Neuroinflammation in Alzheimer's disease

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Introduction

Alzheimer's disease (AD) represents the most common cause of dementia, accounting for roughly 70% of cases and as such a major health care challenge. Neuropathologically, AD is characterized by extracellular deposition of misfolded and aggregated beta-amyloid peptides (Aβ) as well as formation of intraneuronal tangles made of hyperphosphorylated tau. In addition, Alois Alzheimer had already described the histological abnormalities of astroglia and microglia, yet for a long time activation of these innate immune cells and their joint inflammatory reaction have been regarded as non-relevant, bystander reaction. Epidemiological, clinical, genetic as well as experimental studies have challenged and changed this view over the past two decades substantially. Immune mediated mechanisms have become a field of intense research and drug development. Consequently, one must consider which immunological process at which time point can be harnessed for therapeutic intervention. While in general such immune modulation may include preventive, disease modifying or even acute therapeutic strategies, it is commonly accepted that clinically silent or even inapparent disease stages may hold the greatest potential for such interventions. Importantly, the identification and definition of AD pre-stages, such as subjective cognitive impairment and mild cognitive impairment may allow together with fluid and imaging biomarker findings to delineate the time, duration and site where immune processes modification will successfully interfere with disease pathogenesis and progression. In this review, we summarize and weight the current knowledge on immune processes in AD. From human evidence, we will go further to the contributions of individual cellular compartments and the involved immune mechanisms.

Evidence for an inflammatory component in Alzheimer's disease

AD brain pathology The term "plaques" was introduced in 1898 for structures which are nowadays well-known as amyloid plaques in AD brain, even before Alois Alzheimer described the disease[2,3]. Glial cells surrounding these plaques were described and it was speculated that these plaques were from glial origin[2,3]. By now, it is well-established that microglia are activated and increased in AD brain, (1) being associated with Aβ plaques[4-6], [7] neurofibrillary tangles[8], (3) complement factors[4], and that they (4) produce immune mediators such as cytokines, chemokines, inflammasomes and radical oxygen species[4,5,9-14]. Microglia are involved already in the asymptomatic and symptomatic disease stages[15,16] and likely play a role in the clinical and pathological disease phenotype[17].In humans, associations have been reported for microglia with Aβ and hyperphosphorylated (p)tau, but not between Aβ and ptau consistent with microglia playing a pivotal role in the AD pathogenesis[18]. Diffuse Aβ plaques are present in the brains of middle-aged and elderly cognitively normal people[19], and the homeostatic markers of microglia (Iba1, P2Y12) respond to the appearance of Aβ[20]. While neuritic plaques defined by the presence of Aβ, ptau and microglia are a more specific feature of AD[21] with microglia expressing phagocytic markers CD68 and Macrophage Scavenger Receptor (MSR)-A[22]. Of note, there is a wide variety in Aβ deposits with different involvement of microglia in human AD brains[23]. Aβ in neuritic plaques tends to be more fibrillar, with dense cores, and has a more varied composition with the presence of $A\beta_{40, 42, 43}$, N-terminus truncated Aβ and other post-translationally modified forms[24-26]. AD cases with an atypical clinical presentation show a different spreading and morphology of pathological hallmarks, associated with different levels and spatial localization of microglia activity[17,27]. This supports the hypothesis that the spatial activation of microglia is involved in both the clinical and pathological presentation of the disease. In conclusion, microglia are involved early in disease and are instrumental for the morphology of Aβ deposits, spreading of pathology and the clinical presentation of AD patients[21].

Fluid biomarkers of inflammation While these pathological assessments require brain material, evidence for an ongoing chronic inflammatory disease component in humans has been further substantiated by probing of inflammatory fluid biomarkers primarily in cerebrospinal fluid or blood samples and by the development of microglial PET tracers such as TSPO ligands. Although the first studies on biofluid-based biomarkers for inflammation – most of all CSF or blood-based protein

markers – date back nearly 30 years[28], an unmet demand for reliable biomarkers capable of monitoring the various aspects of AD neuroinflammation remains. Moreover, since at present disease non-specificity of most inflammatory markers limit their value as trial outcome measures or further clinical use. Studies on "classical" inflammation markers, like CRP or pro-inflammatory cytokines, are large in number but have shown limited consistency in meta-analyses[29,30]. Quantitation of inflammatory mediators such as cytokines in CSF can be hampered by sensitivity of detection technologies[31], but novel ultra-sensitive immunoassays including Single molecule array (Simoa), proximity extension assay (PEA) and nucleic acid-linked immuno-sandwich assay (NULISA) or measurement in brain-derived exosomes might overcome such limitations[32-34]. For CSF, few proteins have emerged as robust markers to monitor neuroinflammation in AD due to their reproducible relation to pathological features of the disease: soluble TREM2 (sTREM2) as a marker of microglial activation, YKL-40 as an astroglial inflammation marker, and glial fibrillary acidic protein (GFAP) as a marker of general astrocytic activation[35-37]. Interestingly, the GFAP signal in AD is robustly replicated in serum and plasma; plasma/serum GFAP concentration increases in close association with onset of cerebral amyloid plaque pathology[38], which likely reflects astrocytic activation to the pathology[39]. Extensive proteomics studies that include validation in biofluids describe several other inflammatory messengers within sets of proteins affected by AD pathology[40]. Furthermore, novel immunoassays might enable detection of proteins like NLRP3 or ASC as biomarkers of inflammasome activation[41,42]. By their nature, CSF or blood based-fluid biomarkers will not allow for ascribing an inflammatory process to specific brain areas or regions and thus also neither its longitudinal spread over the entire disease trajectory.

Molecular Imaging/PET Also technically more demanding such questions can be answered by molecular imaging techniques including positron-emission tomography, that allow for temporal and spatial analysis of the living human brain. To visualize microglial activation by molecular imaging in human brain, radiopharmaceuticals have been developed targeting the 18 kD translocator protein (TSPO) within the mitochondrial membrane[43]. Current research aims towards the development of radiotracers targeting microglial receptors (e.g. P2X7R, P2Y12R, CX3CR1) which will allow to relate their detection more to specific microglial functions[44,45]. In the 2nd generation of TSPO tracers, two radiotracers (DPA-714, PBR28) have shown higher binding potential (2-3-fold higher) in comparison to first generation PK11195 and reduced background activity[46]. In AD, it has been demonstrated, that increased PBR28 binding (temporal, parietal) correlates to cognitive impairment and atrophy[47] as well as regional tau and amyloid deposition[48]. In a longitudinal set-up (2.7 years) n=14 amyloid-positive patients in comparison to n=8 amyloid-negative controls had a greater increase in TSPO binding in inferior parietal lobule, precuneus, occipital cortex, hippocampus, entorhinal cortex, and combined middle and inferior temporal cortex[49]. TSPO binding in temporo-parietal regions increased from 3.9% to 6.3% per year. The change in TSPO binding correlated with cognitive worsening. The annual rate of increased TSPO binding in temporo-parietal regions was about 5-fold higher in patients with clinical progression compared with those who did not progress. These results indicate, that in manifest AD, TSPO may serve as a biomarker of AD progression and response to anti-inflammatory therapies[49]. In contrast, in prodromal AD, it has been demonstrated that increased DPA-714 binding in temporo-parietal cortex was positively correlated with MMSE scores and grey matter volume, as well as amyloid load. In addition, n=30 patients with AD were dichotomized into slow or fast decliners after 2 years of follow-up. Excitingly, slow decliners showed higher TSPO-binding than fast decliners[50]. These results demonstrate, that microglial activation appears at the prodromal and possibly at the preclinical stage of AD, and seems to play a protective role at early disease stages[50,51]. Moreover, in patients, an increase of DPA-714 binding was observed at follow-up (mean 13.2% per year; for prodromal AD 15.8%; for manifest AD 8.3%). The positive correlations between increasing DPA-714 binding and clinical outcome measures (CDR, MMSE, hippocampal atrophy) suggests a detrimental effect of increasing neuroinflammation on clinical AD progression[52]. In contrast, high initial DPA-714 binding was correlated with a low dynamic increase of microglial activation and a favorable clinical evolution. Another study has proposed an early and late peak of microglial activation in AD trajectory[53]. Together, PET-based microglial imaging can decipher several microglial phenotypes at various disease stages and

represents a non-invasive biomarker that may be used to assess future immune-modulating therapies in AD.

Immune related genetics While post-mortem brain analysis, detection of inflammatory signals in biofluids and molecular imaging had been around for quite some time, a strong impact on the inflammatory hypothesis in AD came from genome wide association studies (GWAS), which did not only unravel a direct genetic connection of inflammation to disease pathogenesis, but also hold promise for the identification of inflammation-targeting therapeutic interventions. In total, the percentage of disease risk for AD that can be attributed to genetic factors with a heritability has been estimated between 56%-79% in twin studies[54,55]. The development of high-throughput genomic approaches over the last 15 years led to a major improvement in our knowledge of AD genetics[56]. Thus, GWAS and next-generation sequencing approaches have identified over 80 independent genetic loci modulating the risk of AD[57,58]. Pathway analysis using these genetic findings has identified both innate and adaptive immune responses as well as inflammation in general as key contributing pathways for AD pathogenesis[59,60]. So it appeared that AD risk alleles are specifically enriched in active enhancers of monocytes, macrophages and especially microglia[61]**.** In fact, close to 25% of the potential identified AD genetic risk factors could be highly/exclusively expressed by microglia and/or linked to immune-related function[62]. Several of these genes are indeed part of important pathways in microglia including ligand activators (IL34 and APOE), immune receptors (TREM2, SPI1, MS4A4A, MS4A6A HLA-DQA1, and CD33)[63], signaling intermediates (PLCG2, PTK2B, and INPP5D) or effector mechanisms (ABI3 and EPHA1). Besides microglial functions, additional immune-related responses have been linked to the identified genetic signals such as complement machinery (CR1 and CLU)[62] or cytoskeletal machinery (ABI3, EPHA1, and FERMT2)[35]. Recently, the European Alzheimer and Dementia Biobank's (EADB) large meta-GWAS has reaffirmed most previously detected immunological loci. Crucially, it also provided genetic evidence linking the Linear Ubiquitin Chain Assembly Complex (LUBAC) to AD[60]. Comprising SHARPIN, RBCK1, and OTULIN, LUBAC is a high-confidence AD risk factor, unique in forming linear ubiquitin chains and pivotal in inflammation and immunity research. LUBAC is integral to NLRP3 inflammasome activation, impacting innate immune responses and Aβ pathology in AD. It's also involved in autophagy, specifically in modifying TDP-43-positive neuronal inclusions, potentially triggering autophagic clearance. Importantly, the same GWAS study also support the significance of the TNF-α signaling pathway in AD with additional evidences. Genetic loci such as ADAM17, crucial for TNF-α signaling activation[64], and TNIP1, which inhibits this pathway[65], were identified. Other elements include SPPL2A's role in noncanonical TNF-α shedding[66] and PGRN's function as a TNF receptor ligand and antagonist[67]. Finally, an adaptive immune response mediated by HLA-DRB1 (and more specifically the *HLA-DRB1*04* subtype) has been also proposed, potentially by acting against Tau and especially the acylated form at lysine K311[68] which is known to potentiate Tau PHF6 aggregation[69]. Importantly, AD research has also shown that tau pathology dependent on Aβ42-evoked neuroinflammation may be linked to microglia function as connecting both major pathological hallmarks of AD[70-72].

Epigenetics Without any doubt the above described genetic evidence for immune processes has strongly influenced the entire field over the past decade. It is likely that in decades ahead new findings showing how epigenetic changes modulate the AD relevant immune functions and are being transferred vertically from our ancestors, will become equally stimulating. AD arises on the background of complex genome-environment interactions that frequently activate epigenetic mechanisms. These mechanisms add an additional layer of control to the genome. Emerging evidence points to an important role of epigenetics in microglia regulation during AD pathogenesis[38-41]. For example, AD genetic risk variants are mostly centered on specific regulatory regions of microglia characterized by particular epigenetic motifs[73-76]. Microglia, as well as other tissue-resident macrophages, show a high degree of epigenetic heterogeneity between tissues and disease states[77]. They also display lineage-specific characteristics and epigenetically primed responses according to the context and previous events[78,79]. Chromatin compaction[80], DNA methylation[81,82], and histone acetylation[79,83], methylation[79,84,85], phosphorylation[80,86], or lactylation[87] are modified in microglia in response to different stimuli and disease states. Additionally, epigenetic control of microglia is mediated by non-coding RNAs, among which microRNA (miRs) play a prominent role in controlling microglia-specific

gene-expression and proteostasis at the systems level are best studied. Changes in microglia-specific miRs are observed in liquid biopsies of early AD patients and can predict disease progression[88,89]. While such epigenetic alterations can persist and even transmit across generations, they are reversible[90]. Therefore, it is intriguing to note that interventions targeting epigenetic mechanisms, including treatment with DNA methylation[91] and histone deacetylase (HDAC)[92] inhibitors, RNA therapeutics[89,93] and depletion of key components of the epigenetic machinery such as DNA methyltransferase 1 (DNMT1)[94], Tet methylcytosine dioxygenase 2 (TET2)[95], HDACs 1/2[79,96], Sirtuin 1 (SIRT1)[97], Embryonic Ectoderm Development[98] [84] and Jumonji D3 (JMJD3)[85] can modify microglia responses. These effects can differ based on contextual factors and the brain's prior state, leading to contrasting outcomes observed during brain development, homeostasis and disease [99],[96], [100] [77]. In conclusion, epigenetic processes help to shape microglia dynamics and responses to future events[79,101-103] making the epigenome an attractive drug target. Whether this hypothesis will withstand causal validation with epi-genetic editing tools remains to be determined but, at current, it provides an exciting framework for future work.

The Exposome – Can Life-style factors modulate Inflammation?

While genetic and epigenetic influences may still be viewed as "given" and "unchangeable" to date, several life-style behaviors and environmental factors, which are collectively described as the exposome, modify the risk to develop AD. Several of these factors are directly or indirectly linked to the immune system:

Brain trauma Traumatic Brain Injury (TBI) is one of the most important non-genetic, non-age-related risk factors for developing dementia, which correlates consistently with the number and severity of TBIs[104-106]. An association between a single moderate to severe TBI and AD neuropathology is less clear with multiple studies showing no association[107,108], although other studies have found an association between TBI with a loss of consciousness and increased Aβ plaque burden suggesting that the severity of TBI is related to Aβ deposition[109,110]. Notably, exposure to years of repetitive mild TBI such as occurs in contact and collision sport athletes as well as military soldiers is a risk factor for developing chronic traumatic encephalopathy (CTE), a neurodegenerative disease characterized by Tau pathology in the cortical sulci and around blood vessels[111,112]. Both a single moderate-severe TBI and repetitive mild TBIs are associated with chronic vascular injury and blood brain barrier disruption[113,114] as well as a persistent microgliosis[115,116]. Additionally, APP is accumulated in axons with diffuse injury after TBI, increasing the risk for Aβ accumulation[117]. Due to the elevated levels of neuroinflammation common to TBI and AD, it is hypothesized that immune responses after TBI accelerate or even trigger AD-prone neuropathological cascades during normal aging or in individuals with a specific genetic predisposition. Even after mild TBI, microglia and astrocytes remain persistently activated[118], secreting inflammatory mediators such as IL-1β, IL-6, TNFα and ASC that contribute to neurodegeneration post-injury through increased APP transcription[119], γ-secretase expression[120], reduced microglial phagocytosis[121] and pathological posttranslational modifications of Tau such as hyperphosphorylation[70] and acetylation[122]. Furthermore, in a vicious circle the accumulation of toxic peptides and proteins associated with neurodegenerative disorders, may also enhance and perpetuate glial responses to traumatic injury, leading to significantly higher secondary damage and accelerated neurodegeneration[123]. Persistent neuroinflammation following TBI may also mediate the increased risk for other neurodegenerations such as Lewy body disease[107,124] and TDP-43 pathology[125].

Nutrition/diet/midlife obesity sedentary life style Several lifestyle factors influence dementia risk via neuroinflammatory processes[126,127]. Higher physical activity[128,129] associates with reduced dementia risk and lower inflammatory marker in human blood[130,131]. The association with cognitive performance is largely mediated by the amount of activated microglia[132]. In animal models, increased physical activity as well as an enriched environment attenuates the neuroinflammatory response to amyloid pathology resulting in reduced cytokine release[130,133-137], altered microglial phagocytic activity[137-139] and improved cognition[133,134,138-140].-In contrast, a sedentary lifestyle combined with a lack of balanced diet

increases the risk for midlife obesity, midlife hypertension and diabetes[141,142], which are established risk factors for dementia[127]. These processes can induce wide-ranging metabolic changes and systemic chronic inflammation[143,144]. Systemic inflammation and innate immune memory, in turn, can affect neuroinflammatory and neurodegenerative processes in the brain[79,145,146]. Accordingly, pro-inflammatory dietary pattern associates with cognitive decline-related blood-proteome changes[147], high risk for dementia[148] and reduced brain volume[149] while opposite association patterns are observed for a balanced, Mediterranean diet[150-154]. Promoting an active, stimulating lifestyle including a balanced diet (e.g. by multi-domain behavioral interventions[155]) therefore holds promise to prevent dementia and ameliorate neuroinflammation in AD.

Systemic infection/inflammation It has become clear that peripheral inflammation significantly impacts dementia. For example, enhanced cognitive decline has consistently been found in patients with existing AD pathology, who additionally experienced peripheral infections (for review see: Bettcher et al.[156]). A wide range of different infections significantly increase risk for AD and vascular dementia, and increasing numbers of infections increase risk in a cumulative fashion[157]. For both, Aβ and tau, in mice, it has been shown that systemic inflammation, induced by exposure to bacterial lipopolysaccharide exacerbated the respective pathology e.g. through enhanced inflammatory activation and reduced clearance[145,158,159]. Interestingly not only external, bacterial challenges but also sterile inflammatory and autoimmune allergic responses affect brain inflammation[160]. In humans both elevated TNFα and acute systemic inflammatory events were associated with more rapid cognitive decline over the preceding 6 months[157]. Exacerbated pathology is often due to enhanced inflammatory responses in the brain of patients as well as animal models, mechanistically driven by a pre-activation or "priming" of microglia that leads to a severe inflammatory response in the pathologically altered brain and, in turn, drives further functional deterioration[161,162]. Interestingly, epidemiological studies have also provided strong evidence that peripheral inflammation increases dementia risk when the inflammatory insult occurs up to two decades earlier[163]. The mechanisms of these long-term effects are much less clear, but may involve epigenetic reprogramming of microglia, leading to long-lasting immune memory in the brain that is sufficient to alter AD pathology in mouse models[79]. Such epigenetically-driven changes in microglial responses match the concept of innate immune memory as it was developed in peripheral macrophages, where two opposing immune memory states were described: "immune training", where macrophages are primed to mount enhanced inflammatory responses upon exposure to subsequent immune insults, and "immune tolerance", where macrophages are desensitized and show strongly reduced inflammatory activation upon restimulation[162,164]. Whether microglial immune memory also exists in the human brain, however, requires further investigation. While immune training has beneficial functions in the periphery, such as enhanced pathogen clearance, it may drive hyperinflammation in the brain, thereby exacerbating pathology. There is some evidence that AD patients who died with infection show higher levels of brain IL-1β than those who died without infection[165] and LPS-induced systemic inflammation is known to potentiate IL-1β activity, driving further inflammasome activation and exacerbating both amyloid and tau pathology. Conversely, while immune tolerance may lead to immune paralysis in the periphery, increasing the risk for secondary infections, it may be beneficial in the brain by inhibiting detrimental microglial activation[79,164].

Poor oral health/parodontitis Periodontal disease represents a more subtle and chronic form of peripheral inflammation. Further support for an influencing role of oral hygiene comes from works linking microbiome dysbiosis to the development of development in later life[166,167]. Lipopolysaccharide (LPS) from the outer surface membrane of Gram-negative bacteria is a strong immune system activator[168]. *Porphyromonas gingivalis*, with Gram-negative characteristics is considered a keystone bacterium[169] in generalised periodontitis[170]. This bacterium and its virulence factors are found in autopsied AD brains[171-173]. The infection is responsible for causing extensive oxidative damage in a genetically modified apolipoprotein E knock-out ($ApoE^{-/-}$) mouse model, orally infected with *P. gingivalis* to initiate experimental periodontitis[174]. *P. gingivalis* infection and *P. gingivalis*-LPS induced neuroinflammation (glial cell activation) has also been studied in mice models[175-178]. Poole et al., (2015)[177], reported that *P. gingivalis* induced classical complement pathway activation following oral

infections. A subsequent report demonstrated pro-inflammatory cytokines release such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1β in the brain tissues of middle-aged mice by Ding et al., (2018)[179]. Zhang et al., (2018)[178], study highlighted that the Toll-like receptor 4/nuclear factor-kappa B (TLR4/NFkB) signaling pathway was activated. In another study Memedovski et al., (2020)[180] found classical and alternative activation in rat brain microglia, which according to Hanisch (2002)[181], are responsible for secreting cytokines in the human brain. Neuroinflammation, an important element of the AD brain pathology that appears to play a substantial role in the deteriorating cognition and progression of the neuropathological changes (hallmark lesion formation) in AD brains. This has also been demonstrated in mice models of experimental periodontal disease[176,178], which further sustain intrathecal chronic neuroinflammation.

Gut microbiome Next to the oral flora, the gut microbiome may influence immune processes in the brain. Rats receiving fecal transplantation from AD patients show Alzheimer's symptoms[182] and, vice versa, fecal transplantation from healthy mice to AD model animals reduces disease pathology[183,184]. Disease microbiomes can be modified; e.g. the traditional Indian medicine Triphala in AD mice positively affects cognitive parameters and reduces serum Aβ levels by shifting the microbiome to *Bacteriodetes* and *Verrucomicrobiota* phylums with a reduction of *Cyanobacteria*[185]. There are several ways of communication for the gut microbiome and the brain, including the *vagus* nerve, the stress-associated HPA (hypothalamic–pituitary–adrenal) axis, direct or indirect modulation of neurotransmitters and e.g. SCFA (short-chain fatty acids) and other metabolites (reviewed in[186,187]). The BBB (blood-brain-barrier) controls brain entry of peripheral immune cells and immune mediators. Microbiome originated LPS (Lipopolysaccharide) and SCFA impairs the permeability of the BBB[188-190] and affects homeostasis, maturation and activation of microglia e.g. by SCFA binding to FFAR2 (free fatty acid receptor 2) or LPS to TLR4 (toll-like receptor 4)[191,192]. In GF (germ free) mice the BBB has a higher permeability[190]. The BBB permeability in GF mice is rescued by mono-colonization with SCFA-producing bacterial strains[190]. In GF mice there are global defects in microglia morphology and maturity. Temporal eradiation of microbiome leads to severe changes in microglial properties[191]. Microglia in GF animals have enhanced Aβ uptake at early disease stages[193], and protect for tau pathology related neurodegeneration[194]. ABX (antibiotics) microbiome depletion in adult mice disrupts the BBB[195] and allows invasion of peripheral immune cells to the brain. ABX dysbiosis leads to memory impairments[196]. *Bifidobacterium* and *Lactobacillus* species based probiotics therapy after ABX improves BBB integrity and memory deficits in AD mice[185,197]. Brain invading microbial tryptophane indole derivate metabolites[198] have an anti-inflammatory effect on microglia and astrocytes by binding the AhR (aryl hydrocarbon receptor) which then inhibits NF-κB and the proinflammatory phenotype[199,200] (reviewed in[201]). BBB passing primary and microbial processed secondary bile acids bind to microglial TGR5 (Takeda G protein-coupled receptor 5) and induce the anti-inflammatory phenotype[202] by inhibiting the proinflammatory NF-κB pathway via PKA[203,204] and thus the NLRP3 inflammasome[205] as well. The conjugated bile acid TUDCA (tauroursodeoxycholic acid) reduces glial activation in the context of AD, resulting in reduced Aβ plaque formation and cognitive decline[206]. Microbiome alteration as potential treatment to slow down disease progression or to delay disease onset is still understudied and needs to be better understood.

It seems possible that further epidemiological risk factors contribute to AD pathogenesis by stimulating, aggravating or accelerating neuroinflammation. Nevertheless, this may be influenced by the individuum's genetic background. Studying gene-exposome interactions may therefore be important to understand which genetic background in combination with certain life-style factors account for detrimental as well as protective effects.

Which cellular systems drive neuroinflammation in AD?

Microglia The immune system of the central nervous system (CNS) parenchyma consists exclusively of macrophages as innate immune cells whereas many more immune cells like lymphocytes, NK cells, ILCs and others can be found in other CNS structures such as the dura mater[207-209]. These tissue resident CNS macrophages belong to the family of mononuclear phagocytes that are spread across the whole body (such as brain, liver, lung, kidney, testes, skin etc.) and settled there in distinct anatomical compartments[210]. In the CNS, local macrophages exists in two distinct flavors: either as juxta-neuronal macrophages in the parenchyma where are they traditionally called microglia (micro: small, glia: from Greek glue) or as resident macrophages at CNS interfaces such as the leptomeninges, the perivascular space and choroid plexus[211-213]. These border macrophages usually summarized as CNS-associated macrophages (CAMs). Even though CAMs are positioned at strategically important CNS boundaries their functions are only incompletely understood and recently summarized elsewhere[92,214-216]. Notably, microglial cells can be observed widely across the animal kingdom (even in leech, shark etc. to humans) covering more than 450 million years underpinning their obviously essential role for the CNS[217]. For many years their ontogeny was unclear and bone marrow-derived monocytes were considered to be their cells of origin[218]. However, elegant fate mapping experiments have proven their prenatal origin from distinct yolk sac progenitors described as c-kit+ non-committed erythromyeloid progenitors[219,220] that engraft via the CNS surface to the embryonic mouse brain parenchyma at day E9.5 where they locally migrate, expand and finally gain their typical arborized morphology. Nowadays, microglial cells are very long-lived cells existing for few years that divide very slowly at rates of about 0.5 % with considerable differences in various CNS regions in mouse and man[221-223]. Microglial cells in the steady-state CNS undergo self-renewal without any input from circulating hematopoietic cells that are excluded by the tight BBB[224,225]. As typical tissue macrophages, microglial cells are thought to be extremely sensitive and versatile watchdogs of even minute changes of their microenvironment. As such they are considered as tremendously plastic cells that can quickly adopt several functional and morphological phenotypes influences by the environmental cues. The recent advent of several novel single cell technologies and innovative fate mapping studies had shed new light on the transcriptional and cellular heterogeneity of microglia in both mouse and man[226]. Microglial cells are nowadays characterized by distinct transcriptional, epigenetic, and proteomic and functional profiles during development, homeostasis and perturbation[215,227]. During pathology, several microglial states have been defined leading to a perplexing nomenclature of context-associated microglial signatures[215,228-233]. Whether this endless description of putative novel microglial clusters or even subsets is meaningful and whether these reflect real distinct biological conditions remains to be determined in the future.

Microglial transcriptomes and differences between murine and human microglia Nevertheless, the identification of the microglial phenotype associated with neurodegeneration (MGnD)[234] in Alzheimer Disease (AD), also known as DAM[229], has sparked considerable interest for therapeutic targeting, yet the implications in disease progression remained conflicted. We have recently identified a negative role of APOE4, the strongest genetic AD risk factor, in impairing microglial MGnD response to AD pathology in mice and in humans (PMID: 37749326). A similar impairment of microglia expressing another AD risk gene, INPP5D, to induce a response to neurodegeneration was identified, which was restored following the genetic deletion of INPP5D or APOE4[235,236]. Microglial deletion of APOE4 or INPP5D harnessed astrocytes to encapsulate amyloid-b plaques via the induction of LGALS3 and the suppression of TGFβ-mediated checkpoints, associated with reduced pathology and neurodegeneration in mice[236]. In the brains of AD APOE4 carriers, we identified a similar reduction in MGnD signaling and astrocytic activation at sites of pathology. Moreover, reanalysis of two publicly available datasets[237,238] confirmed these findings, demonstrating reduced MGnD signature in AD APOE4 carriers. Taken together, these findings highlight the beneficial role of MGnD-microglia in limiting AD, and that boosting MGnD provides an exciting therapeutic intervention approach for AD. Mouse models of AD only partially recapitulate the complex brain environment encountered in human AD brains. Microglia respond to a plethora of various environmental signals in AD brains, for instance, amyloid plaques, neurofibrillary tangles, synaptic/neuronal loss, myelin debris, and altered intercellular communication between cell types just to name a few. Beyond extrinsic factors, genetic variation in form of single nucleotide polymorphisms (SNPs) associated with elevated AD risk, may lead to impaired

microglial function. Lastly, although the innate immune system is highly conserved between species, mouse and human microglia display significant differences in their gene expression profile[217,238,239]. Bulk analysis of microglia cells isolated from pediatric and human brain tissue of neurotypical controls led to the identification of a homeostatic microglia gene expression signature[239,240]. Homeostatic microglia marker genes include microglia-specific surface receptors such as CX3CR1, P2RY12, and TMEM119. In recent years, the generation of single cell and single nuclei transcriptomic data from isolated human microglia helped to reveal multiple, small subclusters -microglia states- as characterized by the up-regulation of distinct marker genes compared to homeostatic microglia[232,237]. In neurotypical brains, the up-regulation of major histocompatibility class II (MHCII) genes such as CD74 and HLA-DRA indicate that microglia participate in antigen presentation in the brain. Other microglia states include interferon-responsive microglia (e.g., IFITM3, IFIT1, IFIT3, ISG15), inflammatory microglia (e.g., CCL2, CCL3, CCL4), proliferative microglia (e.g., MKI67, PCNA), and a small subset reminiscent of mouse DAM (e.g., APOE, LPL)[232].

Data on gene expression profiles of human microglia states in AD, however, is still limited. Compared to mouse microglia, human microglia show a higher degree of variation, probably due to manifold environmental stimuli in AD pathology but also in terms of technology (e.g., differences in microglia isolation, sequencing technologies, single cell vs. single nuclei, postmortem interval, etc.). Nevertheless, isolation of microglia cells from AD brains and subsequent analysis of the transcriptome gave important insights into microglia states[237,241]. Reflecting the complex environmental changes in AD, signature genes for DAM were found across several microglia clusters while MHCII microglia number was diminished[237]. Comparison with mouse microglia isolated from an amyloid model showed a partial overlap between mouse and human DAM with the common denominator in genes associated with lipid metabolism and lysosomal function[242]. Regressing microglia gene expression against amyloid-beta and phosphorylated-Tau load revealed distinct microglia responses in gene expression to amyloid and tau pathology[241]. However, more studies are needed to dissect microglia states in terms of brain region, disease stage, and pathology. As mentioned above, the gene expression profile of mouse microglia substantially differs from human microglia already under homeostatic conditions. One strategy which allows the investigation of human microglia in response to different environmental stimuli is the transplantation of human iPSC-derived hematopoietic progenitors (HPCs) into the mouse brain of immunodeficient mice[243] overexpressing the human colony-stimulating factor 1 for human microglia survival[244,245]. The presence of amyloid-beta resulted in the transition of iPSC-derived HPCs to DAM with a partial overlap in gene expression signature to mouse DAM 10. Chimeric mouse models allow the investigation of the response of human microglia to a microglia-autonomous genetic perturbation such as the deletion of TREM2. Deletion of TREM2 in human microglia resulted in the loss of the DAM response in amyloid mouse models and also changed microglia function as evidenced by impaired phagocytosis and chemotaxis[246]. Single cell RNA-seq of xenografted iPSC-derived HPCs with the TREM2 R47H loss-of-function variant identified a cluster that resembled atherosclerotic foam cells[247]. Collectively, these transplantation studies may help to provide more biological and mechanistic insights into different microglia cell states in the context of different environmental stimuli. However, limitations of the chimeric models include a mouse environment and immunocompromised background.

Whereas we have gained substantial insights into various microglia cell states and their underlying gene expression profiles in recent years, the transcriptional mechanisms by which different environmental cues in Alzheimer's disease drive these distinct phenotypes are largely unknown. Recent advances in sequencing technologies including ATAC-Seq, ChIP-Seq, and csRNA-Seq just to name a few may help us to infer key transcription factors responsible for context-dependent gene expression of microglia. Transfer of human microglia from the brain into a culture environment results in rapid chromatin remodeling with alterations in chromatin accessibility and active gene regulatory elements, mainly enhancers[239]. A multi-omics study assessing microglia chromatin accessibility and gene expression in AD brains identified SPI1, encoding the lineage-determining transcription PU.1 as a key regulator of microglia in AD[75]. Other transcription factor family candidates include the AP-1 and MI/TFE families, which were shown to be up-regulated in microglia isolated from AD brains[241].

Clarification of the key transcriptional regulators of microglia states may lead to the development of novel strategies targeting microglia phenotypes.

Microglial phagocytosis may be influenced by many of the genes associated with AD that are predominantly expressed by microglia, including *TREM2, PLCG2, ABI3, CD33, PILRA, SIGLEC11, ABCA1, ABCA7, CR1, GRN, CLU* and *APOE*[248]. APOE can opsonize Aβ plaques, synapses or neurons, and then consecutively activate TREM2, PLCg2 and ABI3 to induce microglial phagocytosis, and this pathway is potentially inhibited by CD33, PILRa and SIGLEC11[248]. Thus, most of the known genetic risk for AD is potentially linked to microglial phagocytosis, but it is unclear whether this is via phagocytosis of soluble Aβ, amyloid plaques, dead cells and debris, or live synapses and neurons. Plaque-associated microglia have increased expression of TREM2, which can bind Aβ, inducing phagocytosis of Aβ, causing compaction of Aβ plaques, and reducing Aβ seeding of new plaques[229,234,249,250]. Accordingly, antibodies that increased TREM2 expression and signaling reduced Aβ plaque burden in a mouse model of amyloidosis[98]. Activation of TREM2 can induce the DAM expression profile of microglia, including increased expression of the phagocytic receptors, Axl and Mer[229], which also have increased expression in plaque-associated microglia[251]. Knockout of *Axl* and *Mer* in a mouse amyloid model lowered Aβ phagocytosis 10-fold, and lead to a surprising and selective reduction in the number of dense-core plaques, suggesting that microglial phagocytosis of Aβ via this class of receptors leads to the formation of dense-core plaques by microglia, which is arguably a protective confinement mechanism to prevent the release of toxic Aβ species[251]. Fc receptors have also been shown to mediate microglial phagocytosis of Aβ species bound to immune complexes[252], which is presumed to be one of the mechanisms underlying the amyloid clearing effects of the recently FDA-approved anti-amyloid antibodies to treat AD, aducanumab and lecanemab. Although there are still considerable uncertainties associated with the use of these drugs, they clearly highlight and validate the potential of amyloid clearance by microglia as a promising therapeutic avenue. Nonetheless, in later stages of AD pathology, microglial phagocytosis may contribute to synapse loss (see synapse section below) and neuronal loss. TREM2 can mediate microglial phagocytosis of synapses in amyloid or tau models of AD[253-255]. Mer can mediate microglial phagocytosis of new-born neurons in amyloid mouse models, limiting neurogenesis and seizures[256]. Aggregated Aβ or tau can induce microglial phagocytosis of live neurons in culture or *in vivo*, and this neuronal loss can be prevented by blocking microglial phagocytosis, which also prevented memory loss in mice[257-259]. Thus, microglial phagocytosis of Aβ, synapses and neurons may affect AD onset and progression, and interventions need to focus on the specific receptors involved.

Microglial barrier function Beyond these clearance function, microglia also function as a barrier around sites of degeneration and injury. In AD, microglia cluster around amyloid plaques, wrapping their processes tightly around the plaque surface. This encapsulation creates a physical barrier that limits plaque expansion and leads to a more compact amyloid conformation[260,261]. Surrounding each amyloid plaque are hundreds of axons with spheroid enlargements[262] that disrupt electrical conduction and neural circuit function[263]. Microglia encapsulation of plaques plays a crucial role in protecting axons by limiting their exposure to toxic protofibrillar amyloid[261]. Microglia plaque sensing and encapsulation are disrupted in aging[261] and with hypomorphic TREM2 human variants[264] as well as by deletion of Trem2[264,265] or downstream Dap12 and Syk signaling[266,267] in mice. Additional receptors including MERTK and PIEZO1 may also mediate microglia plaque sensing and barrier formation. Disruption of these signals is associated with more diffuse plaques and greater axonal spheroid formation[264,265] and neuritic tau hyperphosphorylation[268]. In contrast, overexpression of Trem2[269] or treatment with activating TREM2 antibodies[270] enhances microglia encapsulation and reduces plaque-associated axonal pathology. Astrocytes intermingle with microglia at the plaque interface, suggesting a coordinated interaction[271] during barrier formation[271], which may be mediated through Trem2 and ApoE signaling[272]. Overall, the evidence suggests that targeting glial cells in AD to enhance the formation of neuroprotective barriers could yield beneficial therapeutic effects.

Microglial proliferation Microglia numbers may not stay the same in response to any acute or chronic immune challenge. Microgliosis due to increased microglial proliferation represents another key feature of AD, predicting the onset of cognitive decline[273]. An increase in the proliferation of microglia is observed in post-mortem samples from AD patients, in association with upregulation of its key mitogenic machinery, the CSF1R pathway[274-276]. CSF1R gene variants are also strongly associated to LOAD susceptibility[277]. These studies have been reinforced and expanded by studies in models of AD-like pathology, helping to elucidate the timing and consequences of microglial proliferation. An accepted mechanistic model linking microglial proliferation to AD progression starts after an early and intimate crosstalk of microglia with nascent Aβ pathology, triggering microglial proliferation, observed using in vivo imaging[261]. Microglial proliferation increases progressively in proximity to Aβ plaques, in a CSF1R-dependent manner[276]. Prevention of microglial proliferation via inhibition of the tyrosine kinase activity of CSF1R impedes the degeneration of synapses, ameliorating cognition without modifying the levels of Aβ in the APP/PS1 model[276], as well as the 3xTg[278] and 5xFAD models[279,280] of AD-like pathology. Microglial proliferation can be prevented by alternative agents such as minocycline, rendering similar beneficial effects over AD-like pathology[281]. The inhibition of CSF1R is also a disease-modifying mechanism in a model of tauopathy, leading to reduced neurodegeneration and an improvement of behavioral performance. Functionally, prevention of microglial proliferation induces a repolarization of these cells to a homeostatic phenotype[276,282]. Interestingly, inhibition of microglial proliferation is linked to a prevention of the onset of replicative senescence in microglia, associated with the specification of the DAM phenotype[283]. Collectively, these studies provide solid evidence identifying microglial proliferation as a mechanism underpinning the contribution of the cells to the disease and identify CSF1R as a promising target for therapy. This body of evidence underpinned promising drug discovery programs[284], and in coming years the field will collect valuable clinical information about their potential efficacy in AD.

Microglial immune metabolism Although representing just 2% of our body mass, the brain is one of the most metabolically active organs and consumes the most energy, predominantly in the form of glucose. Glucose is broken down into pyruvate (known as glycolysis), where it can enter the Krebs cycle to be fully metabolized to CO_2. This process also reduces NAD to NADH, which is subsequently used for oxidative phosphorylation (oxphos) and ATP generation. Recent advances in immunology have uncovered the sophisticated role that glycolytic signaling has on powering inflammatory activity in macrophages and peripheral immune cells, yet we are still uncovering the extent to which these processes are used by microglia in the brain. In primary microglia, Aβ can trigger glycolysis with a corresponding reduction in oxphos[285]. This switch to glycolysis activated the mTOR-HIF-1α pathway, that in turn directly regulated the production of inflammatory cytokines including IL-1β[285]. Similar effects have been found in murine models of AD, where microglia from APP/PS1 mice have increased glycolytic activity[286]. This was recently shown to be sex dependent as microglia from aged female APP/PS1 mice are more glycolytic and inflammatory than their male counterparts, with a corresponding reduction in phagocytic ability[287]. Interestingly, microglia are metabolically flexible and not solely reliant on glucose. Instead, they can also use amino acids such as glutamine, or fatty acid oxidation to fuel important surveillance and migratory activities[288]. Recent studies indicate that microglial and macrophage glycolysis and mitochondrial function decline significantly with aging, leading to an energy depleted state that disrupts homeostatic myeloid responses such as phagocytosis and inflammation resolution. Several mechanisms have been identified that contribute to this change. With age and immune stimulation, myeloid cells lose their capacity for *de novo* NAD+ biosynthesis because of a distal breakdown in tryptophan metabolism[289]. Moreover, with aging, glucose is shunted away from glycolysis and towards production of glycogen, an effect driven by increased signaling by the immune modulator Prostaglandin E_2 (PGE_2) via its EP2 recepto[290]. EP2 signaling also disrupts glutaminolysis in aging myeloid cells, an alternative source of energy that fuels the TCA and mitochondrial respiration via anapleurosis. Inhibition of EP2 signaling genetically and pharmacologically restores microglial and macrophage bioenergetics and homeostatic immune responses and reverses age-associated cognitive decline. Recent studies have also identified TREM1 (Triggering Receptor Expressed in Myeloid cells-1), an amplifier of detrimental inflammatory

responses, as a disruptor of homeostatic myeloid glucose metabolism that contributes to cognitive decline in aging and models of amyloidosis (Wilson et al., Nat Neuroscience, *in press*). Thus myeloid metabolism directs immune responses in microglia and macrophages, which in turn regulate cognitive function in aging and models of neurodegeneration.

Microglia senescence / fate Cellular senescence is a hallmark of ageing and age-associated diseases including AD. Senescent cells are characterized by an irreversible proliferation arrest and profound changes in their metabolism and behavior, preventing them from executing their physiological function. In addition, senescent cells frequently display a senescence-associated secretory phenotype (SASP) that is characterized by the release of various proinflammatory factors[291]. SASP factors were detected in the brain, cerebrospinal fluid and serum of patients suffering from AD[292-295] and are associated with aged and potentially senescent microglia[296]. Interestingly, microglial-mediated inflammation especially via the common SASP factor interleukin (IL)-1β was shown to contribute to tau spreading and tau-mediated neurodegeneration[70,158,297,298]. In line with this, microglia have been identified as a putative senescent population in tauopathies including AD[283,294,299,300]. Senescent microglia developed before the onset of neurofibrillary tangle deposition in human P301S *tau*-transgenic mice (PS19 mice). Using single cell RNAseq, these microglia were found to represent a subset of DAM[301]. Remarkably, removal of senescent cells, either genetically or with senescence-targeting pharmacological means, alleviated tau pathology, *tau*-mediated neurodegeneration and cognitive deficits in this model[299], suggesting that senescent microglia contribute to disease progression. Cellular senescence can be induced via multiple pathways. The sustained proliferation of microglia in Aβ-depositing APP/PS1 mice promoted replicative senescence, ultimately fueling Aβ accumulation and synaptic defects[283]. Furthermore, microglia internalizing *tau* aggregate-bearing neurons or monomeric *tau* from the extracellular space enter a senescent state and present with a SASP[302,303], that might modulate AD pathology, neuronal function and neurodegeneration.

Astrocytes provide vital physiological functions for normal development and maintenance of the CNS – particularly for neuron health and function[304]. The altered response of astrocytes during acute infection or brain injury and in chronic disease states is referred to as astrocyte 'reactivity' and any one particular reactive response may include several heterogeneous reactive 'sub-states' – each with distinct transcriptomic profiles and (likely) functional outcomes[304,305]. The response of astrocytes to neurodegenerative diseases like AD have been linked to inflammatory responses of microglia and peripheral immune cells, pathological proteins like amyloid and Tau, barrier leakage, and many other pathological indications. While there are many initiators of astrocyte reactive states in AD, the main historical hallmarks are hypertrophy of fine processes, upregulation of cytoskeletal proteins like GFAP and Vimentin, as well as increased expression of innate immune-related genes like Lipocalin 2 (Lcn2), the protease inhibitor α1-antichymotrypsin (Serpina3n), and many components of the cholesterol synthesis pathway[238]. These transcriptomic and morphological changes often occur long before cognitive deficits. Reactive astrocytes are associated with senile plaques, and while there is restructuring of astrocyte gross morphology their domain architecture is preserved, indicative of isomorphic, non-proliferative astrogliosis[306] and proliferation or scar formation is uncommon, except for around amyloid plaques later in disease progression. Other reported altered functional changes in reactive astrocytes include decreased phagocytosis, decreased glutamate uptake, loss of endfeet-polarization and expression of AQP4 water channels, and secretion of neurotoxic compounds[307]. In particular, astrocytes in AD up-regulate expression of monoaminoxidase-B that translates to an increased synthesis of GABA (thus increasing tonic inhibition counteracting neuronal hyperexcitability but also casing cognitive impairments) and increased production of H_2O_2; similarly, H_2O_2 is produced by increased activity of urea cycle, implemented in detoxification of ammonium and utilization of β-amyloid[308,309]. Oxidative stress is further augmented by age-dependent decline in astrocyte anti-oxidative system[306], thus precipitating direct neuronal injury. A substantial sub-population of astrocytes in AD demonstrate atrophy and loss of homeostatic support, further aggravating neuronal damage[310]. Given that astrocytes interact with up to 2 million synapses in the human brain[311], changes in synapse forming functions likely have major contributing roles to cognitive decline. Synaptic uncoupling of neurons projecting between brain regions, particularly in the hippocampus likely

decrease memory function. The neurotoxic reactive astrocyte sub-state also likely plays an active role in the degeneration of neurons and synapses[307], while other putatively protective reactive astrocytes seem more prevalent in the early stages of disease and may help maintain CNS integrity by limiting infiltration of peripheral immune cells[305]. How astrocytes also response directly to Aβ deposits, remains under investigation, but decreased astrocyte AQP4 levels could slow clearance of such pathogenic proteins through the glymphatic system (formed between the blood vessel endothelium and astrocyte end feet). Loss of cholesterol synthesis machinery is also important for understanding modulation of neuroinflammation in the context of AD. As almost sole producers of cholesterol in the CNS, astrocytes are integral for the biosynthesis of cell membranes in the brain and spinal cord. Cholesterol is also an important trophic molecule for microglia, and evidence suggests that astrocytes expressing the AD-associated APOE4 allele are less competent at producing and secreting cholesterol. This could initiate a feedback loop between decreased cholesterol, driving microglial reactive states, which in turn feedback to drive reactivity in astrocytes[312]. Indeed, this astrocyte-microglia crosstalk is important for the maintenance of many physiological microglial functions including synapse pruning and debris clearance.

Lymphocytes and the adaptive immune system Besides the innate immune system, presented in particular by microglia and macrophages, the adaptive immune system is increasingly recognized as being involved in the pathogenesis of AD. The disruption of the blood-brain-barrier in AD[313] resembles an essential requirement for the possibility of peripheral lymphocytes including B- and T-cells to enter the brain parenchyma. Indeed, pathology in transgenic AD mice is associated with infiltration of B cells into the brain parenchyma and with immunoglobulin deposition at Aβ plaques (PMID: 33846335). Furthermore, in the absence of B cells Aβ plaque burden was reduced suggesting that B-cells might contribute to AD pathogenesis. Importantly, the absence of B-cells reversed behavioral and memory deficits presenting B-cells as promising targets in AD therapy development. One of the most remarkable changes that accompany immune system aging relates to the function and maintenance of T cells (primarily T helper cells), which are key orchestrators of the immune system. Whereas the population of naïve T cells shrinks with age, central memory, effector memory, and exhausted T cells accumulate and often show dysregulated properties[314-316]. Low-grade chronic systemic inflammation, which accompanies and/or is caused by processes such as tissue senescence and altered metabolism[317], acts as an additional component that contributes to the dysfunctional properties of age-related T-cell subsets. A compelling key question is whether the emergence of such dysregulated T-cell subsets could set the ground for the development of AD[318]. A support for this was evident in a recent study in humans, demonstrating increased frequencies of pro-inflammatory $CD8^+$ $CD45RA^+$ T effector memory (TEMRA) cells in peripheral blood of individuals with MCI and AD, as well as their clonal expansion in the CSF, suggestive of antigen-specific reactivation[319]. CD8 T cells were also observed within the meningeal tissues and the brain parenchyma of people with AD[319], overall suggesting the neurotoxic capacity of dysregulated and/or antigen-experienced CD8 T cells in the pathophysiology of AD[319]. In accordance, recent reports in murine models of Tau pathology evidenced an instrumental role of T-cell infiltration in Tau-related neurodegeneration, neuroinflammation and cognitive deficits[320,321], in association with clonal expansion of selected T cells, although their antigen specificity remains unknown[320]. These observations are also reminiscent of earlier reports showing increased frequencies of late-stage differentiated effector memory $CD4^+$ TEMRA cells in the blood[322] and clonal expansion of $CD4^+$ T cells in the CSF[323] of AD patients compared to healthy controls, and enhanced circulating Aβ-specific $CD4^+$ T cells in elderly individuals and people with AD[324]. However, their putative role in AD pathogenesis remains to be further defined. Nevertheless, their identity as tissue-resident memory T-cells has been confirmed through transcriptome analysis[325]. Moreover, the fact that the CD8 T cells within the brain parenchyma are in direct contact with microglia cells suggests a regulatory cross-talk between the two cell types[326]. The latter was elegantly illustrated in a recent study identifying the CXCL16–CXCR6 axis orchestrating and retaining $CD8^+$ T cells in brains of mice with AD pathology[327]. *Cxcr6* deficiency reduced accumulation and clonal expansion of CD8 T cells in the brains, and the ablation of $CD8^+$ T cells ultimately increases proinflammatory cytokine production from microglia, together suggesting beneficial roles for brain CD8 T cells in AD pathogenesis. In contrast, the

observed direct contact of the CD8 T cells with neurites argues for the possibility of a neurotoxic activity[319], this, however, requires further experimental evidence. Nevertheless, antibody-mediated depletion of CD8 T cells in transgenic AD mice resulted in changes in the expression of neuronal genes in the brain. Moreover, the infiltration of CD8 T cells into a 3D culture system resembling an AD pathology led to an increase in neuroinflammation and neurodegeneration[328]. In summary, it is still unclear if CD8 T cells are friends or foes in term of AD pathology. Both have been described, and it might well depend for example on the stage of pathology. The topic certainly urges for further investigation, in particular since immune-therapeutics targeting CD8 T cells are established in other fields such as cancer are ready to repurposed for their use in neurodegenerative diseases such as AD. Besides, clinical studies further suggest an altered homeostasis and suppressive function of regulatory T cells (Tregs) — $CD4^+$ T cells that suppress excessive immune responses — in patients with AD[329,330]. Of note, studies in mouse models of AD-like amyloid pathology deficient in adaptive immune cells have shown either decreased[331] or worsened brain pathology[332,333], supporting a complex role of T cells in disease progression, with both detrimental and beneficial effects. In this line, blockade of PD1—a checkpoint ligand and one of the key markers of exhausted T cells—was suggested to facilitate the recruitment of monocyte-derived macrophages into the brain along with ameliorating the disease process[334], although PD1 deficiency worsened disease progression in another model of AD-like amyloid pathology[335]. Furthermore, Aβ-specific Th1 cells (secreting IFN-γ), injected into the ventricles of 5xFAD mice, not only migrate into the brain parenchyma, but also stimulate the expansion of MHCII+ microglial cells with improved capacity of Aβ uptake[333]. Genetic engineering of these T cells to overexpress BDNF facilitated neuronal repair[336]. In addition, Tregs were shown to critically control anti-Aβ $CD4^+$ T cell responses[337] and Tregs selective amplification via low-dose IL-2 treatment modulates the activation of microglia and restores cognitive functions in a mouse model of AD-like amyloid pathology[333,334,338]. Recent reports further evidenced that Tregs also contribute to modulate and fine tune the balance of reactive astrocyte subtypes in AD-like pathology[1]. Altogether, these studies support an intricate interplay of T cell immunity with innate neuroinflammation in AD. It is thus intriguing to suggest that the evolvement of dysregulated T cells with aging facilitate neurotoxic inflammation and the progression of AD. Further characterizing immune senescence processes as well as antigen specificity of disease-associated dysregulated T cells, and their impact on neurotoxic inflammation, may thus pave the way toward therapeutic approaches that target peripheral adaptive immunity and immune senescence, for rebalancing a proper peripheral-central immune crosstalk essential to promote neural fitness or even repair in the AD brain.

Oligodendroglia Independent lines of evidence suggest causal links between oligodendrocytes in the aging brain, secondary neuroinflammation and Alzheimer's neuropathology. Oligodendrocytes make myelin for rapid impulse propagation and provide metabolic support to myelinated axons[339], extending beyond white matter tracts. Notably, there is extensive intracortical myelination of projection neurons and interneurons[340], persisting well into the second and third decade of human life. Importantly, with advancing age cortical myelin decreases in abundance, showing an inverse correlation with the onset of pathologies that become the hallmark of Alzheimer's disease[341]. Specifically, the late and thinly myelinated regions of the human brain appear to be the first to develop Alzheimer pathology[342]. Underlying the myelin loss is a gradual deterioration of myelin integrity, initially documented by electron microscopy in aging primate brains[343]. This degeneration includes the cytoplasmic channels within myelin[344] required for delivering metabolic support to the encapsulated axon[345,346]. Thus, advanced aging of the cortex is associated with axonal perturbation, myelin degeneration and secondary inflammation[347], the latter triggered by axon loss and the ingestion of myelin debris by microglia leading to their proinflammatory activation[348-350]. Combining mouse models of AD with oligodendrocyte-specific defects that cause the prematurely white matter aging phenotype it was possible to demonstrate that myelin dysfunction drives amyloidosis and plaque formation[351]. Interestingly, increased brain amyloid is a consequence of both, more Aβ processing in affected nerve fibers and a distinct molecular phenotype of the disease-associated microglia. The latter become visibly distracted from plaques by dysfunctional myelin, leading to less efficient clearing of Aβ deposits.

Peripheral immune cells Circulating innate immunity cells such as neutrophils and monocytes migrate into the AD brain and may contribute to disease pathogenesis. Neutrophils accumulate in the AD brain and the peak of neutrophil infiltration in mice with AD-like disease coincides with the onset of memory loss[352]. Indeed, transient neutrophil depletion during early disease in AD models reduces cognitive deficit and neuropathology, suggesting these cells have a detrimental role[352,353]. Neutrophils adhere in brain vessels and migrate into the parenchyma but they also obstruct blood flow by plugging in brain capillaries, thus contributing to disease development through multiple vascular mechanisms[352-354]. Soluble oligomeric Aβ1-42 triggers the rapid activation of LFA-1 integrin, leading to neutrophil adhesion, whereas Aβ deposits promote neutrophil arrest and spreading in brain venules but also determine the intraparenchymal localization of these cells[352]. LFA-1 integrin plays a key role in neutrophil extravasation and intracapillary plugging and its blockade has therapeutic effects in mouse AD models[352]. Neutrophils are highly reactive cells that release multiple cytotoxic molecules during AD, including myeloperoxidase, elastase and IL-17[352,355,356]. They also deploy neutrophil extracellular traps in the vasculature and inside the parenchyma, thus contributing to BBB dysfunction and brain damage[352]. Notably, circulating neutrophils have a hyperactivated phenotype in AD patients compared to control subjects, and neutrophil abnormalities correlate with faster cognitive decline[357-360]. Neutrophil indicators could therefore be suitable as disease biomarkers. MONOCYTES: In AD mice, circulating monocytes migrate into the brain via the CCR2-CCL2 axis and contribute to the clearance of Aβ[361,362], although this beneficial effect has recently been challenged in the context of AD[363,364]. A dysfunctional monocyte compartment characterized by changes in blood monocyte subsets and phenotypes has been reported in patients with dementia, further highlighting alterations of peripheral innate immunity cells as potential pathological drivers in AD[358,365]. Understanding the phenotype of neutrophils in AD may reveal new disease biomarkers and new therapeutic approaches targeting neutrophil-dependent detrimental mechanisms.

Contribution of peripheral immunity and their crosstalk with microglia in AD Several Alzheimer's disease (AD) risk factors are expressed in microglia and peripheral immunity including the immune checkpoints HAVCR2 (TIM3), INPP5D (SHIP1) and CD33 play a critical role in suppressing immune effector functions. The beneficial effect of targeting immune checkpoints to harness immunity was reported to mitigate AD pathology. CD33 was shown to inhibit monocyte[366] and microglial uptake of amyloid-β , and its deletion reduced pathology in AD mice[367]. Deletion of Inpp5d in microglia was sufficient to protect against neuronal dystrophy in transgenic AD mice[235,368] (*Yin, in press). Furthermore, recent studies identified that APOE4, the strongest genetic risk factor for late-onset AD, impairs microglial response by inducing TGFβ -mediated checkpoints (*Yin, **Liu, in press). Mechanistically, APOE4-mediated induction of TGFβ signaling impaired MGnD response via upregulation of microglial homeostatic checkpoints, including INPP5D in mice. In addition, APOE4 genotyping prior to treatment considerations with recently approved AD therapies was recommended due to increased incidence of ARIA[369-371] and reduced response to Lecanemab[372]. Therefore, a combinatorial strategy targeting amyloid-β and immune checkpoints to restore MGnD response to neurodegeneration (MGnD) may provide a promising therapeutic intervention for AD

Vascular cells Alzheimer himself described an increase in endothelial proliferation and growth in the first case of AD reported[2], suggesting that vascular cells become activated during the progression of the disease. Many reports have described vascular anomalies including i) the existence of a major brain microvascular pathology[373,374] and insufficient angiogenesis[375-378], ii) a deficient clearance of Aβ due to an altered blood-brain barrier (BBB)[379], and iii) the accumulation of hypoxic markers in the brain of AD patients and models[380-385]. It has also been suggested that the vascular network associated to Aβ plaques is early altered both in AD patients[386-389] and models[390-392], where vascular holes surrounded by hyper-vascularized areas were found associated with Aβ deposits. A recent multifactorial data-driven study have shown that vascular dysfunction is an early event in the AD pathology[393] and a snRNA-seq analysis have suggested specific changes in AD associated with endothelial cells and pericytes[394] and observed an enrichment in the expression in vascular cells of AD risk genes[394]. Mechanistically, vascular activation has been associated with i) accumulation of Aβ in the wall of brain vessels in the form of cerebral amyloid angiopathy (CAA)[395]; ii) brain pericytes contraction[396]; iii)

clotting of blood vessels by neutrophils[352,353]; iv) infiltration of peripheral immune cells in the brain parenchyma[397] due to the concomitant neuroinflammation[398,399]; and v) reduction in the number of vessels through non-productive angiogenesis, which activate microglia to disassemble blood vessels around Aβ plaques[380], suggesting and interesting cross-talk between microglia and blood vessels in AD. In addition, perivascular microglia, astrocytes and pericytes may also directly affect BBB patency in AD[400,401]. Importantly, the pathological leakage across the BBB induced by these cells may in turn also modulate innate immune cell function in the brain, indicating a vicious circle of vascular injury leading to perivascular inflammation and vice versa[402]. In addition to these cellular changes, major functional mechanisms of the cerebral vasculature, such as the local increase of blood flow in response to neuronal activity, i.e. neurovascular coupling, are also altered in AD models and patients[403]. In animal models, these detrimental effects are mediated by Aβ inducing the CD36-mediated generation of reactive oxygen species in perivascular macrophages[404], as well as by phosphorylated tau disrupting the synthesis of the vasodilator nitric oxide evoked by synaptic activity[405]. These changes are exacerbated by additional vascular effects on the capillary level, such as pericyte-mediated vasoconstriction[396]. All of these structural and functional vascular changes likely act synergistically together with direct effects of Aβ to disrupt white matter integrity in AD[406,407].

Glymphatics The role of the blood-brain barrier (BBB) in the removal of amyloid beta (Aβ) from the brain is well established, largely driving the elimination of Aβ[408]. However, this is not the sole route of Aβ removal. Typically, tissue metabolites are cleared through the lymphatic network that pervades most body tissues. The central nervous system (CNS) parenchyma, however, lacks this comprehensive lymphatic vasculature, leading many to presume over the decades, or even centuries, that the brain, due to its "immune privilege" status, has no lymphatic connection to the peripheral immune system. This belief was disproved in 2015 when functional lymphatic vessels were identified just outside the parenchyma of the brain[409] and spinal cord[410], specifically in the outermost layer of their meningeal covering, the dura mater. While these vessels are outside the CNS parenchyma, they serve as a lymphatic conduit for the CNS, delivering brain and spinal cord-derived molecules to the draining lymph nodes[409]. To effectively drain CNS-derived molecules, including Aβ, these meningeal lymphatics must interact with the so-called glymphatic system, a conceptual model for understanding cerebrospinal fluid (CSF) flow through the brain[411]. Arterial pulsations drive CSF from peri-arterial to intra-parenchymal spaces, and this CSF is then reabsorbed at the peri-venule spaces with the aid of the glial Aqp4 molecule[412,413]. When the "dirty" CSF, containing brain metabolites such as Aβ, leaves the brain, it traverses the meningeal layers, a process observed in both mice[414] and humans[415]. However, the exact path that the CSF takes remains elusive. Upon reaching the dura mater, brain-derived molecules are sampled by dural antigen-presenting cells, and the remaining molecules are removed by the meningeal lymphatics[414,416]. Impairment of these meningeal lymphatics, either through pharmacological or genetic manipulation or complete ligation at the entry of the draining lymph node, results in increased deposition of amyloid plaques in the brain parenchyma and their occurrence in previously plaque-free meninges[417-421]. Moreover, dysfunctional lymphatics hinder the effectiveness of anti-amyloid antibodies in plaque clearance and lead to side effects like a compromised BBB and abnormally activated microglia, mirroring the microglia phenotype seen in humans with AD[422]. Given that the functionality of meningeal lymphatics declines with age[422], it's plausible that these lymphatics (or the "brain's sink") must be operational for patients to benefit from anti-amyloid therapy (and possibly other therapies). Future therapies should aim to combine plaque removal with strategies that enhance the function of the meningeal lymphatics.

Immune mediators and immune receptors

DAMPs and Pattern recognition receptors Damage-associated molecular patterns (DAMPs) are molecules released upon cellular stress, tissue injury or cell dead and are considered as endogenous danger signals[423]. DAMPs include a high and diverse class of molecules which activate innate immune system through multiple pattern recognition receptors (PRRs), which include TLRs, NLRs, AIM2-like receptors, RLRs and CDRs[423]. DAMPs accumulated in AD patients´ brains react with the immune system

and contribute non-trivially to several aspects of the pathology and accelerate the disease progression[424]. The most relevant is Aβ, which is able to activate microglia via multiple surface receptors. Microglia can phagocytize Aβ through CD36, inducing the formation of TLR2-TLR6 heterodimer and NFKB activation[425], and via CD14, a coreceptor of TLR4, TLR6, TLR9, α6β1 integrin and SCARAq[424,426-428]. Upon TLR activation, Aβ initiates NLRP3 inflammasome activation, promoting the release of inflammatory cytokines[429]. Furthermore, Aβ is able also to activate NLRP1 expressed in neurons and oligodendrocytes through different mechanisms, including TLR4 binding[430]. However, Aβ is not the only damp found in AD brains. It has shown that other significant DAMPs as HMGB1, Chromogranin A, S100 proteins, circulating DNA and mt-DNA, ceramides and P2X7R have a significant contribution in the activation of the immune system in AD[423,430].

Trem2/ApoE APOE is the primary transporter of lipids and cholesterol in the brain; it also has immunomodulatory functions that are entwined with the microglial receptor TREM2. APOE is an activating ligand of TREM2 and TREM2 signaling sustains microglial production of APOE in the brain. TREM2 directly binds numerous ligands including lipidated as well as recombinant non-lipidated APOE[431-434]. Upon binding APOE, TREM2 transmits intracellular signals that promote microglia activation. However, the TREM2 variant R47H, which is associated with increased risk of Alzheimer's disease (AD), is unable to bind APOE[431-433]. Thus, direct APOE–TREM2 interactions may sustain microglia responses to AD pathology. Microglial transition from a homeostatic to an activation state in mouse models of Aβ accumulation is partially dependent on both TREM2 and APOE[250,435]. Interaction between TREM2 on microglia and APOE within Aβ plaques may be crucial for compaction: Aβ plaques in both APOE- and TREM2-deficient mice display filamentous morphology and are associated with axonal dystrophy[272]. Though TREM2 affinity for APOE isoforms may be similar[431,432], APOE variants are recognized and engulfed by TREM2 at varying rates, suggesting that APOE4 may have a more marked impact than other isoforms[246]. During homeostasis, APOE is mainly secreted by astrocytes. However, microglia, particularly those wrapped around Aβ plaques, secrete large amounts of APOE in AD patients and mouse models of AD[229,234,238,436]. This is largely dependent on TREM2: very little APOE is produced by microglia either expressing the TREM2 R47H variant[247,437] or lacking a functional Trem2 gene[229,250]. Thus, APOE-TREM2 interactions may constitute an autocrine circuit that sustains microglia responses to Aβ plaques.

Complement factors The complement system is a key contributor and regulator of inflammation, both in the periphery and in the CNS. It has been known for over 4 decades that complement components C1q and C3 are associated with pathological hallmarks of AD (plaques and tangles)[4,438,439], with multiple more recent studies using advanced technologies to demonstrate increased expression of complement proteins (reviewed in[440]) and generation of activation fragments in brain of AD and mouse models of AD[441,442]. If excessive, complement activation can lead to detrimental inflammation and neurotoxicity via the C5a and C3a fragments which signal through their receptors and synergize with other innate immune signaling pathways such as TLRs and RAGE[443,444], and via the generation of terminal membranolytic complex (C5b-9), all of which are relevant to Alzheimer's disease progression[445-447]. The role of C3 and the receptors for its diverse activation fragments in AD is clearly complex and regulated by time and location ([448,449] and reviewed in[450]). C3 knockout mice show protection from neurodegeneration[451], spine loss[442], and excessive microglial-mediated synapse loss[442], and C3aR is a modulator of microglial function[441,452]. C5ar1 expression is upregulated in AD brain[453,454]. In mouse models of AD, antibody to the proinflammatory complement activation fragment C5a, genetic ablation of C5aR1 or pharmacologic antagonism of C5aR1 resulted in less inflammatory microglia and astrocytes, preservation of neuronal complexity, reduction of cognitive loss and suppression of synapse engulfment by microglia[454-457]. In addition, classical complement activation (via C1, C2, C4 and C3) has a substantial role in synapse pruning during neural development and adult plasticity, but aberrant or unregulated activation leads to excessive synapse elimination in AD mouse models ([253,458,459] and as reviewed in[460]). However, induction of C1q expression is an early response to injury, prior to upregulation of other complement components in brain, and protective roles of C1q have been well documented (enhancement of phagocytosis, suppression of microglial medicated inflammation, and neuroprotection) (reviewed in[461]). As a result, unintended immunocompromising consequences of

targeting this component must be considered. In contrast, novel approaches to modulate neuronal activators of the complement cascade may be selective and effective for different subtypes of AD[462]. Thus, while a powerful arm of the immune system, protecting from infection and enhancing removal of cell debris, activation of the complement cascade by pathological protein accumulation, signals of weak or dying cells/synapses and disease associated cellular debris contributes to the progression of AD. Therapeutic approaches must selectively target detrimental consequences, while maintaining beneficial complement-mediated immune and cognitive functions.

Cytokines During AD, cytokine production is initiated by DAMPs or Ab activating pattern recognition receptors and can be regulated at multiple steps, including cellular release. In the brain, cytokines are released by microglia, astrocytes, lymphocytes, pericytes and other cells, and act on neighboring cells, including the releasing cells, to drive neuroinflammation in different directions, depending on the cytokine. For example, in microglia, activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome generated interleukin-1β (IL-1β), which reduced microglial clearance of Aβ, the release of Aβ-degrading enzymes, such as insulin-degrading enzyme and neprylisin, and stimulated the production of nitric oxide and subsequent immune cascades[429]. Neurons exposed to microglia-derived IL-1β show spine loss and reduced hippocampal long-term potentiation (LTP)[429,463]. Reduced LTP has also been reported for interleukin 2, interleukin 6 (IL-6), tumor necrosis factor α (TNFα) and other cytokines[464-467]. IL-1β can cause neurofibrillary tangle formation and tau pathology through a IL-1 receptor mediated, CamKII dependent mechanisms in rodent models of AD[70]. NLRP3 inflammasome activation can also result in microglial pyroptosis, release of ASC speckles and further seeding of Aβ deposition[468]. More recently generation of type I interferons and other cytokines through the cGAS-STING pathway, activated by cytosolic DNA in microglia, neurons and other cells has become a focus of research[469-471]. Type I interferons are elevated in AD, and genetic deficiency for the type I interferon receptor (IFNAR1) can be protective in some mouse models of AD[472]. IL-1α (a type 1 interferon), IFN-γ, GM-CSF, IL-10 and IL-13 are elevated in AD brains in association with neurofibrillary tangles[473]. IFN-γ, from infiltrating T lymphocytes, can increase microglial activation and Ab deposition in amyloid mouse models, prevented by anti-IFN-γ antibodies[474]. IL-10 is generally anti-inflammatory, but knockout of the IL-10 gene in an amyloid mouse model, reduced amyloidosis, synaptic loss and cognitive deficits, while increasing microglial activation and phagocytosis[475]. IL-12 and IL-23 share a subunit and are elevated in AD, while depletion of the subunit by genetics or antibodies reduced amyloid load and cognitive deficits in an amyloid mouse model PMID: 23178247. Some cytokines may be protective, for example, IL-33 is depleted in AD brains, and IL-33 knockout resulted in tau pathology and neurodegeneration in mice[476], whereas IL-33 injection reduced microglial activation, Aβ plaques, synaptic loss and cognitive deficits in an amyloid mouse model[477].

COXx/prostanoids As key mediators of inflammation, prostanoids were initially implicated in AD pathogenesis based on cross-sectional and longitudinal epidemiologic studies showing reduced risk for AD in individuals taking non-steroidal anti-inflammatory drugs (NSAIDS) which inhibit both cyclooxygenase (COX)-1 and -2[478,479]. Although clinical trials of NSAIDS and COX-2 selective inhibitors were abandoned due to lack of clear benefit and potential cardiovascular risks[480], continued preclinical work highlights unique roles for these enzymes in the context of AD. For example, COX-1 is constitutively expressed by microglia[481], and its activity was associated with memory impairment in inflammatory models[482,483] and both amyloid and tau pathology in transgenic mice[484]. In addition, cyclooxygenases have been implicated in communication across the blood-brain barrier[188,485], and therefore might play roles linking peripheral inflammation to dementia and AD progression[486]. Other data demonstrate unique roles for specific prostanoids and their G protein-coupled receptors. For instance, prostaglandin E2 acting on EP2 receptors reduced amyloid phagocytosis in several models[487,488] and worsened spatial memory performance in APP/PS1 and aging mice[290,487], possibly by driving age-associated changes in myeloid cell inflammatory and metabolic states[290]. Moreover, EP1 receptors facilitate excitotoxic injury in ischemic and AD models[489,490]. Such findings support interventional targets that are more specific than general COX inhibitors.

iNOS and nitric oxide Neuroinflammation and activation of microglial into the M1 phenotype are associated with numerous neurodegenerative conditions including AD[424]. One major hallmark of neuroinflammation is aberrant NO production by microglial-expressed inducible nitric oxide synthase (iNOS or NOS2), a factor held responsible for aggravating pathology. iNOS generates high levels of NO with stimulation of microglia by lipopolysaccharide[446]/interferon-g resulting in a rate of NO production at ~140pmol/min/million cells[491]. In the presence of reactive oxygen species (ROS) following NADPH-oxidase activation, various reactive nitrogen species (RNS) are generated including the potent oxidant peroxynitrite which enhances nitrosative stress and causes oxidative damage, nitrotyrosination and S-nitrosylation of proteins, lipids and DNA. Evidence suggests that iNOS protein expression during the pathology of AD and other neurodegenerative conditions is the major source for NO-mediated protein post-translational modifications likely rendering many target proteins dysfunctional[492-495]. In AD, 3-nitrotyrosination of y-secretase, triose-phosphate isomerase, tau or Ab itself may aggravate the pathology[496-500]. These modifications can induce a positive feedback loop by which chronic and uncontrolled neuroinflammation causes further excessive microglial activation, resulting in release of additional pro-inflammatory cytokines and chemokines and damage to the nervous system. In contrast to iNOS-derived NO, Ca-dependent neuronal NOS (nNOS) activity leads to NMDA-dependent peak NO production of ~2fmol/s (~120 pmol/min) in the entire hippocampus which increases in aged 3xTg-AD mice due to higher nNOS protein expression[501]. This enhanced NO production was also seen in APP/PS1 mice due to increased interaction between carboxy-terminal PDZ-ligand (CAPON) and nNOS[502], a mechanism which when disrupted prevented memory defects and dendritic loss in this model. Additional evidence suggests that tau nitrotyrosination is caused by the enhanced nNOS-CAPON interactions in AppNL-G-F mice[503]. These data confirm a NMDAR-nNOS-dependent route contributing to AD pathology, consistent with earlier studies and clinical trials, where application of the NMDA receptor antagonist, memantine, an open-channel blocker, reduces excitotoxicity and ameliorates AD pathology[504]. There are various hypotheses as to where excitotoxicity and the well-described neuroinflammation originates. Classically, accumulation of Aβ aggregates and cell debris are involved in a neuroinflammatory response and augmented NO production. Indeed both fibrillary and oligomeric forms of Ab directly activate microglial cells including iNOS expression and NO production[505-507]. Recent studies suggest a role for a gut microbiota dysbiosis in neuroinflammation. The gut microbiota have been found differing from healthy controls in AD patients. Gram-negative bacteria can cross the blood–brain barrier (BBB), contribute to systemic neuroinflammation[508-510] thereby generating and releasing neuroinflammatory molecules such as LPS, capsular proteins, fimbrillins and flagellins which can further enter the CNS via a compromised BBB[511]. In agreement with these findings, post-mortem AD samples exhibit higher amounts of LPS, E coli K99 and other Bacteroidetes[510,512] and conversely, preventing a dysbiosis in a mouse model of AD can alleviate symptomatic cognitive decline[513]. To target NO-mediated cytotoxicity in neurodegenerative conditions, one therapeutic approach is to suppress overall NO production, either pharmacologically or genetically. This method showed promising outcomes in a variety of model systems where NOS inhibition or iNOS deletion prevented or slowed disease progression[514,515]. However, clinical trials have not yet achieved any beneficial effects, although phase I and II trials (NCT02167256, NCT01864655) with Src family kinase inhibitors such as saracatinib to suppress transcription factor NFκB[516] necessary for iNOS expression, were performed[517,518]. Perhaps due to the advanced stage of the disease there were no clinical benefits found reiterating the need for identifying a critical window in which these agents could exert the most clinical efficacy[519,520].

Mutual interaction between Immune mechanisms and neurodegeneration

*Inflammatory regulation of APP processing /A*β Inflammation can have detrimental effects in AD by exacerbating the generation of Aβ. It was proposed that pro-inflammatory cytokines could enhance the transcription of the Amyloid Precursor Protein (APP), and/or affect Aβ aggregation and generation[521-523]. BACE1 and APP expressions can become increased by incubation with pro-inflammatory mediators such as cytokines and ROS[524-527] or by events leading to chronic gliosis, such as traumatic brain injury and stroke[528-531]. Other reports have suggested that inflammatory cytokines

can regulate γ-secretase activity by inducing the expression of interferon-induced transmembrane protein 3 (IFITM3), which binds to γ-secretase, rising amyloid-β levels[532]. Interestingly, peripheral infection, including oral administration of a periodontal pathogen can lead to an increase in APP and BACE1 expression[176]. On the other hand, studies in animal models of amyloidosis have revealed that low grade peripheral inflammation by injection of LPS exacerbates amyloid pathology, affecting Aβ clearance mechanisms[145,533,534] or Aβ generation[535,536], while other reports have shown the opposite effects, with a reduction in Aβ when LPS is injected intra-cranially[537,538] or when mice are primed with low doses of LPS before Aβ deposition[146]. The effect of inflammation on APP and BACE1 expressions has been related to the presence of consensus binding sites for various transcription factors that are known to be regulated by inflammation (such as SMAD, NFκB, PPARγ and STAT1) in the BACE1 and APP promoters[524,539-541]. In addition, changes in inflammatory markers have been associated with alterations in epigenetic reprogramming[542], including the expression of miRNAs regulating the expression of genes involved in Aβ generation and tau phosphorylation (such as BACE1 and GSK3)[530].

Tau Evidence from the past years revealed that tau pathology can spread from cell-to-cell by a so far unknown mechanism. Accordingly, tau can be found in the extracellular space and potentially enters cells trans-synaptically, a phenomenon thought to be involved in disease progression[543-545]. In experimental tau-transgenic mouse models, tau pathology and tau spread were shown to be driven by activated microglia, potentially via release of the pro-inflammatory cytokine IL-1β[158,297]. In line with this, microglia depletion led to reduced tau transfer between neurons[546]. However, the presence of extracellular tau can not only be a potential continuous thread for neurons directly, but also the immune system in the brain. Recently, tau was identified as an activator of the NLRP3 inflammasome, an important defense pathway in microglia. NLRP3 inflammasome activation was detected in brains and CSF[547] of tauopathy patients and loss of inflammasome function markedly reduced progression of tau pathology as well as tau seeding downstream of Aβ[70]. In another study, hyperphosphorylated and misfolded tau from tauopathy brains activated microglial NF-kB and NLRP3 inflammasomes containing ASC[547]. Notably, myeloid-cell restricted deletion of myeloid differentiation primary response protein 88 (MyD88), a common adaptor protein for IL-1Receptor/TLR4, or ASC rescued tau pathology, and improved cognitive function in hTau mouse model of tauopathy. Importantly, suppression of tau via doxycycline or neutralizing pathological tau via Qb-virus like particle (VLP)-based vaccination significantly reduced NLRP3 and ASC levels in rTg4510 mouse model of tauopathy[547]. Together, these studies neuronally-derived tau can serve as DAMPs and trigger microglial innate immune responses. Strategies to block tau alone and/or tau-microglia interaction could be potential therapeutic strategy against tauopathies, including AD.

Synapses and Axons It is becoming increasingly clear that microglia play crucial roles at the neuronal synapse (thus the term “quadripartite synapse”)[234,548]. Microglia constantly contact synapses and contribute to synaptic homeostasis and function throughout lifespan[548-550]. Among the diverse functions microglia perform[100,550], one key microglia-mediated mechanism during development is to coordinate developmental synaptic pruning via the classical complement cascade[551,552]. Interestingly, this process becomes reactivated in a region-specific manner in various models of neurologic disease, including those of AD[553]. In both amyloid-[451,459] and tau-[442,554] based mouse models. These studies have shown that C1q, the initiating factor of the classical complement cascade, and/or C3, a downstream factor in the cascade, are upregulated and localized to synapses. This subsequently leads to aberrant elimination of the ‘tagged’ synapses by microglia[459]. Interestingly, this microglia-mediated synapse loss has been implicated to mediate synapse loss and dysfunction not only in AD models but also models of other neurologic diseases involving synaptopathy[555-558] as well as in aging[451,559] and cross-species[560]. These results strongly suggest that microglia play crucial roles in determining synapse fate across aging and disease[553]. Several immune and neuronal proteins have emerged as potential upstream regulators of microglia-mediated phagocytosis and production of C1q in AD-relevant models (for e.g., phosphatidyl serine (PtdSer), SPP1, TREM2, and neuronal pentraxin Nptx2)[561-563]. Still, further investigations are necessary to determine how specific synapses are being targeted and eliminated while others remain intact[564]. This could include molecules that negatively regulate complement proteins, such as the newly identified complement inhibitor SRPX2, or molecules that negatively

regulate microglial phagocytosis, such as CD47 and SIRPα. Another important consideration is that microglia-mediated synapse elimination may not always be detrimental in neurodegeneration. For example, it has recently been shown that microglia-mediated elimination of synapses can protect circuits from hyperexcitability in AD-related neurodegeneration. It is possible that synapse elimination early on in neurodegeneration is serving a beneficial function to protect neurons from excitotoxicity and detrimental in a circuit if this biology propagates uncontrolled, leading to cognitive decline. Thus, further elucidating the timing and circuit specificity of microglia and complement-mediated synapse elimination during neurodegeneration will improve our ability to therapeutically target these mechanisms in disease.

Therapeutic modulation of brain immunity in preclinical models Given the compelling evidence that manipulation of the immune system could provide disease modifying therapies for AD, there have been extensive studies to evaluate potential immune manipulation in preclinical models of AD relevant pathologies. Though there are multiple mechanisms to explain efficacy of anti-Aβ immunotherapies, data from both successful and failed human AD clinical trials support the concept that preferential targeting of deposited Aβ and subsequent microglial activation underlies efficacy. Thus, these interventions represent a major translational success for the field as the potential proof of concept and this mechanism of action was first obtained in amyloid depositing mouse models.

Numerous additional immune therapies are now being evaluated both in preclinical studies with several therapies in human clinical trials. There is however little consensus regarding how to best evaluate these novel therapies in preclinical models and which models should be used. As the balance of positive (e.g., amyloid and/or tau reduction, synaptic integrity) and negative effects (e.g., excessive synaptic pruning, overt toxicities, impacts on peripheral immune status) of any manipulation may limit therapeutic benefit, the field would be well-served to utilize a rigorous and systematic approach to evaluate these therapies in models before human trials. Indeed, the examples of immune modulation that have opposing effects on amyloid and tau pathologies in mice, illustrate why we should insist on a more rigorous and systematic approach to testing these novel therapies before moving them into human testing. Few in the field would be comfortable with advancing a therapy for AD that had opposing effects on the classic core pathologies. Yet, most immune interventions are advanced to the clinic without rigorous testing in both models, and with only limited study of impacts on the peripheral immune system. To increase probability of translational success and reduce the potential for doing harm we might consider using systems level omic studies both at a cellular and multiorgan level to assess potential benefits and liabilities of novel immune therapies. Indeed, immune manipulation in an elderly population with AD or at risk for AD, raises many safety concerns, and we should try to de-risk these interventions as much as possible.

Clinical trials and future therapeutic targets The modern-era study of neuroinflammation in AD began in 1982 with the report from Eikelenboom and Stam of complement components decorating amyloid plaques[4,6] These results were fortified by additional studies coming from the McGeers[9] and Joe Rogers[10] the later 1980s. Given that the implication of inflammation in AD pathogenesis predates articulation of the amyloid hypothesis[565], and given an assumption that such inflammation must harm surrounding tissues, one may wonder why no agents have been approved for modification of AD pathogenesis by modulation of inflammation, and none in late-stage clinical trials. Clinical trials to date have resulted in null, or in some instances negative (suggesting harm), findings (reviewed up to 2018 in[566], section 6). These trials tested anti-inflammatory agents of different categories and, in some instances, employed strategies to avoid exposure at later stages of the disease process, enrolling relatively "young-elderly" cognitively normal individuals with a parental history of AD[567]. The most concerning result emerged from a trial that tested the ability of the discontinued COX2-selective agent rofecoxib to prevent "conversion" of MCI to AD dementia, producing a statistically significant hazard ratio of 1.46 (p=0.011) in favor of incident dementia. Such findings have likely discouraged more recent trial efforts, as a search for 'neuroinflammation Alzheimer's disease' under 'controlled clinical trials' retrieved only 26 citations as of 6th November 2023. The more recent citations report approaches such

as Boswellic acids[568]; organic acids purified from plant resins), caloric restriction[569] and oral hygiene intervention[570]. Investigators described phase 1 trials of Lomecel B mesenchymal stem cells in patients with mild AD (MSCs[571,572]; rebranded "medicinal signaling cells" by one of their discoverers to diminish the implied stemness of the cell product[573]). Recipients of Lomecel B showed no safety signals, and measurements of plasma cytokines, hippocampal volume and MMSE produced variable results with no clear dose-response or biomarker-clinical relationship. A senolytics cocktail of Dasatinib and Quercetin has been trialed in a small number of early AD patients (NCT04063124; study design reported in[574], with results at clinicaltrials.gov. There were no deaths or severe adverse events (SAE); CSF Dasatinib was detected at ~3% of the plasma Cmax and Quercetin was not detected; CSF total tau decreased by an estimated 3% and Ab1-42 increased by about 10%. Effects on other putative biomarkers or cognition measures were marginal. One high-profile initiative (NCT05450549) using a brain-penetrant TREM2 antibody, DNL919, was discontinued following observation of moderate, reversible hematologic toxicity in a single ascending dose (SAD) safety study in healthy volunteers (n=80;https://investors.denalitherapeutics.com/news-releases/news-release-details/denali-therapeutics-reports-second-quarter-2023-financial). The judgment of those involved was that the therapeutic window in AD patients would be too narrow to justify continued efforts to advance this compound. A recent thoughtful Perspective piece[575] asked the analogous question about amyloid-lowering agents: why did it take 30 years to gain the first approvals for this approach? Their answers point to the fundamentals of drug development, and they highlight the overwhelming importance of biomarkers of target pathologies: amyloid and tau positron emission tomography (PET), buttressed by cerebrospinal fluid (CSF) biomarkers. From the present review and from examining the clinical trial literature, it becomes apparent that we (the community of neuroinflammation / neurodegeneration researchers and developers) lack a unifying hypothesis which would enable the generation of panels of core-pathology biomarkers. Our field would be well-advised to consider ways to accelerate clinical development, given underlying biological uncertainty. For example, basket trials performed within a platform trial structure allow the establishment of a combined, enlarged placebo group and standardized protocols, against which to evaluate multiple agents simultaneously. At the same time, considering how to enhance diversity of trial populations promises to augment the potential for real-world success.

Next generation models and open questions

This review has highlighted the multiplicity of roles that each of many cell types are exerting on the brain parenchyma to contribute to "neuroinflammation" along the trajectory to Alzheimer's disease (AD). It is thus clear that the target in AD is not a given cell type of subtype but rather a community of cells whose intercellular communication accelerates AD pathophysiology[576]. Disruption of these communications is an important therapeutic target, and it will require more sophisticated human *in vitro* induced pluripotent stem cell- (iPSC) derived model systems than are generally available today, as it will require not only co-culturing multiple cell subtypes together but ensuring that each of them is in its relevant cell state. Further, complexity will need to be balanced with reproducibility, which is critical to reduce sources of variation in the assays that will be deployed to answer specific mechanistic questions. These challenges are being addressed by many groups, and, while no one model system is ideal today, some in vitro systems are showing promising results in capturing some features of disease pathophysiology such as response to Aβ toxicity[577] or enhanced reproducibility. Further, simpler model systems of cellular monocultures derived from iPSC have already shown that certain *in vitro* measures correlate with complex traits captured during life, such as cognitive decline[7,578]. An added challenge is that iPSC-derived cell types, and even cell lines, display heterogeneity in cell states even in monocultures[579], next generation models will thus need a higher level of characterization to either account for the diversity of cell states or, preferably, polarize the component cell types to the target cell states needed for an experiment; work in microglia-like cells is showing the way forward using small molecules[580]. The recent development of chimeric models where human microglia is transplanted into the mouse brain opens new avenues to tackle some of the challenges listed above.

They provide a complex platform in which human cells are placed into a living brain "bioreactor", where they can interact with other CNS and systemic components and be exposed to relevant disease challenges[282,581,582]. Initial characterization of this model showed that transplanted human microglia recapitulate several baseline transcriptomic, proteomic and functional aspects of human primary cells[244,581,583]. The analysis of human microglia transplanted into the brain of AD mice revealed that they display a wide heterogeneity of cell sates that mimic time-dependent phenotypes and transcriptional features of AD[246,582]. An additional key advantage of chimeric models is the wide range of patient derived iPSC lines that could shed light on the impact of single or poly-genetic risk associated to AD[582], as well as relatively straight forward genetic modifications that can be introduced at stem cell level and can help translating from cell state to function. Although transplantation studies may provide relevant biological and mechanistic insights into different AD genetics, microglia cell states and functions, they come with limitations as the human cells are placed in a mouse immunodeficient host.

With enhanced multicellular *in vitro* and *in vivo* models, we will not reproduce the human brain, but we will have a manipulable approximation of cellular communities with which to test mechanistic questions and obtain reproducible results that can inform therapeutic pipelines. Key questions to pursue include defining how different microglial cell states translate into function within the brain, prioritizing node(s) in the intercellular communication network of a pathophysiologic cellular community for perturbation such that the community is driven towards protective states. One does not necessarily have to perturb all cells in a community equally; perhaps perturbing a key driver cell subtype can then effect the desired changes in the other cell types of the community. *In vitro* models with a pseudo-vascular component or refined chimeric systems with re-introduction of adaptive immune cells via T-cell transfer are particularly interesting as leveraging the propagation of immune responses from the periphery to the CNS would be ideal for a therapeutic, avoiding the many challenges of blood:brain barrier penetration.

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