Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. Typically, the disease progresses in a prolonged, inexorable manner [1]. Patients initially show symptoms of mild cognitive impairment, which may include some memory loss. As the disease progresses, more severe memory loss occurs (e.g., retrograde amnesia) leading to confusion and lack of orientation. The patient is often institutionalized in this period, as it becomes increasingly difficult for family members to cope with the constant requirements of care. In later stages of the disease, apathy and stupor can occur, and the patient becomes bedridden.

The histopathology of AD is characterized by gliosis and tissue atrophy caused by both synaptic and neuronal loss, which are most pronounced in the frontal and temporal cortices [2]. Proteinaceous deposits are seen in both the intracellular and extracellular compartments of the brain, typically in the hippocampus and neocortex. The intracellular deposits consist of neurofibrillary tangles that are made up of paired helical filaments of a hyperphosphorylated form of the cytoskeletal protein tau [3]. Extracellular amyloid plaques are found most commonly in the hippocampus and neocortex and may be diffuse or compact in nature [4]. Amyloid is also deposited as cerebral amyloid angiopathy within small- to medium-sized arterioles [5]. Although neurofibrillary tangles are associated with a number of different types of neurodegenerative disease, the presence of numerous compact or neuritic amyloid plaques is a hallmark feature of Alzheimer’s disease. For this reason, it may be argued that accumulation of the β-amyloid protein (Aβ) is a key step in the pathogenic mechanism of Alzheimer’s disease. In contrast, although the density of neurofibrillary tangles correlates more closely with the cognitive symptoms, it is now commonly thought that tangles are a secondary feature or the underlying disease process [6].

1.1 The Role of Aβ in AD

Glenner and Wong [7] first identified the major protein component of vascular amyloid, which was a low-molecular-weight, 4-kDa polypeptide, now referred to as the β-amyloid protein (Aβ). Subsequent studies established that the same protein was the major component of amyloid plaques [8]. The complete amino acid sequence of Aβ led to the identification of its precursor, the β-amyloid precursor protein (APP) [9].

APP has features of an integral type I transmembrane glycoprotein, with a large ectodomain containing the N-terminus and a small cytoplasmic domain containing the C-terminus (Fig. 1.1). Multiple mRNA splicing of exons can generate several different isoforms of APP that lack domains homologous to Kunitz-type protease inhibitors (KPI domain) and the OX-2 antigen as well as a domain encoded by an exon that regulates O-linked glycosylation by chondroitin sulfate. The Aβ sequence itself comprises part of the ectodomain of the protein and extends into, but not all the way through, the transmembrane domain [9, 10].

Soon after its identification, APP was shown to undergo ectodomain shedding by an enzyme
dubbed the $\alpha$-secretase. The $\alpha$-secretase cleaves APP within the $\beta\delta$ sequence, adjacent to lysine-16, thereby destroying the sequence [11, 12]. Recently studies suggest that enzymes of the ADAM family of metalloproteases are responsible for this activity [13, 14]. Other studies have demonstrated that APP can also be cleaved at the N- and C-terminal ends of the $\beta\delta$ sequence by enzymes dubbed $\beta$- and $\gamma$-secretase, respectively, to generate the full-length $\beta\delta$ sequence [15]. Amyloidogenic processing by $\beta$- and $\gamma$-secretase is a normal, albeit minor, pathway of APP processing. The $\beta$-secretase has been unequivocally identified as an aspartyl protease termed BACE1 (an acronym for $\beta$-site APP cleaving enzyme-1) [16–19]. The $\gamma$-secretase comprises a complex of several proteins including presenilin-1, presenilin-2, Aph1, Pen2, and nicas-trin. However, other protein components of this complex may also exist [15].

There is considerable evidence that the accumulation of $\beta\delta$ in the brain is toxic to neurons and that this toxicity underlies the neurodegeneration that occurs in AD (Fig. 1.1) [20]. $\beta\delta$ peptides are toxic to cells in culture [21], and this toxicity is associated with aggregation of the peptide [22]. Recent studies support the view that the most toxic species are the low-molecular-weight, soluble oligomers of $\beta\delta$ [23].

Despite many studies that have shown that $\beta\delta$ can disrupt biochemical events within neurons, direct proof that the accumulation of $\beta\delta$ is the cause of AD has been lacking. Nevertheless, evidence that this is the case has slowly been accumulating. Some of the strongest evidence that $\beta\delta$ accumulation is the cause, rather than an epiphenomenon, of AD has come from the finding of familial AD mutations present in the APP gene [24]. All of these mutations have been found to cluster around the $\beta\delta$ sequence, and all of them have so far been shown to directly or indirectly cause an increase in forms of $\beta\delta$ that aggregate [25]. For example, although the most commonly produced form of $\beta\delta$ contains 40-amino-acid residues ($\beta\delta40$), a minor form containing 42 residues is also formed. This minor form aggregates into amyloid fibrils much more readily than $\beta\delta40$ [26]. The first mutation to be identified in the APP gene, the London mutation, involves a single base change at codon 717, which encodes a form of APP that is more readily cleaved to produce $\beta\delta42$. To date, at least 10 familial AD mutations are known to occur in APP [27].

The direct involvement of APP and $\beta\delta$ in the pathogenesis of AD is also strongly supported by studies on transgenic mice. A number of transgenic lines have been developed in which human APP is expressed [28]. Many of these mice develop amyloid plaques. In addition, other features of AD pathology such as neuritic dystrophy, abnormal tau phosphorylation, gliosis, synaptic loss, and behavioral abnormalities have been observed. Although human APP mice do not develop neurofibrillary tangles, this is probably due to differences between mouse tau and human tau isoforms. Indeed, in double transgenic mice expressing both mutant human tau and APP, $\beta\delta$ is seen to increase tau deposition [29].

Mutations in the APP gene account for only a very small percentage of all familial Alzheimer’s disease (FAD) cases. Shortly after the identification of the first familial AD mutation in the APP gene, mutations were identified in two other genes, PS1 encoding presenilin-1 and PS2 encoding...
presenilin-2, located on chromosomes 14 and 1, respectively [30, 31]. Both presenilin proteins are components of the γ-secretase complex, and familial AD mutations within the PS1 and PS2 genes alter γ-secretase processing in a way that leads to the production of more Aβ42 [32].

In general, mutations in the APP, PS1, and PS2 genes lead to early-onset forms of AD. In contrast, the apolipoprotein E (apoE) gene located on chromosome 19 is a risk factor for late-onset AD [33]. There are three forms of apoE, termed E2, E3, and E4. The E4 variant is a risk factor for late-onset AD, whereas the E2 may be protective. Although the reason for this is still unknown, it is undoubtedly related to Aβ production, aggregation, or clearance from the brain. Individuals with the E4 allele have more Aβ deposition within the brain [34]. In addition, APP x apoE knockout transgenic mice develop little amyloid deposition in their brains, unlike normal APP mice [35]. Thus, studies on the role of apoE in AD provide strong support for the Aβ hypothesis.

1.2 Anti-Aβ Therapies for AD

The idea that Aβ is a primary causative agent in AD leads inevitably to the view that an effective therapy based on inhibiting the production, aggregation, clearance, or toxicity of Aβ may be achievable. One of the most promising but controversial approaches in recent years has been Aβ immunization. Studies show that in transgenic mice, immunization with Aβ42 leads to the generation of an immune response [36]. Anti-amyloid antibodies bind to amyloid plaques and appear to facilitate their removal from the brain, leading to an improvement in cognitive performance compared with nonimmunized control animals. Unfortunately, clinical trials of this approach in humans have been halted because a small percentage of individuals immunized with Aβ have developed a severe meningocencephalitis [37]. Nevertheless, there is some evidence that patients who develop a strong immune response to Aβ without the associated brain inflammation may benefit from this approach [38].

1.3 Current Status of the Aβ Hypothesis of AD

There is now very strong evidence that accumulation of oligomeric or fibrillar Aβ in the brain is a key event in the pathogenesis of AD. Perhaps the most important unresolved question is the mechanism by which Aβ causes its neurotoxic effect. It is also unclear what form of aggregated Aβ is the most neurotoxic. Another major question is how many unidentified genetic risk factors there are and how these risk factors affect Aβ production, aggregation, or clearance. If anti-Aβ therapies can be used successfully for the treatment of AD, then the remaining concerns about the role of Aβ in the pathogenesis of AD will have been answered.

References


