PERSPECTIVE

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The case for rejecting the amyloid cascade hypothesis

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Alzheimer's disease (AD) is a biologically complex neurodegenerative dementia. Nearly 20 years ago, with the combination of observations from biochemistry, neuropathology and genetics, a compelling hypothesis known as the amyloid cascade hypothesis was formulated. The core of this hypothesis is that it is pathological accumulations of amyloid-β, a peptide fragment of a membrane protein called amyloid precursor protein, that act as the root cause of AD and initiate its pathogenesis. Yet, with the passage of time, growing amounts of data have accumulated that are inconsistent with the basically linear structure of this hypothesis. And while there is fear in the field over the consequences of rejecting it outright, clinging to an inaccurate disease model is the option we should fear most. This Perspective explores the proposition that we are over-reliant on amyloid to define and diagnose AD and that the time has come to face our fears and reject the amyloid cascade hypothesis.

For over 100 years, scientists have recognized a strong correlation between the clinical signs of late-life dementia and the presence in brain of abnormal protein deposits. In AD, these deposits contain aggregated peptide fragments of various proteins, including the amyloid precursor protein (APP), the microtubule-associated protein tau and others. With the discovery that *APP* mutations can act as fully penetrant AD genes, a compelling hypothesis known as the amyloid cascade hypothesis was put forward. This hypothesis states in essence that the APP fragments themselves are the root cause of AD. This view of the disease has obvious appeal. It suggests a relatively straightforward set of criteria by which the disease can be diagnosed and several equally clear paths by which it might be prevented if not cured. As seductive as this narrative might be, however, the dementing illness that we recognize as AD is associated with a complex biology and biochemistry, as well as a pattern of brain disintegration that cannot easily be explained by a simple linear disease model. Indeed, there are growing amounts of data, including a number of failed clinical trials, suggesting that the model is insufficient at best. While the amyloid cascade hypothesis has been exceptionally useful in galvanizing research in the field, continued acceptance of this disease model has led us to be over-reliant on amyloid to define and diagnose AD, as well as to measure the effectiveness of any potential new treatment. This Perspective explores the proposition that the time has come to formally reject the amyloid cascade hypothesis.

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Alzheimer's disease: an overview

By all measures AD is an enormous public health problem that will only grow in severity as the population of the world ages. Oft-cited figures suggest that an individual's risk of developing AD doubles every 5 years after the age of 65 (ref. 1). More recent estimates of prevalence[2] are slightly lower, but they still point to a twenty-first-century demographic where one person in nine over the age of 65, and about one in three over the age of 85, will have AD. The most prominent AD symptoms include difficulty remembering names and recent events as well as loss of executive functioning. There are also behavioral symptoms such as apathy and depression that form an integral part of the disease process. At later stages motor signs appear such as difficulty speaking, swallowing and walking[3]. Although the disease is widely viewed as originating in limbic regions, in particular entorhinal cortex[4], at autopsy an affected brain shows a dramatic shrinkage in virtually all neocortical areas, with thinning of the mantle and expansion of the ventricles. Subcortical structures are lost as well, including 75% or more of the cells of the basal nucleus of Meynert, the dorsal raphe and the locus coeruleus[5–7]; other regions, such as the substantia nigra, are largely spared. On the basis of the pattern of phosphorylated tau deposits, it has recently been argued that AD pathology may actually originate in the brain stem[8]. In addition to the deposits of amyloid and tau, there are early signs of synaptic loss extending to a loss of spine density and dendritic complexity. A compelling case can and has been made that AD begins at the synapse[9–14]. By any measure, therefore, AD is a widespread neurodegenerative disease.

The genetics and biochemistry of Alzheimer's disease

AD is fundamentally a disease of old age: well over 90% of all cases are first diagnosed after age 65. Earlier ages of onset are rare and are usually associated with a dominant genetic mutation. These mutations have identified the misprocessing of the type I membrane protein APP (amyloid precursor protein) as a potential driver of early onset AD[15–17]. Normally, APP is cleaved close to the membrane by an extracellular protease known as the α-secretase. This liberates a soluble extracellular fragment, sAPPα. A second cut is made within the membrane by a complex of proteins known as the γ-secretase. The catalytic subunit of this secretase is one of the presenilin proteins, encoded by either the *PSEN1* or *PSEN2* gene. This second cut liberates an intracellular peptide known as AICD (amyloid intracellular domain) and a small residual peptide between the α- and γ-secretase cuts. The pathway initiated by the α-secretase is apparently benign. In other situations, however, a pathogenic variation of this sequence occurs. The extracellular cut in APP is made farther from the membrane by a separate enzyme, an aspartyl protease known as the β-secretase, followed once again by γ-secretase cleavage. The 40- to 42-amino-acid fragment remaining between the β and γ cleavage sites is the amyloid-β (Aβ) peptide. It is this small fragment that aggregates

to form oligomers and ultimately the macroscopic plaques that form one of the hallmarks of AD pathology. Much has been written on this topic, and the interested reader can consult any of a number of excellent reviews[1,15,17–20].

Note that three of the players in this sequence—APP, PSEN1 and PSEN2—are encoded by the only three identified genes leading to the early onset, familial form of AD (fAD). The congruence of AD genetics and APP processing forms a powerful argument in favor of the idea that Aβ is the cause of fAD. More evidence in favor of a direct role for Aβ is found in the observation that the fAD mutations in each of these three genes all tend to favor the increased production of the aggregation-prone 42-amino-acid form of Aβ ($Aβ_{42}$) both *in vivo* and *in vitro*. This connection extends to the recent discovery of an APP mutation (A673T, an alanine-to-threonine mutation very near the β-secretase cleavage site) that significantly lowers Aβ production and is protective against AD as well as against cognitive decline in the non-AD population[21]. And yet, I would argue that the genetics by itself points only to the involvement of APP and its processing by presenilin. It does not directly address the question of whether the Aβ fragment itself contributes to fAD. Further, if Aβ were the direct link between the fAD mutations and disease symptoms, it is at least odd that no mutation or variant in either the β- or α-secretase has been found that either leads to fAD or protects against it. As will be discussed below, the linkage between Aβ and AD is probably indirect.

In contrast to the rarity of fAD, the sporadic form of AD (sAD) is quite prevalent. Sporadic AD first appears clinically after the age of 65. Over a dozen genes have been found to increase lifetime AD risk (a list is maintained at the Alzforum web site, http://www.alzgene.org/). The most important of these is the gene for apolipoprotein E (*APOE*)[15,16,22]. A pair of polymorphisms that leads to a two-amino-acid switch in the normal amino acid sequence produces the APOE4 variant of the protein. This variant has subtly altered lipid-binding properties and, when heterozygous, is associated with a fourfold increased risk of AD. Individuals homozygous for *APOE4* have an approximately eightfold elevation in risk. The prototypical function of APOE is to transport lipids in the body; but it is known to transport Aβ as well. The other AD risk factor genes that have been identified in addition to *APOE* all have quantitative effects that are considerably less than that of *APOE*. Curiously, given the data supporting a role for APP and Aβ in fAD, nonfamilial forms of AD do not appear to involve genes for either APP or its processing genes (secretases) as risk factors.

Despite these promising insights into both fAD and sAD and evidence for the central role of APP and the γ-secretase in fAD, it is safe to say that we still have an incomplete picture of the biology underlying the devastating loss of brain mass and function that accompanies AD. This lack of precision begins with the diagnosis, the criteria for which have been recently laid out by McKhann *et al.*[23]. As they point out, "AD dementia is part of a continuum of clinical and biological phenomena … [and is] … fundamentally a clinical diagnosis." And while they support the use of biomarkers, including amyloid detected either in cerebrospinal fluid or through positron emission tomography (PET), they state that "to make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied." They go on to say that one might imagine that AD starts with Aβ pathophysiology initiating a hierarchical sequence in which other biomarkers are essentially downstream. But they urge caution for diagnostic purposes and assert quite directly that "the reliability of such a hierarchical scheme has not been sufficiently well established for use in AD dementia."[23]

The amyloid cascade hypothesis

The hierarchical scheme that McKhann *et al.*[23] refer to is known as the amyloid cascade hypothesis. The idea that amyloid deposits are the driving force in both familial and sporadic AD was proposed in the early 1990s (ref. 24). Since then the details have evolved[25–27] but the core elements of the hypothesis have remained fairly constant. In a recent description[28], it was summarized in the following way. "Over time, an imbalance in Aβ production and/or clearance leads to gradual accumulation and aggregation of the peptide in the brain, initiating a neurodegenerative cascade that involves amyloid deposition, inflammation, oxidative stress, and neuronal injury and loss. … Oligomeric and fibrillar forms of Aβ cause long-term potentiation impairment and synaptic dysfunction, and accelerate the formation of neurofibrillary tangles that eventually cause synaptic failure and neuronal death." These and other restatements of the amyloid cascade hypothesis are more nuanced than the original, yet the basic structure of the hypothesis remains unchanged: a linear pathway that begins with Aβ formation and ends with the dementia we know as AD.

Testing the hypothesis

The amyloid cascade hypothesis, like all good hypotheses, makes clear, testable predictions. As it is currently stated, there are two basic types of experiments that should be done to test its validity. The first type would involve taking healthy people and adding amyloid to their brains. According to the hypothesis, they should get AD. The second test would be to take people who already have AD and remove the amyloid from their brains. According to the hypothesis, they should get better; or at least they should not get any worse.

The first test has been done in humans and in mice. Although the full interpretation of the findings in human brain is still being discussed[29], there is evidence from autopsy studies and from live imaging using PET ligands such as PiB (the ^{11}C-labeled Pittsburgh compound B)[30] or its ^{18}F-labeled cousins, florbetapir, flutemetamol, florbetaben and others[31]. These studies are all in substantial agreement with one another: individuals can present with few if any clinical symptoms of dementia and yet carry substantial amyloid burdens in their brains[32,33]. That is basically an experiment of nature that fulfills the first test—adding amyloid to healthy people's brains. They should have Alzheimer's dementia, but they do not. Such individuals are not rare; rather, they account for a quarter to a third of all older individuals with normal or near-normal cognitive function. Having a detectable amyloid burden by PET scanning increases the risk that a healthy individual or a person with mild cognitive impairment will progress to AD by about fourfold[34]. But data are still accumulating on the question of how long amyloid deposits can persist without major cognitive illness. It is already clear, however, that the time will be measured in years, not in weeks[35].

The existence of this group of individuals (healthy, but amyloid positive) is a substantial challenge to the amyloid cascade hypothesis. It is clearly possible to have amyloid deposits without dementia; therefore amyloid is not sufficient to cause disease. And since the deposits are the macroscopic result of a process that starts with smaller oligomeric aggregates, we may speculate that these plaque-positive individuals have been oligomer-positive for even longer periods of time; they should thus be well along the disease pathway. Yet the absence of any overt signs of dementia in 25% to 30% of such individuals suggests that they are not.

The situation in the mouse is even more dramatic. A variety of human APP constructs have been introduced into the mouse genome, with or without second or third AD-associated transgenes[36–41]. These lines of mice produce substantial deposits of amyloid in their brains

beginning as early as 4 months of age. They tend to do poorly on the Morris water maze test of spatial memory and to show other modest cognitive symptoms; but most of the classic AD-associated pathologies never develop. No neurofibrillary tangles appear, and while there is synaptic loss, there is little or no neurodegeneration. Indeed, mice can live three-quarters of their lives with dense deposits of amyloid, yet while they suffer from behavioral symptoms , these symptoms bear little resemblance to those of people with even mild dementia. Indeed, recent evidence suggests that in transgenic mice that express the Aβ peptide only, in the absence of APP overexpression, plaques develop but virtually no cognitive deficits appear[42]. This finding resonates with the concerns raised above about the human genetics of AD and the extent to which they implicate APP processing or Aβ itself.

To be sure, the mice are only models of human fAD; tellingly, mice do not naturally develop any significant late-life Alzheimer-related pathology. While we can acknowledge these caveats, the mouse and human data validate each other. Simply stated, you cannot produce an Alzheimer's-like dementia by exposing a mammalian brain to amyloid deposits. Note that this interpretation of the data does not imply that Aβ is not neurotoxic; it is[43–45]. But the data offer the strong suggestion that Aβ is not sufficient to cause the complex symptomatology of AD and that there is more to the AD story than Aβ alone.

The second test of the amyloid cascade hypothesis has also been done: amyloid has been removed from the brains of individuals with AD and from mice with engineered familial forms of the disease. Here the tests have been less definitive and the evidence is mixed. In mouse models of AD, a variety of different techniques have proven effective in preventing amyloid deposits, and in many situations macroscopic plaques can be removed after they have formed. Active and passive immunization against the Aβ peptide, as well as strategies that enhance Aβ clearance and treatments that reduce inflammation, have all been shown to be effective means of clearing plaques from the mouse brain[46,47]. And in these cases, the behavior of the mice improves, most often to levels of performance approaching those of wild-type animals. The data, therefore, are consistent with the amyloid cascade hypothesis: remove amyloid from their brains and mice get better.

A closer look at the mouse data, however, raises questions of interpretation. Consider that while the plaque burdens in the mice were high, in study after study, the improvements that are seen after amyloid clearance approach 100%. Thus, in stark contrast to the human trials, the condition in the mouse can be fully cured. This reminds us that while our AD mice may have problems in their neural networks, their problems are reversible; none of the models involves appreciable (irreversible) neurodegeneration. They have behavioral abnormalities, but the rapid[46,48] and nearly complete[46,48–50] restoration of normal behavior makes it likely that there is little or no permanent damage associated with their conditions. These models may reproduce some of the early stages of AD, but they do not capture the full range of brain damage that occurs during the course of the human disease.

This second type of test has also been done in humans, where the results are not promising. On the basis of the success of the immunization protocols developed in mice, analogous studies were initiated in humans with early sAD. Unfortunately, adverse events required the termination of the initial trial[51]. Even with an abbreviated immunization schedule, however, several of the participants were found to have generated anti-amyloid antibodies. Follow-up studies in these 'responders' have shown that they reacted just as the mice did: their plaque burdens were substantially reduced[52]. Cognitive testing conducted over many years, however, now suggests that, despite a greatly reduced plaque load, their dementia has not improved and most likely is continuing to worsen[53]. Two recent reports of human trials using anti-amyloid antibody therapy also failed to meet their stated endpoints even after 80 weeks of therapy[54,55]. These examples join a discouraging list of failures of advanced stage clinical trials based on the premises of the amyloid cascade hypothesis[56]. Thus in humans, removing plaques from the brain does not cure AD and may not prevent its continued advance. It is perhaps simplistic to characterize these findings as a definitive test. Nonetheless, at first pass the data are inconsistent with the amyloid cascade hypothesis: remove amyloid from their brains and people still have AD.

These findings deserve consideration beyond the question of whether they prove or disprove the amyloid cascade hypothesis. The individuals who entered into the vaccine trials were diagnosed with AD, and most would agree that even now, years after their immunization, they still have AD. But their plaque burden has been dramatically reduced. In this case, we know that their loss of Aβ was induced by the immunotherapy, but it is not impossible to imagine that a natural process (such as autoimmunity or exaggerated clearance) could spontaneously occur in the brain of someone with AD and also remove their plaques. The success of the human trials in reducing amyloid burden forces us to confront the fact that when we see an individual with dementia but no plaques, he or she might very well have AD. The implication is that just as there can be plaques without AD, there can also be AD without plaques.

Rejecting the amyloid cascade hypothesis

Note that none of these data argue that Aβ is not involved in AD. Along with APP and the secretases, it can and should remain a central part of our thinking on the pathophysiology of the disease. Further, even if Aβ proves to be correlated with AD and nothing more, the correlation is still robust. Its presence is pervasive in aging and in AD brains, and there are powerful genetic data arguing for its connection to some of the core mechanisms of fAD. Further, the amyloid cascade hypothesis continues to have many strengths as well as weaknesses (**Table 1**); thus, Aβ and APP should be included in any revised hypothesis of the origins of AD. Yet the weight of the evidence from sAD is fairly compelling that amyloid at any stage of aggregation is not by itself sufficient to cause AD. At this juncture, therefore, it would make sense to propose that it is time to reject the amyloid cascade hypothesis and search for alternative explanations for the cause(s) of human AD. I would emphasize that in proposing this rejection I am arguing only that a simple linear pathway tracing disease progression from Aβ to AD is inadequate as a formal hypothesis and that thus this specific disease model should be rejected.

Instead of rejecting the hypothesis, however, the field has essentially redefined the disease. The result is a dangerous circular logic that is holding back the field. It has been proposed that if people have plaques in their brain but are cognitively normal, they nonetheless have an early, 'preclinical' stage of AD[57]. Since amyloid deposits are integral to defining AD, and since we can detect amyloid before the onset of overt cognitive decline, the argument is that the amyloid pathophysiology must precede the clinical symptoms and therefore defines an early disease stage. This argument only makes sense, however, if we have complete confidence that Aβ directly causes AD. The evidence above argues that such confidence is not justified. The concept of a preclinical stage of AD is a useful one; but, as with the diagnosis of AD itself, to list amyloid deposits as a required part of the definition of its existence is supported neither by the data nor by the clinical experience. It is the equivalent of saying that once plaques are found in the coronary arteries, a person is having a heart attack and, if there are no plaques in the arteries, no myocardial event can be defined as a heart attack. This is not a useful concept. Rather, in both heart

Table 1 Strengths and weakness of the amyloid cascade hypothesis

	Strengths	Weaknesses
Genetics	• fAD: *APP* and *PSEN* genes are the only genes identified • sAD: *APOE* variants affect AD risk and also Aβ clearance • Rare A673T *APP* mutation lowers Aβ production and protects against AD	• fAD: No α-secretase (*ADAM10*) or *BACE* mutations yet found • sAD: *APP*, *PSEN*, *BACE* and *MAPT* (tau) polymorphisms show little association • *MAPT* mutations associate with frontotemporal dementia
Biochemistry	• Amyloid comes from APP after cleavage by γ-secretase (PSEN) • Conditions that favor γ-secretase cleavage to the longer $A\beta_{1-42}$ favor aggregation and AD • APOE4 increases risk of AD and slows clearance of Aβ	• Transgenic mice expressing only Aβ suggest amyloid alone is not sufficient[42] • Other biochemical deficits are present in AD and are sufficient to create dementia
Animal models	• Overexpression of human APP in mouse produces plaques • Mouse transgenics for human APP show memory deficits • Aβ is toxic to neurons in culture • Overexpression of human APP in fruit flies produces neurodegeneration	• Overexpression of human APP in mouse does not produce tangles, neurodegeneration or AD-like dementia • *PSEN* transgenics show neither plaques nor tangles nor neurodegeneration • Memory deficits in transgenics correct quickly and completely
Pathology	• Amyloid plaques are more frequent in AD-affected brains	• Tangles correlate better with neurodegeneration than plaques do • Individuals with substantial plaque burdens can have normal cognition
Clinical findings	• Presence of plaques on imaging associated with increased AD risk • In some subjects with amyloid burdens and early dementia, anti-amyloid therapy improves cognition[a]	• After AD begins, immunoclearing of plaques does not improve cognition[a] • By definition, there is no AD without plaques and plaque deposits without dementia is preclinical AD • No phase 3 clinical trial based on the hypothesis have been successful • Inhibition of γ-secretase increases AD symptoms
Epidemiology		• Certain nonsteroidal anti-inflammatory drugs reduce AD risk by half

[a]As this paper was going to press, the results of the Biogen trial of BIIB037, a humanized Aβ monoclonal antibody, were announced. Though this was only a pilot study of carefully selected individuals, subjects showed cognitive improvement after anti-Aβ therapy.

and brain, the plaques define risk, not disease. This is not merely a semantic point. If we use the deposits to define the disease but there can be plaques without AD, then we will include individuals in our clinical studies even if they are healthy in reality. Equally problematic, if there can be AD without plaques, we will exclude people from our studies (or include them as controls) erroneously.

Where to next? Alternative models of the disease process

Our goal for moving forward should not be to eliminate the various APP breakdown products from our thinking, but we do need to reposition them in our schema. I have argued before[58] that since age is the single most accepted and most powerful risk factor of AD, it makes sense to start with age and keep it central to any hypothesis of AD pathogenesis. While age must be at the foundation of any theory of AD, a review of the literature suggests that there are a number of alternative ways of viewing the disease[59]. The dementia we know as AD evolves from a progressive loss of integrity in the brain's neuronal networks, a gradual decrease in synaptic density, an increasing neuritic atrophy and eventually a widely dispersed cell loss. But what causes these degenerative changes? Without question, AD can be viewed as a disease of amyloid. Yet AD can also be viewed as a tauopathy. There is evidence supporting the view that AD represents a failure of autophagy[60] and/or lysosomal function[61]. A good argument can also be made that a loss of Ca^{2+} homeostasis, due perhaps to excitotoxic activity, lies at the heart of AD[62–68]. Several researchers have suggested that AD represents a failure of neuronal cell cycle control[69–78]. A strong case can be made for the central role of neuroinflammation[79–83], and this argument has been expanded[58] to propose that AD requires three steps: (i) an injury that initiates a disease process distinct from normal aging, (ii) the establishment of a chronic inflammatory state and (iii) a cellular change of state that permanently alters the biology of the cells. A genetic etiology is plausible as well. For fAD, the situation is already clear, but perhaps the right combination of risk factor genes is all we need to establish sAD. Progressive oxidative damage[84] that accumulates with age[85] or DNA damage[73,86–93] have both been argued to be root causes of the disease. And it has been proposed that the real problem in AD is a loss of mitochondrial function[94–96], or a complex senescence phenotype[97]. Or maybe it is all about glucose metabolism[98,99] or a general metabolic compromise[100].

I propose that it is the length of this list of alternatives that serves as the best explanation for our hesitancy to reject the amyloid cascade hypothesis—the heart of our fears. Were we to reject it, we would move from simplicity to complexity. We would instantly be faced with a long list of disease-causing options; yet we would have no clear guidance as to how to focus our quest to understand and treat AD. I submit, however, that the true risk lies precisely in not rejecting the hypothesis. The answer to the question of which option shall we choose is probably fairly simple: choose them all (**Fig. 1**). We can assume that there is a common final path to AD and still entertain the notion that there are many ways to access that path. Amyloid is a frequent contributor to the AD disease process, but the evidence suggests that it is neither necessary nor sufficient. Each of the processes listed above probably contributes in important ways to the development and progression of the disease.

Rejecting the hypothesis is not a defeat or an admission of failure. The biology of AD is perhaps one of the most complex systematic malfunctions of the nervous system that we know. Indeed, for a disease with the prevalence and complexity of AD, the real surprise would be if there were in fact a single, linear pathway that led from healthy brain aging to AD. In truth it is likely that we will need to address all of the listed options if we are to cure AD or completely prevent it. This is a daunting task, but it is likely that each treatment will make a difference, so that our victories will be small and incremental but frequent—a hopeful concept. Removing tau deposits from the brain may help some symptoms; rebalancing Ca^{2+} homeostasis may help with others. Returning autophagy to normal might add to the therapy and

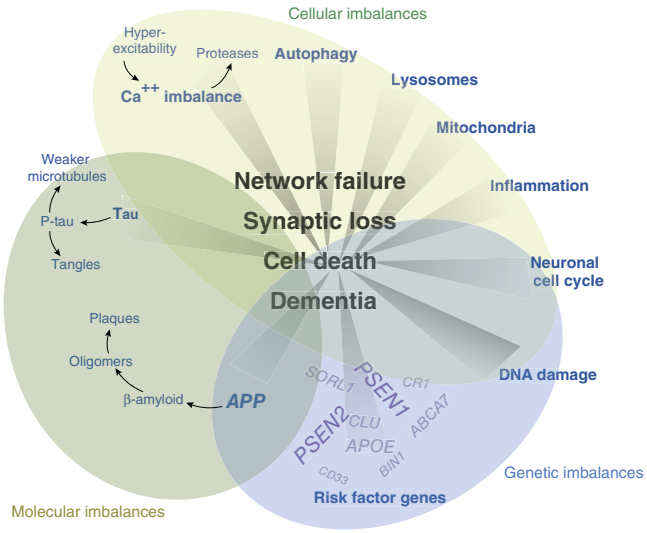

Figure 1 The degenerative events that ultimately produce the clinical symptoms of AD are fed by numerous deficiencies. The symptoms are shown in large bold type at the center, the deficiencies in bold around the periphery. Wedges indicate the paths leading from the deficiencies to the final spiral of degeneration. One of these deficiencies includes the many risk factor genes that have been identified. A partial listing is indicated over the star shape thus labeled. *PSEN2*, *PSEN1* and *APP* are emphasized to indicate their status as fAD genes. A few of the downstream consequences of the primary degenerative events are also shown. These include the creation of β-amyloid from APP and tangles from tau via phosphorylation (P-tau). The causes of AD can be roughly grouped into three categories (shaded ovals): cellular events (light green), genetic events (blue) and molecular events (dark green). Missing entirely from the diagram are the many ways in which various elements interact with the others. Thus, for example, inflammation can enhance the deposition of Aβ and Aβ in turn can influence the deposition of tau and impair synaptic function, possibly also affecting Ca^{++} release.

blocking further neuroinflammation or neuronal cell cycle activity might also help. Reducing oxidative or DNA damage might be useful. Removing amyloid will likely make a difference, but the odds are high that this will not be the end of the story. As the vaccine trials have shown, dementia can and does persist even when amyloid plaques are removed from our brain. Our circle of exploration has been focused for too long on a single disease hypothesis. It is time to listen to our own data, reject it and move forward.

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