Chapter 1
Cellular Immunity and Multiple Sclerosis: Current Understanding

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Abstract We here focus on a single representative neuroimmunological disease, multiple sclerosis (MS), and illustrate how cell-mediated immunity, in which immune reactions occur independently of antibodies but are dependent on the recognition of antigens by T cells, contributes to the disease mechanism, especially with respect to the dynamics of relapse and remission. The findings from the most useful animal model of MS, the experimental autoimmune encephalomyelitis (EAE), and recent genome-wide association studies clearly demonstrated the causative role of cell-mediated immune response in MS. However, we are witnessing a rapid increase of prevalence of MS as evident in Japan, which hardly explained by genetic factors or established environmental factors, such as vitamin D or smoking habit. We will introduce new players of immunology, such as innate lymphoid cells or gut microbiome, which may provide a clue to the mystery.

1.1 Introduction

Multiple sclerosis (MS) is an autoimmune disease affecting the central nervous system (CNS), of which pathogenesis has been intensively investigated for many years. Although basic research aiming at the cure of MS would cover broad ranges of subjects and use various methodologies, immunology-driven research could be regarded as being the most successful in the past, because of its contribution to the development of new drugs. Before T cell antigen receptor gene was cloned and sequenced, it was already known that adoptive transfer of lymphoid cells but not immune sera into syngeneic rodent could recapitulate the neuroinflammation associated with experimental autoimmune encephalomyelitis (EAE), an animal model of MS. Afterward, T cell lines and clones reactive to myelin basic protein (MBP)

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have been established, which are able to induce EAE upon adoptive transfer [1–3]. Similar MBP-specific T cell clones were isolated also from the peripheral blood of patients with MS [4, 5], allowing us to believe that pathogenesis of MS is mediated by autoreactive T cells. Because of ethical reasons, encephalitogenic potentials of human MBP-reactive T cells have been explored only ex vivo. However, in 2000, Roland Martin and his colleagues have reported that an MBP peptide analogue designed to inactivate MBP-specific T cells would activate those T cells and induce relapses of MS [6]. They failed to develop a new drug on the concept of altered peptide ligand (APL) but ironically revealed that MBP could be a target autoantigen in MS. Peripheral blood T cells from patients with MS are also sensitized against other autoantigens, including proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG). Because of the presence of numerous antigenic epitopes recognized by autoimmune T cells in MS, antigen-specific therapy for MS is thought to be a challenge.

1.1.1 MS Disease Course

MS is described as a chronic inflammatory demyelinating disease of the central nervous system (CNS). The term "chronic" does not always mean "progressive"; rather, the disease is mostly characterized by repetitive attacks of neurological deficits with various degrees of recovery. Attacks, also called relapses, typically occur at different ("multiple") CNS locations and at different ("multiple") times [7]. Clinically, each attack is usually visualized as lesion(s) or plaque(s) by magnetic resonance imaging of the brain or the spinal cord. MS is not a so-called common disease, like diabetes or cancer; however, it is the most common neurologic disease in young adults in Western countries. Moreover, epidemiological studies suggest that it is increasing worldwide. Its prevalence among the Japanese population has increased by more than tenfold within a few decades [8, 9]. The reason for this increase is unclear, but environmental factors may be involved (discussed later). Our knowledge of MS has progressed according to our general knowledge of medicine and biology [10]. The etiology of MS has been a mystery for a long time, but the critical role of the immune system is now well accepted.

Although the disease course for most patients usually starts with relapsing-remitting type (RRMS), it typically transitions into secondary progressive type (SPMS). SPMS is characterized, clinically, by slowly progressive neurological deficits without recovery and is usually accompanied by a decreased rate of relapses. Some patients initially experience a progressive course without any episodes of relapse (i.e., primary-progressive MS or PPMS). Recently, a simple, up-to-date version of the clinical course classification has been proposed as follows [11]: (1) RRMS and (2) progressive course. These two courses can co-occur with different contributions in each patient and clinical stage.

Based on numerous studies, the following basic theory explaining these two conditions has been proposed: (1) relapse and remission are controlled mainly by
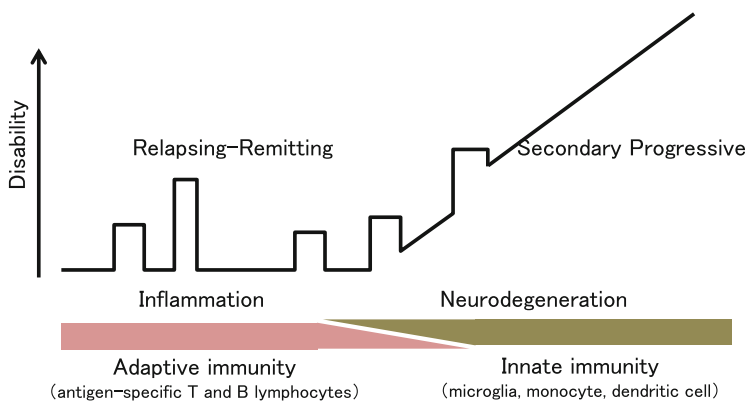
Fig. 1.1 Clinical course of MS and a proposed pathomechanisms. At the stage of Relapsing-Remitting course is driven by the adoptive immunity with the central role of CD4+ helper T cells, whereas later stage of secondary progressive disease is driven mainly by innate immunity including brain-resident microglia, monocytes (Modified from Ref. [12])

the adaptive immune system, in which CD4$^+$ T cells play a pivotal role, and (2) progression is less dependent on adaptive immunity, and more influenced by the innate immune system, in which microglia, monocytes, and dendritic cells serve decisive roles (Fig. 1.1) [12, 13]. Although this is still a working hypothesis, accumulating evidence supports the basic concept.

The mechanism of relapse has been extensively studied, resulting in the development of several effective drugs to reduce MS relapse rates, providing proof of concept regarding the understanding of relapse. However, the mechanism of progression has not been sufficiently elucidated, making it an important issue in the field of neuroimmunology. It should be mentioned that relapse and progression are not completely independent phenomena. Rather, it is suggested that they are fundamentally associated with each other [14]. Very recently, Oki, Raveney, and Yamamura have revealed that CD4$^+$ T cells expressing transcription factor Eomes are involved in the pathogenesis of chronic EAE model and SPMS [15]. As such, chronic neuroinflammation associated with microglial activation is under control of inflammatory T cells which appear to be distinct from Th1 or Th17 cells.

1.2 The Immunology of Relapse

As mentioned above, the disease course for the majority of MS patients starts with a clinical pattern of RRMS [16]. Let us start by describing the importance of helper T (Th) cells in the pathogenesis of MS, especially in relapses.

1.2.1   EAE: A Model of MS

For decades, the mechanisms of MS relapse have been studied extensively using the experimental autoimmune encephalomyelitis (EAE) animal model [17]. Around 40 years ago, it was shown that the injection of a defined protein of the myelin sheath (e.g., myelin basic protein (MBP)) combined with an adjuvant causes either acute or chronic EAE (active EAE) in recipient animals [18]. Encephalitogenic potentials of proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) were demonstrated much later until synthetic peptides were available for EAE studies. EAE can be induced by adoptive transfer of in vitro activated CD4+ Th cells that are specifically reactive to myelin antigens (passive EAE) [19]. The disease course of EAE, such as monophasic or chronic progressive, depends on the genetic background or antigen type, reminiscent of the variety of clinical courses of MS. In 2009, Pollinger et al. reported that a new transgenic mouse model showed a relapsing-remitting course of EAE [20]. Because Th cells play decisive roles in the pathogenesis of EAE, extensive studies have examined human Th cells in MS.

Some evidence shows the role of Th cells in the pathogenesis of MS. For example, Th cells that are reactive to myelin antigens can be detected in patient blood samples. Histopathological studies of lesions have revealed the accumulation of oligoclonal Th cells [17], suggesting that T cells reactive to specific antigens are recruited to and expand in the lesions (antigen specificity). These and other findings support the autoimmune nature of the disease, with a special role of Th cells in the pathogenesis of MS. However, the antigen(s) recognized by such oligoclonal T cells are not yet identified and are a topic of further investigation.

1.2.2   Genetic Factor

According to epidemiological data, the concordance rate in MS of monozygotic twins is about 30 %, showing a contribution of genetic factors. The most significant genetic risk factor for MS is major histocompatibility complex (MHC) class II (HLA-DR and HLA-DQ), and MHC class I is additionally involved. In 2011, a genome-wide association study of 9772 Caucasian individuals was reported [21]. Association of MHC classes I and II, IL-2 receptor, and IL-7 receptor was confirmed. Moreover, 29 newly identified genes demonstrating associations were involved in CD4+ Th cell function or differentiation, which are related to adaptive immunity. In addition, about a half of the associated genes were the same as those associated with other autoimmune diseases such as type 1 diabetes, Crohn's disease, and rheumatoid arthritis. These results indicate that MS is primarily an autoimmune disease, in which the role of adaptive immunity is related to genetic factors, suggesting the adaptive immune component is causal but not a result of the disease. However, the contribution of each allele was small, suggesting substantial contributions of environmental factors.

There are many potentially useful directions for further investigation. Genome-wide association studies evaluate only common variants. There is a possibility that minor variants also play roles in MS. Additionally, the genetic backgrounds that influence the disease phenotype of MS (MS heterogeneity) should be examined. Other important questions are related to the interaction between environmental factors and genetic factors and the role of gene-gene interactions (i.e., epistasis). Moreover, it is not yet clear whether different ethnic groups, such as the Japanese population, share the same genetic risks with Caucasians.

1.2.3 The Mechanism of Relapse

The initiation mechanisms of EAE (and presumably MS relapse as well) are usually divided into the following three stages: (1) activation of autoreactive CD4+ T cells in the peripheral lymphoid organs, (2) migration of activated T cells through the blood-brain barrier (BBB) to the CNS, and (3) events involved in CNS tissue damage [7]. The last process involves the infiltration of various cell types, such as monocytes or CD8+ T cells.

Such autoreactive, invading T cells are termed pathogenic or encephalitogenic T cells. In the first stage, T cells react to various CNS components, presumably including myelin antigens such as MBP and may become activated. The mechanisms of activation are not completely understood, but it is thought to occur after microbial infection or exposure to other inflammatory stimuli, which activate the innate immune system. Two potential underlying mechanisms have been proposed. The first, called molecular mimicry, considers that autoreactive T cells cross-react with an infectious agent. The second, referred to as bystander activation, assumes that autoreactive T cells are activated as a result of nonspecific inflammatory events that occur during infection [7].

Activated T cells may then migrate to the CNS by crossing the BBB, which is a functional unit that sequesters the CNS from the systemic environment for CNS homeostasis. The topic of BBB will be discussed in Chap. 4. The effectiveness of drugs that suppress MS relapse provides proof of concept supporting the importance of the second step. For example, natalizumab, a humanized anti-VLA4 integrin antibody, blocks migration of T cells into the CNS at the BBB level, whereas fingolimod, an S1P1 receptor antagonist, traps the T cells in the lymph nodes. Both drugs reduce relapse rates, emphasizing the importance of the T cell migration step in relapse [22, 23].

1.3 What Are Pathogenic T Cells?

1.3.1 From Th1/Th2 Dogma to the Discovery of Th17 Cells

Since the 1990s, there has been a widely accepted dogma in immunology in which Th cells are categorized into two functionally antagonistic subsets: Th1 and Th2 [24]. Th1/Th2 balance theory was proposed to describe the immune mechanism of autoimmune diseases and allergies. According to the established dogma, EAE/MS is a representative Th1 disease, meaning that Th1 cells predominate over Th2 cells. Th1 (which produces interferon-γ: IFN-γ) but not Th2 (which produces interleukin (IL)-4) cells are regarded as pathogenic in EAE/MS. In fact, treating MS patients with IFN-γ worsens the disease, providing direct evidence of the pathogenic role of IFN-γ in MS [25]. Moreover, an altered peptide ligand of MBP administered to MS patients in a phase 2 clinical trial revealed a potential encephalitogenic effect via the activation of Th1 cells [6].

In 2003, a breakthrough was achieved as described in a report by Cua et al. [26]. - IL-12 is a critical cytokine to induce Th1 cells. However, IL-12-deficient mice, which lack Th1 cells, developed EAE, suggesting that Th1 cells are unrelated to EAE. Instead, IL-23-deficient mice were completely protected from EAE. IL-23 is similar to IL-12, but important to induce IL-17 production, instead of IFN-γ. To sum up the results of several studies, the IL-23-IL-17 pathway, which induces pro-inflammatory cytokines, such as IL-6, tumor necrosis factor-α (TNF-α), and granulocyte-macrophage colony-stimulating factor (GM-CSF), is critically involved in the pathogenesis of EAE [27]. A few years later, IL-17-producing Th cells were shown to be induced in vitro by IL-6 and TGF-β in mice and to express the characteristic transcription factor RORγt; they were classified as a new Th subset that is fundamentally different from Th1 and Th2 cells [28]. The number of cells needed to induce EAE in an adoptive transfer model was much smaller in Th17 cells than in Th1 cells, implying strong pathogenicity of Th17 cells [29]. Interestingly, however, IL-17-deficient mice are only partially protected from EAE [30]. Moreover, the therapeutic effect of IL-17 blockage was moderate [31], suggesting an insufficient pathogenic role of IL-17.

1.3.2 Diverse and Flexible Th17 Cells

Recent studies have revealed that Th17 cells are more diverse in function (i.e., they exhibit heterogeneity) and more flexible during development (i.e., they are plastic) than originally thought. The possibility of the in vivo transition between regulatory T cells (Treg) and Th17 cells has been reported. Zhou et al. reported that Tregs could be converted into Th17 cells in vivo [32]. Conversely, another report has shown that IL-17-producing Th cells could exert regulatory function [33]. Similarly, phenotypic changes for Th17 cells and Th1 cells have been reported. IL-17A

reporter mice were generated to track IL-17A expression in vivo [34]. EAE of the reporter mice depended on the ex-TH17 cells; IFN-γ and other pro-inflammatory cytokines were produced exclusively by IL-17-producing cells before conversion.

The epigenetic mechanism underlying such Th cell plasticity was examined by generating genome-wide histone H3 lysine 4 (H3K4) and lysine 27 (H3K27) trimethylation maps for various Th cell subsets [35]. Genes encoding transcription factors for Th cell differentiation, such as T-bet, Foxp3, or Rorc, exhibited a broad spectrum of epigenetic states, resulting in high plasticity of differentiated effector T cells.

1.3.3 Pathogenic and Nonpathogenic Th17 Cells

How do such heterogeneity and plasticity of Th17 cells connect to pathogenic and nonpathogenic phenotypes? In one study, Th17 cells generated in response to IL-23 signaling, independently of TGF-β signaling, efficiently induced EAE [36]. These pathogenic Th17 cells co-expressed RORγt and T-bet. Another group has reported that TGF-β3 together with IL-6 induces pathogenic Th17 cells [37]. TGF-β3 was produced by developing Th17 cells in an IL-23-dependent manner, again implying a critical role of IL-23. Th1-related T-bet may be a key factor in inducing the pathogenic functions of Th17 cells, although another study did not reproduce these results [38]. Several factors probably cooperate to determine the fates of various Th17 cell types. Supporting this hypothesis, a study by Kuchroo et al. demonstrated a dynamic regulatory network with as many as 39 regulators controlling Th17 cell differentiation [39]. A model has been proposed in which mouse Th17 cells are related to a wide spectrum of effector phenotypes (Fig. 1.2) [40]. In this model, TGF-β and IL-23 play major antagonistic roles in shifting the Th17 phenotype toward regulatory (nonpathogenic) and alternative (pathogenic) phenotypes, respectively, although other cytokines also contribute to the fine-tuning of the spectrum. The nonpathogenic Th17 subtype is characterized by the production of IL-9 and IL-10 and the expression of c-Maf and AhR, whereas the pathogenic Th17 subtype is distinguished by IFN-γ, GM-CSF, and IL-22 signatures with T-bet expression. Two simultaneously published papers suggested that GM-CSF is required for the acquisition of pathogenicity in Th17 cells [41, 42], supporting this model.

1.3.4 Pathogenic Th17 Cells in MS

Using MS patient samples, a potentially pathogenic role of human Th17 cells has been reported. The frequency of Th1 and Th17 cells in the cerebrospinal fluid (CSF) of patients with RRMS during relapse has been investigated [43]. Both Th1 and Th17 cells are significantly more abundant in the CSF than in the peripheral blood.
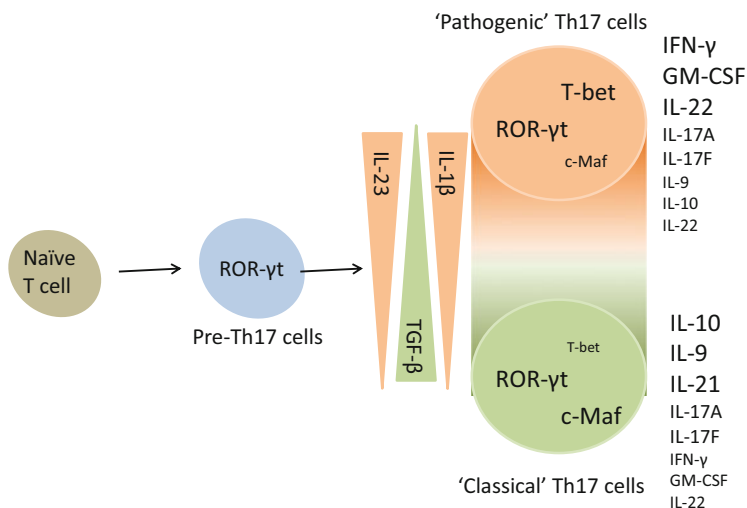
Fig. 1.2 Spectrum view of Th17 cells. pre-Th17 cells which express RORgt will be skewed into either 'classical' or 'pathogenic' depending on different cytokine milieu. Classical type of Th17 cells are induced by abundant TGF-b to produce IL-10 etc, play an important role in tissue homeostasis. On the other hand, pathogenic type of Th17 cells are induced by IL-23 or IL-1b to produce IFN-g or GM-CSF etc, exert an autoimmunity as shown in EAE model (Modified from Ref. [10])

Interestingly, adhesion molecules such as CD49d, CD6, and the melanoma cell adhesion molecule MCAM/CD146, which mediates T cell attachment to endothelial cells, were expressed more abundantly in Th17 cells than in Th1 cells. Together with other features such as the high proliferative capacity and reduced susceptibility to suppression, these Th17 cells are regarded as pathogenic. Another group has reported that lymphocytes from the peripheral blood of MS patients in relapse show an increased propensity to expand into IFN-γ-producing Th17 cells than those of controls [44]. These cells preferentially crossed an in vitro BBB model [45]. In addition, the importance of IL-1 and IL-12 in the induction of pathogenic IL-17/IFN-double-producing phenotype has been emphasized [46]. Another line of research defines the pathogenic human Th17 cell subset based on chemokine receptor expression. In one study, a fraction of CCR6+CXCR3hiCCR4loCCR10-CD161+ cells expressing a P-glycoprotein (multidrug resistance type 1 protein: MDR1) displayed a pro-inflammatory phenotype with a transcriptional signature akin to that of pathogenic mouse Th17 cells [47]. Such MDR1+Th17 cells are enriched and activated in the guts of patients with Crohn's disease and are refractory to glucocorticoids, possibly conferring a treatment-resistant phenotype. We reported that CCR2+CCR5+Th cells exhibit an IL-17/IFN-γ-double-producing phenotype and are enriched in the CSF of relapsing MS patients. Interestingly, this subset possessed a high BBB invasive capacity when activated in vitro [48].

1.3.5 Th Cell Types and Heterogeneity of MS

Following the discovery of Th17 cells, new Th subsets, such as IL-9-producing Th9 or IL-22-producing Th22 cells, were recognized. Interestingly, in EAE, different Th subsets cause different disease phenotypes. For example, in vitro induced Th17, Th1, Th2, and Th9 cells cause EAE with different pathologies, both with respect to severity and anatomy [49]. Other studies have shown that Th1 cells are more likely to induce a classical-type EAE, which mainly affects the spinal cord, whereas Th17 cells tend to induce an atypical-type EAE characterized by the presence of brain or cerebellar lesions [50–52]. Collectively, these studies suggest that various Th phenotypes mediate CNS inflammation, possibly via different immunological mechanisms. There is a good possibility that heterogeneity in the anatomical distribution of MS patients is related to variation in Th subsets.
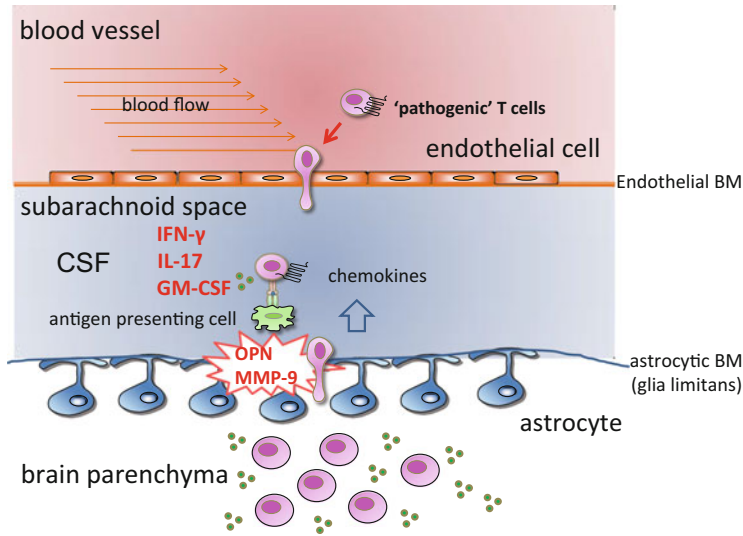
1.4 Transmigration of Pathogenic T Cells

1.4.1 The Blood-Brain Barrier

The pathogenicity of T cells is fundamentally coupled to the invasion capacity into the CNS through the BBB. The important role of the BBB in neuroimmunology is described in Chap. 4, and we will not go into the details here.

The transmigration of T cells into the CNS is a multistep process characterized by a series of sequential steps that proceed in the following order: rolling, activation, arrest, crawling, and transmigration. The transmigration step can be further subdivided into (1) transmigration from blood vessels to the perivascular space (where CSF is filled) and (2) transmigration from perivascular space to the CNS parenchyma (through glia limitans formed by astrocytic end feet). The precise mechanism of transmigration has not yet been elucidated; however, the development of multicell culture systems recapitulating the BBB is beginning to uncover the molecular mechanism regulating this step [53, 54]. Moreover, a live cell imaging technique has been developed, enabling us to observe in vivo trafficking of lymphocytes at the BBB during the course of EAE [55]. T cell-antigen-presenting cell interactions appear to be necessary for migration into the CNS, suggesting an antigen-specific process is involved in this step (Fig. 1.3).

1.4.2 Key Molecules Involved in MS Relapse

One of the key factors in the transmigration of T cells into brain parenchyma is matrix metalloproteinases (MMPs) [56, 57]. MMPs are a family of proteolytic enzymes capable of remodeling and degrading the extracellular matrix and have

Fig. 1.3 A model in which 'pathogenic' T cells migrate from periphery to brain parenchyma, through subarachnoid space, triggering MS relapse. With activation by putative myelin autoantigen such as MBP, 'pathogenic' T cells gain the capacity to pass through the BBB. MMP-9 presumably degrades parenchymal basement membrane of the BBB, and OPN augments CNS inflammation

important roles in development and physiology. Previous studies have revealed that several MMPs, including MMP-2, MMP-7, MMP-8, MMP-9, and MMP-14, are upregulated in the serum, CSF, and brain tissues from MS patients [58]. In particular, the role of MMP-9 (gelatinase B) has been emphasized [59–61].

Another key molecule mediating CNS inflammation in MS is osteopontin (OPN). The involvement of OPN in EAE and MS was first demonstrated by Steinman and colleagues [62]. OPN is a member of a family of small integrin-binding proteins, termed SIBLING proteins, which execute various biological functions, including inflammation [63]. The injection of OPN induces relapses in the EAE model, and OPN knockout mice are protected against CNS inflammation, suggesting a critical role of this molecule in EAE. OPN transcripts are also greatly upregulated in human MS lesions [64], and increased OPN levels in plasma in RRMS patients have been reported [65–68]. Moreover, OPN binds to α4β1 integrin on T cells to stimulate expression of pro-inflammatory mediators, including Th1 and Th17 cytokines, and promotes the survival of autoreactive T cells by inhibiting apoptosis [69, 70]. As natalizumab is an inhibitor of α4 integrin, it can block OPN signaling, which may be one mechanism for preventing relapses [62]. OPN is produced by macrophages, microglia, astrocytes, and CCR2+CCR5+ T cells [48].

1.5 New Players in Cell-Mediated Immunity in MS

1.5.1 Commensal Gut Microbiota and Gut Immunity

As previously described, the number of MS patients in Japan has increased dramatically during a single generation [8, 9]. It is difficult to explain such a rapid increase by improvement of diagnostic tool or the established environmental risk factors such as vitamin D, smoking, Epstein-Barr virus, and others [71]. Recent developments in the field of gut immunity and commensal microbiota are beginning to provide important clues [72].

The mammalian immune system plays an essential role in maintaining homeostasis with gut microbial communities. At the same time, resident bacteria profoundly shape mammalian immunity and contribute to the mutualistic relationships between bacteria and hosts. It is not an exaggeration to say that gut microbiome is a kind of ecosystem.

Many studies have examined the role of gut microbiota and EAE. The development of regulatory T cells and Th17 cells depends on the gut microbiota. Our group and others have reported that changing the microbiota of an experimental mouse model actually changes the disease course of EAE [73, 74]. Even one strain of bacteria could influence the disease course. A segmented filamentous bacterium was shown to be critical to the induction of Th17 cells in mice and contributed to EAE [75, 76]. In a spontaneous CNS inflammatory mouse model, the disease did not develop under germ-free conditions but showed signs only after commensal microbiota were induced [77]. These mouse studies indicate the important role of microbiota in the pathogenesis of MS [78]. Actually, dysbiosis of disease cases (abnormal microbiome structure or balance) has been reported in various autoimmune diseases such as inflammatory bowel diseases [79]. Just recently, our group proved moderate dysbiosis of Japanese RRMS patients, with a striking depletion of species belonging to *Clostridia* XIVa and IV clusters [80]. Interestingly, the other species classified in the same clusters were reported to inducing Treg [81]. However, the functional significance of the depleted species is needed to be elucidated.

1.5.2 Innate Lymphocytes

Recently, an increasing number of studies have examined a group of immune cells that link innate and adaptive immunity. Natural killer, or NK, cells, γδ T cells, innate lymphocytes (ILCs), invariant NKT (iNKT) cells, and mucosal-associated invariant T cells (MAIT cells) are members of this group.

Unlike conventional αβT cells, which possess unique T cell receptors, they basically lack such antigen specificity. For example, iNKT cells and MAIT cells are characterized by very limited T cell receptor diversity owing to their expression of a single α-chain (Vα24-Jα18 in human iNKT cells and Vα7.2-Jα33 in human

MAIT cells). One important feature of ILCs is the ability to produce various cytokines.

iNKT cells are a unique subset of lymphocytes that recognize glycolipid antigens presented by CD1d [82]. α-Galactoceramide (α-GalCer) is an antigen of iNKT cells that activates iNKT cells to produce various cytokines, both pro-inflammatory and regulatory, including both IFN-γ and IL-4. In MS, a decreased frequency of iNKT cells [82] and a possible regulatory role of iNKT cell via IL-5 have been reported [83]. An α-GalCer analogue called OCH, which has a shorter sphingosine chain, was discovered to selectively stimulate IL-4 production from iNKT cells, ameliorating the disease course of EAE [84]. Various preclinical studies have led to drug development targeting MS. OCH is now under a clinical trial including healthy subjects and patients with RRMS.

MAIT cells are enriched in the gut (as can be inferred from their name, mucosal associated) but are represented at a substantial frequency (several %) in blood lymphocytes in humans [85]. In mice, MAIT cells exert regulatory roles in EAE, suggesting a similar role in MS [86]. MAIT cells are decreased in the peripheral blood [87] and are detected in MS lesions, although the on-site role has not been elucidated. MAIT cell antigens have long been enigmatic. However, it was recently reported that vitamin B2 derivatives function as MAIT cell antigens. Intriguingly, they are produced by the gut microbiome [88], providing an explanation for the lack of MAIT cells in germ-free mice. Regarding NK cells, it has been reported that NK cells of MS patients in remission produce IL-5 and exert a supportive effect on the maintenance of remission [89].

1.5.3   Role of B Cells

There is a growing body of evidence that suggests a prominent role of B cells in MS pathogenesis. Intrathecally synthesized oligoclonal bands in the CSF of MS patients have been an important diagnostic hallmark [90]. Histopathological examination has revealed that the accumulation of IgG or a complement is most often observed in MS lesions [91]. B cell depletion by the anti-CD20 antibody rituximab reduces the number of MS relapses [92]. Moreover, plasmapheresis and immunoabsorption therapy, which deplete humoral factors including antibodies, is beneficial in a subset of patients [93]. B cells can contribute to MS pathogenesis in multiple ways, including antigen-presenting cells, cytokine producers, and antibody producers. Here, we describe a few examples. Meningeal lymphoid follicle structures have been reported in a subset of SPMS patients [94]. They contain germinal centers, in which affinity maturation and clonal expansion of B cells occur inside of the CNS, probably affecting the progressive course of the disease. BAFF (B cell-activating factor belonging to the TNF family) is a factor that promotes the survival and development of B cells. It has been reported that the serum BAFF level of MS patients increased after the administration of IFN-β therapy [95]. There is discussion regarding why some patients who receive IFN-β exhibit increased disease

activity [96]. One explanation is that an increased BAFF level promoted B cell-mediated autoimmunity, which increased disease activity.

1.6 Concluding Remarks

In this chapter, we focused on cell-mediated immunity of MS and mainly described the role of pathogenic T cells in MS pathology. Numerous studies have been performed on this topic, not only revealing various roles of T cells in MS but also enabling the development of drugs to treat RRMS. We would like to mention here that other cell subsets, including those that we could not describe here, including CD8+ T cells and monocytes, are also involved in MS. In particular, the role of innate immune cells in the progressive phase of MS is a particularly interesting topic.

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