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INVITED REVIEW

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Multifactorial glial responses and their contributions to Alzheimer's disease continuum

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Abstract

Alzheimer's disease (AD) is the most common neurocognitive disorder. Various factors are intricately intertwined before clinical symptoms appear, although both amyloid-β peptide deposition and neurofibrillary tangle formation (i.e. pathological hallmarks of the AD brain) are established. Among such factors, glial responses have been increasingly recognized as important roles in the progression of these pathologies and viewed as one component of the AD continuum. However, the detailed molecular and cellular mechanisms of glial function underlying AD pathogenesis remain to be elucidated. Recent studies showed that peripheral immunity, gut microbiota or environmental factors influence brain pathophysiologies through communication with glial cells in the brain. This disease complexity makes understanding AD etiology difficult and hinders the development of effective therapeutic strategies to tackle this disease. Conversely, aged patients often suffer from multiple – not a single – diseases as multimorbidity, and AD pathogenesis might be related to pathologies caused by other diseases. Hence, investigating AD as a systemic disease has become critical for identifying therapeutic interventions. This review aimed to summarize current knowledge on AD research and share perspectives for understanding glial functions regarding AD pathophysiology.

KEYWORDS
Alzheimer's disease continuum, Alzheimer's disease, astrocyte, brain–periphery interaction, glial response, microglia, multimorbidity

1 | INTRODUCTION

Alzheimer's disease (AD) is a common cause of neurocognitive disorder in the elderly and imposes tremendous social issues on modern society. However, a definitive solution to AD has yet to be established. Recently, interventions with anti-amyloid antibodies, such as aducanumab[1] and lecanemab,[2] are effective in some patients with early AD. This implies that a proof of concept has been obtained that amyloid-β (Aβ) removal therapy from the preclinical stage might reduce disease progression. Conversely, clinical trials with anti-tau antibodies against AD or anti-synuclein antibodies against Parkinson's disease therapies have been inconclusive at present,[3,4] and so far, strategies targeting the upstream of the amyloid cascade appear to be promising. However, clarifying the molecular and cellular mechanisms underlying AD pathogenesis, and developing fundamental disease-modifying drugs is necessary to fully prevent and treat AD.

Recent discoveries of many plasma and cerebrospinal fluid biomarkers identified that pathological changes that characterize AD occur sequentially in an overlapping manner before the clinical onset.[5,6] AD is now referred to as a continuum rather than a discrete disease

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entity by covering both biological and clinical stages of AD during disease progression (Figure 1a).[7] This so-called "AD continuum" is based on the amyloid cascade hypothesis where senile plaque formation represents a primary hallmark of AD.[8] Particularly, familial AD mutations on the *APP* (amyloid precursor protein) and *PSEN1/2* (presenilin-1/2) genes strongly drive Aβ production and plaque formation in the brain, causing the earlier onset of AD.[9] In addition, genetic risk factors of AD also involve abnormal Aβ metabolism that in turn aids plaque formation.[5] Subsequently, the appearance of neurofibrillary tangles (i.e. the accumulation of hyperphosphorylated tau) finally leads to neurodegeneration.[8]

Although the pathological cascade of the AD continuum is supported by the genetical,[9,10] pathological[11] and live-imaging studies,[12] the underlying mechanisms that connect each pathology remain elusive. Current evidence hints at the role of the glial cell population, because these cells can respond and contribute to the development of pathological hallmarks of AD. Importantly, inflammation that differs in degree and elicited molecular pathways should also occur continuously at distinct levels of the AD continuum (Figure 1a). The consequent inflammatory burden is likely to accumulate and become diverse over the disease progression, highlighting that further insights into the AD pathogenesis can be provided by untangling the mixed inflammatory environment in the AD brain. Even more complicated, other mediators can also modulate the glial reactivity and possibly affect the AD pathogenesis (for instance, adaptive immune cells in the brain, altered gut microbiota and co-existing brain or systemic pathology; Figure 1b). The present review outlines how glia play key roles in the development of the AD continuum, and how peripheral mediators or multimorbidity might influence the continuums of AD pathology and glial reactivity.

2 | GLIAL CELL NETWORK IN THE AD CONTINUUM

Recently, glial cells have been recognized to play a major role in the pathogenesis of neurodegenerative disorders, including AD.[13] In

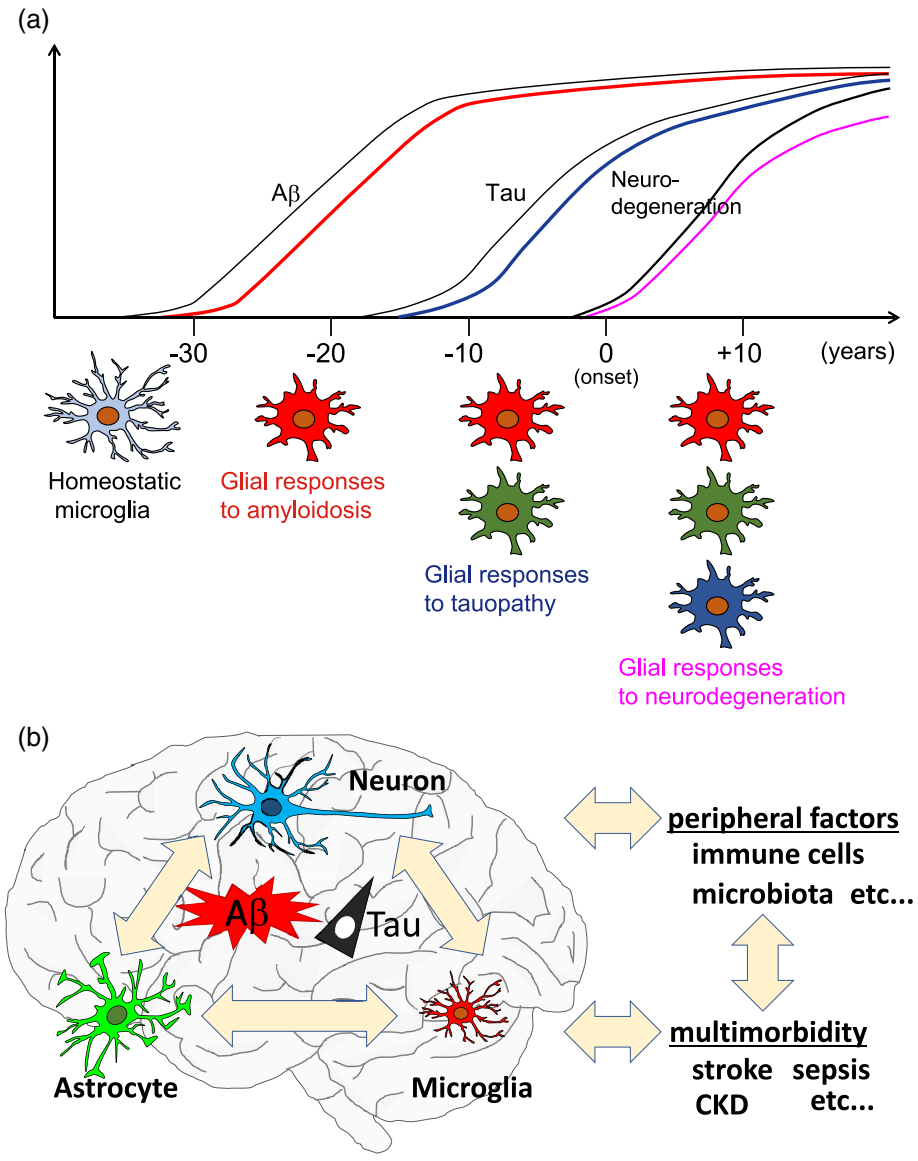

FIGURE 1 The complex inflammatory milieu along with the Alzheimer's disease (AD) continuum. (a) The pathological trajectory of AD is best described by a temporal continuity of pathological hallmarks, whereby aggregates of β-amyloid (Aβ) and later hyperphosphorylated tau protein accumulate in the brain, followed by neuronal cell death (black lines). Traditionally, inflammatory responses have been simplified as "neuroinflammation" and integrated into the "AD continuum" as an additional facet of AD pathology. Nevertheless, every sequence of AD pathology is known to stimulate the glial cells differently. Amyloid pathology first elicits the Aβ-related inflammation (red line), whereas tau accumulation and neurodegeneration generate overlapping, but different, inflammatory signatures or glial cell behavior at the middle (blue line) and late spectrum (purple line) of the AD continuum. This results in mixed glial responses and creates a heterogeneous inflammatory environment in the brain. (b) Glial response to the AD continuum can be intensified by peripheral mediators (such as the infiltrated T cells and altered gut microbiota) and co-existing chronic diseases (including stroke, sepsis and chronic kidney disease [CKD]).

particular, factors expressed in glial cells, such as triggering receptors expressed on myeloid cells 2 (TREM2), have emerged as a focus of attention, following the genome-wide association study of rare variants of AD.[14] TREM2 is expressed specifically in microglia, and is the initiator of glial responses by binding to various ligands, including Aβ.[15] Deletion of TREM2 function was shown to reduce microglial phagocytosis and accelerate Aβ accumulation.[16] This has led to a growing interest in the diversity of microglial functions. Previously, microglial subtypes were limited to the classical classification of M1 and M2,[17] but recent RNAseq analyses have shown that microglia can be classified into a variety of types. In particular, functional analysis of TREM2-expressing disease-associated microglia has become a hot topic.[18] These results showed that microglial abnormalities affect other glial cells, such as astrocytes and oligodendrocytes.[19] Furthermore, the diversity of gene expression signatures of microglia, astrocytes and oligodendrocytes in the brains of patients with AD has been shown.[20,21] Conversely, RNAseq analysis has been carried out in various AD model mice. Such datasets from 5×FAD mice (Gene Expression Omnibus database [GSE150934]),[22] APP/PS1 mice (the dataset will be deposited soon), 3×Tg-AD mice (GSE92926),[23] *App*$^{NL\text{-}G\text{-}F}$ knock-in mice (GSE127893)[23–26] and rTg4510 (the dataset will be deposited soon)[25] are available. Interestingly, microglial proprieties in the Aβ and tau pathology models appear to differ, suggesting the existence of pathology-specific microglial subtypes.[13] Gene expression in the amyloidosis model also shows the presence of model-specific microglial subtypes, but gene expression in the disease-associated microglia appears to be similar. However, the direct extrapolation of the gene expression profiles of microglia to humans might be debatable. Additionally, RNAseq analysis showed that the genetic background of the model mice also results in microglial diversity, and rare variants found in genome-wide association study (such as ApoE, TREM2 and Sorl1) seem to be affected by the genetic background of model mice.[27] Both differences between models, and between humans and animal models (including sex differences in glial cells) should be considered.[28] Capturing the pathophysiology in the AD brain from the analysis using animal models of AD is important while considering these factors. Additionally, the aspect of homeostatic microglial dysfunction is important.[25,29] In particular, not only the massive activation of glial cells, as characterized by disease-associated microglia, but also a decreased maintenance of homeostatic function for the brain environment preservation, are thought to be extremely important in the onset of diseases. The diversity of other brain cells (e.g. astrocytes) needs to be taken into account, similar to microglial subtypes.

Whereas inflammatory responses are generally important defense responses for the body, chronically maintained inflammation caused by sustained glial activation is regarded as a pathological trigger for various disorders. This chronic neuroinflammation is mediated by not only microglia, but also other cell types that are simultaneously stimulated as a whole (namely, glial cell network responses). Epidemiological studies have long suggested that anti-inflammatory drugs might be effective for AD prevention and treatment.[13,30] This is congruent with the increased expression of pro-inflammatory cytokines (including, but not restricted to, interleukin-1β [IL-1β], IL-6 and tumor necrosis factor) in the AD brain at post-mortem.[31] Notably, nuclear factor-κB (NF-κB) is a well-established upstream transcriptional factor for inflammation initiation and cooperates with an inflammatory platform, termed inflammasome.[32,33] In particular, the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome appears to contribute to Aβ and tau pathogenesis.[34,35] Recently, neuronal cell death by pyroptosis (an inflammatory cell death downstream of the NLRP3 inflammasome) has been found to be involved in the AD brain through the activation of the NLRP3 inflammasome exclusively in microglia (but neither in astrocytes nor neurons).[36] Conversely, NLRP3 inflammasome might not be involved in the early stage of amyloidosis, and further scrutiny is needed under chronic conditions as a non-inflammatory response of glial cells (in preparation). Furthermore, one of the inflammasome components, including apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), can form speck-like aggregates by itself and contribute to pathological deterioration,[37] and act as a cross-seed for Aβ.[38] Additionally, NF-κB is activated and involved in the expression of cytokines in astrocytes derived from induced pluripotent stem cells of patients with AD,[39] suggesting that NF-κB is a common pro-inflammatory regulator in both microglia and astrocytes. Research on drug development targeting NF-κB is underway, and future trends are attracting attention.[40] Of note, other investigators reported the roles of oxidative stress involving reactive oxygen species,[41,42] metal/lipid metabolism[43,44] and aging,[45] thus clarification of how these factors are intricately intertwined would provide more insights into AD pathogenesis.

The amyloid cascade hypothesis proposes that Aβ accumulation triggers the formation of tau pathology. For example, the formation of neurofibrillary tangles in tau transgenic (Tg) JNPL3 mice is accelerated by the coexistence of Aβ accumulation.[46] Furthermore, treatment with immunosuppressive agents including FK506 suppressed the tau pathology formation in P301S-Tau-Tg mice,[47] suggesting that glial cells are involved in tau pathology formation. Conversely, non-pathological neurofibrillary tangles, which are confined to the entorhinal cortex until Braak stages I–II, seem to spread and expand extensively in the brain after Braak stages III–IV, when Aβ pathology spreads into the entorhinal cortex and hippocampus according to Braak's classification of AD pathology.[48] Additionally, the early symptoms of dementia are evident around Braak stages III–IV, and this tau propagation is hotly debated as having important implications for pathogenesis and dementia symptoms. Interestingly, tau propagation was accelerated in mice with Aβ pathology,[49] and even more exaggerated in tau-humanized *MAPT* knock-in mice when tau seeds extracted from patients with AD were inoculated into mice.[50] Microglial contribution to the uptake and release of tau seed has been recently reported using animal models.[51] Consistently, positron emission tomography imaging studies in humans revealed that tau propagation was correlated with microglial activation along the Braak stage.[52] Furthermore, glial roles in neurodegeneration (that is, the final stage of the AD continuum) were recently documented as in pyroptosis,[36] necroptosis[53] and phagoptosis,[54] reflecting different glial responses to

amyloid and tau pathology within the AD continuum.[13] Together, the glial cell network in the AD brain should be carefully investigated, because it is subtle and dynamic, transforming from moment to moment as the disease progresses in the AD continuum.

3 | BRAIN–PERIPHERY INTERACTIONS IN AD PATHOGENESIS

Recent studies showed that the peripheral body environment could influence the central nervous system (CNS) in various ways. For this reason, a more holistic research approach would enhance our understanding of AD pathology. Noteworthily, this particular viewpoint has therapeutical potential, because many CNS-targeting drugs have pharmacokinetic difficulties in crossing the blood–brain barrier (BBB). Several of these peripheral targets highlighted previously include the brain border, adaptive immune system and intestinal microbiota.

Because the CNS was considered to be an immune-privileged system,[55] the majority of research focused on the brain resident immune cells in the AD brain that could acquire the aggressive phenotypes.[18,56] Increasing lines of evidence highlighted the importance of a tightly regulated CNS border where meningeal lymphatic vessels and skull bone marrow maintain the immune cell dynamics in the brain.[57–60] This brain border is also known as the key component of the glymphatic system that mediates clearance of toxic proteins in AD.[61] For example, extracellularly injected Aβ and tau can be removed into the cerebrospinal fluid through aquaporin-4.[62–65] Meningeal lymphatic vessel occlusion (through reactive oxygen species production by Visudyne-mediated photoconversion) aggravated Aβ deposition in the meningeal lymphatic vessels and brain parenchyma of 5×FAD mice.[65]

Lymphocyte infiltration into the brain parenchyma also contributes to the pathogenesis of AD. A multifactorial data-driven analysis based on the multimodal brain images and biomarkers showed that vascular dysregulation was an early pathological event during disease progression.[66] The leaky BBB in patients with early AD was associated with cognitive decline.[67] More T cells were observed in the hippocampus of patients with AD than in those with other cognitive impairments and mental diseases.[68] Of note, Down syndrome is pathologically related to AD, because the trisomy of chromosome 21 produces an extra copy of the *APP* gene.[69,70] The highest T cell infiltration was recorded in those with Down syndrome possessing AD pathology, substantiating the notion that the presence of T cells in the brain is correlated with amyloid pathology.[68] In support, compromised BBB integrity and robust $CD8^+$ T cell extravasation were found in APP/PS1 mice.[71,72] The roles of these infiltrating T cells are as yet unclear, but the transcriptomic analysis showed the involvement in synaptic plasticity dysfunction.[72] These results collectively suggest that amyloid pathology impairs vascular functions, which in turn leads to T cell extravasation and T cell-mediated neuronal damage. Meanwhile, the detection of extravascular $CD3^+$ T cells was also correlated with tau protein accumulation.[71] T cells were observed in the brain of multiple models of tauopathy, which lack Aβ deposition (for example, THY-Tau22 mice and rTg4510 mice).[73,74] Depletion of T cells by administering anti-CD3 antibody rescued the spatial memory deficits in these mice, hinting at the possible involvements of T cells in synapses.[75] Altogether, brain border manipulations that prevent the T cell infiltration or dampen neurotoxic T cell function seem to be therapeutically beneficial for AD.

Gut microbiota alteration affects the physiology and AD pathology in the brain.[76] The gut microbiota is the microorganisms that live in the digestive tracts, and its composition affects the metabolism of diet and drugs, the immune cell regulation, and the brain function.[77] The gut microbiota regulates brain function through the parasympathetic nervous systems and sympathetic nervous systems in physiological conditions in mice.[78,79] Fecal microbiota transplantation from young mice attenuates age-dependent learning impairment and microglial phenotypic changes associated with aging.[80] Gut microbiota-derived N^6-carboxymethyl lysine (a major advanced glycation end-product) is accumulated in the serum and brain of aged mice, and promotes microglial reactive oxygen species production.[81] Likewise, N^6-carboxymethyl lysine and other advanced glycation end-products increase in diabetic vasculature, and contribute to the development of atherosclerosis and increase the endothelial permeability to macromolecules.[82] Diabetes mellitus is associated with an increased risk of developing AD and cognitive dysfunctions, and these findings suggest that the metabolic control system, including intestinal bacteria, plays an important role in AD development.[83] This is supported by previous findings in patients with AD where N^6-carboxymethyl lysine levels were elevated or accumulated in plasma, neurons and endothelial cells in the brain.[84,85] Indeed, the elimination of gut microbiota by rearing mice in a germ-free environment led to reductions of Aβ and tau phosphorylation in the brain of 3×Tg mice.[86] The authors also suggested that this germ-free effect was masked by fecal transplantation from patients with AD, but not healthy controls.[86] In contrast, fecal transplantation from the wild-type mice ameliorated Aβ and tau pathologies in $ADLP^{APT}$ mice (novel APP-Tg mice with *MAPT* mutations).[87] One of the possible mediators might be short-chain fatty acids that are known to be derived from gut microbiota, and microglial contributions have been suspected. Supplementing short-chain fatty acids in APP/PS1 mice increased the Aβ plaque load and changed the microglial transcriptomic signature.[88] Conversely, gut microbiota depletion by an antibiotic cocktail (ABX) reduced Aβ load in APP/PS1 mice, which was diminished by microglial depletion with colony-stimulating factor 1 receptor inhibitor.[89] Interestingly, Aβ or phosphorylated tau deposition attenuation by ABX treatment was observed only in male mice, reflecting possible sex differences in microglial responses.[90,91] Overall, age- and disease-associated changes in gut microbiota composition and metabolism might serve as therapeutic targets for AD, although detailed mechanisms remain to be elucidated.

4 | MULTIMORBIDITY IN AD PATHOGENESIS

Age serves as an unambiguous risk factor for AD, but also for various other diseases, raising the awareness of the concept of "multimorbidity" – the presence of two or more chronic diseases in the same

individual.[92,93] Notably, multimorbidity was documented in 43% of patients at the time of dementia diagnosis, with a linear correlation between the number of conditions and dementia risk when elderly individuals ($n = 206\,960$) were followed up for up to 15 years.[94] Another prospective cohort study of middle-aged individuals ($n = 10\,095$) showed that the onset of multimorbidity, especially before the age of 55 years, doubled the risk of subsequent dementia during the follow up over 32 years.[95] The top five chronic conditions associated with dementia were Parkinson's disease, mental disorders, stroke, chronic kidney disease (CKD) and depression among the 13 diseases that defined multimorbidity in this study,[95] whereas other studies indicated hypertension, coronary heart disease, diabetes and pain.[94,96] Additionally, a recent population-based study ($n = 989\,800$) highlighted the importance of infection due to a twofold increase in dementia incidence in elderly survivors of sepsis.[97] These lines of evidence delineate possible, albeit probably multilayered, interactions between multimorbidity and dementia. In this context, multimorbidity is likely to accelerate or worsen the progression of AD pathology, because AD is characterized by a pathological trajectory over decades.[5] Here, we concentrate on three chronic conditions that can frequently shape multimorbidity in patients with AD and relate to glial responses to the co-existing pathology.

Stroke confers well-acknowledged risks for subsequent dementia, because post-stroke dementia represents one of the major vascular cognitive impairments that occur within 6 months post-stroke.[98] Indeed, a 5-year longitudinal study of 2080 patients with varying stroke severity confirmed a 50-fold increase in dementia among those with severe stroke and an acceleration of the estimated onset by 25 years.[99] Although conflicting evidence is available,[100] elderly patients with ischemic stroke showed higher retention of Aβ positron emission tomography radiotracer, Pittsburgh compound B, in the ipsilateral peri-infarct region with neocortical retention remaining normal.[101] Congruently, ischemic stroke (modeled by middle cerebral artery occlusion and bilateral carotid artery stenosis) in APP-Tg mice worsened the amyloid pathology[102,103] or induced de novo leptomeningeal Aβ deposition.[104] Meanwhile, patients with ischemic stroke had a heightened binding of tau positron emission tomography tracer (^{18}F-THK-5451) in the peri-ischemic and remote areas 3 months post-stroke.[105] In line with this, 3×Tg-AD mice manifested increased levels of tau phosphorylation after bilateral carotid artery stenosis and unilateral carotid artery occlusion.[103,106]

Previous studies indicated the involvement of several signaling pathways in the aggravation of amyloid and tau pathology. Notably, stroke can induce acute cerebral hypoxia in patients and animal models.[107,108] Tissue reperfusion has frequently failed due to persistent occlusion of the capillaries by clogged neutrophils ("no-reflow" phenomenon) even after a clot removal and recanalization of occluded vessels.[109] On this ground, hypoxia-related pathways (for example, hypoxia-inducible factor 1) are likely to be activated, thereby modulating both amyloid and tau pathology. To illustrate, hypoxia-inducible factor 1α upregulated β-secretase enzyme 1, and promoted Aβ production in APP-Tg mice and 3×Tg-AD mice after hypoxia and bilateral carotid artery stenosis, respectively.[103,110,111] Meanwhile, activated leptin signaling and impaired autophagy activity have been suggested as potential mechanisms for increased tau phosphorylation.[103,106] Nevertheless, others argued that leptin reduced tau phosphorylation[112] and hypoxia promoted autophagy.[113] These inconsistencies obscured the current understanding of how tau phosphorylation increased post-stroke, warranting further investigations in the future.

Furthermore, not all patients with stroke manifest cognitive decline during the recovery, and this differentiation has been proposed by pre-existing amyloid pathology upon stroke onset. Patients who were positive for Pittsburgh compound B in the brain at the time of stroke diagnosis presented a progressive deterioration of cognitive functions over 3 years, whereas negative patients did not.[114] Intriguingly, recent preclinical findings suggested that stroke lesion was exaggerated in the presence of Aβ, as evidenced by twice larger infarct sizes in APP-Tg mice than wild-type mice after middle cerebral artery occlusion.[115,116] One could speculate plausibly that tissue damage is more pronounced in patients with AD after stroke onset, contributing to worsening brain atrophy and cognitive decline through exaggeration of glial responses.

Our understanding of stroke–AD multimorbidity is also largely restricted to ischemic stroke and can be strengthened by considering intracerebral hemorrhage. This underestimation might be due to the less common onset of hemorrhagic stroke than ischemic stroke in the general population[117] and patients with AD.[118] Nevertheless, patients with ischemic stroke frequently showed hemorrhagic transformation (accounting for 27%),[119] and elevated BBB permeability was detected at the very early stages of AD before cognitive decline.[120] Evaluation of hemorrhagic stroke in patients with AD and the relevant animal models is currently sparse, and this will be another focus of future research in this field.

Elderly patients with sepsis (that is, life-threatening organ dysfunctions caused by dysregulated host responses to infections) can irreversibly impair cognitive functions in those who survived sepsis through systemic inflammation.[33] Brain structural changes in the medial temporal lobe – the brain region vulnerable to AD – and altered cognition were documented in those who survived sepsis and COVID-19 infection.[121–123] Notably, falls that necessitate hospitalization were recorded in one-third of patients with dementia,[124] and patients with AD had a threefold higher risk of hip fracture, which could cause sepsis in the elderly after the surgery.[125,126] This is corroborated by motor dysfunctions in patients with mild cognitive impairment and AD, as well as mouse models.[127–130] Studies investigating the effects of systemic inflammation on AD pathology were flourishing, and reported multifactorial mechanisms that drove these changes. For instance, intraperitoneal injection of Gram-negative bacterial cell wall component, lipopolysaccharide, increased Aβ deposition in APP-Tg mice and *App* knock-in mice.[131,132] The same was true for APP-Tg mice that underwent cecal ligation and puncture that simulated polymicrobial infection.[133] Proposed mechanisms that enhance amyloid pathology include: (i) reduction of Aβ phagocytosis by microglia, possibly due to microglial migration toward blood vessels;[131–134] (ii) secretion of glia-derived proteins that can cross-seed Aβ peptides (as exemplified by ASC specks);[37,131] and/or (iii) upregulation of cytokine-responsive proteins that regulate APP processing (e.g. interferon-induced

transmembrane protein 3).[135] Likewise, systemic lipopolysaccharide injection into Tau-Tg mice acutely boosted tau phosphorylation and chronically exacerbated neuronal loss in the cortex.[136] A similar increase in tau phosphorylation in the hippocampus was found after biweekly injections of lipopolysaccharide in young and aged 3×Tg AD mice.[137,138] Some reasoned alteration of cyclin-dependent kinase 5 and glycogen synthase kinase 3β activities at different ages of mice,[137,138] whereas others pointed to different kinases, such as p38 mitogen-activated protein kinase.[139] Importantly, the effects of systemic inflammation are not limited to the amyloid and tau pathology, hence adding a further complexity of its consequences. For example, systemic inflammation can decrease the number of synapses in the hippocampus,[140,141] generate long-lasting innate immune memory in microglia that modulates amyloid pathology,[142] dampen neurogenesis in the hippocampus[143] and increase the BBB permeability.[144]

Finally, emerging evidence has implicated the association of CKD with mild cognitive impairment and dementia.[144,145] At present, AD neuropathology exacerbation by persistent renal dysfunctions in patients is unknown, but likely, because the uremic toxins in the blood include pro-inflammatory cytokines that can elicit systemic inflammation (e.g., IL-1β, IL-6, IL-8 and tumor necrosis factor).[146] In support, unilateral nephrectomy for 6 months worsened Aβ pathology, promoted tau phosphorylation and augmented spatial memory deficits in APP-Tg mice.[147] The underlying mechanism remains unexplored, but AD pathology aggravation might be mediated through systemic inflammation or, alternatively, hypertension in view of the intermittent link between CKD and cardiovascular disease.[148] Prolonged angiotensin II infusion accelerated Aβ deposition in APP-Tg mice,[149] and augmented tau phosphorylation in the cortex of wild-type mice.[150] However, neuroinflammatory responses to CKD and their contributions to AD pathology exacerbation remain unclear, thus requiring more investigations to address the CKD–AD cross-talks in the future.

5 | CONCLUSION

The present review has outlined the recent findings on the pathological roles of glial cells in the AD continuum. To develop preventive, disease-modifying and ultimately curative therapies, it is essential to decipher the whole spectrum of AD pathogenesis with a particular focus on the immune responses. Glial cells are indeed responsive to both amyloid and tau pathologies and, consequently, shape unique transcriptional signatures that govern their functions. Likewise, altered gut microbiota, stroke and systemic inflammation modified both glial phenotypes and AD pathology in mouse models, and likely, in patients with AD. Still, trends in research fields that are relatively novel tend to concentrate on non-glial cells, and more detailed examinations of glial populations are strongly encouraged in the future.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DISCLOSURE OF ETHICAL STATEMENTS

Approval of the research protocol: N/A.
Informed Consent: N/A.
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