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EXPLORING THE MOLECULAR CIRCUITS AT BRAIN BORDERS PARTICULARLY THE ROLE OF B-CELL RICH LYMPHOID STRUCTURES IN THE MENINGES IN DRIVING GRAY MATTER INJURY IN MULTIPLE SCLEROSIS

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ABSTRACT

In Multiple Sclerosis, long-term disability and neurodegeneration depends on injury of gray matter, which is one of the central determinants. Even though historically treated as a white matter disorder, Multiple Sclerosis is currently considered to have an early cortical demyelination, synaptic changes, and neuronal degeneration that have a strong impact on the disease progression, especially during its progressive phases. The meninges appear to be dynamic immune niches in which inflammation can become compartmentalized and structured into B-cell rich tertiary lymphoid structures. These systems maintain persistent immune responses in the form of chemokines like CXCL13 and CCL19/CCL21 and survival factors like BAFF and APRIL thereby maintaining the B-cell persistence, plasma cell maturation, and intrathecal antibody generation. Diffused Soluble inflammatory mediators of tertiary lymphoid structures such as cytokines, antibodies and complement components cause neuronal degeneration, microglial and astrocytic activation, oxidative damage, and synaptic dysfunction. Coalescing neuropathology, cerebral fluid biomarker and advanced imaging, and animal model findings associate the tertiary lymphoid structures of the meninges with subpial cortical demyelination and rapid progression. Although B-cell therapeutic approaches and associated pathway therapies are promising, more mechanistic research and valid in vivo biomarkers are needed to establish approaches that are effective in preventing or restricting cortical neurodegeneration.

Keywords: *Multiple Sclerosis, Gray matter, Meninges, B-cells, Tertiary Lymphoid structures, Neurodegeneration, Cerebrospinal fluid*

1. INTRODUCTION

Inflammatory central nervous system (CNS) based chronic inflammatory diseases have been now identified to have a significant pathological component of long-term disability and neurodegeneration risk through the injury of gray matter, especially in multiple sclerosis. To decades, MS has been viewed as a predominantly white matter demyelinating disease; nonetheless, substantial amounts of neuropathological and neuroimaging data have shown that damage to gray matter is both extensive and early occurring, and plays a strong role in the clinical course, cognitive deterioration, and permanent neurological loss (Calabrese et al., 2015; Filippi et al., 2012). Progressive types of MS are particularly

characterized by cortical lesions, so continuous neurological damage can be out of proportion to acute inflammatory processes that can be seen on traditional MRI (Calabrese et al., 2015; Lassmann, 2018). These results indicate that other processes other than the traditional peripheral immune infiltration into white matter lesions are key in the progression of disease.

The key characteristic of the MS lesions of the gray matter is the existence of extensive cortical demyelination, with a subpial distribution in many cases. Specifically, even primary MS cases have been reported to be characterized by inflammatory cortical demyelination, which allows considering cortical pathology not only to be a late onset side effect of the disease but also to be a facilitator of the disease progression (Lucchinetti et al., 2011). Subpial lesions are superficial cortical layers, usually including more than one gyrus, and it has been theorized that the meningeal compartment could be a source of diffusible inflammatory mediators into the adjacent cortex (Calabrese et al., 2015; Magliozzi et al., 2007). This extrinsic injury model of injury is opposed to the classical concept of MS lesions based largely on perivascular inflammation into the deep lying parenchyma and emphasizes the significance of immune activity in CNS borders.

Over the past years, brain border immunity has completely transformed the way we look at Neuroimmune interactions. Immune surveillance and immune responses at the anatomical interfaces are now considered to take place in the CNS in specialized locations, such as the meninges, perivascular space, and choroid plexus (Rua & McGavern, 2018). Meninges are also becoming more known as an active immune system as opposed to a passive cover. These include resident immune cells (e.g., border associated macrophages), infiltrating lymphocytes and antigen presenting cells, which have the ability to coordinate inflammatory cascades in CNS autoimmunity (Rustenhoven et al., 2021). Also, meningeal lymphatic vessels have been identified to be functional, offering a mechanistic definition of antigen drainage and immune communication between the CNS borders with peripheral lymphoid tissues (Louveau et al., 2015). The combination of these findings suggests that the meninges is an immunologically privileged site that is able to support chronic inflammation.

B-cells have been found to play a significant role in the progressive neuroinflammatory pathology among immune populations at brain boundaries. B-cell depletion therapies (e.g., anti-CD20 monoclonal antibodies) have been shown to be effective in reduction of the activity of inflammatory diseases with high clinical efficacy, and it can be demonstrated that B-cells possess more roles than the production of antibodies such as antigen presentation, cytokine secretion, and the organization of immune microenvironment (Hauser et al., 2017). Markedly, B-cells may accumulate in the meninges in a diffuse or highly structured aggregates of ectopic lymphoid structures (ELFs) or ectopic lymphoid follicles (ELFs) in patterns of diffuse infiltrates to highly organized aggregates in progressive MS (Magliozzi et al., 2007). TLS represent organized immune structures which develop in non-lymphoid tissues during chronic inflammation and are able to replicate secondary lymphoid organ behavior, such as segregated B-cells and T-cells spaces, follicular dendritic cell like networks and chemokine directed immune cell recruitment (Pitzalis et al., 2014). The fact that they are found in the meninges indicates that chronic inflammation may be compartmentalized and local self-sustaining within the borders of the CNS.

Notably, severe cortical pathology has been closely indicated to be linked with meningeal TLS. The initial pioneer research on secondary progressive MS has shown that patients with follicles of meningeal B-cells demonstrate a greater area of subpial cortical demyelination and a more severe clinical prognosis (Magliozzi et al., 2007). Later studies have confirmed that meningeal inflammation is common in MS and is strongly associated with a lesion in cortex, which attests to the existence of a pathogenic relationship between meningeal immune aggregates and the damaging of gray matter (Howell et al., 2011). The implications of this association are significant since they indicate the possibility of inflammation as a cause of progressive disability being partially

compartmentalized beyond the CNS barriers and thus less reachable by systemically administered therapeutic agents (Lassmann, 2018; Reali et al., 2020). Moreover, B-cell based meningeal inflammation has been linked to cortical demyelination as well as to more widespread neurodegenerative alterations that include microglial activation, neuronal damage, and synaptic loss phenotype leading to irreparable impairment (Calabrese et al., 2015; Lassmann, 2018).

Molecularly, TLS development and maintenance is maintained by distinct immune circuits of chemokines and survival factors. One of such B-cell attracting chemokines is CXCL13 and it is important to note that it signifies via CXCR5 and plays a core role in recruiting and organizing B-cells as follicle like structures (Pitzalis et al., 2014). Equally, CCL19 and CCL21 recruit T-cells and dendritic cells via CCR7 and compartmentalize immune cells (Pitzalis et al., 2014). Another factor facilitating the survival and maturation of B-cells is BAFF (B-cell activating factor) and APRIL (a proliferation-inducing ligand) which can promote B-cell and plasma cell survival and increase intrathecal immune response (Reali et al., 2020). These molecular circuits enable the meningeal TLS to act as a chronic inflammatory niche that can produce soluble mediators (cytokines, antibodies, complement related molecules) that can diffuse into the cortex and cause downstream functioning of microglia and astrocytes (Rua & McGavern, 2018).

Thus, the study of the molecular pathways that act at the brain boundaries especially in the ones that sustain B-cell enriched meningeal TLS is now critical to defining the pathogenesis of gray matter damage. This understanding can be used to discover new therapeutic sites to disrupt compartmentalized inflammation, inhibit cortical neurodegeneration, and delay the development of disability. The present review summarizes the existing information regarding meningeal immune architecture, TLS related molecular signaling, mechanistic events that connects border immunity to gray matter injury, and the role of B-cells as organizers and amplifiers of chronic meningeal inflammation.

2. Meninges as a Compartmentalized Neuroimmune Niche

The historical interpretation of the central nervous system (CNS) as an immune privileged organ has been reconsidered radically during the last decade. Besides the restricted access of immune cells to the parenchyma due to the blood-brain barrier, the active immune surveillance of the brain parenchyma has been firmly established in recent years at a set of connected anatomical interfaces that are now known as brain borders. They are the meninges, choroid plexus, perivascular spaces, and the cerebrospinal fluid (CSF) compartments, which serve as immune cell traffic control sites, antigen presentation sites, and inflammatory signaling sites (Rua & McGavern, 2018). These regions are not passive defensive guard, instead, they are dynamic immunological checkpoints that mediate communication between the peripheral immune system and CNS tissue and hence regulate protective immune responses and pathological neuro inflammation.

Among such interfaces, meninges are particularly important Neuroimmune niche, as they are organized in a particular anatomic structure and are additionally nearest to cortical surface. The meninges are separated into three layers that are dura mater, arachnoid mater as well as pia mater. The dura mater is highly vascular and harbors populations of immune cells analogous to the peripheral tissues, and the leptomeninges (arachnoid and pia) are quite analogous to the subarachnoid space and are directly connected to the cortical parenchyma (Rustenhoven et al., 2021). This proximity interaction forms a micro environment where soluble inflammatory mediators that are generated in the meningeal compartment can enter deep cortical layers. This setup is consistent with the already known outside-in model of cortical pathology in multiple sclerosis (MS) in which subpial demyelination and neuronal damage are correlated with underlying meningeal inflammation (Calabrese et al., 2015).

The meninges are also structurally modified to help in immune surveillance. Channels of venous sinuses and vascularity in the dural layer allow the entrance of immune cells that can enter the meningeal spaces and there can be exposed to

CNS derived antigens in the CSF and interstitial fluid. This organization permits activation of immune at CNS borders despite either no or limited invasion of immune cells into the brain parenchyma, which indicates that the meninges forms a key interface between systemic immunity and neural tissue (Rua & McGavern, 2018).

One of the biggest steps towards the study of brain border immunity was the finding of functional meningeal lymphatic vessels. These vessels facilitate drainage of CSF, immune cells and CNS derived antigens in deep cervical lymph nodes, which connects CNS to the peripheral immune organs (Louveau et al., 2015). This route offers a presentation and immune priming route to the peripheral lymphoid tissues which were not previously known, thereby solving a long held enigma on how the CNS antigens would be presented and primed. Notably, the immune regulation is not restricted to passive clearance of the fluid by meningeal lymphatic, but is actively involved. Change in lymphatic drainage in chronic neuroinflammation might extend the period of antigen presentation and sustained immune activation in CNS boundaries, which leads to compartmentalized inflammatory responses (Rua and McGavern, 2018).

The microenvironment of the meningeal immune comprises a wide variety of resident and invading immune cells. Border associated macrophages (BAMs) are involved in sampling antigens and tissue homeostasis whereas the dendritic cells are also involved in antigen presentation and initiation of adaptive immune responses. There are T lymphocytes, and they are normally found in a healthy state and are amplified in times of inflammation, both CD4+ and CD8+. B-cells and plasma cells that secrete antibodies are accumulated in chronic neuroinflammatory conditions and innate immune cells of mast cells and neutrophils might be utilized in acute inflammatory processes. It has been recently shown that the areas around the dural sinuses are specialized zones of neuroimmune interaction, which enables communication and activation of immune cells without necessarily invading the CNS parenchyma (Rustenhoven et al., 2021). Such compartmentalized immune response is specifically applicable to progressive MS where disease progression seems to be a product of inflammation persistence in CNS associated spaces as opposed to recurrent rounds of peripheral immune invasion.

The meningeal compartment is additionally accessible to the immune cells via vascular pathways between skull and vertebral bone marrow to the dura. The pathways offer a localized supply of myeloid and lymphocytes that could maintain chronic inflammation without depending on the circulation of the system and potentially lead to the maintenance of compartmentalized immune responses in progressive disease (Cugurra et al., 2021).

Progressive MS is a slow development of the neurological loss with the decrease of the acute inflammatory lesion activity in contrast to the relapsing disease. The development of compartmentalized inflammation, with immune responses being locally maintained in the meninges, along perivascular spaces, and other CNS border areas is one of the proposed explanations of this clinical pattern (Lassmann, 2018). In this context, inflammatory loop continues behind anatomical barriers which restrict clearance of immune cells and therapeutic penetration leading to chronic neurodegenerative events. Extensive cortical demyelination, microglial proliferation, loss of neurons, and more adverse clinical outcome have been closely linked with meningeal inflammation (Howell et al., 2011; Magliozzi et al., 2007). The meninges thus serve as an inflammatory center capable of providing cytokines, chemokines, antibodies, and factors of complement that leak into the surrounding cortical tissue and lead to the destruction of gray matter (Calabrese et al., 2015).

The positive spatial relationship between subpial cortical lesions and meningeal inflammation also underlines the fact that brain border immunity is significant in the inflammatory degeneration of the gray matter. Subpial demyelination can hardly be explained by the principle of deep parenchymal immune infiltration but is biologically plausible when the inflammatory source of the meninges is regarded as a significant source of inflammatory mediators and immune effector molecules. The

meninges can hence be considered dynamic immunological systems which determine the disease processes in the CNS. The distinct cellular structure, anatomy and lymphatic interrelation of this compartment result in the conditions under which the formation of B-cell rich immune aggregates and tertiary lymphoid structures develop, which are becoming increasingly important contributors to cortical damage and disease pathogenesis in MS.

3. B-cell Rich Meningeal Tertiary Lymphoid Structures (TLS)

The presence of chronic inflammation in the central nervous system (CNS) may result in the formation of structured immune complexes that are called tertiary lymphoid structures (TLS) or ectopic lymphoid follicles. The structures emerge in non-lymphoid tissues in the case of sustained immune stimulation and have structural and functional similarities with secondary lymphoid organs, such as lymph nodes, such as sectionalized B and T-cell spaces, stroma organization, and local immune activation (Pitzalis et al., 2014). TLS have been documented in numerous chronic inflammatory diseases, such as auto-immune diseases, infections and cancer where they are able to maintain local immune response. TLS within the meninges of the neuro inflammatory diseases, especially the progressive multiple sclerosis (MS), has become an important pathologic finding that is closely related to cortical gray matter damage (Magliozzi et al., 2007; Howell et al., 2011).

Meningeal TLS in MS usually lie in the leptomeninges and they are commonly found in deep cortical sulci near the pial surface. Their physical location close to the cortex helps to prove the idea of an outside-in mechanism of tissue damage, where inflammatory mediators spread out of the meningeal compartment to the underlying gray matter, a process that leads to subpial cortical demyelination and neurodegeneration (Calabrese et al., 2015). Histopathological examination has demonstrated that the follicles of B-cells are correlated with an earlier disease onset, more aggressive disease progression, and greater level of cortical demyelination (Magliozzi et al., 2007). Later studies established that extensive meningeal inflammation especially when systematized into B-cell rich aggregates is strongly associated with amplified cortical lesion burden, amplified microglial reactivity and amplified neuronal loss in progressive MS (Howell et al., 2011; Reali et al., 2020). These results indicate that TLS are a type of compartmentalized inflammation and may be maintained without any peripheral immune activity and lead to neurodegeneration persistence (Lassmann, 2018).

This complexity of functional and active immune microenvironment is reflected in the cellular composition of meningeal TLS. The center of follicle like areas consists of B-cells, especially of the CD20+ memory B-cells, which have many functions, such as antigen presentation, cytokine production, and differentiation to antibody producing plasma cells (Reali et al., 2020). These B-cell clusters are surrounded by CD3+ T lymphocytes which present co-stimulatory signals to enable B-cell activation and survival (Howell et al., 2011). TLS is associated with the presence of plasma cells in or around it, and this may be why these cells contribute to the production of intrathecal immunoglobulins, which is a characteristic of the cerebrospinal fluid of MS patients (Reali et al., 2020). Furthermore, stromal components that are similar to follicular dendritic cells, as well as macrophages and dendritic cells, aid in lymphoid architecture organization and antigen retention and presentation, which further maintain local immune response (Pitzalis et al., 2014). Notably meningeal TLS are highly heterogeneous in their extent of organization, being diffuse B-cell invading, or complete follicle like structures with germinal center like appearances. This heterogeneity indicates that TLS might be dynamic phases of lymphoid neogenesis, which may affect their inflammatory capability, response to therapy, and relations to disease severity (Serafini et al., 2004; Pitzalis et al., 2014).

The development and homeostasis of meningeal TLS are controlled by molecular pathways participating in the development of lymph nodes. These are majorly the lymphoid chemokines that regulate the recruitment and spatial organization

of immune cells. CXCL13-CXCR5 is the core of B-cells attraction and follicle formation whereas CCL19/CCL21-CCR7 is the place of T-cells and dendritic cells attraction to form T-cell zones (Pitzalis et al., 2014). B-cell survival factors, including B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL) in addition to chemokine signaling, facilitate long-term B-cell persistence, class switching and plasma cell survival, thus facilitating chronic intrathecal immune activity (Reali et al., 2020). Lymphotoxin signaling via the LT alpha/LT beta. LT beta receptor pathway also plays a role in stromal remodeling and formation of stable lymphoid architecture, and is also essential to sustained TLS neogenesis (Pitzalis et al., 2014).

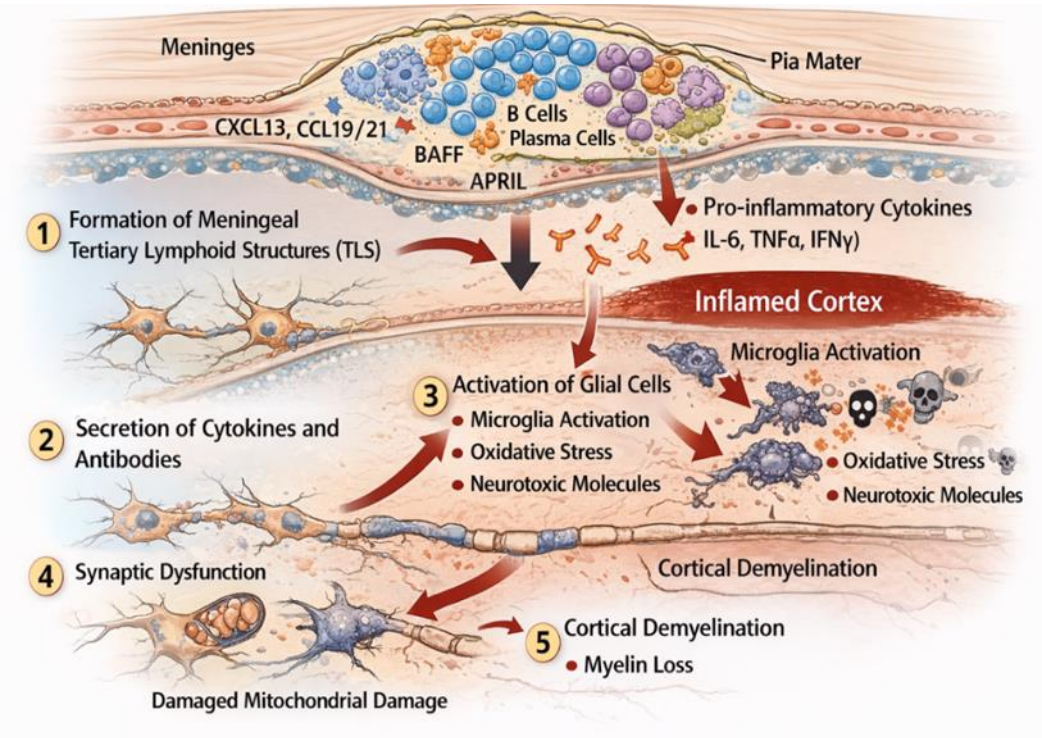

Figure 01: B-cell Rich Meningeal Tertiary Lymphoid Structures in Multiple Sclerosis.

The development of meningeal TLS that is rich in B-cells, plasma cells, T-cells, and stromal cells which then secrete cytokines (IL-6, TNF, IFN), and antibodies. These stimulate microglia and astrocytes leading to the dysfunction of the synapses, mitochondrial injury and demyelination of the cortices. (Calabrese et al., 2015)

Meningeal TLS play a role in the injury of the gray matter in a variety of interrelated ways. Chronic T-cell activation and production of cytokines is maintained by local antigen presentation by B-cells, which forms an inflammatory loop in the CNS compartment (Lassmann, 2018; Reali et al., 2020). In addition to pro-inflammatory cytokines, tumor necrosis factor alpha, interleukin-6, and interferon-g, plasma cell derived antibodies may encourage complement activation and synaptic or myelin injury, and pro-inflammatory cytokines may diffuse into neighboring cortical tissue (Calabrese et al., 2015). The glial activation causes oxidative stress, mitochondrial dysfunction, loss of synapses and eventual neuronal damage. Significantly, the existence of TLS also offers a structural foundation to a continuous and compartmentalized inflammation and can explain why the onset of progressive disease and neurodegeneration can proceed despite peripheral immunity being suppressed (Lassmann, 2018).

4. Molecular Circuits Linking Meningeal TLS to Gray Matter Injury

One of the main questions of neuro immunology is how a peripheral localization of inflammatory processes at the borders of the central nervous

system (CNS) especially the meninges, can cause damage to the underlying cortical gray matter. There is growing evidence of an outside-in approach of pathology where meningeal compartment produced inflammatory mediators infiltrate adjacent cortical tissue and trigger neurodegenerative cascades (Calabrese et al., 2015; Magliozzi et al., 2007). This process is particularly applicable to the progressive multiple sclerosis (MS), when inflammation is confined to CNS peripheral areas even though peripheral immune infiltration declined (Lassmann, 2018). Meningeal tertiary lymphoid structures are structured inflammatory centers that are able to maintain immune activation in an interconnected circuit of molecules and thus preserve chronic inflammatory signaling with the capacity to induce grey matter injury.

The networks between chemokines are also important to form and sustain meningeal TLS by controlling the recruitment, maintenance, and spatial orchestration of lymphocytes. The CXCL13–CXCR5 axis is the most important of these, in terms of the B-cell trafficking and follicular organization. High levels of CXCL13 are also strongly linked to B-cell compartmentalization and generally regarded as a viable indicator of TLS activity (Pitzalis et al., 2014). Simultaneously, the CCL19/CCL21-CCR7 interaction makes T-cells and dendritic cells recruit and allows structuring T-cell areas and efficient antigen presentation. A combination of these chemokine circuits allow diffuse meningeal inflammation to progress to fixed and self-sustaining immune aggregates that further generate inflammatory mediators despite an absence of a continued systemic immune response.

B-cell mediated inflammation in TLS is additionally maintained by the survival and differentiation signals given by tumor necrosis family members, especially B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL). These molecules facilitate the survival, differentiation of B-cells into plasma cell and sustained presence of antibody secreting cells (Reali et al., 2020). Specific clinical significance is attached to the BAFF/APRIL axis since long-lived plasma cells do not express CD20 and hence they are insensitive to anti-CD20 drugs. Consequently, trophic support mediated by BAFF/APRIL can also be a source of sustained intrathecal antibody production and tissue destruction in progressive MS even in the face of systemic B-cell depletion (Lassmann, 2018; Reali et al., 2020).

In meningeal TLS B-cells also can act as effective antigen presenting cells with the ability to maintain T-cell activation locally. B-cells facilitate the growth of pathogenic CD4 + T-cells and release of pro-inflammatory cytokines by presenting antigen through major histocompatibility complex class II molecules, as well as by providing co-stimulatory signals (Lassmann, 2018). This local TB interaction enables immune mechanisms to be maintained in CNS compartments without reliance on peripheral lymphoid organs and in effect turn meningeal TLS into immunological reactors in place of the susceptible cortical tissue (Calabrese et al., 2015).

Diffusion of soluble inflammatory mediators into the superficial layers of the cortex is one of the best associations between meningeal inflammation and cortical pathology. In TLS and the surrounding meningeal infiltrates, immune cells generate cytokines, including tumor necrosis factor- 6, interferon- 6, lymphotoxin family members, and can provoke oligodendrocyte stress, astrocyte reactivity and microglial activation (Calabrese et al., 2015; Howell et al., 2011). Anatomical evidence of this mechanism is the characteristic subpial gradient of cortical demyelination, whereby there is a decrease in the severity of the lesion with the distance of the lesion site to the pial surface (Magliozzi et al., 2007).

Along with the toxicity induced by cytokines, plasma cells related to TLS help with the production of immunoglobulin in the area and the development of oligoclonal bands. Such antibodies can be involved in tissue damage by direct binding to the neural targets and complement cascade activation, which facilitates inflammatory phagocytosis and apoptosis of synapses (Calabrese et al., 2015; Lassmann, 2018). A plausible way through which intrathecal humoral immunity contributes towards

neurodegeneration is complement mediated tagging of synapses to eliminate.

The microglia can be considered as essential downstream effectors that can convert meningeal immune signals into both structural and functional brain injuries in the gray matter. The sustained exposure of microglia to cytokines, chemokines, antibodies, and complement components transfer the microglia to a pro-inflammatory phenotype that is associated with the generation of reactive oxygen species, mitochondrial dysfunction, and excessive synaptic pruning (Calabrese et al., 2015; Lassmann, 2018). Activated microglia are also found regularly in areas of the cortex between inflamed meninges and are closely related to progressive neuronal loss and clinical impairment (Howell et al., 2011).

Table 01. Molecular Pathways Linking Meningeal TLS to Gray Matter Injury in Multiple Sclerosis.

Molecular Pathway (Ligand -receptor)	TLS Function	Cortical Effect	Therapeutic Targeting	Sources
CXCL13- CXCR5	Recruitment of B-cell and organization of follicle	Subpial demyelination	CXCL13 Inhibition	Magliozzi et al., 2007
CCL19/CCL21–CCR7	T-cell positioning and aggregation	Sustained cortical inflammation	CCR7 pathway blockade	Krumbholz et al., 2005
BAFF–BAFFR	B-cell survival	Persistent antibody production	BAFF inhibition	Krumbholz et al., 2005
APRIL–TACI/BCMA	Plasma cell maintenance	Ongoing humoral injury	APRIL targeting	Serafini et al., 2004
Lymphotoxin (LTα / LTβ – LTβR)	Stromal organization	Chronic inflammatory niche	LTβR inhibition	Pitzalis et al., 2014
Immunoglobulins–Complement receptor	Amplifies antibody effects	Synaptic loss	Complement inhibitors	Howell et al., 2011
Pro-inflammatory cytokines (TNF-α / IL-6 – Cytokine receptors)	Sustains TLS signaling	Microglial activation	Cytokine modulation	Lassmann, 2018

These interrelated conditions create a pathogenic loop where chemokine-mediated recruitment contributes to the evolution of TLS formation, BAFF/APRIL signaling to the T-cell keeps B-cells alive, and the production of glial activation and tissue damage happens locally grow on the production of cytokines and antibodies. The ensuing discharge of neural antigens and signals of damage also strengthens immune response and normalizes the niche of inflammatory processes of the meninges. The mechanism of this feedback is a mechanistic way to explain why gray matter degeneration is persistent in progressive MS and how limited treatments that focus mainly on peripheral immune activity are (Lassmann, 2018; Reali et al., 2020). In turn, the disruption of molecular circuits at brain boundaries, e.g. at CXCL13 mediated recruitment, BAFF/APRIL survival pathways, lymphotoxin signaling, complement activation, or microglial effector

functions, is a valuable approach to therapeutics to interfere with compartmentalized neurocentral inflammation. TLS stromal cells, such as population of fibroblastic reticular cell like and follicular dendritic cell like networks, are critical in chemokine gradient maintenance, antigen retention and structural stability. The non-hematopoietic elements are also becoming known as important regulators of chronic inflammation and have become viable therapeutic targets to disrupt TLS persistence at CNS border points (Pitzalis et al., 2014; Rustehoven et al., 2021).

5. Meningeal TLS as Drivers of Gray Matter Injury

Well supported human neuropathological, imaging, and clinical evidence supports the direct association of subpial cortical demyelination, neuronal injury and progressive disability in multiple sclerosis (MS) with inflammatory immune niches in CNS borders with B-cell enriched meningeal tertiary lymphoid structures (TLS) in particular. Convergent evidence of autopsy-based histopathology, cerebral spinal fluid (CSF) biomarkers, modern magnetic resonance imaging (MRI), and clinical outcome studies support the fact that meningeal inflammation is a factor in an outside-in mechanism of gray matter injury. All of them lead to the finding that immune aggregates in the meninges are not transitions but pathophysiological agents of cortical neurodegeneration, particularly in later stages of the progression (Magliozzi et al., 2007; Howell et al., 2011; Calabrese et al., 2015).

Ectopic B-cell follicle like structures in the meninges of secondary progressive MS (SPMS) patients were first shown by neuropathological studies. These structures were closely linked to a premature disease, faster disease progression, and widespread subpial cortical demyelination which released a first indication that structured meningeal immunity is interconnected with intense gray matter pathology (Magliozzi et al., 2007). Later studies also verified that meningeal inflammation is prevalent in MS and that it is associated with the burden of cortical lesions, microglial activation, and neuronal loss (Howell et al., 2011). Notably, MS usually involves cortical demyelination with little lymphocyte infiltration of the parenchyma, which confirms the hypothesis of involvement of diffusible meningeal origin inflammatory mediators in tissue lesion (Lassmann, 2018; Calabrese et al., 2015). Previous studies also showed transected neurites, apoptosis of neurons, and the destruction of synapses in cortical lesions, which showed that the pathology of the gray matter is also characterized by demyelination and neurodegeneration (Peterson et al., 2001; Wegner et al., 2006).

The spatial relationship between inflammatory infiltrates and cortical damage is a major character that can sustain a causal role of meningeal inflammation. Cortical lesions are most evident in the superficial layers at the pial surface and less intense as one gets deeper in keeping with a gradient of meninges to cortex inflammatory exposure (Magliozzi et al., 2007; Howell et al., 2011). Besides focal lesions, diffuse neuroaxonal injury and extensive microglial activation has been noted in normal appearing gray matter implying the chronic exposure of the brain to the inflammatory mediators (Kutzelnigg et al., 2005). It is important to note that inflammatory cortical demyelination has been observed as soon as in the early MS, meaning that gray matter pathology starts early and can be further increased through continued meningeal inflammation (Lucchinetti et al., 2011).

TLS like organization is also supported by the cellular structure of the inflammation of the meninges. Histological examination shows that there are aggregates with B-cells, T-cells, plasma cells, and networks that resemble follicular dendritic cells, and these are compatible with characteristics of tertiary lymphoid structures (Magliozzi et al., 2007; Howell et al., 2011). These findings are consistent with the more general idea of lymphoid neogenesis in chronic inflammatory diseases (Aloisi and Pujol Borrell, 2006; Pitzalis et al., 2014). These structures can also play a role in disease, as B-cells in these structures can perform antigen presentation, secrete cytokines, and produce local antibodies, which is facilitated by the therapeutic effectiveness of B-cell depleting therapies in MS demonstrated to date (Hauser et al., 2017).

Biomarker research also gives more evidence towards humoral immunity being compartmentalized in the CNS. The occurrence of oligoclonal IgG bands (OCBs) in the CSF is indicative of continued intrathecal immunoglobulin production and also one of the most regular immunological manifestations of MS (Dobson and Giovannoni, 2019). Intrathecal inflammation and disease activity have been linked to elevated levels of B-cell chemoattractant CXCL13 in CSF and has been linked to continued B-cell recruitment and TLS related pathways at CNS borders (Khademi et al., 2011; Pitzalis et al., 2014). Simultaneously, higher serum and CSF Neurofilament light chain levels are sensitive indicators of neuroaxonal injury and are negatively associated with disease progression, which is an indirect sign of continued neurodegeneration that might have been caused by chronic meningeal inflammation (Disanto et al., 2017).

Compartment specific inflammation activation signatures of MS tissues have been further illustrated using single-cell and spatial transcriptomic analysis, which comprise enlarged B-cell clones and pro-inflammatory myeloid phenotypes to provide molecular scale evidence of local immune tissue to drive gray matter damage (Schafflick et al., 2020).

Mechanisms between cortical injury and meningeal inflammation in vivo are further supported by imaging studies in vivo. Leptomeningeal enhancement (LME) identified with post contrast MRI is believed to be a radiological measure of inflammatory activity of the meninges. LME has been found in MS subtypes, and it is related to more significant cortical lesion burden, cortical thinning, and poor clinical outcomes (Absinta et al., 2015). According to longitudinal studies, LME is likely to remain throughout the age, which is in line with chronic compartmentalized inflammation as opposed to acute inflammatory flares (Zivadinov et al., 2017). The relation between LME and progressive cortical atrophy gives significant in vivo evidence to the role of meningeal inflammation in causing gray matter degeneration.

The idea of compartmentalized CNS inflammation is also supported by clinical and pathological investigations of progressive MS. The progression of the disease is marked by the transition of acute peripheral inflammatory activity to chronic active lesions, diffuse tissue damage, and perivascular space and meninges compartmentalization inflammation (Frischer et al., 2015; Lassmann, 2018). Despite the positive clinical effects of the B-cell depleting therapies, the disease progression was not eliminated completely, which indicates that compartmentalized immune niches such as TLS and long-lived plasma cells might still remain beyond CNS barriers and partially inaccessible to systemic treatment (Hauser et al., 2017; Lassmann, 2018).

Together, human studies continuously show that meningeal inflammation is strictly related to cortical pathology, that B-cell rich TLS like structures are related to severe and early onset gray matter damage, and that biomarkers and imaging results indicate that compartmentalized immune activity persists in the CNS. These results firmly back up a hypothesis where persistent immune reaction on the boundary of the brain cause progressive neurodegeneration by the long-term exposure of cortical tissue to inflammatory agents.

6. Links between Brain Borders Immunity, TLC, and Gray Matter Injury

Experimental models have played an important role to the determination of causation forces between immune activity at the borders of central nervous system (CNS) and neurodegenerative outcomes. Human research has good associative evidence that meningeal inflammation and B-cell rich tertiary lymphoid structures (TLS) are associated with cortical damage, but animal and translational research can be used to control the study of whether these immunologic mechanisms directly mediate gray matter damage. The most commonly used model of multiple sclerosis (MS) like disease is experimental autoimmune encephalomyelitis (EAE) due to its ability to recreate major pathological events, such as T-cell mediated CNS inflammation, demyelination, neuroaxonal damage, and impairment of

functions (Robinson et al., 2014). Even though classical EAE is white matter-based, the antigen specificity differences, genetic makeup, and chronicity of the disease may cause cortical damage, progressive neuro degradation, and intense meningeal immune penetration. Such results show that not only parenchymal invasion by immune cells is involved in CNS inflammation but also immune activation in meningeal and perivascular compartments (Ransohoff et al., 2015).

The body of evidence growing out of EAE studies suggests that accumulation of immune cells is often accrued to the meninges and are linked to underlying cortical injury. The immune cells of the meninges under chronic neuro inflammatory conditions release soluble mediators, chemokines, and pro-inflammatory cytokines that diffuse into the adjacent cortical tissue supporting the outside-in-model of gray matter injury suggested in progressive MS (Calabrese et al., 2015). In experimental studies, it is shown that meningeal inflammation may cause microglial activation under inflamed areas, superficial cortical demyelination and neuronal dysfunction, which is mechanistic evidence that meningeal immune response actively takes part in cortical pathology and not a bystander phenomenon (Ransohoff et al., 2015).

TLS such as immune aggregates in the meninges can also be as a result of chronic neuro inflammation in animal models. Lymphotoxin signaling, ongoing stimulation with antigens, and chemokine gradients (CXCL13 and CCL19/CCL21) as well as stromal cell remodeling that facilitates the organization of immune cells have been found to be essential in the formation of ectopic lymphoid structures in peripheral autoimmune diseases (Pitzalis et al., 2014). Like mechanisms would occur in the CNS where chronic immune activation would favor B-cell aggregation and plasma cell localization in the meninges. These experimental results have mechanistic explanations of human neuropathological evidence of follicle like B-cell aggregates in secondary progressive MS (Magliozzi et al., 2007).

The pathogenic mechanisms of B-cells in compartmentalized CNS inflammation are further emphasized by experimental studies of the multifaceted pathogenicity. B-cells also play important roles in the production of antibodies, as well as the antigen presentation to the CD4+ T-cells, the synthesis of pro-inflammatory cytokines, and the creation and sustenance of antigens sites in the CNS (Hauser et al., 2017; Ransohoff et al., 2015). Animal models show that B-cell depletion diminishes the disease severity and inflammatory activity in situations where B-cell mediated mechanisms are dominant as are seen with anti-CD20 therapies in MS, and that B-cells play a central role in disease progression (Hauser et al., 2017).

The chemokine signaling pathways are important in the establishment and sustenance of TLS in experimental systems. Recruitment and organization of follicles are dependent on CXCL13, whereas T-cell and dendritic cell positioning are mediated by CCL19 and CCL21, and the stromal networks stabilize TLS structural architecture (Pitzalis et al., 2014). There is evidence in the human cerebrospinal fluid (CSF) research that a high level of CXCL13 is an indicator of intrathecal inflammatory responses and MS disease activity (Khademi et al., 2011). These observations are further developed by experimental models that have shown that CXCL13 is no longer a biomarker but is a functional element of the molecular network that supports immune aggregates that are rich in B-cells on a chronic basis.

Microglia are important effectors transmitting immune signals into neurodegeneration downstream of meningeal inflammation. Activated microglia play a role in oxidative stress, synaptic pruning, axonal injury, and enhancement of local inflammatory reactions in chronic neuro inflammatory models (Ransohoff et al., 2015). The outcomes are consistent with the human research, which demonstrated enhanced microglial stimulation and neural degeneration in the cortical areas that were in close proximity to the meningeal inflammation (Howell et al., 2011; Wegner et al., 2006). Experimental models, however, in spite of the usefulness of their

mechanistic value, possess significant limitations. EAE is not a complete replica of the progressive MS-like long-term compartmentalized inflammation, animal models of TLS like structures might have a different structural and functional structure compared to those in humans, and most models have more white matter than the cortical process. Therefore, experimental results can only be considered as mechanistic support but not an exact replication of the human disease pathology (Robinson et al., 2014; Lassmann, 2018).

The chronic antigen exposure, viral stimulation, or adoptive transfer of B-cells into experimental systems have added to the literature the capacity to model meningeal immune aggregation and cortical pathology and provided new platforms onto which TLS specific therapeutic approaches and molecular pathways in progressive MS can be studied (Ransohoff et al., 2015).

7. Therapeutic Targeting of Meningeal TLC and Brain Borders Molecular Circuits

The identification of the fact that meningeal TLS is chronic immune niches that causes gray matter damage has some significant therapeutic implication. The strategies to be used to combat progressive MS can potentially require a combination of actions on various elements of the compartmentalized immune response such as B-cells recruitment and survival pathways, TLS organization, intrathecal antibody and cytokine generation, and downstream neurotoxicity mediated by microglia. This methodology is especially applicable by the fact that inflammation in the progressive disease is to some degree localized in the CNS and is less susceptible to treatment aimed at the primary inhibition of peripheral immune response (Lassmann, 2018).

B-cell depleting therapy provides strong clinical evidence to define the pathogenic role of B-cells in MS, and ocrelizumab, a monoclonal antibody against CD20 reduces the relapse level and MRI inflammation in relapsing MS, and even delays the disease progression in primary progressive MS (Hauser et al., 2017; Montalban et al., 2017). The therapeutic benefit of anti-CD20 therapy, though, may not be high in meningeal TLS because CD20 is not expressed on long-lived plasma cells, CNS compartmentalization may restrict the penetration of antibodies, and intrathecal immunoglobulin production may not be reduced by peripheral B-cell depletion (Lassmann, 2018). These observations indicate that further measures are required in order to disconnect long-lasting intrathecal cellular responses.

One of the strategies is to target B-cell survival factors. B-cell activating factor (BAFF) and a proliferation inducing ligand (APRIL) enhance B-cell survival, plasma cell survival, and prolonged antibody production at the sites of inflammation (Reali et al., 2020). BAFF/APRIL signaling inhibitors can potentially reduce the long lived plasma cell survival in meningeal TLS and in turn undermine tissue damage by chronic antibody deposition.

There are also chemokine pathways that control TLS formation that are promising targets of therapy. According to (Pitzalis et al. 2014), CXCL13 is at the heart of the B-cell recruitment and follicular structure organization, and the high levels of CSF CXCL13 are associated with MS intrathecal inflammation. The CXCL13 CXCR5 axis may be a potential limiting factor in B-cell trafficking into the meninges and TLS stabilization, as well as in compartmentalized inflammation, but these interventions are under study.

Inhibitors of the tyrosine kinase (BTK) of Bruton are becoming an especially promising approach since BTK signaling also controls the B-cell receptor stimulation, as well as the inflammatory reaction of the myeloid cells. Since TLS require adaptive and innate immune cell interactions, BTK inhibition may disrupt various elements of compartmentalized CNS inflammation and retain partial immune functionality and possibly reach superior CNS penetration as compared to depletion therapies.

Besides the effect on the organization of immune cells, downstream effector mechanism focused therapies can minimize tissue damage. Meningeal TLS generated intrathecal antibodies have the potential to trigger the complement pathways, resulting in the loss of synapses and neuronal damage (Calabrese et al., 2015). Even in the case

of the presence of TLS structures, complement inhibition would have the effect of alleviating neurotoxicity. Similarly, microglial activation is also a valuable neuroprotective approach because microglia are the mediators of oxidative damage, mitochondrial dysfunction, and synapse loss in chronic neuro inflammation (Ransohoff et al., 2015). Microglial inflammatory signaling, oxidative stress, and neuronal resilience could be modulated to slow the gray matter degeneration in progressive disease (Lassmann, 2018).

The development of imaging and biomarkers can allow the targeted approach to brain border immune pathology in a personalized way. Cortical injury and faster cortical atrophy has been linked to leptomeningeal enhancement (LME) on contrast enhanced MRI, indicating that this is an indication of active meningeal inflammation (Absinta et al., 2015; Zivadinov et al., 2017). Parallel to that, compartmentalized inflammation and treatment response may be tracked with the support of such molecular biomarkers as CSF CXCL13 (Khademi et al., 2011), serum or CSF neuro-filament light chain as a neuroaxonal harm indicator (Disanto et al., 2017), and oligoclonal band status (Dobson and Giovannoni, 2019). The combination of these strategies contributes to a change in the initial therapeutic strategies based on a mechanism toward immune circuitry at the borders of the CNS that propagates the gray matter damage progressively. An enhanced CNS penetrant in future therapeutic approaches might then necessitate enhanced ability to target long-lived plasma cells and stromal support networks, and the creation of biomarkers that can be utilized to monitor compartmentalized meningeal inflammation in vivo (Lassmann, 2018; Rustenhoven et al., 2021).

Table 02. Therapeutic Strategies Targeting Brain Border Immunity in Multiple Sclerosis

Strategy	Target / Mechanism	Impact on Compartmentalized CNS Inflammation	Sources
Anti CD20 monoclonal antibodies	Reduces CD20+ B-cells that cause meningeal and CNS inflammation.	Reduces B-cell drive immune activity and may disrupt meningeal aggregates	Roach & Cross (2021)
Bruton tyrosine kinase inhibitors	In B-cells and microglia BTK signaling inhibit	Inhibits inflammatory responses in the meninges and decreases leptomeningeal increase in the model.	Howell et al. (2020)
Treatment targeting broad B-cell	Attack B-cell surface molecules in order to suppress broad B-cell activity.	May suppresses B-cell pathogenicity, antigen, and cytokine manufacture	Kanatas et al. (2023)
S1P receptor modulators	Disorderly lymphocyte diffusion out of lymphoid tissue.	Lessens the lymphocyte infiltration in CNS sections.	Álvarez Bravo et al. (2022)
Axis modulation of BAFF/APRIL	B-cell survival signals (BAFF/APRIL) modified	In meningeal niches changes chronic B-cell survival	Rahmanzadeh et al. (2018)

8. Future Research Directions

Although there is an increasing body of evidence to suggest that immune activity at central nervous system (CNS) boundaries also plays a role in cortical pathology, a number of critical gaps in knowledge exist about the molecular pathways that run at brain boundaries, how such B-cell rich meningeal tertiary lymphoid structures (TLS) form and what their functional role is in causing injury to the grey matter. The question concerning causality is one of the primary problems that remain unsolved. The direct relationship between post-mortem studies has also always indicated that meningeal TLS is closely related to severe subpial cortical demyelination, neuronal loss, and rapid disease progression in multiple sclerosis (MS) (Magliozzi et al., 2007; Howell et al., 2011). It is, however, not clear whether TLS actively promote cortical damage or rather they develop as a secondary effect of persistent neurodegeneration. To answer this question, longitudinal studies comprising the combination of the latest imaging technologies, including leptomeningeal enhancement (LME), spatial transcriptomic, and detailed neuropathological correlation, will be needed (Absinta et al., 2015; Zivadinov et al., 2017).

The other important gap is in regard to the heterogeneity and molecular identity of meningeal immune aggregates. In not all infiltrates, the structural and functional requirements of the actual TLS are fulfilled, commonly encompassing follicular dendritic cell networks, germinal center like responses, and purposeful chemokine gradients. There are cases of some structures being early or incomplete lymphoid neogenesis. Such heterogeneity may be the explanation of interpatient variations in the extent of cortical pathology, disease progression, and response to the therapy (Pitzalis et al., 2014; Lassmann, 2018). Additional research is required to classify meningeal immune structures based on the cellular constituents, the condition of B-cell differentiation, plasma cell densities, and molecular markers through high resolution immunophenotyping and transcriptomic analyzes. Meningeal B-cells antigenic specificity is also not well characterized. Despite the fact that the B-cells are known to work as the antigen presenting cells and the cytokine producers in the case of MS, the exact antigens that support the TLS activity are not entirely comprehended (Hauser et al., 2017). These include myelin, neuronal or synaptic proteins, viral antigens or neoepitopes produced during tissue injury. It will be critical to determine the specificity of the antigen in identifying whether TLS mediated pathology occurs through the primary mechanisms of autoimmunity, persistent infection, or self-maintaining inflammatory feedback (Lassmann, 2018).

Moreover, the structural and stromal elements which assist in the formation of TLS in the meninges have not been well defined. Lymphoid neogenesis in the peripheral tissues relies on stromal cell remodeling, lymphotoxin signaling, and chemokine (Pitzalis et al., 2014). Only the similar functions of meningeal fibroblasts, endothelial cells, perivascular macrophages and meningeal lymphatic vessels are starting to be investigated. This brain border microenvironment could be the reason behind ongoing chronic immune niches to progress MS despite peripheral inflammation dropping (Calabrese et al., 2015; Lassmann, 2018).

There is also need to improve experimental models. Despite the useful mechanistic understanding of experimental autoimmune encephalomyelitis (EAE), it is not a complete, lasting replication of long-term compartmentalized inflammation, stable meningeal TLS, or extensive infiltration of the subpial cortex (as in progressive MS) (Robinson et al., 2014; Ransohoff et al., 2015). Test treatments of the pathways involving TLS will require development of models that are more representative of chronic meningeal inflammation and cortical neurodegeneration.

Translating access to meningeal TLS is a significant issue that faces therapeutic access challenges. These compartments are found in secure CNS environments and much of the contemporary immunotherapy is focused on peripheral immunity. Even the most efficient anti-CD20 therapy can fail to get rid of long-lived plasma cells and to suppress intrathecal immune responses completely (Hauser et al., 2017;

Lassmann, 2018). To enhance CNS penetration and directly affect TLS maintenance pathways including CXCL13 CXCR5 signaling, lymphotoxin pathways, and plasma cell survival via BAFF/APRIL engagement, future therapeutic intervention should be based on these indicators (Reali et al., 2020).

Lastly, validated biomarkers, which can detect TLS induced pathology in vivo are required. LME is an attractive imaging biomarker yet not a standardized and sensitive imaging platform (Absinta et al., 2015; Zivadinov et al., 2017). Also, cerebral spinal fluid CXCL13 indicates intrathalamic illness but does not select TLS (Khademi et al., 2011). The future research should focus on the development of combined imaging and the molecular biomarker panel that can identify the presence of border inflammation and predict the further progression of cortical injury. Although serum Neurofilament light chain can be used to assess neuroaxonal injury, it is not a particular measure of meningeal immune response (Disanto et al., 2017).

9. Conclusion

Literature has built up to support that brain border immunity is a pivotal approach in the pathophysiology of progressive neuro inflammatory disease. The idea that the meninges may support compartmentalized CNS inflammatory B-cell rich TLS like structures is supported by human neuropathological findings, advanced imaging findings, biomarker studies, and experimental evidence. Those organized immune niches have a close relationship with subpial cortical demyelination, microglial activation, neuronal loss, and progressive cortical atrophy (Magliozzi et al., 2007; Howell et al., 2011; Calabrese et al., 2015).

Meningeal TLS are organized inflammatory niches which the chemokine and survival signals of CXCL13 CXCR5 and BAFF/APRIL signatures support long-term survival of B-cells and antibody secreting plasma cells in CNS compartments (Pitzalis et al., 2014; Reali et al., 2020). This peripheral localization of immune reactions facilitates an outside-in model of gray matter damage, where soluble cytokines, antibodies, and complement factors will leak into the underlying cortex and induce microglia mediated neurodegenerative mechanisms (Lassmann, 2018).

The clinical effectiveness of the B-cell depletion methods, such as anti-CD20 monoclonal antibodies, offers good clinical data highlighting the principal role played by B-cells in MS pathogenesis (Hauser et al., 2017; Montalban et al., 2017). However, the continuous development of the disease in most patients suggests that compartmentalized inflammatory response in meninges and TLS driven immune circuits are yet to be fully managed with the current treatment options. The further studies must thus aim at identifying TLS heterogeneity and antigen specificity, better experimental models of progressive disease, more reliable imaging and fluid biomarkers of border inflammation, and the development of therapeutic agents that are able to disrupt TLS maintenance and at the same time protect the neurons and synapses.

The molecular and cellular interactions at CNS borders helps to offer a single framework of explaining progressive cortical pathology and introduce novel possibilities of targeted therapeutic intervention to prevent the occurrence of gray matter damage and long-term neurological disability.

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