terminal APP, and increased β-amyloid formation.

Another study used a mouse model of Niemann-Pick type C disease—which exhibits genetically induced cholesterol accumulation in late endosomes and lysosomes—to link altered function of endosomes and lysosomes with increased γ-secretase activity and enhanced β-amyloid formation.

These results underscore the importance of the endocytic-lysosomal pathway in Alzheimer disease pathogenesis. Niemann-Pick type C disease exhibits several Alzheimer disease-like pathologic features, including abnormal autophagic activity, lysosomal dysfunction, and neurofibrillary tangles. Furthermore, Alzheimer disease-like pathologic features in brains of individuals with Niemann-Pick type C were found to be influenced by the ApoE ε4 genotype. These various results suggest that the activity, substrate preference, and products of secretases depend on their subcellular localization, which, in turn, indicates that regulation of the sorting of secretases could provide potential therapeutic targets.

Disruption of the endocytic-lysosomal and autophagic-lysosomal systems could affect other cellular functions that, in turn, could contribute to Alzheimer disease pathogenesis. For example, the endocytic pathway is important for receptor-mediated signaling, including trophic factor signaling. Thus, abnormalities in this pathway could...
interfere with trophic factor signaling.\textsuperscript{113} In cultured hippocampal slices, lysosomal dysfunction results in accumulation of phosphorylated tau and tangle-like structures.\textsuperscript{114}

The autophagic-lysosomal system plays an important role in the regulation of mitochondria, essential organelles for cell survival and cell death. Autophagic-lysosomal dysfunction could result in the accumulation of aged and damaged mitochondria, which could release factors leading to cell death.\textsuperscript{115} Changes in mitochondrial gene expression and function are common in aged mammalian brains,\textsuperscript{116} and mitochondrial dysfunction has been reported in brains of patients with Alzheimer disease.\textsuperscript{115} Therefore, antioxidative treatment\textsuperscript{117-119} and estrogen replacement therapy\textsuperscript{120,121} to improve mitochondrial function have been proposed as potential treatments for patients with Alzheimer disease.

**Conclusion**

After several decades of intensive research, substantial progress has been made in understanding the basic mechanisms of Alzheimer disease. Researchers now understood how APP is sequentially processed by $\beta$-secretase and $\gamma$-secretase to form APP$_{s\beta}$, APP C-terminal fragment, and $\beta$-amyloid. Furthermore, genetics studies have identified the cause for early-onset FAD. Mutations in FAD-related genes are associated with accumulation of $\beta$-amyloid, which has been cited as strong evidence for the amyloid cascade hypothesis.

More recent studies have led to modification of the amyloid cascade hypothesis. The toxic $\beta$-amyloid fibrils are no longer viewed as the foul players. Instead, the $\beta$-amyloid oligomers are seen as the culprits. A recent report\textsuperscript{101} that mutations in the PS1 gene lead to lysosomal dysfunction—by impacting the maturation of the lysosomal proton pump—poses another challenge to the amyloid cascade hypothesis. Results from that study\textsuperscript{101} suggest that lysosomal dysfunction occurs upstream of altered $\beta$-amyloid levels, either by decreasing $\beta$-amyloid degradation or by increasing specific $\beta$-amyloid generation (because of changes in pH in endosomes and lysosomes or because of modified targeting of secretases and of APP and its metabolites).

Considering the large amount of published studies covering every aspect of cell functions in Alzheimer disease, it is reasonable to conclude that multiple pathways likely contribute to Alzheimer disease pathogenesis and that combined approaches, including osteopathic manipulative treatment, should be considered for Alzheimer disease management.

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