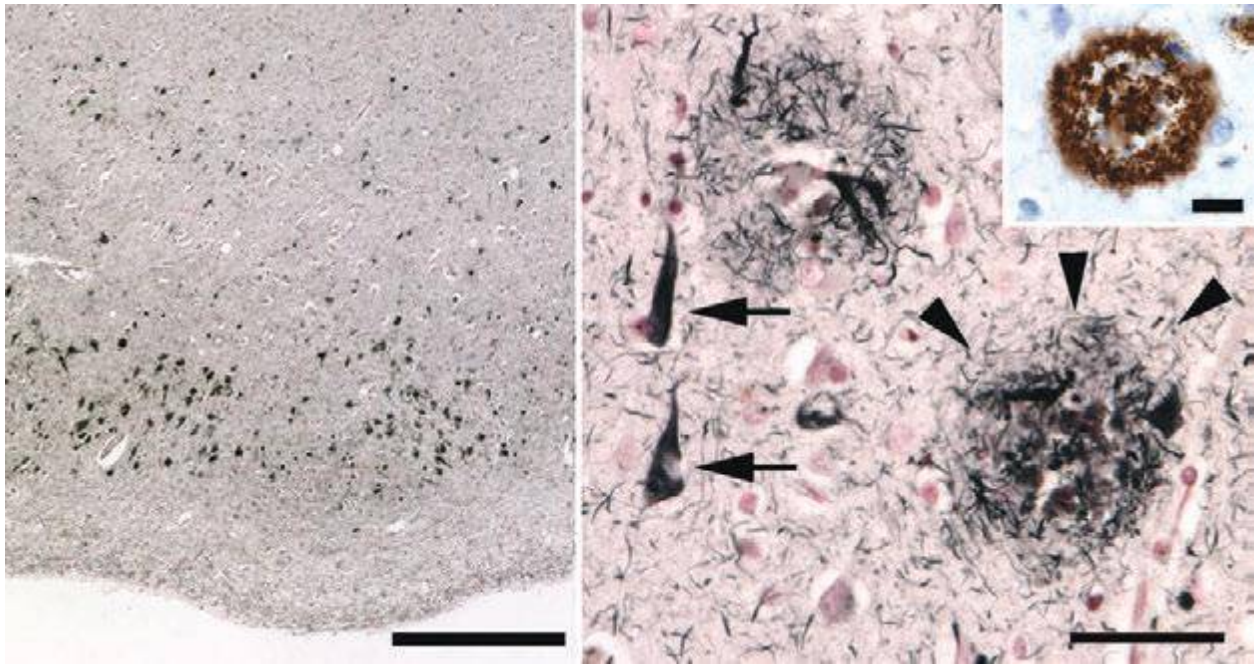

A B

FIGURE 448-1 Neuropathology of Alzheimer's disease. *A.* Early neurofibrillary degeneration, consisting of neurofibrillary tangles and neuropil threads, preferentially affects the medial temporal lobes, especially the stellate pyramidal neurons that compose the layer 2 islands of entorhinal cortex, as shown. ***B.*** Higher magnification view reveals the fibrillary nature of tangles (*arrows*) and the complex structure of neuritic plaques (*arrowheads*), whose major component is Aβ (*inset* shows immunohistochemistry for Aβ). Scale bars are 500 μM in ***A***, 50 μM in ***B***, and 20 μM in ***B*** inset.

normal brain aging but dominate the picture in AD. Increasing evidence suggests that soluble amyloid species called *oligomers* may cause cellular dysfunction and represent the early toxic molecule in AD. Eventually, further amyloid polymerization and fibril formation lead to neuritic plaques, which contain a central core of amyloid, proteoglycans, Apo ε4, α-antichymotrypsin, and other proteins. Aβ is a protein of 39–42 amino acids that is derived proteolytically from a larger transmembrane protein, *amyloid precursor protein* (APP), when APP is cleaved by β and γ secretases (Fig. 448-2). The normal

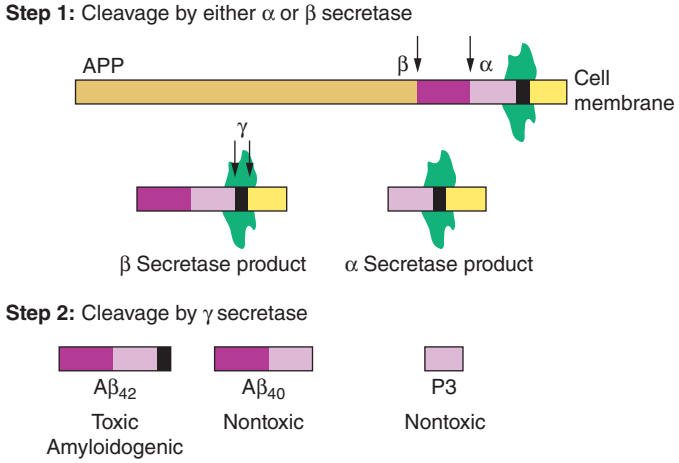

FIGURE 448-2 Amyloid precursor protein (APP) is catabolized by α, β, and γ secretases. A key initial step is the digestion by either β secretase (BASE) or α secretase (ADAM10 or ADAM17 [TACE]), producing smaller nontoxic products. Cleavage of the β secretase product by γ secretase (Step 2) results in either the toxic $A\beta_{42}$ or the nontoxic $A\beta_{40}$ peptide; cleavage of the α secretase product by γ secretase produces the nontoxic P3 peptide. Excess production of $A\beta_{42}$ is a key initiator of cellular damage in Alzheimer's disease (AD). Therapeutics for AD have focused on attempts to reduce accumulation of $A\beta_{42}$ by antagonizing β or γ secretases, promoting α secretase, or clearing $A\beta_{42}$ that has already formed by use of specific antibodies.

function of the Aβ peptides remains uncertain. APP has neurotrophic and neuroprotective properties. The plaque core is surrounded by a halo, which contains dystrophic, tau-immunoreactive neurites and activated microglia. The accumulation of Aβ in cerebral arterioles is termed *amyloid angiopathy*. NFTs are composed of silver-staining neuronal cytoplasmic fibrils composed of abnormally phosphorylated tau protein; they appear as paired helical filaments by electron microscopy. Tau binds to and stabilizes microtubules, supporting axonal transport of organelles, glycoproteins, neurotransmitters, and other important cargoes throughout the neuron. Once hyperphosphorylated, tau can no longer bind properly to microtubules and redistributes from the axon to throughout the neuronal cytoplasm and distal dendrites, compromising function. Finally, patients with AD often show comorbid DLB or vascular pathology. In animal models of AD, diminishing neuronal tau ameliorates the cognitive deficits and seizures, even though $A\beta_{42}$ continues to accumulate, raising hope for tau-lowering therapies in humans. Biochemically, AD is associated with a decrease in the cortical levels of several proteins and neurotransmitters, especially acetylcholine, its synthetic enzyme choline acetyltransferase, and nicotinic cholinergic receptors. Reduction of acetylcholine reflects degeneration of cholinergic neurons in the nucleus basalis of Meynert that project throughout the cortex. There is also noradrenergic and serotonergic depletion due to degeneration of brainstem nuclei such as the locus coeruleus and dorsal raphe, where tau-immunoreactive neuronal cytoplasmic inclusions can be identified even in individuals lacking entorhinal cortex NFTs.

GENETIC CONSIDERATIONS

Several genes play an important role in the pathogenesis of AD. One is the *APP* gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40 years, and many develop a progressive dementia superimposed on their baseline mental retardation. The extra dose of the *APP* gene on chromosome 21 is the initiating cause of AD in adult Down's syndrome and results in excess cerebral amyloid production. Supporting this hypothesis, some families with early age-of-onset familial AD (FAD) have point