Alzheimer's Disease

Modernizing Concept, Biological Diagnosis and Therapy

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Current Conceptual View of Alzheimer's Disease

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Abstract

The dementia known as Alzheimer's disease (AD) has been recognized as a clinical entity for nearly 100 years. The neurodegeneration that occurs during the course of the disease is complex, progressive, extensive and defies easy description. Over the years, many different hypotheses have been put forward to explain the underlying biology of AD. While the most widely known of these is the amyloid cascade hypothesis, other models have also received consideration. These alternative views recognize the role of tau, the failure of lysosomal function, abnormalities in autophagy, the loss of cell cycle control, the failure of calcium homeostasis, the establishment of a chronic inflammation and so forth. There are strengths and weaknesses to each of these conceptualizations of the disease, and this review attempts to summarize them. The chapter ends with a proposal that, befitting its complexity, the most productive way to view AD may be as a true composite of all of these mechanisms.

Alzheimer's disease (AD) is arguably the most complex neurodegenerative disease to afflict the human brain. By the final stages of the disease, affected individuals are unable to interact with their surroundings or care for themselves in any meaningful way. Functional deficits appear in virtually every domain of cognition and behavior. At a structural level there are losses of neuronal processes and cell bodies in diverse regions from brainstem to olfactory bulb. These are described in more detail in the following chapter by Schneider and colleagues [pp. 49–70] as are the accumulations of abnormal deposits of many different proteins, which are also scattered widely throughout the brain. Compounding this picture of brain devastation, AD is relentlessly progressive and remarkably common. As detailed in the previous chapter, estimates of prevalence in individuals over age 85 are widely cited to be greater than 50%. And yet, in the vast majority of all cases, no overt signs of impending brain illness are apparent before the age of 60. This is a huge puzzle for anyone seeking to understand the biological basis of AD as it seems nearly unimaginable that a brain that

has performed normally for 60+ years could fall apart so completely during a 10- to 20-year span of time. Finally, AD is almost uniquely human. None of the most common experimental animal model systems naturally develops anything resembling the catastrophic degeneration that is seen in AD.

The challenges we face in attempting to conceptualize such a common, age-restricted, nearly uniquely human illness, are immense. Fortunately, we have made substantial progress in recent years in unraveling the mysteries of this modern 'plague', but as of this date it seems fair to say that we have still not achieved consensus on the answer to two deceptively simple questions, 'What is AD and where does it come from?' The goal of this chapter is to review the status of our various attempts to answer these questions.

The Biology of Aging

AD does not strike the young. There are no reported cases of infantile or juvenile-onset AD; even the most virulent cases of familial AD do not appear until the fourth decade of life. Thus, to fully conceptualize AD, we must first understand what is meant by brain aging. Progress in our understanding of the biology of the aging process itself has been remarkable. And this progress has led us to the realization that aging is deeply tied to the most fundamental of all of life processes – nutrition.

In the 1980s, researchers were exploring the possibility that age might be a regulated phenomenon. If so, they reasoned there should be genes whose mutation would extend the typical lifespan of an organism. Using the emerging model organism *Caenorhabditis elegans*, they discovered a single recessive mutation that could extend the life of a wild-type nematode by nearly 50% [1]. They called the mutation *Age1*, and its discovery set off a search for other such genes. From these pioneering studies, a unifying principle emerged. Most 'longevity' genes have functions that relate to the insulin/IGF receptor pathway, which regulates the energy utilization of the cells of the body [2]. The cells of the brain become aware of a rise in serum insulin or insulin-like growth factor (IGF-II) levels through the insulin/IGF-II receptor. Ligand binding initiates a series of signals through the PI3 kinase pathway that resonate through a diversity of critical pathways. One is the stress response pathway. PI3 kinase activates Akt, which then signals through Foxo1 and SIRT1. When translocated to the nucleus, the result is an enhancement in synthesis of stress response genes. A second pathway targeted by insulin-induced PI3 kinase is one of the cell's core signaling proteins, mTOR (mammalian target of rapamycin) [3]. The mTOR protein is another member of the PI3 kinase family and its downstream targets include potent regulators of the protein translation system – again a central function of a cell's biochemistry. mTOR also represses the autophagy pathway in part by phosphorylating the Atg13 protein.

The linkage of this pathway to aging was unexpected at first. The smooth response of the insulin/IGF-II receptor would seem relevant only to a moment-to-moment

regulation of energy utilization, yet researchers who study the aging process were repeatedly confronted with the observation that the rate of aging in an organism is highly correlated with the rate of flux through this pathway. The most dramatic demonstration of this relationship is that in organisms from yeast to mammals, caloric restriction (which reduces flux through the insulin/IGF receptor pathway), increases lifespan by as much as twofold. Increasing flux through the pathway, by contrast, accelerates the aging process. To date, this relationship is effective only over a relatively small range; restricting food intake is not the key to immortality. From the vantage point of an age-related disease such as AD, however, the key consideration is that these 'aging' pathways are intertwined with the most fundamental processes of life. And as the risk of developing AD increases with age, we must consider that the origins of AD itself are linked to many of these same processes.

Aging cannot be 'cured'. We must therefore accept that human beings are destined to live with a progressive increase in the risk of developing AD throughout their lives. But while it is linked to aging, AD is not normal aging. It is a pathological process that diverges from the normal biology of brain and body. We must recognize that the task of preventing AD becomes more and more difficult with each year of life; but if we can understand the biology of AD and how it links to the biology of the aging process, we presumably can intervene to either delay its onset or blunt its effects on our nervous system.

Current Theories of Alzheimer's Disease

The time and resources – public and private – that have been put towards uncovering the causes of AD are immense, rivaling those that have been brought to bear on the War on Cancer and the Human Genome Project. As a result, there is no dearth of ideas as to the causes of AD. Some of these theories are more widely accepted than others, but as of this writing, none has been disproven. This begs the question of whether AD might best be viewed as the sum of many mechanisms – some known and probably some that have yet to be discovered. This is an unsatisfying answer to the questions, 'What is AD and where does it come from?' But it is fully consistent with the prevalence of the disease, and with its complex biology and pathological appearance. The following sections briefly summarize several of the better known views of AD.

Alzheimer's Viewed as a Proteinopathy

This is the historical root of our understanding of the disease. In 1906, Alois Alzheimer published the first description of a particularly aggressive form of senile dementia. He took the time in his description to include his results using the newly evolving techniques of heavy metal staining. He reported two types of unusual deposits, which we

now know as senile plaques and neurofibrillary tangles. From the correlation of these odd brain lesions with the dementia he concluded that the deposits themselves possibly caused the disease. As neurologists and neuropathologists explored this correlation, they developed an appreciation that the presence of visible tangles and plaques were correlated with disease, but they served as imperfect guides to the sites of neuronal loss. The neurofibrillary tangles of hyperphosphorylated tau were better correlated with the sites of neurodegeneration over a wider range of areas, and with the associated behavioral changes. This period of clinicopathological correlation received a biochemical boost when Glenner and Wong [4] identified the main plaque constituent as macromolecular aggregates of a short peptide that was termed β-amyloid (Aβ). During this same period, other laboratories reported that the tangles that had been identified by Alzheimer consisted of paired helical filaments whose main constituent was a hyperphosphorylated form of the microtubule-associated protein, tau [5, 6]. These discoveries offered clear and compelling disease mechanisms that led from defects in protein processing, to the accumulation of abnormal intra- and extracellular deposits, to the blockage of normal neuronal functioning and ultimately to the atrophy and death of neurons.

Amyloid

After the discovery of the sequence of the Aβ peptide, research soon showed that Aβ was derived from the transmembrane portion of a previously unknown type I transmembrane protein. Because of its relationship to the amyloid-containing plaques, this new protein was named the amyloid precursor protein (APP). When a mutation of the APP gene was subsequently identified as an autosomal dominant form of early-onset AD, the convergence of biochemistry, histopathology and genetics offered nearly overwhelming proof that the key to AD was amyloid. Additional genetic evidence strongly supported this case (see below). The conceptualization of AD as a β-amyloid disease was crystallized in what has become known as the amyloid cascade hypothesis (fig. 1) [7, 8].

According to this hypothesis, AD has two possible initiation points. For familial (genetic) forms of AD, the disease begins with a genetic predisposition to incorrectly process the APP gene, leading to a relentless accumulation of Aβ, in particular its most amyloidogenic form, the 42-amino-acid peptide known as $A\beta_{1-42}$. For sporadic (late-onset) forms of AD, the disease begins with a slow, age-related accumulation of extracellular Aβ that may be influenced by many factors, but has no specific proximal cause. Eventually, in both early- and late-onset forms of AD, this Aβ load reaches a tipping point that starts the amyloid cascade. Single Aβ peptides begin to associate, first in dimers and small molecular weight oligomers. Gradually the oligomers grow in size until microscopically visible plaques form. As the aggregates grow in size a series of neurodegenerative events begins to unfold. Monomeric Aβ peptide has synaptic activity and likely functions as a neuromodulator during normal neuronal activity. The smaller Aβ oligomers – dimers to 12-mers – also have synaptic activity [9, 10];

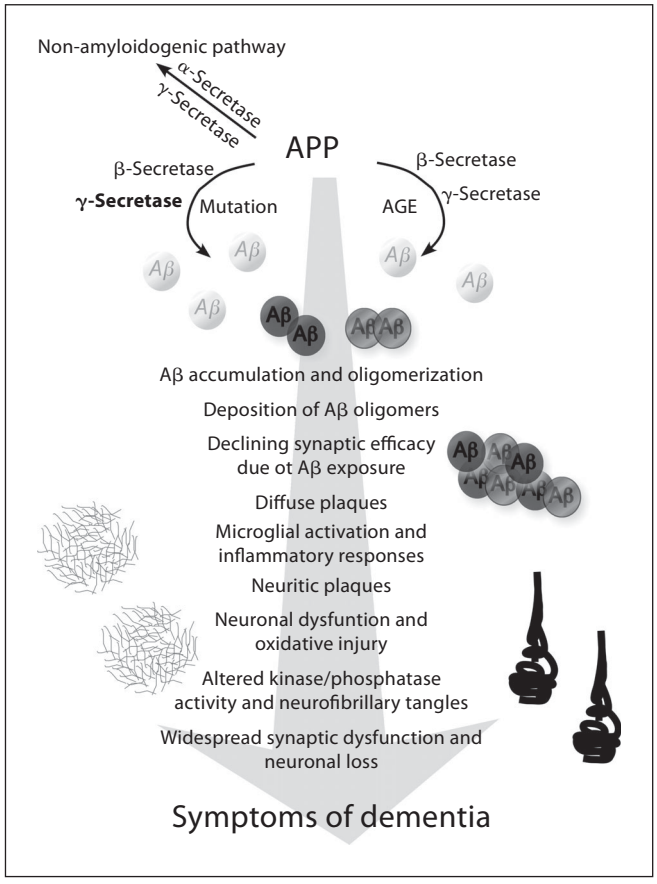

Fig. 1. The amyloid cascade hypothesis [7, 8].

but they have been found to have potent neurotoxic properties as well [11–14]. As the amyloid cascade continues, the aggregating Aβ reaches macromolecular proportions and thus the first plaques appear. Additional pathogenic events add to the destruction: the immune system responds, creating a chronic inflammatory state; neuronal dysfunction moves beyond the synapse leading to the hyperphosphorylation of tau which leads to neuronal cytoskeletal defects and problems with axonal transport. The end result of this multifaceted degenerative cascade is widespread system failure and the progressive symptoms of AD.

Strengths and Weaknesses

The amyloid cascade hypothesis is, by any measure, the most cited conceptualization of the pathogenesis of AD. It has a number of strong points that account for its preeminence. It incorporates both the genetics and the pathology of AD with a single clear program of events. It successfully predicts the reproduction of the memory deficits that are observed in APP-based mouse models of familial AD. It is broad-based and

incorporates the known changes in related processes such as tau hyperphosphorylation, oxidative damage and neuroinflammation. Finally, it has offered a lexicon of terms that have helped researchers from around the world to discuss the disease in a consistent fashion. It is not without its critics, however. A conceptual weakness in the hypothesis is that it is largely silent on the mechanisms that lead to the slow accumulation of amyloid that is a required part of the model of sporadic AD. An additional, more powerful criticism is the finding of significant amyloid deposition in individuals with little or no cognitive impairment. According to the amyloid cascade hypothesis, once Aβ begins to aggregate in the brain of an individual and the tipping point is reached, the clinical symptoms of AD should become apparent. But cross-sectional studies, performed either at autopsy or in living patients with plaque imaging, have repeatedly shown that between a quarter and a third of apparently healthy, non-demented individuals carry significant plaque burdens [15, 16]. The mouse models of familial AD carry a similar message. A variety of transgenes – alone or in combination – have been described that produce heavy Aβ plaque deposition in mouse cortex. Despite the fact that the mice carry this amyloid burden for three quarters or more of their lives, none of the models shows significant neurodegeneration or behavioral problems beyond deficits of long-term memory and spatial orientation that do not capture the human condition with any degree of fidelity. The lack of correlation between the anatomical sites of plaque deposition in human brain and neurodegeneration is a related weakness, as is the lack of correlation between plaque burden and cognitive performance. Finally, the results of clinical trials based on this hypothesis have been discouraging. The failure to show efficacy is widely agreed to be due to the fact that by selecting subjects for study who were already afflicted with mild dementia or cognitive impairment, the studies were all begun too late in the disease process to be effective. Current articulations of the model, however, make no prediction that this should be the case.

Tau

AD can also be seen from the vantage point of the neurofibrillary tangle – the second of the abnormal brain deposits identified in Alzheimer's initial report. Conceptualizing AD as primarily a tauopathy is consistent with the amyloid cascade hypothesis in that it views the underlying pathogenic mechanism as a problem of protein misfolding and aggregation. For all of its prominence as a component of the neurofibrillary tangle, tau has no specific hypothesis, equivalent to the amyloid cascade hypothesis, which describes its complete role in the etiology of AD. The general thesis is that the changes of age and disease lead to a faulty regulation of the levels of tau phosphorylation, which alter its ability to interact with its normal protein-binding partners, primarily microtubules. These failed interactions are envisioned as part of the process that drives AD forward. It is a consistent observation that the level of phosphorylation is a key regulatory change that alters the affinity of tau for the microtubule; more heavily phosphorylated forms of tau have weaker affinity for microtubules. As tau binding stiffens the microtubules,

reductions in tau/tubulin association will lead to more a more pliable and flexible cytoskeleton. This flexibility is required during certain cellular processes (mitosis and early developmental movements are prime examples), but in the context of a stable adult neuron, the loss of structural integrity and smooth functioning axonal transport can be destructive.

In addition to this loss of function, the enhanced propensity for phosphorylated tau to form aggregates of varying sizes adds a complimentary toxic gain of function as there is evidence that macromolecular assemblages of tau are not good for neurons. As with Aβ, there is evidence that it is the smaller, oligomeric, structures that are more toxic than the larger tangle-forming aggregates [17–19]. Tau-based theories of AD have also advanced in recent years by a series of new discoveries. For example, tau is required for the neurotoxicity observed in Aβ/APP AD models [20, 21]. Further, unlike APP-based mouse models, transgenic animals carrying mutant forms of tau can develop a significant neurodegeneration phenotype [22, 23]. *Drosophila* models make this point particularly well [24]. It is also increasingly apparent that tau has functions beyond those of a simple microtubule-associated protein. For example, the association with the Src-family kinase, Fyn, has broadened the view of the normal function of a tau [25]. Tau hyperphosphorylation increases its affinity for Fyn offering opportunities for impact on functional as well as structural properties of the neurons.

Strengths and Weaknesses

The strengths of the cell biological connections between the tau protein and the health and survival of the neuron are much more direct than with β-amyloid. The anatomical correlations between hyperphosphorylation of tau and the appearance of neurodegeneration in AD are tight and occur early in the disease process [26]. Transgenic mice carrying human tau, both mutant and wild-type develop neuronal cell loss in addition to the hyperphosphorylation phenotype [23], and a similar neurobiology is at work in the fruit fly. Despite these observations, there are weaknesses in using tau as the key to the conceptualization of AD. The most important of these is that the genetics are not in agreement. Not only have mutations in *MAPT* (tau) not been associated with AD, the mutations in *MAPT* that do lead to neurological illness are found in association with a different disorder – FTDP-17 (frontotemporal dementia with parkinsonism linked to chromosome 17) [27]. A second major weakness is that while the tau transgenics will develop hyperphosphorylation and pre-tangle pathology, true neurofibrillary tangles are rare and none of the models develops any degree of plaque pathology. A final weakness facing any theory that is reliant on tau to explain AD is that there is no clear mechanistic explanation for how the disease initiates. Several tau kinases including Cdk5 and GSK3β have been identified and implicated as causative factors in AD, but no generally accepted explanation exists as to what triggers these kinases to malfunction in the temporal and anatomical pattern that leads to AD.