MECHANISMS OF DISEASE

Alzheimer's Disease

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MORE THAN 35 MILLION PEOPLE WORLDWIDE — 5.5 MILLION IN THE United States — have Alzheimer's disease, a deterioration of memory and other cognitive domains that leads to death within 3 to 9 years after diagnosis. Alzheimer's disease is the most common form of dementia, accounting for 50 to 56% of cases at autopsy and in clinical series. Alzheimer's disease combined with intracerebral vascular disease accounts for another 13 to 17% of cases.

The principal risk factor for Alzheimer's disease is age. The incidence of the disease doubles every 5 years after 65 years of age, with the diagnosis of 1275 new cases per year per 100,000 persons older than 65 years of age.[1] Data on centenarians show that Alzheimer's disease is not necessarily the outcome of aging[2]; nevertheless, the odds of receiving the diagnosis of Alzheimer's disease after 85 years of age exceed one in three. As the aging population increases, the prevalence will approach 13.2 to 16.0 million cases in the United States by mid-century.[3]

Many molecular lesions have been detected in Alzheimer's disease, but the overarching theme to emerge from the data is that an accumulation of misfolded proteins in the aging brain results in oxidative and inflammatory damage, which in turn leads to energy failure and synaptic dysfunction.

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PROTEIN ABNORMALITIES IN ALZHEIMER'S DISEASE

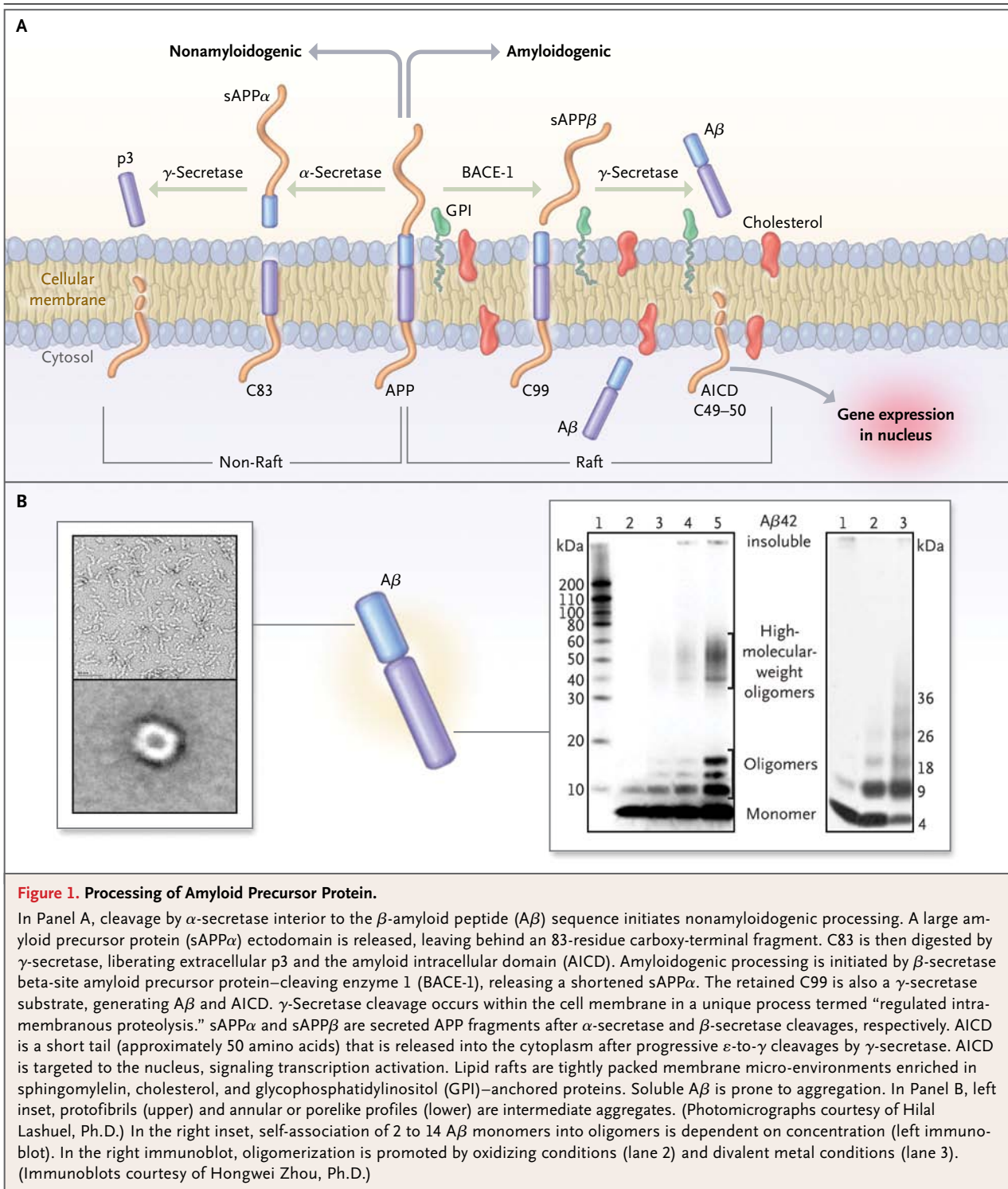### β-AMYLOID

Cerebral plaques laden with β-amyloid peptide (Aβ) and dystrophic neurites in neocortical terminal fields as well as prominent neurofibrillary tangles in medial temporal-lobe structures are important pathological features of Alzheimer's disease. Loss of neurons and white matter, congophilic (amyloid) angiopathy, inflammation, and oxidative damage are also present.

Aβ peptides are natural products of metabolism consisting of 36 to 43 amino acids. Monomers of $A\beta_{40}$ are much more prevalent than the aggregation-prone and damaging $A\beta_{42}$ species. β-amyloid peptides originate from proteolysis of the amyloid precursor protein by the sequential enzymatic actions of beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), a β-secretase, and γ-secretase, a protein complex with presenilin 1 at its catalytic core[4] (Fig. 1). An imbalance between production and clearance, and aggregation of peptides, causes Aβ to accumulate, and this excess may be the initiating factor in Alzheimer's disease. This idea, called the "amyloid hypothesis," is based on studies of genetic forms of Alzheimer's disease, including Down's syndrome,[5] and evidence that $A\beta_{42}$ is toxic to cells.[6,7]

Aβ spontaneously self-aggregates into multiple coexisting physical forms. One form consists of oligomers (2 to 6 peptides), which coalesce into intermediate assemblies[8,9] (Fig. 1). β-amyloid can also grow into fibrils, which arrange themselves into β-pleated sheets to form the insoluble fibers of advanced amyloid plaques.

Soluble oligomers and intermediate amyloids are the most neurotoxic forms of

Figure 1. Processing of Amyloid Precursor Protein.

In Panel A, cleavage by α-secretase interior to the β-amyloid peptide (Aβ) sequence initiates nonamyloidogenic processing. A large amyloid precursor protein (sAPPα) ectodomain is released, leaving behind an 83-residue carboxy-terminal fragment. C83 is then digested by γ-secretase, liberating extracellular p3 and the amyloid intracellular domain (AICD). Amyloidogenic processing is initiated by β-secretase beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), releasing a shortened sAPPα. The retained C99 is also a γ-secretase substrate, generating Aβ and AICD. γ-Secretase cleavage occurs within the cell membrane in a unique process termed "regulated intramembranous proteolysis." sAPPα and sAPPβ are secreted APP fragments after α-secretase and β-secretase cleavages, respectively. AICD is a short tail (approximately 50 amino acids) that is released into the cytoplasm after progressive ε-to-γ cleavages by γ-secretase. AICD is targeted to the nucleus, signaling transcription activation. Lipid rafts are tightly packed membrane micro-environments enriched in sphingomyelin, cholesterol, and glycophosphatidylinositol (GPI)–anchored proteins. Soluble Aβ is prone to aggregation. In Panel B, left inset, protofibrils (upper) and annular or porelike profiles (lower) are intermediate aggregates. (Photomicrographs courtesy of Hilal Lashuel, Ph.D.) In the right inset, self-association of 2 to 14 Aβ monomers into oligomers is dependent on concentration (left immunoblot). In the right immunoblot, oligomerization is promoted by oxidizing conditions (lane 2) and divalent metal conditions (lane 3). (Immunoblots courtesy of Hongwei Zhou, Ph.D.)

Aβ.[10] In brain-slice preparations, dimers and trimers of Aβ are toxic to synapses.[11,12] The severity of the cognitive defect in Alzheimer's disease correlates with levels of oligomers in the brain, not the total Aβ burden.[13] Neuronal activation rapidly increases Aβ secretion at the synapse, a process tied to the normal release of vesicles containing neurotransmitters. Physiologic

levels of synaptic Aβ may dampen excitatory transmission and prevent neuronal hyperactivity.[14]

The proteases neprilysin and insulin-degrading enzyme regulate steady-state levels of Aβ. Neprilysin, a membrane-anchored zinc endopeptidase, degrades Aβ monomers and oligomers.[15] A reduction in neprilysin causes accumulation of cerebral Aβ.[16] Insulin-degrading enzyme, a thiol metalloendopeptidase, degrades small peptides such as insulin and monomeric Aβ.[17] In mice, deletion of insulin-degrading enzyme reduces Aβ degradation by more than 50%.[18] Conversely, overexpression of neprilysin or insulin-degrading enzyme prevents plaque formation.[19]

Clinical trials of a γ-secretase inhibitor (LY450139) (ClinicalTrials.gov number, NCT00765115),[20] aggregation blockers, vaccination with Aβ, and monoclonal antibodies against various Aβ epitopes are in progress. The antibodies bind Aβ, thereby triggering complement and Fc-receptor–mediated phagocytosis by microglia, or enhance clearance of Aβ, or both.[21] Vaccination in a phase 2a trial (NCT00021723)[22] resulted in encephalitis,[23] and follow-up of immunized patients showed no cognitive or survival benefit despite diminution of plaques.[24] A phase 2 trial of passive immunization resulted in vasogenic cerebral edema in some patients (NCT00112073). Phase 3 trials of two monoclonal antibodies against Aβ (NCT00574132 and NCT00904683) and of 10% intravenous immune globulin are under way (NCT00818662).

TAU

Neurofibrillary tangles, which are filamentous inclusions in pyramidal neurons, occur in Alzheimer's disease and other neurodegenerative disorders termed tauopathies.[25] The number of neurofibrillary tangles is a pathologic marker of the severity of Alzheimer's disease. The major component of the tangles is an abnormally hyperphosphorylated and aggregated form of tau. Normally an abundant soluble protein in axons, tau promotes assembly and stability of microtubules and vesicle transport. Hyperphosphorylated tau is insoluble, lacks affinity for microtubules, and self-associates into paired helical filament structures (Fig. 2). Enzymes that add and those that remove phosphate residues regulate the extent of tau phosphorylation.[26]

Like Aβ oligomers, intermediate aggregates of abnormal tau molecules are cytotoxic[27] and impair cognition.[28,29] Insoluble helical filaments

may be inert, however, since decreases in axonal transport and neuron number are independent of the burden of neurofibrillary tangles.[30] These helical filaments sequester toxic intermediate tau species, a process that may be protective.[31]

More than 30 mutations of *Tau* on chromosome 17 have been detected in frontotemporal dementia with parkinsonism.[32] By contrast, *Tau* mutations do not occur in Alzheimer's disease, and the extent of neuron loss is out of proportion to the number of neurofibrillary tangles.[33] Nevertheless, increased levels of phosphorylated and total tau in the cerebrospinal fluid correlate with reductions in scores on cognitive examinations.[34] Elevated levels of phosphotau amino acids T181, T231, and total tau in the cerebrospinal fluid together constitute a biomarker test with good accuracy for predicting incipient Alzheimer's disease in patients with mild cognitive impairment.[35] Experimental evidence indicates that Aβ accumulation precedes and drives tau aggregation.[36-38] Moreover, Aβ-induced degeneration of cultured neurons and cognitive deficits in mice with an Alzheimer's disease–like illness require the presence of endogenous tau.[39,40]

Increased oxidative stress, the impaired protein-folding function of the endoplasmic reticulum, and deficient proteasome-mediated and autophagic-mediated clearance of damaged proteins — all of which are also associated with aging — accelerate the accumulation of amyloid and tau proteins in Alzheimer's disease.[41,42] Agents capable of counteracting these changes are not available, but trials of small-molecule inhibitors of β-amyloid (e.g., scylloinositol) (NCT00568776) and tau oxidation and aggregation (e.g., methylene blue) (NCT00568776) are under way.[43] Polyphenolic extracts from grape seeds (e.g., resveratrol), which stimulate aging-suppressor genes, also show promise as therapeutic agents.[44]

THE SYNAPSE IN ALZHEIMER'S DISEASE

SYNAPTIC FAILURE

Alzheimer's disease may be primarily a disorder of synaptic failure.[45] Hippocampal synapses begin to decline in patients with mild cognitive impairment (a limited cognitive deficit often preceding dementia) in whom remaining synaptic profiles show compensatory increases in size.[46] In mild Alzheimer's disease, there is a reduction
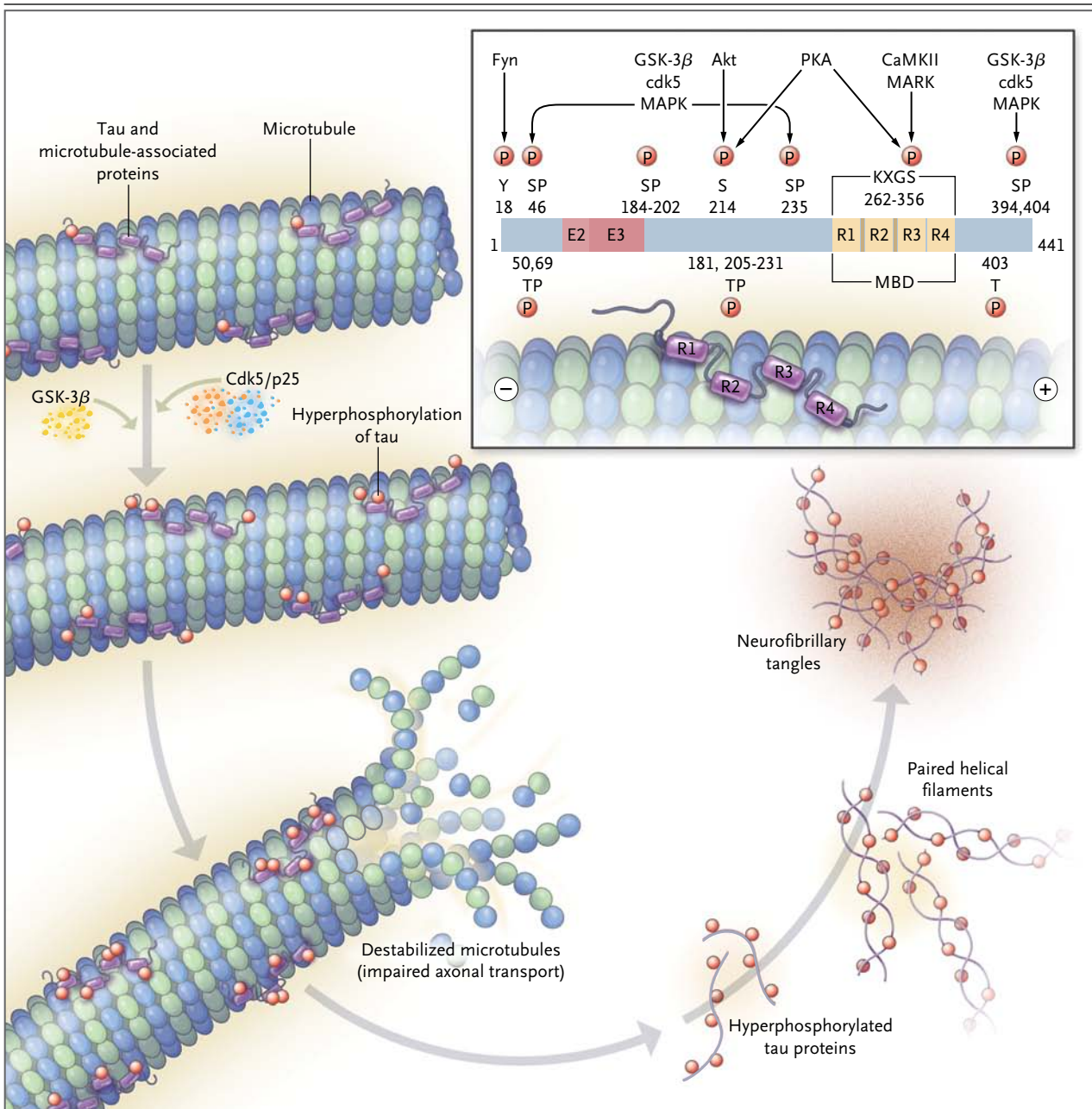
Figure 2. Tau Structure and Function.

Four repeat sequences (R1-R4) make up the microtubule-binding domain (MBD) of tau. Normal phosphorylation of tau occurs on serine (S; inset, above horizontal bar) and threonine (T; inset, below horizontal bar) residues, numbered according to their position in the full tau sequence. When followed by proline (P), these amino acids are phosphorylated by glycogen synthase kinase 3 (GSK-3β), cyclin-dependent kinase (cdk5) and its activator subunit p25, or mitogen-activated protein kinase (MAPK). Nonproline-directed kinases — Akt, Fyn, protein kinase A (PKA), calcium–calmodulin protein kinase 2 (CaMKII), and microtubule affinity-regulating kinase (MARK) — are also shown. KXGS (denoting lysine, an unknown or other amino acid, glycine, and serine) is a target motif. Hyperphosphorylated sites specific to paired helical filament tau in Alzheimer's disease tend to flank the MBD. Tau binding promotes microtubule assembly and stability. Excessive kinase, reduced phosphatase activities, or both cause hyperphosphorylated tau to detach and self-aggregate and microtubules to destabilize.
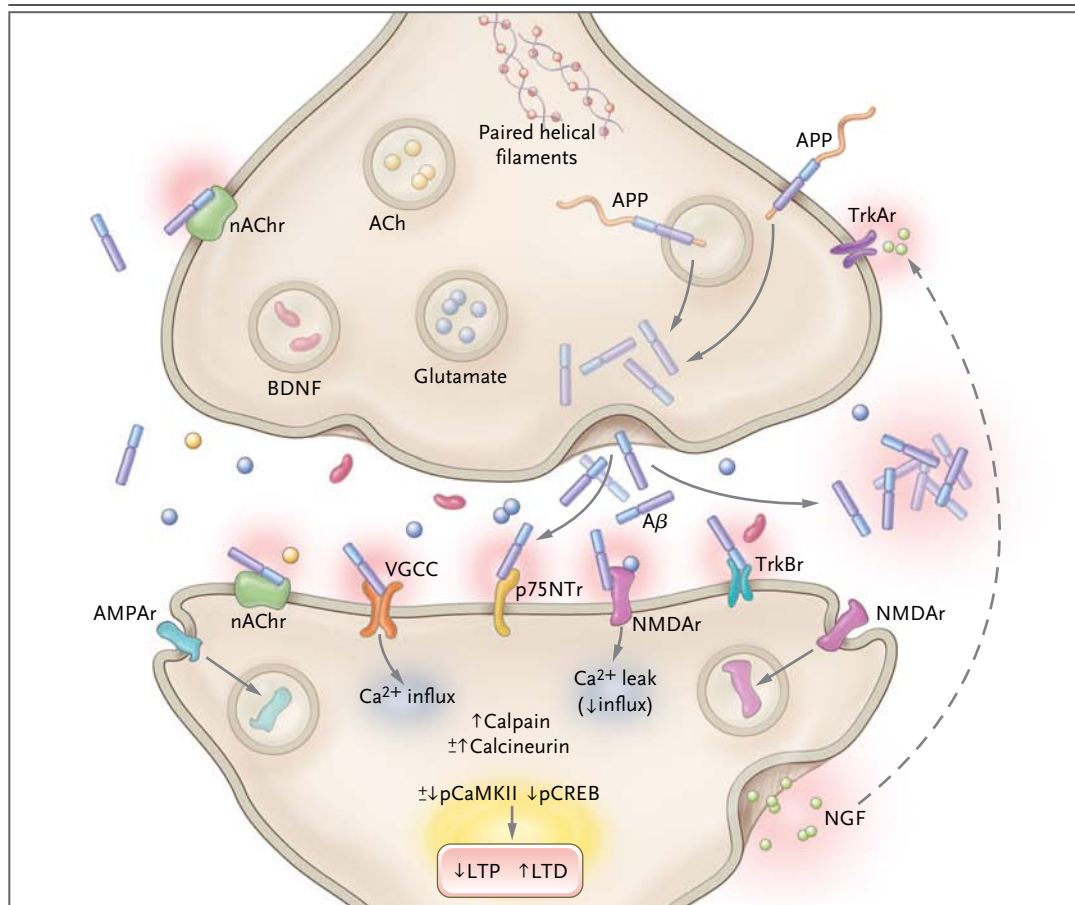
Figure 3. Synaptic Dysfunction in Alzheimer's Disease.

Synaptic loss correlates best with cognitive decline in Alzheimer's disease. A control synapse is shown at the top of the figure. At the bottom of the figure, an "Alzheimer's disease synapse" depicting the pleiotropic effects of the β-amyloid peptide (Aβ) is shown. Rings represent synaptic vesicles. Experimental application and expression of Aβ, especially oligomers, impair synaptic plasticity by altering the balance between long-term potentiation (LTP) and long-term depression (LTD) and reducing the numbers of dendritic spines. At high concentrations, oligomers may suppress basal synaptic transmission. Aβ facilitates endocytosis of receptors of N-methyl-D-aspartate (NMDAr) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAr). Aβ also binds to the receptors of p75 neurotrophin (p75NTr) and brain-derived neurotrophic factor (the BDNF receptor, also known as the tyrosine kinase B receptor [trkBr]), exacerbating a situation in which levels of BDNF and nerve growth factor (NGF) are already suppressed. Aβ impairs nicotinic acetylcholine (ACh) receptor (nAChr) signaling and ACh release from the presynaptic terminal. Numbers of hippocampal synapses decrease in mild cognitive impairment in which remaining synaptic profiles show compensatory increases in size. APP denotes amyloid precursor protein, pCaMKII phosphorylated calcium–calmodulin–dependent protein kinase 2, pCREB phosphorylated cyclic AMP response-element-binding protein, trkAr tyrosine kinase A receptor, and VGCC voltage-gated calcium channel.

of about 25% in the presynaptic vesicle protein synaptophysin.[47] With advancing disease, synapses are disproportionately lost relative to neurons, and this loss is the best correlate with dementia.[48-50] Aging itself causes synaptic loss,[51] which particularly affects the dentate region of the hippocampus.[52]

Basal transmission of single impulses and "long-term potentiation," an experimental indicator of memory formation at synapses, are impaired in plaque-bearing mice with Alzheimer's disease and after Aβ peptide has been applied to brain slices.[11,53] Subsequent to this impairment, signaling molecules important to memory are in-

hibited. Disruptions of the release of presynaptic neurotransmitters and postsynaptic glutamate-receptor ion currents[54,55] occur partially as a result of endocytosis of N-methyl-D-aspartate (NMDA) surface receptors[56] and endocytosis of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid surface receptors[57] (Fig. 3). The latter further weakens synaptic activity by inducing a lasting reduction in currents after a high-frequency stimulus train. A similar shift in the balance between potentiation and depression in synapses occurs with normal aging. Intraneuronal Aβ can trigger these synaptic deficits even earlier.[58]

DEPLETION OF NEUROTROPHIN AND NEUROTRANSMITTERS

Neurotrophins promote proliferation, differentiation, and survival of neurons and glia, and they mediate learning, memory, and behavior. The normally high levels of neurotrophin receptors in cholinergic neurons in the basal forebrain are severely reduced in late-stage Alzheimer's disease (Fig. 3). Injection of nerve growth factor can rescue basal neurons in animal models,[59] and a phase 1 trial of treatment with the *NGF* gene in Alzheimer's disease showed improvement in cognition and brain metabolism.[60] In Alzheimer's disease and mild cognitive impairment, levels of brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, are depressed,[61] a finding reproduced experimentally with $Aβ_{42}$ oligomers.[62] BDNF treatment in rodents and nonhuman primates supports neuronal survival, synaptic function, and memory,[63] suggesting that BDNF replacement is another option for the treatment of Alzheimer's disease.[64]

The deficiency of cholinergic projections in Alzheimer's disease has been linked to the buildup of Aβ and tau. Presynaptic α-7 nicotinic acetylcholine receptors are essential for cognitive processing, and their levels increase in early Alzheimer's disease,[65] before decreasing later.[66] Experimental studies show that Aβ binds to α-7 nicotinic acetylcholine receptors, impairing the release of acetylcholine and maintenance of long-term potentiation.[67] The level of muscarinic acetylcholine receptors, or receptor coupling, is reduced in the brains of patients with Alzheimer's disease. Pharmacologic stimulation of the postsynaptic muscarinic type 1 (M1) acetylcholine receptors activates protein kinase C, favoring processing of amyloid precursor protein that does not yield amyloid.[68] Furthermore, activation of nicotinic acetylcholine receptors or M1 receptors limits tau phosphorylation.[69,70] Although cholinesterase inhibitors improve neurotransmission and provide mild palliative relief in Alzheimer's disease, they lose efficacy over time. The use of agonists and modulators of α-7 nicotinic acetylcholine receptors is under investigation. Clinical trials of selective M1 agonists have shown improvements in cognition[71] and reduced Aβ levels in the cerebrospinal fluid,[72] but these agents are toxic.

MITOCHONDRIAL DYSFUNCTION

Aβ is a potent mitochondrial poison, especially affecting the synaptic pool.[73] In Alzheimer's disease, exposure to Aβ inhibits key mitochondrial enzymes in the brain and in isolated mitochondria.[74,75] Cytochrome *c* oxidase is specifically attacked.[76] Consequently, electron transport, ATP production, oxygen consumption, and mitochondrial membrane potential all become impaired. The increase in mitochondrial superoxide radical formation and conversion into hydrogen peroxide cause oxidative stress, release of cytochrome *c*, and apoptosis (Fig. 4).

The accumulation of Aβ within structurally damaged mitochondria isolated from the brains of patients with Alzheimer's disease[77] and transgenic brains[76] is consistent with other evidence of intraneuronal Aβ in Alzheimer's disease.[78] Alcohol dehydrogenase is one such mitochondrial-binding target of Aβ.[79] Similar changes occur in normal cells that have been repopulated with mitochondrial DNA (mtDNA) from patients with sporadic Alzheimer's disease.[80] Both in Alzheimer's disease and in the normal aging process, mtDNA sustains high levels of oxidative damage.[77] This instability and the irreparability of the brain's mitochondrial genome allow the gradual accumulation of mtDNA mutations.[81] Fragmentation (or fission) of mitochondria from the oxidation of a dynamin-like transporter protein may cause synapse loss in Alzheimer's disease.[82] The antihistamine dimebolin hydrochloride, a putative mitochondrial stimulant, has been reported to improve cognition and behavior in patients with mild-to-moderate Alzheimer's disease.[83]

OXIDATIVE STRESS

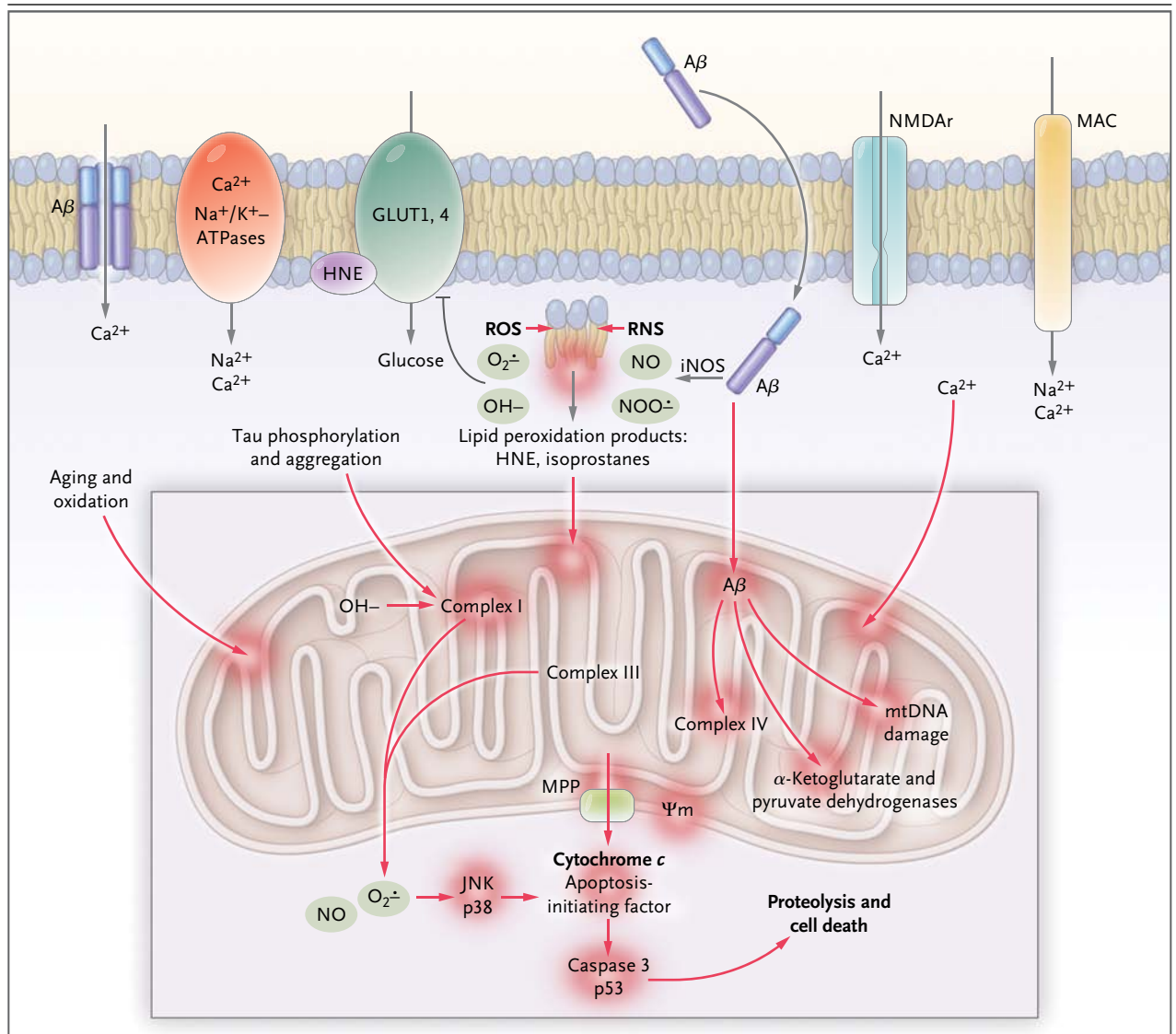Dysfunctional mitochondria release oxidizing free radicals, and in Alzheimer's disease and the nor-

Figure 4. Oxidative Stress and Mitochondrial Failure.

A β-amyloid peptide (Aβ)–centric scheme depicts production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Their peroxidative attack on cell and organelle membrane lipids yields the mitochondrial toxins hydroxynonenal (HNE) and malondialdehyde. Oxidative damage to membrane-bound, ion-specific ATPases and stimulation of calcium (Ca²⁺) entry mechanisms — for example, glutamate (N-methyl-D-aspartate [NMDA]) receptors (NMDAr), membrane-attack complex (MAC) of complement, and ion-selective amyloid pore formation — cause cytosolic and mitochondrial Ca²⁺ overload. Cellular Aβ directly attacks electron transport complex IV (cytochrome c oxidase) and key Krebs-cycle enzymes (α-ketoglutarate and pyruvate dehydrogenase) and damages mitochondrial DNA (mtDNA), leading to fragmentation. Lipid peroxidation products also promote tau phosphorylation and aggregation, which in turn inhibit complex I. Exaggerated amounts of ROS and RNS are generated at complexes I and III. As the mitochondrial membrane potential (MPP) collapses and permeability-transition pores (ψm) open, caspases are activated. Aβ also induces the stress-activated protein kinases p38 and c-jun N-terminal kinase (JNK), as well as p53, which are further linked with apoptosis. Substrate deficiencies, notably NADH and glucose, combine with electron transport uncoupling to further diminish ATP production. Alcohol dehydrogenase was recently identified as the mitochondrial-binding target for Aβ. Endoplasmic reticulum contributions are shown. GLUT1, 4 denotes glucose transporter 1, 4.

mal aging brain, they cause considerable oxidative stress.[84,85] Experimental models show that markers of oxidative damage precede pathological changes.[86] Aβ, a potent generator of reactive oxygen species[87] and reactive nitrogen species,[88] is a prime initiator of this damage. The receptor for advanced glycation end products mediates Aβ's pro-oxidant effects on neural, microglial, and cerebrovascular cells.[89] Mitochondrial hydrogen peroxide readily diffuses into the cytosol to

participate in metal ion–catalyzed hydroxyl radical formation. Stimulated microglia are a major source of the highly diffusible nitric oxide radical. These reactive oxygen species and reactive nitrogen species damage several molecular targets. Peroxidation of membrane lipids yields toxic aldehydes,[90] which impair critical mitochondrial enzymes.[77,91] Other essential proteins are directly oxidized, yielding carbonyl and nitrated derivatives.[92] Subsequently, increases in membrane permeability to calcium, other ionic imbalances, and impaired glucose transport[93] aggravate the energy imbalance.

Elevated levels of free divalent transition metal ions (iron, copper, and zinc) and aluminum are linked with reactive oxygen species–mediated damage and neurodegeneration in several ways.[94-100] These metal ions also promote aggregation of tau and changes in its conformation or phosphorylation.[95] Zinc, typically thought to be a toxin in Alzheimer's disease, might at lower concentrations actually protect cells by blocking Aβ channels[96] or compete with copper for Aβ binding.[97]

Although animal models and most cross-sectional studies in aging populations show an association between antioxidant intake and cognitive performance, randomized trials of antioxidants have generally failed.[98] Therapeutic chelation of divalent metals is potentially harmful because essential enzymes rely on coordination with them. In a pilot phase 2 trial (NCT00471211), PBT2, a safe compound derived from clioquinol that attenuates metal proteins,[99] showed some efficacy.

INSULIN-SIGNALING PATHWAY

Another metabolic disturbance of emerging importance in Alzheimer's disease and tied into synaptic and energy homeostasis involves insulin signaling in the brain. Subgroups of patients with advanced Alzheimer's disease have high fasting insulin levels and low rates of glucose disposal (peripheral resistance).[100] Glucose intolerance and type 2 diabetes are considered to be risk factors for dementia.[101] Levels of insulin receptors, glucose-transport proteins, and other insulin-pathway components in the brain are reduced in some studies of Alzheimer's disease[102] (central resistance). Insulin (mostly bloodborne) and brain-derived insulin-like growth factor I initiate signals in the brain by activating the phosphatidylinositol-3-kinase–Akt (also known as protein kinase B) pathway and the mitogen-activated protein kinase–extracellular signal-regulated kinase pathway,[103] but it is unclear whether signaling is up-regulated (compensatory) or down-regulated (pathologic) in Alzheimer's disease. Aging and life span are also influenced by insulin.[104] Resistance to insulin signaling renders neurons energy-deficient and vulnerable to oxidizing or other metabolic insults and impairs synaptic plasticity. Moreover, the higher serum glucose levels that are common in normal aging directly damage hippocampal structures,[105] up-regulate the tau kinase, glycogen synthase kinase 3β,[106] and reduce levels of insulin-degrading enzyme in the brain in Alzheimer's disease.[107] Treatment with thiazolidine drugs (peroxisome-proliferator-activated receptor [PPAR] agonists), which activate insulin-responsive gene transcription) prevented Alzheimer's disease–associated changes and cognitive decline in transgenic mice[103,108] and had significant effects in subpopulations of patients with Alzheimer's disease.[109]

VASCULAR EFFECTS

In Alzheimer's disease, vascular injury and parenchymal inflammation perpetuate the cycle of protein aggregation and oxidation in the brain; damage from strokes and white-matter lesions contribute greatly to cognitive decline. Ischemic disease affects 60 to 90% of patients with Alzheimer's disease, with major infarctions representing one third of vascular lesions in autopsy cases. Conversely, one third of putative cases of vascular dementia have coincidental pathological features of Alzheimer's disease. Although clinically and radiographically "pure" cases of vascular dementia are recognized,[110,111] most cases of dementia are in fact mixed. Pervasive pathological changes include cerebral amyloid angiopathy,[112] affecting more than 90% of patients with Alzheimer's disease, capillary abnormalities, disruption of the blood–brain barrier, and large-vessel atheroma.[113] None of these changes alone explain the symmetric reductions of cerebral blood flow in patients with Alzheimer's disease, which are more likely to reflect regional energy underutilization.[114,115]

Another hypothesis holds that clearance of Aβ along diseased perivascular channels and through the blood–brain barrier is impeded in Alzheimer's disease. The source of vascular Aβ (mostly 40 amino acid form) is heterogeneous, comprising neurons, degenerating myocytes, and the circulation. Amyloid deposition in the arteriolar

wall enhances vasoconstriction in ex vivo studies.[116] Aβ is also cytotoxic to endothelial[117] and smooth-muscle[118] cells, conferring a predisposition to lobar hemorrhage in advanced age. The "neurovascular uncoupling" hypothesis proposes that deregulation of Aβ transport across the capillary blood–brain barrier is caused by the imbalanced expression of low-density lipoprotein receptor–related proteins and receptors for advanced glycation end products, which mediate Aβ efflux and influx, respectively[119] (Fig. 5).

Short of prophylaxis against stroke, there are few specific therapies for the vascular changes in Alzheimer's disease. Centrally acting angiotensin-converting–enzyme inhibitors were associated with reductions in yearly cognitive decline in one observational study.[120] Patients with hypertension who are receiving medication have fewer neuropathologic features of Alzheimer's disease.[121] Folic acid reduces homocysteine levels and may lower the risk of Alzheimer's disease, but it does not improve cognition in established Alzheimer's disease.[122,123] A phase 2 study of inhibitors of receptors for advanced glycation end products in mild-to-moderate Alzheimer's disease (NCT00566397) is under way. Concern has been expressed about the safety of Aβ immunotherapy because of the possibilities of increased vascular amyloid, microhemorrhages, and vasogenic edema as the efflux of Aβ into vascular compartments is stimulated.[124]

INFLAMMATION

Activated microglia and reactive astrocytes localize to fibrillar plaques, and their biochemical markers are elevated in the brains of patients with Alzheimer's disease.[125] Initially, the phagocytic microglia engulf and degrade Aβ. However, chronically activated microglia release chemokines and a cascade of damaging cytokines — notably, interleukin-1, interleukin-6, and tumor necrosis factor α (TNF-α)[126] (Fig. 5). In common with vascular cells, microglia express receptors for advanced glycation end products, which bind Aβ, thereby amplifying the generation of cytokines, glutamate, and nitric oxide.[89,127] In experimental studies, chemokines promote the migration of monocytes from the peripheral blood into plaque-bearing brain.[128]

Fibrillar Aβ and glial activation also stimulate the classic complement pathway.[129] Tangles and plaques contain complement cleavage products, C1q and C5b-9, indicating that opsonization and

autolytic attack are under way.[126] Stimulated astroglia also release acute-phase reactants, alpha$_1$-antichymotrypsin, alpha$_2$-macroglobulin, and C-reactive protein, which can both aggravate and ameliorate Alzheimer's disease. Although inflammatory (and oxidative) events are implicated in a breakdown of the vascular blood–brain barrier in Alzheimer's disease, it is not certain that this leads to monocyte or amyloid influx from the circulation in humans.[130,131]

The contradictory roles of microglia — eliminating Aβ and releasing proinflammatory molecules — complicate treatment.[132] Nonsteroidal antiinflammatory agents have been reported to lower the risk of Alzheimer's disease and slow progression of the disease, but only in prospective observational studies.[133,134] Their mechanisms of action include selective reduction of Aβ_{42},[135,136] inhibition of cyclooxygenase-2 or the prostaglandin E$_2$ receptor, stimulation of phagocytosis by microglia, and activation of PPAR-γ. Recent randomized trials of nonsteroidal antiinflammatory agents[137] and a trial of a derivative, tarenflurbil (Flurizan) (NCT00105547), did not show evidence of reducing the risk of Alzheimer's disease or slowing cognitive decline. In addition to the Aβ-immunization efforts, various TNF-α and complement factor blockers and agents that promote phagocytosis are being investigated.[138]

CALCIUM

Loss of calcium regulation is common to several neurodegenerative disorders. In Alzheimer's disease, elevated concentrations of cytosolic calcium stimulate Aβ aggregation and amyloidogenesis.[139,140] The presenilins modulate calcium balance. Presenilin mutations cause about one half of the few cases of Alzheimer's disease (<1%) that are of the early-onset, familial type. These mutations might disrupt calcium homeostasis in endoplasmic reticulum.[141,142] However, the main effect of the mutations is to increase Aβ_{42} levels, which in turn increases calcium stores in the endoplasmic reticulum and the release of calcium into the cytoplasm.[143] The relevance of these mechanisms to sporadic Alzheimer's disease is unclear.

A chronic state of excitatory amino acid (glutaminergic) receptor activation is thought to aggravate neuronal damage in late-stage Alzheimer's disease.[144] Glutamate increases cytosolic calcium, which in turn stimulates calcium-release channels in the endoplasmic reticulum. How-
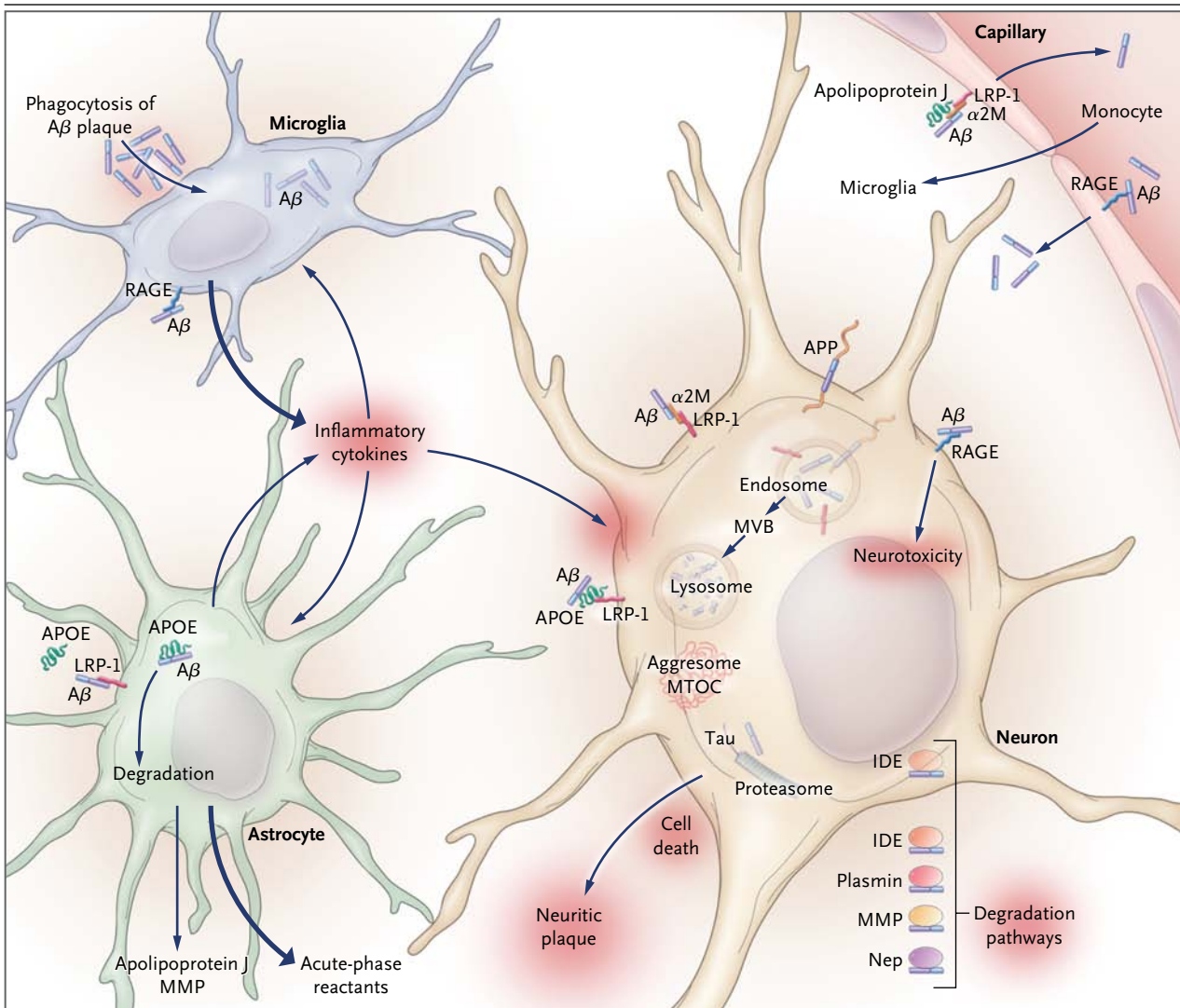
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Figure 5. Inflammation and Mechanisms of Aβ Clearance.

β-amyloid peptide (Aβ) is formed within intracellular compartments (the endoplasmic reticulum, Golgi apparatus, and endosomes) or it can enter multiple cell types through the low-density lipoprotein receptor–related protein. The ubiquitous apolipoprotein E (APOE) and α2-macroglobulins (α2M) are chaperones in this process and in the genesis of extracellular plaques. Microglia directly engulf Aβ through phagocytosis. Astrocytes also participate in Aβ clearance through receptor-mediated internalization and facilitation of its transfer out of the central nervous system and into the circulation. Microglia and astrocytes are recruited and stimulated in Alzheimer's disease to release proinflammatory cytokines and acute-phase reactants. Receptors for advanced glycation end products (RAGE) molecules transduce extracellular Aβ toxic and inflammatory effects and mediate influx of vascular Aβ. The inflammatory milieu provokes neuritic changes and breakdown of the vascular blood–brain barrier. In addition to cell-mediated reactions, Aβ clearance occurs through enzymatic proteolysis, mainly through neprilysin (Nep) and insulin-degrading enzyme (IDE). Aβ oligomers block proteasome function, facilitating the buildup of intracellular tau and accumulation of Aβ into "aggresomes." APP denotes amyloid precursor protein, MMP matrix metalloproteinase, MOTC microtubule-organizing center, and MVB multivesicular body.

ever, the evidence of excessive excitatory amino acid mechanisms in Alzheimer's disease is modest. Aβ forms voltage-independent, cation channels in lipid membranes,[145] resulting in calcium uptake and degeneration of neuritis.[146] Indirectly, glutamate activates voltage-gated calcium channels. The L-type voltage-gated calcium-channel blocker, MEM 1003, is in a phase 3 trial, and memantine, an NMDA-receptor blocker, is approved by the Food and Drug Administration.

AXONAL-TRANSPORT DEFICITS

Another internal derangement that is probably an effect rather than a cause of Alzheimer's dis-

ease is a reduction in the transport of critical protein cargoes to the synapse. Molecular motors of the kinesin family drive vesicles and mitochondria destined for the synaptic terminal along axonal microtubules. The kinesin superfamily heavy-chain protein 5 and its associated kinesin light chain 1 facilitate "fast" anterograde transport. Tau forms the cross-bridges that maintain the critical spacing between microtubules.

The riddle of Alzheimer's disease is entwined with the elusive goal of finding the biologic function of amyloid precursor protein. It was exciting when amyloid precursor protein, BACE-1, and presenilin 1 were reported to undergo fast anterograde transport[147] into terminal fields where Aβ and other proteolytic derivatives are released.[148] Impairment of transport causes amyloid precursor protein, vesicle, and kinesin accumulations in axonal swelling, local Aβ deposition, and neurodegeneration.[149,150] However, whether amyloid precursor protein functions as the critical cargo vesicle receptor for the motor protein complex remains unclear.[151] Furthermore, an essential role is not evident from studies of amyloid precursor protein–deficient mice, which are viable, with only subtle synaptic and learning defects.[152,153]

The anatomical distribution of pathological features in Alzheimer's disease nonetheless suggests that microtubules are dysfunctional, since tau is primarily deranged in the source of cortical projections.[154] In addition, defects in the white-matter tract are observed in patients at all stages of Alzheimer's disease[155] and in animal models.[156] Pharmacologic disruption of microtubules and inhibition of tau phosphatases cause similar axonal swelling and synaptic failure.[157] Since paclitaxel reverses these defects in mouse models,[158] inhibitors of tau polymerization, phospho tau peptide vaccines,[159] and other microtubule stabilizers[160] are being investigated.

ABERRANT CELL-CYCLE REENTRY

In league with secondary deregulations of calcium and transport, a failure in the normal suppression of the cell cycle in Alzheimer's disease has been hypothesized.[161] Markers of aberrant cell-cycle reentry are detected in all stages of Alzheimer's disease and in mild cognitive impairment,[162] but they are most prominent at the G_1–S-phase boundary.[163] This may progress to completion of DNA replication, resulting in tetraploid neurons and activation of mitotic cyclins, but mitoses are absent.[164] Cyclin-dependent ki-

nase–inhibitor proteins, which maintain cell-cycle exit, are also deranged in Alzheimer's disease.[165] Oxidative stress and DNA-damaging agents, including Aβ and the carboxyl-terminal 99 amino acid BACE-1 product C99, all initiate DNA replication and death in cultured neurons.[166] The event inciting cell-cycle reentry in Alzheimer's disease is unknown. Furthermore, whether it is pathogenic or just reflects a survival response to repair damaged DNA[167] is unclear.

CHOLESTEROL METABOLISM

A defect in cholesterol metabolism is an appealing hypothesis because it ties together the apolipoprotein E (*APOE*) genetic risk, amyloid production and aggregation, and vasculopathy of Alzheimer's disease. However, proof is also lacking for this hypothesis. Cholesterol is an essential component of neuronal membranes and is concentrated in sphingolipid islands termed "lipid rafts." Rafts are ordered platforms for the assembly of β-secretases and γ-secretases and processing of amyloid precursor protein into Aβ[168] (Fig. 1 and 2). Aβ generation and aggregation are promoted and clearance from the brain is reduced when an overabundance of esterified cholesterol decreases membrane lipid turnover. Glial-derived APOE is the primary cholesterol transporter in the brain. A major determinant of the risk of late-onset Alzheimer's disease is the APOE isoform inheritance pattern (APOE2, APOE3, or APOE4)[169]; a single E4 allele increases the risk by a factor of 4, and two E4 alleles increase the risk by a factor of 19.[170] APOE4 is not only a pathological chaperone, promoting Aβ deposition[171] and tau phosphorylation,[172] but it is also the least effective of the three in promoting healthy membrane lipid turnover and the uptake of lipoprotein particles.

High serum cholesterol levels in midlife increase the risk of Alzheimer's disease.[173] In observational studies, use of statins was shown to be associated with a reduced risk. Statins appear to reduce the membrane pool of free cholesterol.[174] Other actions of statins that are not dependent on cholesterol include reductions in inflammation[175] and isoprenoids and up-regulation of both α-secretase[176] and vascular function. One prospective trial of statins showed cognitive improvements in patients with mild Alzheimer's disease,[177] but a recent multicenter trial did not.[178] Thus, the benefit of statins remains controversial. An alternative pharmacologic approach is to

limit the esterification of cholesterol.[179] Improvement of membrane biophysics and function through ingestion of n–3 fatty acid supplements has also been studied (NCT00440050).[180]

CONCLUSIONS

An effective treatment for sporadic Alzheimer's disease rests on the translation of the disease pathways we have discussed, as well as additional molecular mechanisms or new risk genes (e.g., apolipoprotein J) defined by gene-expression profiling and whole-genome association studies,[181,182] into specific pharmacologic targets. Examples of recently discovered proteins encoded by these risk genes and mechanisms include apolipoprotein J (clusterin), another Aβ chaperone,[183] TOMM40, a transporter of proteins across the mitochondrial membrane, and Sortillin-related receptor, which functions to partition amyloid precursor protein away from β-secretase and γ-secretase; this is consistent with observations that levels are reduced in the brains of patients with Alzheimer's disease and mild cognitive impairment.[184,185] Another potential risk factor for sporadic Alzheimer's disease, general anesthesia, promotes tau insolubility and Aβ oligomerization,[186,187] deficiency of estrogen in the brains of postmenopausal women,[188] and chronic activation of the glucocorticoid axis.[189] However, their underlying mechanisms are diverse, and whether any of these factors lead to amyloid deposition and tauopathy in humans is unknown. Prospective studies also show that cognitive leisure activity and training can lower the risk of dementia[190]; findings from these studies provide support for the concept of building a "cognitive reserve." The figure in the Supplementary Appendix (available with the full text of this article at NEJM.org) summarizes the heterogeneity of pathways that could initiate and drive Alzheimer's disease. There is no single linear chain of events. Complicating matters, some changes are not pathologic but reactionary or protective. Thus, the development of a multitargeted approach to prevent or symptomatically treat Alzheimer's disease, as used in current practice for other multigenic disorders, is needed.[191] Recent studies point to brain atrophy and other pathologic conditions, not severe amyloid or tangle load, in accounting for dementia in the oldest old (persons 80 years of age or older).[192] It remains possible that many of these mechanisms, including the amyloid hypothesis, are minor or wrong and that some critical aging-related process is the disease trigger.

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