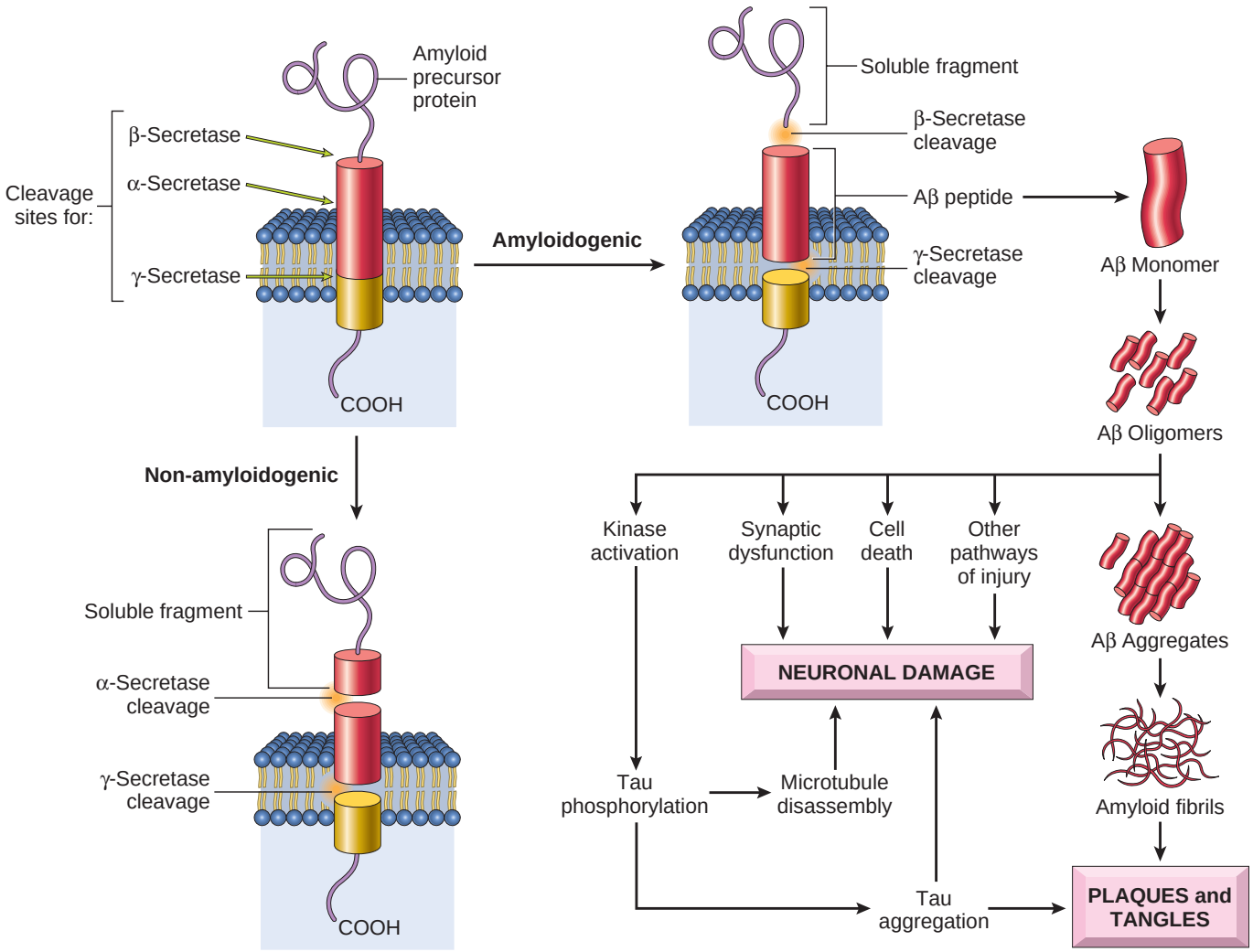

Figure 28-36 Protein aggregation in Alzheimer disease. Amyloid precursor protein cleavage by α-secretase and γ-secretase produces a harmless soluble peptide, whereas amyloid precursor protein cleavage by β-amyloid–converting enzyme (BACE) and γ-secretase releases Aβ peptides, which form pathogenic aggregates and contribute to the characteristic plaques and tangles of Alzheimer disease.

- *Role of tau.* Because neurofibrillary tangles contain the tau protein, there has been much interest in the role of this protein in AD. Tau is a microtubule-associated protein present in axons in association with the microtubular network. With the development of tangles in AD, it shifts to a somatic-dendritic distribution, becomes hyperphosphorylated, and loses the ability to bind to microtubules. The formation of tangles is an important component of AD, and the increased tangle burden in the brain over the course of the illness eventually appears to become independent of the Aβ. The mechanism of tangle injury to neurons remains poorly understood but two possible pathways have been suggested. First, the aggregates of tau protein elicit a stress response and second, the microtubule stabilizing function of tau protein is lost.
- *Other genetic risk factors.* The genetic locus on chromosome 19 that encodes apolipoprotein E (ApoE) has a strong influence on the risk of developing AD. Three alleles exist (ε2, ε3, and ε4) based on two amino acid polymorphisms. The dosage of the ε4 allele increases the risk of AD and lowers the age of onset of the disease, such that individuals with the ε4 allele are overrepresented in populations of patients with AD. This ApoE isoform promotes Aβ generation and deposition, although the mechanisms have not been established. Overall, this locus has been estimated to convey about a quarter of the risk for development of late-onset AD. Genome-wide association studies have identified several other loci that contribute to the risk of AD. The connection between these genetic loci and the pathogenesis of AD remains to be explored.
- *Role of inflammation.* Both small aggregates and larger deposits of Aβ elicit an inflammatory response from microglia and astrocytes. This response probably assists in the clearance of the aggregated peptide, but may also stimulate the secretion of mediators that cause damage. Additional consequences of the activation of these inflammatory cascades may include alterations in tau phosphorylation, along with oxidative injury to the neurons.

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