Akt activation in pheochromocytoma PC12 cells, suggesting that kinase activation is also involved in the survival promoted by NGF (*24*). The implication from the new work is that the Akt signaling pathway is able to prevent apoptosis of neurons after NGF treatment. Does activated Akt protect cells from programmed cell death promoted by other stimuli and physiological conditions? Interestingly some reports (*25*) indicate growth factor–induced neurite outgrowth in PC12 cells is inhibited by wortmannin, suggesting yet another role for Akt.

Are other PH domain–containing protein kinases (about 12 at the last count) also recruited to the membrane and activated by PI 3-kinase? Only time will tell if they are all as interesting as Akt.

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NEUROSCIENCE

Alzheimer's Disease: Genotypes, Phenotype, and Treatments

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New research findings on Alzheimer's disease (AD) emerge at a furious pace, at first appearing to obscure rather than illuminate a unified mechanism of disease that could simplify the search for therapies. But several recent reports, coupled with earlier observations from many laboratories, now suggest a clarifying pattern—that all four known genetic alterations underlying familial AD increase the production or deposition (or both) of the amyloid β protein (Aβ) in the brain. Moreover, studies of humans with AD or trisomy 21 (Down syndrome), and of transgenic mouse models, all indicate that Aβ accumulation in the cerebral cortex is an early and invariant event in the development of AD pathology, preceding other brain lesions and clinical symptoms by many years or decades.

The central quest of research on AD is to identify the steps in its pathogenesis that, if inhibited, would slow or prevent the disease. All AD patients develop neuritic plaques in brain areas subserving memory and cognition. These plaques consist of extracellular masses of Aβ filaments intimately associated with dystrophic dendrites and axons, activated microglia, and reactive astrocytes. Virtually all patients also have many neurofibrillary tangles, intraneuronal bundles of paired helical filaments composed of highly phosphorylated forms of the microtubule-associated protein, tau. Aβ also accumulates in many nonfilamentous extracellular deposits that lack altered neurites and glia (diffuse plaques). These are composed of the slightly longer and more amyloidogenic 42-residue form of Aβ ($Aβ_{42}$), whereas neuritic plaques contain both $Aβ_{42}$ and the far more abundantly produced $Aβ_{40}$ peptide. Aβ is formed by specific endoproteolytic cleavages of the β-amyloid precursor protein (βAPP), which is encoded by a gene on chromosome 21, and is constitutively secreted by both brain and nonbrain cells into extracellular fluids throughout life.

βAPP missense mutations located at or near the sites of endoproteolysis are a rare cause of familial AD (see table). All of these βAPP mutations have been studied in transfected or primary cells, and all increase Aβ secretion, particularly $Aβ_{42}$ (*1*, *2*). Furthermore, plasma Aβ levels are significantly increased in some mutation carriers, even presymptomatically (*2*). As a result, it is now widely accepted that βAPP mutations cause AD by enhancing the cleavages that generate Aβ, thereby promoting amyloidogenesis. There is no evidence that normal βAPP function is impaired by the mutations, probably because only a small fraction of all βAPP molecules in the cell actually undergoes the Aβ-generating cleavages, even in individuals with the mutations.

The second gene to be implicated in familial AD is apolipoprotein E (apoE). Inheritance of one or two apoE4 alleles increases the likelihood and decreases the age of onset of AD (*3*). The only consistently confirmed phenotypic clue to its mechanism is that AD patients carrying apoE4 alleles show a significant, dose-dependent increase in the density of Aβ deposits (in particular, those contain-

Chromosome	Gene defect	Age of onset	Aβ phenotype
21	βAPP mutations	50s	↑ Production of total Aβ peptides or of $Aβ_{42}$ peptides
19	apoE4 polymorphism	60s and older	↑ Density of Aβ plaques and vascular deposits
14	Presenilin 1 mutations	40s and 50s	↑ Production of $Aβ_{42}$ peptides
1	Presenilin 2 mutations	50s	↑ Production of $Aβ_{42}$ peptides

Genetic factors predisposing to Alzheimer's Disease: Relationships to the β-amyloid phenotype. Additional chromosomal loci exist but are not yet specifically identified.

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ing $A\beta_{40}$) compared to patients carrying no apoE4 alleles (*4–6*). Precisely how the apoE4 protein enhances Aβ deposition is under intensive study, but a leading theory is that it permits increased formation of Aβ fibrils.

The third and fourth familial AD genes to be identified, presenilin (PS) 1 and 2, encode highly homologous, multitransmembrane proteins (*7*). More than 30 mutations in PS1 and 2 in PS2 have been identified to date. A selective and highly significant increase of $A\beta_{42}$ occurs in the plasma and in media from cultured skin fibroblasts of patients with PS mutations, and this rise can be detected presymptomatically (*2*). Importantly, simple transfection of mutant PS cDNAs into cultured peripheral cells selectively increases $A\beta_{42}$ secretion, indicating that this is a direct phenotypic effect of the mutations and requires no neural or other AD-related influence (*8*). Transgenic mice expressing mutant PS1 also show increased $A\beta_{42}$ levels in brain (*8, 9*). Finally, direct analysis of the brains of patients bearing PS1 mutations demonstrates a significant increase in the density of $A\beta_{42}$-containing plaques compared to that found in patients with sporadic AD (*10*).

The recognition that all four known familial AD genes enhance Aβ production or deposition (or both), even in simple in vitro systems, fits well with five previous findings about the AD process. (i) Patients with trisomy 21 (Down syndrome), who invariably develop classical AD neuropathology by age 50, overproduce Aβ from birth and show diffuse $A\beta_{42}$ plaques as early as age 12, decades before they get neuritic plaques, tangles, and other AD lesions (*11*). (ii) Normal older humans, particularly those carrying apoE4 alleles, can get diffuse Aβ deposits before or without developing the lesions and symptoms of AD (*5*), indicating that Aβ deposition precedes AD pathology rather than arising as an effect of it. (iii) Filamentous aggregates of Aβ can injure cultured neurons and activate microglia, and blocking filament formation generally precludes this cytotoxicity (*12*). (iv) Transgenic mice expressing mutant human βAPP genes exhibit the age-related development of diffuse and neuritic plaques, microglial activation, astrocytosis, and changes in neuronal cytoskeletal proteins including tau (*13, 14*), and this process can even be accompanied by memory deficits (*14*). However, the mice have not yet shown typical neurofibrillary tangles nor significant loss of neuronal cell bodies. (v) Humans get other amyloid deposition diseases (sometimes due to missense mutations in the precursor protein of the amyloid), and decreasing the production of the responsible protein sometimes ameliorates the disease (*15*).

Taken together, the available evidence favors a model of the disease in which diverse gene defects (some of which remain to be identified) lead to enhanced production, increased aggregation, or perhaps decreased clearance of Aβ peptides (see the table). These effects allow accumulation first of the highly self-aggregating $A\beta_{42}$ peptide (*16*) and later the $A\beta_{40}$ peptide. The gradual cerebral buildup of Aβ in first soluble and then particulate forms (the microscopically detectable consequence of which is diffuse plaques) appears to result in local microglial and astrocytic activation, with concomitant release of cytokines and acute-phase proteins (*17*). By means of these "inflammatory" changes or by direct Aβ neurotoxicity, local neurons and their processes can be injured, causing profound metabolic changes—likely including altered tau phosphorylation and paired helical filament formation in some plaque-associated neurites and in tangle-bearing cell bodies. Filamentous Aβ may alter glia and neurons by causing changes in calcium homeostasis as well as oxidative injury from free-radical formation. The clinically important consequence of these various events is synaptic loss and mutiple neurotransmitter deficits.

In summary, genetic, neuropathologic, and transgenic modeling studies all point to Aβ accumulation as a necessary but not, by itself, sufficient step for the pathogenesis of AD. Aβ is an early pathogenic factor in all known forms of familial AD, but it must be followed by many molecular and cellular changes before sufficient injury to limbic and association cortices results in symptoms of dementia. The major argument against a central role for Aβ in the genesis of AD has been the finding of some, or sometimes many, Aβ deposits in the brains of individuals dying with normal cognition. But these deposits are overwhelmingly diffuse plaques; mentally normal subjects show few neuritic plaques and neurofibrillary tangles. In this sense, diffuse plaques of $A\beta_{42}$ may be to AD what fatty streaks of cholesterol are to atherosclerosis: very early lesions that may or may not progress to mature, symptom-producing lesions, depending on many factors, including the longevity of the host. It has also been pointed out that the total number of Aβ deposits shows only a modest correlation with degree of dementia. But this is precisely what one would expect from an initiating factor; downstream events occurring closer to the onset of symptoms (such as synaptic loss) would show a stronger quantitative relation to clinical impairment.

The exciting conclusion that flows from recent progress in defining the genotype-to-phenotype relationships in familial AD is a growing consensus about a common early mechanism as a therapeutic target in many, if not all, forms of the AD syndrome. The most effective treatments for complex, chronic diseases are usually those that interrupt an obligatory early step, occurring before a progressive cascade of cell-damaging events. In this context, at least four broad classes of AD drugs can now be envisioned: (i) protease inhibitors that partially decrease the activities of the enzymes (β- and γ-secretase) that cleave Aβ from βAPP; (ii) compounds that bind to extracellular Aβ and prevent its aggregation into cytotoxic amyloid fibrils; (iii) brain-specific anti-inflammatory drugs that block the microglial activation, cytokine release, and acute-phase response that occur in affected brain regions; and (iv) compounds such as antioxidants, neuronal calcium channel blockers, or antiapoptotic agents that interfere with the mechanisms of Aβ-triggered neurotoxicicity. Aiming at these targets does not preclude efforts to improve current symptomatic treatments for AD such as cholinergic replacement. In the future, one can envision an array of therapeutics, each of which addresses a particular step or phase in the pathogenic cascade. The current success in applying molecular genetic and cell biological approaches to the disease predicts that this future is closer than one might think.

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