Amyloid, tau, pathogen infection and antimicrobial protection in Alzheimer’s disease – conformist, nonconformist, and realistic prospects for AD pathogenesis

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Abstract

**Background:** Alzheimer’s disease (AD) is a fatal disease that threatens the quality of life of an aging population at a global scale. Various hypotheses on the etiology of AD have been developed over the years to guide efforts in search of therapeutic strategies.

**Main body:** In this review, we focus on four AD hypotheses currently relevant to AD onset: the prevailing amyloid cascade hypothesis, the well-recognized tau hypothesis, the increasingly popular pathogen (viral infection) hypothesis, and the infection-related antimicrobial protection hypothesis. In briefly reviewing the main evidence supporting each hypothesis and discussing the questions that need to be addressed, we hope to gain a better understanding of the complicated multi-layered interactions in potential causal and/or risk factors in AD pathogenesis. As a defining feature of AD, the existence of amyloid deposits is likely fundamental to AD onset but is insufficient to wholly reproduce many complexities of the disorder. A similar belief is currently also applied to hyperphosphorylated tau aggregates within neurons, where tau has been postulated to drive neurodegeneration in the presence of pre-existing Aβ plaques in the brain. Although infection of the central nerve system by pathogens such as viruses may increase AD risk, it is yet to be determined whether this phenomenon is applicable to all cases of sporadic AD and whether it is a primary trigger for AD onset. Lastly, the antimicrobial protection hypothesis provides insight into a potential physiological role for Aβ peptides, but how Aβ/microbial interactions affect AD pathogenesis during aging awaits further validation. Nevertheless, this hypothesis cautions potential adverse effects in Aβ-targeting therapies by hindering potential roles for Aβ in anti-viral protection.

**Conclusion:** AD is a multi-factor complex disorder, which likely requires a combinatorial therapeutic approach to successfully slow or reduce symptomatic memory decline. A better understanding of how various causal and/or risk factors affecting disease onset and progression will enhance the likelihood of conceiving effective treatment paradigms, which may involve personalized treatment strategies for individual patients at varying stages of disease progression.

**Keywords:** Amyloid-beta, Alzheimer’s disease, Amyloid hypothesis, Tau hypothesis, Pathogen hypothesis, Viral infection, Antimicrobial protection
**Background**

Alzheimer’s disease (AD) is the number one cause of age-related dementia, currently with no effective therapy. It represents an imminent threat to the health-span of the senior population. With unprecedented growth of a globally aging population, AD will become an increasing burden to society if left unchecked [1–6]. The clinical manifestations of AD appear with incidental forgetfulness at initial stages, eventually progressing to mild cognitive impairment to full-blown AD with noticeable difficulties in cognitive functions such as memory, planning and organizing. Patients at later stages of AD not only suffer severe decline in cognitive functions, but also may experience drastic personality and behavioral changes, with an eventual incapacity to independently carry out daily functions [7–10]. Although these clinical symptoms may be indicative of AD onset, definitive diagnosis requires the detection of three pathological hallmarks in the brain, namely, extracellular amyloid (plaques) composed of Aβ peptides (graded by Thal phases [11, 12]), intracellular neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau (categorized through Braak staging [13–15]), and degeneration in brain regions such as the entorhinal cortex, hippocampus, and cerebral cortex during late stages of onset [7, 16]. Previously, these pathological features associated with AD could only be confirmed by postmortem analysis. With rapidly evolving developments in the brain imaging field, it is currently possible to observe amyloid and tau aggregates and degeneration within the central nervous system (CNS) during ante-mortem stages [17–22]. Given the current advances in neuroimaging, together with the identification of diagnostic biomarkers in cerebrospinal fluid (CSF) and/or blood [23–31], the possibility of diagnosing and monitoring AD from early onset to terminal stages of AD progression, and characterizing the efficacy of various therapeutic treatments has become more promising.

It has been debated whether pathological hallmarks, such as plaques and NFTs have an active role in driving disease progression, or whether they merely reflect progression and severity of the disease. Postmortem studies and neuroimaging results indicate the appearance of pathological features associated with AD in the brain decades before the onset of cognitive symptoms [7, 19, 32]. Should the pathologies function as drivers of the disease, removal or reduction of these pathological features will naturally be beneficial in preventing, slowing down or even reversing the disease progression. In the case where the pathological hallmarks are merely byproducts of disease onset, then targeting these markers would have little or no beneficial effect, necessitating the search for the primary trigger for AD onset.

Multiple hypotheses have evolved regarding the primary initiator of AD onset based on clinical observations, which is supported by results derived from various experimental model systems. In this review, we will briefly discuss four influential hypotheses for AD: the amyloid cascade hypothesis that has dominated the field for decades, the tau hypothesis that gained much more attention following repeated clinical failures using Aβ-centered targeting strategies, the pathogen hypothesis that has gained supporting evidence from recent publications, and the “antimicrobial protection hypothesis” that revisits the amyloid hypothesis in the context of microbial pathogen response. Although other important AD-related hypotheses exist which involve mitochondrial/oxidative stress, insulin-resistance, cerebrovascular dysfunction, and neuroinflammation, etc., we defer our discussion here to many excellent reviews that comprehensively discuss these topics (e.g. [33–49]).

Due to the vast literature related to the topics covered in this review, we are limited to the number of studies cited in our discussion below; thus, we apologize to the authors whose contributions have advanced the field, but whose work are not referenced herein.

**Main text**

**Amyloid cascade hypothesis**

The amyloid cascade hypothesis (referred to as the “amyloid hypothesis” hereon) has undoubtedly had the greatest influence on AD research for nearly three decades. The amyloid hypothesis originally proposed a role for amyloid plaques as a causal initiator for all downstream pathological events in AD onset, including NFTs and neurodegeneration in the CNS [50]. The hypothesis has been modified since to propose a primary role for soluble Aβ oligomers as the critical driver in AD progression [51–56]. The amyloid hypothesis lends strong support from genetic evidence in familial AD (fAD) comprising a small percentage of hereditary AD cases and countless experimental model systems. However, the key question remains whether familial AD is equivalent to sporadic AD (sAD), representing over 95% of all AD cases. Several recent reviews have summarized arguments supporting and contradicting the amyloid hypothesis [57–60].

Amyloid plaques are pathological aggregates comprising amyloid-β (Aβ) peptides, derived from sequential proteolysis of amyloid precursor protein (APP) by β- and γ-secretases. Autosomal dominant mutations all reside in three genes, APP, PSEN1 and PSEN2, with the latter two encoding the catalytic subunit of the γ-secretase complex [2, 61–63]. These mutations are invariably linked to increased generation/accumulation of the aggregation-prone Aβ42 peptide. While sporadic AD manifests usually at the age of seventy to eighty or
older, fAD mutations may trigger early AD onset (before the age of 65 years old) [64], and sometimes can be as early as age 30 in the mutation carriers (https://www.alzheimers.net/10-13-14-early-onset-alzheimers/). Although fAD patients represent less than 5% of the AD population, their pathological and clinical characteristics provide critical genetic evidence that increased Aβ42 levels in the CNS can almost invariably aggravate AD onset. Aβ accumulation in sporadic AD has been thought to be primarily derived from reduced Aβ clearance rather than enhanced Aβ generation from clinical analyses in human CSF [65]. In support of the notion that sAD is associated with impaired Aβ efflux in the CNS, expression of human apolipoprotein E4 (apoE4), the most potent risk factor for sAD characterized to date, is seen to potently reduce Aβ clearance and increases Aβ plaque load [37, 66–68]. Thus, an imbalance between Aβ production and clearance potentially leads to Aβ accumulation in both familial and sporadic cases of AD, where different mechanisms drive elevations in Aβ levels in the CNS.

With respect to how Aβ accumulation can trigger AD onset, thousands of publications have proposed various mechanisms describing how Aβ can mediate neuronal dysfunction in vitro and in vivo. A non-exhaustive list of toxic effects associated with Aβ include impairments in synaptic plasticity and synaptic loss as observed in human AD brain [54–56, 69–72], dysregulation of calcium homeostasis which occurs prior to synaptic impairment [73–80], dysfunctional axonal trafficking [81–85], functional perturbation of cellular organelles such as lysosomes, endoplasmic reticulum, Golgi and mitochondria [86–95], and induction of astrogliosis and neuroinflammation [96–103]. Although most mouse models expressing human β-amyloid fail to induce NFTs comprising mouse tau within the murine lifespan [104–106], the presence of Aβ-oligomers or APP with fAD mutation(s) is invariably associated with increased tau pathology in tau transgenic mice [107, 108], tauopathy models in rats [109], non-human primates [110], and in 3D human iPSC (induced pluripotent stem cell)-derived neuronal cell culture systems [111–114]. Moreover, neurodegeneration has been observed in human iPSC-derived neurons grafted into the brain of 5xFAD transgenic mice [115], suggesting that human neurons may be more susceptible to Aβ toxicity compared to mouse neurons. In short, regardless of whether Aβ accumulation is caused by amyloidogenic APP processing or reduced Aβ clearance, a vast sum of literature supports the role of Aβ elevation in triggering deleterious events associated with neurodegeneration.

Despite this, the amyloid hypothesis is also unable to satisfy many observations that counter the significance or potency of Aβ in sAD [58, 60, 116–118]. Inconsistencies with respect to a primary role for Aβ in triggering AD onset include: [1] poor correlation between amyloid plaque load and severity of cognitive impairment/degeneration in human brain; further, many individuals feature an abundant amyloid plaque load in the brain without manifesting deficits in cognitive function [119–126], [2] most human β-amyloid mouse models are not associated with NFT pathology as mentioned above, and [3] many Aβ-centered clinical trials show little or no efficacy (as reviewed in [116, 127, 128]). Alternative explanations may preclude outright rejection of the amyloid hypothesis [57, 58, 129, 130]; it may be more favorable to modify or elaborate on the amyloid hypothesis to accommodate its inability to comprehensively predict the outcomes mentioned above. For example, a potential delay in Aβ-mediated proteotoxicity due to intrinsic neuroprotective mechanisms within the brain would account for cognitively non-impaired individuals with elevated amyloid loads. A pathogenic synergy may be apparent between Aβ and tau, which would also explain a poor correlation between amyloid load and cognition: the formation of neuritic plaques which feature amyloid filaments that coincide with swollen/dystrophic neurites correlate with early cognitive impairment more accurately than amyloid or tau pathology alone [131, 132]. Animal models may fail to fully recapitulate human AD pathology due to the cross-species differences in tau, and/or the short life-span of rodents in comparison with human beings. Failures in Aβ-targeted clinical trials may result from the disease stages of the participants upon treatment, or specificity of the Aβ species targeted by certain drugs in the trial, in addition to many other factors (e.g. drug potency). With promising results from a Phase II clinical trial characterizing protective effects of an anti-Aβ protofibril antibody (BAN2401), targeting the toxic forms of Aβ may yet be protective: News release from Eisai and Biogen indicates a dose-dependent reduction in plaque load and reduced clinical decline in drug-treatment groups compared to placebos in an 856 mild cognitive impairment (MCI) patient cohort (http://investors.biogen.com/news-releases/news-release-details/eisai-and-biogen-announce--detailed-results-phase-ii-clinical).

In summary, it is likely that Aβ and amyloid plaques are necessary but may not be sufficient to initiate all the downstream events required for AD pathogenesis, especially in sporadic AD. However, Aβ pathology is unlikely to be an inconsequential epiphenomenon in AD pathogenesis, despite instances where seniors accumulate plaques in the brain for decades without showing overt cognitive deficits. In sporadic AD, dysregulated Aβ homeostasis may initiate late in life and gradually precondition the brain to be more susceptible to other internal and/or external insults during aging, while in fAD, chronic imbalance in Aβ levels derived from inherited amyloidogenic dominant mutations may erode
endogenous defense mechanism and manifest AD pathology to an early AD onset. Despite certain inadequacies with the amyloid hypothesis, strategies underlying therapeutic AD drug design will need to consider newly discovered physiological roles for Aβ in microbial infection and pathogen response as reviewed in the discussion of “the antimicrobial protection hypothesis” below.

**Tau hypothesis**

Given that Aβ pathology correlates poorly with cognitive decline, a central role for tau in driving AD onset has also been considered. The tau hypothesis proposes that tau is a fundamental pathogenic initiator that triggers all the downstream pathological events during AD onset. Unlike amyloid accumulation, pathological Braak stages - characterized tau tangles primarily comprising hyperphosphorylated tau, correlates more tightly with cognitive impairment and AD severity [13, 14, 120, 133–135]. The progressive onset of tau pathology and distinctive spatial propagation of tau tangles characterized using conventional postmortem pathological analysis and recent methods in tau PET imaging, implicates tau as a better prognostic indicator for neurodegeneration and cognitive deficits in AD compared to amyloid pathology [13, 14, 136–141]. Contrary to frequently observed instances of high brain amyloid with no apparent cognitive impairment, the occurrence of non-symptomatic individuates with advanced Braak pathology (Braak stages V-VI) is comparatively rare [142, 143]. Moreover, van Rossum et al reported that CSF total-tau and phosphorylated-tau (which are markers of CNS injury) are associated with rapid progression from MCI to late-stage dementia [144, 145]. These observations indicate that tauopathy can be a key factor driving AD onset and progression. This notion is supported by studies demonstrating a critical role for tau in mediating toxic effects derived from Aβ using tau deletion models in vitro and in vivo [146–153]. Should tau be an essential driver in AD onset, therapeutically targeting tau may effectively attenuate disease onset and AD pathogenesis.

Tau is a soluble microtubule-binding protein localized primarily to axons in adult neurons under normal physiological conditions. Tau directly binds microtubules, thereby promoting its assembly and stability. Six tau isoforms are derived from splice variation, where tau is also subject to regulation through various posttranslational modifiers (reviewed in [154–159]). Besides its predominant localization to axons, tau has also been detected at lower levels in dendrites, and at the plasma membrane, Golgi complex, rough endoplasmic reticulum, nucleus and nucleolus, (reviewed [159–161]). Tau function extends beyond microtubule-binding, and includes roles in regulating synaptic function [161], protecting RNA and DNA in early stress response [162, 163], and affecting nucleocytoplasmic transport via direct interaction with nucleoporins [164]. A majority of studies so far have focused on tau hyperphosphorylation, since pathological tau phosphoforms are prone to aggregation and feature various deficiencies in physiological functions, in addition to driving dominant effects in toxicity [165–167]. In addition to hyperphosphorylation, tau acetylation and glycosylation can also aggravate AD-associated tau pathology, whereas tau O-GlcNAc modification is likely protective and is seen to attenuate tau pathology in several transgenic models [168–175]. Additional posttranslational modifications such as truncation [176–179], ubiquitylation [180, 181], SUMOylation [182], and nitration [183–185] have been reported for tau, with aberrant modifications found to be associated with either hyperphosphorylation, increased tau aggregation or mis-localization of tau in vivo or in vitro (recently reviewed [159, 186, 187]).

Pathological tau dysfunction is primarily thought to be derived from a loss in microtubule binding, thereby leading to many downstream events in cellular dysregulation such as impairment in mitochondrial transport and functions [188–192], synaptic deficits [170, 193–196], defective axonal transportation [197–200], and enhanced stress granule formation [201–208]. Tau dysfunction can also alter neurogenesis in various mouse models; a transgenic line expressing human tau features reduced adult neurogenesis prior to the formation of pathological tau aggregates [209]. Conversely, models expressing human tau constructs that are refractory to aggregation exhibit increased neurogenesis [210]. Interestingly, tau deletion confers resistance to impairments in neurogenesis induced by chronic stress compared to wild type littermates, implicating a role for tau in suppressing neurogenesis [211]. A role for tau in AD-associated neuroinflammation has also been proposed, where inflammation can either be protective or deleterious to CNS function depending on the duration and extent of the inflammatory response (e.g. recently reviewed in [212–215]). In addition to driving neuroinflammation, the formation and distribution of pathological tau aggregates may be consequently modulated through pro-inflammatory triggers [216–219]. Although tau aggregates have been proposed to spread through prion-like mechanisms [220], these models fail to explain certain spatiotemporal aspects of NFTs in human postmortem brain [221]. How tau aggregates propagate in the brain is still actively under investigation. As an intracellular protein component, tau spreading requires extrusion and uptake from the extracellular environment via exome-dependent or independent mechanisms as indicated by various assays in vitro and in vivo [222–226]. AD is also associated
with insulin resistance in the brain, which can both manifest in or occur independently of diabetes [227–230]; tau protein and insulin signaling pathways in the brain can also interact to exacerbate disease onset in aging and AD [231–233]. Future study will further define pathways and mechanisms by which tau can potentially modulate AD onset.

Although mounting evidence indicates an indispensable role for tau in AD, the tau hypothesis is still subject to criticism. Importantly, while tau mutations have been found to be associated with human tauopathy disorders such as frontotemporal lobar degeneration with tau inclusions (FTLD-tau), Pick's disease, progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), and chronic traumatic encephalopathy, without amyloid accumulation [154, 234–237], these mutations are not linked to AD. This suggests that tau pathology may be induced as a downstream consequence of AD onset. However, hyperphosphorylated tau can be detected in the absence of tangles in young human brain as early as 14 years of age [14, 238, 239], where intraneuronal tau aggregates can be found across a large age group, indicating that tau pathogenesis is not necessarily dependent on age and AD-related toxicity. This also suggests that tau alone may not be a sufficient driver for AD onset. To complicate matters, the protective APOE variant in AD, APOE ε2, is associated with increased risk for tauopathy disorders such as PSP, CBD, and AGD [240–242]. Should tau be an upstream trigger for AD onset, it will be difficult to reconcile how protective APOE variants (APOE2) can be a risk factor for tauopathy. Several biomarker studies using human CSF demonstrate that ratios comprising Aβ42/total-tau and Aβ42/phospho-tau may accurately indicate transition from normal to mild cognitive impairment, and full AD onset [243–245], reiterating the importance of both markers in AD diagnosis. It is still currently unclear how Aβ and tau interact, and how these interactions lead to terminal cognitive phenotypes associated with AD. In the face of failures from amyloid-focused clinical trials, tau-targeting strategies have recently received growing attention. Although selective tau-aggregation blockers [246] or tau-reactive antibodies (https://clinicaltrials.gov/ct2/show/NCT00818662) have yet to succeed in meeting primary endpoints, additional efforts to develop active or passive vaccines and alternative strategies to modulate tau post-translational modification are being pursued [247] (recently reviewed in [59, 248]). Continued efforts are also currently being pursued with tau as an immune target; additional anti-tau antibodies are currently being developed and tested in preclinical stages (e.g. [249–254]).

Similar to the role for Aβ in the context of the amyloid hypothesis, tau appears to also be necessary but insufficient as a primary initiator for AD. This is complicated by the observation that cognitively normal individuals can manifest brain amyloid or tau pathologies, or a combination of both [255, 256], which necessitates the identification of other mediators and modulators of AD.

The “pathogen hypothesis” and “Antimicrobial Protection Hypothesis”
The “pathogen hypothesis”, or “infection hypothesis” in AD, suggests that chronic infection by viral, bacterial, and/or fungal pathogens may be a trigger for sporadic AD onset during aging. Candidate pathogens have been proposed in the literature over the years, including oral herpes - herpes simplex virus type 1 (HSV-1), genital herpes HSV-2, human herpesvirus 6A (HHV-6A) and HHV-7, Epstein Barr virus (EBV), cytomegalovirus, human immunodeficiency virus (HIV), gut bacteria, liver bacteria Helicobacter pylori, periodontal pathogens (bacteria linked to gingivitis), bacteria Chlamydiaphila pneumoniae that causes pneumonia, and others (recently reviewed in [257–261]). These pathogens may invade the CNS directly by translocating across the blood-brain-barrier and/or the brain-CSF barrier, through the trigeminal nervous system and oral-nasal pathway, or by penetrating the gastrointestinal tract [258, 262–267]. Moreover, pathogens may also secrete toxins circulating to the brain to dysregulate neurological functions associated with AD [260, 261, 268–277].

This concept that AD may be derived from infection was initially postulated by Dr. Oskar Fischer, who was regarded as Dr. Alzheimer’s rival when he independently reported the observation of pathological hallmarks associated with 12 dementia cases in 1907 [278–280]. Evidence in support of the pathogen hypothesis first appeared in 1991 from a group led by Dr. Ruth Itzhaki, who has become one of the strongest advocates of the pathogen hypothesis in recent decades. This hypothesis was not well-accepted in the AD field until recent multi-omic studies surveying large populations have provided additional support to the infection hypothesis [281, 282].

The pathogen hypothesis has gained support from a recent study using large datasets across multiple independent clinical cohorts [282]. Combining multi-omic analyses on genomic, transcriptomic, and proteomic datasets, the study observed frequent viral infection in normal human brains. Interestingly, viral DNA and RNA from certain viral strains, namely human herpesvirus 6 (HHV-6) and herpesvirus 7 (HHV-7), were more abundant in AD samples, where viral DNA and RNA abundance were found to correlate with aggravated AD pathology [282]. AD risk has also been reported in association with chronic periodontitis in a ten-year retrospective, population-based study from
Taiwan in 9291 patients diagnosed with chronic periodontitis in comparison with 18,672 non-infected patient controls [283]. Another recent study tracking HSV infection in 8362 infected individuals vs 25,086 sex- and age-matched controls in a Taiwan population observed that HSV infection significantly correlated with a higher risk of dementia later in life, where anti-herpetic treatment can greatly reduce risk of dementia onset [281]. Although no definitive conclusions can be made with respect to a causal role for HSV infection in AD, since APOE status and clinical AD characterization is lacking in the study, dramatic reduction in dementia risk with anti-herpetic treatment suggests that viral infection may be a serious risk factor that increases likelihood of dementia onset if left untreated. These recently discoveries have drawn increased attention to the pathogen hypothesis in AD which has been viewed skeptically for past two decades.

Although these recent findings do not sufficiently provide evidence as to whether viral infection is definitively causal to AD onset, these results provide compelling indication that viral infection may be a prevalent risk factor in dementia, and implicate a potential role for anti-viral strategies in AD therapy. The anti-viral agent valacyclovir (Valtrex) has been approved for testing in clinical trials by the FDA earlier this year for patients testing positive for herpes simplex virus-1 (HSV-1) or HSV-2 with mild dementia potentially due to AD [https://clinicaltrials.gov/ct2/show/NCT03282916].

Skepticism towards the pathogen hypothesis in the AD field likely stems from early published studies that derived data from small cohorts and sample sizes, and contradicting results from different groups; in addition, some studies fail to account for APOE status in AD and control groups. For example, the first study characterizing the presence of HSV-1 DNA in human postmortem brain samples was based on postmortem tissues from 8 AD patients and 6 normal controls, where HSV-1 DNA was detected in both AD and control samples [284]. Although, Dr. Itzhaki’s group [284–290] together with others [291–296] have since confirmed the presence of viral DNA in human brain from different cohorts, conflicting results have been reported as to whether viral infection positively correlates with AD. For instance, while results from Dr. Itzhaki’s group indicates a positive correlation between viral infection and AD onset, other reports failed to determine any correlation between viruses and AD [295–297]. HSV1 viral DNA is also found to be prevalent in human trigeminal ganglia, a sensory ganglion extending into the human brain; HSV1 infection has been reported across all age groups (from 0–10-year old up to over 90 age groups) and appears to be independent of gender [298]. Since studies have shown that women are more prone to AD and given that HSV1 infection appears to be gender independent, this may suggest that viral infection may not be a primary trigger for AD onset.

The validity of the pathogen hypothesis is further confounded by differential effects of APOE ε2, ε3, and ε4 alleles encoding apolipoprotein E2, E3, and E4 (apoE2, E3 and E4) variants. Although mechanisms for APOE-dependent AD onset remain under active investigation, it has been well established so far that APOE ε4 is the strongest risk factor for sAD, while ε2 appears to be protective in AD onset (recently reviewed in [37, 299]). Exactly how different apoE isoforms may affect viral infection in the body and CNS remains unclear; which makes it difficult to delineate contributions from viral infection to AD vs those from different apoE isoforms. For example, results indicating a positive correlation between HSV1 infection and AD risk comprises an imbalance in APOE ε4 carriers in AD and controls; where the percentage of APOE ε4 alleles was found to be > 10 times higher than controls in a study from 46 AD patients and 77 non-AD donors [300]. With respect to whether viral DNA correlates with amyloid plaque formation in AD [290], 5 out 6 AD patients were APOE ε4 carriers, where there was none APOE ε4 carrier in the control cases (the control group was made up of one APOE ε2 carrier and four APOE ε3/ε3 individuals). Although results from these studies indicate a positive association between HSV1 and AD, these results remain correlating and fail to establish viral infection as a primary trigger for AD onset. For instance, viral infection could possibly be a consequent event rather than instigator of AD onset; given that HSV1 DNA is localized to amyloid plaques, the proportion of HSV1 DNA in amyloid plaques in control patients was significantly reduced compared to AD brain as a consequence of lower plaque loads [290]. Alternatively, APOE alleles may modulate viral entry into the brain, whereby viral infection would be a consequence of APOE status rather than a causal factor for AD onset. Given these limitations, it is difficult to conclude that viral infection as an independent risk factor for AD, let alone causing AD.

In addition to the potential association of HSV1, HHV-6, and/or HHV-7 with AD, the gastrointestinal microbiome has also been proposed to play a role in AD pathogenesis by affecting the brain-gut-liver axis. Vogt et al. describe decreased Firmicutes and Bifidobacterium and increased Bacteroidetes in fecal samples from AD patients in comparison with controls (n = 25/group) [301]. Xu and Wang have identified AD-associated metabolites using an integrated computational approach utilizing publicly available databases including the human metabolome database [302]. MahmoudianDehkordi recently reported reduction of primary bile acid (cholic acid) and elevated bacterial-derived secondary bile acid (deoxycholic acid) in serum samples from AD patients [303]. Dysbiosis of microbiota and viruses can produce
toxic metabolites that may breach the gut epithelial barrier, affect brain function, contribute to local and systemic inflammation, and cause dysregulation of tryptophan metabolism in the intestine that affect the production of various neurotransmitters including acetylcholine, gamma-aminobutyric acid (GABA), and serotonin (reviewed in [258, 304, 305]). Using a mouse amyloid plaque model, Minter et al have reduced amyloid plaque load in APP_SWE/PS1 transgenic mouse brain by combinatorial antibiotic treatment [306, 307]. Harach et al observed that germ-free APP transgenic mice exhibited drastically reduced plaque pathology [308]. These observational and in vivo experimental studies support the notion that microbiota (bacteria, viruses, and bacteriophages etc) inhabiting within human body can contribute to AD pathology.

Many other lingering questions remain with respect to the pathogen hypothesis, and we refer readers to several excellent recent reviews that explore various aspects of this hypothesis [259, 260, 277, 309].

In parallel with recent progress in support of the pathogen hypothesis, a protective physiological role for Aβ as an antiviral peptide has been discovered [310–314]. It was initially proposed by Soscia et al when they reported Aβ40 and Aβ42 peptides inhibit the overnight growth of 8 out of a total of 12 types of bacteria and fungi tested [310]. Later, two groups found that Aβ could also inhibit replication of H3N2 and H1N1 influenza A virus in vitro [313], HSV-1 replication in fibroblast, epithelial, and neuronal cell lines [314]. Initial evidence in vivo indicate that 5xFAD mice and Aβ-expressing transgenic nematodes (Caenorhabditis elegans) survive longer than the control groups after exposure to gut pathogens (yeast Candida albicans or bacteria Salmonella enterica serovar Typhimurium) [311]. APP-knockout mice, on the other hand, have shortened survival after pathogenic challenge [311]. A recent publication from Drs. Tanzi and Moir’s group provided further evidence to support a protective antimicrobial role for Aβ. Using 3D human neural cell cultures and 5xFAD mice, these researchers demonstrated that HSV-1, HHV-6A, or HHV-6B infection accelerated β-amyloid deposition, where Aβ inhibits HSV-1 infection in the host cells and prolongs host survival after HSV-1-induced encephalitis in 5xFAD mice [312]. The antimicrobial effect of Aβ is mediated via its heparin-binding domain. These in vitro and in vivo results strongly support the hypothesis that Aβ peptides play an important role in brain's innate immune system by entrapping invading pathogens, thereby protecting the brain from infection. The “antimicrobial protection hypothesis” in AD has been discussed extensively in a recent review article [315], detailing antimicrobial abilities of Aβ and drawing comparisons of Aβ with other well-known antimicrobial peptides (AMPs) [315]. Given that dysregulation of the other known AMPs can lead to host cell toxicity, AD may be triggered by chronic activation of sustained inflammation due to elevations in Aβ in response to an elevated microbial burden during aging.

In summary, evidence so far in support of the infection hypothesis indicates that the presence of viruses may be a risk for AD; however, due to the prevalence of pathogen existence within the human body throughout life, definitive evidence is lacking that infection is causal to AD. Similar to the amyloid hypothesis, the antimicrobial hypothesis indicates that Aβ accumulation is a key to AD pathogenesis. It is likely that sophisticated protective mechanisms have evolved for human brains to confer resilience to stress and dysfunction for decades in life. So far, multi-omics human data suggest HHV-6A and HHV-7 to be prominently associated with AD across 3 independent cohorts [282]. Defining the causal or consequential role of pathogen infection remains a challenge. The discovery of Aβ-mediated antimicrobial activity and pathogen-dependent effects in inducing Aβ aggregation have connected these two factors together with neuroinflammation, which represents a double-edged sword in AD pathogenesis. Human stem cell- or iPSc-derived 3D culture or organoid culture systems are possible experimental systems to study a role for pathogens in AD, in which exposures of different infectious agents can be clearly managed. Studying effects of pathogen in animal models may require sterile animal house facilities to control the effects from specific bacteria, viruses, or fungi in AD pathogenesis.

Conclusions & Future Prospective
Recent advances of the pathogen and Aβ-antimicrobial hypotheses have shifted an ever-evolving view of the etiological origin of AD. It provides novel insights for future therapeutic strategies in combining anti-amyloid strategies with anti-viral approaches to be tested in clinical trials. New discoveries published recently indicate that APP mRNA in the brain can be reverse-transcribed into DNA and reinserted into the genome, resulting in thousands of APP variants with point mutations, insertions, deletions and so on. This phenomenon is much more pronounced in brains of sporadic AD than those of non-AD controls [316]. These findings pose additional questions regarding whether viral infection has any contribution to the substantially high amount of APP variants in sAD brain. Authors of the paper also suggest that FDA-approved combined anti-retroviral therapy for HIV infection may be potentially effective in treating sAD, Down syndrome and fAD patients.

Many unanswered questions remain for AD pathogenesis; for example, do different isoforms of apoE and/or different apoE aggregation status (monomer, oligomer, and/or lipidated particles) play any role in modulating
antimicrobial Aβ activity? What are the physiological events or mechanisms that link Aβ and tau pathology in AD? In addition to Aβ, do tau oligomers, α-synuclein oligomers also confer any antimicrobial effects in infected cell types in the CNS? Should the infection model/antimicrobial model be valid, will chronic viral infection in the amyloid mouse models lead to tau pathology and neurodegeneration during aging, representing an improved model system for AD?

Unlike familial AD, sporadic AD may evolve from a combination of various genetic and environmental factors. Neuroinflammation, tau pathogenesis, and viral infection have all been implicated to play important roles in AD; however, these factors do not appear to be pathogenic triggers that are specifically relevant to AD. Thus, specific causal mechanisms that drive AD onset have yet to be clearly defined, which may lead to the identification of new therapeutic targets. It is now widely accepted that sporadic AD is a complicated syndrome. Future preventative and therapeutic approaches very likely require a personalized combination of different targeting strategies based on specific genetic profiles and preclinical or clinical stages at the time of diagnosis and treatment.

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HL drafted the manuscript; TYH and HL performed critical editing; CL and HZ participated in constructive outline, discussions, and editing. All authors read and approved the final manuscript.

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