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REVIEW

Microglial priming of antigen presentation and adaptive stimulation in Alzheimer's disease

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Abstract

The prominent pathological consequences of Alzheimer's disease (AD) are the misfolding and mis-sorting of two cellular proteins, amyloid-β and microtubule-associated protein Tau. The accumulation of toxic phosphorylated Tau inside the neurons induces the increased processing of amyloid-β-associated signaling cascade and vice versa. Neuroinflammation-driven synaptic depletion and cognitive decline are substantiated by the cross talk of activated microglia and astroglia, leading to neuron degeneration. Microglia are the brain-resident immune effectors that prove their diverse functions in maintaining CNS homeostasis via collaboration with astrocytes and T lymphocytes. Age-related senescence and chronic inflammation activate microglia with increased pro-inflammatory markers, oxidative damage and phagocytosis. But the improper processing of misfolded protein via lysosomal pathway destines the spreading of 'seed' constituents to the nearby healthy neurons. Primed microglia process and present self-antigen such as amyloid-β and modified Tau to the infiltrated T lymphocytes through MHC I/II molecules. After an effective conversation with $CD4^+$ T cells, microglial phenotype can be altered from pro-active M1 to neuro-protective M2 type, which corresponds to the tissue remodeling and homeostasis. In this review, we are focusing on the change in functionality of microglia from innate to adaptive immune response in the context of neuroprotection, which may help in the search of novel immune therapy in AD.

Keywords Microglia · Antigen presentation · Neuroimmunomodulation · T cell infiltration · Immunotherapy · Tauopathy · Alzheimer's disease

Abbreviations

BACE1	Beta secretase 1
PTMs	Post-translational modifications
BBB	Blood–brain barrier
CNS	Central nervous system
ROS	Reactive oxygen species
NO	Nitric oxide
iNOS	Inorganic nitric oxide synthase
CD	Cluster of differentiation
MHC	Major histocompatibility complex
TGFβ	Transforming growth factor β
TNFα	Tumor necrosis factor α
IL	Interleukin
IFN	Interferon
T_H	Helper T cell
T_{reg}	Regulatory T cell
KO	Knockout
CR	Complement receptor
NFκB	Nuclear factor κ for B cell
mTOR	Mammalian target for rapamycin
Akt	Protein kinase B
ATP	Adenosine tri-phosphate
APC	Antigen-presenting cell
TREM2	Triggering receptor expressed on myeloid cells 2
ApoE	Apolipoprotein E
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
p38-MAPK	p38-mitogen-activated protein kinases
CSF1R	Colony-stimulating factor-1 receptor

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Emergence of microglia in Alzheimer's disease

Alzheimer's disease (AD) is a progressive neurodegenerative disease with continuous loss of neuronal connections, memory loss, cognition impairment, demyelination and loss of co-ordination between neuro-muscular junctions. The risk factors for AD are aging, oxidative stress, genetic and loss-of-function mutation, epigenetic regulation and auto-immunity [1]. AD is mainly associated with misfolding and modification of microtubule-binding protein Tau (MAPT) and transmembrane protein amyloid precursor protein (APP), which leads to the formation of neurofibrillary tangles (NFTs) and extracellular senile plaques, respectively. Misfolded proteins undergo cellular proteostasis machinery either by ubiquitin–proteasomal system (UPS) or by selective autophagy–lysosomal degradation. Misfolded or modified target proteins often interfere with the ubiquitin tagging for UPS pathway or block the functionality of component proteins involved in chaperone-mediated autophagy or microautophagy, resulting in unfolded-protein response (UPR) in neurons [2]. Like most of the neurodegenerative disease, AD is a multi-factorial disorder, arising due to protein aggregation and overactivation of resident immune effectors leading to the oxidative tissue necrosis, neuronal circuit loss and ultimately neurodegeneration [3].

Innate immune response is mediated by tissue-resident macrophage, i.e., microglia in central nervous system (CNS). Microglia are the myeloid cells, differentiated from mesodermal origin of embryonic yolk sac though the alternative hypothesis focuses on blood-derived monocytic lineage or neuro-ectodermal origin [4]. Recently, microglia have come under limelight due to multiple contributions in CNS homeostasis, tissue repair and emerging role in neurodegenerative disease such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), experimental acute encephalomyelitis (EAE) and amyotrophic lateral sclerosis (ALS). Microglia play a constant role in the random surveillance of neuronal circuits and consecutive phagocytosis of misoriented synapse via complement-driven elimination, called synaptic pruning [5]. Microglia also mediate the maintenance of ion homeostasis, neurotransmitter recycling and repair of damaged neurons by secreting neurotropic factors in CNS [6]. Microglia sense the invading pathogens in CNS, become activated with increased inflammatory response and phagocytic activity for the rapid clearance of death signals [7]. Initially, the function of microglia was questioned as antigen presenter due to lack of MHC expression and migration to secondary lymphoid organ for T-lymphocyte reactivation. But recent evidences have proved the potential of microglia as bold antigen-presenting cell (APC) via MHC II with co-stimulatory molecules, elicitor of adaptive activation and T cell clonal proliferation [8].

Proteopathic stimulation leads to exacerbation of the microglial phenotype with increased phagocytosis and pro-inflammatory state, which ultimately eventuates the improper synaptic loss and propagation of prion-like proteins within healthy neuronal circuits [9, 10]. Depending on the inflammatory microenvironment, microglia perform either pro- or anti-inflammation state with increased phagocytosis and neuronal regrowth [11]. Microglia along with astrocytes shape the CNS immune status by secreting various cytokines in a time-dependent manner. Both microglia and astrocytes present antigen via MHC class II molecule complexes with self-peptide to infiltrate $CD4^+$ T cells in drainage lymphoid and stimulate adaptive immune response in CNS. The dialogs between microglia and T cell pass the messages on residential neuron for repair, matrix reconstitution and remodeling of connecting circuits [12]. Here, we explore the interaction of microglia with CNS-resident cells and will propose a model for requisite antigen presentation T-cell activation in CNS during neurodegenerative AD condition.

Neuroimmunomodulation of AD

AD pathogenesis can be explained by several hypothesis. The foremost well-accepted theory comes with the 'Amyloid-β cascade' which signifies the deposition of extracellular protein aggregates by abnormal proteolytic cleavage of APP due to enzymatic activation and genetic variation of BACE1 [13]. Second theory was proposed on 'Tau pathology' which states that the Tauopathy occurs before amyloid-β signaling cascade [14]. Hyperphosphorylation of Tau leads to the oligomerization and tangle formation inside the neuron, which is colonized around the membrane–raft microdomain and mainly secreted by heparan sulfate proteoglycan (HSPG) in ATP-independent membrane permeabilization [15] or by exosomal vesicular release [16]. Intracellular accumulation of Tau dramatically increases amyloid-β processing in the AD brain [17]. Besides that, degeneration of cholinergic neurons and level of GABA alteration are evidenced in AD patients which leads to aberration of neuronal network related to learning and memory [18]. 'Neuroimmunomodulation' is an emerging concept of AD pathogenesis that occurs well in advance of Tau hyperphosphorylation and amyloid-β signaling cascade (Fig. 1). Innate immunity is governed by glial priming upon exposure to low concentration of highly reactive soluble Tau and amyloid-β oligomers [19], which results in the secretion of inflammatory chemical mediators [20]. A differently proposed hypothesis is based on the constant peripheral–central

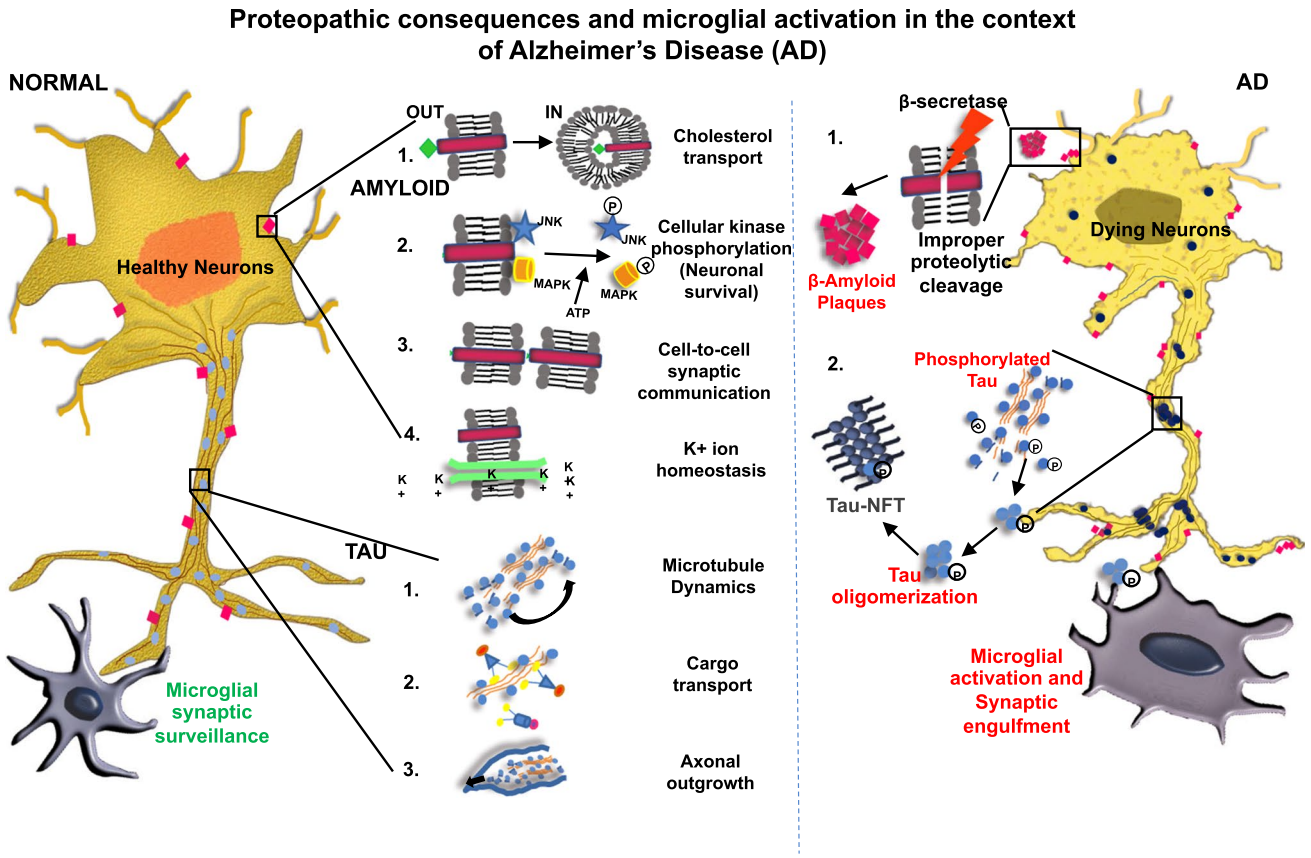

Fig. 1 Proteopathic consequences and microglial activation in the context of Alzheimer's disease (AD). Two proteins involved in AD are amyloid-β and Tau, mediating its normal physiological functions in membrane and cytosol, respectively. amyloid-β is mainly involved in cytoplasmic membrane such as in cholesterol transport, cell-to-cell communication signaling in synapses and K^+ ion homeostasis in neurons whereas microtubule-associated protein Tau is involved in microtubule dynamics, treadmilling, cargo transport and axonal outgrowth. In neuro-diseased condition, amyloid-β protein become proteolytically cleaved and aggregated as senile plaques in brain parenchyma. Tau becomes post-translationally modified (PTMs) which alters its affinity towards microtubule and become intracellular neurofibrillary tangles (NFTs). The deposition and release of these two proteins in synapses are recognized by microglia. Microglial activation leads to the engulfment of synapses via bulk phagocytosis, which subsequently leads to neuronal connection loss and death

inflammatory process due to the presence of genetic variant of ApoE, altered expression of kinases Akt, mTOR and downstream STAT3 transcriptional activation [21]. This scenario is adjoined with high circulatory TNFα, CCL3/4 level, overexpression of TREM2 and ApoE on microglial membrane [22], leading to glial priming and AD pathology [23]. CNS inflammation can also be triggered by pathogenic viral and leptomeningeal bacterial infection [24]. It has been reported that systemic inflammation and LPS-Pg induce gliosis with increased amyloid-β and p-Tau level [25], pro-inflammatory cytokine expression (IL1β, IL6, TNFα) in hippocampus [26] with BACE1 activation in AD patient brain [27]. Similarly, the AD patient with terminal peripheral infection showed more plaque deposits and the expression of microglial activation marker Iba1, HLA-DR (MHC), CCR4 and gathering of $CD3^+$ T cells in brain parenchyma [28]. During lymphocytic choriomeningitis virus (LCMV) virus infection, $CD11c^+$ microglia are shown to interact with $CD8^+$ and $CD4^+$ T cells directly, which leads to proliferation and memory response in brain, ultimately causing neuronal degeneration [29].

Microglial surveillance in CNS

Microglia are immune-competent macrophages in CNS, mediating various functions during development, maintenance of tissue homeostasis, surveilling microenvironment and protecting from invading pathogens. Microglia are originated from erythro-myeloid progenitor cell from yolk sac unlike other tissue-resident macrophages from bone-derived monocytes or other glial astrocytes and oligodendrocytes from neural stem cell [30]. Quiescent microglia are small cells with extended morphology for constant surveillance, have exceptionally longer life span than other macrophages and also gain the property of continuous proliferation [31].

During development, microglia fine-tune the synaptic connections [32] in a process called circuit pruning [33] via C1q complement-mediated phagocytosis [34]. Microglia express a variety of membrane receptors, which continuously detect the chemical signals secreted by neurons in brain parenchyma, for example, the concentration of released neurotransmitter GABA, glutamate, extracellular ATP, K^+ and Ca^{2+} ions via ionophoric receptors [35]. Microglia also sense the proportion of secreted and membrane-bound chemokine CX_3CL_1 on neurons by delta chemokine receptor CX_3CR_1, where secreted isoforms are associated with normal physiological condition [36]. A myeloid-specific receptor TREM2 (target receptor for erythroid myeloid type 2) is a microglial marker, which is involved in sensing anionic lipid molecules. Similarly, ApoE receptor recognizes ApoE-bound lipids. Both TREM2 and ApoE receptors are involved in neuro-glial energy metabolism. TREM2 is a direct regulator of microglial activation in AD pathology [37], which can sense the membrane phospholipid phosphatidylserine, flagged during apoptosis of neurons [38]. Glycosylation plays another important role in neuro-glial cross talk. The interaction between neuronal membrane sugar moiety and microglial receptor acts as an inhibitory signal from complement-mediated phagocytosis of unusual synapses [39]. Despite being immune effector, microglia express a negligible amount of MHC molecules during developmental and physiological states with unaltered phagocytic property [40]. But the scenario of microglial surveillance and tissue homeostasis gets reversed during pathological situations.

Misfolded protein processing in microglia

Cellular proteostasis involves a balance between the synthesis and the recycling of proteins through either UPS or autophagic lysosomal pathway. Dysregulation of UPS is one of the emerging causes of neurodegenerative diseases such as AD and PD. Similarly, PTM proteins and aggregates interfere with chaperone-mediated degradation pathway and the depleted lysosomal machinery leads to misfolded protein response in neurodegeneration [41]. Patho-proteins are recognized by chaperone hsc70 and targeting to lysosomes where the reactive irreversible oligomeric complexes of Tau block its translocation into lysosomal lumen and create steric hindrance for chaperon-mediated degradation of physiological protein's turnover [42]. Different mutations impact diversely on patho-protein accumulation and microglial activation. For e.g., Tau ThyT22 mutant shows more phosphorylated and soluble aggregation, which emphasizes on higher microglial toxicity as compared to P301S Tau variant in mouse model [43]. While the aggregation-resistant variant of Tau-Tau$^{RD\Delta KPP}$, which mainly expresses in developing hippocampus to enhance neurogenesis and to reduce microglial-astroglial activation [44]. Activated microglia uptake patho-proteins by phagocytosis, receptor-mediated endocytosis and exosomal membrane fusion or by passive diffusion. Hydrophobic patches exposed to the protein aggregates allow them to readily interact with lipid-carrier receptors ApoE and low-density lipoprotein receptor (VLDR), which subsequently leads to internalization by cellular machinery [45]. Due to PTMs of patho-proteins, it becomes insoluble and deposits in the extracellular matrix (ECM) having more potentiality to be engulfed by bulk phagocytosis [46]. Iba^+ microglia are found to surround the extracellular hyaluronic glycosaminoglycans along with amyloid-β plaques and Tau tangles in AD brain [47]. Upon phagocytosis, the endosomal vesicles are fused with lysosomes and the maturation of phago-lysosomes leads to the degradation of missorted proteins [48]. The degraded peptides are spread as seed components by overactivated microglia to the neighboring healthy cells as evident in AD patients and rTg4510 mouse brain [49]. The PTM proteins, which are tagged with ubiquitin or other modification (acetylation, methylation and phosphorylation), can be degraded via chaperon-mediated ubiquitin–proteasomal (UP) pathway in microglia. UP system cleaves the c-terminal region of the target protein and the immuno-proteosomal complex allows it to bind to B-pocket of MHC molecules [50]. Transporter associated with antigen processing protein (TAP1/2) is ATP cassette that helps in the transfer of cytosolic-processed antigen to the endoplasmic reticulum for MHC binding [51]. Phosphorylated Tau protein (p262/181) was shown to accumulate within the catalytic 20S immuno-proteasomal compartment in Tau-transgenic mouse model, depicting the function of impaired UPS pathway [52]. Accumulation of glycated proteins is the signature of age-related neurodegeneration where the cross-linking of proteins increased the rigidity of APP or Tau proteins for proper proteolysis [53]. Cleaved protein products, glycated peptides and phosphoproteins are insisted in the generation of neo-epitopes as the candidates of microglial activation in AD condition [54]. Additionally, microglia show an induction of lysosomal machinery with increased immunoreceptor tyrosine-based activation motif and in antagonistic case ITIM (ITIM/ITAM)-related phagocytic genes around the plaque niche in aged TgCRND8 transgenic AD mouse model, very similar to human AD brain [55].

Primed microglia orchestrated with cytokines and surface receptors

Depending on the milieu and stimulator, microglia can be activated in different ways. (i) 'Classical activation—M1 type': upon tissue insult, pro-inflammatory activation occurs and leads to the production of TNFα, IL1β, superoxides,

nitric oxide, ROS and proteases; (ii) 'Alternative activation—M2 type': after adequate inflammation, tissue repairing and extracellular matrix reconstitution are required which are associated with IL4, IL13, IL10 and TGFβ secretion; (iii) 'Acquired deactivation': due to the presence of excess apoptotic signals, IL10 and TGFβ levels, microglial deactivation occurs with robust phagocytic activity [56]. Aged brain contains high level of IL6, IL12 and nuclear localization of NFκB but compromising IL10 level, which depicts the general scenario of central inflammation [57].

Initially, microglia can sense the auto-antigen via membrane-bound pathogen recognition receptors (PRRs), which is a key player in innate immune response. A nonspecific molecular pattern on patho-proteins is recognized as death signal by microglial PRRs such as Toll-like receptor 4 (TLR4) which signals through adaptor protein MyD88/IRF7 and ultimately leads to the activation of central inflammatory mediator NfκB [58]. Hyperphosphorylated Tau which are induced with high glucose level are sensed by TLR9–p38 MAPK signaling cascade in microglia [59]. Another PRR–NLRP3 (NOD-like receptor pyrin domain-containing-3) is involved in the formation of inflammasomes along with adaptor complex caspase1–ARC and protein aggregates leading to microglial activation [60]. Co-culture of microglia and neuronal stem cells significantly reduces the formation of NLRP inflammasomes and attenuate caspase1–IL1β effector function by impairing p38–MAPK signaling cascade [61] which proves the inflammasome pathway as a potential therapeutic target [62]. Extracellular protein burden is sensed by microglial GPCR–CB2, an endogenous cannabinoid receptor that is expressed more on immune cells. CB2 is found to surround the amyloid plaques and Tau deposits in AD brain [63]. As an effector of GPCRs, Phospholipase-C mediates the cytoplasmic hike of Ca^{2+} level from the organelles. Microglial calcium-sensing receptor (CaSR) forms complex with amyloid-β or p-Tau oligomers and induces the microglial inflammatory states. In turn, the administration of CaSR antagonist has reduced the amyloid-β- and p-Tau-mediated neurotoxicity with improved lysosomal–autophagosomal proteostasis [64], less secretion of reactive nitrogen species (RNS) and vascular endothelial growth factor A (VEGF-A) from glia [65].

Tau oligomers and fibrils directly induce IL6 and prostaglandin expression in activated microglia [66]. In parallel line, Perea et al. suggested that extracellular dephosphorylated Tau rather than hyperphosphorylated state effectively induces pro-inflammatory response through p38–MAPK [67] and NMDA signaling pathways in microglia [68]. Thus, selective blocking of α-isoform of MAPK downregulates the inflammatory molecules—IL1β and IFNγ—and rescues neurodegeneration by decreasing p-Tau181 level from later stage of AD [69]. The relative concentration of secreted chemokine CX_3CL_1 with its membrane-bound isoform plays an important role in microglial activation wherein the decreased level of sCX_3CL_1 is observed in CSF of AD brain [70]. Overexpression of full fractalkine (CX_3CL_1) or only chemokine domain ($CX_3CL_1^{\Delta 105}$) improves the cognitive function and VEGFα signaling for neuro-vasculature repair but without improving the hyperphosphorylation of Tau [71] and $CD45^+$ microglial activation in rTg4510 mousemodel [72]. On the contrary, CX_3CR_1-deficient mice showed reduced accumulation of amyloid-β and Tau-NFTs and cytokine secretion with increased phagocytic activity of microglia [73].

Microglial surface receptor TREM2 signals through its adaptor protein TYROBP/DAP12 [74]. DAP12 is found to be associated with neuronal injury in APP/PS1 [75] and Tauopathy [76] mouse model. Secretary TREM2 (sTREM2) in CSF can be considered as early biomarker for neuroinflammation-associated AD [77, 78]. TREM2 haplo-insufficiency causes higher microglial activation with excess production of pro-inflammatory cytokines and increased Tauopathy in aged transgenic mouse model as compared to TREM2 KO mice [79]. Genetic knockdown or transcriptomic silencing of discoidin receptor (DDR1/2), which is a tyrosine kinase collagen-activated receptor, is evidenced with increased amyloid-β and Tauopathy in transgenic mouse model. DDR1/2 are found to have a direct relation with reduced TREM2 level on microglia [80]. Exceptionally, Jiang et al. reported that overexpression of TREM2 downregulates IL1β level, inhibits GSK3β activity, Tau phosphorylation and increases Arg1, synaptophysin expression in traumatic mouse model [81]. Microglial CD33 senses sialic acid of neuronal membrane, which acts as an inhibitory signal from glial activation. But, the loss of sialic acid tags the neuronal membrane with complement factors—C1q and C3—which results in the phagocytosis and elimination of synapses leading to cognitive decline. Deletion of C3aR1 and C1q improves the cognitive impairment and post-synaptic neuronal loss through signal transducer and activator of transcription-3 (STAT3) transcriptional activation and subsequently reduces micro-astroglial inflammation [82, 83].

Microglial turnover is one of the emerging aspects in terms of age-related neurodegeneration. A particular structural and functional alteration arises in aged microglia with increased apoptosis, depicted as cytoplasmic 'beading' and 'twisting' termed as 'Dystrophic' microglia [84, 85]. Senescent microglia showed 'primed' phenotype with exaggerated immune activation, reduced phagocytosis and motility [86], while the CSF1R-dependent replenishment of microglia population increases the cognitive memory and synaptogenesis without altering immune profile of homeostatic microglia [87]. Senescent microglia are found to colocalize with degenerating neurons where the aged microglia feature with increased clumping, dysfunctionality [88] and expression of MHC II, ED1, particularly in the white matter of

Tauopathy model [89, 90]. There is controversial evidence of repopulating circulatory monocytes in brain-resident microglial population [91] while the other groups claim the building of neo-population are from CNS-derived microglia as evidenced with myeloid-specific TMEM119^{+} and P2RY12^{+} glial cells in replenished aged brain of animal model [92, 93]. Based on the above-mentioned facts, short-term administration of CSF1R inhibitor and subsequent withdrawal can be a feasible treatment for therapeutic targeting in neurodegenerative condition.

Astro–micro-gliosis

During neurodegenerative condition, activated microglia and reactive astrocytes both play a conjoint role in the initiation, progression and resolution of inflammation. Major functions of astrocytes in CNS are ion homeostasis, energy metabolism and formation of primitive mechanical blood–brain barrier (BBB). Astrocytes sense brain microenvironment [94] through a cation-specific mechano-sensitive ion channel Piezo1 which certainly discriminates between soft tissue and amyloid-β/NFT-contained stiff deposits. Piezo1 expression is found to be upregulated in TgF344-AD rat model as well as peripheral infection which signifies the possible activation of astrocytes through both systemic and CNS inflammation in AD [95]. Similar to microglia, astrocytes can be categorized into two types: A1—neurotoxic and A2—neuroprotective. Activated microglia secrete high levels of TNFα, IL1α and C1q which convert the quiescent astrocytes into A1 type [96]. Upon activation through patho-proteins and microglia, A1 astrocytes produce high level of intermediate filaments—glial fibrillary acidic protein (GFAP) and Vimentin [97]. However, GFAP and Vimentin KO in APP/PS1 mice showed twofold higher deposition of amyloid-β plaques and altered phenotypes of astrocytes in brain [98]. MicroRNA-miR142 is overexpressed with increased transcription of GFAP and colony stimulatory factor 1 (CSF1) through STAT3 and TNF-receptor 2 (TNFR2) pathway in Tauopathy mouse model and AD brain which signifies the activation of both microglia and astrocytes in diseased condition [99]. Rodent astrocytes upregulate the MHC II expression upon IFN-γ treatment which induces T-cell differentiation and proliferation in vitro [100]. Intracellular ATP released through NMDA receptor and sCX_3CL_1 from apoptotic neurons and injured astrocytes, are subsequently sensed by P_2RY_{12} purinergic receptor and CX_3CR_1 on microglia respectively, which together are aiding in synaptic remodeling [101]. A1 astrocytes have higher activity of monoamine oxidase-B (MAO-B), which results in the excess production of hydrogen peroxide (ROS) and leakage of GABA. The administration of MOA-B inhibitor—selegiline—can reduce the astrocytic reactivation in AD mouse model [102].

In a different glance, astrocyte-derived TGFβ1 deactivates microglia and diminishes neurotoxicity through Smad3-dependent transcriptional activation which is reported to be impaired in AD brain [103]. Similarly, secretory growth factor from astrocytes activates microglia through MAPK–ERK signaling cascades which employ neuronal repair and survival [104]. Tau-bearing neurons express high amount of phosphatidylserine, milk-fat-globule EGF factor8 (MFGE8) which facilitate the glial phagocytosis of living neurons while blocking the secretion leading to reduced gliosis in P301S mouse model [105]. Blocking several approaches such as NFAT (nuclear factor for activated T cell) signaling and NFκB KO in astrocytes resulted in less microgliosis and release of less C1q and CR3 in amyloid-β pathology [106]. Microglial activation is blocked by administrating Captopril—angiotensin converting enzyme (ACE) antagonist—decreases TNFα, IL1, NO production in LPS-induced BV2 microglia, while long-term Captopril treatment showed significant reduction of amyloid-β pathology and microglial activation in AD model [107]. High-mobility group box 1 (HMGB1) protein, a pro-inflammatory cytokine and transcription factor can be a potential immune therapeutic target for the regulation of neuronal injury as well as deactivation of astro–microglial response [108]. Lastly, a 3D organotypic model of AD brain, containing co-culture of neurons, astrocytes and microglia leads to the production of chemokines CCL2, CCL3/4 and CCL5; cytokines IL6 and IL8 along with anti-inflammatory markers IL10, TGFβ which signifies the process of astroglial chemotactic cross talk in CNS immunity [109]. Bioinformatics studies support the physical association of $CXCR_4$ with four microglial genes CXCL12, TLR2, RALB and CCR5, which was clearly explained in clinical samples of AD brain and Tauopathy mouse model [110]. A central ApoE-driven network coincides with CCL3/4 signaling cascade during gliosis which reveals a potential mechanism for higher susceptibility of AD in females [22]. Understanding the functionality of chemokine–chemokine receptor interactions in micro-astrogliosis such as CCL2/CCR2, CX3CL1/CX3CR1, CCL5/CCR5, CXCL10/CXCR3, CCL11/CCR3 and CXCL1/CXCR1 can be established as potential immunotherapy in amyloid-β and Tau pathology [111, 112] (Fig. 2).

CNS antigen presentation on demand

Brain was initially thought to be a immune-privileged site where the events such as antigen presentation and cell-mediated adaptive immune response were known to be least abundant. Microglia are excluded from the group of APCs because of their inability to express MHC molecules and migrate to lymph nodes to stimulate T-cell proliferation. But in current studies, microglial synaptic surveillance allows

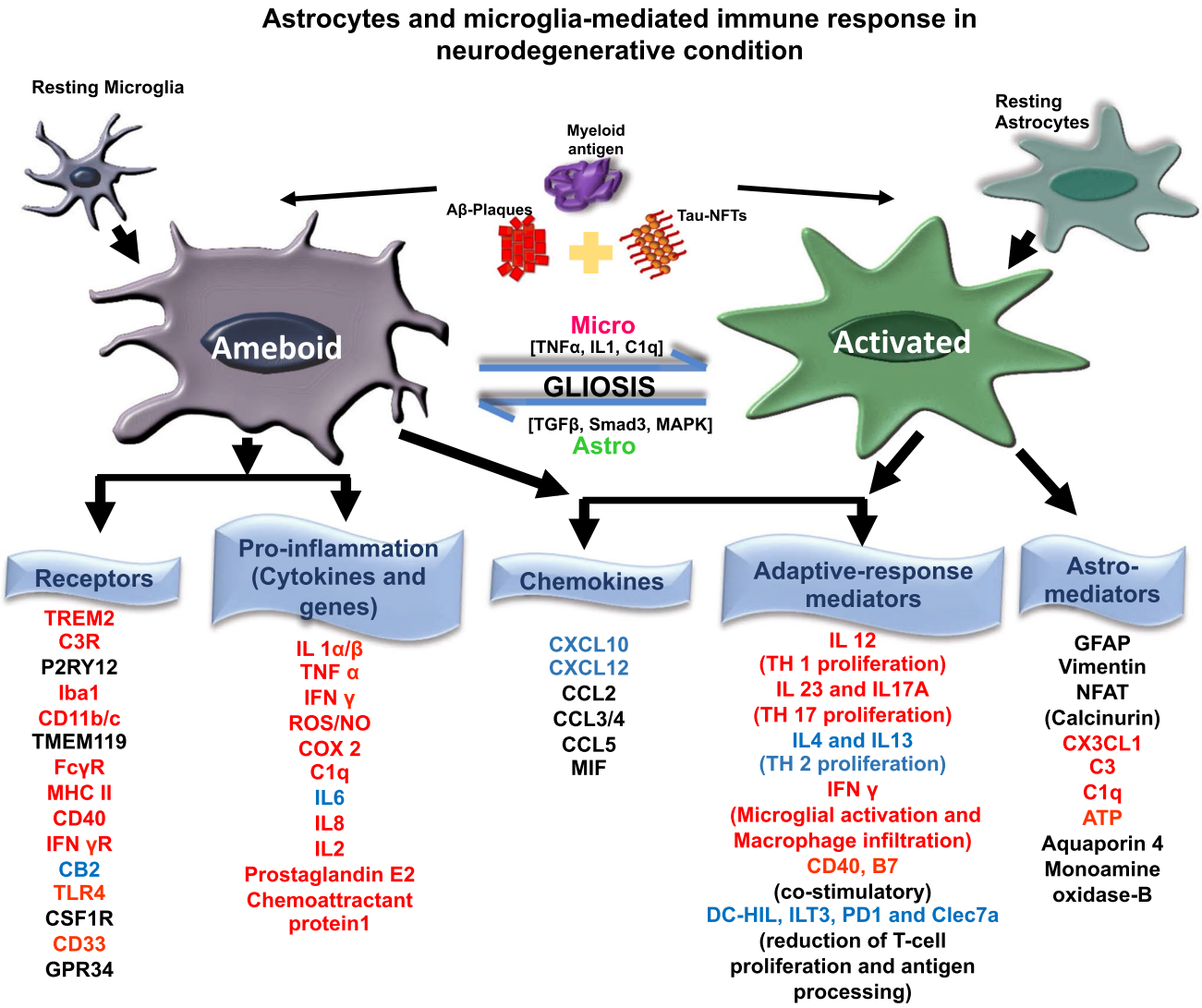

Fig. 2 Astrocytes and microglial-mediated immune response in neuro-disease condition. Depending on the inflammatory state, microglia and astrocytes can switch between two states: M1 and M2; A1 and A2, where M1 and A1 signify the pro-inflammatory and neurotoxic states, and M2 and A2 depict the anti-inflammatory and neuroprotective stages, respectively. Upon activation by toxic proteins or tissue insult, microglia secretes high level of toxic cytokines and membrane receptor thus eventually activating astrocytes. Astrocytes upon activation express high level of intermediate filament and produce ROS. But astrogliosis leads to the production of TGFβ and activates MAPK–ERK signaling cascade that helps in neuron regeneration and repair. The pro-inflammatory markers and mediators are coded as 'red', which corresponds to M1 and A1 types and anti-inflammatory as 'blue' indicating M2 and A2 types. Molecules coded in 'black' function in physiological condition or are contributing minutely in the mediation of microglial activation

this immune effector to sense and present antigen inside the brain parenchyma. Primed microglia present antigen by MHC II and co-stimulatory (CD 40, CD33, CD86, B7) molecules along with increased phagocytic activity [113]. Moreover, glia limitans—astrocytes, brain endothelial cells (BECs)—also have the property of antigen presentation with loaded MHC II expansion and increased expression of co-stimulatory and adhesion molecules such as ICAM and VCAM allowing the homing of circulating lymphocytes [114]. Higher level of CSF-ICAM1, YKL40, Flt1 along with p-Tau level are considered as risk factors in early AD patient without dementia [115]. Additionally, peripheral dendritic cells (DCs), B cells, and marginal macrophages potentiate the cumulative antigen presentation to circulatory T lymphocytes in brain due to auto-antigen diffusion and creating a microenvironment a lymphatic drainage [116]. Primary brain pericytes ($PDGFR\beta^{+}$) isolated from APP-SweDI mouse model differentiate into $CD11b^{+}$ microglia-like cell (moderate $Iba1^{+}$) with moderate phagocytic and antigen-presenting capacity [117]. Microglia can phagocyte myelin antigen and present to activate T lymphocytes via MHC II in vitro [113], which proves the functionality of

APCs in microglia. Silencing of transcriptional activator CIITA that regulates the MHC II expression leads to the increased pathology and no recovery from disease [118], which signifies that MHC II expansion is essential during neuroinflammation.

T-cell raid and adaptive immune boost up in CNS

T cell is the major effector of adaptive response, recently reported to invade CNS during inflammation, mechanical brain and spine injury, trauma, infection and neurodegeneration. Though the presence of auto-reactive T cells in circulation is not obvious, the peripheral T cells infiltrate CNS through various gateways: (i) via trespassing the endothelial blood–brain barrier; (ii) by invading leptomeningeal barrier; or (iii) by breaking the mechanical barrier of choroid plexus. Infiltration of T cell shapes the adaptive immune makeup in CNS for not only the clearance of patho-proteins but also repairing the damaged neurons via secreting neurotropic factors [116]. The phenotypic functionality of microglia is dependent on cytokine expression as well as corresponding T-cell proliferation. For example, $CD11c^+$ microglia express more amounts of IFNγ and IL17A for the T_H1 and T_H17 responses and CR4 complement-mediated activity while $CD11c^-$ microglia showed detectable amounts of IL8, IL 12 and IL23 cytokine profile [119]. Antigen-reactive $CD4^+$ effector lymphocytes extravasate brain parenchyma to react with CNS phagocytes which subsequently shows phenotypic activation with increased IFNγ and IL17A in experimental acute encephalomyelitis (EAE) model [120]. Tau-specific microglia induce the infiltration of antigen-reactive T cells and monocytes into the brain [121]. In MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-induced PD model, $CD4^+$ T effectors are associated with increased dopaminergic neuronal survival and M2 microglial phenotype while MHC KO mice shows increased death of neurons [122]. However, $CD4^-$ mice showed increased disease pathology in ALS mouse model, suggesting the necessity of $CD4^+$ effector lymphocytes in CNS [123]. In AD brain, infiltrated T cells are found in proximal association with microglia in hippocampal slices [124]. But in AD mouse model, hyporeactive and suppressive $CD4^+$ T cells are evidenced in marginal parenchyma, depicting the function of 'antigen tolerance' during AD condition [125]. Similarly, $CD8^+$ effector T cells have been shown to localize with activated microglia in AD [126]. $CD3^+$ $IL17A^+$ T_H17 cells significantly localize in AD patient brain while $CD25^+$ T_{reg} cells are more prominent with phospho-Tau (T181) level which clearly depicts T_{reg} cells as a potential marker for Tau-mediated neurodegeneration [127]. Recent report also emphasizes on the presence of T_{reg} cells with reduced pathology, NFκB activation and microglial activation in AD brain [128] (Fig. 3).

Consequences of microglia–T cell's bipartite function

During neurodegeneration, $CD4^+$ T_H cells mediate neuroprotective functions along with the axis of T_{reg} cells upon microglial antigen presentation that subsequently results in the reconstitution of CNS homeostasis [129]. T_{reg} cells showed increased level of TGFβ, which performs diverse functions, including anti-inflammation, tissue repair, ECM deposition and most importantly it switches adaptive regulation as well as microglial phenotype [130]. Blockage of CD40–CD154 interaction reduces the microglia–T cell-mediated-neuronal damage and increases the production of TGFβ and IL10 in amyloid-β-immunized AD mouse model [131]. Produced IL4 and IL23 directly act as anti-inflammatory mediators, resulting in the reduction of pro-inflammatory cytokine—IL6, IL8, IL1β, TNFα—and ROS level. M2 microglia induce the production of neurotropic factors—IGF1 (insulin-like growth factor 1), Arginase, FIZZ1 (found in inflammatory zone 1), YM1, CD206 and CD163 (mannose receptor) [132]. CD206 and scavenging receptor—CD163—initiate phagocytosis during the resolution of inflammatory process with effective debris clearance. Arginase acts in a competitive equilibrium with iNOS for the substrate arginine and reduces NO production. YM1 attached to HSPG increases the docking of growth factors on cell membrane [133]. FIZZ directly induces the ECM–collagen formation, reduction of apoptosis and elicit $CD4^+$ T-cell response [134]. $YM1^+$ and $TNFα^-$ microglia are found to be surrounded by amyloid-β plaques in AD mouse model. Intracerebral injection of IL4 and IL13 significantly reduced amyloid-β load and upregulated IGF1 and YM1. Microarray analysis of AD brain samples showed increased levels of TNFα, IL1β, MHC II, IFNγ, Arginase1 and CD206, which deciphers the mixed phenotypic expression of microglia [135]. Antibody-mediated opsonization by microglia which is reducing the Tau aggregate overload, an evidence of antibody-mediated adaptive effector function [136]. Some of the immune suppressors of microglia involved in shaping adaptive immunity are DC-HIL, PD1, ILT3, Clec7a, etc. DC-HIL's function is modulated by TGFβ, which inhibits T-cell receptor-mediated clonal proliferation [137] while microglial PD1 reduces the IFNγ-primed microglial activation [138]. ILT2 prevents $CD4^+$ T-cell proliferation and downregulates antigen processing and microglial activation [139]. Clec7a directly reduces TREM2 expression, leading to microglial deactivation [140]. Antigen presentation and bipartite functionality of microglia–T cell duo in CNS are essential for protective scenario of neurodegeneration and

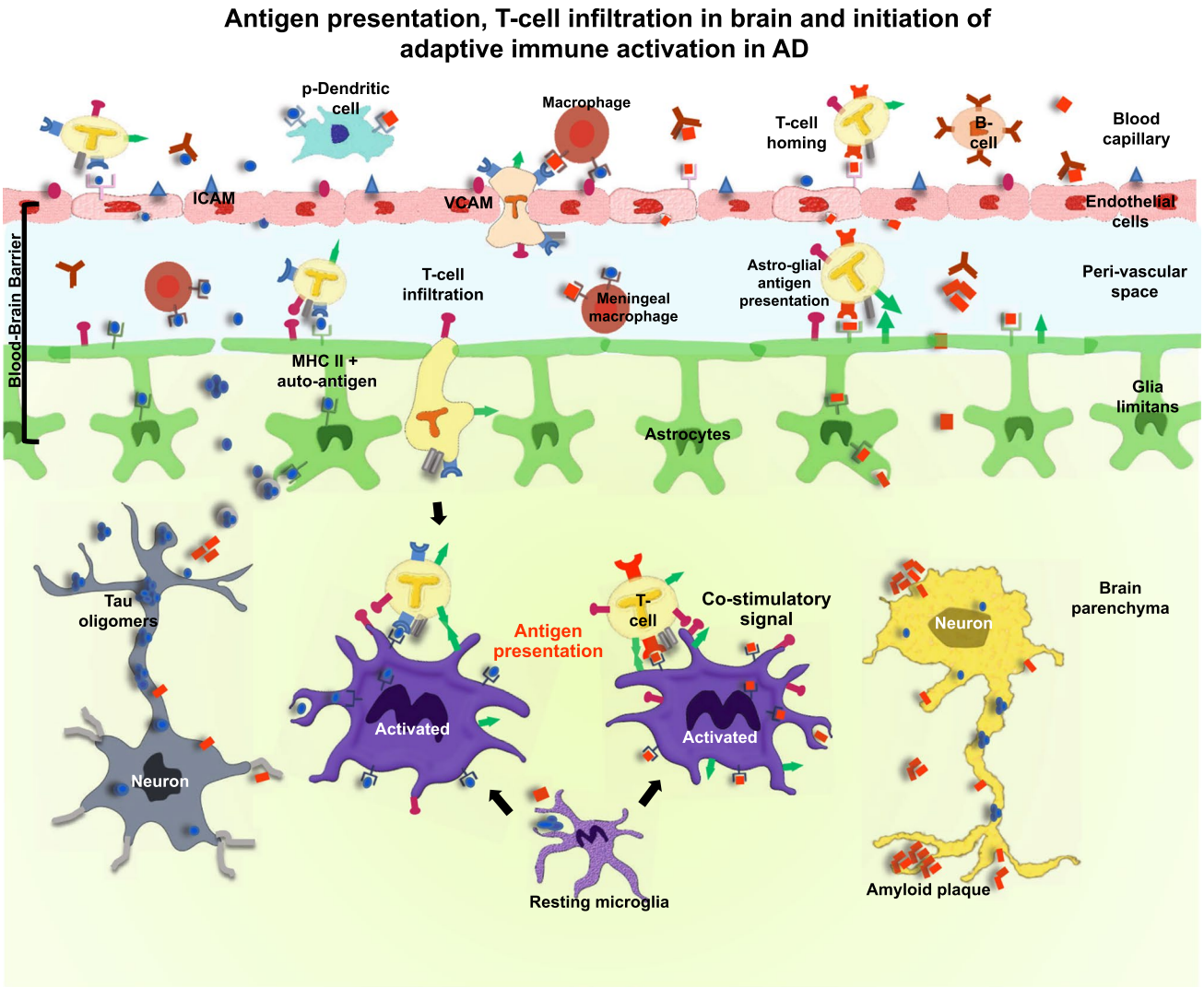

Fig. 3 Antigen presentation T-cell infiltration into brain and initiation of adaptive immune activation in AD. A lymphatic antigen drainage such as the leakage of soluble Tau and amyloid-β oligomers from CNS activates the marginal dendritic cells and meningeal macrophages to present antigens to peripheral adaptive immune system. Brain endothelial cells can present antigen and express high levels of adhesion molecules ICAM and VCAM which in turn cause the homing of auto-reactive T lymphocytes in brain. Further, the extravasation of $CD4^{+}$T cell into the brain parenchyma via breaking glia limitans allows it to access microglial antigen presentation. Microglial–T-cell cross talk converts the microglial phenotypes towards M2 state and modulates the adaptive immune response towards neuroprotection (Red: high risk/relevance; blue: moderate; black: less involvement/deleterious)

neutralization of glia-mediated inflammatory outburst in AD (Fig. 4).

Targeting microglia as a candidate of immune therapy

Recent developments prove the emerging role of microglia in the facilitation of early inflammatory events followed by neurodegeneration. But the dual functionality of microglia in bridging the innate–adaptive immunity and tissue remodeling manifests new interests in the degenerating milieu of AD. Direct reduction of microglial number by inhibiting CSF1R is not an actual target to combat AD as seen in rTg4510 mouse model [141]. Instead of whole microglial population, aged senescent glia [142], $P16^{INK\Delta4A+}$ cells can be a potential target for the prevention of gliosis, hyperphosphorylation of Tau and reservation of cognitive function [143]. Zhang et al. suggested that hypoxic condition can develop amyloid-β and p-Tau level with increased M1 microglia phenotypes ($TNF\alpha^{+}$ $CD86^{+}$ $IL6^{+}$) and decreased Arg^{+} $IL4^{+}$ $IL10^{+}$ M2 type through the impairment of NFκB signaling [144]. A way different intervention, hyperbaric oxygen therapy reduces micro–astrogliosis and pro-inflammatory cytokine—IL1β and TNFα—level as

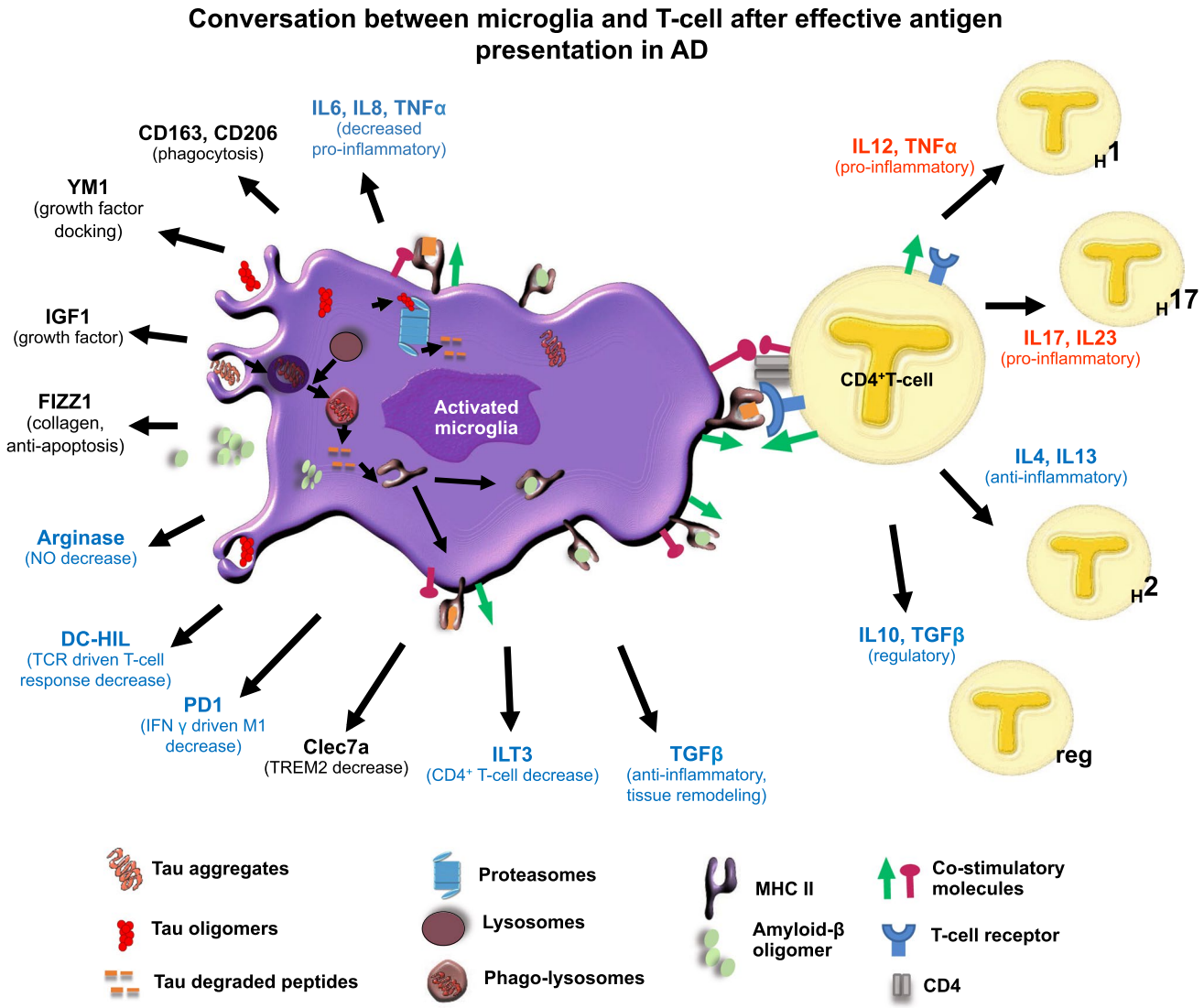

Fig. 4 Conversation between microglia and T cell after effective antigen presentation in AD. Microglia process the engulfed Tau and amyloid-β protein oligomers (aggregates) either by UPS or phago-lysosomal compartment and present the auto-antigens through MHC II molecules in CNS parenchyma. Upon infiltration of T lymphocytes into the brain, microglia present self-antigen with increased co-stimulatory signaling. By conversing with T cell, microglia alter their phenotype from pro- to anti-inflammatory state and secrete a diverse group of cytokines, which converts the naïve T cell into T_{reg} and T_H17 response, thus, resolving the inflammatory burst. Additionally, microglia secrete a variety of tissue-remodeling factors, which allows the damaged neurons to repair and express more surface molecules involved in phagocytic clearance of toxic protein aggregates in CNS. The pro-inflammatory mediators: 'red', anti-inflammatory: 'blue', and proteins involved in growth factors signaling or tissue remodeling: 'black'

well as amyloid-β and p-Tau burden in 3XTg mouse model [145]. Another approach, electroacupuncture, declines oxidation, nitrosylation, pro-inflammation with decreasing amyloid-β and p-Tau-mediated neurodegeneration, followed by increasing acetylcholine neurotransmitter [146].

Future directions

The identification of processed and MHCII-loaded auto-antigenic peptide of Tau and amyloid-β by CNS-resident

immune cells (microglia, astrocytes) is essential for T-cell reactivation, which can be a lead for cell-mediated immunity and antibody-mediated immunization therapy. Cross-reactivity helps in immune therapy as passive immunization with anti-Tau antibody inhibits Tau as well as protects from amyloid-β pathology in CNS. The relative amount of antigen drainage in CNS for normal and pathological condition to elicit adaptive immune response can be an advanced topic for future research and clinical identification of early disease condition. The phenotypic switching of microglia from M1 to M2 type through IL4/ IL13-TGFβ cytokine therapy is an alternative approach for shaping the innate immunity in neurodegeneration. Thus, the immunotherapeutic strategy to change T-cell reactiveness can modulate the overlapping functionality of innate and adaptive arms of CNS inflammatory environment.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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