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Potential importance of B cells in aging and aging-associated neurodegenerative diseases

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Abstract

Our understanding of B cells as merely antibody producers is slowly changing. Alone or in concert with antibody, they control outcomes of seemingly different diseases such as cancer, rheumatoid arthritis, diabetes, and multiple sclerosis. While their role in activation of effector immune cells is beneficial in cancer but bad in autoimmune diseases, their immunosuppressive and regulatory subsets (Bregs) inhibit autoimmune and anticancer responses. These pathogenic and suppressive functions are not static and appear to be regulated by the nature and strength of inflammation. Although aging increases inflammation and changes the composition and function of B cells, surprisingly, little is known whether the change affects aging-associated neurodegenerative disease, such as Alzheimer's disease (AD). Here, by analyzing B cells in cancer and autoimmune and neuroinflammatory diseases, we elucidate their potential importance in AD and other aging-associated neuroinflammatory diseases.

Keywords

B-cell; Bregs; Alzheimer's disease; Neurodegeneration

Introduction

Aging often leads to decline in the brain functions and memory loss. It is a risk factor for the development of Alzheimer's disease (AD), a progressive neurodegenerative disorder of the elderly. Per amyloid cascade theory, an aberrant cleavage of the amyloid precursor protein (APP) with the gamma (γ) secretase complex results in brain accumulation of amyloid β-

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peptides (Aβ), which in turn induces a chain of inflammatory events, such as deposition of neurofibrillary tangles (NFTs) of hyper phosphorylating tau protein and activation of microglia (MG) and astrocytes [1], leading to gradual synaptic dysfunction and neuronal degeneration in multiple interconnected brain regions [2, 3]. This is also an inflammatory disease that involves upregulated and sustained expression of IFN-I, IFNγ, IL-12, IL-23, TNFα, IL-6, and IL-1β [4, 5] produced locally by activated MG and astrocytes [6–9] and by peripheral innate immune cells, such as MO, neutrophils, NK cells, and perivascular macrophages [10–12]. They disrupt the integrity of blood-brain-barrier (BBB); impair MG functions, such as phagocytosis and removal of Aβ deposits; reduce adult hippocampal neurogenesis; and exacerbate cognitive decline [13–19]. As in cancer and autoimmune diseases, production and activity of proinflammatory cytokines is regulated by immunosuppressive cytokine IL-10 [20] and TGFβ1 [21, 22]. Healthy adult CNS also constitutively expresses TGFβ2 and 3 [23], while TGFβ1 is induced in AD brains [24] from Aβ-stimulated MG and astrocytes [25]. It protects neurons from Aβ toxicity [26] and its deficiency leads to neuronal death and microgliosis [21].

As a double-edged sword, inflammation is also needed for the activation of MG to clear Aβ [11, 27] and to promote adult hippocampal neurogenesis by monocytes [10]. T cells infiltrate the CNS [28, 29] as important regulators of the maintenance and adult neurogenesis [30]. However, upon their activation, for example, by myelin olygodendrocyte protein (MOG), they promote multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE, a murine model for MS). Similarly, infiltration of pathogenic IFNγ and TNFα-producing T cells (Th1) in the brain parenchyma [31] is thought to cause cerebral vasculature leakage [32] and meningoencephalitis in some patients with AD immunized with Aβ vaccine [33, 34]. The loss of IFNγ signaling in AD mice or T cells in RAG-deficient AD mice blocks MG activation and Aβ deposition [18]. Conversely, regulatory T cells (Tregs, which block Th1 responses) can reverse Aβ-induced brain inflammation and impaired cognition in AD mice [35], presumably explaining the inverse correlation between Treg presence and mild cognitive impairment in AD patients [36]. However, Tregs can instead promote AD in 5xfAD mice, as they block IFNγ-dependent beneficial gateway of the brain's choroid plexus (CP) needed for the infiltration of inflammation-resolving immune cells in the CNS [37]. Tregs also crosstalk with B cells and their regulatory subsets (Bregs), an important group of adaptive immune cells that actively control outcomes of cancer and autoimmune diseases.

The role of B cells in AD remains poorly understood and even thought to be inessential [38] despite the fact that they are implicated in neuropsychiatric disorders [39] and depressive-like symptoms [40, 41] and that Aβ is immunogenic and induces antibody (Ab) response in AD patients and mice. Passive administration of Aβ-specific Ab [42, 43] or active immunization with Aβ can reduce Aβ deposits in AD patients [34, 44] and mice ameliorating severity of the disease [45–47]. Even non-amyloid IgG is recently shown to be beneficial, as it activates MG phagocytosis and thereby reduces Aβ deposits and, conversely, its loss in RAG-5xfAD (due to its inability to generate mature B cells besides T cells and NK cells) accelerates AD [48]. On the other hand, IgG and its immune complexes can induce harmful activation of MG and neuronal neurotoxicity, for example, upon inflammation in old age. Aging not only increases inflammation but also dysregulates the

composition and function of immune cells. By reducing B-cell lymphopoiesis and naive B cells, it impairs Ab response to neoantigens and pathogens while enriching for B7-DC$^+$ ABC B cells that induce polarization of Th17 and Th1 cells [49]. Recently, we found that old humans, macaques, and mice also accumulate a different type of potentially pathogenic B cells [50]. These cells (designated 4BL cells) express high levels of 4-1BBL and membrane (m)TNFα and belong to innate B1a cells, which upon aging lost their immunosuppressive function and instead acquired a superb ability to induce cytolytic CD45RA$^+$ CD8$^+$ T cells to self-antigens [51]. Contrary to young B1a cells that support tumor growth, 4BL cells efficiently retard tumors in old mice. Since young B1a cells and B1a-like B10 cells protect from experimental autoimmune encephalitis (EAE) and colitis [52, 53], our findings raise an interesting question whether aging B/4BL cells can contribute to aging-associated neurodegenerative diseases. To answer this question, here, we analyze the role of B cells in seemingly different diseases, such as cancer and autoimmune and neuroinflammatory diseases, as epidemiological studies positively and negatively correlate them with AD, respectively [54–56]. First, we discuss the role of peripheral inflammation. Then, we analyze the pathogenic and protective activities of humoral immunity in AD. Although almost no report exists on the immunoglobulin-independent function of B cells in AD, to extrapolate their potential importance, we also provide in-depth analysis of B cells and Bregs in clinically relevant diseases, such as cancer and autoimmune diseases, including multiple sclerosis (MS).

AD is an age-associated inflammatory disease

A growing number of studies link function of the CNS with peripheral inflammation and activation of innate immune cells. In healthy brain, monocyte (MO) infiltration in perivascular space, in choroid plexus (CP) and meninges is linked with protective functions [57]. They alone or upon differentiation into perivascular macrophages can reduce Aβ deposits [58] via Aβ efflux by BBB neonatal Fc receptor [59]. As important cells that surveil inflammation, CCR2$^+$ MO activated by normal gut microbiome are thought to be necessary for adult hippocampal neurogenesis [10]. As such, adult hippocampal neurogenesis can be impaired upon loss of CCR2$^+$ MO [10] and commensal microbiota in gem-free mice or after treatment with broad-spectrum antibiotics [60]. Similarly, the CCR2 deficiency reduces MO infiltration in the CNS causing brain microhemorrhages and mortality of transgenic AD mice [10]. However, peripheral inflammation can also disrupt adult hippocampal neurogenesis and induce aging-associated cognitive decline [13–15]. It is a risk factor for AD [61] and various neuropsychiatric disorders [39] and depressive-like symptoms [40, 41]. Peripheral blood (PB) and CNS fluids of AD patients is enriched in proinflammatory cytokines, such as IL-6, IFN, IL-1, and TNFα [4, 5], which activate reactive astrocytes and MG [6, 7]. Note that IFNγ exhibits both pathogenic and protective functions depending on where and what cells produce it. While it activates MG [17] impairing their phagocytosis of Aβ [62], it controls immune cell trafficking into the brain of mice by inhibiting the negative effects of IFN-I in CP [63]. CP [64, 65] and recently discovered brain lymphoid structures [66] are the main gateways of immune cells into the brain.

Neuroinflammation [67] and brain functions in rodents and humans [68, 69] are controlled by gut commensal microbiota, whose pathological role increases in aging. First, aging

markedly affects microbial composition in the gut reducing their diversity and shifting the *Firmicutes/Bacteroidetes* ratio toward inducers of inflammation [70, 71]. A proinflammatory *Escherichia/Shigella* taxon is increased and an anti-inflammatory taxon, *E. rectale* is reduced in patients with cognitive impairment and brain Aβ amyloidosis [72]. The microbiome change disrupts intestinal barrier, which is also increased in elderly [73], causing leakage of endotoxin and other factors [74] that impair blood-brain-barrier (BBB), activate MG and astrocytes, and induce accumulation of Aβ deposits [1, 61]. Alone or with T cells in the brain parenchyma [31], peripheral inflammation also triggers production of inflammatory cytokines leading to long-lasting alterations of MG (upregulation of MHCI and II) [75] and cerebral vasculature [32]. As such, IFN-I [16], IFNγ [17, 18], and other proinflammatory cytokines (TNFα and IL-1) are linked with aging cognitive decline, at least in part, as inhibitors of adult hippocampal neurogenesis [13–15].

T cells also produce less IFNγ and do not proliferate in the brain of transgenic AD mice, suggesting that the loss of their immunosurveilling functions may lead to Aβ accumulation and progression of the disease [76]. Moreover, the normal function and maintenance of healthy brain need cytokines. For example, IL-4 from meningeal T cells supports memory maintenances [77] while neuronal and glia-derived TNFα regulates synaptic strength via exocytosis and endocytosis of AMPA and GABA receptors, respectively [78]. IFNγ regulates neuronal connectivity and social behavior via induction of GABA on inhibitory neurons [79]. This normal use of cytokines and their balance shifts from the maintenance to damage during neuroinflammation. While M2 macrophages and microglia produce anti-inflammatory cytokine IL-10 and mediate tissue remodeling, neurogeneration, and remyelination through stimulation of oligodendrocytes [80], peripheral inflammation induces MO-to-M1 macrophage differentiation that exacerbate brain inflammation via producing TNFα, IL-12, IL-23, CXCL9, CXCL10, reactive oxygen, and nitrogen species [81]. The M1/M2 balance and the nature of inflammation affect function of B cells. For example, proinflammatory cytokines IL-1β and IL-6 produced in response to gut microbiota can induce differentiation of IL-10^{+} Bregs in the spleen and in the mesenteric lymph nodes [82].

Protective and pathogenic roles of immunoglobulin

The B-cell compartment consists of multiple B-cell subsets classified in two main categories: conventional B cells (also known as B2 cells) and the innate-like B1 cells. Mature B2 cells consist of follicular B cells (FO B) and the marginal zone B cells (MZB). B1 cells are represented by B1a (mainly produce IgM) and B1b (produce IgA and IgM) cells that mostly located in the pleural and peritoneal cavities, although a minor population (<5% of B cells) can be found in the spleen. While antibody (Ab) production from B2 cell and some B1b cells requires help of T cells (TD), B1a cells produce Ab in T cell independent fashion. In fact, B1a and marginal zone B cells (MZB) are the main producers of so-called natural Ab that protect from blood-borne bacteria and maintain tissue homeostasis (i.e., removal of apoptotic bodies, mucosal commensal bacteria, intestinal microbiota [83–86]). The importance of B2 cells in production of Aβ neutralizing antibody (Ab) [87, 88] was first noted in HIV patients before the advent of antiretroviral therapies, where about 50% of patients suffered from dementia associated with Aβ accumulation in brain and cerebrospinal

fluids [89]. Aging also impairs TD Ab production by reducing lymphopoiesis and subsequently, naïve T and B cells and increasing antigen-experienced memory and mature conventional B2 cells [90–93]. It also increases B1 cells and production of natural Ab [94, 95].

Ab can infiltrate into healthy brain (albeit inefficiently, only 0.1% of IgG in circulation) by passive diffusion through BBB [96, 97], which is enhanced upon BBB disruption in systemic inflammation, aging, and AD [98, 99]. The Ab influx in the brain is a double-edged sword. On one hand, as first proposed by Morris and Muller in the late 1960s [100], immunoglobulin (Ig) is a potent and beneficial “non-specific” immune suppressor in autoimmune diseases [101–103]. It can induce inhibitory signaling from FcγRIIB in target cells [104] or activate FcγR on DCs to produce immune-suppressive factors [105]. In AD mice, as shown in an elegant study by Marsh et al. [48], non-amyloid reactive IgG promotes Aβ clearance upon association and activation of MG phagocytosis. Thus, the ablation of B cells in RAG enzyme-deficient 5xfAD mice markedly increases β-amyloid pathology. This probably explains the benefit of intracranially injected non-specific IgG in Aβ clearance in AD transgenic mice [106] and patients with AD [107, 108]. Despite its failure to improve cognition in Phase II trial, infusion of IgG (the formulation designated Gammagard) significantly reduced Aβ load and cognitive decline in a subset of patients with ApoE4 risk allele [107, 108]. Similarly, a passive administration of Aβ-specific Ab [42, 43] or an active immunization with Aβ(1–42) vaccine can also be beneficial in AD patients [34, 44] and mice [45, 46]. For example, as we reported, Aβ vaccine alleviates AD pathology and thereby reverse the AD-associated mortality in 3xTg-AD mice that develop onset of the disease late in life [47]. On the other hand, it can also be expected that Ab is harmful in AD, as the disease as well as systemic inflammation and aging upregulate Fc receptors in perivascular macrophages and resident cells in the CNS, such as MG and neurons [97]. Their ligation with therapeutic and endogenous Ab can lead to neurodegeneration via inducing a harmful inflammation [109, 110]. Auto-Ab to glutamatergic and dopaminergic neurons can exacerbate AD and Parkinson disease (PD) [111], while Ab to the synaptic NMDA receptor is thought to contribute to dementia and psychosis in patients with progressive cognitive dysfunction [112, 113].

The pathogenic role of B cells

Independently of Ab, B cells exhibit effector functions depending on the nature and strength of a signal/inflammation and immune environment, such as differentially expressed Th1- and Th2-type cytokines [114]. By producing IFNγ and TNFα, B cells activate inflammatory macrophages (Mϕ) and inhibit regulatory immune cells [115, 116], while MZB and B1a cells use IL-10 in immunosuppression [117, 118]. As antigen-presenting cells [119], B cells present cognate antigens (Ag) in activation of $CD4^+$ T cells and $CD8^+$ T cells [120, 121] and lipid Ag on their CD1d in induction of NKT cells [122]. By producing cytokines, they facilitate differentiation of $CD8^+$ T cells [123], Th1, Th2, Th17, Tfh, and Treg cells [124–128]. However, whether these functions are affected in aging remains poorly understood. Old mice are enriched in anergic and exhausted age-associated B cells ($CD21^-CD23^-$ABCs) [129] and B7-DC^+ ABC B cells that induce Th17 and Th1 cells [49]. We recently discovered a different type of B cells that accumulate in elderly humans, macaques, and mice, the

activated B1a cells expressing 4-1BBL and mTNFα (designated 4BL cells) [50, 51]. While 4-1BBL is only transiently expressed in normal B cells after a combined stimulation with BCR and CD40 [130], this TNF superfamily type 2 transmembrane protein is usually expressed by Mϕ and DC [131] to activate NK, CD8 T cells and splenic DCs upon engagement with its receptor 4-1BB/CD137 [132–135]. In synergy with B7 and ICAM, it can also induce proliferation of naïve $CD4^+$ T cells when antigen is limiting [136]. Despite unaltered 4-$1BBL^+$ antigen-presenting cells, such as DCs, surprisingly, 4BL cells function as the main inducers of antigen-specific $perforin^+$ GrB^+ $CD8^+$ T cells in aging [50, 51], explaining the accumulation of highly differentiated GrB^+ $CD45RA^+$ $CD8^+$ T cells often detected in elderly humans [90].

As in aging, PB of patients with moderate-severe AD is also enriched in memory B cells such as IgG^+ $CD27^-IgD^-$B cells [137], although a clinical relevance of this increase remains unknown. B cells are pathogenic in MS/EAE, lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 (T1D) and type 2 (T2D) diabetes mellitus, and Graves disease (GD), as their depletion with anti-CD20 Ab (rituximab) ameliorates these diseases [138–140]. Similarly, the ablation of memory $CD27^+$ B cells, $CD19^{High}CXCR3^+$ B cells, or autoreactive memory IgM^+ B cells [140–143] can also alleviate these diseases due to, at least in part, reduction of self-reactive and pathogenic Ab and T cells [144]. The $CD27^+$ $CD19^+$ $CD138^+$ or $CD138^-$ memory B cells are present in CSF of MS patients, which can be found on both sides of BBB [145]. Ex vivo stimulation with myelin olygodendrocyte protein (MOG) induces higher levels of TNFα, IL-12, and IFNγ in B cells from primary progressive MS as compared to relapsing-remitting MS (RRMS) or benign MS patients [146]. By presenting soluble or attached to Mϕ and DC antigens [147, 148], B cell prime naïve $CD4^+$ T cells [149] to low antigen concentrations [150] and induce Th1 and Th17 cells implicated in the CNS autoimmunity [151, 152]. The MHC class II^+ B cell-induced activation of myelin-specific T cells [153] and subsequent demyelination and axonal loss in MS/EAE [154] are reversed upon B-cell depletion or if mice are B-cell deficient [119, 153]. B cells also promote stroke-associated dementia in mice [155] and humans even the decade following the stroke [156, 157].

The protective role of B cells

As originally reported by Shimamura and colleagues about 30 years ago in mice immunized with a high dose of sheep erythrocytes [158], B cells can also elicit immunosuppression and thereby protect from autoimmunity. Thus, loss of B cells [159] or their essential components (CD19) [160] can instead promote autoimmune diseases and EAE. This protective function is, at least in part, mediated by Bregs (the definition first used by Mizoguchi to describe protective B cells in mice with colitis [161]), a diverse group of B cells that regulate effector immune responses by promoting tolerance of $CD4^+$ and $CD8^+$ T cells [162, 163] and inducing Tregs and other immune suppressive cells [164–166] and Tr1 cells [167]. To date, they are represented by murine B10 regulatory cells ($CD1d^{High}CD5^+$ B cells) [160], T2-MZP Bregs ($CD43^-CD21^{High}CD23^{Low}CD2^{High}$ IgD^+ IgM^+ $CD93^{Int}CD1d^{High}CD19^+$ transitional-2 marginal zone B-cell precursor) [168], $CD1d^{High}$B1b cells ($CD5^-B220^{Low}CD11b^+$ $CD23^-CD24^+$ $CD62L^+$ IgM^+ $CD1d^{High}$) [118, 161], Tim-1^+ $CD1d^{High}CD5^+$ Bregs [169], IL-33^+ Bregs ($CD19^+$ $CD25^+$ $CD1d^{High}IgM^{High}$

$CD5^{-}CD23^{-}Tim1^{-}$) [170], and IL-35^{+} Bregs ($CD1d^{High}CD5^{+}$ $B220^{+}$ B cells) [171]. The loss of Bregs or suppressive B cells in humans also lead to autoimmune diseases, such as $CD19^{+}$ $CD24^{High}$ $CD38^{High}$ B cells [172], IL-10 producing memory $CD24^{High}CD27^{+}$ B-cells (a human counterpart of B10 cells) [173], IL-10 and TGFβ-producing $CD25^{High}CD27^{High}CD86^{High}CD1d^{High}$ B cells [174], and GrB^{+} $CD25^{+}$ B cells [175]. The cerebrospinal fluid of MS patients is enriched in perforin-expressing $FoxP3^{+}$ $CD25^{+}$ $CD19^{+}$ B cells (Bregs) [176].

Cancer also uses Bregs, although not every subset reported in autoimmune protection. T2-MZP Bregs are increased and negatively associate with cytolytic $CD8^{+}$ T cells in mice with squamous carcinoma induced by 7, 12-dimethylbenz[α] anthracene/terephtalic acid (MBA/TPA) [177] and human colorectal cancer [178]. It also generates unique cancer-associated Bregs, such as GrB^{+} Bregs in humans with breast, ovarian, colorectal, and prostate carcinomas [179]; IL-10 and TGFβ-expressing $FoxP3^{+}$ $CD5^{+}$ $CD19^{+}$ B cells that accumulate in patients with esophageal cancer [180]; and $CD25^{+}$ $CD20^{Low}$ tBregs we originally found in BALB/c mice with 4T1 breast cancer [128] and C57BL/6 mice with spontaneous ovarian cancer [181] and in humans with B-CLL [182]. tBregs differ from other Bregs and LPS- or BCR-activated suppressive B cells [183, 184], as they are poorly proliferative $CD25^{High}$B7-$H1^{High}CD81^{High}CD86^{High}CD20^{Low}CD62L^{Low}IgM^{Int/Low}$ B2 cells that express constitutively active Stat3 without detectable CD5. Their regulatory activity does not require B7-H1/PD1, Fas/FasL, IL-10, IL-27, and IL-35. While suppressive activity of most Bregs is enhanced after stimulation of Toll-like receptors (TLRs), the TLR-9 stimulation instead converts tBregs into inducers of cytolytic CD8+ T cells [128].

Most suppressive B cells/Bregs use IL-10 to directly or indirectly (via inducing other regulatory immune cells) regulate immune responses. Thus, IL-10 deficiency alone can lead to spontaneous autoimmunity due to hyper activation of T cells [185], as it is an important immunoregulatory cytokine that promotes Th2-type cytokine responses and inhibits Th1, Th17, $CD8^{+}$ T, and NK cells [52, 160, 168, 172, 173, 186–188]. It is also a prosurvival factor for murine and human B1 cells [189–191]. B1a cells, B10 cells, and MZB require stimulation with TLR ligands, IL-21, or IL-35 to upregulate IL-10 and thereby efficiently protect mice from EAE, experimental autoimmune uveitis (EAU), lupus, and collagen-induced arthritis [117, 171, 192–195]. Bregs also inhibit autoimmune and antitumor $CD8^{+}$ T cells utilizing IL-10 [188, 196]. B cells/Bregs use IL-10 in regulation of MO and Mϕ [197]. B10 cells downregulate surface FcγR on Mϕ using IL-10 and retard therapeutic efficacy of B-cell lymphoma-depleting antibody [198]. By utilizing IL-10 and natural Ab, cancer-associated B cells and B1 cells induce M2 polarization of Mϕ and TAMs [199, 200]. We recently reported that myeloid-derived suppressive cells (MDSCs), the key inhibitors of antitumor effector cells [201], also require cancer B cells/tBregs [181]. tBregs evoke regulatory and thereby prometastatic function of MDSCs via triggering the TgfβR1/TgfβR2 signaling axis [181]. Thus, loss of tBregs or their downstream Tregs is sufficient to abrogate lung metastasis despite unaltered expansion of MDSCs in response to cancer [128, 182, 202]. Bregs also mediate IL-10-independednt regulation [203, 204]. Human GrB^{+} Bregs disable antitumor T cells by degrading their TCR-ζ with granzyme B [179]. Activated B cells express TGFβ [186, 205], which alone or as a complex with Ig is immunosuppressive [206, 207]. They also produce galectin-1 and other potentially cytotoxic factors that induce

apoptosis and anergy Th1 cells and $CD8^+$ T cells [205, 208–210]. Most human $CD25^{High}CD27^{High}CD86^{High}CD1d^{High}CD19^+$ B cells [174] and murine B cells and Bregs utilize TGFβ and IL-10 to induce $FoxP3^+$ $CD25^+$ $CD4^+$ Tregs and iTregs, respectively [128, 166, 174, 205, 211, 212]. However, TGFβ is not needed in some $CD1d^+$ Breg-mediated induction of $FoxP3^+$ Tregs [164, 213]. They mostly used IL-10 [164, 213] possibly to maintain FoxP3 expression [214]. IL-10 also induces Tr1 cells ($FoxP3^-IL\text{-}10^{High}$ Tregs [167] and effector-memory Tregs (TREM) [215, 216], although it remains unknown whether Bregs can induce them. Bregs also expand Tregs via IL-35 and suppress EAU by inhibiting pathogenic Th-17 and Th1 cells [171].

Despite importance of Bregs in autoimmune diseases and cancer, little is known whether Bregs participate neurodegenerative diseases and, particularly, in AD. The protective role of B cells in EAE, which is originally reported by Wolf and colleagues in 1996 [159], is now expanded to various suppressive B cells and Bregs, such as B10 cells, plasmablasts [52, 187, 217] and IgM^+ $CD138^{High}TACI^+$ $CXCR4^+$ $CD1d^{Int}$ $Tim1^{Int}$ plasma cells [218]. Bregs inhibit activated Mϕ and MOG-specific Th17 and Th1 cells via IL-10 and IL-35 [52, 218], presumably explaining reduction of $IL\text{-}10^+$ Bregs and memory $CD27^+$ IgD^-CD19^+ B cells in PB of patients with RRMS [219]. Conversely, $CD25^+$ $CD19^+$, $FoxP3^+$ $CD25^+$ $CD19^+$, $FoxP3^+$ $CD19^+$, and $perforin^+$ $CD25^+$ $CD19^+$ Bregs increased in PB of non-active RRMS patients as compared to MS patients with active disease [176]. Interestingly, these Bregs appear to function as our tBregs $CD25^{High}CD19^+$ that promote metastasis [128, 182], as both inhibit proliferation of TCR-activated $CD4^+$ T cells [176] - the feature rarely linked to Bregs. Recently, a new type of $BTLA^+$ Bregs is found in MS patient [146]. They increase upon disease remission and become reduced in active MS. Their function appears to control cytokine production from TCR-induced T cells via BTLA/HVEM axis [146]. Similarly, B10 cells ($CD24^{High}CD38^{High}CD19^+$ Bregs) are increased upon rituximab therapy-induced amelioration of myasthenia gravi [220].

Concluding remarks

Peripheral inflammation plays an important role in the pathology of age-associated neurodegenerative diseases and AD, which is mostly thought to involve activated innate immune cells and Th1 cells. However, the role of B cells, which also actively sense and respond to the environmental cues, remains poorly understood and is even considered to be non-essential. The question is why to date almost nothing is known about B cells in AD when they participate in numerous clinically relevant diseases, such as cancer, autoimmune diseases, and MS/EAE and modulate neuroinflammation and CNS injury?

Can it be due to the dysregulation of B cells in aging humans and mice, which accumulate new types of potentially pathogenic B cells not seen in young? If so, the modeling studies in young mice cannot fully capture this change in the context of aging-associated diseases. Thus, unless tested in old mice, the role of 4BL cells (memory/innate B cells), which retard tumor growth by inducing cytolytic GrB^+ $CD8^+$ T cells via 4-1BBL/4-1BB axis [50] and $B7\text{-}DC^+$ ABC B cells that induce Th17 and Th1 cells [49] in AD will be hidden. One may argue that B cells are not known to infiltrate the brains of mice and humans with AD. Bregs can be missed within the overwhelming numbers of other cells in the CNS due to their low

numbers, as for example, they account for less than 10% of B cells in tumor-bearing mice. On the other hand, B cells can remotely affect AD, as they express a full array of cytokines and other factors implicated in this disease. They can induce or impair MG phagocytosis and clearance of Aβ and promote adult hippocampal neurogenesis or neurodegeneration. Thus, the inflammation-activated CNS is expected to differ in responses to humoral factors or/and innate and adaptive immune cells. Harmful Th1 cells can be reactivated by loss of $CD19^{+}$ $CD24^{High}$ $CD38^{High}$ B cells (Bregs?) in humans with SLE [172] or after depletion of B cells/Bregs with rituximab, causing anecdotal exacerbation of ulcerative colitis and induction of psoriasis in patients with psoriatic arthropathy and colitis, GD, and non-Hodgkin lymphoma [221–224]. In summary, we propose that, as important activators and regulators of almost every cell type involved in AD, including Tregs (whose numbers increase in aging), cytotoxic $CD8^{+}$ T cells, NK cells, and M1/M2 macrophages [128, 140, 199, 200, 225], B cells can affect the pathogenesis of AD and other age-associated neurodegenerative diseases.

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