



Review

# Neuroinflammation in Alzheimer's Disease

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**Abstract:** Alzheimer's disease (AD) is a neurodegenerative disease associated with human aging. Ten percent of individuals over 65 years have AD and its prevalence continues to rise with increasing age. There are currently no effective disease modifying treatments for AD, resulting in increasingly large socioeconomic and personal costs. Increasing age is associated with an increase in low-grade chronic inflammation (inflammaging) that may contribute to the neurodegenerative process in AD. Although the exact mechanisms remain unclear, aberrant elevation of reactive oxygen and nitrogen species (RONS) levels from several endogenous and exogenous processes in the brain may not only affect cell signaling, but also trigger cellular senescence, inflammation, and pyroptosis. Moreover, a compromised immune privilege of the brain that allows the infiltration of peripheral immune cells and infectious agents may play a role. Additionally, meta-inflammation as well as gut microbiota dysbiosis may drive the neuroinflammatory process. Considering that inflammatory/immune pathways are dysregulated in parallel with cognitive dysfunction in AD, elucidating the relationship between the central nervous system and the immune system may facilitate the development of a safe and effective therapy for AD. We discuss some current ideas on processes in inflammaging that appear to drive the neurodegenerative process in AD and summarize details on a few immunomodulatory strategies being developed to selectively target the detrimental aspects of neuroinflammation without affecting defense mechanisms against pathogens and tissue damage.

**Keywords:** Alzheimer's disease; neuroinflammation; immunosenescence; inflammasome; mitochondria; microglia; astrocytes; DAMPs; SASP



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## 1. Introduction

Aging is characterized by dysregulated immune [1] and metabolic homeostasis [2,3] where there is chronic sterile low-grade inflammation or inflammaging [4] that involves cellular senescence [5,6], immunosenescence [7–10], mitochondrial dysfunction [11,12], defective autophagy [13,14] and mitophagy [15,16], dysregulation of the ubiquitin–proteasome system [17,18], activation of the DNA damage response [19,20], meta-inflammation or metaflammation from chronic overnutrition or obesity [21,22], and gut microbiota dysbiosis [5,23–25]. These are reflected by changes in circulating immune markers including C-reactive protein (CRP) [26], interleukin-6 (IL-6) [27], tumor necrosis factor alpha (TNF- $\alpha$ ) [28] and its soluble receptors (tumor necrosis factor receptor I (TNFR-I) and tumor necrosis factor receptor II (TNFR-II)) [28], vascular cell adhesion molecule I (VCAM-I) [29], d-dimer [30], and sirtuin signaling [31,32]. The drawback of chronic subclinical inflammation is that it is an essential risk factor for increasing the incidence of degenerative diseases such as AD [33–35]. There are currently an estimated 728 million persons aged 65 years or over in the world. In the next 30 years, this number is expected to more than double to exceed 1.5 billion in 2050 (<https://www.un.org/development/desa/pd/news/world-population-ageing-2020-highlights> (accessed on 20 March 2021)). Thus, the aging population vulnerable to inflammaging will significantly increase over the next few decades.

AD is a chronic devastating neurodegenerative disorder in which increasing age is the strongest non-modifiable disease risk factor [36,37]. There are currently no effective therapies for AD [38,39]. It is clinically characterized by the progressive deterioration of memory and other cognitive functions [40]. It is the leading cause of dementia, affecting 50 million people worldwide [41]. Its neuropathological hallmarks include extracellular  $\beta$ -amyloid ( $A\beta$ ) plaques and intracellular hyper-phosphorylated tau ( $p$ - $\tau$ ) in neurofibrillary tangles, accompanied with synaptic and neuronal loss [40–42]. AD can be classified as (i) familial or early-onset AD (EOAD) or (ii) sporadic or late-onset AD (LOAD) [43]. Both share almost similar pathophysiology [44,45]. Three causative genes, including presenilin 1 (PSEN1) [46], presenilin 2 (PSEN2) [47], and amyloid precursor protein (APP) [48], are involved in the pathogenesis of EOAD in an autosomal-dominant trait [49,50]. LOAD, however, comprises most AD cases (>95%) where the greatest risk factor is advanced age [51], while the common genetic risk factor is an allelic variation in apolipoprotein E (Apo E) [52]. Recent large scale studies of AD genetics, employing genome-wide association studies (GWAS), whole exome sequencing (WES), and whole genome sequencing (WGS), have defined additional genes whose variants contribute to increased risk [53,54]. These include Clusterin (CLU), Sortilin-related receptor-1 (SORL1), ATP-binding cassette subfamily A member 7 (ABCA7), Bridging integrator 1 (BIN1), phosphatidylinositol binding clathrin assembly protein (PICALM), CD2 associated protein (CD2AP), Complement component (3b/4b) receptor 1 (CR1), CD33, triggering receptor expressed on myeloid cells 2 (TREM2), and phospholipase D3 (PLD3) [55–57]. Intriguingly, more than 50% of validated gene variants are implicated in innate immune and microglial functions [58–60], including the top two AD risk genes, APOE and TREM2 [61,62]. Epigenomic analysis shows that AD GWAS loci are preferentially enriched in enhancer sequences involved in innate immune processes [63,64] as well as endocytosis, cholesterol/sterol metabolism, and synaptic function [55,65,66]. TREM2 enhances the rate of phagocytosis in microglia and macrophages; modulates inflammatory signaling; and controls myeloid cell number, proliferation, and survival [67], and it has been revealed that triggering TREM2 receptor in microglial cells is closely associated with the pathogenesis of AD [68]. TREM2 modulates microglial functions in response to  $A\beta$  plaques and tau tangles [69,70]. In early AD, the absence of TREM2 leads to increased amyloid pathology that progressively becomes worse owing to the loss of phagocytic  $A\beta$  clearance [69]. In AD, TREM2 variants arise in part because of their reduced capacity to phagocytose  $A\beta$  [71].

While compelling evidence indicates that AD has a multifactorial etiology [72–74], neuroinflammation plays a central role in its etiopathogenesis [75,76], owing to its capacity to exacerbate  $A\beta$  and  $\tau$  pathologies [77]. In vivo positron emission tomography (PET) studies provide direct evidence of increased microglia activation (inflammation) in the brains of AD patients [78–80]. The levels of pro-inflammatory cytokines in AD patient serum and post mortem brain are elevated [81,82], and  $A\beta$  can activate the brains' innate immune cells [83,84]. The sustained inflammatory response in AD brains [85–87] extends beyond a reaction to neuronal loss [88] and involves microglia, astrocytes, oligodendrocytes, mast cells, cytokines, and chemokines, as well as complement [89]. These collectively play an integral role in the onset and progression of the disease [88,90,91]. Other early-onset processes involved in the etiology of the disease include mitochondrial dysfunction resulting in altered glucose metabolism [92] and oxidative stress [93]; chronic hypoperfusion [94]; and neuronal cell cycle re-entry that leads to neuronal tetraploidization (NT) [94], trisomy 21 mosaicism [95], and synapse loss [96]. These processes may synergistically interact to facilitate the neurodegenerative process in AD [93,97].

Here, we focus on recent progress made in understanding the role of inflammation in the etiopathogenesis of AD and describe a few immunomodulatory strategies being developed to selectively target the detrimental aspects of neuroinflammation without interfering with the defense mechanisms against pathogens and tissue damage.

## 2. Mediators of Neuroinflammation

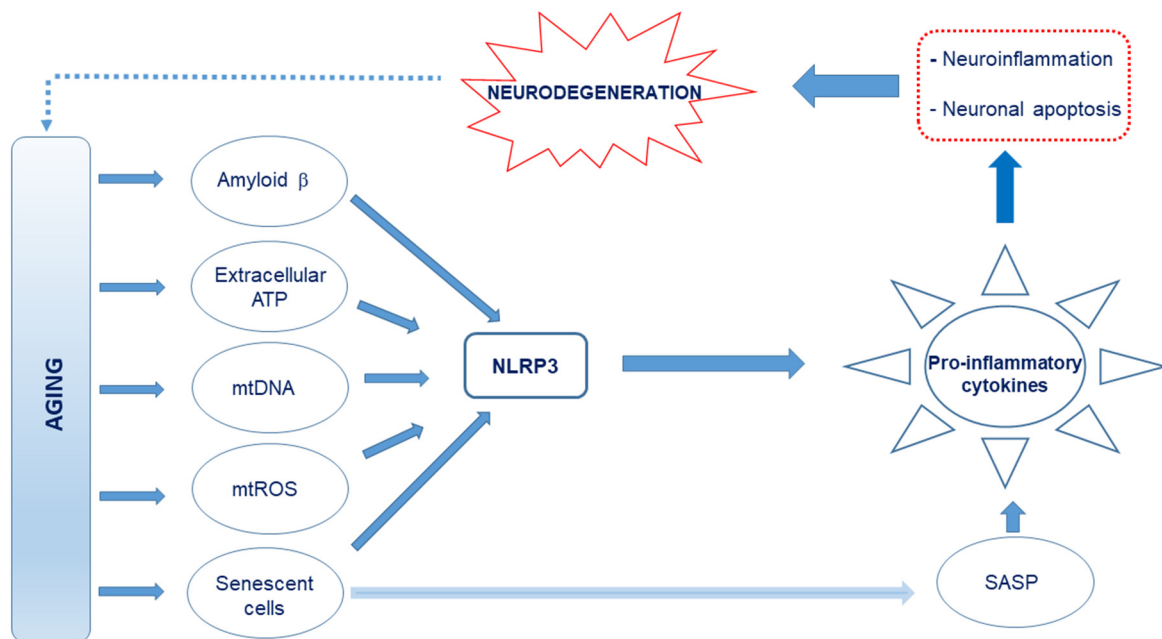
### 2.1. Microglia

Microglia are the CNS's immune cells [98] and are different from peripheral and other tissue-resident macrophages [99–104]. They arise from yolk-sac fetal macrophages and are unique in their capacity for self-renewal [105–107]. Other tissue macrophages develop from precursors that emerge later in life [103,104]. They constantly survey their milieu and assess ongoing synaptic activity, mediate synaptic pruning, clear debris, and provide trophic support for neurons [108]. In pathological situations such as chronic stress, the blood brain barrier (BBB) may become compromised, allowing peripheral hematopoietic cells to cross into neural tissue and become part of the parenchymal microglia/macrophage pool [109,110]. In response to CNS insults such as neuronal injury or infection, microglia become activated to produce pro-inflammatory factors (M1 phenotype) or anti-inflammatory factors (M2 phenotype) [111]. An exquisite balance of anti-inflammatory mediators to heal and repair tissues and pro-inflammatory mediators to clear cellular debris and aggregated misfolded proteins is essential for the maintenance of a healthy CNS [27,111]. With advancing age, microglia acquire an activated phenotype and release pro-inflammatory cytokines such as IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 [112–114]. In AD, microglia react to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) [115–117] to assume a M1 phenotype, leading to an exacerbation of inflammation and an acceleration of disease progression [88] (Figure 1). Preliminary findings implicate a link between A $\beta$  and neuroinflammation [118]. In AD brain slices, activated microglia surround both extracellular A $\beta$  plaques and neurons containing neurofibrillary tangles (NFTs) [119,120]. It is thought that A $\beta$  activate microglia, which then secrete IL1 $\beta$ , IL6, and TNF $\alpha$ , as well as (C-C motif) ligand (CCL 2/4/11), which lead to the recruitment of more microglia and astrocytes to the A $\beta$  locus [121]. Microglia phagocytize A $\beta$  through a range of cell surface receptors, including cluster of differentiation (CD)-14, toll-like receptor (TLR)-2, TLR4,  $\alpha$ 6 $\beta$ 1 integrin, CD47, and scavenger receptors such as CD36 [122–125]. In AD, the accumulation of A $\beta$  throughout the brain results partly from the failure of microglia to remove extracellular A $\beta$  [126–128] and AD cortical specimens reveal that the microglia surrounding plaques have impaired A $\beta$  uptake [127,129,130]. It has been shown in human and animal studies that inflammation influences APP processing overall [131,132]. Initially, microglial activation may serve to eliminate A $\beta$  [126,133–135], but their chronic activation may amplify the amyloid cascade [133,136] and lead to neurotoxicity [137,138]. In rat intraventricular hemorrhage (IVH) model of AD, A $\beta$  accumulation tracks with neuroinflammation and may contribute to the cognitive impairment [139]. There is no consensus, however, regarding the relationship between in vivo microglial activation and A $\beta$  plaque burden [140–144]. A $\beta$  has recently been suggested to be an antimicrobial peptide that fibrilizes in order to activate the innate immune defense system and protect the host from a wide range of infectious agents [145].

### 2.2. Astrocytes

Astrocytes are the most abundant cell type in the CNS and a critical part of the tripartite synapse [146]. They are highly sensitive to their environment and rapidly respond to CNS needs and insults [147]. They also regulate the maturation of neurons and help maintain their function [147,148]. They are found in various states of activation and can be neuroprotective (reducing inflammation and stimulating repair) or neurotoxic (promoting inflammation that may result in neurodegeneration) [149,150]. They respond to inflammatory molecules such as cytokines and chemokines and are able to detect aggregated proteins such as A $\beta$  [148,151,152]. They hypertrophy upon activation and upregulate glial fibrillary acidic protein (GFAP) expression [153,154]. Reactive astrocytes are a distinct trait of AD patient brains [155] and are also a feature of AD mouse model brains [156–158]. Intralaminar astrocytes are atrophied and severely disrupted in post-mortem AD brains [159]. In the 3xTg, which contain three mutations associated with a familial AD (APP Swedish, MAPT P301L, and PSEN1 M146V) mouse model, atrophic astrocytes appear in the entorhinal cortex (EC) as early as 30 days and are present until A $\beta$

plaques begin to emerge at 12 months of age [160]. This phenomenon also occurs in other AD mouse models including the 5xTG-AD, PDAPP-J20, and Swiss 3 mice [161–164]. When astrocytes are created from familial and sporadic AD-induced pluripotent stem cells (iPSC), they have an atrophic phenotype in vitro [165]. Inhibiting astrogliosis in AD mouse brains results in A $\beta$  accumulation with increased histopathology [166] and they are associated with cognition [167]. This may result in a breach of the blood brain barrier (BBB), leading to an infiltration of peripheral immune cells, aggravating neuroinflammation and inducing neurotoxicity by impairing glutamate homeostasis [168,169], and generating altered Ca<sup>2+</sup> signaling [170].



**Figure 1.** Schematic representation of the proposed causes of neuroinflammation in Alzheimer’s disease (AD). Age-related release of damage-associated molecular patterns (DAMPs) such as A $\beta$ , extracellular ATP, and cell debris such as circulating mitochondrial DNA, which are capable of interacting with the Nod-like receptor 3 (NLRP3), creates an oxidative and neuroinflammatory environment through the excessive production and release of pro-inflammatory cytokines and reactive oxygen and nitrogen species (RONS). Further, mitochondrial reactive oxygen species (mtROS) and senescence-associated secretory phenotype (SASP) factors from the senescent cells, which also drive senescence in nearby cells, produce pro-inflammatory cytokines. This culminates in neuroinflammation and neuronal apoptosis.

### 2.3. Oligodendrocytes

The main function of oligodendrocytes is to provide support and insulation to the axons by forming myelin sheaths around nerve fibers. Their involvement in AD is not fully understood, although emerging evidence implicates their potential role in pathogenesis and progression of AD [171]. Tsai et al. recently reported that oligodendrocytes are severely impaired in AD [172] and, indeed, there is focal loss of oligodendrocytes and a reduction in myelin proteins near A $\beta$  plaques [173–175]. A $\beta$  not only impairs the survival and maturation of oligodendrocyte progenitor cells (OPCs), but also hampers the formation of the myelin sheath [176]. Neuroinflammation and oxidative stress may also contribute to oligodendrocyte dysfunction and death [175].

### 2.4. Myeloid Cells Other Than Microglia

The other monocytic cells found in the CNS include perivascular macrophages that line blood vessels of the brain, macrophages within the choroid plexus, and meningeal macrophages in the leptomeninges [177]. Dendritic cells, monocytes, and granulocytes are found in the meninges and are recruited to the brain during or after an insult or

other pathology [178,179]. The CNS-resident macrophages express scavenger receptors (SR) and TLRs that facilitate phagocytosis and degradation of A $\beta$  [180,181]. In SR knock out mouse models of AD, A $\beta$  accumulates in the parenchyma and the animals have cognitive deficits [124,182]. In the CD11c-DNR mouse model of AD, which expresses a dominant-negative form of the TGF- $\beta$  receptor under the control of the CD11c promoter, the brain levels of A $\beta$  are reduced by up to 90%, the A $\beta$  plaques and cerebral vasculature are surrounded by macrophages [183], and the behavior of the animals is significantly improved [183]. The migration of peripheral monocytes is dependent on C-C chemokine receptor type 2 (CCR2) [184]. Blocking transforming growth factor (TGF)- $\beta$  signaling increases peripheral myeloid cell infiltration into the CNS and significantly reduces A $\beta$  burden [183]. It is still not exactly clear how myeloid infiltration into the brain contributes to damage or clearance of pathological proteins.

### 3. Defective Autophagy and Neuroinflammation

Cells degrade protein aggregates and damaged organelles by autophagy and defective mitochondria by mitophagy [185–188]. With advancing age, autophagy gradually subsides and this decline is linked to defective mitochondria and results in inflammaging [189]. Damaged cellular and organelle components that accumulate as a result of inadequate autophagy are released as damage-associated molecular patterns (DAMPs) [190–192]. Dysfunctional mitochondria that are not eliminated by mitophagy release large amounts of mitochondrial DNA (mtDNA) into the cytosol and, together with ROS [193,194], metabolites such as ATP, fatty acids, A $\beta$ , succinate, per-oxidized lipids, advanced glycation end-products, altered N-glycans, and HMGB1 are also recognized as DAMPs and trigger an innate immune inflammatory response [195,196] by directly activating TLR9. This initiates the transcription of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , IL-1 $\beta$ , and MMP-8 [197] and activates the Nod-like receptor 3 (NLRP3) inflammasome, a key regulator of inflammation [198–200], to activate caspase-1 and facilitate IL-1 $\beta$  and IL-18 maturation as well as gasdermin D-mediated pyroptotic cell death [201–203]. These inflammatory responses can be blocked by Pro-IL-1 $\beta$  degradation in autophagosomes [204]. Further, the mitochondrial derived peptide (MDP) known as mitochondrial open reading frame of the 12S ribosomal RNA type-c (MOTS-c) [205] reduces inflammation by inhibiting cytokines such as TNF- $\alpha$  and IL-6, while simultaneously promoting an anti-inflammatory response. MOTS-c stimulates IL-10 as well as signal transducer and activators of transcription 3 (STAT3) and aryl hydrocarbon receptor (Ahr), which inhibit NF $\kappa$ B expression and pro-inflammatory cytokine production [206]. Another mitochondrial peptide, humanin, also has anti-inflammatory effects [207,208]. The chronic sterile low-grade inflammation elicited [4] may culminate in immunosenescence [209] and compromise neuronal function [32]. This may partly explain why dysregulated NLRP3 inflammasome activation is observed in AD [210,211]. Eliminating damaged and dysfunctional mitochondria by mitophagy may prevent the hyperinflammation triggered by NLRP3 inflammasome activation [212].

### 4. Mitochondrial Dysfunction and Immunometabolism

Mitochondrial dysfunction with decreased oxidative phosphorylation (OXPHOS) and increased glycolysis is observed in AD microglia [213]. Microglia exhibit high metabolic flexibility to cope with their high energy demands [214]. Microglial activity becomes compromised with age as mitochondrial activity declines with age and especially in age-related diseases such as AD [215] and they have a low mitochondrial turnover [213,216]. Exposure to A $\beta$  and tau activates a proinflammatory phenotype that is accompanied by a shift of the metabolic profile from OXPHOS to glycolysis. If the inflammatory process is prolonged, bioenergetic failure involving both glycolysis and OXPHOS occurs [217]. In the 5XFAD mouse model of AD, enhancing glycolytic metabolism restores microglial phagocytic activity [217]. Increased mitochondrial fragmentation is seen in cellular and animal models of AD and is associated with the increased pro-inflammatory cytokine production and neurotoxicity [213]. These mitochondrial perturbations in activated mi-

croglia are propagated to other cell types, including astrocytes and neurons, exacerbating the disease outcome [213]. Increased glycolysis and upregulated expression of glucose transporters as well as glycolytic enzymes in activated microglia are a well-established phenomenon [218,219]. Increased microglial glycolysis is often coupled with the increased secretion of proinflammatory cytokines, exacerbating neurotoxicity, and escalating ongoing neurodegeneration [219,220]. Glycolysis is upregulated in microglial cells during the early phase of AD, coupled with increased phagocytic activity followed by an “immune tolerant” phase, during which glycolysis and oxidative phosphorylation were both disrupted, with less phagocytic potential [217]. Microglial activities can be restored through increasing metabolic functions with interferon-gamma (IFN- $\gamma$ ), resulting in increased microglial clustering around A $\beta$  plaques, phagocytosis, and TNF- $\alpha$  production. Conversely, in AD models, oxidative phosphorylation increased phagocytosis and migration and reduced proinflammatory cytokine production [221].

### 5. Oxidative Stress and Neuroinflammation

Neuroinflammation and oxidative stress are key pathologic signatures of AD [222–225]. RONS are produced by all aerobic cells, and while they are essential signaling molecules [226,227], a redox imbalance is detrimental and plays an important role in the inflammatory process in aging as well as in AD [226,228,229]. While cells of innate immunity produce copious amounts ROS within the central nervous system (CNS), it is not clear whether neuroinflammation induces oxidative stress or if it is the elevated levels of ROS that cause neuroinflammation [230,231], especially in a situation where there is already excess oxidant production in the face of age-associated weakened antioxidant defense [230,232].

Elevated RONS levels damage primary cellular components including lipids, proteins, and DNA [226]. Increased oxidative stress biomarkers (i.e., malondialdehyde (MDA), glutathione peroxidase (GSH-Px), and protein carbonyl (PC)) correlate with raised levels of inflammatory cytokines and both are associated with low cognitive performance in institutionalized elderly people [233]. Mitochondria are the most important source of intracellular ROS and mitochondrial dysfunction leads to significant ROS increase [226]. Alternative mechanisms that produce ROS include NADPH oxidase (NOX), immune activation, xanthine oxidase (XO), arachidonic acids (AA) metabolism, and so on [226,234]. mtDNA mutations that accumulate with age disrupt the mitochondrial respiratory chain and lead to excessive mitochondrial ROS (mtROS) production, which, in turn, accelerates the emergence of new mtDNA mutations, leading to cellular senescence, further aggravating the inflammaging process. A vicious oxi-inflamm-aging cycle is thus created in aging and exaggerated in AD [235,236].

### 6. Cellular Senescence and Neuroinflammation

Stimuli such as mitochondrial dysfunction, persistent DNA damage, and exposure to DAMPs can initiate cellular senescence [237,238]. Senescent cells accumulate with aging and secrete proinflammatory and matrix-degrading molecules as part of a senescence-associated secretory phenotype (SASP), which is linked to age-related tissue inflammation and disease [239]. Senescent cells are deleterious to non-senescent neighboring cells. They develop a SASP and secrete cytokines, chemokines, ROS, and proteases that create a noxious microenvironment [240–242] that promotes inflammaging [243]. Senescent neurons have been described in old rodent and human brains [244,244,245], suggesting a proliferation-independent senescence-like mechanism in post-mitotic cells including neurons [246]. This concept is described as “amitosenescence” and involves an attempt by post-mitotic cells (particularly neurons) to re-induced cell cycle [247,248]. SASP may account for several observed disease phenotypes in AD [249–252]. The SASP is a very heterogeneous phenotype [253] and the secreted components vary on the basis of cell type and triggering factors, but generally consist of interleukins (IL-1 $\alpha$ , IL-1 $\beta$ , and IL-6), chemokines (IL-8 and growth-regulated- $\alpha$  protein), growth factors (fibroblast growth factor 2 and hepatocyte growth factor), metalloproteinases (interstitial collagenase (also known as

MMP1), stromelysin 1 (also known as MMP3), and collagenase 3 (also known as MMP13)), as well as other insoluble proteins and extracellular matrix components [254–256]. Their effects are mainly paracrine, but may become systemic as some of the soluble mediators may get into the circulation [257–259]. Prominent SASP regulators include p38MAPK, NF- $\kappa$ B C/EBP $\beta$ , GATA4, and mechanistic target of rapamycin (mTOR) [260–262]. Senescent markers are up-regulated in the astrocytes of AD patients and A $\beta$  elicits senescence in astrocytes in vitro via ROS accompanied by p38, IL-6, and IL-8 up-regulation [263]. When rat astrocytes are cultured, they exhibit signs of senescence including intense SA- $\beta$ -gal staining, elevated ROS production, and bioenergetic deficits. This compromises their ability to maintain neurons and adversely affects the aging brain [264,265]. Depleting human astrocytes of glutathione in vitro activates SASP-associated pathways (NF- $\kappa$ B and p38MAPK) and IL-6 secretion [266]. In vitro, both human and rodent astrocytes upon replicative or stress induced senescence become flattened and enlarged and adopt senescence-associated heterochromatin formation (SAHF) and have elevated levels of p53, p21CIP1, p16INK4a, and SA- $\beta$ -gal [267,268]. Further, oligodendrocyte precursor cells (OPCs) in an AD mouse model show a proinflammatory phenotype along with increases in p16 and p21 expression near A $\beta$  plaques, and A $\beta$  can induce senescence in cultured OPCs [252]. Mouse models of A $\beta$  plaque accumulation lend credence to the fact that OPCs localize to plaques. In the 3xTg-AD mice AD [269],158], hypertrophic OPCs infiltrate and accumulate around A $\beta$  plaques [270] and in the TgAPP/PS1 mouse model, the OPCs surrounding A $\beta$  plaques have increased Cdkn2a mRNA expression, and SA  $\beta$ -gal and IL-6 levels (SASP factor) reflect what is seen in the human brain. This suggests that extracellular protein accumulation may negatively impact OPC function [252]. While IL-6 and TGF- $\beta$  mRNA are upregulated in AD patients [271,272], an inflammatory response from resident immune cells is also prominent in AD [88]. Generally, senescent cells are cleared by natural killer cells (NKs) [273–275] and macrophages [276–278]. The CNS being under relative immune privilege, T-cells, NKs, and peripheral macrophages normally have limited access to the meninges and choroid plexus and far-limited access to the CNS parenchyma [279–281]. However, this immune privilege is not absolute, and cells of the CNS are sensitive to inflammatory events occurring both within and outside of the brain [282]. In the aging brain and especially in the AD brain, the BBB is compromised, leading to peripheral immune cell infiltration [283,284,284–286]. This allows the infiltration of peripheral immune cells [287] and possibly infectious pathogens. Although microglia are the CNS resident macrophages, there is no evidence that they selectively kill senescent cells [261]. Getting rid of CNS senescent cells would require infiltrating CD4<sup>+</sup> T-cells, as peripheral macrophages appear to depend on these cells to kill senescent cells outside the CNS [277]. As the clearance of senescent cells in the CNS is limited in non-aged healthy individuals, senescent cells, SASP, and secondary senescence may continue in the brain for several years or even decades.

## 7. Meta-Inflammation (Metaflammation)

Late life obesity/metabolic disease and diabetes (T2DM) contribute to low-grade non-resolving inflammation and neuroinflammation [91,288] and increase the risk of developing AD [289]. AD has been referred to as “type 3 diabetes” [290,291]. Adipose tissue inflammation in obesity is sterile, chronic, and low grade and affects the metabolic control of nutrient flow in adipose tissue, liver, muscle, and pancreas by inducing insulin resistance, and it differs from the typical inflammatory response to pathogens [292–295]. Indeed, peripheral insulin resistance leads to decreased insulin signaling in CNS that is associated with an alteration in brain metabolism and activation of inflammatory pathways [296]. Hyperglycemia in T2DM increases AD risk by exacerbating microglia and astrocyte-mediated neuroinflammation and neuronal injury [297]. Individuals with advanced age, obesity, T2DM, or hypercholesterolemia are more likely to be affected by AD [298,299].

## 8. Exercise and Inflammation

Endurance exercise (EE) has anti-inflammatory properties that can reduce the risk of several metabolic disorders [300–302]. Some of these effects arise from the IL-6 secreted from skeletal muscles into circulation in response to EE [303] and include the acute phase of immune response [304] as well as glucose and lipid metabolism [305,306], and have been shown to reduce the risk and severity of many chronic diseases, and the benefits extend to the brain [302]. One of the long-term immunometabolic adaptations is mediated by energetic stress, which induces beneficial molecular adaptations in adipose tissue and immune cells [307]. In the brain, this results in the upregulation of IL-10 that activates mouse microglia and astrocytes [308,309]. The modulatory effects of exercise on inflammation both centrally and peripherally have a protective effect on cognitive function and may be beneficial to patients with AD [310,311], as it elevates levels of circulating growth factors (such as insulin-like growth factor 1, IGF-1) and neurotrophins (such as the brain-derived neurotrophic factor, BDNF) [310,312].

## 9. Gut Microbiota and Inflammation

The gut microbiota is less diverse with age and contains more Bacteroides, compared with the higher presence of Firmicutes in younger adults [313–315]. There is also a correlation between microbial diversity, frailty scores, and environmental factors such as dietary pattern in elderly individuals [313,316]. These changes can initiate dysbiosis, and the prevalence of pathogenic species in the intestinal microbial composition results in elevated levels of systemic proinflammatory markers (IL-6, IL-8, TNF- $\alpha$ , and CRP) [313,316] associated with the pathogenesis of AD [317,318]. The microbiota can also modulate events in the brain via vagus nerve activation, neuropeptide and neurotransmitter release, short-chain fatty acids (SCFA),  $\alpha$ -amino- $\beta$ -methylaminopropionic acid (BMAA), and lipocalin-2 release [319–321]. These signals reach the brain and influence the microglial maturation and activation [322], facilitating immune surveillance, regulation of hypothalamic-pituitary-adrenal (HPA) axis, synaptic pruning, and clearance of debris [323]. Further, neurobehavioral complications associated with peripheral infections may be facilitated by advancing age because hippocampal processing is more easily disrupted when the peripheral innate immune system is stimulated in older animals [324,325].

## 10. Complement in the Brain

While complement proteins are mainly synthesized in the liver, complement proteins and their cognate receptors and regulators are expressed throughout the CNS [326–329]. The intact blood–brain barrier (BBB) restricts and prevents access of complement proteins from the periphery. Local production is, therefore, particularly important for innate immune defense in the healthy brain. Even in the healthy brain, however, there are regions where the BBB is compromised, particularly in the aged normal brain where evidence of barrier loss in and around the hippocampus has been described [330], and this is more severe in the AD brain [327]. In the post-mortem AD brain, complement protein and activation products surround plaques and tangles [326]. Numerous mediators are implicated, including ROS and activation of tissue metalloproteinases, but the dominant pathway to BBB breakdown is inflammation, either central or systemic [331,332]. BBB impairment in AD may be much more subtle, localized to areas of pathology, and affecting specific transport processes—e.g., the transport of A $\beta$  [284,333]. C3a/C3aR signaling via intracellular Ca<sup>2+</sup> mediates vascular endothelial cadherin junction and barrier integrity in an in vitro model of the BBB. Microglial reactivity can be inhibited by inactivation of C3aR1, and this restores hippocampal and cortical volumes in aged brains, suggesting an association between impaired BBB, inflammation, and neurodegeneration [334,335]. Complement plays complex roles in brain homeostasis and likely has both protective and exacerbating effects on disease [327]. Evidence suggests that complement restricts A $\beta$  plaque formation and aids clearance of plaque components, but also contributes



to the switch of microglia and astrocytes into activated neurotoxic cells that drive the pathology [336–339].

## 11. Possible Intervention for Neuroinflammation in AD

In chronic inflammation, the initial response is not adequately resolved, leading to the accumulation of TNF, IFNs, and IL-6 as well as immune cells, apoptotic cells, and debris at the site of insult/injury, compromising functional homeostasis [340]. While there are concerted efforts to develop compounds that target specific facets of inflammation, viable strategies should seek to resolve neuroinflammation without impacting the defense mechanisms against pathogens and tissue damage. We depict a few immunomodulatory strategies being developed to delay the onset and/or progression of AD.

### 11.1. Targeting TNF- $\alpha$

TNF- $\alpha$  plays a central role in the initiation and maintenance of the inflammatory response, and effects of TNF- $\alpha$  in the CNS can be either homeostatic or pathophysiological [341,342]. It regulates synaptic plasticity, microglial activation, astrocyte-induced synaptic strengthening, and glutamatergic transmission in the healthy CNS [343,344], while in pathological conditions, the copious amounts of TNF- $\alpha$  released by microglia mediate a chronic inflammation that leads to neuronal dysfunction and cognitive impairment [344], as seen in transgenic mouse models of AD [345]. 5XFAD/Tg197 AD/TNF double-transgenic mice develop a human TNF- $\alpha$  (huTNF- $\alpha$ ) expression induced A $\beta$  plaques deposition and arthritis. Systemic treatment with infliximab, an anti-huTNF- $\alpha$  antibody that does not cross the BBB, protects neurons, reduces gliosis, and prevents infiltration of peripheral immune cells without altering brain huTNF- $\alpha$  levels [346,347]. In AD patients, TNF- $\alpha$  not only co-localizes with A $\beta$  plaques in the brain, but the levels are also elevated in the plasma and cerebrospinal fluid (CSF) and correlate with the severity of the disease [348]. TNF- $\alpha$  specific monoclonal antibodies such as infliximab, adalimumab, and the recombinant fusion proteins etanercept have been developed for peripheral inflammatory conditions and have been demonstrated to be effective and well tolerated in patients with a wide range of inflammatory conditions [349]. These drugs have been tested on AD rodent models via central and peripheral routes of administration [345,350]. Adalimumab significantly attenuated neuronal damage and neuroinflammation, decreased beta secretase-1 protein expression and A $\beta$ 1-40 plaques, and improved cognitive functions in A $\beta$ 1-40-injected mice [351,352], suggesting possible clinically meaningful outcomes in patients with AD. Indeed, patients with rheumatic disorders that are treated with TNF-blocking agents have a lower risk for developing AD [353]. XPro1595, a second-generation TNF- $\alpha$  inhibitor, targeting only the soluble form of TNF- $\alpha$ , thus preserving the neuroprotective transmembrane TNF- $\alpha$  signaling pathways [354], has been evaluated in three different mouse models of AD. Peripherally administered, XPro1595 reduces brain amyloid deposition and age-dependent increase in activated immune cells and improves synaptic function [355,356]. Locally administered, XPro1595 reduced pre-plaque A $\beta$  pathology in 3 $\times$ TgAD mice [357] with concomitant reduction in microglia activation and improvement of synaptic and cognitive functions in aging rats [358]. While new TNF- $\alpha$  inhibitors that are able to cross BBB are being developed [359], the use of the above compounds is limited to peripheral targeting of TNF- $\alpha$  as they are not able to readily cross the BBB [345].

An alternative approach under consideration for AD is the development of inhibitors of TNF- $\alpha$  synthesis [343]. Thalidomide and its derivatives, also referred to as immunomodulatory imide drugs (IMiDs), target the 3'-untranslated region (3'-UTR) of TNF- $\alpha$  mRNA, inhibiting TNF- $\alpha$  cytokine production. Compared with similar anti-inflammatory drugs, currently marketed IMiDs have improved BBB permeability and bioavailability, making them viable candidates for neurological disorders [360]. Chronic thalidomide administration significantly reduces both astrocytes and microglia activation, and A $\beta$  generation in brains of APP23 transgenic mice through inhibition of  $\beta$ -secretase (BACE1) [361,362]. 3,6'-dithiothalidomide (3,6'-DT) effectively lowers TNF- $\alpha$ , nitrite, and secreted amyloid

precursor protein (sAPP) levels in vitro in LPS-activated macrophage-like cells. It also significantly reduces central and systemic TNF- $\alpha$  production and neuroinflammatory markers and restores hippocampal neuronal plasticity in LPS-challenged rats [363,364]. Chronic 3,6'-DT administration ameliorates A $\beta$ -induced neuroinflammation and microglial activation, preventing neurodegeneration and improving memory in an AD mouse model of stereotaxic intracerebroventricular A $\beta$ 1-42 [365] and reduces multiple hallmark features of AD, including glia activation, phosphorylated tau protein, APP, A $\beta$  peptide, and A $\beta$ -plaque number along cognitive dysfunction in 3 $\times$ Tg-AD mice, and leads to synaptic preservation [363,366]. When treated with 3,6'-DT from 4 months of age, these mice showed only A $\beta$  deposition within neurons, but no plaque or  $\tau$  pathology is evident. This is associated with an increase in TNF- $\alpha$  levels and improved working memory performance [363,366]. These promising preclinical studies using IMiDs indicate their potential of progressing from the bench to clinical trials and, eventually, to the bedside of AD patients.

### 11.2. Senolytics

Senescent cells secrete proinflammatory cytokines, chemokines, and tissue-damaging proteases that negatively impact their surrounding microenvironment and accelerate aging and age-related diseases [367]. Senolytics are drugs that selectively eliminate senescent cells [368,369] and apparently provide beneficial effects in rodent models of aging [370], although a causal link between senescent cell accumulation and AD is yet to be established. Dasatinib, a tyrosine kinase inhibitor with BBB penetrance, decreases microgliosis and is neuroprotective in preclinical models of AD [371,372]. Quercetin is a naturally occurring flavonoid that ameliorates AD pathology and protects cognitive and emotional function in aged triple transgenic AD disease model mice [373]. In combination, Dasatinib and Quercetin (D + Q) have favorable side effect profiles, which makes them attractive for in-human trials [368,374,375]. Fisetin (F) is flavonoid senolytic occurring in many plants, fruits, and vegetables that is widely available as a nutritional supplement [369,376]. In old mice, intermittent F administration enhanced cognitive function [375]. Intermittent administration of senolytics into a  $\tau^+$  mouse line (rTg(tauP301L)4510) with mild  $\tau$  overexpression that exhibit neurocognitive symptoms only after 22 months (equivalent to 70 human years) decreases brain senescent cells, neuroinflammation, and gliosis; enhances neuron density; partially restores lost cortical brain tissue; and decreases ventricular enlargement [250]. These changes are associated with the clearing of 35% of proinflammatory senescent NFT-containing neurons. Zhang et al. have demonstrated that D + Q clear brain senescent oligodendrocytes, decrease neuroinflammation, and improve memory acquisition and retention [252]. Senolytics are selective for senescent, but not normal oligodendrocyte lineage cells derived from human brains as well as in the transgenic mice [375]. In AD patient brains and brains of rTg4510 mice, only Olig2 and NG2 expressing OPCs that are associated with A $\beta$  plaques exhibit a senescence like phenotype, while astrocytes, microglia, and oligodendrocytes that are exposed to A $\beta$  do not. Treating these mice with senolytics selectively eliminates senescent cells, ameliorates inflammation and cognitive decline, and reduces A $\beta$  accumulation [252,377].

### 11.3. Targeting the Inflammasome

Targeting the NLRP3 inflammasome is gaining traction as a therapeutic strategy in inflammatory diseases [378,379]. Several approaches endeavor to inhibit the activation of the NLRP3 inflammasome and reduce microglial cytokine production [380]. The NLRP3 inflammasome significantly contributes to neuroinflammation and age-related cognitive decline and is potently activated by A $\beta$  [381]. Novel specific inhibitors of the NLRP3 inflammasome are currently in pre-clinical or clinical trials [382] (ifmthera.com/pipeline). MCC950 (also known as CP-456,773 and CRID-3), a potent inhibitor of NLRP3, promotes microglial clearance of A $\beta$ , reduces A $\beta$  accumulation, and improves cognitive function in APP/PS1 mice [383–386]. Both MCC950 and Inzomelid, another potent, selective, brain-penetrant NLRP3 inflammasome inhibitor, are expected to move into Phase II trials for a range of disorders, including Parkinson's, Alzheimer's

and, motor neurone disease (<https://www.europeanpharmaceuticalreview.com/news/111201/patents-for-nlrp3-inflammasome-inhibiting-compounds-granted-in-us-and-europe/>). Accessed on 20 March 2021).

#### 11.4. Targeting Immune Checkpoints

The PD-1 (programmed cell death-1) receptor (an inhibitory immune checkpoint receptor (ICR)) is expressed on the surface of activated T cells. Together with its widely expressed ligand PD-L1, PD-1 plays an important role in maintaining immune homeostasis and self-tolerance [387,388]. Persistent antigen stimulation and inflammation in pathological situations increase T cell surface expression levels of ICRs [389]. This leads to their interaction with their ligands on antigen presenting cells (APCs) that “exhausts” the T cells, inducing a hypofunctional state [390,391]. This mechanism could be manipulated to either quench or enhance the immune response as a therapeutic target and depends on recruited immunosuppressive regulatory T cells (Treg) [392]. This anti-PD-1/PD-L1 based immunotherapy has been effectively utilized for many cancers [393], and is now also a therapeutic strategy in AD animal models to induce a robust immune response against neurotoxic proteins [394]. Indeed, immunoneutralization of tumor necrosis factor-related apoptosis inducing ligand (TRAIL), a modulator of Treg cell functions, reduces neuroinflammation in a mouse model of AD [395]. In AD mouse models with advanced amyloid pathology, using PD-1 immune checkpoint blockers to overcome immune tolerance induces a robust systemic IFN- $\gamma$  response with subsequent recruitment of monocyte-derived macrophages (M $\Phi$ ) to the brain. This results in cerebral clearance of A $\beta$  and improved cognition [396,397]. Altering the brain immunological environment by inhibiting the PD-1/PD-L1 axis in a mouse model of tau pathology mitigates cognitive deficits and cerebral pathology [398]. Supporting these findings, it has been shown that functional PD-1 is expressed in hippocampal neurons and anti-PD-1 treatment rescues synaptic transmission and plasticity and potentiates learning and memory [388]. In the 5XFAD AD mouse model and DM-hTAU mouse model of frontotemporal dementia, neuroinflammation and cognitive deficits are shown [398]. Although the immune checkpoint blockade based-therapy represents a promising therapeutic strategy for AD and age-related dementia, further research is needed before PD-1/PD-L1 based clinical trials are conceived for these disorders. In fact, it is important to note that several PD-1 antibody inhibitors developed for other indications activate the peripheral immune system, but fail to modulate monocyte-derived macrophage infiltration and progression of brain A $\beta$  pathology in three different models of AD [399,400]. A different study using the same PD-1 checkpoint blockade [396,398] reported only a modest improvement of locomotor activity without any effect on cognition or tau pathology in a transgenic AD model [401]. PD-1 inhibitors may be able to reduce plaque load and improve cognition [396].

#### 11.5. Targeting CD38

Daratumumab, a first-in-class humanized monoclonal antibody against the CD38 epitope, was approved and indicated for multiple myeloma patients refractory to conventional therapy [402]. CD38 is a NAD glycohydrolase that is expressed by neurons, astrocytes, and microglial cells and plays an important role in neuroinflammatory and brain repair processes [403]. Its role in AD was evaluated and it was found that deleting CD38 significantly reduces both soluble A $\beta$  and plaque levels and improves spatial learning in mice [404]. In an APP<sup>swe</sup>PS1 $\Delta$ E9 mouse model of AD, loss of CD38 results in significant reduction of A $\beta$  plaques and an improvement of learning performance. In these APP<sup>swe</sup>PS1 $\Delta$ E9.CD38<sup>-/-</sup> mice, both  $\beta$ - and  $\gamma$ -secretase activities are reduced, suggesting that the loss of CD38 is neuroprotective in this AD model [404]. So, while there is still no direct evidence implicating CD38 in NDDs, it might be a novel therapeutic target for modulating A $\beta$  production and neuroinflammation in AD.

### 11.6. Targeting CD33

CD33 has been identified by GWAS among the leading risk factors for AD [405]. In the brain, it is exclusively expressed by microglia and infiltrating macrophages [406,407], and it has been shown in CD33<sup>-/-</sup> mouse models that knocking out CD33 reduces A $\beta$  levels and amyloid plaque load in the brain [407]. As APP processing is not altered in these animals, the phenotype likely results from a more efficient phagocytic clearance of A $\beta$ . Other studies have shown that overexpression of ectopic CD33 in microglial line BV-2 cells reduces A $\beta$  uptake [407]. Indeed, subtype-selective sialic acid mimetic called P22 binds to CD33 and increases uptake of the toxic A $\beta$  into microglial cells [408], making the sialic acid-binding site on CD33 an attractive pharmacophore for developing therapeutics that promote clearance of the A $\beta$ .

### 11.7. Targeting IL-12/IL23

Inhibition of the IL-12/IL-23 pathway by genetic ablation or pharmacological manipulation significantly reduces cerebral A $\beta$  load and cognitive deficit [409]. IL-12 and IL-23 subunit p40 production by microglia is increased in the APPPS1 AD mouse model. Genetic ablation of the IL-12/IL-23 signaling molecules p40, p35, or p19 reduces cerebral A $\beta$  load and the biggest effect comes from ablation of p40 or its receptor complex [409].

Moreover, immunizing of AD transgenic mouse models with A $\beta$ 42 prevents A $\beta$  plaque formation along with decreased expression of the IL-12R $\beta$ 1 receptor in T cells [409,410]. Co-blockade of IL-12 and IL-23 via targeting of p40 reduces A $\beta$  burden [409,411,412]. Indeed, antibodies against p40, IL-12, or IL-23 (European patent EP2661445A2) have been developed for the prevention or treatment of AD.

### 11.8. Targeting Th1 Response

Glatiramer acetate (GA) (Copaxone), a synthetic analog of myelin basic protein [413], the first disease-modifying drug approved for treatment of multiple sclerosis (MS) [414] can be used to safely boost T-cell responses without the risk of autoimmune disease, as it weakly cross-reacts with myelin-derived autoantigens [415]. It is thought to mediate its effects by stimulating Th2 response, possibly by suppressing the inflammatory Th1 response [416], increasing the frequency and function of Treg cells, modulating CD8<sup>+</sup> T cells, and exerting an immunomodulatory effect on B cells [417]. In APPSWE/PS1dE9 double-transgenic, immunization with GA results in cerebral recruitment of pro-healing, highly phagocytic monocytes (Mo) and M $\Phi$ , greatly alleviating cerebral A $\beta$  burden, reducing microgliosis and astrogliosis, resulting in improved hippocampal-based cognitive functions [418]. Further, T cell-based vaccination with GA in the same animal model of AD leads to enhanced neurotrophic support and hippocampal neurogenesis [419]. In APP-Tg mice, nasal vaccination with a proteosome-based adjuvant plus GA activates pro-healing microglia and robustly reduces A $\beta$  fibrils levels [420]. GA-stimulated M $\Phi$  protect neurons from A $\beta$ -mediated synaptotoxicity both in vivo and in vitro [401] and enhances cerebral recruitment of Mo-derived M $\Phi$  and reversing loss of cortical and hippocampal excitatory synapses in mouse models of AD. GA immunization enhances the expression of hippocampal early growth response protein 1 (Egr1), a protein negatively correlated with hippocampal A $\beta$  plaque burden [421]. GA-based vaccination could provide a new viable avenue for immune therapy for AD.

### 11.9. Targeting Microglial P2Y6 Receptor

GC021109 is a small molecule that specifically targets microglial purinergic P2Y6 receptors, promoting their phagocytic activity and inhibiting the release of pro-inflammatory cytokines. It has been shown to be safe in a phase 1 trial of AD ([www.alzforum.org/therapeutics/gc-021109](http://www.alzforum.org/therapeutics/gc-021109); [www.clinicaltrials.gov/ct2/show/study/NCT02386306](https://www.clinicaltrials.gov/ct2/show/study/NCT02386306)) Accessed on 20 March 2021).

#### 11.10. Cyclosporine and Tacrolimus

Cyclosporine and Tacrolimus are inhibitors of calcineurin and are used as immunosuppressive agents to prevent post-transplant organ rejection and for the treatment of autoimmune diseases and tuberous sclerosis tumors [422]. They have been shown to downregulate APP mRNA and protein expression in primary cultures of neonatal rat astrocytes [423]. Tacrolimus significantly quenches A $\beta$ - and LPS-stimulated secretion of pro-inflammatory cytokines and increases microglial uptake of fibrillar A $\beta$  in vitro. It also reduces spleen cytokine levels, microgliosis, and A $\beta$  plaque burden in APP/PS1 mice [424] and ameliorates dendritic spine density deficits in plaque-bearing AD model mice [425]. When APP/PS1 AD transgenic mice were treated with FK506, microgliosis, cytokine levels, and A $\beta$  plaque load were significantly reduced [424]. In Streptozotocin (STZ)-treated mice, Cyclosporine and Tacrolimus significantly reduce biochemical and histopathological alterations and age-related memory deficits, demonstrating their potential as therapeutic agents in cognitive dysfunctions, probably owing to their anti-amyloid, anti-oxidative, and anti-inflammatory properties [426,426].

#### 11.11. Targeting p38MAPK

Another novel therapeutic agent in the pipeline includes the orally active p38 MAPK $\alpha$  inhibitor Neflamapimod [VX-745] that is being developed as a disease modifying drug for AD [427], with phase 3 trials slated for late 2021. It is able to reduce IL-1 $\beta$  levels (NCT02423200) [428] and improve patients' attention and executive function.

#### 11.12. CNS Targeting Anti-Complement Agents

In vivo tests in Tg2576 that overexpress the human amyloid precursor protein (hAPP) 695 isoform that harbors the Swedish double mutation found in some cases of familial AD, and 3xTg, which contain three mutations associated with familial Alzheimer's disease (APP Swedish, MAPT P301L, and PSEN1 M146V) mouse models of AD, have shown that the cyclic hexapeptide PMX205 that potently and noncompetitively inhibits complement C5a Receptor 1 (C5aR1) decreases A $\beta$  and  $\tau$  deposits, reduces activated glia, and improves cognition, while not affecting the levels and physiological functions of C1q and C3 [429]. ANX-M1/ANX005, a humanized immunoglobulin G4 recombinant antibody against C1q developed by Annexon Biosciences, is safe at high doses (200 mg/kg) and is neuroprotective, preventing synaptic loss when A $\beta$  fibrils are injected into the lateral ventricles [430]. It has proceeded to clinical trials [431]. C3aR antagonist SB290157 could decrease amyloid load and microgliosis [432]. It is important to recognize that complement may be neuroprotective early in the disease process by clearing debris, meaning that an intimate understanding of the therapeutic window where complement inhibition is most effect is crucial [326].

#### 11.13. Novel Non-Steroidal Anti-Inflammatory Derivatives

CSP-1103 (also known as CHF 5074 or Itanapraded) is a non-steroidal anti-inflammatory derivative lacking cyclooxygenase inhibitory activity. It is a microglia modulator that has the potential to inhibit A $\beta$  plaque deposition, reduce tau pathology, restore normal microglial function by increasing phagocytosis, and decrease production of pro-inflammatory cytokines [433]. It is currently in phase III clinical trials.

#### 11.14. Calorie Restriction (CR)

CR has been shown to improve lipid and glucose metabolism, quench inflammation, and improve cardiovascular health [434]. This is thought to be via key nutrient and stress-responsive metabolic signaling pathways including IIS/FOXO, TOR, AMPK, Sirtuins, NRF2, and autophagy [435] that additionally work towards lifespan extension by CR [434]. Ultimately, the age-related proinflammatory upregulation of NF $\kappa$ B, IL- $\beta$ , IL-6, TNF- $\alpha$ , and ROS is attenuated [436,437] and the beneficial effects include enhanced cognitive response [437].

### 11.15. Metformin

The biguanide drug metformin is a hypoglycemic drug widely prescribed to treat T2DM and metabolic syndrome [438,439]. Its mode of action is to simulate CR, and it increases lifespan and limits the onset of age-associated diseases across species [440,441]. It activates AMP-activated kinase (AMPK) [442], enhances autophagy and mitochondrial function, and quenches inflammaging [443].

### 11.16. Endurance Exercise

Endurance exercise (EE) is neuroprotective against AD [444,445]. Exercise activates continuous oxidative stress that induces a series of counteractive mechanisms. These enhance mitochondrial function and mitigate ROS-induced neurotoxicity, i.e., mitohormesis [446,447], and this is especially important in the hippocampus, which is particularly sensitive to oxidative stress [448]. EE also activates anti-inflammatory pathways [449,450].

### 11.17. Melatonin

N-acetyl-5-methoxytryptamine (Melatonin), which is synthesized from tryptophan, is able to activate both proinflammatory pathways. It is also capable of suppressing proinflammatory processes including NO release, activation of cyclooxygenase-2, NLRP3, gasdermin D, TLR-4 and mTOR signaling, cytokine release by SASP, and A $\beta$  toxicity under different conditions [451,452]. In addition, it activates SIRT1 and upregulates Nrf2 while quenching NF $\kappa$ B activity and the release of IL-4 and IL-10, thus shifting microglia polarization towards an M2 phenotype [452].

### 11.18. Resveratrol

Resveratrol has been shown to affect aging and lifespan in mammals [453]. It is a potent natural SIRT1 activator that helps prevent aging-related decline in heart function and neuronal loss [454]. Resveratrol can also attenuate the phosphorylation of the mammalian target of rapamycin (mTOR) and S6 ribosomal protein (S6RP) while ameliorating inflammation [455]. Several cellular and animal studies show that SIRT1 is neuroprotective in neuroinflammation and neurodegenerative diseases. There are, however, conflicting results on the effects of resveratrol on AD subjects [456]. In one study, AD subjects who received resveratrol for 52 weeks had a significant reduction in the expression of cerebrospinal fluid matrix metalloproteinase 9 (MMP-9) and inflammatory markers [457], but in another clinical trial of AD, resveratrol had no beneficial effects [458]. A 26-week resveratrol treatment of healthy older adults improved memory performance and hippocampal functional connectivity [459]. These findings suggest that SIRT1 may be the potential target treatment of neuroinflammation and neurodegenerative disorders [460].

### 11.19. Antioxidants

Given the close association between oxidative stress and inflammaging [461,462], targeting detrimental ROS at the production stage without affecting ROS signaling may improve immune function and ameliorate neuroinflammation [463]. Mitochondria-targeted antioxidants potently sequester reactive oxygen intermediates (ROIs) and confer greater protection against oxidative damage in the mitochondria than untargeted cellular antioxidants [464,465]. These mitochondria-targeted antioxidants such as (10-(6'-plastoquinonyl) decyltriphenyl-phosphonium) (SkQ1), MitoQ, MitoTEMPOL, and MitoVitE prevent apoptosis by mitigating the oxidative damage more effectively than untargeted antioxidants such as 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox) [466]. Other such antioxidants include the following: 4,5-dihydroxybenzene-1,3-disulfonate (Tiron), which accumulate within the mitochondria by permeabilizing the mitochondrial membrane [467] and astaxanthin, a mitochondrion-permeable antioxidant, that can penetrate the blood-brain barrier and is effective in preventing and treating macular degeneration [468,469].

### 11.20. Probiotics

Gut microbiota are altered in the elderly; therefore, supplementation with specific strains of *Lactobacilli* and *Bifidobacteria* along with fructooligosaccharides and galactooligosaccharides may be beneficial [470–472]. They have been shown to attenuate inflammation by down regulating IFN- $\gamma$  and TNF- $\alpha$  and upregulating IL-10 [473,474]. Alteration of the gut microbiota can induce changes in brain activity, which raise the possibility of therapeutic manipulation of the microbiome in AD and other neurological disorders. This field of research is currently undergoing great development, but therapeutic applications are still far away [475]. The gut flora of cognitively impaired individuals and those with brain amyloidosis have an increased abundance of the pro-inflammatory species *Escherichia/Shigella*, while the abundance of anti-inflammatory species *E. Rectale* is reduced [476]. Fecal samples from elderly AD patients with AD induce a lower expression level of p-glycoprotein (a key mediator of intestinal homeostasis) in intestinal epithelial cells in vitro. p-glycoprotein dysregulation leads to inflammatory disorders of the intestine. Altered gut microbiota with disrupted intestinal homeostasis and induced inflammation may lead to neurodegenerative diseases like AD [476] via the gut–brain axis pathway [477]. Thus, remodeling the gut microbiota may be a novel therapeutic strategy for AD [473,474,478,479]. Altering gut microbiota through probiotics is a potential therapeutic strategy in AD [480–483].

### 11.21. Nutraceuticals

The nutraceutical NT-020, which is a proprietary blend of blueberries, green tea, vitamin D3, and carnosine, has been shown to reduce inflammation in elderly rats and prevent age-related cognitive decline and enhance neurogenesis [484–488]. Treating aged rats with NT-020 increases neurogenesis and serum from these animals' rescued aged hippocampal neural stem/precursor cells (NPCs) and bone-marrow derived mesenchymal stem cells (MSCs) from age-related reduction in cell proliferation as measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assays and serum from aged rats treated with NT-020 was not different from serum.

### 11.22. Essential Vitamins and Minerals

Vitamins and minerals play major roles in boosting the immune system to protect against certain infections and inflammation [489–492]. Vitamin E supplementation enhances IL-2 production and induces naive T cell proliferation [493–495]. Vitamin C is a potent water-soluble antioxidant and plays an important role in maintaining redox homeostasis within cells and is protective against ROS released by phagocytes [496–499]; therefore, it modulates the pro-inflammatory signaling pathways [500,501]. It also augments humoral response and cell-mediated immunity [500]. By accumulating within phagocytic cells, it enhances chemotaxis and phagocytosis [502] and is essential for apoptosis and clearance from the site of infection of spent neutrophils by macrophages to decrease potential tissue damage. Vitamin C also reduces inflammation by blocking the synthesis of TNF, IL-6, and IL-1 $\beta$  [502], and has been shown in vitro to promote IgG and IgM production [503]. Zinc (Zn) plays an important role as a structural and regulatory catalyst ion for several enzymes and transcription factors, and its deficiency results in significant decline in both the innate and adaptive immune responses and promotes systemic inflammation [504–506]. Zn supplementation is associated with lower TNF- $\alpha$  levels and reduced oxidative stress as well as lower incidents of infection [507–509]. Zinc deficiency activates the NF $\kappa$ B pathway and release of IL-2, IL-6, and TNF- $\alpha$  pro-inflammatory cytokines both in vivo and in vitro [A]. Zinc supplementation elicits inducible regulatory T cells production [510] and decreases ROS production [511].

### 11.23. Flavonoids from *Epimedium* and *Icariin*

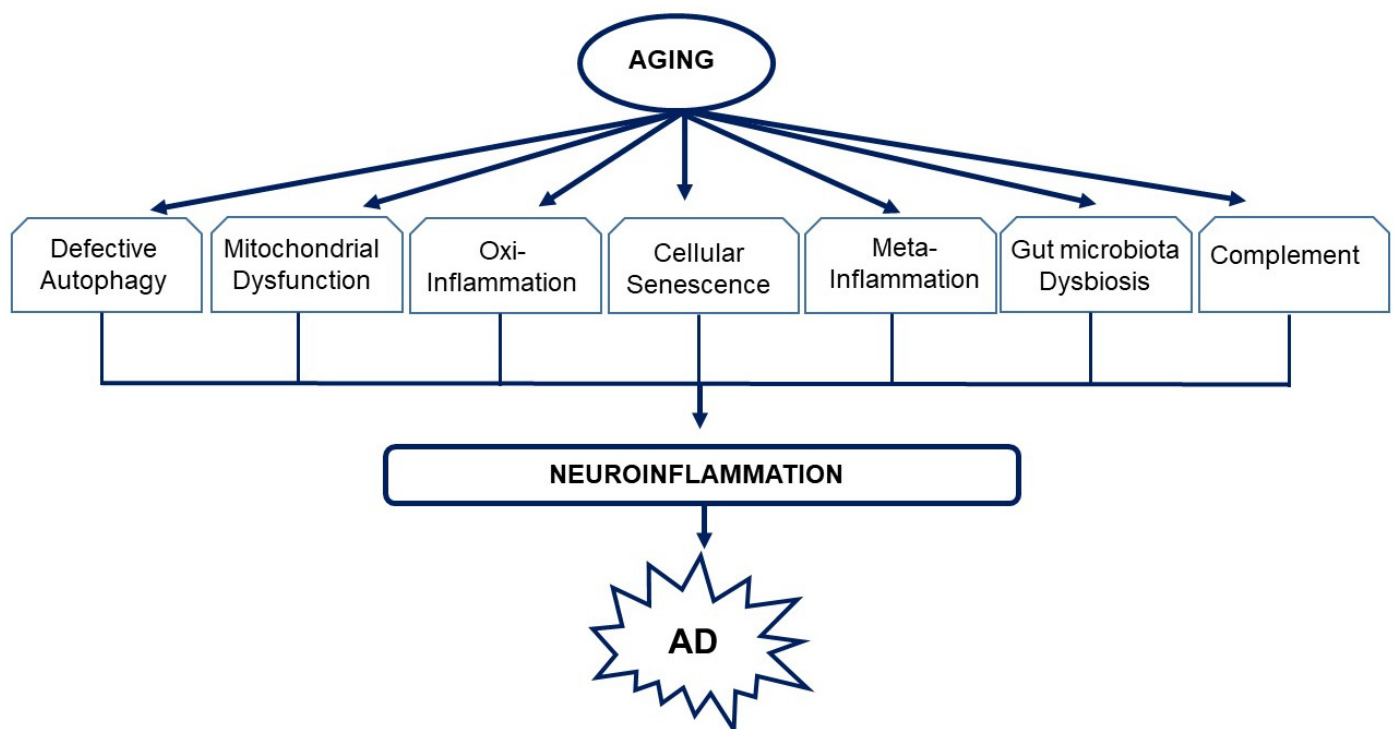
Xia et al. have demonstrated that, in aged rats, Epimedium flavonoids and icariin attenuate the proinflammatory response while enhancing an anti-inflammatory response in inter alia the hippocampus, hypothalamus, and hypophysis, and mitigate neuroinflam-

mation in aging [512,513]. Icaritin acts via the AMPK/mTOR/ULK1 pathway to increase neuronal autophagy and enhance brain function in aged Sprague–Dawley (SD) rats [514]. Moreover, in the bilateral common carotid arteries occlusion (BCCAO) rat model of AD, which manifests as neuronal morphological damage along with A $\beta$  deposition in the hippocampus and cognitive deficits of A $\beta$  in rat hippocampus, oral administration of icaritin reduces hippocampal expression of APP and BACE1, and induces the expressions of insulin-degrading enzyme (IDE) and a disintegrin and metalloproteinase domain 10 (ADAM10). This is accompanied by a decrease in TGF- $\beta$ <sub>1</sub> signaling via inhibition of Smad2/3 phosphorylation [515]. Icaritin also inhibits LPS induced IL-s and TNF $\alpha$  production while increasing expression of NF $\kappa$ B p-p65 and (TLR)4–myeloid differentiation factor 2 (TLR4/MD-2) complex [516]. Tea flowers extract (TFE) has been shown to enhance p-AMPK and SIRT1 expression while reducing acetyl-NF $\kappa$ Bp65 expression, and this is associated with a downregulation of IL-1 $\beta$ , TNF- $\alpha$  levels, inhibiting the pro-inflammatory response through the AMPK/SIRT1/NF $\kappa$ B pathway in aging rats [517].

## 12. Conclusions

While multiple mechanisms likely contribute to the etiology and progression of neurodegeneration in AD, the pathogenic role of neuroinflammation is now well recognized and accepted. A sedentary lifestyle and unhealthy diet can accelerate the aging-associated chronic low-grade inflammatory process linked to neurodegeneration in AD. While a lack of pre-clinical models that can reliably mimic changes in both immune system and inflammatory machinery has complicated efforts to fully elucidate the underlying disease mechanism in a manner that would enable the manipulation of different pathways in order to delay the onset and/or progression of the disease, we describe a few that pivot on the inflammatory process (Figure 2). We discuss approaches including immunotherapeutic targeting immune checkpoint inhibitors, pharmaceuticals that selectively target the SASP microenvironment, and other detrimental aspects of neuroinflammation without affecting defense mechanisms against pathogens and tissue damage. Lifestyle changes that incorporate long-term EE regimen, CR/CR-mimetics and nutraceuticals, or a combination of these interventions may ameliorate inflammaging and its progression into AD. Remodeling the aging gut microbiota using probiotics or fecal transplants is likely to dampen the pro-inflammatory milieu and modulate the neurochemical and neuro-metabolic signaling pathways of the brain and protect against neuroinflammation. As there is a huge potential for therapies that modulate the neuroimmune response in AD, it is important to define the inflammatory stages to correlate to each phase of AD progression and clarify which processes are protective and which ones are detrimental, as well as identify suitable times, modes, and sites of intervention. This may facilitate a focused and functional therapeutic approach to alleviate age-related stress on the intracellular organelles, tissues, and systems and delay AD progression in aging.





**Figure 2.** The interactions between aging and neuroinflammation in the pathogenesis of AD. With age, several cellular and molecular mechanisms elicit chronic sterile low-grade inflammation. This interaction of exogenous and endogenous risk stimuli, including defective autophagy, mitochondrial dysfunction, oxi-inflammation, cellular senescence, meta-inflammation, gut microbiota dysbiosis, and complement, triggers neuroinflammation. The resulting inflammatory mediator secreted drives the pathophysiological mechanisms of AD.

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### Abbreviations

AA	Arachidonic acid
A $\beta$	Amyloid beta
ABCA7	ATP-binding cassette subfamily A member 7
AD	Alzheimer's disease
Ahr	Aryl hydrocarbon receptor
AMPK	AMP-activated kinase
APP	Amyloid precursor protein
BBB	Blood–brain barrier
BIN1	Bridging integrator 1
BMAA	$\alpha$ -Amino- $\beta$ -methylaminopropionic acid
CCR2	C-C chemokine receptor type 2
CD	Cluster of differentiation
CD2AP	CD2 associated protein

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CLU	Clusterin
CNS	Central nervous system
CR	Calorie restriction
CR1	Complement component (3b/4b) receptor 1
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DAMPs	Damage associated molecular patterns
EE	Endurance exercise
EOAD	Early-onset Alzheimer's disease
GFAP	Glial fibrillary acidic protein
GA	Glatiramer acetate
GWAS	Genome-wide association studies
HMGB1	High mobility group box 1
ICR	Inhibitory immune checkpoint receptor
IFN $\gamma$	Interferon gamma
IMiDs	Immunomodulatory imide drugs
LOAD	Late-onset Alzheimer's disease
MDA	Malondialdehyde
MMP-9	Matrix metalloproteinase 9
Mo	Monocytes
MTOR	Mechanistic target of rapamycin
mtROS	Mitochondrial reactive oxygen species
M $\Phi$	Macrophages
NF $\kappa$ B	Nuclear factor $\kappa$ B
NLRP3	Nod-like receptor 3
NOX	NADPH oxidase
OPC	Oligodendrocyte precursor cells
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death ligand-1
PICALM	Phosphatidylinositol binding clathrin assembly protein
PLD3	Phospholipase D3
PSEN1	Presenilin 1
PSEN2	Presenilin 2
ROI	Reactive oxygen intermediates
ROS	Reactive oxygen species
RONs	Reactive oxygen and nitrogen species
S6RP	S6 ribosomal protein
sAPP	Secreted amyloid precursor protein
SASP	Senescence-associated secretory phenotype
SCFA	Short-chain fatty acids
SORL1	Sortilin-related receptor-1
STAT3	Signal transducer and activators of transcription 3
T2DM	Type 2 diabetes mellitus
TGF- $\beta$	Transforming growth factor beta
TLR	Toll-like receptor
TNF- $\alpha$	Tumor necrosis factor alpha
TNFR-I	Tumor necrosis factor receptor I
TNFR-II	Tumor necrosis factor receptor II
TRAIL	Tumor necrosis factor-related apoptosis inducing ligand
Treg	Regulatory T cells
TREM2	Triggering receptor expressed on myeloid cells 2
VCAM-I	Vascular cell adhesion molecule I
WES	Whole exome sequencing
WGS	Whole genome sequencing
XO	Xanthine oxidase

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