CURRENT OPINION

Targeting Infectious Agents as a Therapeutic Strategy in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most prevalent dementia in the world. Its cause(s) are presently largely unknown. The most common explanation for AD, now, is the amyloid cascade hypothesis, which states that the cause of AD is senile plaque formation by the amyloid β peptide, and the formation of neurofibrillary tangles by hyperphosphorylated tau. A second, burgeoning theory by which to explain AD is based on the infection hypothesis. Much experimental and epidemiological data support the involvement of infections in the development of dementia. According to this mechanism, the infection either directly or via microbial virulence factors precedes the formation of amyloid β plaques. The amyloid β peptide, possessing antimicrobial properties, may be beneficial at an early stage of AD, but becomes detrimental with the progression of the disease, concomitantly with alterations to the innate immune system at both the peripheral and central levels. Infection results in neuroinflammation, leading to, and sustained by, systemic inflammation, causing eventual neurodegeneration, and the senescence of the immune cells. The sources of AD-involved microbes are various body microbiome communities from the gut, mouth, nose, and skin. The infection hypothesis of AD opens a vista to new therapeutic approaches, either by treating the infection itself or modulating the immune system, its senescence, or the body's metabolism, either separately, in parallel, or in a multi-step way.

Key Points

Experimental and epidemiological data increasingly support the involvement of infections in the development of Alzheimer's disease (AD), with the sources of AD-involved microbes being various body microbiome communities from the gut, mouth, nose, and skin.

Infection results in neuroinflammation, leading to and sustained by systemic inflammation, causing neurodegeneration, and the senescence of the immune cells preceding the clinical manifestations.

The infection hypothesis and the Antimicrobial Protection Hypothesis of AD open the way to new therapeutic approaches.

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Published online: 26 May 2020

1 Introduction

Presently, Alzheimer's disease (AD) is one of the most important public health concerns [1]. It remains the most common cause of dementia in the world [1–4]. Despite huge scientific efforts and financial outlay, we still do not know what is the cause of this disease, which is perhaps more appropriately defined as a syndrome [5–7]. More than 1000 clinical trials have failed, and all ongoing attempts to identify treatment do not seem to be promising [8–10]. The prevailing hypothesis to explain the pathomechanism(s) of AD puts the amyloid beta peptide (Aβ) at center stage and is defined as the beta amyloid cascade hypothesis [11–13]. All attempts to modulate by any means the concentration of Aβ in patients' brains have resulted so far in a failure to improve the clinical status of patients suffering from any stage of AD. Thus, there is an urgent need to reconsider the causes of AD, which may and should lead us to the discovery of new innovative measures to prevent and treat AD [8–10]. A new hypothesis has emerged, which puts infection or microbial/microbiome challenge in the forefront of AD [5, 14].

△ Adis

AD is a chronic disease, and the pathophysiological processes leading ultimately to its overt symptoms start decades before the clinical manifestations may appear, triggered by age-related changes [15, 16], such as immune system modifications, inflammaging (increased levels of proinflammatory cytokines without overt signs of any inflammation), increase in gut leakage, and microbiome shift (dysbiosis), as well as the appearance of senescent cells in the gut and the brain; all factors that favor the development of AD [5, 7]. This makes it very difficult to cure, but in the meantime, this may convey hope as it can be prevented in the "incubation period" preceding the appearance of cognitive decline to avoid the full-blown disease, if appropriate predictive biomarkers can be discovered. It is, however, of interest that the development from the emergence of the first clinical symptoms [mild cognitive impairment (MCI (MCI))] to full-blown AD takes about 10–15 years. This time may also be used to slow down the progression or even cure it if the cause(s) of AD could be found or if biomarkers could allow it to be efficiently tracked.

2 What is the Prevailing Hypothesis and Why Is It Unsatisfactory?

Since the first description of AD by Alois Alzheimer, extracellular Aβ plaques and intracellular hyperphosphorylated tau deposition (called neurofibrillary tangles) unrelated or only indirectly related to the formation of Aβ have become the pathological hallmarks of AD [17, 18].

This gave rise to the amyloid hypothesis of AD which has been adopted by the majority of the AD scientific community. Everything in AD research, clinical trials and ultimately in memory clinics has been oriented and driven by the Aβ hypothesis [12, 19, 20].

However, the lack of useful and productive progress toward mechanistic understanding of AD calls for a revaluation of the Aβ cascade hypothesis. The amyloid hypothesis states that the production of Aβ from its amyloid precursor protein (APP) in neurons and astrocytes by β-secretase (BACE) together with a presenilin-containing complex called γ-secretase is the primary cause of AD [21–23]. Thus, the formation of Aβ is the starting point that initiates all the other observed pathological phenomena associated with AD and culminates in the deposition of amyloid plaques in the brain [13]. It also triggers the intracellular deposition of hyperphosphorylated tau. Both of these phenomena (formation of plaques and of neurofibrillary tangles) result in neurodegeneration (synapse degeneration and then neuronal cell death) and, more importantly, neuroinflammation [24–30]. It has subsequently been found that AD has many different genetic risk (susceptibility) factors, such as ApoE-ε4, TREM-2, and TOMM40 [31–37].

However, as appealing as this hypothesis may appear, many observations made over decades have spoken against it. One of the most important, yet constantly overlooked details is that these hallmarks exist in the brain of 20–30% of non-demented healthy elderly, while in contrast, an almost identical proportion of patients suffering from AD do not have these hallmarks [5, 38]. Evidence suggesting a role for events preceding and precipitating deposition of Aβ-containing plaques emerged almost a decade ago from the laboratory of Dr. Rudolf Tanzi, who had demonstrated the antimicrobial properties of Aβ and first described it as an antimicrobial peptides (AMP) [39]. These crucial observations were later confirmed by other laboratories, which found that Aβ acts as an AMP against many different microorganisms [40, 41], which suggested the "Antimicrobial Protection Hypothesis" of AD. Moreover, several different microorganisms have been demonstrated in the brains of AD patients [42–53]. Nevertheless, the most important argument against the Aβ hypothesis of AD is, as already mentioned, the lack of success of almost all trials that directly targeted Aβ accumulation through vaccination or monoclonal antibodies or its production by the BACE inhibitors [54, 55]. An additional finding supports the antimicrobial role of Aβ generated in the brain, as a decrease in Aβ production during the clinical trials lead occasionally to the emergence of some type of infections in the brain [56]. Thus, based on these facts, the infection hypothesis of AD pathogenesis was developed, slowly conceptualized, and finally clearly published in a recent editorial [14]; see Fig. 1. Other possible hypotheses of mechanisms leading to AD have also been advanced [57–59].

3 Other Existing Theories

It should be mentioned that over the years a few researchers have promoted different ideas about AD etiology. Among them was the vascular hypothesis, which appeared in the 1990 s [59]. A study in nuns (The Nun Study) demonstrated that even if, pathologically, amyloid plaques could be detected in the brain, the clinical diagnosis of AD was established only when these lesions were accompanied by atherosclerotic lesions in the brain, regardless of the age of the nun [60]. Later, it was shown that ischemia and shear stress were also able to generate the production of Aβ [61, 62]. These ideas led to the integration of vascular problems and associated diseases (e.g., hypertension) as risk factors for AD [63, 64].

Another theory, the mitochondrial cascade hypothesis, authored by Swerdlow et al. [65], proposed that mitochondrial dysfunction resulting from aging, genetic
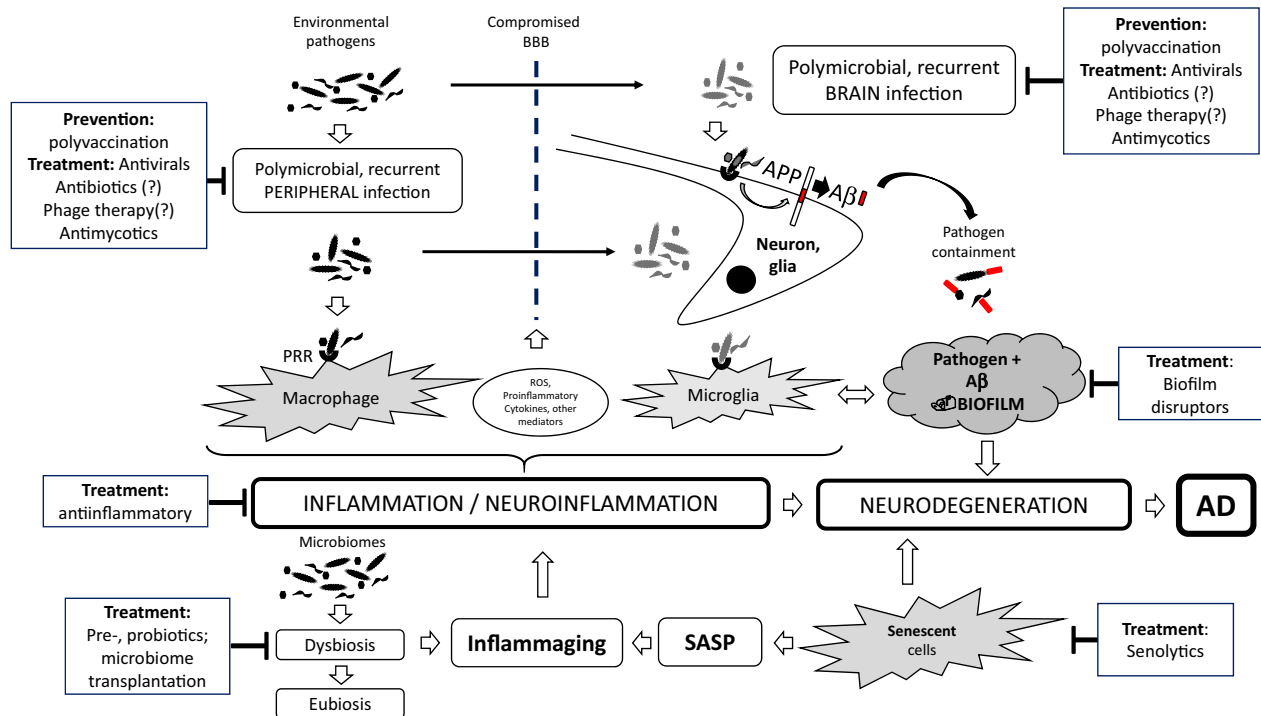
Fig. 1 Possible intervention checkpoints according to the infection hypothesis. This figure depicts the various putative players in the development of AD, considering the infection hypothesis as well as the individual future targets for intervention. *Aβ* amyloid beta peptide, *AD* Alzheimer's disease, *APP* amyloid precursor protein, *BBB* blood–brain barrier, *PRR* pattern recognition receptors, *ROS* reactive oxygen species, *SASP* senescence-associated secretory phenotype

predisposition, or environmental factors results in the production of reactive oxygen species (ROS) that damage brain cell functions, resulting in typical AD pathology. The mitochondrial cascade hypothesis, similarly to the Aβ hypothesis, cannot stand alone as a causative factor for neurodegeneration, but requires internal or external stresses acting on various brain cells, such as neurons, microglia, and astrocytes. All infections stimulate ROS production and may interact directly with mitochondria, perturbing mitochondrial DNA (mtDNA) and mitochondrial homeostasis (fission, fusion, and mitophagy), leading to mitochondrial dysfunction [58]. Thus, this hypothesis can be easily integrated into the infection hypothesis.

4 What Evidence Supports The Infection Hypothesis for AD?

There are numerous epidemiological and experimental discoveries that support that AD may be an infectious disease. Already, many years ago, epidemiological evidence has linked the treatment of rheumatoid arthritis (RA) to the prevention of AD. McGeer et al. [66] showed that RA patients who are receiving anti-inflammatory treatment develop AD much less often than others. This observation was confirmed by an updated meta-analysis of cohort studies [82]. Sixteen cohort studies, including 236,022 participants, published between 1995 and 2016, were included in this systematic review. Current evidence suggests that nonsteroidal anti-inflammatory drug (NSAID) exposure might be significantly associated with reduced risk of AD, but again, the need for prospective studies with individual NSAIDs is badly needed. Initially, this protection was suggested to be linked to the decrease in the neurotoxic effect of Aβ-induced neuroinflammation [67, 68]. However, more recently, RA was linked to the mouth bacterial pathogen *Porphyromonas gingivalis* [69–73]. Thus, the question may arise of whether the treatment of RA inflammation, which indirectly also decreased AD progression by reducing neuroinflammation, could somehow treat the common root, namely an infectious origin.

Epidemiologically, the first and strongest evidence was brought to the community by dentists [74–77]. They observed that people who suffer from periodontitis develop AD much more often than those who do not present this alteration in the mouth [78, 79]. Since these epidemiological observations, numerous experimental data have supported the link between periodontitis-induced systemic inflammation, oral dysbiosis, and altered immune response and AD [77, 80–89]. It should, however, be mentioned that some

studies did not confirm these associations [90]. Increased AD incidence was linked to the presence of biofilms produced by the cornerstone bacteria *P. gingivalis* [80, 91]; however, recently, other bacteria were found to be involved, such as *Treponema denticola* and *Tannerella forsythia* [81]. The bacterial effect might be direct (bacteria entering the brain via the lingual nerve or the olfactory bulb) or indirect via their virulence products that stimulate the production of Aβ; the effect is the same: appearance in the brain of a structure resembling bacterial biofilm, called senile or Aβ plaques [75, 77, 78, 87, 92]. Indeed, it was recently postulated that amyloid plaques are biofilms [48]. This was recently supported by a study demonstrating the presence of one of the most important virulence factors of *P. gingivalis*, gingipain, in the brains of healthy and AD patients [52]. This latter group showed also [by quantitative polymerase chain reaction (qPCR)] the presence of *P. gingivalis* in the brains of healthy subjects as well as in the brains of patients suffering from AD [52]. Our unpublished data also demonstrated by qPCR the presence of *P. gingivalis* in AD brains (manuscript in preparation).

Yet another bit of information associating the development of AD with bacterial infections is the role of calreticulin (CRT) and galectin-3 in the brain. The decreased expression of CRT in the neurons of AD patients was first demonstrated almost 2 decades ago [93]. CRT is a multifunctional protein, which has since been associated with a chaperone function for APP; thus, the more CRT is present in the neuron, the more stable the APP becomes and less Aβ is produced resulting in its aggregates (plaques) [94]. On the other hand, CRT production is upregulated by Aβ oligomers, at least in vitro [95]. Serum levels of CRT are considered a negative biomarker of AD development and progression [96]. This may make sense, as CRT has been very recently shown to be secreted also by activated macrophages and microglia and to act as an opsonin facilitating the phagocytosis of bacteria invading the brain (albeit so far only in a rat model) [97]. Thus, we could imagine/propose a scenario where an infection leads to production and release of Aβ, which aggregates and upregulates the production and secretion of CRT, which in turn binds/opsonizes bacteria for microglia-executed phagocytosis; thus, more intracerebral infection could lead to decreased levels of CRT (as it would be used up by opsonization and phagocytosis), which would favor AD.

Very recently a study in Taiwan showed that those suffering from herpes simplex virus-1 (HSV-1) infection and treated with antiviral drugs had a reduced incidence of AD [98]. This retrospective cohort study from Taiwan showed the 10-year incidence of dementia in a group of 8362 subjects aged 50 years or over who were newly diagnosed with HSV-1 or HSV-2 infection was 2.56-fold greater than that in the control group (95% confidence interval 2.351–2.795; $P < 0.001$). More strikingly, anti-herpetic medication reduced the risk of developing dementia by approximately 91%. These results strongly support a potential causative link between HSV-1 infection and AD, mainly in genetically susceptible subjects [36]. This observation suggests that AD is linked somehow to viral infections [53, 99–101]. However, this still does not clearly demonstrate whether HSV-1 is the cause or the consequence of AD, but highly suggests that HSV-1 may be also involved in its pathogenesis. Interestingly, decades ago, Itzhaki showed experimentally that HSV-1 DNA is present in the brain plaques of persons suffering from AD [43]. This indicated that viral infection may play a role in the development or progression of AD and that the secretion of Aβ may be a reactive phenomenon to control infection. It may have some AMP effect or may be a general acute phase reaction to a strong stress as many other peptides in the organism during infection, such as LL-37, are affected [102, 103]. Very recently, the Lovheim group demonstrated an association between HSV-1 carriage and declining episodic memory function, only among ApoE-ε4 carriers, while the other alleles such as ε2 and ε3 did not show such an association in cross-sectional and longitudinal studies of a large population-based cohort [37]. Thus, the Lovheim group [36, 37] showed for the first time in a prospective epidemiological analysis that the host genetic background interacts with HSV-1 carriage to increase the risk for developing AD. The primary strengths of their studies include many cases with closely matched controls from the same population, combined with thorough clinical AD diagnosis. These studies further confirm the interaction between ApoE-ε4 heterozygosity (APOE-ε2/ε4 or ε3/ε4) and HSV-1 carriage, which increased the risk of AD by approximately fivefold, whereas the presence of only one factor did not. A calculated genetic risk score (GRS), based on nine additional risk genes (ABCA7, BIN1, CD33, CLU, CR1, EPHA1, MS4A4E, NECTIN2, and PICALM), also correlated with anti–HSV-1 immunoglobulin G (IgG) for increased risk of subsequent AD. The present findings suggest that the ApoE-ε4 allele and other AD genetic risk factors might potentiate the risk of developing HSV-1–associated AD. Another very recent study in a cohort in Bordeaux, France, further confirmed these relationships between ApoE4 and HSV-1 being a strong risk factor for AD development [104]. Together, these data could provide new insights into the possible mechanisms by which the genetic treat of ApoE-ε4 associated with HSV-1 carriage may be involved in the development of AD.

Almost at the same time, Miklossy and others have demonstrated the presence of other microbes, such as the spirochete *Borrelia burgdorferi,* in blood, cerebrospinal fluid, and brain tissue [105, 106]. They also hypothesized that this

bacterium may produce a biofilm that would constitute the amyloid plaque, protecting bacteria from various stress in the brain [107]. Balin et al. have demonstrated the existence of *Chlamydia pneumoniae* in plaques [50]. They later observed that systemic infection with *C. pneumoniae* in turn increased the occurrence of AD [51]. All these data have converged to promote and justify the development of the infection hypothesis, stating that accumulation of Aβ is not the primary cause of AD, but is itself the consequence of infection. Aβ would then play its pathogenic role as stated by the amyloid hypothesis [5, 108].

Subsequently, the demonstration of *Treponema* in plaques reinforced the infection hypothesis. In the sexually transmitted infection syphilis, caused by *Treponema pallidum*, the tertiary stage is accompanied by a particular dementia status [109], which occurs in most cases several decades after the primary infection [109]. This is a very important similitude as this makes plausible the role of a bacterium of the genus *Treponema* in the pathogenesis of AD. Furthermore, another virus, HIV, has been associated with neurodegenerative disorders [HIV-associated neurodegenerative disorder (HAND)] [110, 111]. A neurodegenerative disorder related to HIV infection has been reported to cause a severe form of dementia [112]. Since the efficacious treatment of HIV by combination antiretroviral therapy (cART), patients live much longer with the virus, reaching old age, and their neurocognitive disorder has become much milder in its clinical manifestations [113–115]. In these patients, HAND resembles AD more and more, even including the production of Aβ in response to the virus [116, 117]. Interestingly, HIV suppresses production of Aβ at early stages of the infection as a protection against the AMP role of Aβ, which reinforces its AMP role [118].

The latest microorganisms abundantly found post-mortem in the brains of AD patients are pathogenic fungi [119]. The most important species were *Candida albicans* and the *Malassezia* sp. [120, 121]. We do not know how fungi may be involved in the development of AD, and this needs further investigations.

All this experimental evidence points toward the involvement of microbes in the pathogenesis of AD [14] (Table 1). These results also indicate that it would be very difficult to identify one microorganism as the unique cause. It was suggested that AD is a polymicrobial disease [120, 122]. Nevertheless, one bacterium may be more important than the others, namely *P. gingivalis.* Its cornerstone role in periodontitis, where it orchestrates the formation of biofilms, could be duplicated in AD. In support of this theory, a recent paper found the *P. gingivalis* virulence factors, gingipains, in the post-mortem brains of AD patients [52]. In summary, all of the experimental data gathered so far, suggest a potential causality between infections and AD [123].

Table 1 The most frequently involved microorganisms in Alzheimer's disease

Viruses
HSV-1
HIV
HHV-6 and HHV-7
Bacteria
Borrelia burgdorferi
Treponema denticola
Chlamydia pneumoniae
Porphyromonas gingivalis
Fungi
Candida albicans
Malassezia furfur

HHV human herpesvirus, *HSV* herpes simplex virus

Before further describing the putative pathomechanism that could explain how microorganisms may induce AD, we will describe the changes in the immune system that are a necessary corollary to allow infections to promote AD development, a process that may be the target for future treatments.

5 The Innate and Adaptive Immune System in AD

The immune system has the role to defend the organism against external and internal challenges [124, 125]. In many circumstances, the immune system may be activated for a longer period than necessary when a challenge is maintained for a long time or is reactivated from time to time [126]. This means that inflammation that plays a beneficial role in acute infection may become chronic and detrimental to the host organism and even generate disease [126].

In the case of AD, neuroinflammation is a fundamental part of its pathogenesis [13, 16, 24, 127–130]. According to the amyloid hypothesis, neuroinflammation is generated and maintained chronically by Aβ [13]. In the infection hypothesis, it is the result of the penetration of the microbes or their products into the brain and is meant to help in the elimination of the infection, at least at the beginning of the pathogen invasion into the brain [15]. However, as infection becomes chronic, neuroinflammation also becomes chronic and destructive [40, 41]. Neuroinflammation in AD is characterized by microglial and astrocyte activation, inflammasome activation via NLRP3, complement activation, and altered cytokine production shifted towards pro-inflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 [131]. All of these characteristic

features of neuroinflammation may be found typically during infections as well [132].

Indeed, in AD, neuroinflammation is sustained mainly by the systemic and the local innate immune system. Systematically, the activated innate peripheral immune cells such as natural killer (NK) cells, neutrophils, and monocytes are, on the one hand, able to cross the blood–brain barrier (BBB) and create destruction in the brain directly or by their products, such as the pro-inflammatory cytokines or chemokines, which cross the BBB and act on resident brain immune innate cells, such as microglia and astrocytes, as demonstrated in humans and in animal models of sepsis [133–137]. Furthermore, Bu et al. have shown in an association study that the systemic infectious burden measured by antimicrobial antibodies increased the risk of AD [138]. This study points again towards the polymicrobial nature of AD. Thus, peripheral infections, inflammation, and stress were linked to microglial activation via the NFκB/NLRP3 pathway via pro-inflammatory cytokines [139–141]. Together, these data suggest that systemic immune activation has central effects and vice versa [77, 82, 142].

The brain has a powerful innate system composed of microglia (brain macrophages), astrocytes, and even neurons. They may destroy microorganisms or produce efficient antimicrobial peptides, the most important being the cathelicidin LL-37 [143–145]. Microglia, in response to stress, develop an inflammatory response (pathogen-associated molecular patterns or damage-associated molecular patterns) and secrete pro-inflammatory cytokines [146–148]. Importantly, microglia may also modulate astrocyte reactivity by IL-1α, TNF-α, and C1q, and such stimulated astrocytes may acquire a pro-inflammatory A1 phenotype [149, 150]. These "good" innate cells may be turned into "bad" cells by several microbial products, including lipopolysaccharides (LPS) and gingipains, resulting in their loss of ability to eliminate invaders and decrease the Aβ burden, and in the activation of their senescence as well as in increasing their attack against neurons [89, 131, 151, 152]. In summary, under microbial pressure, the brain's innate immune system deviates from a defensive to a killing role, resulting in neuroinflammation, senescence and neuronal death. Again, one trigger suspected to play a pathogenic role in AD is microbes and their products such as LPS.

The demonstration by Soscia et al. that Aβ is an AMP gave a new impetus to the infection hypothesis [39]. They tested Aβ against bacteria and fungi and found it more powerful than even LL-37. More recently, we and others have demonstrated that, like LL-37, Aβ may also inactivate viruses, including HSV-1 [41], influenza [153], and retroviruses [118]. It was also shown that when infected by HSV-1, neurons were able to secrete substantial amounts of Aβ, which inhibited HSV-1 infection of other neurons [154]. This indicates that Aβ is not only a pathological peptide as supposed originally, but has a well-defined physiological role and is produced under very well-defined conditions. Moreover, Aβ was more powerful than interferon (IFN) type I. Recently, an interesting finding showed that Aβ may also have anticancer properties [155] as well as BBB repair properties [156]. The most important cells producing Aβ are neurons and astrocytes. This is not surprising as the latter together with microglia play a crucial role in the brain host defense either clearing waste or secreting defensins [157, 158].

The role of Aβ as an AMP has since been tested in many animal and experimental models. It was shown in a murine model of *Salmonella enterica* and *Salmonella typhimurium* infection that endogenous as well as exogenous Aβ could prevent infection in the brain [159, 160]. These authors hypothesized that the mechanism of action of Aβ was by formation of amyloid aggregates (plaques) using the microbial surface [161]. This led to the formulation of the Antimicrobial Protection Hypothesis [162]. However, they never linked biofilm formation to plaque formation, as had been hypothesized by Miklossy [48]. Together these data again strongly support the notion that Aβ is a newly recognized member of the large AMP family combating infections in humans.

All these findings provide an answer to why evolution would promote, and even select for, an enzymatic system (β- and γ-secretase) if the result had no pro-survival value and, as believed, was only detrimental (leading to AD). Now, based on the convincing observations described above, we can say that generation of Aβ has a clear pro-survival role.

In fact, both secretases have multiple targets with distinct, different physiological roles, which likely evolved in early vertebrates many million years before APP and Aβ [163–165]. Also, the APP and its cleavage products seem to be multifunctional. Yet, based on their studies, Moore et al. venture to say, "Although not as deeply conserved as BACE1, the Aβ peptide has been conserved for at least 430 million years. This indicates that Aβ, too, has essential functions that have thus far escaped discovery" [165], which indirectly supports our notion that antimicrobial effects of Aβ might be an (evolutionarily conserved) "bonus" feature.

The adaptive immune system also showed important changes in AD [166]. Naïve T cells decreased and CD8+ memory T cells increased. This situation is identical to what is observed during normal aging, but also in chronic infections, independent of age, such as cytomegalovirus (CMV) infections [167, 168]. This suggests that just like the innate immune system, the adaptive immune system is also chronically stimulated and its capacity to fight infections is not always efficient [169]. Thus, the immune system shows similar properties in AD patients to those found in many other chronic infectious diseases with, of course, specificities typical to its localization in the brain.

Furthermore, this constant stimulation of the immune system via what is called inflammaging results in the exhaustion of the immune cells, resulting in an increase of cellular senescence, which is also evident in microglial cells [170]. This cellular senescence, via the senescence-associated secretory phenotype (SASP), further supports and amplifies the notion of inflammaging [171–174]. SASP of microglia and astrocytes is sustained by the activation of two main intracellular inflammatory pathways that are intimately linked with NFκB and the inflammasome pathways [175–177]. The NOD receptor pathway via NLRP3 mediates the production of IL-1β, IL-18, and caspase-1, which increase in AD brains. Moreover, IL-1β has been shown to contribute to the permeability of the BBB, favoring the passage of microorganisms and their by-products [7, 178, 179]. These pathways may not only induce senescence but also what is called pyroptosis, which is an inflammation-triggered programmed cell death, especially in microglia [180].

6 What is the Pathomechanism that Microorganism(s) Use to Cause AD?

We suggest two overlapping pathways for microbes to induce AD.

The first involves direct migration of the microorganisms to the brain via either the lingual nerve or the olfactory bulb and crossing the permeabilized BBB, composed mainly of astrocytes, endothelial cells, and pericytes [181, 182]. For a long time, the brain was considered a privileged organ, as it was protected by a well sealed BBB; however, it has been shown that even in the early stages of AD, the BBB becomes more permeable [183]. This also may occur during the process of aging [184] as well as during systemic inflammatory responses elicited by microbial infections such as viruses or bacteria, with or without direct brain infection [185, 186]. Microbes have evolved to be able to make the BBB permeable, partly by subverting pericytes and/or endothelial cells by inducing either their apoptosis or by using the complement system receptor 3 (CR3) to their advantage to make their way to the brain [187–189]. Neurons would respond by producing Aβ, to try to destroy the invading microbes [39–41]. In the meantime, the microglia and astrocytes are also stimulated and produce other antimicrobial peptides, pro-inflammatory cytokines, free radicals, and proteases to destroy the microorganism [158, 190, 191]. Moreover, the complement system is activated, and this favors phagocytosis [192]. Finally, the adaptive immune system is also activated either to produce cytotoxic effector CD8 + T cells or antibodies via B cells [193]. Thus, in a normal situation, the invading microorganism may be totally eliminated or imprisoned in biofilm, seen as plaques, which protect the microbial community from destruction [48]. This process may occur for decades preceding clinical manifestations of AD, and many reactivation or reinfection cycles may lead to chronic neuroinflammation and plaque deposition resulting in massive neuronal death.

Another non-mutually exclusive pathway may be the passage not of the entire microorganism but only its virulence factors, such as LPS, gingipains, extracellular RNAs, or peptidyl arginine deiminase (PAD) enzymes [52, 86–89, 194, 195] or other. These substances may occur permanently in the organism and originate from any of the microbial communities/reservoirs of the organism, such as gut microbiome, mouth, or neurobiome [196–200]. These microbial products or metabolites may mediate their deleterious actions by being incorporated in extracellular vesicles (EVs) [201]. Indeed, many microorganisms, including *P. gingivalis*, are also able to release EVs containing gingipain and fimbriae, which modulates intestinal permeability as well as the function of the innate immune system, thus favoring an inflammatory status [88, 202, 203]. In this way these by-products will stimulate the immune system with the production of inflammatory mediators, which will chronically induce the same processes as the direct presence of the microorganism itself [89, 204].

As mentioned, these microbes or their virulence products may originate from various microbial reservoirs in the body including microorganisms that have reached the brain via the first pathomechanism. The most important microbial reservoir in humans is in the gut, which leads to the notion of the gut–brain axis. This means that there is a constant communication between the gut and the brain and vice versa throughout life [205–208]. Indeed, the direct presence of microbes and/or their by-products has been demonstrated in the brains of AD patients, but interestingly also in the brains of healthy aged subjects, hence the notion of a "neurobiome" [52]. Studies of the gut microbiome in aged people showed a tendency towards an increase in Gram-negative bacteria [209], which was also shown in MCI patients [210]. This becomes even more problematic when the immune system manifests some maladaptation with aging which permits the clinical development of AD through the translocation of microbes that are normally commensal (dysbiosis) [211–213] and are contained within the gut by the local immune system which has induced a tolerogenic state [214]. It has also been demonstrated that dysbiosis of the gut microbiome may promote various inflammatory disorders which have provoked microglial activation during the development of AD [211, 215–217]. Thus, this suggests that the gut microbiome or better, its dysbiosis, is involved in regulating microglial activation and neuroinflammation in AD.

Another important axis for the development of AD could be the mouth–brain axis, involving mainly *P. gingivalis* [77, 218]. *P. gingivalis* produces various virulence factors such as LPS, flagella, and toxic proteases called gingipains [219].

The LPS may activate astrocytes and transform them to the proinflammatory A1 phenotype by stimulating Toll like receptor (TLR)-4 [220]. Gingipains have been found in the brains of healthy subjects and AD patients, and have been proposed to be involved in the pathophysiology of AD [52]. In periodontitis, these virulence factors, mainly gingipains (lysine-gingipain and arginine-gingipain A/B), have been shown to play a role in host colonization, inactivation of the host immune response, and iron and nutrient acquisition [221, 222]. Gingipains may also activate various innate receptors such as TREM1, TREM2, TLR-4, CR1, and NLRP3 [223–226], which may result in the activation of the inflammasome [227]. This activation in turn facilitates plaque formation and may amplify the inflammatory reaction via release of ASC specks [228, 229]. Interestingly, the activation of this inflammasome results in pyroptosis which eliminates the cell infected by *P. gingivalis* and limits replication of this bacteria [230]. Furthermore, this phenomenon does not always require the presence of live *P. gingivalis*; released gingipains may penetrate cells and have similar effects [231, 232]. These processes involving the mentioned receptors, the inflammasome, and *P. gingivalis* or its gingipains will ultimately kill neurons and favor amyloid plaque deposition and IL-1β release. This will further help to permeabilize the BBB. Gingipains are also able to cleave IgG1 and IgG3, mainly by gingipain K, and in this way, the adaptive branch of the immune defense of the organism can be compromised [233, 234]. Another important virulence factor of *P. gingivalis* is peptidylarginine deiminase (PPAD), which catalyzes the citrullination of both bacterial and host proteins [235, 236]. PPAD helps *P. gingivalis* evade destruction by neutrophils by impairing phagocytosis and bacteria-induced NETosis [235]. Furthermore, when PPAD citrullinates cationic antimicrobial peptides such as LP9 and LL-37, it efficiently neutralizes them [237]. Gingipains can also deactivate them by proteolytic degradation [238, 239], which may be followed by PPAD citrullination of exposed arginine residues. All of these products from *P. gingivalis* help it to evade elimination by both the innate and adaptive immune systems. It is of note that the direct role of *P. gingivalis* and its products in the development and progression of AD, even if they have been found in the brain of AD patients, will require further studies.

Inflammaging is sustained by an imbalance between the innate and adaptive immune systems together with the senescence of the cells constituting the central nervous system (CNS), including neurons, microglia, and astrocytes. The concomitant processes of inflammaging, programmed cellular senescence, and dysbiosis further favor the leakage of the gut, resulting in the passage of bacteria (pathogenic and/or commensal) [238] and their products into the brain, including those which may contribute to AD, such as the curli [239].

One other recently described phenomenon which can lead to sustained neuroinflammation is the mechanism of "trained" innate immunity [240]. This process captures the constant inflammatory state seen in the innate immune system during aging, AD, and other chronic diseases [126]. Once monocytes have been activated, any new unrelated stimulation will result in higher response from these cells [241]. This property of the innate immune system is reminiscent of memory in the adaptive immune system and can lead to maintenance of a basic, constant activation in cells like microglia, which will likely contribute to constant neuronal destruction.

All these experimental results point to the fact that Aβ is deposited in the brain decades before the clinical manifestation of AD, suggesting that AD is related to chronic mutually sustaining inflammatory processes in the CNS and in the periphery as a result of a long-lasting antimicrobial response culminating in plaque deposition [15, 162, 242, 243].

Whatever the pathway that microorganisms employ to cause AD, better understanding of these processes could suggest new innovative strategies to prevent or intervene in the progression of AD.

7 What are Possible Interventions Targeting the Prevention or Cure of AD?

The obvious treatments which come to mind are treatments by specific agents aimed at containing or direct elimination of the aforementioned microorganisms, such as antivirals, antibacterials, and antifungal products. In the case of viruses, the most relevant would appear to be the antiviral drugs that penetrate the BBB and which are very effective even in herpes viral encephalitis, such as valacyclovir [101, 244, 245]. Unfortunately, although HSV-1 has been implicated in AD, we do not know if other viruses are also involved, and even for HSV-1, we do not know exactly when and how it may cause AD (and, as mentioned above, rather assume that the cause is prolonged and polymicrobial). It may be experimentally challenging to determine when, how, and at what dose to use such agents [100]. Nevertheless, each time that we have an infectious burst such as herpes labialis or herpes genitalis or zoster, we should treat the patients most vigorously, regardless of age. If we consider data from the Taiwanese study mentioned above, each of these treatments should decrease the incidence of AD. Other viruses may also be involved, and so we will have to discover antiviral agents that cross the BBB to control them.

Are there any direct trials targeting any stages of AD with antiviral treatment? In fact, there is one ongoing, one which has been just finished, and some may be actively planned [100]. This is due to the uncertainty of the viral mechanisms causing AD. Another factor is knowing at what time to treat.

Considering the long "incubation period" of AD, it would be logical to treat any viral infection at any time it manifests itself, which would be of great advantage in decreasing the deleterious effect not only on the immunobiography/inflammaging, but also the viral contribution to the chronicity of such an accumulation of burden involving several infections. To avoid unnecessary treatment of non-susceptible individuals, one of the best periods would be when memory problems are starting to appear in the subjective memory complaint (SMC) and MCI stages. In this way, we could assess whether this treatment would at least delay the progression towards AD. Logically, a pulse repeated intervention would be needed, but this again would have to be demonstrated. The advantage of valacyclovir and related drugs is that they have very few side effects even in elderly subjects. The epidemiological study from Taiwan seems to indicate that it could be a rewarding intervention. If successful in SMC or MCI, it could be envisaged at earlier times.

Devanand in his paper of 2018 [100] mentions a phase II, proof-of-concept, randomized, double-blind, placebo-controlled, 18-month treatment trial of 130 patients (65 valacyclovir, 65 placebo) with mild AD [Mini-Mental State Examination (MMSE) range 20–28] who tested positive for antibodies to HSV-1 or HSV-2. Valacyclovir dosage will be 2–4 g daily. The dose range was stated safe and is known to lead to CNS penetration with high cerebrospinal fluid (CSF) levels, which should increase the chance of efficacy. The hypothesis was that, in comparison with patients treated with placebo, patients treated with valacyclovir would show a smaller decline on the Alzheimer's Disease Assessment Scale–Cognition 11-item scale (ADAS-Cog11) (cognitive measure; 0–78 weeks) and the Alzheimer's Disease Cooperative Study–Activities of Daily Living scale (ADCS-ADL) (function measure; 0–78 weeks). The authors state that if the trial is successful, they will continue with a phase III trial. Indeed, there is a trial registered as ClinicalTrials.gov Identifier NCT03282916. This trial plans to use valacyclovir in MCI/AD patients to establish whether this treatment will restore or decrease cognitive functions. We should wait for the results of these trials to be published in forthcoming years, probably in 2022. Another study, the VALZ-Pilot study (NCT02997982), investigated the effects of valaciclovir treatment in individuals with AD or MCI of AD type. This study enrolled 36 persons for 4 weeks treatment then followed them for another 12 months. The study finished in March 2020, and no results are available yet. It will be interesting to have the results to plan larger phase III studies. A study (Apovir study) used Apovir (Apodemus AB, Solna), a combination of the experimental anti-enterovirus agent pleconaril, originally developed to treat the common cold, and the hepatitis C treatment ribavirin. This was reported at the Clinical Trials on Alzheimer's Disease (CTAD) conference in Barcelona (2018) (https://www.ctad-alzheimer.com/files/files/CTAD%20ABSTRACT.pdf) as a phase 2a clinical trial including 69 people with mild AD given Apovir or placebo for 9 months. There was a very high dropout rate in the Apovir group because of side effects. However, the ADAS-Cog improved slightly in patients taking Apovir versus placebo, by 3 points. This result was considered inconclusive, and the authors suggested that further studies were merited. These data were not yet published. Currently, there are no other ongoing clinical trials with antivirals for AD.

It is worthwhile to mention that several antibiotics have been tried to treat or at least to slow down the progression in prodromal as well as in mild to moderate AD [246]. The most used antibiotics in these clinical trials were doxycycline, minocycline, and rifampin. In a clinical trial, Loeb et al. (2004) [246] used oral doxycycline at 200 mg and rifampin 300 mg daily for 3 months in prodromal and mild to moderate AD. The end point was Standardized Alzheimer's Disease Assessment Scale cognitive subscale (SADAScog) score at 6 months. This trial concluded that there were no major adverse events, and therapy with doxycycline and rifampin may have a therapeutic role in patients with mild to moderate AD; however, the mechanism could not be established, as it seemed unlikely to be due to the effect on *C. pneumoniae*. A few years later Molloy et al. [247] published the DARAD trial, which used doxycycline and rifampin for treatment of AD. This was a multicenter, blinded, randomized, 2×2 factorial controlled trial set at 14 geriatric outpatient clinics in Canada for 12 months. This study did not confirm the results of Loeb et al. [246]; instead, there was a significant deterioration in SADAScog over time with both rifampin and doxycycline in comparison with placebo. Another recent clinical trial, with minocycline, reported by Howard et al. [248], used an experimental design of 1:1:1 in a semifactorial design for patients to receive minocycline (400 mg/day or 200 mg/day) or placebo for 24 months. This clinical trial also found that minocycline did not delay the progress of cognitive or functional impairment in people with mild AD during a 2-year period and also found that 400 mg of minocycline was poorly tolerated in this population. These contradictory results can be explained by the fact that antibiotics target directly the infectious agents, which may not be present at the stage of the disease when they were used. The diferences in patient selection as well as the period of administration and various cognitive outcomes may also explain the apparent contradictions. Furthermore, as recently reported by Balducci and Forloni [249], doxycycline, which crosses the BBB, has had compelling preclinical results in mouse models of AD against Aβ oligomers and neuroinflammation. However, by targeting β-amyloid oligomers, as have many other trials, it may not be efficacious at the later stages of the disease. Another interesting question is the relationship between microbiota, AD, and dysbiosis. Recently, a review discussed this relationship

[250], raising the possibility that broad-spectrum antibiotics can greatly affect the composition of the gut microbiota, reduce its biodiversity, and delay colonization for a long period after administration, which suggests that the action of antibiotics in AD could be wide and even opposite, depending on the type of antibiotic and on the specific role of the microbiome in AD pathogenesis. All these antibiotics also modulate the neuroinflammation; however, neuroinflammation may be somehow protective at some stages, by countering the microbial presence, rather than being only the cause for neurodegeneration [250]. More studies at different stages of AD are warranted to assess the exact role of antibiotics in the treatment of AD.

It is well known that *P. gingivalis* is almost impossible to eliminate by conventional antibiotics. Two other possibilities exist which would neutralize the virulence factors of these microorganisms. In animal studies, recently developed small molecule inhibitors COR286, COR271, and COR388 have been shown to protect animals from neurodegeneration, decrease the *P. gingivalis* load, and also decrease the burden of Aβ [52]. One small molecule is under clinical trial by Cortexyme to neutralize gingipains [52]. The second strategy involves vaccination of individuals with virulence factors [251–254]. Trials of vaccines to prevent or cure periodontitis are currently being considered [255]. We eagerly await the conclusion of these studies to see whether, by targeting the virulence factors, we can prevent or decrease the progression of AD. Of course, there are other virulence factors which could be targeted from any of the microorganisms. In the meantime, another possibility for treatment would be the use of peptoids (short peptidomimetics), which have been shown to be very effective antimicrobial substances in vitro and in mice [58, 256, 257]. Furthermore, in this line, the expression of natural antimicrobial peptides like LL-37 may be induced systemically [258, 259]. Recently, it was demonstrated to be effective against *Staphylococcus aureus* biofilms [260], and so it may also be useful against other biofilms, such as those created by *P. gingivalis*. The cytotoxic properties of LL-37 may limit its effective use [261, 262]. Nevertheless, new engineered peptides and peptidomimetics may be developed.

However, it should also be noted that considering the polymicrobial nature of AD, one antimicrobial agent might not be enough to treat this disease. A combined multi-target designed treatment should be envisaged.

There may be other possible treatments. The immune system may also be influenced by an anti-inflammatory treatment in a pulse form in later life or as soon as any chronic inflammatory disease manifests itself in the organism. The modulation by probiotics may also be beneficial to maintain the health of various microbiomes in the organism. Recently, a large epidemiological study showed that *Bacteroides* species were less represented in AD patients, suggesting that manipulation of the microbiota may be advantageous for AD

[263]. Recently, a bioengineered curli was used as a restorative therapy for the intestinal barrier [264]. Curli patterned on bacterial models may promote tolerance against certain bacteria in the intestinal tract. They act by inhibiting instead of stimulating the TLRs (TLR-2 and TLR-4) [265].

Furthermore, immunotherapy as in the case of cancer may also be possible. Indeed, microbes have also been shown to pervert T cell co-receptors to decrease immune activation and evade detection [266]. In this context, it is worthwhile to mention that *P. gingivalis* is able to subvert programmed cell death protein 1 (PD-1), to further escape the host immune response [267].

Of course, other general supportive therapies which may reinvigorate the immune system, making the microbiome healthier through nutrition, exercise, or the administration of ketone bodies, may be envisaged. Modulation of dysbiosis by any means may alleviate the burden of neuroinflammation and microglial activation. In this line, a very recent study by Nagpal et al. [268] used modified a Mediterranean-ketogenic diet (MMKD) to modulate the gut microbiome in subjects with MCI. Their data suggested that in MCI patients, the gut microbiome has specific characteristics and MMKD can modulate the gut microbiome and metabolites in association with AD biomarkers such as Aβ in the CSF [270]. However, these authors did not perform any cognitive tests, so their observations remain to be validated at the clinical level. Cunnane's group investigated a medium-chain triglyceride ketogenic diet and showed improvement in the executive functions of MCI patients; however, its effect on the microbiome was not studied [269]. In vitro studies showed that exposure of human macrophages to short-chain fatty acid butyrate may increase macrophage antimicrobial activity through histone deacetylase 3 (HDAC3) inhibition [270]. In small studies in China targeting gut dysbiosis, GV-971 (a mixture of acidic linear oligosaccharides) reversed cognitive impairment by decreasing neuroinflammation [271].

If we consider the role of senescent cells and their secretory phenotype (SASP) in the pathogenesis of AD related to infection, inflammation, and altered autophagy and mitophagy, one obvious treatment would be to eliminate these cells, as has already been suggested as an anti-aging treatment [272, 273]. Indeed, in this context, ciprofloxacin has been shown to modulate the accumulation of senescent DNA in SASP and, as such, played a senolytic role [274]. Further trials would be warranted to confirm this effect. Another molecule which may act as a senolytic is rapamycin, which targets the inhibition of mTOR [275, 276]. Furthermore, recent studies have demonstrated that mTOR inhibition resulted in the restoration of the intestinal barrier damaged by *P. gingivalis* [277, 278]. Interestingly, lithium has been shown also to modulate mTOR and GSK3β, which protect the intestinal barrier by decreasing EC senescence as well as the integrity of the BBB [279]. In this way,

manipulation of mTOR may become a multi-effect treatment eliminating senescent cells, restoring integrity of the gut barrier, and restoring the altered gut microbiota which occurs with aging [280].

Another molecule, azithromycin, an anti–*P. gingivalis* macrolide antibiotic, also has mTOR-modulating properties and has senolytic effects, and may be useful in AD treatment [281, 282]. Concomitantly, other known antibiotics, such as minocycline and rifampicin, aside from inhibiting the NLRP3 pathway, may facilitate the removal of senescent cells [184, 283]. Thus, the use of antibiotics that double as senolytics links infection, inflammation, and cell senescence, which are accentuated by external and internal factors such as aging.

Thus, an obvious means to treat the infectious pathomechanism of AD would be the modulation of NLRP3 activation. This was shown in the case of fluoxetine, a selective serotonin reuptake inhibitor [284]. Indeed, a recent trial showed that fluoxetine has been able to decrease the progression from MCI to AD [285]. Along the same line of evidence, since defective mitochondria stimulate the NLRP3 pathway, the elimination of these defective mitochondria by increasing mitophagy may also be an effective therapy. Interestingly, some antibiotics, such as tetracycline, seemed to be able to increase mitophagy in AD [286]. Obviously, direct inflammasome inhibitory substances may also have a therapeutic role in AD. Among the most promising, as already mentioned, are short-chain fatty acids such as butyrate [287].

Another interesting therapeutic approach may stem from observations showing that glucagon-like peptide-1 (GLP-1) facilitates immune tolerance [288, 289] and may be upregulated by LPS stimulation. This generated the suggestion that GLP-1 may behave as an AMP [290]. Moreover, GLP-1 seemed to inhibit the development of A1 inflammatory astrocytes [291]. This has led to a new trial in AD using a well-known drug used in type 2 diabetes, liraglutide, which is a GLP-1 receptor agonist [292].

Yet another group of molecules which may be considered in AD therapy because they target the infection hypothesis at its origins are iron chelators [293]. Iron is essential for bacterial growth; thus, its chelation may enhance body defenses and diminish the microbial load. Moreover, recently, iron has also been shown to contribute to cell senescence [294] via stimulation of the mTOR pathway and inhibition of mitophagy [295]. Thus, iron chelators such as deferoxamine are mTOR inhibitors [296]. A natural in vivo iron chelator, lactoferrin, has been shown to bind LPS and thus to deactivate NLRP3 [297]. It has also been demonstrated to be an AMP with anti–*P. gingivalis* activity [298, 299]. So, lactoferrin may become a powerful treatment for AD [300–303].

New developments may include small molecules that target mitochondria such as MitoQ, Mdicvi-1, and SS31, which have proved to be efficient in preventing mitochondrial

dysfunction and restoring mitochondrial homeostasis in cell cultures and in experimental animals; however, their use alone or in combination in humans awaits clinical trials [304]. In addition to iron chelators, mito-modulators have also been proposed to counteract the dysfunction of mitochondria in AD that has possibly been induced by microbial by-products such as gingipains. The overproduction of ROS associated with infection and microglia stimulation may be targeted by endogenous antioxidants such as reduced glutathione (GSH) [305] as well as by exogenous antioxidants, which are found in various nutrients as well as in diets such as the Mediterranean diet [306].

However, the most rewarding treatment would be prevention. In this way, we can imagine that vaccines against the microorganisms that are involved may be developed. An agent capable of destroying biofilms would also be a major breakthrough to treat the mouth microbiome and as such prevent AD.

Figure 1 and Table 2 summarizes potential interventions.

8 Can We Learn from "Why" to Find "How" to Prevent or Treat "When"?

While various interventions are possible, we still have not identified the reason(s) why a pathogen would migrate to the brain. Understanding the events leading to pathogenic migration and colonization of the brain should help develop prophylactic strategies to reduce AD onset.

The direct relationship between amyloid plaques and presence of pathogens in the brain has not been firmly established despite strong circumstantial evidence. We do

Table 2 Potential interventions

Targeting microorganisms directly
Antiviral agents
Antibacterial agents (antibiotics)
Antifungal agents
Immune-modulating treatment
Vaccination
Anti-inflammatory treatment
Checkpoint inhibitors
Cell biological treatment
Senolytics
Antimicrobial peptides
Iron chelators and mito-modulators
Supportive treatment
Probiotics/prebiotics
Ketone bodies
Nutritional support
Physical exercise

know that amyloid plaques are also present in individuals without AD. Similarly, individuals with atherosclerotic plaques are not all equally at risk of calcification and blood vessel disruption. This strongly suggests that pathogen migration to the brain may be independent of amyloid plaque formation per se.

Is it then possible to prevent this migration? Would that be enough to prevent the onset of AD? The contribution of ApoE isoforms in the susceptibility to AD can also be due to the fact ApoE4 facilitates entry to the brain [307]. Burgos et al. [308] have found that mice in a humanized mouse model expressing human ApoE4 have high levels of HSV-1 in the brain compared to ApoE3 humanized mice, while no difference was observed in viral load in other organs. A systematic study of other pathogens would be necessary to understand the array of pathogens that might gain increased access to the brain with the ApoE4 carrier.

Other mechanisms such as crossing the BBB have been put forward. Lachenmaier et al. [309] demonstrated that *Toxoplasma gondii* modulated gene expression of brain endothelial cells to promote its own migration through the BBB. They suggested that this enhanced migration could be via a "Trojan horse" mechanism with infected cells having a CD11b + CD11c ± phenotype. Another intriguing characteristic of *T. gondii* invasion of the brain was its propensity to develop low metabolic activity [310] upon entry into the CNS. This fine activity balance may also exist for a series of other pathogens located in the brain, but it may be disrupted during acute events.

Current concepts and data would imply that the brain of individuals without AD is free of pathogens. However, it appears that many or most individuals have microorganisms in their brain, as revealed by the recent report of a brain symbiotic ecosystem where restricted types of microorganisms can survive without inducing pathology (neurobiome) [52].

Could this be the result of an efficient immune cell–pathogen interaction specific for the brain environment? The logical consequence would be that a trigger is needed to disrupt this fine equilibrium just as in the gut where the well-arranged balance between microbes and the intestine is periodically disrupted and results in dysbiosis.

It is largely unknown which acute stress or repetitive acute stresses may be responsible for the activation of the metabolic switch leading to pathogen proliferation and subsequent sequelae. This will require intense research. A few possibilities exist: [1] brain inflammation associated with microvasculature defects; (2i) severe gut dysbiosis associated with leakage sensed in the brain; [3] acute infectious disease; and [4] major organ failure leading to transfer of biological reserves from the brain to the corresponding organ/system. Independent of the cause, understanding the brain symbiotic ecosystem (neurobiome/neurodysbiosis) and its regulation will enable better control of the events associated with AD onset.

9 Searching for New Directions in Drug Discovery

The *National Alzheimer's Project Act* by world leaders mandates a plan, which articulates the ultimate goal of preventing or effectively treating AD by the year 2025 [311]. To propose a possible pathway, it is important to put into perspective past failures, discuss novel opportunities, and understand the feasibility of delivering a drug by 2025. Several decades of research on competing hypotheses for explaining the cause of AD [e.g., cholinergic [312], amyloid [313], tau [314], glucose synthase kinase 3 [315], inflammation [316]] led to the development of drugs that reached clinical trials but failed. Despite billions of euros spent worldwide on drug development and clinical trials based largely on animal modeling, these have repeatedly failed to translate into effective interventions [317]. Under these hard-to-accept empirical observations, it is imperative to consider alternative hypotheses (e.g., the infection hypothesis), but also to consider drug development and research strategies that shy away from transgenic animal models that do not accurately reproduce human AD.

Indeed, recent technological leaps in stem cell research have led to the ground-breaking development of lab-grown human mini-brains, which reproduce the hallmarks of AD [318, 319]. This alternative model allows for testing of various in vivo–based hypotheses and extract correct and complex information. Combining these advances to the infection hypothesis of AD, as well as the Antimicrobial Protection Hypothesis of AD [160], provides clear targets and the framework for novel AD drug designs. Indeed, since Aβ is a powerful antimicrobial peptide that targets and neutralizes AD pathogens, it is reasonable to consider the development of a cocktail of novel and more powerful antimicrobial peptides based on the Aβ template. To achieve these ultimate goals, we envisage a multi-stage, closed-loop framework between in silico drug screening and drug testing in mini-brains as follows. First, data mining in existing databases (e.g., cAMP) and antimicrobial activity prediction via rational design [320] should generate analogs with improved activity. Second, state-of-the-art molecular simulations should be employed to determine the mechanism of action of Aβ against AD pathogens. Third, by combining information gained from step 1 and 2, and with further determination of physical–chemical descriptors of the generated analogs and Aβ, these can be used to train and screen potential antimicrobial peptides candidates via advanced machine-learning drug discovery software.

This final stage should involve testing against user-desired properties (e.g., half maximal inhibitory concentration (IC50)), as well as multiomics analysis. In this way, antimicrobial peptides sequences can be ranked in terms of the desired property, and those of poorest quality are rejected, allowing a new population to be selected.

Note that biofilm experiments in neural tissue based on multiomics data from patients and deceased frozen brains can be recreated in mini-brains and tested. Moreover, modern high-throughput technologies enable rapid and efficient simultaneous acquisition of multiomics data in the course of a single experiment [321]. This is significant since it departs from traditional experimental studies, which are usually carried out to isolate the effects of a single mechanism and not to investigate the interactions of many mechanisms. This leads to a set of results that seem conflicting; thus, it is difficult to interpret or understand the interactions of the underlying mechanisms leading to the pathogenesis of the disease.

The observables of such a modeling approach could in principle be integrated with a drug discovery process and therefore lead to a systematic and holistic screening of antimicrobial peptides with high therapeutic efficacy against AD pathogens. Therefore, novel biological models and experimental approaches, as well as multiomics acquisition devices provide unique opportunities to study and accelerate drug development in the context of novel hypotheses of AD by coupling it to advanced data analysis and state-of-the-art in silico drug screening. Moreover, this proposed pathway has the potential to reduce the overall cost of drug development.

10 Conclusion: Perspectives

It seems clear that it will be difficult to find one pathogen to explain the whole spectrum of AD in the spirit of the infection hypothesis. From the available data, it seems that we should think instead about a causative polymicrobial community which affects the immune/inflammatory reactions in the brain and in the periphery, and which interacts with various factors such as genetics, environment, and age. Thus, more properly, AD may be considered a complex syndrome involving dysregulation of the brain's immune system. Obviously, future treatments (and/or prevention) of AD will not be one simple molecule but a multimodal complex treatment. This will combine most probably antimicrobial, senolytic, and anti-inflammatory agents with pro-mitophagy treatments. In this way, prevention and even treatment of AD will most probably become feasible. Many clinical investigations and trials will be necessary before we can arrive at this stage.

Compliance with Ethical Standards

Conflict of interest The authors, Tamàs Fülöp, Usma Munawara, Anis Larbi, Mathieu Desroche, Serafim Rodrigues, Michele Catanzaro, Andrea Guidolin, Abdelouahed Khalil, François Bernier, Annelise E. Barron, Katsuiku Hirokawa, Pascale B. Beauregard, David Dumoulin, Jean-Philippe Bellenger, Jacek M. Witkowski, and Eric Frost, declare that they have no conflict of interest related to this article.

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