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Multiple sclerosis pathogenesis: missing pieces of an old puzzle

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Abstract: Traditionally, multiple sclerosis (MS) was considered to be a CD4 T cell-mediated CNS autoimmunity, compatible with experimental autoimmune encephalitis model, which can be characterized by focal lesions in the white matter. However, studies of recent decades revealed several missing pieces of MS puzzle and showed that MS pathogenesis is more complex than the traditional view and may include the following: a primary degenerative process (e.g. oligodendroglial pathology), generalized abnormality of normal-appearing brain tissue, pronounced gray matter pathology, involvement of innate immunity, and CD8 T cells and B cells. Here, we review these findings and discuss their implications in MS pathogenesis.

Keywords: degeneration; heterogeneity; inflammation; multiple sclerosis; neuropathology; oligodendrocyte; pathogenesis.

Introduction

Multiple sclerosis (MS) is the most common non-traumatic neurological cause of disability in young adults. After more than one century, pathogenesis of MS is not fully understood.

The history of MS shows that early researches on MS were extremely influenced by concomitant studies on post-vaccine encephalitis (Rivers et al., 1933, Schwentker and Rivers, 1934; Rivers and Schwentker, 1935; Freund et al., 1947; Baxter, 2007; Ransohoff et al., 2015). Considerable similarities between MS and post-vaccine encephalitis were more appreciated following the development of experimental autoimmune encephalitis (EAE), the animal model of post-vaccine encephalitis (Kabat et al., 1947; Morgan, 1947; Baxter, 2007).

The EAE model can be produced by different methods that can provide a pool of CNS antigen-specific CD4 T cells in blood (Lassmann, 2007). The EAE model represents a wide range of MS characteristics, e.g. lesions disseminated in time and space, lesions more detectable in spinal cord, perivascular distribution of lesions, abnormal inflammatory profile of blood and cerebrospinal fluid (CSF; Adams and Kubik, 1952). In addition to the EAE model, considering CNS as an absolute immune-privileged organ (Galea et al., 2007; Shechter et al., 2013) fortified the peripheral T cell-mediated autoimmunity hypothesis of MS.

According to the traditional view, myelin-reactive CD4 T cells that are escaped from central tolerance in the context of a defective peripheral tolerance can be primed following encountering CNS-sequestered antigens, molecular mimicry, or bystander activation (Olson et al., 2001; Steinman and Zamvil, 2006; Harkiolaki et al., 2009; Munz et al., 2009; Ji et al., 2010; Dendrou et al., 2015). Then, activated autoreactive T cells enter the CNS through a breach in the blood-brain barrier (BBB) or the blood-CSF barrier and initiate an inflammatory attack against the myelin, which results in the formation of distinct lesions in the white matter (WM) of MS brains (Kivisakk et al., 2009; Shechter et al., 2013).

Thanks to the extensive research on EAE, some immunomodulating drugs, e.g. glatiramer acetate (Teitelbaum et al., 1971), mitoxantrone (Lublin et al., 1987), and natalizumab (Yednock et al., 1992), which are highly effective in reducing relapse rate and inflammatory activity of the disease, were discovered. However, as research on MS and EAE model proceeds, an increasing body of evidence shows that the two conditions are not the same. Indeed, studies revealed that several immunomodulating agents, e.g. monoclonal anti-tumor necrosis factor antibody cA2 (van Oosten et al., 1996), could suppress EAE development but are not effective to ameliorate MS severity.

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Overall, discoveries over the last decades revealed that the EAE-derived explanation of MS could not cover all dimensions of the disease pathophysiology and that

1. MS lesions are not a uniform consequence of CD4 T cell-mediated autoimmunity; lesions are heterogeneous, and CD8 T cells and B cells are involved more than expected;
2. MS is not a disease exclusively affecting the WM; the gray matter (GM) is vastly diseased even in early stages of the disease;
3. CNS pathology in MS is not confined to lesions; normal-appearing brain tissue (NABT) is largely abnormal;
4. MS is not a disease with a pure autoimmune pathology that is originated outside the CNS and produces vasocenteric lesions; non-autoimmune processes inside the CNS as oligodendrocytopathy may initiate the formation of non-vasocenteric lesions as well.

Here, we review the progresses made in recent decades to provide a discussion on the inflammatory and degenerative sides of MS pathogenesis in WM and GM to show that MS pathogenesis is more complex than a CD4 T cell-mediated CNS autoimmunity, leading to the formation of focal and homogeneous demyelinating lesions.

WM in MS

MS lesions are heterogeneous: a review of recent neuropathological studies

MS is generally believed to be a heterogeneous disease in terms of clinical phenotype, genetics, radiological findings, and response to therapy. The seminal study by Lucchinetti and colleagues (Lucchinetti et al., 2000) provided pathological substrates for MS heterogeneity and showed that the target of injury and demyelinating mechanisms may differ among patients. The study showed four different immunopatterns of active lesions based on oligodendrocyte destruction, remyelinating capacity, involvement of humoral immunity, and distance of lesions from vessels. Immunopattern I lesions are well bordered and perivascular with equal loss of all myelin components, lack of complement and immunoglobulin (Ig) deposition, in a background of infiltrated T cells and activated macrophages/microglia. In addition, these lesions show a variable loss of oligodendrocytes at the active lesion edge with subsequent reappearance in inactive center. Newborn oligodendrocytes resheath thin layers of myelin around axons in lesion, so-called remyelinated shadow plaque. Immunopattern II is the most common type of active lesions and is distinguished from pattern I by deposition of Ig and complement proteins. The ill-defined immunopattern III lesions in contrast to the two first patterns are not centered on vessels. Lesions of immunopattern III contain infiltrating T cells and macrophages without deposition of humoral immunity proteins. Strikingly, there is a considerable loss of oligodendrocytes with morphological features of apoptosis at active plaque edge. One other exclusive feature of immunopattern III lesions is the preferential loss of myelin-associated glycoprotein (MAG), which is located in distal periaxonal myelin layers, suggesting a primary distal dying-back oligodendrocytopathy (Rahmanzadeh et al., 2018). Immunopattern IV lesions are rare and are characterized by non-apoptotic death of oligodendrocytes in peri-lesional WM without reappearance in inactive center.

Therefore, at least two distinct demyelinating processes may be responsible for lesion genesis in MS; in one the primary target of injury is suggested to be oligodendrocytes and in the other myelin components.

The WM lesions of EAE animals resemble MS lesions of immunopatterns I and II (Barclay and Shinohara, 2017), and EAE cannot illustrate pathophysiology of MS in patients with immunopattern III and IV lesions. In this respect, Felts et al. (2005) introduced an animal model, named LPS model, in which local injection of bacterial lipopolysaccharide (LPS) into the spinal cord WM produces focal WM pathology resembling pattern III lesions.

Other studies (Barnett and Prineas, 2004; Henderson et al., 2009) on early MS lesions obtained from patients with early MS who died during or very close to a relapse attributed four immunopatterns to different stages of lesion development, thereby challenging the heterogeneity of MS lesions, and suggested three stages during the temporal evolution of a lesion: (1) extensive oligodendrocyte apoptosis without considerable inflammation and demyelination along with the presence of activated microglia (pattern III-like region); (2) areas with active demyelination that include degenerating myelin and considerable quantity of activated macrophages/microglia with very low quantity of T cells and other inflammatory cells; (3) recently demyelinated region with pronounced quantity of myelin-laden macrophages, presence of oligodendrocyte precursor cells and early signs of remyelination, and high quantity of lymphocytes, along with Ig and complement deposition (pattern II-like region). However, further studies using longitudinal biopsy/autopsy samples of MS patients revealed that immunopattern of MS lesion may persist over time (Metz et al., 2014).

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Rodriguez, through repeated electron microscopic study of active lesions taken from patients with early MS, showed that the oligodendrocytopathy and myelin distortion, e.g. degenerating inner cytoplasmic channels of myelin, may precede infiltration of inflammatory cells, and it has been suggested that this sublethal oligodendrocyte injury may be reversible (Rodriguez and Scheithauer, 1994; Cui et al., 2017).

A recent paper (Rahmanzadeh et al., 2018) comprehensively reviewed neuropathological studies showing that oligodendrocytopathy may precede inflammatory events in the formation of MS lesion and suggested oligodendrocyte injury independent of CNS autoimmunity and viral infection of myelin cytoplasmic channels as possible underlying mechanisms for demyelination with preferential MAG loss in MS lesions.

Recently, Kuhlmann and colleagues (Kuhlmann et al., 2017) proposed a simplified classification system to represent the temporal development of MS lesions. Based on this updated system, lesions will be classified into three main subtypes (active, mixed active/inactive, and inactive) with or without ongoing demyelination. Lesions with macrophages/microglia throughout the lesion area are considered to be 'active'. 'Inactive' lesions are considered to represent the late stages of lesion development and are completely lacking macrophages/microglia. 'Mixed active/inactive' lesions contain an inactive center and an active rim of macrophages/microglia at the lesion border. As the demyelinating activity within active and mixed active/inactive lesions could be ongoing or passed, these lesions could further be classified into 'demyelinating' or 'post-demyelinating'.

In addition to a variety of demyelinating processes and targets of injury, ample evidence show that there is heterogeneity in remyelinating capacity as well. Remyelination of a lesion may be complete, so-called shadow plaque, or partial in remyelinated shadow areas. It has been shown that the extent of remyelination of MS lesions may differ among patients and also in various CNS regions of a given patient (Patrikios et al., 2006; Patani et al., 2007). In addition, although in most of the patients a variable oligodendrocyte loss in active demyelinating areas is followed by repopulation of oligodendrocyte progenitor cells (OPCs) in inactive lesion center, in a minority of patients inactive areas of lesion similar to active demyelinating edge are totally empty of oligodendrocytes (Lucchinetti et al., 1999). Although the underlying mechanisms responsible for remyelination failure in MS have not been well determined, it has been shown that a defect in OPC migration to the site of pathology and also in OPC differentiation to myelinating oligodendrocytes may be involved (Kuhlmann et al., 2008; Boyd et al., 2013; Schultz et al., 2017).

Taken together, recent neuropathological studies show that

1. The pathology of MS is heterogeneous, and different mechanisms may underlie MS pathogenesis;
2. Heterogeneity among demyelinating lesions seems to be inter-individual, not intra-individual, and the immunopattern of MS lesion may persist over time;
3. The EAE model could not illustrate the MS pathophysiology of patients with lesions of immunopatterns III or IV;
4. Besides heterogeneity in demyelinating processes, there is a remarkable difference in remyelinating capacity among MS patients as well (Box 1).

Degenerative side of MS pathogenesis

Oligodendrocyte pathology

Oligodendrocyte destruction is an important neuropathological finding, which was detected frequently in MS samples and was conceptualized to be a result of autoimmunity attack against myelin (Bruck et al., 1994; Kuhlmann et al., 1999; Lucchinetti et al., 1999). The strongest evidence supporting this view come from observations showing the presence of myelin basic protein (MBP)-specific T helper cells in MS brains (Oksenberg et al., 1993). Furthermore, MBP peptides coupled with HLA-DR2 on macrophages at sites of demyelination have been detected in MS lesions (Krogsgaard et al., 2000).

However, recent neuropathological observations show that pathology may spread from oligodendrocytes to myelin and suggest a primary oligodendrocytopathy (Rahmanzadeh et al., 2018). In this regard, preferential loss of MAG, which is located in the innermost myelin layers adjacent to axons, in non-vasocenteric lesions of immunopattern III (Lucchinetti et al., 2000) may indicate a dying-back oligodendrocyte pathology (Lucchinetti et al., 2000; Henderson et al., 2009) that precedes inflammatory infiltration and myelin destruction (Barnett and Prineas, 2004; Henderson et al., 2009).

It was suggested that oligodendrocyte death and CNS autoimmunity may be two steps in MS pathology rather than a dichotomy, and in addition, it was hypothesized that autoimmunity may be secondary to oligodendrocyte pathology (Matute and Perez-Cerda, 2005; Stys et al., 2012). In this respect, several studies by inducing oligodendrocyte apoptosis in animals have investigated this hypothesis. Indeed, a recent study using a genetic

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Box 1: Sources of heterogeneity in MS.

According to the diagnostic criteria of MS (Thompson et al., 2018), any interplay of genetic and environmental factors able to produce CNS WM lesions disseminated in time and space may be labeled as MS. Therefore, MS, by definition, is a heterogeneous disease, especially in terms of clinical course, severity, and response to therapy.

The majority of MS patients shows a relapsing-remitting course at the beginning of the disease and then enters the progressive phase a few decades later. However, about 20% of MS patients show a gradual accumulation of disability from onset, called primary progressive MS. In addition, MS patients show a wide variety of severity from more benign forms to fulminant forms, e.g. Balo's concentric sclerosis and Margburg's MS variants, which may be highly fatal (Lublin et al., 2014).

Recent studies suggest that the heterogeneity among MS population in severity and clinical course may partly be answered by this fact that each pathology may affect different patients with varying extents. Indeed, it has been shown that although an early GM pathology may be the first presentation of MS in some patients (Calabrese and Gallo, 2009; Popescu et al., 2011) or an extensive pathology, which involving up to hundreds of gyral plaques, may affect some patients, a few cortical lesions may be detectable in other patients even in the late progressive phase (Kidd et al., 1999).

The heterogeneous response of MS patients to immunomodulatory therapies, e.g. IFN-β, glatiramer acetate, mitoxantrone, and natalizumab, is appreciated for a long time (Haghikia et al., 2013). The seminal study of Lucchinetti et al. (2000) shows that different immunopathogenic processes may be involved in lesion formation in different patients. Indeed, it has been shown that therapeutic plasma exchange was efficacious in patients containing immunopattern II lesions, while patients with lesions of other immunopatterns did not show any improvement in neurological complications (Keegan et al., 2005). In accordance, Stork et al. (2018) recently confirmed that patients with pattern III MS lesion do not respond to apheresis therapy. Furthermore, recently it has been shown that MS lesions of immunopatterns II and III may differ from immunopattern I in some CSF characteristics (Jarius et al., 2017). This study showed that OCBs are more prevalent and BBB integrity seems to be more preserved in patients with immunopattern I than the two other immunopatterns.

There is growing body of evidence suggesting that heterogeneity in different aspects of MS cannot be considered as a 'variety within an entity' (Lucchinetti et al., 2000; Barnett and Prineas, 2004). Indeed, as the neuropathological studies suggest, MS may be initiated by a CNS autoimmunity or a primary CNS degenerative process such as oligodendrocyte degeneration (Barnett and Prineas, 2004; Breij et al., 2008; Metz et al., 2014). Therefore, MS may more be a syndrome than a single disease entity. In parallel, neuromyelitis optica, which was long believed to be a form of MS, was distinguished from MS in the last decade, and it has been shown that the disease may be of an astroglial origin (Lennon et al., 2004; Lassmann et al., 2007; Lucchinetti et al., 2014).

model, in which oligodendrocyte apoptosis occurs due to expression of diphtheria toxin fragment A, showed that a late-onset demyelinating disease with characteristics of autoimmunity, e.g. infiltrating lymphocytes in CNS and myelin-specific T cells in peripheral lymphoid organs, may slowly develop over a long time (Traka et al., 2016).

Oligodendrocytes owing to unique biological properties are believed to be of utmost vulnerability to pathological conditions. High metabolic rate needed for production of high amount of myelin, high amount of intracellular iron, and lack of anti-oxidative agents may make oligodendrocytes susceptible to overwhelming oxidative stress (Thorburne and Juurlink, 1996). The need to high amount of energy for myelin production also makes them susceptible to ischemic events (Juurlink, 1997). The expression of numerous glutamate receptors such as AMPA (Tanaka et al., 2000), kainite (Alberdi et al., 2006), and NMDA (Karadottir et al., 2005) makes oligodendrocytes vulnerable to increased extracellular glutamate (Domercq et al., 2007). In addition, inflammatory cytokines are able to exert their deleterious effects on oligodendrocytes via death receptors expressed on their surface. The best example of this kind is the interaction of tumor necrosis factor (TNF)-α and receptor P55 that may lead to oligodendrocyte apoptosis in neuroinflammatory conditions (Jurewicz et al., 2005). In this regard, different pathological processes have been proposed to be the potential triggers of early oligodendrocyte pathology in MS lesions including viral infection (Itoyama et al., 1980), ischemia-hypoxia (Aboul-Enein et al., 2003), glutamate toxicity (Matute et al., 2001; Groom et al., 2003; Sanchez-Gomez et al., 2003), inflammatory mediators, reactive oxygen species, and impaired energy homeostasis of oligodendrocytes (Dowling et al., 1996; Bonetti and Raine, 1997; Trapp et al., 1999).

Axonal pathology

Works published by Ferguson's (Ferguson et al., 1997) and Trapp's (Trapp et al., 1998) groups using postmortem samples showed that there is an extensive axonal transection in active lesions and in lesser extents in expanding border of preexisting lesions and inactive ones. In keeping with pathological reports, magnetic resonance spectroscopy detected lower *N*-acetyl-aspartate (NAA) level (De Stefano et al., 2001), a marker of healthy neurons and

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axons, in MS lesions. In addition, diffusion tensor imaging (DTI) revealed a reduced integrity of axonal fibers (Inglese and Bester, 2010), which may indicate axonal injury in MS.

The extensive axonal pathology in active lesions was attributed to direct and indirect effects of inflammation. Inflammation may directly injure axons via secretion of proteolytic enzymes, cytokines, and free-radical species (Hohlfeld, 1997), compromising the mitochondrial respiration (Bo et al., 1994; Liu et al., 2001; Smith et al., 2002) and inducing the expression of neurotransmitters and their receptors (Lipton and Rosenberg, 1994; Pitt et al., 2000; Matute et al., 2001; Friese et al., 2014) and CD8 T cell-mediated cytotoxicity (Babbe et al., 2000). Furthermore, inflammatory processes in active lesions may be accompanied by edema that, in turn, via reduction of blood supply may injure neurons.

Although axonal injury is more extensive in active lesions, which are more detectable in relapsing-remitting MS (RRMS), it has been shown to be more symptomogenic in progressive MS in which there are no sufficient axonal fibers to compensate the ongoing axonal loss (Friese et al., 2014). As the disease proceeds, lack of neurotrophic supports from oligodendrocytes and myelin, e.g. myelin roles in axonal cytoskeleton integrity (Griffiths et al., 1998; Brady et al., 1999; Uschkureit et al., 2000; Lappe-Siefke et al., 2003), may partly be responsible for neurodegeneration in chronic lesions. In addition, innate immunity, which drives inflammation during disease progression, may perpetuate inflammation-induced mechanisms of axonal injury, especially mitochondrial failure and glutamate excitotoxicity (Groom et al., 2003).

In contrast, there is an increasing body of evidence suggesting that axonal injury may in part occur independent of focal demyelination. First, prominent axonal injury is evident in relapse-free less inflammatory primary-progressive form of MS (Kutzelnigg et al., 2005). Second, diffuse reduction of NAA level in normal-appearing white matter (NAWM) may be detected very early in RRMS when there is a low number of WM lesions. Third, immunomodulating therapy, initiated early in patients with RRMS or clinically isolated syndrome (CIS), could not halt the axonal pathology detectable in progressive stage (Kappos et al., 2009). In accordance, quantitative magnetic resonance imaging (MRI) studies show that the extent of axonal injury in NAWM cannot be correlated with WM lesion load and location (De Stefano et al., 2003). Furthermore, a longitudinal study using coupled magnetic resonance spectroscopy and T1-weighted MRI showed an increase in lipid level, indicative of axonal pathology, in advance of BBB rupture at the sites of future demyelinating lesions (Narayana et al., 1998).

It has been suggested that several mechanisms may be responsible for axonal injury independent of demyelination in MS. First, oligodendrocytes provide trophic support for neurons, and also, myelin has important role in maintaining the integrity of axons. Therefore, a preceding oligodendrocytopathy may cause axonal injury and neuronal demise via disrupted 'oligodendrocyte-neuron crosstalk'. Indeed, Oluich et al. (2012) showed that selective ablation of oligodendrocytes may lead to structural and functional disturbances in nodes of Ranvier and paranodes in areas with preserved expression of myelin proteins such as MAG and cyclic nucleotide phosphodiesterase. In addition, mice with disturbed expression of myelin proteins such as proteolipoprotein-null mice show axonal degeneration (Griffiths et al., 1998). Second, inflammatory cells, especially cytotoxic CD8 T cells, may attack neurons or oligodendrocytes and cause axonal injury (Bitsch et al., 2000; Neumann et al., 2002). Third, antibody- or complement-mediated axonal damage may occur in MS as autoantibodies against neuronal and axonal antigens, e.g. proteins around the Ranvier's nodes such as neurofascin (Mathey et al., 2007; Yan et al., 2014) and contactin-2 (Derfuss et al., 2009) and ion channels such as potassium channel KIR 4.1 (Srivastava et al., 2012; Brickshawana et al., 2014) and calcium-activated chloride channel anoctamin 2 (Hohlfeld et al., 2016a,b), have been detected in body fluid of MS patients. In addition, cytokine, excitotoxicity, and viral infections could also be considered as potential causes for primary axonal pathology in MS (Haines et al., 2011).

Inflammatory side of MS pathogenesis

As CD4 T cells are the main pathogenic inflammatory cells responsible for EAE, they were expected to be more involved in MS pathogenesis than other inflammatory cells (Steinman, 1996). Several observations augmented this concept. First, transfer of autoreactive CD4 T cells extracted from EAE animals is sufficient to produce many of the presentations of MS (Ben-Nun et al., 1981; Zamvil et al., 1985; Madsen et al., 1999). In addition, genetic surveys demonstrated that HLA-A2 alleles coding MHC class 2 regions strikingly increase the risk for MS (Olerup and Hillert, 1991; Krogsgaard et al., 2000). However, agents exclusively depleting CD4 T cells fail to considerably attenuate relapse rate and inflammatory activity of the disease (van Oosten et al., 1997; Hohlfeld and Wekerle, 2001), while the broader spectrum drugs with additional effects on other immune cells are more efficacious (Coles et al., 1999; Paolillo et al., 1999). Therefore, involvement

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of immune system in MS should not be confined to CD4 T lymphocytes.

CD8 T cells

Although the number of CD8 T cells is lower than half of CD4 T cells in blood and CSF of healthy subjects (Kivisakk et al., 2003), the former outnumbers the latter in MS lesions (Booss et al., 1983; Babbe et al., 2000) and in blood and CSF of MS patients (Jacobsen et al., 2002; Skulina et al., 2004; Junker et al., 2007). Furthermore, it has been shown that the axonal injury in MS lesions could be well correlated with the quantity of CD8 T cells but not CD4 T cells (Bitsch et al., 1999). In addition, it has been shown that an HLA-A3 allele that encodes MHC class 1 regions may independently double the risk for MS (Fogdell-Hahn et al., 2000; Burfoot et al., 2008).

These findings along with more effectiveness of drugs with additional effect on CD8 T cells, e.g. alemtuzumab and fingolimod, suggest a role for cytotoxic CD8 T lymphocytes in MS (Coles et al., 1999; Kappos et al., 2006).

It was suggested that CD8 T cells directly injure every cell expressing MHC class 1 including endothelial cells and microglia in healthy brains (Hoftberger et al., 2004) and all neuroectodermal cells in inflammatory milieu as MS lesions (Neumann et al., 1995; Hoftberger et al., 2004). Although the main mechanisms thereby CD8 T cells act remain yet unknown, it seems that direct cell contact-mediated lyse plays an important role (Friese and Fugger, 2005; Goverman et al., 2005). Indeed, it has been shown that in MS lesions, cytotoxic materials such as perforin and granzymes inside the CD8 T cells are polarized toward the oligodendrocytes and axons (Neumann et al., 1995). Besides, CD8 T cells via secretion of inflammatory mediators such as interferon (IFN)-γ and TNF-α may recruit and activate macrophages (Wallstrom et al., 2000; Laplaud et al., 2004). In accordance, it has been shown that both direct cytotoxicity and release of soluble mediators are required for the induction of EAE using MBP-specific CD8 T cells (Huseby et al., 2001).

It should be noted that although this paper discusses the destructive functions of CD8 T cells, their protective regulatory roles are reported in the literature as well (Antel et al., 1986; Tennakoon et al., 2006).

B cells and plasma cells

The oligoclonal immunoglobulin bands (OCBs) constitute the sole immunological element of MS diagnostic criteria (Thompson et al., 2018). However, the importance of Ig-producer B cells was not appreciated until recently that the dramatic effect of anti-CD20 monoclonal antibodies (Hauser et al., 2008; Kappos et al., 2011), e.g. rituximab and ocrelizumab, on inflammatory activity and relapse rate of MS patients was shown. In addition, the presence of B cells in perivasculare cuff and parenchyma of MS brains (Meinl et al., 2006) and also the deposition of Ig and complement on myelin sheaths in MS lesions of immunopattern II (Lucchinetti et al., 2000) highlight the importance of B cells in MS pathophysiology. B cells and plasma cells may exert their effects through different ways, antibody-mediated processes aimed at destructing the myelin, oligodendrocytes, axons, and neurons (Mathey et al., 2007; Derfuss et al., 2009; Yan et al., 2014) and antigen presentation to T helper cells.

In addition, CSF of MS patients is suggested to be extremely B cell-fostering, and germinal-center-like B cell-containing structures are shown in the meninges (Pashenkov et al., 2003; Krumbholz et al., 2005, 2006, 2007). In more details, increased amount of chemokines such as CXCL 13 in CSF may chemo-attract B cells into the CSF (Krumbholz et al., 2006; Hiepe et al., 2011); elevated amount of B cell-activating factor of the TNF family and a proliferation-inducing ligand may improve survival of B cells (Krumbholz et al., 2005; Mackay and Schneider, 2009); and the lymphotoxin-α overexpressed along outer layers of meningeal vessels (Corcione et al., 2004) may aggregate and reorganize B cells into lymphoid-like structures.

OCBs were detected in about 90% of patients with CIS and have been shown to be a prognostic factor for CIS transformation to MS (Tintore et al., 2001; Cameron et al., 2009).

Although the source of OCBs is not well determined until now, it has been shown that Ig transcriptome of CSF B cells is compatible with proteome of OCBs (Obermeier et al., 2008). This finding along with the observation that re-arrangement of Ig genes differs between B cells in CSF and blood may indicate that immunoglobulins are produced by B cells that undergo maturation and clonal expansion within CSF (Colombo et al., 2000). In parallel, it has been shown that B cells within CSF contain highly mutated Ig genes indicative of a response to CNS antigens (Andreau et al., 1998). Although the accurate identification of these antigens remains elusive, several autoreactive antibodies, especially against myelin proteins, have been detected so far (O'Connor et al., 2005).

B cells, similar to T lymphocytes, following activation secrete different sorts of cytokines. As a result, B cells, other than activating T cells via antigen presentations,

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may induce T cell differentiation as well. Although some B cell-secreted cytokines such as IL-6 and IL-17 may promote T cell differentiation toward Th1 and Th17 cell, some other cytokines such as IL-4 and IL-10 may augment Th2 responses (Lund, 2008). Therefore, B cells may have both pro-inflammatory and anti-inflammatory roles in MS. Indeed, although most B cell-targeting therapeutics, e.g. rituximab and ocrelizumab, substantially reduce inflammatory activity of the disease, atacicept trials (Kappos et al., 2014) show that depletion of wider range of B cell lineage may be deleterious as a subpopulation of B cells may have anti-inflammatory roles. In keeping with clinical trials, animal studies show that IL-10 secreted by B cells ameliorates EAE severity and has a critical role in post-relapse recovery (Fillatreau et al., 2002).

Of note, infection of B cells and plasma cells with Epstein-Barr virus (EBV) may be important for pathogenicity of B cells in MS. EBV infection may induce development of autoreactive B cells through various ways including cross-reactivity between EBV and CNS antigens, infecting the preexisting autoreactive B cells to increasing their survival and pathogenicity and bystander destruction of CNS by EBV-specific cytotoxic CD8 T cells (Pender and Burrows, 2014). Indeed, a recent analysis of CSF that evaluated the reactivity of CSF IgG to numerous proteins found that the two most reactivities were against EBV proteins EBNA1 and BRRF2. In parallel, examinations of MS brains showed the presence of EBV-infected B cells in MS lesions, meningeal follicles, and cervical lymph nodes (Serafini et al., 2014).

Involvement of innate immunity in MS

CNS-resident microglia and monocyte-derived macrophages, the main components of innate immunity in MS brains, through antigen presentation to T cells, secretion of inflammatory mediators, and myelin phagocytosis, are involved in the formation of MS lesions. Myelin- or lipid-laden microglia/macrophages are detected in high quantities in focal MS lesions of various stages. In addition, it has been shown that microglia/macrophages are diffusely activated throughout the NAWM in MS (Kutzelnigg et al., 2005). This generalized involvement of innate immunity is more pronounced in progressive MS and along with slowly expanding preexisting MS lesions seems to be partly responsible for disease progression and cortical atrophy in progressive MS (Marik et al., 2007; Mahad et al., 2015). Microglial cells have been detected in close association to injured axons and degenerating neurons in MS brains. In this regard, it has been suggested that the cascade of 'microglial activation, oxidative stress, and mitochondrial failure' may drive the neuro-axonal pathology in progressive forms of the disease (Mahad et al., 2015).

Besides the destructive roles, phagocytes have been shown to augment remyelination through phagocytosis of distorted myelin and secretion of anti-inflammatory/neuroprotective factors as nerve growth factor and brain-derived neurotrophic factor (Napoli and Neumann, 2009, 2010). However, it is not well determined whether the beneficial roles of phagocytes are confined only to microglia or blood-borne macrophages could also be involved (Yamasaki et al., 2014).

Interestingly, examinations of early MS lesions by Lassmann's group (Marik et al., 2007) show that microglial activation may be the first finding in so-called 'pre-demyelination' lesions. In such lesions, there are preferred MAG loss, edema, negligible axonal injury, and pronounced microglial activation. Pre-demyelinating lesions are suggested to be an earlier stage of the development of pattern III MS lesions. Therefore, innate immunity may be involved in lesion genesis in a subpopulation of MS patients.

Normal-appearing white matter

The name of MS, which historically dates back to the first observations by Charcot, highlights the presence and importance of sclerotic lesions in the CNS WM of MS patients. MRI, owing to its high sensitivity to WM lesions, allowed researchers to study the clinical impact of MS lesions (Barkhof, 2002). Subsequent studies showed that WM lesions can only marginally be correlated with clinical assessments, so-called clinico-radiological dissociation (Box 2) (Barkhof, 2002). Although this paradox, between WM lesion load and clinical disability, was first attributed to the heterogeneity in brain plasticity and cortical reorganization among patients, the following studies using quantitative MRI showed that NAWM is considerably abnormal. Indeed, magnetic transfer imaging (MTI) revealed reduced MT ratio (Filippi et al., 1995; Loevner et al., 1995; van Waesberghe et al., 1997; Schmierer et al., 2004; Loitfelder et al., 2012), DTI showed reduced fractional anisotropy and increased apparent diffusion coefficient (Cercignani et al., 2002; Rovaris et al., 2002; Vrenken et al., 2006a,b,c; Inglese and Bester, 2010; Rocca et al., 2016), magnetic resonance spectroscopy showed a reduction in absolute amount of metabolites such as NAA (Birken and Oldendorf, 1989; Fu et al., 1998; De Stefano et al., 2001), and T1 and T2 relaxation times are increased in NAWM of MS patients related to normal subjects;

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Box 2: An answer to clinico-radiological paradox of MS.

Conventional T1- and T2-weighted MRI are of considerable sensitivity to WM lesions and constitute an inseparable part of MS diagnosis, management, and research (Thompson et al., 2018). However, CNS lesion load detected by these methods shows only a weak correlation with clinical disability (Barkhof, 2002).

Several MRI-pathology correlational studies showed that the signal abnormality at lesion site on conventional MRI may represent a wide spectrum of pathology such as inflammation, edema, demyelination, and gliosis. More importantly, MRI cannot differentiate between ongoing demyelination and ongoing remyelination as both contain low myelin content. As a result, the severity of lesion pathology is not taken into account on MRI records. Furthermore, neuropathological and imaging studies revealed that other pathological mechanisms may be involved in MS and routine MRI are not sensitive to them, e.g. GM and NABT pathology.

As cortex contains low myelin content and also intra-cortical lesions are typically small, inflammation and ensuing demyelination in cortex do not produce sufficient contrast to be detectable by conventional MRI (Hulst and Geurts, 2011).

In addition, pathological studies revealed that myelinated NAWM may include several pathology as oligodendrocytes apoptosis (Barnett and Prineas, 2004), microglial activation (Marik et al., 2007), and axonal injury (De Stefano et al., 2001) undetectable by routine MRI. In this regard, Bjartmar and colleagues detected 20% axonal loss secondary to a recent lesion in a region without any sign of myelin pathology (Bjartmar et al., 2001). As myelin can remain unchanged for years following injury to corresponding axon, it has been suggested that NAWM may contain extensive axonal injury embedded in myelin, a pathology that cannot be detected by conventional MRI.

Taken together, an increasing body of evidence shows that there are several pathology undiscoverable by conventional MRI but of utmost importance in clinical disability as follows: (1) degenerative such as processes as axonal injury and oligodendrocytopathy; (2) NABT pathology; (3) GM lesions; (4) differentiation between ongoing de- and re-myelination; and (5) differentiation between distinct lesion immunopatterns. Therefore, the clinico-radiological dissociation in MS may partly be answered by recent findings.

all findings indicate NAWM pathology in MS patients (Griffin et al., 2000; Parry et al., 2002; van Walderveen et al., 2003; Vrenken et al., 2006a,b,c).

In this respect, a few pathological studies that examined NAWM showed a generalized inflammatory process including perivascular cuffs of macrophages, activated microglia, and a diffuse infiltration of T cells (Kutzelnigg et al., 2005). As pathological findings are more pronounced in regions close to focal WM lesions and there is an equal loss of myelin and axons (Barnett and Prineas, 2004; Kutzelnigg et al., 2005; Marik et al., 2007), the abnormalities of NAWM were believed to be a result of focal lesion-induced secondary degenerative processes including anterograde Wallerian degeneration, retrograde apoptosis of cell body, and migratory neuronal demise due to loss of trophic support from injured neurons (Bruck, 2005). However, imaging studies provided evidence suggesting that a primary process in NAWM in advance of blood-brain breakdown may precede the formation of WM lesions: (1) positron emission tomography scanning detected a diffuse microglial activation in NAWM of CIS patients that is also prognostic for MS development (Giannetti et al., 2015); (2) NAWM abnormalities are not well correlated with T2-weighted MRI lesion load (Rovaris et al., 2001, 2002; Rocca et al., 2003); (3) a longitudinal analysis of MS patients using MTI and T1-weighted MRI showed that MTI can detect an ongoing abnormality at sites of future lesions several months prior to their appearance on post-contrast T1-weighted MRI (Filippi et al., 1998); and (4) longitudinal perfusion study coupled with conventional MRI showed that an increase in cerebral blood flow and volume not only precedes BBB breakdown but also precedes apparent diffusion coefficient changes (Wuerfel et al., 2004).

In keeping with MRI results, examination of samples obtained from MS patients with various phenotypes (RRMS and secondary- and primary-progressive MS) showed that NAWM is diffusely abnormal (Kutzelnigg et al., 2005). In patients exhibiting lesions of immunopattern II, NAWM contains numerous small areas of perivascular infiltration along with demyelination and axonal pathology. It is long believed that confluence of such demyelinating inflammatory lesions may later form larger MS plaques (Gay et al., 1997; Bitsch et al., 1999). However, NAWM of patients exhibiting immunopattern III lesions showed several areas of microglial activation that resembles the initial stages of lesion formation (Marik et al., 2007).

Collectively, results of neuropathological and imaging studies suggest that NAWM is vastly abnormal and may contain some pathogenic processes that may precede the formation of focal lesions.

GM in MS

GM lesions

For a long time, MS was believed to be a disease preferentially affecting the WM. In this regard, lack of

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techniques sensitive to GM pathology, e.g. histopathological staining and imaging methods (Hulst and Geurts, 2011; Walker et al., 2011; Popescu and Lucchinetti, 2012; Zivadinov and Pirko, 2012), was the main obstacle to study GM in MS. However, subsequent studies using modern techniques, especially immunohistochemistery for detection of MBP and proteolipoprotein (Bo et al., 2003a,b) and also unconventional MR imaging as double inversion recovery (Redpath and Smith, 1994; Geurts et al., 2005; Bagnato et al., 2006; Simon et al., 2010), revealed that GM is not intact in MS and this damage is clinically relevant. Interestingly, studies show that GM lesion load better than WM lesion load could be correlated with physical disability and cognitive impairment in MS (De Stefano et al., 2003; Amato et al., 2004; Dalton et al., 2004; Tiberio et al., 2005; Sanfilipo et al., 2006) and may also be a predictor for the disease severity (Magliozzi et al., 2007).

Pathological studies showed that GM lesions can be classified, based on their location, into three main subtypes: subpial lesions that extend from pial surface to deeper cortical layers, intra-cortical lesions that are embedded in the cortex and are usually small and perivascular, and leukocortical lesions that affect adjacent WM and GM (Peterson et al., 2001; Bo et al., 2003a,b; M. Vercellino et al., 2005; Kutzelnigg et al., 2007; van Horssen et al., 2007). It has been suggested that different pathogenic processes may be involved in the formation of GM lesions of different locations. Inflammation is less pronounced in cortical lesions than WM ones, likely as GM has lesser myelin and denser cellular content. Among GM lesions, it has been shown that inflammation is more pronounced in leukocortical lesions and almost absent in cortical lesions (Vercellino et al., 2005; van Horssen et al., 2007). GM lesions similar to WM lesions temporally evolve (Popescu et al., 2011). In this respect, the active GM lesions of early MS were shown to be highly inflammatory and to contain myelin-laden macrophages, infiltration of lymphocytes (more CD8 and less CD4 T cells), and microglial activation, while chronic GM lesions lack the macrophages and lymphocytic infiltration and BBB breakdown (Lucchinetti et al., 2011). The non-inflammatory feature of chronic cortical lesions has been attributed to rapid resolution of inflammation and rapid repair in cortex (Merkler et al., 2006).

It has been shown that subpial lesions are the most common type of cortical lesions in progressive MS. Some results show that subpial lesions may be produced by diffusion of CSF inflammatory mediators, e.g. TNF-α, IFN-γ, matrix metalloproteinases, and cytokines, into the CNS (Calabrese et al., 2015).

It has been suggested that follicle-like structures containing B cells may be detectable in some MS patients (Popescu and Lucchinetti, 2012). Such structures have also been reported in other inflammatory and autoimmune conditions such as rheumatoid arthritis and Sjogren's disease and were attributed to a systematic reorganization of B cells into lymphoid-like organs (Young et al., 1984; Schroder et al., 1996). This process mostly occurs in sulci where CSF stasis leads to long-term gathering of B lymphocytes, T cells, and follicular dendritic cells (Serafini et al., 2004; Howell et al., 2011). These meningeal structures have been linked to the prolonged duration, higher inflammatory activity, and faster progression of the disease (Magliozzi et al., 2007).

Normal-appearing gray matter

Similar to NAWM, it has been shown that the normal-appearing gray matter (NAGM) is diffusely abnormal in MS. Pathological investigation revealed considerable axonal and neuronal injury in NAGM of MS patients compared with healthy subjects. Moreover, it has been shown that there may be no significant differences between subpial cortical lesions and NAGM in relation to neuroaxonal pathology (Kutzelnigg et al., 2005).

In keeping with pathological studies, unconventional MRI studies confirm that GM in MS patients are diffusely abnormal. Using MTI, it has been shown that MT ratio of NAGM of MS patients compared with healthy population is reduced and this reduction can better be correlated with disability than MT ratio of other CNS areas, e.g. NAWM (Samson et al., 2014). In parallel, DTI showed reduced fractional anisotropy and increased MD levels in NAGM of MS patients (Filippi, 2015).

Another radiographic finding that may signify diffuse abnormality of GM is GM atrophy that increases during the course of the disease (Kutzelnigg and Lassmann, 2005). It has been shown that GM atrophy is the best imaging finding that can be correlated with cognitive impairment in MS patients (Calabrese et al., 2009).

Conclusion

According to the traditional theory, MS pathogenesis is governed by autoreactive CD4 T cells in blood that invade the CNS, a process that leads to the formation of sclerotic lesions in the WM of MS brains. However, studies of recent decades show that MS pathogenesis is more complex and may include several other processes.

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Degenerative processes are present in MS, e.g. oligodendroglial or neuroaxonal destruction, and may even be responsible for disease genesis and even the CNS autoimmunity in MS (Stys et al., 2012). Compartmentalized inflammatory activity in meninges may vastly be involved in cortical lesion formation, even in early stages of the disease, and may contribute to disease progression. The immune system involvement in MS is more complex than a CD4 T cell-mediated inflammation against myelin, and CD8 T cells, B cells, and innate immunity are more involved than expected.

Routine MRI techniques are not sensitive enough to explore diffuse NABT pathology, GM abnormality, and axonal injury that may occur independently from frank demyelination. Given that such abnormalities are associated with clinical disability of MS patients, the longstanding dilemma of 'clinico-radiological paradox' could partly be appreciated (for detailed discussion, see Box 2). In addition, neuropathological studies revealed that MS lesions are heterogeneous and may underlie the diversity in clinical course and response to therapeutics seen in MS (for detailed discussion, see Box 1).

In conclusion, new discoveries in the recent decades highlight that MS is a disease in which various inflammatory and non-inflammatory processes work together to produce focal and diffuse pathology in CNS. Furthermore, such findings may provide a wealth of targets, e.g. innate immunity, oligodendroglial and neuroaxonal pathology, B cells and B cell-related factors such as B cell-activating factor of the TNF family and a proliferation-inducing ligand, for generation of more effective therapeutics.

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