Infectious etiology and amyloidosis in Alzheimer's disease: The puzzle continues

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Recent studies have renewed the debate on infectious etiology in late-onset Alzheimer's disease. Bocharova *et al.* reported that abundant expression of human beta amyloid (Aβ) in the mouse brain (5XFAD animals) failed to protect against acute herpes simplex virus type 1 infection relative to control mice. While this study does not confirm the antiviral actions of Aβ, it neither supports nor disproves the hypothesis that infection with microbial pathogens is the major cause of Alzheimer's disease.

Alzheimer's disease (AD) is a devastating and progressive neurodegenerative disorder and the most common form of dementia in the elderly. AD is associated with the pathological deposition of neurofibrillary tau tangles and extracellular amyloid β (Aβ) plaques as well as with chronic neuroinflammation. Numerous studies showed that specific microbial infections, including with herpes simplex virus type 1 (HSV1), *Chlamydia pneumoniae*, and several types of spirochaete are linked to AD etiology, as these pathogens have been detected in some AD brains, particularly in senile plaques (1). HSV1 is the most common of these and strongly links human pathogens to AD etiology (supported by over 100 publications reporting direct or indirect association), whereas only a handful of reports are contradictory. The following lines of evidence support this connection: (i) the presence of viruses and other microbes in the brain of most elderly individuals; (ii) in AD brains, pathogen signatures like HSV1 DNA specifically colocalize with AD amyloid plaques; (iii) active HSV1 infection can trigger chronic neuroinflammatory responses that lead to herpes simplex encephalitis, known to cause severe damage in brain regions associated with memory and cognitive functions; (iv) circulating levels of anti-HSV antibodies, an indicator of HSV1 reactivation, is positively correlated with AD pathology; (v) HSV1 infection activates neurotoxic pathways and causes an AD-like phenotype in mice, while in clinical studies, treatment with antiherpetic drugs like valacyclovir show improved cognitive functions in patients with AD compared with controls; and (vi) key features of AD pathology are transmissible upon intracerebral injection of AD brain homogenates (1, 2), indicating that microbial infection could represent an important contributor to late-onset AD and supporting "the Aβ antimicrobial protection hypothesis." This hypothesis proposes that Aβ deposition is an early response against microbial infection, which consequently drives chronic neuroinflammation and neurodegeneration, which is not necessarily contrary to with the established "amyloid hypothesis" that proposes that amyloidosis of Aβ is the root cause of AD (1). Recently, contrasting evidence was provided to continue the debate on the antiviral role of Aβ and the causative role of HSV1 infection in AD and to highlight that chronic neuroinflammation could represent a central mechanism in infectious etiology of late-onset AD (Fig. 1).

Previously, an elegant and high profile study by Eimer *et al.* (3) reported that human Aβ interacts with viral surface glycoproteins, which mediates Aβ oligomerization and viral entrapment, leading to protection against HSV1 infection in AD mice and 3D human neuronal cell cultures. Others also showed that Aβ amyloidosis protects against bacterial and fungal infections in animal and worm models of AD (4), suggesting that in addition to various genetic, biochemical, and environmental factors, microbial infection could represent one of the possible triggers of amyloidosis in AD neuropathology (Fig. 1).

In a recent article in the *Journal of Biochemistry*, Bocharova *et al.* (5) questioned the antiviral properties of Aβ and the role of viral infection in AD pathology in contrast to the findings of Eimer *et al.* (3), demonstrating protective antiherpetic actions mediated by human Aβ-expressing mice (5XFAD mice). Bocharova *et al.* used three different age groups of 5XFAD mice expressing transgenes for mutant human amyloid precursor protein and human presenilin 1, one of the four core proteins of the gamma secretase complex that generates Aβ from amyloid precursor protein, with five AD-linked mutations. WT control and 5XFAD mice were infected with three different doses of two strains of HSV1 ranging from 5- to 10-fold below or above the dose lethal to 50% of the mice (LD_{50}). Despite the use of different viral strains, doses, and ages of the animals, survival analysis revealed no statistically significant differences between 5XFAD and WT mice, which confirmed the lack of protective effect of the 5XFAD genotype against HSV1-induced encephalitis (5). Bocharova *et al.* also noted the region-specific or cell-specific tropisms of HSV1 strains that were not affected in 5XFAD mice compared with controls, which suggested that host–

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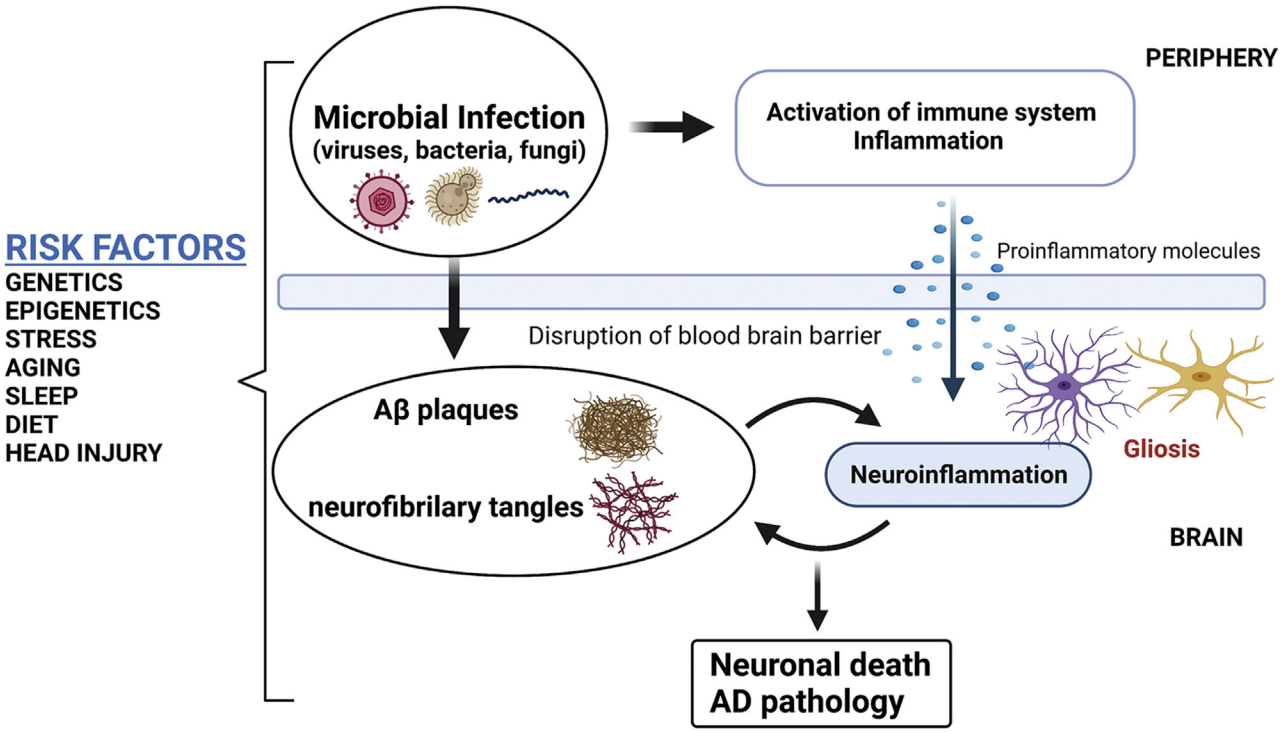

Figure 1. Schematic presentation of AD pathogenesis according to the "Aβ antimicrobial protection hypothesis" and the "amyloid β hypothesis." Chronic microbial infections activate the immune system and lead to sustained inflammatory responses, which allow penetration of microbial pathogens and/or their products to cross the blood–brain barrier. In the brain, they colocalize with Aβ and induce Aβ fibrillation to form senile plaques. Disruption of the blood–brain barrier causes penetration of peripheral inflammatory molecules as well as inflammatory cells into the brain and promotes gliosis. Furthermore, various risk factors, including genetics, stress, sleep, diet, head injury, and aging, influence disease progression. Together, these form a vicious inflammatory response, perpetuated by chronic infections or reactivation, which further stimulate chronic neuroinflammation. This process eventually leads to neuron death and AD pathology. AD, Alzheimer's disease.

pathogen interactions remained unaltered by Aβ overexpression. Also contrary to the study by Eimer *et al.* (3), Bocharova *et al.* found no evidence of HSV1-induced Aβ aggregation and Aβ-mediated viral entrapment. This observation was attributed to the microglia transitioning to a chronic reactive stage and subsequently phagocytosing the virus in Aβ aggregate-dense brain regions. Reactive microglia, often seen in human AD brains, might cause chronic neuroinflammation in response to recurrent reactivation or repetitive HSV1 infections (6). This repeated and sustained microglia activation could eventually potentiate deregulated chronic neuroinflammation and development of AD pathology (7).

These studies raise obvious fundamental questions, such as what are the targets for antimicrobial actions of Aβ in human? It is noteworthy to mention that mouse models are not natural hosts for HSV1 and hence do not adequately mimic spontaneous viral shedding or recurrent symptomatic diseases in humans (8). Furthermore, antimicrobial proteins show varying activity against different microbial pathogens, and therefore, the lack of protection against HSV1 infection in 5XFAD mice contrasts the strong protective effects against bacterial and fungal infections (5). This could correlate with diverse microbial infections in human brain. The discrepancies between the two studies could also be due to the use of different doses and variations of HSV1 strains. Nevertheless, the current work neither supports nor refutes the hypothesis of the viral etiology of late-onset AD. Indeed, since no protection was found against acute HSV1 infection in 5XFAD mice, it indicates that viral pathogens could even increase the risk of late-onset AD through multiple Aβ-dependent and independent mechanisms.

In the future, it would be of interest to examine the antimicrobial actions of Aβ against diverse microbial pathogens, including several types of spirochete, *Treponema pallidum*, *C. pneumoniae*, and the protozoan *Toxoplasma gondii*, implicated in human brain diseases. Certainly, HSV1 is not the sole contributor to late-onset AD, as it is a multifactorial disease with many contributing factors (including other potential pathogens). HSV1 may contribute to a minority of AD cases, and even this etiology may depend on the presence or the absence of other risk factors such as genetic factors (apolipoprotein E4 variant carriers), age, stress, sleep, diet, head injury, cardiovascular disease, and many others (7). Collectively, these contradictory studies question the contributory role of HSV1 to AD development and the antiviral activity of Aβ. Fundamentally, the findings of Bocharova *et al.* (5) support the notion that chronic infections with viral, bacterial, and fungal pathogens might cause deregulated neuroinflammatory responses, which subsequently increase amyloidosis in the brain and contribute to AD pathogenesis (2, 9, 10). Thus, inflammatory responses against infections might provide the missing link between infectious etiology and late-onset AD, if such a link exists.

It is worth mentioning that the infectious etiology in late-onset AD is a puzzle not yet solved, as—at least so far—no

specific microbial infection has been conclusively linked to causation of AD in humans. However, interesting data from many laboratories renewed the concern of infectious etiology in late-onset AD, which will provide new opportunities for anti-inflammatory therapy development.

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Abbreviations—The abbreviations used are: AD, Alzheimer's disease; HSV1, herpes simplex virus type 1.

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