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Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis

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Abstract: Alzheimer's disease is the most common form of dementia and the most common neurodegenerative disease. It manifests as a decline in short-term memory and cognition that impairs daily behavior. Most cases of Alzheimer's disease are sporadic, but a small minority of inherited forms allow gene identification which, together with neuropathology, yields important clues about the wider causes. Environmental and metabolic risk factors, including inflammation and vascular impairment, play a role in disease onset and progression. While neuronal atrophy and a loss of synapses occur throughout the cerebral cortex, we lack a full understanding of how this arises. The known hallmarks of Alzheimer's disease include amyloid-β plaques and neurofibrillary tau tangles and while extensive research has been carried out throughout the past few decades, the exact role of these protein aggregates in the disease remains elusive. In this chapter, we discuss mechanisms that have been implicated, including inflammation, mitochondrial dysfunction, oxidative stress and changes in protein clearance.

Keywords: amyloid-β plaques; etiology of Alzheimer's disease; dementia; neurodegeneration in Alzheimer's disease; neurofibrillary tau tangles

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INTRODUCTION

Around 50 million people worldwide suffer from dementia (1). About two thirds have Alzheimer's disease (AD) (2), an irreversible neurodegenerative disorder involving a decline in memory and executive function, and personality change (3). It is named after Alois Alzheimer who first characterized AD in 1906 (4). AD results in synapse loss and neuronal atrophy predominately throughout the hippocampus and cerebral cortex. It is characterized by amyloid plaques and neurofibrillary tau tangles (NFTs), aggregates of misfolded proteins, throughout the brain. Both genetics and environmental factors are believed to play a role in AD. While there are a small number of cases due to dominant genetic mutations (5–7), a majority of AD cases are sporadic and have no single genetic cause. Environmental and metabolic risk factors such as diabetes, cerebrovascular disease, poor diet, head injury and stress are linked to increased dementia risk. The leading hypothesis as to how AD begins and progresses, the amyloid hypothesis, though quite widely accepted, leaves many questions. In particular it remains unclear "what is the best drug target?" and "what lies upstream of the rise in amyloid-β (Aβ) in sporadic cases?." We still lack a fundamental understanding of how AD comes to fruition, and therapies to help individuals fight the disease. AD is a chronic disease manifesting as loss of memory, language, cognition and problem-solving skills, changes in behavior and ultimately death. While the primary signs are memory loss and executive dysfunction, they are often preceded by changes in language and vision (8). Additionally, not all types of memory are equally affected. People with AD have severely impaired episodic, semantic and working memory, yet long-term memory, such as procedural memory, tends to remain intact (9, 10). Clinically, AD is classified into seven stages (Table 1) (11). Patients often die 3–10 years after onset of symptoms (12) with complications arising from immobility, such as pneumonia or blood clots (13, 14).

TABLE 1 **The seven clinical stages of Alzheimer's disease (Global Deterioration Scale) (11)**

	Symptoms and characteristics
Stage 1	Persons appear cognitively normal, but pathological changes are happening in the brain.
Stage 2	Prodromal stage: mild memory loss, but generally this is indistinguishable from normal forgetfulness.
Stage 3	Progression into mild cognitive impairment (MCI). Individuals may get lost or have difficulty in finding correct wording.
Stage 4	Moderate dementia; poor short-term memory. Individuals forget some of their personal history.
Stage 5	Cognition continues to decline and at this point individuals need help in their daily lives. They suffer from confusion and forget many personal details.
Stage 6	Severe dementia. Requiring constant supervision and care. Patients fail to recognize many of their family and friends and have personality changes.
Stage 7	Individuals are nearing death. They show motor symptoms, have difficulty communicating, are incontinent and require assistance in feeding.

ETIOLOGY

Both genetic and environmental risk factors play a role in the manifestation of AD. The greatest risk factor is age. At age 65, the likelihood of having AD is about 3%, rising to over 30% by age 85 (15). The incidence of AD under the age of 65 is less certain, but estimates suggest that this age group accounts for around 3% of AD cases (15). Although overall numbers are increasing with the ageing population, age-specific incidence appears to be falling in several countries (16–18).

AD can be classified by when the disease manifests, and whether it is inherited. Early-onset Alzheimer's disease (EOAD) occurs before age 65, whereas late-onset Alzheimer's disease (LOAD) accounts for over 95% of cases (19) and manifests beyond age 65. Familial AD shows Mendelian (usually dominant) inheritance, while sporadic AD shows no simple familial link (20). Nearly all EOAD are familial as these cases are due to mutations in *APP*, *PSEN1* or *PSEN2*, and a vast majority of LOAD are sporadic. Genome wide association studies (GWAS) and sequencing have now provided more than 20 risk loci in total that contribute to sporadic cases (21), but often there is no identifiable genetic cause.

Aβ precursor protein

Aβ precursor protein (APP) was the first gene shown to have autosomal dominant mutations causing AD. As the precursor of the aggregated peptide in amyloid plaques, its discovery in 1991 by John Hardy and colleagues (5) led to the "amyloid hypothesis," which states that the toxic build-up of Aβ starts a cascade of events, leading to neuronal death and disease (22, 23). There are now over 50 known *APP* mutations, accounting for approximately 10% of familial cases. Widely studied ones include the London (V717I) (24), Swedish (KM670/671NL) (25), Indiana (V717F) (26) and Artic (E693G) (27) mutations, and most cluster around cleavage sites for β and γ-secretase (28). Research suggests that many of these mutations increase Aβ production, or the Aβ 42:40 ratio, leading to increased amyloid accumulation. In very rare instances, *APP* duplication or promoter mutations can cause AD (29, 30). Interestingly, studies have also found that there is an *APP* mutation (Icelandic—A673T) which lowers Aβ and protects against AD (31).

Presenilins

Presenilin 1 (*PSEN1*) and Presenilin 2 (*PSEN2*) encode the catalytic components of γ-secretase, an enzyme complex involved in APP processing (32). Presenilin mutations cause autosomal dominant AD, with *PSEN1* variants being the most commonly known Mendelian genetic cause, estimated to account for around 30–50% of familial EOAD cases (33, 34). Research shows that *PSEN1* and *PSEN2* mutations alter Aβ production, similar to *APP* mutations (35) but paradoxically tend to confer loss of function, raising questions as to how this fits the amyloid hypothesis (36, 37).

Other genetic risk factors

Other genes known to have variants associated with AD risk include *TREM2* (38), *APOE* (39), *CLU* (40–42), *SORL1* (43), *BIN1* (42) and *PICALM* (40, 42). APOE

(apolipoprotein E) is a protein involved in fat metabolism, and its E4 allele is the most common genetic risk factor for AD with an allele frequency of ~13.7% (44, 45). Heterozygosity for this allele increases the risk 3-fold (39). Although rarer, the variant *TREM2*^{R47H} (triggering receptor expressed on myeloid cells 2) has a similar effect size (46). TREM2 is a receptor expressed on multiple cell types of the immune response, and its association supports a role for inflammation in AD pathogenesis.

Down syndrome

By age 65, up to 80% of Down syndrome (DS) individuals develop dementia (47). As with other instances of EOAD, amyloid and tau pathology begin much earlier than in LOAD, even at <40 years of age (48–50). DS results from the trisomy of chromosome 21, where the *APP* gene is located, and having three copies of this gene is sufficient to increase Aβ levels. However, the increased risk of developing the disease may also be due in part to triplication of other genes on chromosome 21 (47, 51, 52).

Inflammation

Sporadic AD often results from a combination of genetic and environmental risk factors, with cerebral hypoperfusion (53) and inflammation (54) being among the most common. Inflammation due to trauma, sepsis and infection has been linked to both short- and long-term cognitive impairment (55–57). Traumatic brain injury, and even bone fractures in the elderly, are implicated in dementia risk (58, 59). Higher levels of inflammatory markers such as interleukin 6 (IL-6) associate with greater risk of AD and vascular dementia (60). AD patients often have higher levels of certain inflammatory markers and activated microglia and astrocytes in the brain, which tend to surround plaques and tangles (61, 62). Finally, higher levels of these markers are associated with faster cognitive decline (63).

Cerebral, cardiovascular disease and diabetes

There is a strong link between vascular disease and dementia. Cardiovascular disease, including high blood pressure and heart attack, and cerebrovascular disease such as ischemia are associated with increased risk of AD (64). Metabolic and lifestyle risk factors for developing vascular diseases, including poor diet, obesity, high cholesterol and sedentary lifestyle, are also risk factors for dementia (65, 66). Poor diet and high cholesterol can produce metabolic changes both systemically and in the brain, and alter oxygen levels (67). Additionally, type 2 diabetes approximately doubles the risk for dementia (68–70).

Other environmental risk factors

The list of environmental and metabolic risk factors discussed here is not intended to be comprehensive, especially as the nature of epidemiology in populations with diverse genetics and lifestyle means that important mechanisms will not always

generate conclusive evidence. Other risk factors implicated include pollution, stress and heavy metal exposure (71–76). Many of these risk factors share some common characteristics with one another which can thus make it difficult to determine how their presence affects the brain. Some may act through similar mechanisms, such as inflammation or oxidative stress, which will be discussed later in this chapter.

NEUROPATHOLOGY

AD is characterised by synapse loss, followed by the atrophy of neurons throughout the cerebral cortex, with the medial temporal lobe being the most severely affected (77–79). Pathology appears to start within the hippocampus and entorhinal regions and spreads subsequently throughout the fronto-temporal cortices. It reaches as far as the striatum and thalamus, usually with sparing of the cerebellum (80–83). On a macroscale level, MRI scans show shrinkage of these regions (84). In particular, pyramidal cells of the CA1 of the hippocampus are vulnerable to morphological changes and cell death, consistent with the main symptom of memory loss (85, 86). The appearance of Aβ plaques and NFTs precedes clinical symptoms suggesting that by symptom onset, there have been years of pathological changes making early intervention difficult.

Aβ plaques

Senile plaques are primarily made of a variety of 36–43 residue-long amyloid peptides that undergo fibrilization to form Aβ sheets that are resistant to degradation (87). They often co-localize with neuronal debris and activated microglia and astrocytes (88), and first appear in the frontal, temporal and occipital lobes of the neocortex. They spread throughout neocortical areas as well as the hippocampal formation and entorhinal region, and eventually spread further throughout the cerebral cortex to the striatum and thalamus (83) (Figure 1). Amyloid pathology appears to precede that of tau, with NFTs only being found in regions where amyloid was already present. Numerous studies have shown that cognitively unimpaired elderly individuals can also have significant Aβ deposition (89–91), while on the contrary, others have reported a correlation of deposition to cognitive decline (92) and dementia severity (93). A recent study has more specifically shown that differences in Aβ oligomer concentration may be a better correlate of disease (94, 95). It is likely that differences in methodology are responsible for the varying conclusions from these studies. It has also been suggested that cognitively normal persons with high plaque levels may have "prodromal" disease, with Aβ pathology that precedes cognitive changes (96, 97).

Neuronal fibrillary tau tangles

NFTs are intraneuronal aggregates of hyperphosphorylated tau protein, encoded by the microtubule associated protein tau (*MAPT*) gene (98) (Figure 1). NFTs are

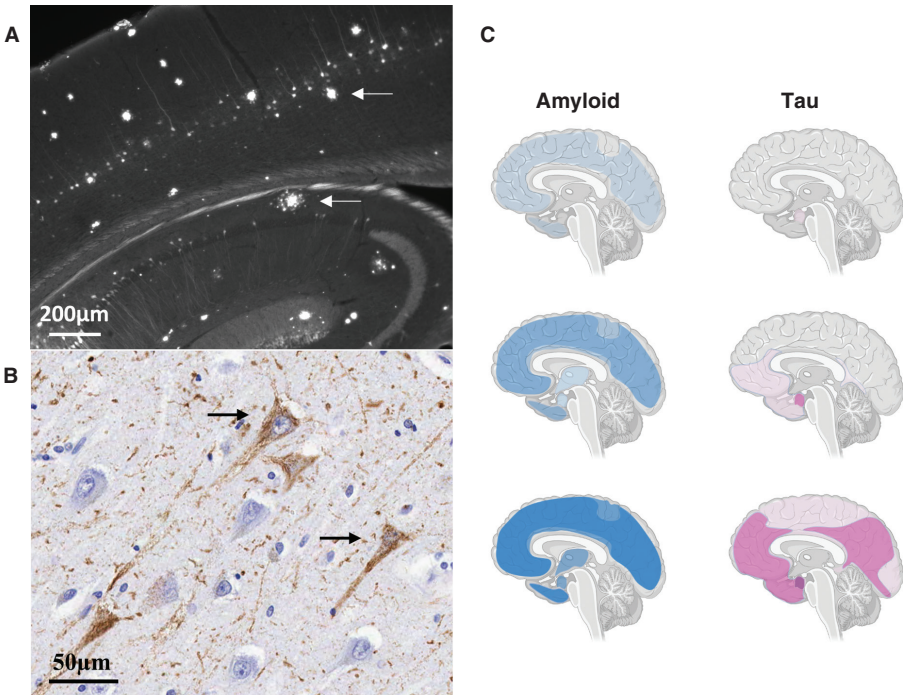

Figure 1. Amyloid and tau pathology. (A) Thioflavin S staining of Aβ plaques in the cortex of a CRND8 APP transgenic mouse. (B) AT8 staining of neurofibrillary tau tangles (NFTs) within an aged human CA1 region of the hippocampus. (C) The spread of amyloid and tau pathology throughout the brain during AD, adapted from Braak and Braak 1991 (83).

composed of paired helical fragments (PHFs) of tau fibrils approximately 20 nm in diameter (Figure 2). Like plaques, they spread throughout the brain as disease progresses, beginning near the entorhinal cortex. Braak staging is commonly used as a means of defining the progression of disease as determined by tau pathology. In stages I–II, tangles appear in the trans-entorhinal region; in stages III–IV, tangles have spread to the limbic system and start to show in the neocortex; in stages V–VI, pathology is present throughout the neocortex (83) (Figure 1). In addition to AD, several other neurodegenerative diseases are classified as tauopathies due to the presence of NFTs; these include Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration and frontotemporal dementia (FTD) (99). While aggregates of amyloid and tau have both been associated with neuronal loss and toxicity, they have a poor correlation with cognitive decline as AD progresses. On the contrary, the loss of synapses is one of the strongest correlates to cognitive decline in AD (100). Familial cases and PET imaging have allowed us to identify changes in both Aβ and tau prior to changes in brain structure and symptom onset (101). A combination of psychological and cognitive testing, scans and CSF and blood tests (to rule out other neurological disorders) are required to obtain the diagnosis of AD. Ultimately though, definitive confirmation of the disease requires post-mortem histopathology.

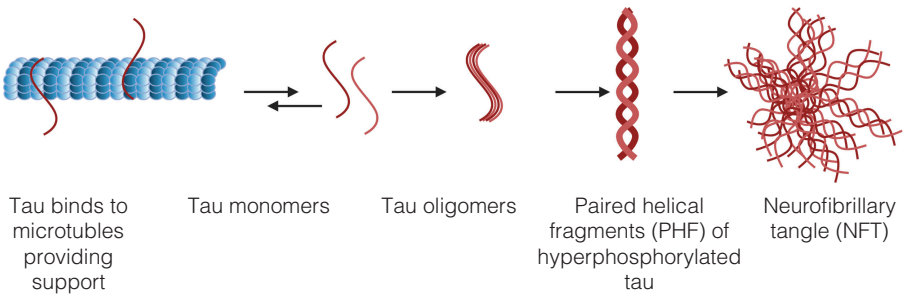

Figure 2. Microtubule-associated protein Tau (MAPT) aggregation results in the accumulation of neurofibrillary tau tangles (NFTs). Tau is believed to play a role in the stabilization of microtubules. Hyperphosphorylated tau polymerization leads to the creation of insoluble paired helical fragments (PHFs), which further aggregate into NFTs.

PATHOGENESIS

The mechanism of AD pathology and neuronal loss remains elusive. The roles of both Aβ and tau have been extensively researched in the past few decades, yet we are still unsure of their role in disease. A variety of mechanisms have been proposed to explain what occurs in the pathogenesis of AD. It is possible that different combinations of risk factors in different patients activate the disease in different ways, and that these converge on a common pathway of degeneration.

Aβ and APP

The amyloid hypothesis remains the dominant hypothesis in AD research due to the causal mutations found in both *APP* and presenilin genes. APP is processed via either the amyloidogenic or non-amyloidogenic pathway. For Aβ, APP is sequentially cleaved by the β- and γ-secretases, releasing the peptide into the cytosol (Figure 3). Functions of APP and Aβ are largely unknown, but they are thought to play a role in signal transduction for neuronal development, growth and survival (102, 103). While genetic mutations may explain Aβ accumulation in EOAD, it is still unclear how this occurs in LOAD. Aβ accumulation has been proposed to cause neuronal death via a number of mechanisms, including excitotoxicity, synaptic disruption, oxidative stress and mitochondrial dysfunction. Excitotoxicity can occur when NMDA receptors are continually activated, either by Aβ directly or by a downstream mechanism. In conjunction with synapse loss, both AD patients and animal models show reductions in the synaptic proteins synaptophysin and PSD-95 (104–108). Aβ oligomers accumulating in an AD brain (109) may be even more toxic than fibrils or plaques. Soluble oligomers appear to amass in a different manner compared to plaques and appear early in pathogenesis (110). Oligomers can disrupt cognitive function (111) and inhibit long-term potentiation (LTP) (112) *in vivo*, and can be neurotoxic (113) *in vitro*. Interestingly, oligomers tend to cluster near synapses (114) and can induce synapse loss and dysfunction (115). It has also been suggested that changes in another APP

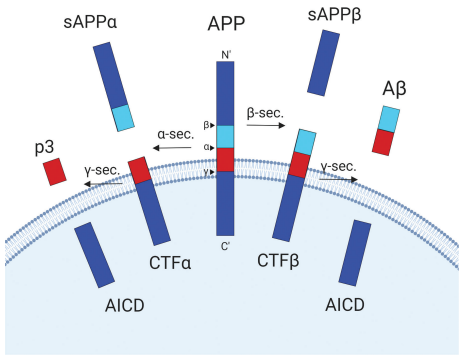

Figure 3. Post-translational processing of Aβ precursor protein (APP) is thought to occur at the cell surface or within endosomes. It includes cleavage by either α- then γ-secretase (non-amyloidogenic), or β- then γ-secretase (amyloidogenic pathway).

processing product could be a contributor to AD (103). Though many APP mouse models present with aspects of AD pathology, most fail to fully recapitulate the neurodegeneration seen in the human AD brain. While this most likely reflects inter-species differences, it also raises questions about the relative importance of APP/Aβ in driving dementia (116).

NFTs and Tau

While no *MAPT* mutations are associated with AD, causal mutations in tau have been found for other neurodegenerative diseases such as FTD, suggesting that tau dysfunction and aggregation can be neurotoxic. Tau's major role is thought to be that of a cytoskeletal protein, interacting with tubulin to help assemble and stabilize microtubules (117). In humans there are six isoforms of tau generated by alternative splicing of exons 2, 3 and 10. The incorporation of exon 10 leads to four microtubule-binding repeats (4R tau) instead of three (3R tau), altering how tightly the protein binds to microtubules and its propensity to aggregate (118). Healthy adult humans express similar amounts of 3R and 4R tau. Research has shown that the ratio between the two may impact disease, with higher 4R isoforms leading to greater degeneration. In AD, there is a higher ratio of 4R to 3R, and reported downstream consequences include transcriptional alterations in the Wnt signaling pathway (119) and altered axonal transport (120). Prior to NFT formation, tau becomes hyperphosphorylated, and tau phosphorylation not only plays a large role in regulating tau function, but could be the key change resulting in the accumulation, and potential toxicity, of this protein. In fact, multiple tauopathy mutations cause tau to be more readily phosphorylated (117).

Mutant tau mouse models have shown that mutations in this gene can result in severe neurological phenotypes (121, 122). Tau has been hypothesized to induce neurotoxicity via loss of function, gain of function and/or mis-localization. Loss of function of tau occurs when tau is no longer able to stabilize microtubes having an impact on neuronal cytoskeleton, and similarly could lead to deficiencies in axonal transport (123, 124). Higher levels of tau have also been shown to

inhibit vesicle and organelle trafficking, including those carrying APP, and increase levels of oxidative stress (125), as well as have an effect on axonal transport (126). The mis-localization of tau to dendritic spines has been shown to effect cognition and synapses *in vivo* (127, 128). As with APP, it remains unclear as to exactly how tau influences disease progression, but interestingly, Aβ induced toxicity and impairment in LTP has been found to be a requirement for the presence of endogenous tau (129, 130). It has also been suggested that tau and Aβ work together to result in transcriptional deficits (131) and synaptic changes (132) in AD.

Mitochondrial dysfunction and oxidative stress

One of the many processes that is compromised in AD is mitochondrial function. Alterations in mitochondrial morphology, number and transport, reduced cytochrome oxidase activity, deficiencies in metabolic proteins, changes in mitochondrial membrane potential and an increase in oxidative stress have been observed in AD (133, 134). Neurons are highly dependent on mitochondria, and mitochondria accumulate at synapses, helping to power their high metabolic demand. The high level of ROS production which occurs at synapses, in conjunction with insufficient antioxidants, can lead to oxidative stress (134). In addition, the brain is composed of high levels of cholesterols, which are also very vulnerable to oxidative damage (135). Thus, the high energy demands of the brain and its high lipid concentration naturally put it at risk for oxidative damage. Rather than aging driving amyloid pathology, as in the case of the amyloid hypothesis, the mitochondrial cascade hypothesis proposes that genetic and environmental factors determine the rate of mitochondrial decline, which in turn determines the rate of aging and subsequently AD (133). In terms of EOAD, APP or Aβ induces mitochondrial deficits, inducing an increase in the rate of aging, thus making some people susceptible to AD. This has been suggested as a potential link between EOAD and LOAD pathogenesis (136). Supporting this hypothesis, Thy-1-APP mice show reduced mitochondrial membrane potential and ATP synthesis and increased ROS production (137). Similarly, transgenic APP mice have shown an increase in Aβ within synaptic mitochondria, leading to dysfunction and oxidative stress prior to plaque accumulation (138). Paradoxically, oxidative stress, a by-product of mitochondrial deficiency, has been known to affect β-secretase activity (139), which in turn could alter Aβ production.

Insulin

Insulin resistance and a decrease in insulin receptors have been observed in the AD brain (140). Late stages of diabetes also result in insulin resistance in the brain. As cells are heavily dependent upon glucose metabolism for energy production, this can lead to energy deficiencies, potentially leading to oxidative stress. It has also been shown that insulin plays a role in neurotransmission (141) and can be neuroprotective during insults such as ischemia (142). Additionally, it has been reported that insulin and metabolic inhibitors result in increased levels of β-secretase in both wild-type and Tg2576 mice (an APP transgenic model). In Tg2576 mice, this also resulted in an increase in Aβ levels (143). Yet, as others report a protective role of insulin, it is likely that there is a certain level of this hormone which allows the brain to function optimally.

Hypoglycemia and vascular dysfunction

In addition to insulin resistance, the link between diabetes and AD could be due to changes in metabolic proteins, glucose receptors/transporters or even hypoglycemia due to over-medication. Glucose metabolism decreases in the normal aging brain (144) and even further in the AD brain (145). It has also been reported that there is a decline in the expression of glucose transporter at the blood brain barrier (BBB) in both AD patients and animal models of AD (146, 147), as well as in aged wild-type mice (147, 148). In addition, insulin-induced hypoglycemia has also been shown to cause neuronal death *in vitro* and *in vivo* (149). Glucose deprivation can elevate tau levels *in vitro* (150), and hypoglycemia has also been linked to increases in oxidative stress (151). Hypoglycemia could also be the link between cardiovascular and cerebral-vascular diseases and dementia, but whether it be hypoglycemia, hypoxia, a change in another blood component or a combination of these which increases one's risk of disease is still unknown. Finally, abnormal angiogenesis and alterations of vasculature, including changes in blood flow, have been shown in AD patients and animal models of the disease (152–154).

Inflammation

The role of inflammation is a more recent topic of interest in the AD field. As discussed previously, people with inflammation are more likely to develop dementia, and dementia patients with higher levels of inflammatory markers tend to deteriorate more rapidly. Studies in animal models have shown that inflammation can result in cognitive impairment (155), as well as neuronal damage and synaptic loss *in vivo* and *in vitro* (156–159). Although inflammation and the activation of microglia are thought to play a neuroprotective role in acute circumstances, in the long term, this may lead to neurotoxicity, and an increase in Aβ load (155, 160, 161). Aβ itself is thought to activate microglia, attracting them to plaques and enhancing phagocytosis (162–164). Potentially, microglial response to Aβ is protective, but after chronic activation, the microglia begin to play a detrimental role, resulting in a feed-forward loop of degradation (54). Similarly, it has been shown that increased ROS levels increase inflammatory markers, and that immune cells influence the production of ROS (165–168), demonstrating the complex interplay between Aβ, oxidative stress and inflammation.

Tau pathology also appears to be influenced by (169, 170), and have an effect upon (171, 172), inflammation. Research looking at the ability of microglia to phagocytose tau aggregates is conflicting, potentially due to microglia playing an initial role in clearance, but losing their ability to maintain this over extended periods (173). And finally, it has been reported that altering expression of TREM2, which plays a role in inflammation, may have an effect on Aβ levels and plaque-associated macrophages (174).

Ubiquitin-proteasome system

The ubiquitin-proteasome system (UPS) is involved in the degradation of misfolded and excess proteins. It is particularly important for synapse function, where there is high protein turnover (175). Proteins to be degraded go through an

enzymatic process where they are labelled with a polyubiquitin chain which is recognized by the proteasome (176), and subsequently broken down. The proteasome targets monomeric proteins, so is not thought to break down plaques or tangles, but both have been shown to potentially inhibit proteasome activity (177). This could lead to a toxic build-up of excess and misfolded proteins in the brain, and more specifically synapses.

Autophagy lysosome pathway

Autophagy and lysosomal dysfunction are also proposed mechanisms of AD pathogenesis. Autophagy is involved in tau clearance (178), and plays a role in both the generation and clearance of Aβ. APP amyloidogenic processing involves trafficking through the endo-lysosomal pathway (179). Several genes implicated in AD including *BIN1*, *SORL1* and *PICALM* are involved in endosomal recycling, and studies have reported that each may directly play a role in APP endosomal processing (95, 180, 181).

Cholinergic hypothesis

The cholinergic hypothesis was one of the first proposed theories on the manifestation of AD (182, 183). This came to fruition due to abnormal levels of acetylcholine in the AD brain. Cholinergic neurons of the basal forebrain are one of the earliest affected by AD and there is a decrease in choline acetyltransferase (ChAT) transcription and activity in remaining neurons. Studies have also shown a relationship between acetylcholinesterase (AChE) and Aβ accumulation (182). However, as the AD field has moved forward there has been difficulty in linking acetylcholine with other AD pathologies. Indeed, pyramidal neurons are lost in greatest numbers in regions with plaques and tangles and these are, for the most part, glutamatergic neurons (184).

CONCLUSION

Although we have amassed a vast amount of knowledge in the search for a central, unifying mechanism behind dementia and AD, we are still lacking suitable therapies to help slow down the progression of disease. The amyloid hypothesis remains the dominant theory, yet drugs aimed at lowering Aβ levels have been largely unsuccessful. The possibility of NFT and plaque-load being correlative rather than causative with disease progression is entirely possible. There is much overlap between many of the risk factors, both genetic and environmental, and the known pathogenesis, highlighting the complexity of dementia. Similarly, we lack a firm understanding of how familial EOAD and sporadic LOAD ultimately produce the same neurodegenerative outcome. By enhancing our understanding of AD etiology, pathology and pathogenesis, we hope to one day find an effective therapy.

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