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Role of Mast Cells in the Pathogenesis of Multiple Sclerosis and Experimental Autoimmune Encephalomyelitis

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Abstract Multiple sclerosis (MS) is a neurological autoimmune disorder of the central nervous system (CNS), characterized by recurrent episodes of inflammatory demyelination and consequent axonal deterioration. The hallmark of the disease is the demyelinated plaque, a hypocellular area characterized by formation of astrocytic scars and infiltration of mononuclear cells. Recent studies have revealed that both innate and adaptive immune cells contribute to the pathogenesis of MS and its experimental autoimmune encephalomyelitis (EAE) model. Here, we review the current understanding of the role of mast cells in the pathogenesis of MS and EAE. Mast cells may act at the early stage that promote demyelination through interactions among mast cells, neurons, and other immune cells to mediate neuroinflammation. Studies from EAE model suggest that mast cells regulate adaptive autoimmune responses, present myelin antigens to T cells, disrupt the blood–brain barrier, and permit the entry of inflammatory cells and mediators into the CNS. Depletion or limiting mast cells could be a new promising therapeutic target for MS and EAE.

Keywords Central nervous system · Demyelination · Experimental autoimmune encephalomyelitis · Mast cell · Multiple sclerosis

Abbreviations

EAE	Experimental autoimmune encephalomyelitis
IL	Interleukin
MC	Mast cell
MBP	Myelin basic protein
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis

Introduction

Multiple sclerosis (MS) is defined as a chronic inflammatory demyelinating autoimmune disease of the central nervous system (CNS) [1]. Based on clinical presentation and course, the disease is classified in three categories namely relapsing remitting (RR), the most common course characterized by acute attack (relapse) followed by partial or full recovery (remission); the course is primary progressive (PP) and manifested by progressive worsening from onset and secondary progressive (SP) [2, 3]. MS plaque formation is characterized by several pathological features including blood–brain barrier (BBB) leakage, myelin sheath destruction, oligodendrocyte damage and cell death, axonal damage/loss, glial scar formation, and infiltrates of autoreactive T cells, macrophages, microglial cells, ependymal cells, astrocytes, and mast cells (MCs) [4]. Axonal degeneration begins in acute or active MS lesions but does not initially cause neurological disability due to the ability of human CNS to compensate for axonal loss [5]. During the last decades, experimental autoimmune

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encephalomyelitis (EAE) has served as a main approach to understand the mechanisms involved in multiple sclerosis [6]. However, it is not the same disease as MS, due to features such as different locations of demyelination and differences in infiltrated immune cells into plaques [7]. In this model, the injection of myelin components like the myelin basic protein (MBP) [8], the myelin oligodendrocyte glycoprotein (MOG) [9], and the myelin proteolipid protein (PLP) [10] in Freund's Complete Adjuvant (CFA) or Bordetella pertussis toxin (PTX) [11] into susceptible animals leads to a $CD4^+$-mediated autoimmune disease similar to MS and can be adoptively transferred by encephalitogenic $CD4^+$ T cells into a naive animal [12]. The role of innate and adaptive immunity has been studied in the initiation and development of MS and EAE, but the exact immunologic mechanisms are still unknown. Of the innate immune cells, the MCs are underestimated contributors to MS pathogenesis, as they are responsible for releasing cytokines/chemokines to recruit and activate T cell/macrophage, presenting myelin antigen to T cells, and disrupting the BBB to allow activated T cells to infiltrate into the brain [13].

Pathogenesis and Pathologic Features of MS/EAE

MS affects both white and gray matter by neurodegenerative and inflammatory mechanisms. The patients manifest a heterogeneous group of symptoms including paraesthesia, numbness, muscle weakness, gait imbalance, spasticity, cerebellar ataxia, visual impairment, dizziness, urinary dysfunction, fatigue, depression, and cognitive abnormalities [14]. A widely accepted view of MS pathogenesis suggests the involvement of T cells, autoantibodies against myelin antigens, the fixation of complement/opsonization of the myelin sheath, and the oligodendrocyte by macrophages in demyelination process [15]. It should be considered that adoptive transfer of autoantibodies alone does not transfer disease [16]. Most autoreactive T cells are deleted during central tolerance in the thymus; however, in healthy individuals, peripheral tolerance mechanisms such as T_{Reg} function monitor autoreactive T cells. If this tolerance is broken, autoreactive B cells and T cells can be activated in the periphery to become aggressive effector cells by molecular mimicry, novel autoantigen presentation, and recognition of sequestered CNS antigen released into the periphery or bystander activation. $CD8^+$ T cells, differentiated $CD4^+$ T helper 1 (TH1) and TH17 cells, B cells, and innate immune cells infiltrate the CNS and orchestrate inflammation that leads to CNS damage [17]. Earlier studies on the frequency of myelin-reactive T cells in MS are conflicting; while some investigators reported a significantly higher incidence of myelin-specific PBMCs in individuals with MS, others found no difference [18]. The mechanisms whereby activated immune cells participate in MS pathology include (1) direct binding of T cells to myelin epitopes activates macrophages to attack of the myelin sheath by phagocytosis, (2) release of cytotoxic cytokines/soluble toxic mediators such as nitric oxide (NO) from T cells or microglia/macrophages results in destruction of myelin and myelin-producing cells, (3) myelin-specific antibodies bind to myelin and contribute in initiating complement fixation, binding of macrophages, opsonization, and phagocytosis of myelin and oligodendrocytes, and (4) injury to the myelin sheath may render oligodendrocytes vulnerable to environmental toxins or viruses [15] (Fig. 1).

Variety of adhesion molecules, cytokines, chemokines, HLA molecules, and metalloproteases contribute in development of the inflammatory response in brain [19]. Th2 cells attenuate the macrophage activity by recognizing myelin epitopes. They contribute in the remyelination process and in releasing IL-4 and neurotrophic factors such as brain-derived neurotrophic factor (BDNF) [15], the ligand of P2X4 receptors (P2X4R) in the microglia [20]. Many findings support the role of the immune system in the pathogenesis of the disease. For instance, immunomodulatory and immunosuppressive therapy has been shown to have positive effects in disease control [21]. Furthermore, genetic susceptibility in MS has been also studied and the association of genetic risk factors

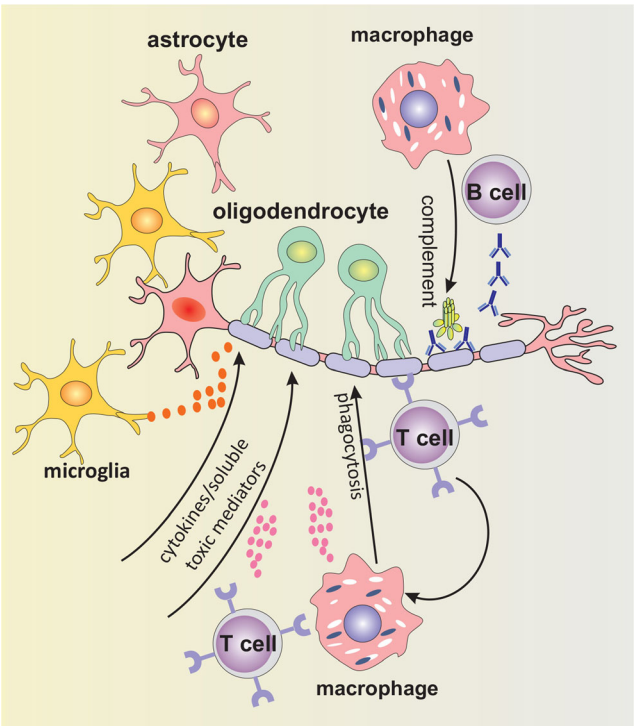

Fig. 1 Mechanisms by which immune cells participate in the pathogenesis of multiple sclerosis. T cells recognize myelin epitopes and activate macrophages to damage myelin by phagocytosis. Cytokines and toxic mediators such as NO released by T cells, microglia, and macrophages cause myelin damage. Furthermore, autoantibodies through binding to myelin and activating complement facilitate phagocytosis mediated by macrophages

such as HLA-DRB1*15 have been reported in the pathogenesis of the disease [22].

Mast Cells in Initiation and Development of MS/EAE

Mast cells develop from $CD34^+/CD117^+$ pluripotent progenitor cells originating in the bone marrow and circulating in the blood as committed precursors. They complete their differentiation under the influence of growth factors such as stem cell factor (SCF) in residing tissues [23, 24]. MC progenitors enter the brain from the leptomeninges during the first stages of development by penetrating blood vessels and residing in CNS associated with vessels. The neurons of rats have been reported to secrete SCF, the prominent cytokine necessary for mast cell survival, proliferation, and differentiation. Interestingly, peptidergic neurons modulate MC activity by secreting neuromediators; for instance, substance P is very effective in inducing histamine release from brain MCs [25].

Upon encountering an allergen (antigen) recognized by IgE bound to the high affinity IgE receptor (FcεRI), mast cells secrete both preformed and newly synthesized mediators [26]. Microscopic observations showed that in brain sections of patients with MS, most MCs were observed in the border zones of the plaques clustered in restricted areas along venules and capillaries, which represent the main area of edema formation in the brain [27]. The penetration of autoreactive T cells into the CNS through the normally impermeable blood–brain barrier under the influence of MCs is a feature reported in literature. They exert such effect through alteration of vascular permeability via releasing the histamine and recruitment of inflammatory cells. To determine whether resident CNS MCs affect T cell infiltration in the brain and spinal cord, Gregory and colleagues primed WT, W/W^v, and reconstituted W/W^v mice (by i.v. transfer of bone marrow-derived MC) with MOG_{35-55} and analyzed T lymphocyte populations in the CNS by flow cytometry (cite the reference here). They observed a reduction in the percentage and absolute numbers of both CD4 and CD8 T cells in the CNS of W/W^v mice as compared to WT controls. In reconstituted mice, CD4 T cells, unlike CD8 T cells (which require signals provided by CNS MC), could infiltrate the CNS. To show the state of T cell activation, CD44 was used activation index. CD8 T cells in the brain and spinal cord of primed WT mice were $CD44^{hi}$, while in W/W^v mice, a significant percentage was found to have naive $CD44^{lo/-}$ phenotype [28] (Fig. 2).

MCs activate lymphocytes and also drive T cell differentiation in favor of Th1, Th2, and also Th17 phenotype by a cytokine profile including IL-4, IL-10, IL-13, TGF-β, TNF-α, and IL-6 [3]. Furthermore, they express IL-4, IL-12, IL-15, and TNF-α and the costimulatory molecules CD154 and OX40L which influence both DC and T cell maturation [28]. Due to wide distribution, MCs are present in the normal brain in the parenchyma and, consequently, can interact with myelin easily [3]. The myelinolytic capacity of MC proteases during degranulation was reported by Johnson and colleagues more than two decades ago. For this purpose, they isolated the peritoneal MCs from male Sprague-Dawley rats, CNS myelinated axons from Hartley guinea pigs, and PNS myelin from frozen bovine spinal roots. Degranulating agents were added to MCs suspended in Tyrode's buffer. Cells were pelleted by centrifugation and the supernatant assayed for β-hexosaminidase as an index of degranulation and for lactate dehydrogenase (LDH) as an index of cell death. For examination of the proteolytic activity of various MC preparations, mast cell lysates or supernatants from mast cells degranulated with Compound 48/80 incubated with protein of either PNS myelin or CNS myelinated axons and myelin protein changes were assessed using SDS electrophoresis.

To examine the effects of MC-derived proteases on various myelin preparations, this group of researches incubated PNS with MC supernatants. They reported that 72 % of the P_0 was broken down after 3 h of incubation with supernatant. They showed that some myelin proteins released from damaged

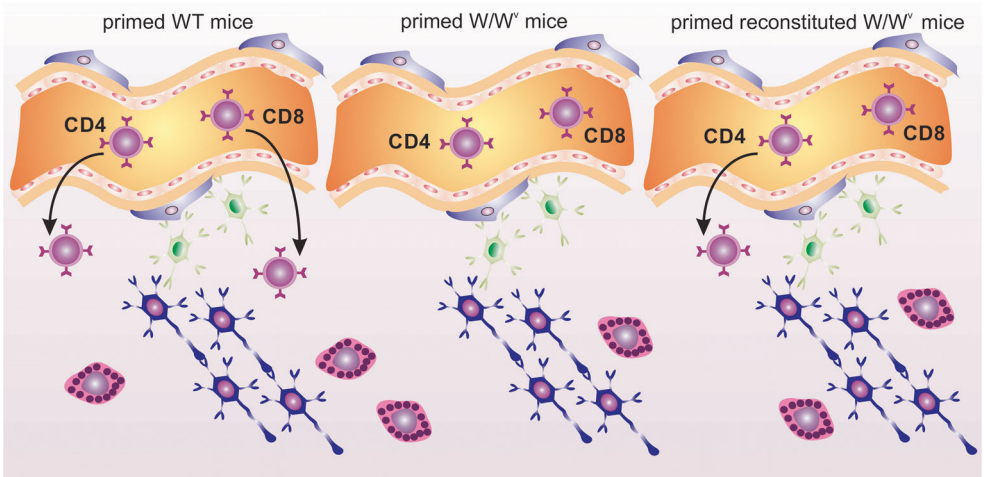

Fig. 2 Gregory and colleagues showed that MOG_{35-55} primed CD4 and CD8 T cells from WT mice could infiltrate the CNS; in contrast, these cells failed to infiltrate in W/W^v mice. CD4 T cells but not CD8 T cells of Primed reconstituted W/W^v mice were found to infiltrate the CNS

myelin sheaths are potent to stimulate MC degranulation [29] (Fig. 3).

MC cytokines such as IL-4, IFN-γ, TNF-α, and MIP1-α may affect immune cell trafficking through direct chemotaxis and/or influence adhesion molecule expression on the endothelium. Furthermore, MCs, by migrating to secondary lymphoid organs, raise the possibility that they can regulate the induction and/or amplification of a polarized Th response [16]. MCs are believed to play a key role in the regulation of vascular permeability by releasing mediators such as histamine [30]. BBB-endothelial cells express histamine receptors, and histamine can increase BBB permeability [31]. Moreover, acute restraint stress and CRH activate MCs and induce mast cell-dependent vascular permeability in rodent as well as in human skin. Human mast cells express CRHR, and activation of which leads to selective release of VEGF possessing neovascularization and vasodilation activity [27]. MCs express TNF-α which contributes in the recruitment of neutrophils to the CNS in blood–brain barrier breach. The presence of MCs and neutrophils together with T cells lead to further inflammatory cell influx and myelin damage [32]. Sayed and colleagues showed that TNF mRNA is strongly expressed in the dura mater of WT, but not W/W^v mice, and that reconstitution with TNF-deficient meningeal MCs cannot restore disease to WT levels [33]. Mast cell tryptase levels increase in the CSF of patients with MS, can activate peripheral mononuclear cells to secrete TNF and IL-6, and stimulate PARs leading to microvascular leakage and widespread inflammation [27]. MC localized within CNS also can be triggered to secrete by direct nerve stimulation or by neuropeptides including substance P (SP), which then leads to leukocyte infiltration [30]. MCs can be activated by myelin and amyloid β-peptide. In turn, activated mast cells participate in the demyelination process and induce apoptotic oligodendrocyte death in vitro [34]. By degrading myelin, MC-derived proteases produce encephalitogenic fragments. Dietsch and colleagues studied the encephalitogenicity of the two most abundant peptides and identified them as residues 69–87 and 69–88. Additional exposure to the MC supernatants removes the COOH terminal histamine from peptide 69–88 to yield peptide 69–87. They showed that immunization with this peptide emulsified in CFA causes the development of clinical EAE [35]. Moreover, myelin instability reported in some demyelinating diseases results in oligodendrocyte (ODC) vesiculation, which characterizes endothelial cells in MS and myelin diffusion into the extracellular environment. At molecular level, peptidyl arginine deiminase (PAD) for example induces myelin vesiculation and MBP proteolysis through converting arginyl residues to citrulline [36]. One of the mechanisms by which MCs contribute in development of EAE is secreting a broad spectrum of cytokines. Gregory and colleagues to provide a line of evidence used a mast cell reconstitution model and investigated the role of MC-derived IL-4 in promoting Th1 responses in vivo. Although IL-4 is best known as a Th2-polarizing cytokine, it has been previously shown to have distinct effects on Th1 responses. In their experiment, MC-deficient (W/W^v) mice were selectively reconstituted with either WT or IL-$4^{-/-}$ BMMCs (referred to as W/W^v + WT and W/W^v + IL-$4^{-/-}$, respectively). Both groups were then immunized with $MOG_{35–55}$ peptide to induce EAE and monitored daily and scored for clinical signs of paralysis. Analysis showed that MC-derived IL-4 influences EAE severity by enhancing encephalitogenicity of Th1 cells. WT, W/W^v, and W/W^v mice reconstituted with WT or IL-$4^{-/-}$ BMMCs were perfused 11 days after immunization, and flow cytometric analysis of CNS-infiltrating $CD44^{hi}$ CD4 T cells (activated cells) was performed. $MOG_{35–55}$ peptide-specific $CD4^+$ T cell responses were measured by intracellular cytokine staining for IFN-γ after a brief in vitro restimulation of splenocytes with antigen and it was revealed that cell obtained from W/W^v + WT mice

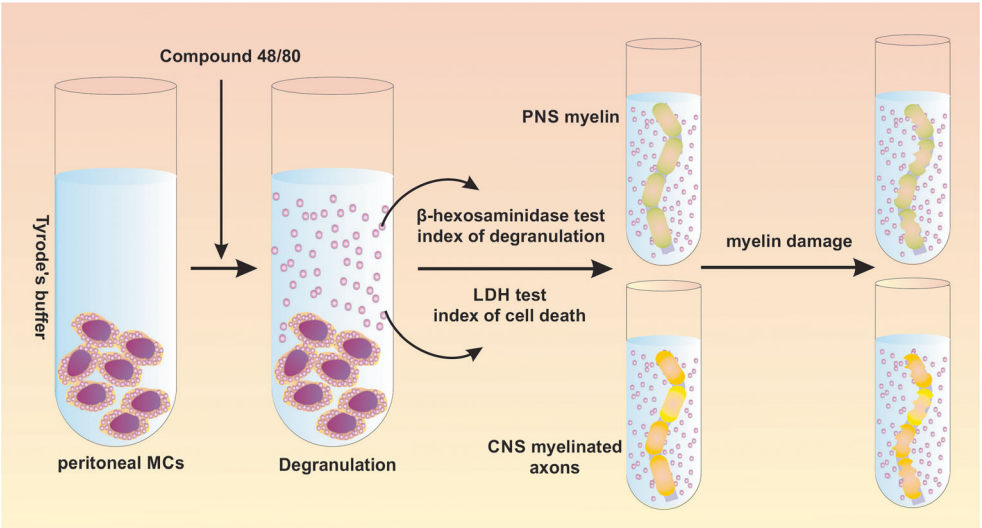

Fig. 3 Male Sprague-Dawley MCs suspended in Tyrode's buffer release proteases when incubated with Compound 48/80. Released proteases damage PNS myelin and CNS myelinated axons. Myelin proteins released from damaged myelin sheaths assessed by SDS electrophoresis

had the strongest response in proportion to other groups [37] (Fig. 4).

Reconstitution of W/W^v mice with wild-type bone marrow-derived MCs (BMMCs) has been a practical approach for studying mast cell functions in vivo. However, details regarding the sites and kinetics of MC repopulation have remained largely uncharacterized until the experience of Tanzola and colleagues examined the kinetics and tissue distribution of green fluorescent protein$^+$ BMMCs in reconstituted W/W^v mice to identify sites of MC influence before and during EAE. This experiment revealed a role for MCs acting outside the CNS to influence disease. In fact, MCs as dynamic immune cells are capable to move to sites of initial T cell activation where they are likely to influence the generation of adaptive immune responses. Tanzola and colleagues

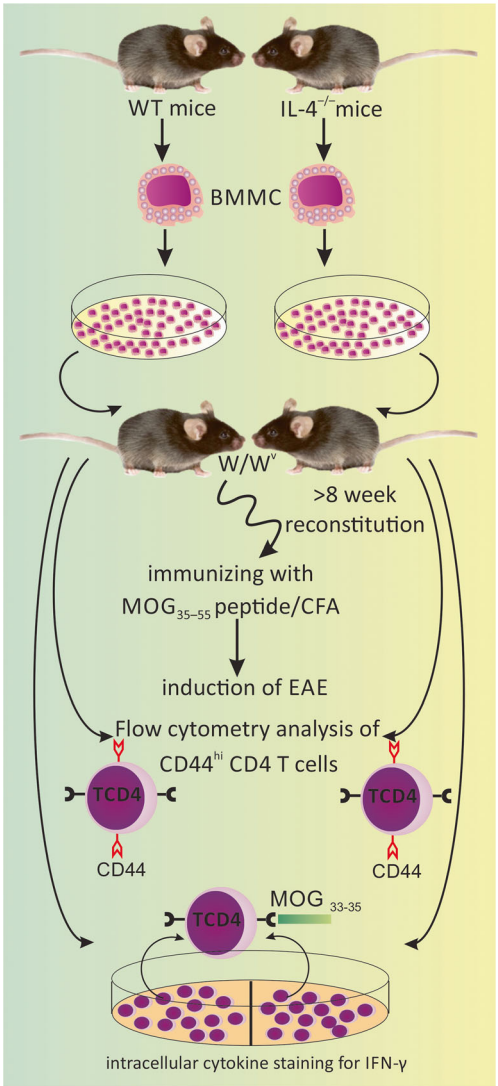

Fig. 4 W/W^v mice reconstituted by WT and IL-4$^{-/-}$ BMMCs were immunized by MOG$_{35-55}$ peptide as myelin antigen to induce EAE. IFN-γ response assessment of infiltrating CD44^{hi} CD4 T cells revealed that W/W^v + WT mice had the strongest responses suggesting that IL-4 has a role in pathogenesis of EAE

used WBB6F$_1$-W/W^v and GFP-transgenic C57BL/6 mice. The bone marrow cells of the GFP-transgenic C57BL/6 mice were harvested in serum-free RPMI 1640 and differentiated in vitro using IL-3 and SCF. The obtained FcεRI$^+$, c-kit^{high} BMMCs were injected to 6- to 8-week-old W/W^v mice. Organs were then harvested and fixed in 4 % paraformaldehyde for 6 h and then flash frozen. Tissue sections were cut by cryostat and analyzed for the presence of GFP using fluorescence microscopy. Furthermore, the slides were stained with toluidine blue to determine the presence of MC granules using a transmitted light microscope. To induce the EAE, this group of researchers introduced the reconstituted W/W^v with MOG$_{35-55}$/CFA and the animals were scored daily for clinical signs of paralysis. They revealed that mast cell numbers in the secondary lymphoid organs change as EAE disease progresses. Moreover, mast cells were not detected in the brain or spinal cord at any point during the course of disease suggesting the presence of a mechanism by which MCs contribute the EAE pathology outside the CNS [38] (Fig. 5).

It should be considered that some MC-derived mediators are neuroprotective [34]. In this regard, angiogenin, a stored mediator which is structurally a homolog of bovine pancreatic RNase A [39], is released to a variety of stimuli, including FcεRI-mediated signals, TLR ligands, and NGF, and promotes the survival and neuritogenesis of motor neurons. Interestingly, it has been reported that nerve growth factor (NGF)-stimulated human MCs release greater amounts of angiogenin compared with those stimulated by FcεRI cross-linking [34]. Most recently, Russi and colleagues described MC inflammasome activity in the pathogenesis of EAE disease. MCs utilize inflammasomes to regulate IL-1β which after releasing interact with its receptor (IL-1R1) on T cells and induce GM-CSF production. Interestingly, GM-CSF regulates the recruitment of CCR2$^+$ monocytes as myelin and nerve damage effector cells [40]. The main pieces of evidence supporting the role of mast cells in pathogenesis of multiple sclerosis and experimental autoimmune encephalomyelitis both at cellular and molecular levels have been listed in Table 1. Furthermore, main interactions of MCs with immune cells within the CNS and MS plaques are depicted in Fig. 6.

Contribution of Innate Immunity in MS Pathogenesis

Macrophages

Phagocytes such as macrophages are mainly responsible for myelin damage and removal within the lesions, and myelin degradation products can be found in phagocytes. Furthermore, they have been shown to promote lesion resolution and tissue repair (remyelination) [50]. During this process, oligodendrocyte progenitor cells (OPCs) respond to

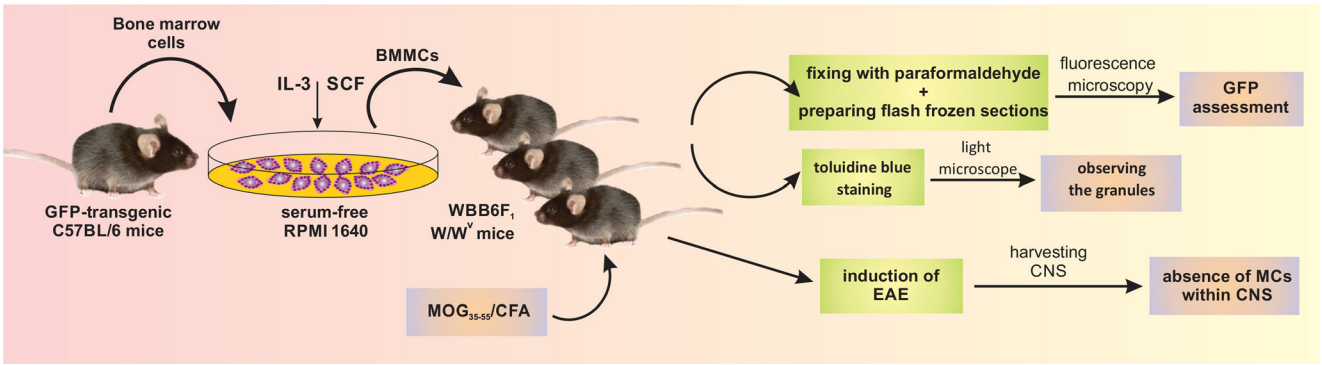

Fig. 5 Reconstitution of WBB6F1-W/W^v mice with BMMCs of GFP-transgenic C57BL/6 mice and inducing EAE by MOG_{35-55}/CFA provided the data regarding to sites and kinetics of MC repopulation. After inducing EAE, mast cells were not detected in the brain or spinal cord at any point during the course of disease suggesting an unknown mechanism by which MCs contribute the EAE pathology outside the CNS

injury by dividing, migrating, and differentiating into oligodendrocytes that reinvest the demyelinated axon with new myelin sheaths [51].

Astrocytes

Astrocytes produce cytokines/chemokines including IL-33 and contribute to MC degranulation [52]. They also interact with mast cells via CD40-CD40L [53].

Dendritic Cells (DC)

Myeloid DCs (Lin^-CD11c^+) in SP/RR-MS patients were found to overexpress activation markers CD40 and CD80 while decreased expression of programmed death ligand-1 (PDL1). Moreover, activated phenotype of mDCs with enhanced production of IL-12 in response to IFN-γ and LPS in both RR- and SP-MS patients is accompanied by an enhanced pro-inflammatory T cell response as defined by increased secretion of TNF-α and IFN-γ. DCs through overexpressing osteopontin, a glycoprotein involved in chemotaxis, activation, and differentiation of Th1 and Th17, promote MS pathology [3]. Through the expression of CCL2, monocytes, and DCs, chemoattractant can be induced in astrocytes which results in recruitment of monocytes and DCs and progression of inflammation within the CNS [54].

Table 1 Role of the mast cells in the pathology of MS and EAE

Pathogenic roles of mast cells in EAE and MS	References
Migration and BBB permeability	[30, 41–43]
Immune cell activation and differentiation	[28, 44]
Promoting demyelination	[35, 36]
Inflammation and immunoregulation	[19, 24, 34, 40, 45–48]
Cell death and apoptosis	[49]

NK Cells

An array of toxicities of NK cells has been reported towards immune and CNS resident cells, including the direct lysis of primary oligodendrocytes and neurons, microglia, astrocytes, DCs, and T cells [55]. Natural killer cell depletion prior to disease induction with myelin antigens led to an increase in EAE severity and mortality. Pronounced cellular infiltrates, CNS inflammation, and demyelination are being reported in NK cell-depleted animals [56].

TLR

An increase of TLR expression within the CNS is observed during MS, even in the absence of microbial involvement [4]. TLRs upon stimulation by their ligands including dsRNA (TLR3), LPS (TLR4), peptidoglycans (PGN; TLR2 with TLR1/6), and viral CpG DNA (TLR9) induce a wide range of immune functions in glial cells, such as secretion of type I interferons (IFN-α/β) [4, 57], pro-inflammatory cytokines, chemokines, and an increase in MHC class I and II expression. TLR-dependent activation of macrophages (Mφ), microglia, and dendritic cells (DCs) results in the production of cytokines such as IL-6, IL-15, and TNF-α which participate in BBB disruption and lymphocyte attraction, inflammation promotion, and modulation of adaptive immunity. In this regard, IL-6 for example promotes Th17 and B cell differentiation. Th17 in return contributes to tissue damage [4].

Contribution of Specific Immunity in MS Pathogenesis

The observation that Igs are elevated in the CSF of MS patients provided the earliest evidence suggesting a role for B cells and antibodies in the pathology of MS. Increased Igs in

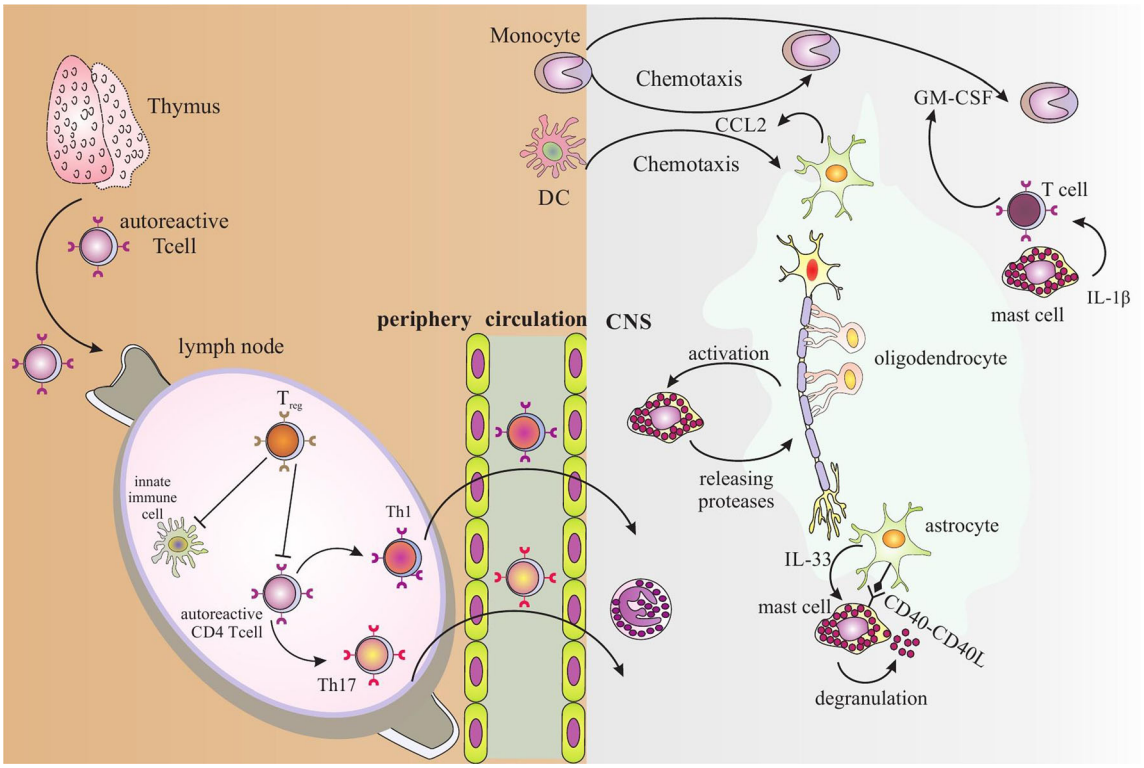

Fig. 6 Autoreactive T cells are released into the periphery from thymus during establishment of central tolerance. They are controlled and monitored by regulatory T (T_{Reg}) cells. In MS, they become activated in the periphery as aggressive effector cells and Th1 and Th17 infiltrate CNS. Mast cells interact with astrocytes, neurons, and T cells for recruiting immune cells and damaging myelinated neurons

the CSF—but not in serum—indicates local Ig production. The mechanisms by which B cells and antibodies contribute to MS pathogenesis include the following: (a) B cells can serve as APCs for autoreactive T cells; (b) B cells provide co-stimulation signals to autoreactive T cells; (c) B cells and tissue-bound Ig can recruit autoreactive T cells to the CNS; (d) idiotope-specific T cells may be activated by CSF Igs, and these T cells sustain B cells that produce such idiotopes; and (e) myelin-specific antibodies can be produced [12]. Histologically, $CD4^+$ T cells are found predominantly in the perivascular cuff, while $CD8^+$ T cells are more prevalent in the center and border zone of the MS lesions [21]. The presence of $CD4^+$ T cells, clonotypic $CD8^+$ T cells, reactive astrocytes, and proliferating oligodendrocytes in acute plaques in addition to pro-inflammatory cytokines such as IL-12 and TNF-α has led to the classical hypothesis that MS is a TH1-cell-mediated autoimmune disease [58]. Myelin-responsive T cells are activated in the lymph node by DCs and downregulate lymph node homing molecules such as CD62L and CCR7. Activated T cells reach the choroid plexus and cross the fenestrated capillaries. Constitutive expression of CCL20 allows $CCR6^+$ cells to cross the ependymal layer into the CSF. They enter into the brain or spinal cord parenchyma. Myelin-responsive T cells upon recognition of their cognate myelin antigen which is presented by DC, resident microglia (MG), or, possibly, infiltrating macrophages become reactivated and produce inflammatory cytokines [59]. Examination of the brain tissue of MS patients has shown clonal expansion of $CD8^+$ T cells in lesions based on T cell receptor analysis. EAE mediated by $CD8^+$ T cells has been reported and transgenic mice with B7-2 (CD86) overexpressing on microglia develop disease mediated mainly by $CD8^+$ T cells. In some conditions, these cells have been shown to directly attach to axons and damage them [54]. $CD8^+$ T cells are observed more frequently than $CD4^+$ T cells in the gray matter and brain samples obtained from autopsies of patients with MS. Moreover, HLA class II molecules are expressed not only at very low levels but also on a limited number of cells in the CNS, while HLA class I molecules, which present antigen to $CD8^+$ T cells, have higher expression in these patients [60]. B cell-activating factor (BAFF) is produced by astrocytes and upregulated in MS lesions and in EAE-affected mice, suggesting that astrocyte-dependent BAFF expression may drive B cell-dependent autoimmunity. In return, B cells affect the astrocyte physiology by producing antibodies against AQP4, the main water channel protein in the CNS which is also expressed on astrocyte end-feet at the BBB. NMO IgG binding to AQP4 triggers complement activation and affects astrocyte physiology resulting in increased BBB, permeability, inflammatory cell infiltration, and impaired glutamate uptake by astrocytes, leading to neurotoxicity [55].

Mast Cells and Autoimmune Diseases

Recent studies have suggested that MCs actively contribute to the development of autoimmune diseases. Functional cross talk between mast cells and T cells has been documented during autoimmune rheumatoid arthritis [61]. Increased mast cell numbers (mast cell hyperplasia) is a common finding in synovium of rheumatoid arthritis (RA) patients where mast cell growth factors and cytokines such as stem cell factor, IL-3, and IL-4 are present. In response to anti-citrullinated protein antibodies (ACPA) and TLR ligands, mast cells are activated and MC-derived IL-8, TNF-α, and leukotrienes act as neutrophil chemoattractants to synovial fluid by which inflammation is actively developed. Monocytes and T cells are recruited to the synovial tissue through chemokines including TNF, CCL2, and CCL5. Moreover, MCs present antigens to $CD4^+$ T cells and induce T cell activation by releasing cytokines [62]. MC-derived chymase is capable to breakdown of extracellular matrix (ECM) and activation of matrix metalloproteinase (MMP) 9 precursor [32]. The development and progression of type 1 diabetes (T1D) result from the autoimmune destruction of pancreatic beta cells following immune cell infiltration specifically targeting the Langerhans islets [63]. $DR^{lyp/lyp}$ rats treated with cromolyn as mast cell stabilizer were reported to have delayed T1D onset [64]. Innate immune cells including mast cells have been implicated in inflammatory bowel disease (IBD) pathology. Increasing MC mediators mainly tryptase, chymase, and histamine suggests that these cells have an important role as inflammation sources in IBD. Neutrophil recruitment to skin through releasing leukotrienes, PAF, and cytokines is considered a key role of MCs in pathogenesis of bullous pemphigoid (BP). Recruited neutrophils release proteolytic enzymes such as elastase and gelatinase B (MMP-9) leading to splitting of epidermis from the dermis. Interestingly, MC chymase MCP-4 activates MMP-9, thus actively participating in induction of blisters [65].

Discussion and Conclusion

Multiple sclerosis is probably the most enigmatic disease of CNS with unknown etiology. Generally, it is believed that an intricate interplay of immunological, genetic, and environmental factors determines the susceptibility to the disease. Unlike many other diseases obtaining the brain tissue from patients with multiple sclerosis seems to be impossible and EAE models have successfully helped us to understand the cellular and molecular mechanisms of disease. In this regard, while gene microarray analysis provides an image of gene expression in MS lesions but it is performed on the specimen obtained from autopsies, thus it only provides information about the late stages of diseases.

Although MCs are defined as tissue (including brain) resident cells, they move through normal brain in the absence of inflammation. Resident and immigrant MCs within the CNS should be phenotypically investigated. One of the mechanisms by which MCs contribute in MS pathology is by acting as APCs by shaping Th1/Th2 responses, but a clear demonstration of this role is still lacking.

To interpret the results of studies aimed to connect the MCs with the pathogenesis of EAE, it should be noted that the mice strain, immunization protocols, type and severity of the disease, and most importantly the scoring system by which EAE development is monitored based on paralysis in mice dramatically can influence the results and may lead to controversies. One of other possible reasons of controversy could be the masking effect of immune cells. $Kit^{W\text{-}sh/W\text{-}sh}$ mice, for instance, show neutrophilia and neutrophils are necessary for developing EAE and BBB permeability. It is believed that neutrophils may mask MC contributions [66].

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