CELL AND MOLECULAR NEUROPATHOLOGY OF ALZHEIMER DISEASE

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Although forms of dementia arising late in life had been identified by Kraepelin and his colleagues in the 1800s, it was not until 1907 that Alois Alzheimer identified the presenile form of dementia with unique neuropathologic features that now bears his name. Alzheimer described a 51year-old woman who presented with personality changes and soon developed progressively worsening memory loss, disorientation to time, and language disturbances but who had relatively normal neurologic function. Mental deterioration progressed, and she died $4\frac{1}{2}$ years later. On autopsy, her brain showed clear evidence of cerebral atrophy. Under the microscope, Alzheimer discovered that many cortical neurons contained argyrophilic fibrous structures—neurofibrillary tangles (NFTs)-now known to be mainly composed of abnormal filamentous forms of the microtubuleassociated protein, tau. Coexisting in the same affected brain regions were extracellular plaquelike lesions. These neuritic or "senile" plaques were later discovered to contain β-amyloid, a fibrillar form of the AB peptide, as their signature constituent. In 1910, Kraepelin proposed that this neuropathologic picture was pathognomic of a new presenile dementing disease and introduced the eponym Alzheimer disease (AD).

Nearly a century later, genetic analyses have shown AD to be the common neuropathologic outcome of different primary etiologic factors (1). Roughly one-third of patients with AD have a familial predisposition, with at least one other affected first-degree relative. In families with early-onset AD arising before the age of 65 years, a type accounting for 2% to 10% of all AD cases, the transmission pattern is consistent with an autosomal dominant disorder with age-dependent penetrance. To date, early-onset familial AD (FAD) has been linked to mutations of three different genes: the amyloid precursor protein (APP) gene and the presenilin 1 (PS1) and presenilin 2 (PS2) genes. Together, these muta-

tions account for nearly half of the families with autosomal dominant early-onset AD (2). In FAD, a single gene defect, interacting with the brain aging process, causes the disease (reviewed in Chapter 83). However, in the other 90% of cases, designated sporadic AD, the emergence of disease is influenced by environmental factors as well as by multiple genes with either neuroprotective or disease-facilitating effects. Although all forms of AD, by definition, share common neuropathologic features, the metabolic antecedents of this pathology in sporadic forms of the disease are poorly understood. Much is known about the genetic forms of AD, yet issues as fundamental as the anatomic and cellular substrate of cognitive decline, the toxic cascades mediating cell degeneration, and the roles of AB, B-amyloid, and tau in the neurodegenerative process are just now being resolved. In this chapter, a discussion of Alzheimer neuropathology provides the starting point for understanding how the diagnosis of AD is made and how clinical symptoms arise and progress. Later sections address the neuroanatomic and cellular basis for dementia and the molecular events that lead to neuropathologic lesions and, ultimately, to the death of neurons. A consideration of current hypotheses on the evolution of cellular pathology identifies common features that help to reconcile the differing views of disease pathogenesis. New studies are beginning to shed light on underlying mechanisms in prevalent sporadic forms of AD, and their review complements a brief discussion of pathogenesis in the rare familial forms here and a more detailed consideration in Chapter 83.

DIAGNOSTIC FEATURES OF ALZHEIMER DISEASE

AD remains a diagnosis based on its histopathologic features. By the time AD can be clinically diagnosed by DSM-IV criteria, neuropathologic features are already quite extensive in some regions of the brain (3,4). Patients with Down

syndrome, for example, develop probable AD by neuropathologic criteria years before clinical dementia can be detected (5). According to the most widely accepted neuropathologic criteria (those of the Consortium to Establish a Registry for Alzheimer's Disease or CERAD), a diagnosis of definite AD can be made in a demented patient when neuritic plaques reach a requisite number, adjusted for age, in the most severely affected regions of the neocortex (6) (e.g., superior and middle temporal gyrus, middle frontal gyrus, inferior parietal lobule, hippocampal/entorhinal cortex, and midbrain) in the absence of other neuropathologic lesions likely to cause dementia. More stringent research criteria require semiquantitative estimates of both neuritic plaques and NFTs (7–9). In the most recent guidelines developed by the National Institute of Health and the Reagan Institute (9), topographic staging of NFT accumulation (7) is incorporated into the criteria and significantly increases diagnostic precision (10).

Neuritic plaques are complex spheric lesions of varying sizes, usually many times larger than a single neuron. These typically contain an extracellular core of β-amyloid surrounded by dystrophic dendrites and axons, loosely organized fibrils of β-amyloid, and many other proteins and protein fragments derived from degenerating cells or liberated from neurons, reactive astrocytes, and phagocytic cells (11). β-Amyloid is a fibrillar form of the β-amyloid peptide (Aβ), a 40- to 43-amino acid peptide derived from the normal processing of a larger ubiquitous membrane glycoprotein, the β -APP (12). As it forms fibrils, $A\beta$ assumes a β -sheet conformation recognizable by probes such as thioflavin S. This conformation distinguishes β -amyloid from the diffuse nonfibrillar deposits of A β that appear several or more years before the neuritic plaques. Diffuse plaques may be widespread throughout the brains of elderly persons with no measurable cognitive impairment. By contrast, neuritic plaques are primarily confined to the neocortex, hippocampus, and amygdala (13).

Although the relationship of diffuse plaques with the development of neuritic plaques is not yet established, studies in transgenic mouse models of cerebral β-amyloidosis have suggested that neuritic plaques originate from diffuse Aβ plaques through a "maturation" process. One possibility to explain this process is based on findings that AB peptide aggregates bind and activate the complement protein C1 and, hence, the classic complement pathway. This, in turn, sets off a local non-immune-mediated, chronic inflammatory response involving microglial activation and stimulation of the acute-phase response (14). This proposed cascade explains the presence within neuritic plaques of additional cell types (microglia, reactive astrocytes) and many proteins, including glial-derived acute-phase proteins, such as α -antichymotrypsin, apolipoprotein E (Apo E), and serum amyloid P, which may, in some cases, accelerate fibrilization of AB. Activated microglia release potentially toxic products, including proinflammatory cytokines (e.g., interleukin-1

and interleukin-6), reactive oxygen species, and proteases, all of which contribute to the local development of dystrophic neurites (15,16). According to a second possibility, not incompatible with the first, primary damage to neurites initiates local A β overproduction, neurite degeneration-regeneration responses, and secondary inflammatory reactions involved in removing cellular debris (17,18). Indeed, ultrastructural studies show that dystrophic neurites contain increased levels of both APP and organellar machinery needed for A β generation. Moreover, neurons injured by various toxic factors produce more A β (19–21).

The NFTs first seen by Alzheimer are skeins of twisted abnormal filaments, whose presence in neurons reflects a global disorganization of the neuronal cytoskeleton (22). The abnormal filaments, which assume a paired helical structure, hence the name paired helical filaments (PHFs), are composed of tau protein. Although its full repertoire of functions is still unclear, tau is known to bind to microtubules and to stabilize their polymeric structure, thereby facilitating the microtubule's function in axonal transport and structural support (23). Over a half-dozen protein kinases regulate the function of tau, including its affinity for microtubules. The observation that the tau in PHFs is hyperphosphorylated has suggested that altered phosphorylation is important for the development of these lesions (24). Other modifications of tau, such as proteolysis and glycation, are also considered to be important for PHF formation and for the resistance of PHF to degradation and removal (25). The importance of tau-related pathology to AD pathogenesis is strongly suggested by the identification of tau mutations in 20% of patients with frontotemporal dementia and in nearly half the patients with frontotemporal dementia who have an affected first-degree relative. In addition, other dementing disorders previously linked to chromosome 17 and characterized by NFT formation in specific neuronal populations are now being found to involve tau mutations or polymorphisms, including progressive supranuclear palsy, corticobasal degeneration, and Pick disease

PHF coexists in tangles together with fragments of various cytoskeletal proteins. Notably, abnormally phosphory-lated neurofilaments may accumulate as the earliest cytoskeletal alteration associated with dystrophic neurite formation (26). Neurites (axons and dendrites) containing abnormal organized cytoskeletal elements are referred to as neuropil threads and are a feature of the dystrophic neurites abundant within neuritic plaques. The appearance of neuropil threads before NFTs develop reflects the slow centrifugal progression of cellular compromise from the synaptic endings toward the neuronal perikaryon over several or more years and indicates that synapse function becomes impaired well before the neuron dies.

Although they are not part of current diagnostic criteria for AD, other characteristic pathologic responses of neurons begin before the first traces of β -amyloid are deposited. One of these responses involves endocytosis, the process by which

the cell internalizes materials that are extracellular or on the cell's surface. Endocytosis allows continuous sampling of the external environment, a process that is important for the uptake of nutrients and for cellular responses to toxic foreign agents. Constant remodeling of plasma membrane receptor topography by endocytosis also allows cells to control how they respond to external signaling molecules. Very early in AD, neuronal early endosomes, which are a major site of AB peptide formation, display prominent morphologic and biochemical alterations reflecting increased activity of the endocytic pathway and appear to be highly specific for AD (27). Individual early endosomes in pyramidal neurons of the Alzheimer brain may enlarge as much as 32fold compared with the normal average endosomal volume (28). These changes coincide with the initial rise in brain production of Aβ peptide, which precedes β-amyloid deposition, and they are detectable even before birth in patients with Down syndrome, a population that invariably develops in AD after the age of 40 years.

Cell stress or injury to neurons also manifests early as robust activation of the lysosomal system, a major cellular degradative pathway. This activation, which involves the proliferation of lysosomes and increased expression of a dozen or more lysosomal hydrolases (29,30), progressively intensifies as neurons become more compromised. Because lysosomal activity controls cell size, up-regulation of this system in AD is likely to be the molecular basis for neuronal shrinkage (31), and it is also believed to contribute to neuritic dystrophy (32,33) and neuronal cell death (34). At end stages of neuronal injury, gradual dysfunction of the lysosomal system is implied by the prominent accumulation within lysosomes of undigested, oxidized proteins and lipids in the form of autofluorescent lipofuscin and ceroid. Although lysosomal system activation is not entirely disease specific, its magnitude in AD is much greater than in other diseases and may reflect a specialized neurodegenerative response characteristic of AD and a subset of related disorders (34).

CELLULAR SUBSTRATES OF DEMENTIA

That AD-related lesions may already be well developed in persons who have apparently normal cognitive function has fueled the debate about the actual neuropathologic substrate of clinical dementia. Attention is increasingly being paid to the roles of less overt pathologic features, such as rising intracellular A β levels, synapse loss, or subtle forms of tau pathology in dendrites or axons. For example, although β -amyloid or "plaque burden" often correlates poorly with cognitive impairment (35), levels of soluble A β peptide may correlate better (36,36a), a concept supporting the possibility that accelerated formation of A β peptide inside the neuron interferes with neuronal function or reflects dysfunction that is present before β -amyloid fibrils form extracellularly

(27). Synapse loss is not revealed by routine neuropathologic analysis but may reach 50% of synapses in affected neocortical areas by late stages of the disease (37,38). A high correlation with cognitive decline has suggested that the loss of synapses may be the cellular basis of dementia, although this hypothesis needs further confirmation. Neurofibrillary change in neurons (NFTs and neuropil threads) is closely associated with synaptic disease, and because it is more easily traced histologically, it is the index most frequently used to correlate structural disease progression to cognitive symptoms.

The progressive appearance of NFTs follows a consistent cytoarchitectonic pattern that parallels the severity of clinical dementia and neuronal cell loss more closely than does the evolution of senile plaques (39–41). The transentorhinal region, particularly layers II and IV of the entorhinal cortex, usually shows the first lesions in AD. By the time the mildest stage of cognitive impairment is detectable, the entorhinal cortex may have one-third fewer neurons than normal. Extrapolations from the rate of subsequent fallout of this cell population suggest that neuronal loss may be initiated up to 7 to 10 years before detectable cognitive symptoms.

The highly predictable development of neurofibrillary degeneration in the entorhinal cortex and its progressive extension into the hippocampus, neocortex, and later into various subcortical structures were the basis for a pathologic staging system developed by Braak and Braak (7,39), which uses cross-sectional data on NFT distribution to distinguish six stages of disease evolution. Inclusion of this grading system into current CERAD criteria for neuropathologic diagnosis of AD significantly increases diagnostic specificity and reduces false-negative diagnoses (10). According to this scheme, disease begins in stage 1 with the involvement of only a few transentorhinal projection cells, and it progresses in stage 2 to involve many entorhinal neurons, particularly those in layer II. In stages 3 and 4, neurofibrillary degeneration remains restricted to limbic regions, but it now begins to invade the hippocampal formation. The two principal targets of the CA1/subicular projection are the accessory nucleus of the amygdala and layer IV of the entorhinal cortex, which provide the principal output from the hippocampus to cortical and subcortical regions. The progression of changes to these targets, which gradually isolates the hippocampus from other brain structures, is associated with impaired cognitive functioning and subtle changes in personality in some persons. By stage 5, cognitive deficits have become broader, and the clinical diagnosis of Alzheimertype dementia can usually be made (10). At this point, NFTs have increasingly appeared in projection neurons within layers II, III, and V of higher-order association cortices (42,43), beginning with the temporal lobe, which is more severely affected than parietal and frontal association cortices. Large cortical projection neurons in layers III and V display the most prominent cytoskeletal alterations, and these cells may be lost to a greater extent than smaller neurons. This pattern of cell loss reflects the special vulnerability of feed-forward and feedback circuitry linking the hemispheres with each other and with the cortex of the limbic lobe and subcortical structures. The basis for the selective vulnerability is poorly understood, but it has been conjectured that it is related, in part, to unique features of the cytoskeleton in these neurons and particularly to the abundance of neurofilament proteins and their relatively low phosphorylation state (44).

Although the cerebral cortex is the primary target in AD, degeneration of subcortical structures may also contribute to memory impairment and their behavioral disturbances (45,46). The nucleus basalis of Meynert provides the major cholinergic input to the cortex and is important for memory, but the variability and timing of cholinergic changes suggest that they may not be the key factors in early cognitive impairment (35). The amygdala receives prominent projections from cortical areas and subcortical areas; degeneration therein is particularly relevant to disease-related impairments in motivated and emotional behavior. Extensive cell loss in the noradrenergic locus ceruleus, which richly innervates the cortex, has been associated with depressive symptoms. Changes in the serotonergic raphe nuclei and involvement of hypothalamic nuclei, including the suprachiasmatic nucleus, may explain commonly observed impairments of sleep and circadian rhythm in AD. Although dopaminergic neurons of the ventral tegmentum are severely depleted, cell loss is only moderate in the substantia nigra, as reflected by the absence of Lewy body pathology and associated extrapyramidal symptoms. The well-documented reductions in levels of various neurotransmitters and their receptors (47) are almost certainly a secondary consequence of the loss or functional deafferentation of these subcortical projection neurons.

INITIATION OF CELLULAR PATHOLOGY

Familial Alzheimer Disease

The identification of genes that, when mutated, cause earlyonset autosomal dominant FAD have provided strong clues to the cellular pathogenesis of AD (see Chapter 83).

Pathogenetic Mechanisms in Sporadic Alzheimer Disease

However, more than 90% of all cases of AD are not caused by single gene mutations, and, in these cases, the origin is less well understood. Although the factors that accelerate β -amyloidogenesis in sporadic AD are not established, clues are emerging from studies of genes that influence the risk of developing late-onset AD. Topping the list of factors that increase AD risk is inheritance of the $\epsilon 4$ allele of the gene encoding Apo E, a protein that transports cholesterol and

certain phospholipids into cells (48,49). The virtual absence of other key plasma apolipoproteins such as Apo A1, C1, and B in the brain emphasizes the critical role of Apo E in this tissue. In addition to its role in lipid transport, Apo E has antioxidant and growth-promoting properties on cells (50,51), and it interacts with Aβ, thereby influencing its endocytosis and clearance (52), its ability to aggregate, and its neurotoxicity (53,54)—effects that may all be relevant to AD pathogenesis. The three isoforms of Apo E, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, vary by only a single amino acid substitution, but they differ markedly in their binding affinities for low-density lipoprotein (LDL) receptors and other proteins. The most common allele, $\epsilon 3$, occurs in the general population with a frequency of 75%, whereas $\epsilon 2$ and $\epsilon 4$ occur with frequencies of 10% and 15%, respectively (1). Inheritance of a single $\epsilon 4$ allele increases the risk of AD threefold, whereas homozygosity for $\epsilon 4$ is associated with an eightfold increase in risk (49). The Apo E ϵ 4 allele appears to lower the age of onset in persons in their sixties and seventies rather than influence the duration and severity of the disease. There is evidence that the $\epsilon 2$ allele confers some protection from the development of late-onset AD and Down syndrome (5).

Additional genes that may influence the risk of developing late-onset disease are being identified at an increasing pace (49,55,56). Among the possible positive risk factors are common population polymorphisms of the APOE promoter (57) and genes encoding the LDL-receptor-related protein (LRP-1) (58-61), α₂-macroglobulin (62), FE65 (63,64), very LDL (VLDL)-R receptor (65), the lysosomal protease cathepsin D (66), the lysosomal cysteine protease inhibitor cystatin C (67), bleomycin hydrolase (68), and interleukin-1 (1A and B) (69,70). In light of the evidence that neuronal endocytosis is altered at the very earliest stages of AD, many of these genetic modifiers of AD risk encode proteins that depend on endocytosis for their function. Apo E, its receptor on neurons (LRP), another LRP ligand (α_2 macroglobulin), and the VLDL receptor all are molecules that traffic through early endosomes as they bring cholesterol or other ligands into the cell. Inheritance of the APOE $\epsilon 4$ allele accentuates endocytic abnormalities in AD (27). Cathepsin D is a major protease of the endosomal-lysosomal pathway previously implicated by other neuropathologic and biochemical data in AD pathogenesis (34). Similarly, cystatin C mutations, which cause the Icelandic form of hemorrhagic cerebral amyloid angiopathy (71), are key regulators of proteases within the lysosomal system. The endocytic pathway is also responsible for the internalization and initial processing of APP at the cell surface. Fe65 binds to the internalization domain of APP and modulates its processing to Aβ (72). Early endosomes are also a principal site of Aβ generation in normal cells and mediate the cellular uptake of A ϵ and APPs (73,74).

The convergence of such a diverse group of etiologically important molecules at a known major site of $A\beta$ produc-

tion has suggested that altered early endosome function may contribute to β-amyloidogenesis in sporadic AD (28). Supporting this hypothesis are studies showing the principal βsecretase in cells resides largely in endosomes (75) and that cathepsin D, a protease with β -secretase activity (76–79), and other "lysosomal" proteases that influence AB formation become more abundant in neuronal early endosomes when the lysosomal system becomes activated in AD. This latter effect reflects not only the markedly increased expression of these proteases but also their enhanced targeting to early endosomes by the cation-dependent mannose-6phosphate receptor (MPR-46), which is also more highly expressed in AD brain (28,80). When these conditions are recreated experimentally in cells by modestly overexpressing MPR-46, Aβ generation is substantially increased (80). Thus, proteases that normally may not even be involved in Aβ formation could, under pathologic conditions, become abnormally routed to cellular compartments where they promote AB generation. This is one mechanism that explains how \(\beta\)-amyloidogenesis may be accelerated in sporadic AD in the absence of a causative gene mutation.

EVOLUTION OF CELLULAR PATHOBIOLOGY

The genetic heterogeneity of AD suggests that the disease may be initiated through distinct cellular cascades, which then converge on the final common pathways responsible for β -amyloidogenesis, neurofibrillary pathology, and, ultimately, neuronal cell death. Secondary and tertiary responses of the brain to the presence of these neuropathologic lesions may further compromise neuronal function, making it difficult to establish what is cause or effect. Current hypotheses on the cellular pathobiology of AD emphasize different aspects of this complex multifactorial process, and, not surprisingly, these "different" views overlap considerably. To illustrate this, three perspectives on cellular pathogenesis are discussed in the following paragraphs; these emphasize metabolic decline, defective cell repair, or Δ 0 toxicity as the driving pathophysiologic mechanism in Δ 1.

From the *metabolic decline* perspective, cellular oxidative stress leading to neurodegeneration is a final common pathway of metabolic insults originating from different sources. According to this view, metabolic disturbances are both a cause and a consequence of β -amyloidogenesis. The onslaught on metabolic function begins with effects of normal aging and specific genetic factors. For example, aging-related cerebral hypoperfusion leading to reduced brain glucose and oxygen utilization impairs energy production at the mitochondrial level and promotes the production of free radicals (81). The detection of regional hypometabolism in AD patients with mild cognitive impairment suggests that such hypometabolism may not be simply a result of neurodegeneration but may also precede it. Moreover, cerebral ischemia, coronary artery disease, *APP* mutations, and some

inherited mitochondrial DNA mutations may increase AD risk, in part, by creating additional oxidative stress through these same pathways (82). Oxidative damage from these and other sources leads to mitochondrial membrane depolarization and increased levels of mitochondrial reactive oxygen species (82a). The resultant oxidative damage to proteins and membranes activates degradative pathways, notably the lysosomal system (31), and in doing so upregulates cathepsins and other proteases (83), which have been implicated in mechanisms of cell death, AB production, and cytoskeletal protein modification (34). Free radicals subsequently impair the function of glucose and glutamate transporters and damage ion-channel adenosine triphosphatases (sodium-calcium pumps), thereby reducing the ability of cells to buffer calcium (84) and rendering them more vulnerable to excitotoxins (85).

Calcium homeostasis is further altered by glutamate and other excitotoxins that stimulate receptor-mediated influx of calcium or, in FAD, by mutations of presenilin that lead to the release of intracellular calcium stores (86,87). Elevated cellular calcium activates major signaling cascades including stress-related protein kinases acting on tau and the cytoskeleton (24,88). Tau hyperphosphorylation decreases its binding to microtubules and promotes loss of microtubule stability and impaired axonal transport (89). NFT formation may compound this effect on transport by imposing physical obstructions to the movement of vital organelles to the axon and synapse. Calcium-activated neutral protease (calpain) systems, which are highly activated in AD brain (90,91), contribute to the truncation and breakdown of cytoskeletal proteins including tau, alter the activity of the protein kinase C cascade, cdk5, and other signaling pathways, and participate in the mechanisms underlying apoptotic and necrotic cell death (92,93). Ultimately, in certain cells, mitochondrial damage leads to the release of cytochrome C, which activates caspases that mediate apoptosis. FAD-linked PS and APP mutations increase the vulnerability of cultured neurons to apoptosis, presumably through one or more of the metabolic pathways discussed above (94-96).

Complementary to the foregoing metabolic decline perspective is a *cell repair* hypothesis, which emphasizes a putative failure by the brain to repair the cumulative neuronal damage arising from normal aging processes, ischemic and environmental insults, and genetic factors. The neurotrophic actions of APP or its mobilization during neuronal injury are most relevant here. Cells normally secrete a proteolytic derivative of APP, designated APPs, which promotes neuron growth and increases neuronal survival after certain types of injury (84). APP expression and distribution dramatically increases after neuronal injury, ischemia or oxidative stress, head injury, and exposure to toxins (97). Cerebrospinal fluid levels of APPs, however, may be reduced. Apo E also figures prominently in the processes of cell repair and regeneration by coordinating the mobilization and re-

distribution of cholesterol needed for myelin and neuronal membrane synthesis (48). Functional synaptic remodeling *in vivo* is markedly compromised in mice lacking the Apo E gene (98). During regeneration, Apo E expression may increase up to 100-fold. The €3 allele seems to be more effective as a growth-promoting or repair factor than the €4 allele, which is linked to an increased risk of AD (99). Because Apo E is synthesized in glial cells, neurons depend heavily on receptor-mediated endocytosis to internalize Apo E−cholesterol complexes, a process that is altered at the earliest stages of AD (27). The increased levels of protease seen in neuronal early endosomes of the AD brain likely promote the degradation of internalized molecules and may prematurely abrogate their trophic or nutrient functions.

A third perspective, commonly referred to as the $A\beta$ cascade hypothesis, places the Aβ peptide at the center of AD pathogenesis based on its neurotoxic properties in either soluble or fibrillar form. AB deposition within senile plaques involves a balance between forces that enhance the overproduction and aggregation of AB and countervailing forces that promote the uptake and degradation of AB from the extracellular space. FAD-linked mutations cause varying degrees of AB overproduction (97), but they may also favor aggregation by increasing the relative production of Aβ42 or mutant Aβ forms that aggregate more easily. Aβ aggregation is also facilitated by additional proteins released by reactive or damaged cells (100,100a). In this regard, Apo E is particularly critical to Aβ deposition (101–103). Cellular uptake and clearance of Aβ involve interactions of an Apo E/Aβ complex with LRP. The influence of Apo E on amyloid deposition is underscored by the observation that Apo E gene ablation abolishes amyloid deposition in transgenic mice overexpressing APP containing the London mutation (104). Microglial function also seems to be critical to Aβ removal (15). In transgenic models of FAD, Aβ deposition is almost completely prevented when microglia are experimentally activated by immunizing mice with AB protein (105).

The fibrillar state of $A\beta$ is considered to be a crucial factor in Aβ neurotoxicity (106,107); however, it is still unclear whether intraneuronal AB accumulation or extracellular soluble AB forms may be relevant to neurotoxicity (108,109). Although a sequence of events after Aβ deposition has not been confirmed, it is hypothesized that AB accumulation within diffuse plaques eventually leads to local microglial activation, cytokine release, increases in astrocyte numbers, and an inflammatory response involving the classic complement cascade, as discussed earlier (14). It has been further proposed that these glial responses and any direct neurotoxic effects of AB initiate a cascade of biochemical and structural changes in surrounding axons, dendrites, and neuronal cell bodies in AD. Aβ-initiated inflammatory and neurotoxic processes generate excessive free radicals and peroxidative injury to proteins and alterations of ionic homeostasis, particularly excessive calcium entry into neurons accompanied by the activation of calpains and kinases acting on cytoskeletal proteins (16,82,84). A β is one of various factors that may stimulate the glycogen synthase kinase pathway, which, among other roles, is involved in both the phosphorylation of tau and still unclarified aspects of presenilin and APP processing (110). Finally, endocytic uptake of A β 42 into cells activates and destabilizes the lysosomal system, and this further compounds the insult to this system from other sources and promotes cell death (111).

Thus, the A β cascade hypothesis ultimately reaches the same metabolic endpoints as the metabolic decline hypothesis, but it distinguishes itself by proposing that A β accumulation is the germinal event, rather than being a secondary, albeit important, consequence of accumulating metabolic or functional deficits within neurons. To become a comprehensive hypothesis of AD pathogenesis, the A β cascade hypothesis still must explain the nature of the initial disturbance that causes A β to accumulate in the 90% of AD cases that are not caused by FAD-linked mutations. Most likely, AD pathogenesis is a multifactorial process, in which A β is necessary but not a sufficient factor.

CONCLUSIONS

In this chapter, a discussion of Alzheimer neuropathology provides the starting point for understanding how the diagnosis of AD is made and how clinical symptoms arise and progress. Later sections address the neuroanatomic and cellular basis for dementia and the molecular events that lead to neuropathologic lesions and, ultimately, to the death of neurons. A consideration of current hypotheses on the evolution of cellular pathology identifies common features that help to reconcile the differing views of disease pathogenesis. New studies are beginning to shed light on underlying mechanisms in prevalent sporadic forms of AD, and their review complements the discussion of pathogenesis in the rare familial forms here and, in more detail, in Chapter 83.

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