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Review article

Current trends in autoimmunity and the nervous system

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ABSTRACT

In the broad field of autoimmunity and clinical immunology, experimental evidence over the past few years have demonstrated several connections between the immune system and the nervous system, both central and peripheral, leading to the definition of neuroimmunology and of an immune-brain axis. Indeed, the central nervous system as an immune-privileged site, thanks to the blood-brain barrier, is no longer a dogma as the barrier may be altered during chronic inflammation with disruptive changes of endothelial cells and tight junctions, largely mediated by adenosine receptors and the expression of CD39/CD73. The diseases that encompass the neuroimmunology field vary from primary nervous diseases such as multiple sclerosis to systemic conditions with neuropsychiatric complications, such as systemic lupus erythematosus or vasculitidies. Despite potentially similar clinical manifestations, the pathogenesis of each condition is different, but the interaction between the ultra-specialized structure that is the nervous system and inflammation mediators are crucial. Two examples come from anti-dsDNA cross-reacting with anti-*N*-Methyl-D-Aspartate receptor (NMDAR) antibodies in neuropsychiatric lupus or the new family of antibody-associated neuronal autoimmune diseases including classic paraneoplastic syndromes with antibodies directed to intracellular antigens (Hu, Yo, Ri) and autoimmune encephalitis. In the case of multiple sclerosis, the T cell paradigm is now complicated by the growing evidence of a B cell involvement, particularly via aquaporin antibodies, and their influence on Th1 and Th17 lineages.

Inspired by a productive AARDA-sponsored colloquium among experts we provide a critical review of the literature on the pathogenesis of different immune-mediated diseases with neurologic manifestations and we discuss the basic immunology of the central nervous system and the interaction between immune cells and the peripheral nervous system.

1. Introduction

Autoimmune diseases represent a broad spectrum of systemic conditions which may also manifest with neuropsychiatric manifestations, while chronic inflammation has been recognized as a crucial contributor to most major acute and chronic central nervous system (CNS) disorders and linked to psychiatric disorders such as depression, anxiety, and bipolar disorder. Further, several immune-mediated diseases target primarily the CNS, thus increasing the interest in the field of neuroimmunology and leading to the identification of new immune-mediated disorders, including anti-neuronal autoimmune encephalitis (AIE) and paraneoplastic neurological syndromes (PNS) [1].

We herein aim at discussing some of the most recent lines of evidence in neuroimmunology, particularly in the neuropsychiatric involvement of systemic autoimmune diseases and primary CNS immune diseases. While possibly not representing the whole progress in neuroimmunology that was observed in the past few years, we chose specific representative issues that appear as the most promising for the near future with putative implications well beyond the CNS. The present article is largely based on a colloquium coined "Neuropsychiatric Manifestation of Autoimmune Diseases" sponsored by the American Autoimmune Related Diseases Association, held on November 21, 2015 in Washington, DC.

2. The bases of CNS immunology

For decades, the CNS was thought to be an immune-privileged site, since neurons are separated from the blood vessels by a physical barrier, the blood-brain barrier (BBB), which exerts both protective and homeostatic functions [2]. The BBB is composed of tightly connected endothelial cells that form a highly restrictive barrier and cells are characterized by restricted pinocytosis and transcytosis potential, and have a peculiar expression of dedicated transporters that regulate the influx/efflux of nutritive/toxic compounds, a reduced expression of leukocyte adhesion molecules and the elaboration of specialized luminal structures involved in tight and adherens junctions that efficiently limit the passive diffusion of blood-borne molecules [3]. The BBB is surrounded by basement membrane, pericytes and processes

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of neighboring astrocytes that concur to the neurovascular unit regulating the barrier function, homeostasis and stability [4]. Further, the BBB is also a key player in maintaining the specialized microenvironment, and enabling the communication with the systemic compartment; however, it may be altered during inflammatory processes, leading to both disruptive and non-disruptive changes, with the former accompanied histological modifications, such as endothelial cell damage or tight junction changes, and thus most likely to be harmful. On the other side, non-disruptive changes occur at the molecular level, and may provide a mechanism for the communication across a morphologically intact BBB, and without unselected compromise of the barrier functions essential to CNS homeostasis. Pro-inflammatory cytokines may influence BBB function, as receptors for IL-1β, IL-6, and TNF-α are expressed on the cerebral endothelium [5–7] and systemic IL-1β and TNF-α cause cerebral endothelial activation, and cyclo-oxygenase (COX) expression [8].

3. What lies at the bases of neuroimmunopathology

Several mechanisms have been proposed in the pathogenesis of acute and chronic CNS disorders and these include fascinating models based on experimental evidence.

First, at a molecular level, adenosine, a nucleoside naturally produced by neurons and glial cells, is known to modulate CNS function through a well characterized set of receptors, called P1 purinergic receptors, and recent studies showed that the axis between adenosine and adenosine receptor (AR) is an important regulator of BBB permeability to macromolecules and cells. Animal studies demonstrated that extracellular adenosine positively regulates the migration of lymphocytes into the brain and spinal cord in a model of autoimmune encephalomyelitis, while the A_{2A} AR deficient mice, when reconstituted with wild-type bone marrow cells, develop only very mild signs of autoimmune encephalomyelitis with virtually no $CD4^+$ T cell infiltration in the spinal cord; moreover, in animal models of neurodegenerative diseases, caffeine, a broad spectrum antagonist, inhibits AR, thus preventing the BBB alteration induced by cholesterol or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [3,9]. AR alters BBB permeability in vivo and may be recruited by NECA, a broad spectrum agonist, while both A_1 and A_2A receptors are stimulated by selective agonists (CCPA and CGS21680) and increase cumulatively and transiently BBB permeability facilitating the entry of intravenously infused macromolecules (including immunoglobulins such as the anti-β-amyloid 6E10 antibody) into the CNS [10]. Another mechanism to induce the CNS entry of intravenously delivered macromolecules is the activation of A_{2A} AR, using Lexiscan, an A_{2A} adenosine receptor agonist [3]. Upon exposure to NECA or Lexiscan, murine brain endothelial cells lower their transendothelial electrical resistance, increasing paracellular space and permeability, and furthermore increase the formation of actinomyosin stress fiber, indicating that ARs signaling initiates cytoskeletal organization and cell shape changes, in a reversible manner. Within tight junctions, A_1 and A_{2A} receptor agonist signaling alters protein expression, i.e. claudin-5 and ZO-1, particularly in cultured brain endothelial cells [10–12]. In human brain endothelial cells, recent studies confirmed that agonist-induced A_{2A} receptor signaling transiently permeabilizes the cell monolayer allowing the passage of both drugs and Jurkat human T cells in vitro in a paracellular type, suggesting that also in humans brain cells respond to adenosine in vitro. Thus, by regulating the expression level of factors crucially involved in tight junction integrity/function, signaling induced through receptors for adenosine acts as a potent, endogenous modulator of BBB permeability in mouse models as well as in human cellular models in vitro.

Second, at a cellular level, the expression of CD39/CD73 is a regulator of tissue barrier function, trough the control of ATP levels [13]. In the BBB, CD73 expression is under a low steady state but sensitive to cAMP and HIF1 through its promoter [14], and can regulate homeostasis by preventing high ATP concentrations, and generating adenosine instead, which contribute to an anti-thrombotic microenvironment [15]. The CD39/CD73 axis regulates also the leukocyte migration induced by chemokines and immune cell adhesion to the endothelium, amplified by high ATP levels and limited by adenosine levels [16–19]. Overall, all mechanisms underlying the BBB alterations is not well understood, however, AR signaling is crucial in controlling BBB permeability and it could be used for a precise time-dependent control, with some reagents targeting ARs that could be used to block the entrance in the CNS of inflammatory cells thus preventing the irreversible damage seen in neuro-inflammatory disorders.

Regardless of the *primum movens*, when inflammatory cells and cytokines are released in the CNS, the microglia, endothelia, astrocytes, ependymal cells and meningeal cells lead to innate immunity activation. In particular, microglial cells upregulate major histocompatibility complex (HLA) and costimolatory molecules, moreover releasing cytokines and chemokines that recruit monocytes, lymphocytes and dendritic cells. Microglial cells are crucial for generating and maintaining the inflammatory milieu, while dendritic cells play a role in antigen presentation to invading T cells [20,21]. In parallel with leukocyte entry, neural antigens are accessible to the periphery, as demonstrated in infections, and thus the adaptive immune response is initiated with antigen specific T cells, which, guided by chemoattractants, cross the BBB and infiltrate the CNS, with $CD4^+$ T cells mainly found in the perivascular cuffs and meninges, while $CD8^+$ also in the parenchyma. When T cells encounter their antigen, $CD4^+$ recruit macrophages, leading to the release of proinflammatory cytokines and toxic molecules (i.e. nitric oxide, IL1, IL6 and TNF), while $CD8^+$ cells might attack also oligodendrocytes and neurons [22]. Furthermore, B cells are involved in the CNS inflammation, and release soluble immunoglobulins directed to membrane bound or soluble antigens [23].

The complex interaction between the CNS and the periphery lead to the discovery of functional meningeal lymphatic vessels, that are crucial to the development of the adaptive immune response. Intriguingly, it has been demonstrated that CNS-derived antigens induce an immune response in the deep cervical lymph nodes and that the CNS functional lymphatic system within the meninges that drains cellular and soluble constituents from the CSF into the deep cervical lymph nodes [24–27]. Meningeal lymphatic vessels enable fluids, macromolecules and immune cells to drain from the CNS to the deep cervical lymph nodes, and with new techniques, it has been demonstrated that lymphatic endothelial cells expressing conventional hallmarks line the dural sinuses and exit the CNS at the base of the skull, with scattered lymphatic valves [26,27]. Meningeal lymphatic vessels may be the route for meningeal antigen presenting cells (APC) and soluble factors from the brain to reach deep cervical lymph nodes, in addition to the previously described routes [26,27]. This APC trafficking could be responsible for the generation of self-reactive T cells. Moreover, CNS lymphatic vessels may be equipped with a unique molecular *armamentarium* to maintain T cells anergy, and failure of such mechanism may potentially underlie the etiology of brain autoimmunity, as in multiple sclerosis (MS). Finally, macromolecules and protein aggregates released from the CNS may be removed by the lymphatic system with a system becoming less efficient with aging and resulting in the deposition of protein aggregates, as observed in Alzheimer's diseases [28].

4. Neuropsychiatric involvement is SLE

SLE is the prototype of systemic autoimmune diseases, with chronic, relapsing-remitting clinical manifestations, which may affect the CNS, beside more classically involved organs [29,30]. Neurologic involvement is coined neuropsychiatric-SLE (NPSLE) and may be a frequent and early manifestation, reported in a variable proportion of patients (12–95%), with an enormous impact on the quality of life and associated with a poor prognosis [31–34]. In fact, neurological symptoms and signs are included in the American College of Rheumatology (ACR) classification criteria for SLE [35] and may include also neuropsychiatric manifestations such as cognitive changes, mood and anxiety disorders, confusional state, and psychosis. NPSLE has been reported to be more frequent in women with a peak incidence at childbearing age, thus suggesting a hormonal dysfunction that might promote the disease development and progression in susceptible individuals [36]. Moreover, non-white individuals have a higher risk of developing SLE and NPSLE, suggesting a genetic predisposition [37].

Clinical manifestation of NPSLE vary widely, with the most common being cognitive dysfunction, in up to 80% of patients, mood and anxiety disorders in 57%, headache in 72%, seizure and stroke, especially in presence of anti-phospholipid antibodies. Uncommon manifestations (<5%) include acute confusion, psychosis, and myelopathy, while rarely (<1%) aseptic meningitis, movement disorders and lupus demyelination have been observed [38]. Cognitive dysfunction is the most common NPSLE manifestation when mild-to-moderate, while the severe form develops only in 3–4% of patients [39]. The most common domains affected are the verbal and visual memory, attention and psychomotor speed [40]. Depression is the predominant psychiatric manifestation of NPSLE, with rates as high as 54% of patient, and might be associated with autoimmune CNS lesions [41]. Overall NPSLE is a complex entity, with partially unknown pathogenesis and almost no biomarker, thus the management and treatment might be challenging. Recently, recommendations for the management of NPSLE were published by the European League Against Rheumatism (EULAR) [39].

The pathogenesis of NPSLE has not been fully elucidated as genetic factors have been intensively investigated, and recently the TRPC6 rs7925662 polymorphism was recognized in NPSLE [42], while other studies identified mutations in TREX1, encoding for three-prime repair exonuclease 1 (also known as DNase III) in NPSLE, while TREX1 polymorphisms are associated specifically with seizures in SLE [43,44]. However, serum autoantibodies, particularly anti-dsDNA, are believed to play a key role in the development of NPSLE as anti-dsDNA may cross-react with anti-*N*-Methyl-D-Aspartate receptor (NMDAR) antibodies. These latter antibodies recognize an extracellular conformation-dependent epitope close to the amino acid 369 of the GlyN1 of the NMDAR, and reduce receptor density on the neuronal surface resulting in neuronal dysfunction, in a reversible manner [1]. Anti-NMDAR antibodies are highly specific for anti-NMDAR encephalitis, but have been reported in up to 49% of SLE cases. Whether this cross-mimicry mechanism may be responsible for the NPSLE remains unclear as antibody-mediated brain lesions require the permeability of the BBB, which may be altered by endothelial dysfunction, due to a pro-inflammatory response; anti-NMDAR/dsDNA antibodies have been reported to be able to enter the brain tissue after altering the BBB and cause neuron damage, leading to memory alterations and stress response in mice. Interestingly, animal studies showed that anti-NMDAR/dsDNA antibodies may affect also the offspring of mothers with SLE while in the uterus, due to the lack of BBB, causing cell death and abnormalities in the fetal neocortex. Epidemiological studies support this hypothesis as children of SLE mothers have higher frequency of cognitive defects compared to controls. In animal studies, anti-NMDAR/dsDNA antibodies were reported to increase the female fetus loss, due to enhanced GluN2A expression in the brain stem of female fetuses. In this view, decoy antigens may represent a therapeutic strategy.

Anti-ribosomal P protein antibodies have been reported at high titers in patients with NPSLE, however the association with specific disease manifestations remains debated, particularly at differentiating phenotypes such as psychosis, mood disorders, and other diffuse or focal manifestations [41]. Nonetheless, experimental evidence showed that anti-ribosomal P protein antibodies recognize neurons within the hippocampus, cingulate and primary olfactory piriform cortex and induce a long-term increase in depressive like behavior [45]. Finally, these antibodies may exert a direct neuropathogenic potential, by inducing a rapid and sustained increase in calcium influx and subsequent apoptosis in rat neurons that express a cell-surface protein termed p331, that was designated as the new neuronal surface *P*-antigen [46].

Additional serum autoantibodies have been associated with NPSLE, including anti-MAP-2 antibodies, which are directed towards a cellular protein essential for cytoskeletal integrity and specific to neurons. Recent evidence shows that antibodies directed towards poly (ADP-ribose) polymerase 1 (PARP-1) are less frequent in NPSLE compared to other SLE phenotypes with no kidney injury or neuropsychiatric symptoms [41]. Serum PARP-1 antibodies influence the repair of single-stranded DNA breaks, suggesting a potential role in NPSLE pathogenesis [41].

Serum anti-phospholipid (aPL) antibodies are commonly detected in SLE, and might cause focal neurological symptoms after vascular events [47]. The aPL family targets are anionic phospholipids which can be detected in plasma membranes and regulate the blood clotting cascade, favoring the activation of procoagulants, promoting thrombosis [48]. In this view, anti-phospholipid antibodies, especially lupus anticoagulant and anti- β2 glycoprotein 1 antibodies, may act as direct contributors to the development of thrombosis and focal neurological manifestations. APL antibodies, especially and anti-β2 glycoprotein-1, have been associated with the following NPSLE manifestations: intractable headaches, ischemic stroke and seizures, notably, being the most predictive antibodies for all of these manifestations [49].

5. Antibody-associated autoimmune disorders

Antibody-associated neuronal autoimmune diseases constitute a newly recognized heterogeneous group of syndromes that result from an autoimmune reaction to neural antigens, mainly divided in two groups: classic paraneoplastic syndromes (PNS) with antibodies directed to intracellular antigens (Hu, Yo, Ri) and autoimmune encephalitis (AIE). PNS occur in patients with active cancer, and are characterized by non pathogenic serum autoantibodies. Conversely, AIE-associated autoantibodies are directed towards easy accessible antigens, such as synaptic receptors and membrane antigens, causing direct neuronal injury [1]. AIE are associated with different antibodies directed mainly towards synaptic receptors, including NMDAR, the α-amino-3-hydroxy-5-methyl-4-isoxazol-propionic acid receptor (AMPAR) or the γ-amino-butyric acid B-receptor (GABAbR) [50–52]. Several patients with AIE have autoimmune comorbidities, including systemic diseases and positivity for other serum autoantibodies, such as antinuclear antibodies (ANA), and

anti-thyroid peroxidase antibodies [53] undetectable in the CSF. Most data on AIE pathogenesis were gathered from NMDAR-antibodies found in NMDAR-encephalitis. NMDAR antibodies, as discussed previously, bind to an extracellular conformational epitope region close to the amino acid 369 of the GluN1 NMDAR subunit and reduce the receptor density causing a reversible direct neuronal dysfunction [54,55]. Other autoantibodies may act through different mechanisms, as GABAbR-antibodies influence receptor function relocating the receptor to extrasynaptic sites [1], while AMPAR antibodies reduce the receptor density at synaptic and extrasynaptic sites, along with a reduction of the AMPAR-mediated miniature excitatory postsynaptic currents [53].

The triggers that stimulate the development of synaptic autoimmunity remains unknown, but infections from herpes simplex virus (HSV) have been proposed, since 20% of patients with HSV encephalitis (HSVE) have relapsing symptoms, especially in children, without viral reactivation, new necrotic lesions, or response to acyclovir. Most patients develop a chorea characterized by dystonia or ballismum, agitation, sleep dysfunction and seizures [53]. These patients in some cases develop anti-NMDAR antibodies, suggesting anti-NMDAR encephalitis as a complication responding to immunotherapy [53].

The crucial issue in the diagnostic workup is the identification of serum autoantibodies, and different techniques are available: tissue-based assay, call-based assay, primary cultures of neurons and immunoprecipitation. Currently, most laboratories use cell-based assays for the diagnosis of AIE, as a highly sensitive and specific assay. Since new autoantibodies may not be identified, tissue-based assays are a good screening method, detecting most of the known antibodies, while immunoprecipitation is used in research settings [1]. Serum autoantibodies are usually tested on the CSF, and are usually always present, while the serum might be negative in 14% of cases, or even show false positive results. Antibody titers may also be determined but their relationship with disease activity and outcome has been investigated only in the context of anti-NMDAR-encephalitis [54]. From a clinical standpoint, AIE manifests with different symptoms, anti-NMDAR encephalitis develops as a multistage process, starting from agitation, memory deficits, and then progressing to coma, hypoventilations and autonomic instability. Patients may experience a prodromic syndrome and in a few days develop progressive anxiety, agitation, psychosis, memory deficits and speech reduction. Encephalitis associated with other antibodies, such as LG1, GABA(B)R and AMPAR, are described as classic limbic diseases, but some additional feature may suggest the target antigen: LG1 is usually associated with hyponatremia, GABA(B)R with seizures and up to 50% of cases with small cell lung cancer; some autoantibodies may cause also systemic symptoms, such as diarrhea or gastrointestinal dysfunction in DPPX-antibodies [1,53].

Recently, autoimmunity has been linked to neurodegeneration, with the characterization of IgLON5-antibody in patients with sleep dysfunctions, abnormal behavior, movements and brainstem symptoms with a chronic progressive disease course. In some patients tau protein aggregation in the hypothalamus, thalamus and brainstem has been observed but it remains unclear whether antibodies have a pathogenic potential or represent an epiphenomenon [56]. The treatment is based on immunomodulators and anti-NMDAR encephalitis usually resolves rapidly after treatment.

6. Multiple sclerosis

Multiple sclerosis (MS) is a chronic disease characterized by a variety of neurological signs and symptoms disseminated in time and space, ultimately causing disability in the white population [57]. MS affects almost 2.1 million people worldwide, and approximately 250,000–400,000 only in the United States [58]. Women are predominantly affected, as for most autoimmune diseases but the etiology remains largely unknown, with genes and environmental factors concurring to the disease onset [59]. The MS concordance is 30% in monozygotic twins and 3% in siblings of patients with MS, suggesting an important role of genes in the development of the disease, and lately the HLA-DR1501 and HLA-DQ0601 alleles, alleles, which encode restriction elements of T cells, are associated with an increased risk of developing MS [60].

The pathogenic mechanisms underlying MS have not been elucidated, also reflecting the different phases and the variability in the evolution of the disease [61,62]. In the early phases, microglia and macrophages activate, but the BBB remains intact with limited inflammatory infiltrate seen in the brain, with virtually no demyelination and astro-gliosis. Later in the disease progression, between 6 and 20 weeks, lesions illustrate the most active phase of the disease, and the inflammatory infiltrate begins to appear in lesions, the BBB starts leaking, and there is evidence of demyelination and reactive astrocytes, along with proliferating oligo-dendroglial cells at the lesion borders. Numerous cytokines and chemokines are released into the lesion, including Th1 and Th2 cytokines. After 20 weeks, the number of inflammatory cells decreases and remyelination occurs even if incomplete [63–65].

For decades, MS has been considered a T cell mediated disease, as myelin-protein-specific T cells can be retrieved from the blood or CSF of patients, with the involvement of plasmacytoid dendritic cells [66]. Both $CD4^+$ and $CD8^+$ T cells are present in MS lesions, with $CD4^+$ T cells being found predominantly in the perivascular cuff, and $CD8^+$ T cells being more prevalent in the center and border zone of the lesion [22]. Myelin-protein-specific T cells may be found in blood or CSF of MS patients, but are highly aspecific, being found also in healthy controls [67]. The importance of B cells is represented by the presence of autoantibodies in patient sera but have been neglected for years. Autoantibodies are present also in the CSF, as demonstrated by the presence of oligoclonal bands or intrathecal IgG production, which remain still the only diagnostic laboratory marker for MS. Recently, dominant B-cell clonotypes, containing replacement mutations in their B-cell-receptor genes, have been identified in CSF and lesions of MS patients, suggesting an antigen-driven selection process; moreover, immunoglobulins (predominantly IgG1) are released into the CSF and lesions of MS patients, while plasmablasts and plasmacells can be identified in the CSF of MS patients, and B-cell cytokines, such as tumor-necrosis factor ligand superfamily member 13B (BAFF), are also detected in MS lesions. Although these findings strongly support a role for the humoral immune response in MS, the specificity and function of this response remains to be determined. A serum antibody that binds aquaporin has recently been described in approximately 50% of patients with MS-related neuromyelitis optica, suggesting that might prove helpful as an early diagnostic biomarker [22]. Moreover, B cells have been reported to influence Th1 and Th17 cells, central lymphocyte lineages in MS. In humans, in vitro B cell depletion in MS reduces Th17 cells after polyclonal stimulation [68], and patients with MS undergoing B cell depletion therapies have lower levels of IL-17 production in vitro [69]. Further, recent studies show that B cells from MS patients are capable of directly supporting neuro-antigen-specific Th17 responses [70].

MS pathogenesis has been investigated also at molecular levels and data support the involvement of the purinergic system signaling, with adenosine, which can control the immune system and inflam-

mation, and adenosine receptors that may be considered as novel potent therapeutic targets in MS [71]. It is suggested that adenosine and the AR are involved in modulation of neuroinflammation in MS and experimental models. The reported dysfunction of the CNS AR shows that signaling of this receptor contributes to MS development in patients and in animal models, with a bidirectional effect in neuroinflammation and brain injury. The expression of A_1R in macrophages in both the brain and blood cells is reduced in MS, which proposes its role in macrophage activation and the CNS inflammation, moreover A_1R regulates severity of the disease in animal models, especially in relation with neurobehavioral and neuropathological outcomes, such as demyelination and axonal damage. On the other hand, A_1R activation reduces the CNS inflammatory response, regulating TNFalpha and IL- 6 levels; however, A_1R activation reduces IL-6 production in MS, while in healthy controls A_1R inhibits TNFalpha levels [72–74].

In patients with MS, magnetic resonance imaging (MRI) studies showed that axonal damage and loss ultimately determine the neurologic disability. Axonal damage occurs in the early stages of the disease: $CD8^+$ T cells directly target neurons, while $CD4^+$ response recruit macrophages, leading to the release of inflammatory mediators and toxic molecules, binding of autoantibodies to neuronal surface antigens, followed by complement activation or antibody mediated phagocytosis of axons [22].

Treatment of MS has significantly evolved in the last years; nonetheless, the disease may still lead to chronic disability and a poor quality of life. Currently, first line treatments include immunomodulating agents, such as interferon-beta, glatiramer acetate (GA), teriflunomide, and dimethyl fumarate [75]. Interferon beta is a naturally occurring polypeptide predominantly produced by fibroblasts, its anti-inflammatory effects are the result of the inhibition of T-lymphocyte proliferation, a shift of cytokine response from an inflammatory response to an anti-inflammatory profile, and reduced migration of inflammatory cells across the BBB [76]. GA is a synthetic polypeptide composed of the most prevalent amino acids in myelin basic protein modulates autoreactive T cells, inhibit monocyte activity and induce bystander immune suppression at lesion sites [22,77]. Teriflunomide is an immunomodulatory agent that selectively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase, required for de novo pyrimidine synthesis, reducing cell proliferation, its therapeutic effect in MS is not fully understood but it is probably mediated by a reduced number of circulating lymphocytes [78]. Dimethyl fumarate is an immunomodulatory agent with anti-inflammatory properties, but the mechanism of action in MS is only partially understood, its activity is primarily mediated through activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway, but it is has also been shown to upregulate Nrf2-dependent antioxidant genes [79]. More recently, new treatments approved for MS therapy are natalizumab, alemtuzumab, and fingolimod, showing important beneficial effects for patients with relapsing-remitting MS. Natalizumab was the first monoclonal antibody approved for MS therapy, it is directed against α4-integrin, and blocks the interaction with its ligands. The mechanism of action is largely through preventing adherence of activated leucocytes to inflamed endothelium, thus inhibiting the migration of inflammatory cells into the CNS [80]. Fingolimod is an oral sphingosine 1-phosphate receptor (S1PR) modulator that subsequent to its phosphorylation binds with high affinity to S1PR, which in turn leads to an internalization and degradation of the receptor in different tissues and cell types, including lymphocytes. As a consequence, fingolimod inhibits the ability of autoreactive lymphocytes to egress from the lymph nodes towards the CNS [81]. Finally, B cell depletion demonstrated impressive and sometimes surprising results with alemtuzumab, a recombinant, humanized monoclonal antibody directed against CD52, a cell surface antigen present at high levels on especially T and B cells. Alemtuzumab acts through antibody-dependent cellular cytolysis and complement-mediated lysis following cell surface binding. The mechanism by which alemtuzumab exerts its therapeutic effects in MS is suggested to be by a depletion and repopulation of lymphocytes that reduces the potential for relapses and thereby delays disease progression [82]. Other B cells depleting therapies have been used in MS: antiCD20, such as rituximab, ocrelizumab, and ofatumumab were effective in MS, rituximab trials were terminated in favor of newer molecules with better biological properties and reduced immunogenicity [83].

7. Autoimmunity in psychiatric disorders

Psychosis is a severe mental condition where thoughts or behaviors are disconnected from reality, manifesting with hallucinations (perceptions in the absence of a stimulus), delusions (fixed false beliefs), and irrational behavior. Schizophrenia is the disease with the highest prevalence of psychosis, followed by bipolar affective disorder. Schizophrenia is associated with a dramatic reduction in the quality of life, and life expectancy, due to multiple medical comorbidities [84]. The pathogenesis of psychosis is multifactorial and in the last decade a neurodegenerative hypothesis has been prevailing, with initial studies demonstrating broad pathological changes in the brain parenchyma, such as ventricular enlargement, decreased gray and white matter volumes, decreased overall brain volume and cognitive decline [85]. However, more recently the etiology of psychosis has been linked to a “disconnection syndrome”, where incoming neural activity is poorly integrated across wide regions of the brain [86]. The immune system has also been extensively investigated, suggesting that an inflammatory autoimmune process may be present in some patients, as supported by the detection of specific autoantibodies against neuronal antigens linking the dysfunction paradigm with immune-mediated mechanisms [85]. Moreover, several immune dysfunctions have been identified in schizophrenia: variants of immune system genes have been identified in genome-wide association studies and these may share a common genetic risk factor that give rise to psychotic disease and autoimmune syndromes. Several cytokines have been identified as disease markers, particularly IL-1β, IL-6, and TGF-β, while IL-12, IFN-γ, TNF-α, and sIL-2R, being overexpressed, independently of psychotic episodes or treatment. The gastrointestinal tract may play a role in triggering autoimmunity and represent the connection between the mental disorder and autoimmune manifestations, and celiac disease is more prevalent in patients with psychiatric disorders and schizophrenia, as reported as early as in the 1950s. Celiac disease and schizophrenia share a genetic predisposition, as a susceptibility locus for schizophrenia was identified in the 6p21 region, which also houses the MHC loci and its resident human leukocyte antigen (HLA) genes, of which the HLA-DQ2 heterodimer or DQ8 haplotype are specific for celiac disease [87]. Moreover, IgA antigliadin antibodies (AGA) (indicative of gluten-sensitivity) and tissue transglutaminase antibodies (tTG) (suggestive of celiac disease) are present in 23% and 5% of patients with schizophrenia, respectively, compared to 3% and 1% of controls [88]. Well representing the dichotomy between celiac disease and gluten sensitivity [89], schizophrenic patients testing positive for AGA and with associated gluten sensitivity may represent a subgroup of people with schizophrenia who have a different etiology or manifestation of schizophrenia related to the chronic inflammatory state. The most recent studies agree that schizophrenia is associated with gluten sensi-

tivity, rather than celiac disease, in a subgroup of patients [90]. Furthermore, AGA might have a pathogenetic role in the development of neuropsychiatric comorbidities, as suggested by animal models in which the injection of sera from patients with celiac disease but no neurologic symptom leads to equilibrium alterations, due to a cross-reactivity between Purkinje cell epitopes and gluten peptides. Moreover, gliadin can activate the cytokine production in monocytes and macrophages [91]. In vitro studies show that murine peritoneal macrophages treated with different concentrations of gliadin induce pro-inflammatory genes, including TNF-α, IL-12, IL-15, IFN-β iNOS, IP-10, and MCP-5, indicating that gliadin and its active peptides are capable of increasing expression of a repertoire of inflammatory genes [92]. In schizophrenia, the lymphocyte response to gluten subfractions is similar to celiac disease [93] and it has been hypothesized that celiac disease and gluten sensitivity may trigger psychiatric and neurologic symptoms in genetically susceptible individuals. Asymptomatic patients may have white matter hyperintensities in frontal and occipitoparietal cortices and gray matter reduction in the cortex and caudate nucleus, and patients who are not on a gluten-free diet demonstrate IgA antibodies to brain blood vessels. Gluten ataxia is a well recognized neurologic complication related with celiac disease. Gluten ataxia is characterized by positive AGA, changes in the cerebellum, and ataxic symptoms including upper or lower limb ataxia, gait ataxia, and dysarthria [94]. In addition to AGA, patients with gluten ataxia have oligoclonal bands in their cerebrospinal fluid, inflammation at the cerebellum, and anti-Purkinje cell antibodies. The sera of patients with ataxia express high reactivity with cytoplasmic proteins of neurons in vitro studies, suggesting a difference in neurological effects of sera from celiac disease patients with no neuropathy and patients with gluten ataxia and neuropathy [95]. Epilepsy is another neurologic manifestation of gluten sensitivity or celiac disease.

Gluten-free diet is the only effective treatment for celiac disease and gluten sensitivity but few studies have investigated the role of diet in the management of schizophrenia, with unconclusive results. Nonetheless, in patients with antibodies to anti-tTG or AGA a gluten free diet may lead to a schizophrenia improvement as well as robust amelioration of the extrapyramidal dysfunction [96].

8. Immune mediated and virus associated encephalomyelitis

Encephalomyelitis represents an inflammatory condition of the brain and spinal cord resulting from the immune response to a viral infection. Indeed, viral encephalomyelitis is an important cause of morbidity and mortality worldwide and numerous encephalitic viruses are emerging and re-emerging due to changes in virulence, spread to new geographic regions, and adaptation to new hosts and vectors [97]. Viruses that cause more frequently encephalomyelitis include herpersviruses, RNA viruses, enterovirus, rhabdovirus, alphavirus, flavivirus, and bunyavirus, while paramyxoviruses and arenaviruses can cause acute encephalitis [98,99]. Despite the large number of viruses known to cause neurologic injury, in most cases the etiologic agent cannot be identified. The infection generally begins outside the CNS, and the immune system prevents the virus entry in the CNS; viruses may then enter the CNS as a consequence of viremia or dissemination from a neighboring organ, such as the nasal olfactory epithelium. In physiological conditions, the BBB inhibits the access to neurons while, when ineffective, the virus may attack neurons. Nevertheless, some viruses (HSV, varicella zoster and rabies) use a specialized CNS entry pathway, as they can enter the nerve terminal in peripheral organs, and then use neural transport mechanisms to transport the virions to the neuron cell body where replication occurs [100,101]. During encephalitis, the virus attacks neurons, while more rarely it may attack the endothelial cells causing vascular complications, or the glial cells causing demyelination, encephalopathy or dementia. Some viruses cause widespread infections of the CNS, while other, such has HSV type I affects the hippocampus, causing behavioral alteration. The neuronal damage can be caused directly by the virus, trough inducing cell apoptosis or necrosis, or by the immune response against the infection [102–104]. The inflammatory response directed towards the infected neurons is the major contributor to the clinical phenotype. As a consequence, the astrocytes and microglial cells become activated and proliferate, monocytes and lymphocytes infiltrate the perivascular space and the parenchyma, neurotoxins, reactive oxygen species are produced, and there in an increase of glutamate and pro-inflammatory cytokines production. The acute process may be fatal, but is crucial for recovery and virus clearance via type I IFN which is essential for the early control of virus replication, and both humoral and cellular arms of the adaptive immune response play important roles in clearance, as mice deficient in all components of adaptive immunity develop persistent nonfatal infection. Virus clearance from infected cells in the brain parenchyma and recovery from infection is a multistep process: first, the virus spread to new cells is inhibited, then clearance of cell-free infectious virus [105]. Subsequently, virus-infected cells must be eliminated or intra-cellular virus replication must be permanently suppressed [105]. The immune system eliminates infected cells and the process, due to the peculiar structure of neurons, leads to permanent damage. The elimination of infected cells may occur by virus induced or immune mediated cytolysis, and T cells are crucial mediators as mature neurons are relatively resistant to cell death: $CD4^+$ and $CD8^+$ T cells exhibit their cytotoxic properties and kill the neurons [106]. Non-cytolytic mechanisms are also enabled to control the infection, and in alphavirus encephalitis IFN gamma and anti-viral antibodies are produced, IFN gamma activates the Jak/STAT signaling pathway to block viral replication in motor neurons without toxicity, antibodies are produced against the E2 viral glycoprotein which is expressed on the cell surface of infected neurons [107–109]. This process does not completely eliminate the viral RNA from neurons, also when the encephalitis is recovered. Long-term immunologic tolerance is required to prevent virus reactivation or the development of a chronic disease, and humoral immunity is thought to play a role with antibodies, which however need either to be produced in the CNS by long-lived resident antibody secreting cells or enter the BBB [110]. The long-term control is not always successful, leading to chronic or recurrent neurologic disease in a subgroup of patients.

9. Neural-immune system interaction in the periphery

The nervous system has been recently recognized as an important partner of the immune system in regulating inflammation, and neuronal pathways are physiological mediators of the immune function. Moreover, neuronal function is altered when the immune system is deregulated and in presence of inflammation. Neurons and immune cells interact with each other, especially within innate immune function and animal studies suggest that the two systems share their phylogenetic origin, and neurons are necessary for the innate immune response. In the periphery, neurogenic inflammation has been identified, and specialized (nociceptor) neurons may detect cytokines and other inflammatory products released by activated cells and mediate inflammatory pain [111,112]. Moreover, neuron release substance P with proinflammatory activities first linked to enhanced production of IL-1, TNF-α, and IL-6 by monocytes, causing vasodilation, and act as

immune cells attractants and activators. Conversely, animal studies indicate that substance P and signaling through the neurokinin-1 receptor on myeloid cells leads to enhanced type 1 immunity by promoting the production of IL-12 and IL-23 [113]. Adaptive immunity is also regulated within this axis, and T cells interact with neuropeptides with sympathetic neurons negatively regulating dendritic cells (DC)-dependent priming of $CD8^+$ T cells during a primary viral infection. Moreover, the sympathetic activity negatively regulate type 1 responses via norepinephrine production by reducing IL-12 production by DCs and by acting directly on T cells which express the β2-adrenergic receptor [113]. These functions cumulatively have protective effects against infections, but in the context of chronic inflammation may play a role in the development of autoimmunity. In the neuro-immune axis, the CNS communicates with the periphery trough different pathways: i.e. infiltration of immune cells in the brain, vagus neurons transmission to the nucleus tractus solitarius. Efferent vagus signaling has also been demonstrated to reduce the excessive release of TNF and other pro-inflammatory cytokines, and has been named the "cholinergic anti-inflammatory pathway", which is mediated by the alpha7nicotinic acetylcholine receptor [114]. These findings lead to the definition of a new immunoregulatory mechanism, the inflammatory reflex, in which the vagus nerve fibers communicate with the immune system to control an excessive pro-inflammatory signaling. Splenic nerves are involved in the control of inflammation, as a subset of splenic T cells containing functional choline acetyltransferase are crucial mediators of the inflammatory reflex. The neurons influence DC migration and motility, and DC have been located in close proximity to sensory neurons in skin, lung, and gut. Moreover, immature DC are responsive to both norepinephrine and neuropeptides [113]. Motility might also be affected, as sensory nerves produce CXCL12 and VEGF-A, which are required for arteriogenesis and vascular branching.

In autoimmune diseases, chronic inflammation favors an inflammatory neuronal configuration characterized by local neuronal imbalance (favoring sensory over sympathetic nerve fibers) and increased systemic sympathetic nerve activity, with the consequence of emptying energy stores and supporting tissue inflammation and destruction [115]. Animal models of inflammatory arthritis show that the sympathetic nervous system may exert both anti-inflammatory and pro-inflammatory properties, depending on the site of its interaction with immune cells [116,117]. Adaptive immunity contributes to the dual effects of the sympathetic nervous system, as it has been demonstrated that activated B-cells decrease inflammation upon β-adrenergic stimulation [118]. However at this stage of disease, the density of sympathetic nerve fibers is reduced in inflamed tissue, and the signaling through the β-adrenergic receptor might be disturbed [119].

In patients with rheumatoid arthritis, a loss of sympathetic nerve fibers and/or maintenance or increase in sensory nerve fibers has been documented, moreover also other chronic inflammatory conditions have been demonstrated to have similar findings [120–122]. Chronic inflammation has also been associated with an increase in systemic sympathetic activity and might be linked to increased cardiovascular risk [123]. In contrast to the increased activity of the sympathetic nervous system, activity of the parasympathetic nervous system appears to be reduced in chronic inflammation.

10. Concluding remarks

The road to understanding the mechanisms of neuroimmunology is fascinating and will likely lead to the disruption of other dogmatic assumptions, similar to what has been observed for the BBB integrity during inflammation over the past decade. The experimental and clinical evidence, associated with the powerful molecular tools, is expected to overcome the limited availability of biological samples from patients and this is likely to encourage the search for new biomarkers or unsuspected mechanisms, such as the microbiota [124,125]. Furthermore, enormous unanswered questions remain to be addressed, as in the case of the immunology of autism spectrum disorder [126] which is expected to provide new data in an exponential fashion [127], thanks to the enormous social pressure related to the growing incidence of the disease, or in overlooked conditions such as myasthenia gravis [128–130]. We are convinced that, despite the specialistic view of neurological disorders, only a multidisciplinary approach to research will provide sufficient insights to address the common key questions on the pathogenesis and etiology of neuropsychiatric immune-mediated diseases.

References

[1] R. Hoftberger, Neuroimmunology: an expanding frontier in autoimmunity, Front. Immunol. 6 (2015) 206.
[2] B.V. Zlokovic, The blood-brain barrier in health and chronic neurodegenerative disorders, Neuron 57 (2008) 178–201.
[3] M.S. Bynoe, C. Viret, A. Yan, D.G. Kim, Adenosine receptor signaling: a key to opening the blood-brain door, Fluids Barriers CNS 12 (2015) 20.
[4] B. Obermeier, R. Daneman, R.M. Ransohoff, Development, maintenance and disruption of the blood-brain barrier, Nat. Med. 19 (2013) 1584–1596.
[5] A. Ericsson, C. Liu, R.P. Hart, P.E. Sawchenko, Type 1 interleukin-1 receptor in the rat brain: distribution, regulation, and relationship to sites of IL-1-induced cellular activation, J. Comp. Neurol. 361 (1995) 681–698.
[6] L. Vallieres, S. Rivest, Regulation of the genes encoding interleukin-6, its receptor, and gp130 in the rat brain in response to the immune activator lipopolysaccharide and the proinflammatory cytokine interleukin-1beta, J. Neurochem. 69 (1997) 1668–1683.
[7] S. Nadeau, S. Rivest, Effects of circulating tumor necrosis factor on the neuronal activity and expression of the genes encoding the tumor necrosis factor receptors (p55 and p75) in the rat brain: a view from the blood-brain barrier, Neuroscience 93 (1999) 1449–1464.
[8] A. Varatharaj, I. Galea, The blood-brain barrier in systemic inflammation, Brain Behav. Immun. (2016).
[9] J.H. Mills, L.F. Thompson, C. Mueller, A.T. Waickman, S. Jalkanen, J. Niemela, et al., CD73 is required for efficient entry of lymphocytes into the central nervous system during experimental autoimmune encephalomyelitis, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 9325–9330.
[10] A.J. Carman, J.H. Mills, A. Krenz, D.G. Kim, M.S. Bynoe, Adenosine receptor signaling modulates permeability of the blood-brain barrier, J. Neurosci. 31 (2011) 13272–13280.
[11] B. Wojciak-Stothard, S. Potempa, T. Eichholtz, A.J. Ridley, Rho and Rac but not Cdc42 regulate endothelial cell permeability, J. Cell Sci. 114 (2001) 1343–1355.
[12] B.E. Dewi, T. Takasaki, I. Kurane, In vitro assessment of human endothelial cell permeability: effects of inflammatory cytokines and dengue virus infection, J. Virol. Methods 121 (2004) 171–180.
[13] S.P. Colgan, H.K. Eltzschig, T. Eckle, L.F. Thompson, Physiological roles for ecto-5'-nucleotidase (CD73), Purinergic Signal 2 (2006) 351–360.
[14] S. Narravula, P.F. Lennon, B.U. Mueller, S.P. Colgan, Regulation of endothelial CD73 by adenosine: paracrine pathway for enhanced endothelial barrier function, J. Immunol. 165 (2000) 5262–5268.
[15] P. Koszalka, B. Ozuyaman, Y. Huo, A. Zernecke, U. Flogel, N. Braun, et al., Targeted disruption of cd73/ecto-5'-nucleotidase alters thromboregulation and augments vascular inflammatory response, Circ. Res. 95 (2004) 814–821.
[16] J. Linden, Cell biology. Purinergic chemotaxis, Science 314 (2006) 1689–1690.
[17] M. Salmi, S. Jalkanen, Cell-surface enzymes in control of leukocyte trafficking, Nat. Rev. Immunol. 5 (2005) 760–771.
[18] D. Petrovic-Djergovic, M.C. Hyman, J.J. Ray, D. Bouis, S.H. Visovatti, T. Hayasaki, et al., Tissue-resident ecto-5' nucleotidase (CD73) regulates leukocyte trafficking in the ischemic brain, J. Immunol. 188 (2012) 2387–2398.
[19] M. Takedachi, D. Qu, Y. Ebisuno, H. Oohara, M.L. Joachims, S.T. McGee, et al., CD73-generated adenosine restricts lymphocyte migration into draining lymph nodes, J. Immunol. 180 (2008) 6288–6296.

[20] F.L. Heppner, M. Greter, D. Marino, J. Falsig, G. Raivich, N. Hovelmeyer, et al., Experimental autoimmune encephalomyelitis repressed by microglial paralysis, Nat. Med. 11 (2005) 146–152.
[21] M. Greter, F.L. Heppner, M.P. Lemos, B.M. Odermatt, N. Goebels, T. Laufer, et al., Dendritic cells permit immune invasion of the CNS in an animal model of multiple sclerosis, Nat. Med. 11 (2005) 328–334.
[22] B. Hemmer, S. Nessler, D. Zhou, B. Kieseier, H.P. Hartung, Immunopathogenesis and immunotherapy of multiple sclerosis, Nat. Clin. Pract. Neurol. 2 (2006) 201–211.
[23] A. Alter, M. Duddy, S. Hebert, K. Biernacki, A. Prat, J.P. Antel, et al., Determinants of human B cell migration across brain endothelial cells, J. Immunol. 170 (2003) 4497–4505.
[24] H.F. Cserr, C.J. Harling-Berg, P.M. Knopf, Drainage of brain extracellular fluid into blood and deep cervical lymph and its immunological significance, Brain Pathol. 2 (1992) 269–276.
[25] S. Kida, A. Pantazis, R.O. Weller, CSF drains directly from the subarachnoid space into nasal lymphatics in the rat. Anatomy, histology and immunological significance, Neuropathol. Appl. Neurobiol. 19 (1993) 480–488.
[26] A. Louveau, I. Smirnov, T.J. Keyes, J.D. Eccles, S.J. Rouhani, J.D. Peske, et al., Structural and functional features of central nervous system lymphatic vessels, Nature 523 (2015) 337–341.
[27] A. Aspelund, S. Antila, S.T. Proulx, T.V. Karlsen, S. Karaman, M. Detmar, et al., A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules, J. Exp. Med. 212 (2015) 991–999.
[28] A. Louveau, T.H. Harris, J. Kipnis, Revisiting the mechanisms of CNS immune privilege, Trends Immunol. 36 (2015) 569–577.
[29] A. Kuhn, A. Landmann, The classification and diagnosis of cutaneous lupus erythematosus, J. Autoimmun. 48–49 (2014) 14–19.
[30] C. Yu, M.E. Gershwin, C. Chang, Diagnostic criteria for systemic lupus erythematosus: a critical review, J. Autoimmun. 48–49 (2014) 10–13.
[31] H. Ainiala, J. Loukkola, J. Peltola, M. Korpela, A. Hietaharju, The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus, Neurology 57 (2001) 496–500.
[32] G.K. Bertsias, D.T. Boumpas, Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations, Nat. Rev. Rheumatol. 6 (2010) 358–367.
[33] A.M. Borowoy, J.E. Pope, E. Silverman, P.R. Fortin, C. Pineau, C.D. Smith, et al., Neuropsychiatric lupus: the prevalence and autoantibody associations depend on the definition: results from the 1000 faces of lupus cohort, Semin. Arthritis Rheum. 42 (2012) 179–185.
[34] A. Unterman, J.E. Nolte, M. Boaz, M. Abady, Y. Shoenfeld, G. Zandman-Goddard, Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis, Semin. Arthritis Rheum. 41 (2011) 1–11.
[35] E.M. Tan, A.S. Cohen, J.F. Fries, A.T. Masi, D.J. McShane, N.F. Rothfield, et al., The 1982 revised criteria for the classification of systemic lupus erythematosus, Arthritis Rheum. 25 (1982) 1271–1277.
[36] Y. Ghodke-Puranik, T.B. Niewold, Immunogenetics of systemic lupus erythematosus: a comprehensive review, J. Autoimmun. 64 (2015) 125–136.
[37] L. Ines, C. Duarte, R.S. Silva, A.S. Teixeira, F.P. Fonseca, J.A. da Silva, Identification of clinical predictors of flare in systemic lupus erythematosus patients: a 24-month prospective cohort study, Rheumatol. Oxf. 53 (2014) 85–89.
[38] J.G. Hanly, ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables, Lupus 13 (2004) 861–864.
[39] G.K. Bertsias, J.P. Ioannidis, M. Aringer, E. Bollen, S. Bombardieri, I.N. Bruce, et al., EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs, Ann. Rheum. Dis. 69 (2010) 2074–2082.
[40] J.G. Hanly, Neuropsychiatric lupus, Rheum. Dis. Clin. North Am. 31 (2005) 273–298.
[41] H. Jeltsch-David, S. Muller, Neuropsychiatric systemic lupus erythematosus: pathogenesis and biomarkers, Nat. Rev. Neurol. 10 (2014) 579–596.
[42] G.A. Ramirez, C. Lanzani, E.P. Bozzolo, L. Citterio, L. Zagato, N. Casamassima, et al., TRPC6 gene variants and neuropsychiatric lupus, J. Neuroimmunol. 288 (2015) 21–24.
[43] B. de Vries, G.M. Steup-Beekman, J. Haan, E.L. Bollen, J. Luyendijk, R.R. Frants, et al., TREX1 gene variant in neuropsychiatric systemic lupus erythematosus, Ann. Rheum. Dis. 69 (2010) 1886–1887.
[44] B. Namjou, P.H. Kothari, J.A. Kelly, S.B. Glenn, J.O. Ojwang, A. Adler, et al., Evaluation of the TREX1 gene in a large multi-ancestral lupus cohort, Genes Immun. 12 (2011) 270–279.
[45] A. Katzav, I. Solodeev, O. Brodsky, J. Chapman, C.G. Pick, M. Blank, et al., Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system, Arthritis Rheum. 56 (2007) 938–948.
[46] S. Matus, P.V. Burgos, M. Bravo-Zehnder, R. Kraft, O.H. Porras, P. Farias, et al., Antiribosomal-P autoantibodies from psychiatric lupus target a novel neuronal surface protein causing calcium influx and apoptosis, J. Exp. Med. 204 (2007) 3221–3234.
[47] J.A. Gomez-Puerta, R. Cervera, Diagnosis and classification of the antiphospholipid syndrome, J. Autoimmun. 48–49 (2014) 20–25.
[48] E. Raschi, C.B. Chighizola, C. Grossi, N. Ronda, R. Gatti, P.L. Meroni, et al., beta2-glycoprotein I, lipopolysaccharide and endothelial TLR4: three players in the two hit theory for anti-phospholipid-mediated thrombosis, J. Autoimmun. 55 (2014) 42–50.
[49] T. Hawro, A. Bogucki, M. Krupinska-Kun, M. Maurer, A. Wozniacka, Intractable headaches, ischemic stroke, and seizures are linked to the presence of anti-beta2GPI antibodies in patients with systemic lupus erythematosus, PLoS One 10 (2015) e0119911.
[50] J. Dalmau, E. Tuzun, H.Y. Wu, J. Masjuan, J.E. Rossi, A. Voloschin, et al., Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma, Ann. Neurol. 61 (2007) 25–36.
[51] E. Lancaster, M. Lai, X. Peng, E. Hughes, R. Constantinescu, J. Raizer, et al., Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen, Lancet Neurol. 9 (2010) 67–76.
[52] M. Lai, E.G. Hughes, X. Peng, L. Zhou, A.J. Gleichman, H. Shu, et al., AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location, Ann. Neurol. 65 (2009) 424–434.
[53] F. Leypoldt, T. Armangue, J. Dalmau, Autoimmune encephalopathies, Ann. N. Y. Acad. Sci. 1338 (2015) 94–114.
[54] N. Gresa-Arribas, M.J. Titulaer, A. Torrents, E. Aguilar, L. McCracken, F. Leypoldt, et al., Antibody titres at diagnosis and during follow-up of anti-NMDA receptor encephalitis: a retrospective study, Lancet Neurol. 13 (2014) 167–177.
[55] M.J. Titulaer, L. McCracken, I. Gabilondo, T. Armangue, C. Glaser, T. Iizuka, et al., Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study, Lancet Neurol. 12 (2013) 157–165.
[56] L. Sabater, C. Gaig, E. Gelpi, L. Bataller, J. Lewerenz, E. Torres-Vega, et al., A novel non-rapid-eye movement and rapid-eye-movement parasomnia with sleep breathing disorder associated with antibodies to IgLON5: a case series, characterisation of the antigen, and post-mortem study, Lancet Neurol. 13 (2014) 575–586.
[57] J.H. Noseworthy, C. Lucchinetti, M. Rodriguez, B.G. Weinshenker, Multiple sclerosis, N. Engl. J. Med. 343 (2000) 938–952.
[58] D. Karussis, The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review, J. Autoimmun. 48–49 (2014) 134–142.
[59] J.A. Hollenbach, J.R. Oksenberg, The immunogenetics of multiple sclerosis: a comprehensive review, J. Autoimmun. 64 (2015) 13–25.
[60] C. Selmi, E. Mix, U.K. Zettl, A clear look at the neuroimmunology of multiple sclerosis and beyond, Autoimmun. Rev. 11 (2012) 159–162.
[61] L. Steinman, Y. Shoenfeld, From defining antigens to new therapies in multiple sclerosis: honoring the contributions of Ruth Arnon and Michael Sela, J. Autoimmun. 54 (2014) 1–7.
[62] A. Ben-Nun, N. Kaushansky, N. Kawakami, G. Krishnamoorthy, K. Berer, R. Liblau, et al., From classic to spontaneous and humanized models of multiple sclerosis: impact on understanding pathogenesis and drug development, J. Autoimmun. 54 (2014) 33–50.
[63] F.W. Gay, T.J. Drye, G.W. Dick, M.M. Esiri, The application of multifactorial cluster analysis in the staging of plaques in early multiple sclerosis. Identification and characterization of the primary demyelinating lesion, Brain 120 (Pt 8) (1997) 1461–1483.
[64] B. Cannella, C.S. Raine, The adhesion molecule and cytokine profile of multiple sclerosis lesions, Ann. Neurol. 37 (1995) 424–435.
[65] B.D. Trapp, J. Peterson, R.M. Ransohoff, R. Rudick, S. Mork, L. Bo, Axonal transection in the lesions of multiple sclerosis, N. Engl. J. Med. 338 (1998) 278–285.
[66] F.V. Duraes, C. Lippens, K. Steinbach, J. Dubrot, D. Brighouse, N. Bendriss-Vermare, et al., pDC therapy induces recovery from EAE by recruiting endogenous pDC to sites of CNS inflammation, J. Autoimmun. (2015).
[67] M. Pette, K. Fujita, B. Kitze, J.N. Whitaker, E. Albert, L. Kappos, et al., Myelin basic protein-specific T lymphocyte lines from MS patients and healthy individuals, Neurology 40 (1990) 1770–1776.
[68] A. Bar-Or, L. Fawaz, B. Fan, P.J. Darlington, A. Rieger, C. Ghorayeb, et al., Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS?, Ann. Neurol. 67 (2010) 452–461.
[69] T.A. Barr, P. Shen, S. Brown, V. Lampropoulou, T. Roch, S. Lawrie, et al., B cell depletion therapy ameliorates autoimmune disease through ablation of IL-6-producing B cells, J. Exp. Med. 209 (2012) 1001–1010.
[70] S.J. Ireland, A.A. Guzman, E.M. Frohman, N.L. Monson, B cells from relapsing remitting multiple sclerosis patients support neuro-antigen-specific Th17 responses, J. Neuroimmunol. 291 (2016) 46–53.
[71] E. Safarzadeh, F. Jadidi-Niaragh, M. Motallebnezhad, M. Yousefi, The role of adenosine and adenosine receptors in the immunopathogenesis of multiple sclerosis, Inflamm. Res. 65 (2016) 511–520.

[72] J.B. Johnston, C. Silva, G. Gonzalez, J. Holden, K.G. Warren, L.M. Metz, et al., Diminished adenosine A1 receptor expression on macrophages in brain and blood of patients with multiple sclerosis, Ann. Neurol. 49 (2001) 650–658.
[73] T.W. Stone, S. Ceruti, M.P. Abbracchio, Adenosine receptors and neurological disease: neuroprotection and neurodegeneration, Handb. Exp. Pharmacol. (2009) 535–587.
[74] J.F. Chen, P.K. Sonsalla, F. Pedata, A. Melani, M.R. Domenici, P. Popoli, et al., Adenosine A2A receptors and brain injury: broad spectrum of neuroprotection, multifaceted actions and "fine tuning" modulation, Prog. Neurobiol. 83 (2007) 310–331.
[75] O. Torkildsen, K.M. Myhr, L. Bo, Disease-modifying treatments for multiple sclerosis - a review of approved medications, Eur. J. Neurol. 23 (1) (2016) 18–27.
[76] S. Dhib-Jalbut, S. Marks, Interferon-beta mechanisms of action in multiple sclerosis, Neurology 74 (1) (2010) S17–S24.
[77] M.K. Racke, A.E. Lovett-Racke, N.J. Karandikar, The mechanism of action of glatiramer acetate treatment in multiple sclerosis, Neurology 74 (1) (2010) S25–S30.
[78] A. Papadopoulou, L. Kappos, T. Sprenger, Teriflunomide for oral therapy in multiple sclerosis, Expert Rev. Clin. Pharmacol. 5 (2012) 617–628.
[79] R.A. Linker, R. Gold, Dimethyl fumarate for treatment of multiple sclerosis: mechanism of action, effectiveness, and side effects, Curr. Neurol. Neurosci. Rep. 13 (2013) 394.
[80] C.H. Polman, P.W. O'Connor, E. Havrdova, M. Hutchinson, L. Kappos, D.H. Miller, et al., A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis, N. Engl. J. Med. 354 (2006) 899–910.
[81] L. Kappos, E.W. Radue, P. O'Connor, C. Polman, R. Hohlfeld, P. Calabresi, et al., A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis, N. Engl. J. Med. 362 (2010) 387–401.
[82] J.W. Brown, A.J. Coles, Alemtuzumab: evidence for its potential in relapsing-remitting multiple sclerosis, Drug Des. Devel Ther. 7 (2013) 131–138.
[83] R. Milo, Therapeutic strategies targeting B-cells in multiple sclerosis, Autoimmun. Rev. 15 (2016) 714–718.
[84] J. van Os, S. Kapur, Schizophrenia, Lancet 374 (2009) 635–645.
[85] K. Pathmanandavel, J. Starling, R.C. Dale, F. Brilot, Autoantibodies and the immune hypothesis in psychotic brain diseases: challenges and perspectives, Clin. Dev. Immunol. 2013 (2013) 257184.
[86] K.J. Friston, Schizophrenia and the disconnection hypothesis, Acta Psychiatr. Scand. Suppl. 395 (1999) 68–79.
[87] E.G. Severance, R.H. Yolken, W.W. Eaton, Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling, Schizophr. Res. (2014).
[88] N.G. Cascella, D. Kryszak, B. Bhatti, P. Gregory, D.L. Kelly, J.P. Mc Evoy, et al., Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population, Schizophr. Bull. 37 (2011) 94–100.
[89] D. Samaroo, F. Dickerson, D.D. Kasarda, P.H. Green, C. Briani, R.H. Yolken, et al., Novel immune response to gluten in individuals with schizophrenia, Schizophr. Res. 118 (2010) 248–255.
[90] B. Porcelli, V. Verdino, L. Bossini, L. Terzuoli, A. Fagiolini, Celiac and non-celiac gluten sensitivity: a review on the association with schizophrenia and mood disorders, Auto. Immun. Highlights 5 (2014) 55–61.
[91] L. Palova-Jelinkova, D. Rozkova, B. Pecharova, J. Bartova, A. Sediva, H. Tlaskalova-Hogenova, et al., Gliadin fragments induce phenotypic and functional maturation of human dendritic cells, J. Immunol. 175 (2005) 7038–7045.
[92] K.E. Thomas, A. Sapone, A. Fasano, S.N. Vogel, Gliadin stimulation of murine macrophage inflammatory gene expression and intestinal permeability are MyD88-dependent: role of the innate immune response in Celiac disease, J. Immunol. 176 (2006) 2512–2521.
[93] J.R. Jackson, W.W. Eaton, N.G. Cascella, A. Fasano, D.L. Kelly, Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity, Psychiatr. Q. 83 (2012) 91–102.
[94] M. Hadjivassiliou, R. Grunewald, B. Sharrack, D. Sanders, A. Lobo, C. Williamson, et al., Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics, Brain 126 (2003) 685–691.
[95] S. Boscolo, A. Sarich, A. Lorenzon, M. Passoni, V. Rui, M. Stebel, et al., Gluten ataxia: passive transfer in a mouse model, Ann. N. Y. Acad. Sci. 1107 (2007) 319–328.
[96] J. Jackson, W. Eaton, N. Cascella, A. Fasano, D. Warfel, S. Feldman, et al., A gluten-free diet in people with schizophrenia and anti-tissue transglutaminase or anti-gliadin antibodies, Schizophr. Res. 140 (2012) 262–263.
[97] D.E. Griffin, Viral encephalomyelitis, PLoS Pathog. 7 (2011) e1002004.
[98] C.A. Glaser, S. Honarmand, L.J. Anderson, D.P. Schnurr, B. Forghani, C.K. Cossen, et al., Beyond viruses: clinical profiles and etiologies associated with encephalitis, Clin. Infect. Dis. 43 (2006) 1565–1577.
[99] D.E. Griffin, Emergence and re-emergence of viral diseases of the central nervous system, Prog. Neurobiol. 91 (2010) 95–101.
[100] G. Ugolini, Use of rabies virus as a transneuronal tracer of neuronal connections: implications for the understanding of rabies pathogenesis, Dev. Biol. (Basel) 131 (2008) 493–506.
[101] M.G. Lyman, L.W. Enquist, Herpesvirus interactions with the host cytoskeleton, J. Virol. 83 (2009) 2058–2066.
[102] M.B. Havert, B. Schofield, D.E. Griffin, D.N. Irani, Activation of divergent neuronal cell death pathways in different target cell populations during neuroadapted sindbis virus infection of mice, J. Virol. 74 (2000) 5352–5356.
[103] C.D. Conrady, D.A. Drevets, D.J. Carr, Herpes simplex type I (HSV-1) infection of the nervous system: is an immune response a good thing?, J. Neuroimmunol. 220 (2010) 1–9.
[104] I.P. Greene, E.Y. Lee, N. Prow, B. Ngwang, D.E. Griffin, Protection from fatal viral encephalomyelitis: AMPA receptor antagonists have a direct effect on the inflammatory response to infection, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 3575–3580.
[105] D.E. Griffin, Recovery from viral encephalomyelitis: immune-mediated noncytolytic virus clearance from neurons, Immunol. Res. 47 (2010) 123–133.
[106] P.S. Vernon, D.E. Griffin, Characterization of an in vitro model of alphavirus infection of immature and mature neurons, J. Virol. 79 (2005) 3438–3447.
[107] R. Burdeinick-Kerr, D. Govindarajan, D.E. Griffin, Noncytolytic clearance of sindbis virus infection from neurons by gamma interferon is dependent on Jak/STAT signaling, J. Virol. 83 (2009) 3429–3435.
[108] S. Ubol, B. Levine, S.H. Lee, N.S. Greenspan, D.E. Griffin, Roles of immunoglobulin valency and the heavy-chain constant domain in antibody-mediated downregulation of Sindbis virus replication in persistently infected neurons, J. Virol. 69 (1995) 1990–1993.
[109] B. Levine, J.M. Hardwick, B.D. Trapp, T.O. Crawford, R.C. Bollinger, D.E. Griffin, Antibody-mediated clearance of alphavirus infection from neurons, Science 254 (1991) 856–860.
[110] W.R. Tyor, S. Wesselingh, B. Levine, D.E. Griffin, Long term intraparenchymal Ig secretion after acute viral encephalitis in mice, J. Immunol. 149 (1992) 4016–4020.
[111] V.A. Pavlov, K.J. Tracey, Neural circuitry and immunity, Immunol. Res. 63 (2015) 38–57.
[112] I.M. Chiu, C.A. von Hehn, C.J. Woolf, Neurogenic inflammation and the peripheral nervous system in host defense and immunopathology, Nat. Neurosci. 15 (2012) 1063–1067.
[113] J. Ordovas-Montanes, S. Rakoff-Nahoum, S. Huang, L. Riol-Blanco, O. Barreiro, U.H. von Andrian, The regulation of immunological processes by peripheral neurons in homeostasis and disease, Trends Immunol. 36 (2015) 578–604.
[114] L.V. Borovikova, S. Ivanova, M. Zhang, H. Yang, G.I. Botchkina, L.R. Watkins, et al., Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin, Nature 405 (2000) 458–462.
[115] G. Pongratz, R.H. Straub, Role of peripheral nerve fibres in acute and chronic inflammation in arthritis, Nat. Rev. Rheumatol. 9 (2013) 117–126.
[116] D. Lorton, C. Lubahn, N. Klein, J. Schaller, D.L. Bellinger, Dual role for noradrenergic innervation of lymphoid tissue and arthritic joints in adjuvant-induced arthritis, Brain Behav. Immun. 13 (1999) 315–334.
[117] P. Harle, D. Mobius, D.J. Carr, J. Scholmerich, R.H. Straub, An opposing time-dependent immune-modulating effect of the sympathetic nervous system conferred by altering the cytokine profile in the local lymph nodes and spleen of mice with type II collagen-induced arthritis, Arthritis Rheum. 52 (2005) 1305–1313.
[118] G. Pongratz, M. Melzer, R.H. Straub, The sympathetic nervous system stimulates anti-inflammatory B cells in collagen-type II-induced arthritis, Ann. Rheum. Dis. 71 (2012) 432–439.
[119] M.S. Lombardi, A. Kavelaars, P.M. Cobelens, R.E. Schmidt, M. Schedlowski, C.J. Heijnen, Adjuvant arthritis induces down-regulation of G protein-coupled receptor kinases in the immune system, J. Immunol. 166 (2001) 1635–1640.
[120] R.H. Straub, F. Grum, U. Strauch, S. Capellino, F. Bataille, A. Bleich, et al., Anti-inflammatory role of sympathetic nerves in chronic intestinal inflammation, Gut 57 (2008) 911–921.
[121] A. Naukkarinen, B.J. Nickoloff, E.M. Farber, Quantification of cutaneous sensory nerves and their substance P content in psoriasis, J. Invest Dermatol 92 (1989) 126–129.
[122] L.E. Miller, H.P. Justen, J. Scholmerich, R.H. Straub, The loss of sympathetic nerve fibers in the synovial tissue of patients with rheumatoid arthritis is accompanied by increased norepinephrine release from synovial macrophages, FASEB J. 14 (2000) 2097–2107.
[123] R.M. Bruno, L. Ghiadoni, G. Seravalle, R. Dell'oro, S. Taddei, G. Grassi, Sympathetic regulation of vascular function in health and disease, Front. Physiol. 3 (2012) 284.
[124] C.T. Ellebrecht, G. Srinivas, K. Bieber, D. Banczyk, K. Kalies, S. Kunzel, et al., Skin microbiota-associated inflammation precedes autoantibody induced

tissue damage in experimental epidermolysis bullosa acquisita, J. Autoimmun. (2015).
[125] J. Peng, S. Narasimhan, J.R. Marchesi, A. Benson, F.S. Wong, L. Wen, Long term effect of gut microbiota transfer on diabetes development, J. Autoimmun. 53 (2014) 85–94.
[126] L. Matelski, J. Van de Water, Risk factors in autism: thinking outside the brain, J. Autoimmun. (2015).
[127] R.A. Luna, T.C. Savidge, K.C. Williams, The brain-gut-microbiome axis: what role does it play in autism spectrum disorder?, Curr. Dev. Disord. Rep. 3 (2016) 75–81.
[128] S. Berrih-Aknin, Myasthenia Gravis: paradox versus paradigm in autoimmunity, J. Autoimmun. 52 (2014) 1–28.
[129] P. Zisimopoulou, P. Evangelakou, J. Tzartos, K. Lazaridis, V. Zouvelou, R. Mantegazza, et al., A comprehensive analysis of the epidemiology and clinical characteristics of anti-LRP4 in myasthenia gravis, J. Autoimmun. 52 (2014) 139–145.
[130] S. Berrih-Aknin, M. Frenkian-Cuvelier, B. Eymard, Diagnostic and clinical classification of autoimmune myasthenia gravis, J. Autoimmun. 48–49 (2014) 143–148.