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Review article

Autoimmunity, neuroinflammation, pathogen load: A decisive crosstalk in neuropsychiatric SLE

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ABSTRACT

Depicting the cellular and molecular bases of the continuous dialogue existing between the peripheral immune and the central nervous systems, as in neurolupus, is fundamental to improve, and better apprehend the role played by immune cells and mediators in the initiation and progression of neurological and psychiatric diseases, which nowadays remain a major public health issue. The relative frequency of neurological symptoms occurring in systemic autoimmunity is particularly worrying as, for example, two-thirds of patients with lupus will eventually experience the disabling effects of neuropsychiatric lupus. Neurolupus is a particularly severe form of lupus with wide-ranging symptoms, which contribute to increased mortality and morbidity in patients. In this context, infections, which suddenly trigger exacerbations of the otherwise mild lupus disease, may drive the progression of neuroinflammation and neurodegeneration *via* different mechanisms involving a network of effector molecules and cells. The complex interaction of neuroimmunology and neuroinfectiology represents a genuine challenge for basic scientists and clinicians to understand the mechanisms that are implicated, and identify possible biomarkers of severity that might predict the development of this devastating form of lupus. The ultimate goal is to design appropriate, personalised therapeutic strategies to improve the outcome of the disease.

Contents

Abbreviations: Abs, antibodies; AID, autoimmune disease; BBB, blood-brain barrier; CMA, chaperone-mediated autophagy; CNS, central nervous system; CSF, cerebrospinal fluid; DAMP, damage-associated molecular pattern; DCs, dendritic cells; ECs, endothelial cells; ICs, immune complexes; IFN, interferon; Ig, immunoglobulin; IL, interleukin; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NMDAR, *N*-methyl-D-aspartate receptor; NPSLE, neuropsychiatric systemic lupus erythematosus; NR2, *N*-methyl-$_D$-aspartate receptor subtype 2; NSPA, neuronal surface P antigen; O&NS, oxidative and nitrosative stress; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; TNF, tumour necrosis factor; UV, ultraviolet.

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1. Introduction

It has long been established that neuropsychiatric (NP) diseases can be elicited by infectious pathogens, diet, or environmental components [1]. Despite intensive investigation, however, the aetiology of most NP diseases as well as autoimmune diseases (AIDs) remains elusive. The interplay of hormonal, immunological, and environmental factors associated to a genetically-predisposed ground appears to be central but nowadays, it is not known how these intrinsic and extrinsic factors associate to trigger the disease, what are the host elements that are involved to orientate the form of the disease in a particular individual, and what regulates acute exacerbation and remission phases in certain AIDs. Autoimmunity may profoundly impact the continuous crosstalk held between the central nervous system (CNS) and the immune system contributing to the emergence of symptoms such as depression, mood and anxiety disorders, or psychosis [2–4]. Some of these symptoms have been reported to occur in neuropsychiatric systemic lupus erythematosus (NPSLE).

In this complex picture, infections have been described as decisive factors that not only trigger but also sustain and exacerbate AIDs. Epidemiological studies show that the occurrence of SLE differs according to countries, to areas of the same country and between social groups. These differences suggest that besides genetic susceptibility and intrinsic factors, environmental elements, notably the infectious environment and the level of hygiene in different world areas, are central in the development of this syndrome [5]. The composition of gut microbiota [6], which may change as a function of diet modification or following medication, can also modulate and aggravate the course of SLE.

After summarizing the current consensus views of NPSLE pathogenesis, this review will focus on the possible ways infectious agents may influence autoimmunity, the mechanisms of neuroinflammation and inflammation-induced behaviour, what they imply in terms of blood-brain barrier (BBB) permeability, brain cytokines and how, nowadays, we progress in our understanding of neurodegeneration in NPSLE. A better understanding this “ménage à trois” (brain, immune system and infectious agents) in a disease where there is still no specific treatment, is pivotal in our quest to design novel therapeutic options based on personalised approaches.

2. Neuropsychiatric systemic lupus erythematosus

2.1. Symptomatology

SLE is a prototypic relapsing-remitting AID identified by elevated titres of inflammatory mediators, hyper-activation of peripheral B and T lymphocytes, production of potentially pathogenic autoantibodies (autoAbs), clearance failure and tissue deposition of immune complexes (ICs). These events precede inflammatory conditions, which may cause end-organ damage [7]. SLE prevalence fluctuates from 40 to 100 cases per 100,000 individuals, and even 40 to 200 among blacks in the US [8,9]. The influence of hormones is central as 90% of patients are female and the vast majority of cases occur during childbearing age. Linkage between genetic and environmental factors (e.g. infections, pollutants, UV radiation, stress) might underpin disease bursts and justify the “waxing and waning” symptoms [10,11]. Although skin, arthritis and renal lesions are the most common manifestations, neurological and NP symptoms occur frequently [12]. When severe, they substantially contribute to the morbidity and mortality rates of patients [13].

NPSLE is a yet poorly understood disease that encompasses some twenty central and peripheral symptoms (Table 1). CNS symptoms largely predominate (93%) and may be diffuse or focal [14]. The majority of NP manifestations appears early in the course of SLE, most of them being not correlated with flare or severity of the disease. NPSLE is essentially clinically-defined by physical examination, brain imaging, and serological, psychiatric and neuropsychological tests. However, despite improved imaging, diagnosing NPSLE still remains a challenge [15–18]. The prevalence of NP events ranges from 14% to 75% [19,20], reflecting important differences in patient selection resulting from the absence of consensus for diagnosing NPSLE. The genetics of NPSLE has rarely been addressed. Of note, the gene *TREX1* involved in apoptosis, oxidative stress and several cerebral diseases has been linked to NPSLE [21]. Larger genome-wide association studies of lupus patients are therefore eagerly awaited.

2.2. Pathogenesis

The pathogenesis of NPSLE is particularly complex. The presence of a chronic inflammatory state is commonly reported but no single pathogenic dysfunction accounts for all NP symptoms, which result from several pathogenic pathways including vascular and neuroinflammatory circuits (Fig. 1) [14,22,23].

Much data demonstrate that some NP symptoms are caused by antiphospholipid Abs, which bind to clotting factors and endothelial cells (ECs), inducing a pro-coagulant state. This mostly results in focal manifestations that can be associated with structural brain abnormalities at autopsy [24]. Both in murine models of lupus [25–28] and in patients [29,30], diffuse manifestations were found to result rather from inflammatory processes and toxicity mediated by Abs binding neuronal cell surface receptors, such as neuronal surface P antigen (NSPA) and *N*-methyl-D-aspartate receptor

Table 1
Neuropsychiatric syndromes described in lupus (ACR[a] classification [145]) (adapted from Refs. [14,146]).

Central nervous system	
Diffuse psychiatric/neuropsychological syndromes	*Focal neurological syndromes*
Mood and anxiety disorders[b]	Stroke[b]
Cognitive dysfunction[b]	Seizures[c]
Headaches[b]	Aseptic meningitis
Psychosis[c]	Movement disorder
Depression	Myelopathy
Acute confusional state	Demyelinating syndrome
Peripheral nervous system	
Autonomic neuropathy[c]	
Cranial neuropathy	
Polyneuropathy	
Mononeuropathy (single/multiplex)	
Myasthenia gravis	
Plexopathy	
Guillain-Barré syndrome	

[a] Abbreviations: ACR, American College of Rheumatology.
[b] Mood and anxiety disorders, cognitive dysfunction, headaches and stroke are very common, but less specific features
[c] psychosis, seizures and neuropathy present greater specificity for neurolupus.

(NMDAR). The occurrence of autoAbs and proinflammatory cytokines in the cerebrospinal fluid (CSF), a liquid secreted within the choroid plexus and diffusing into the cerebroventricular compartments, could either result from leakages in the BBB (passive transfer) or from intrathecal production [31]. Breach of the BBB is critical for the access of Abs directed against NMDAR subunit 2 (anti-NR2, also known as anti-GluN2) to brain neurons [26,32,33]. The BBB can be permeabilised by SLE-linked factors (e.g. cytokines,

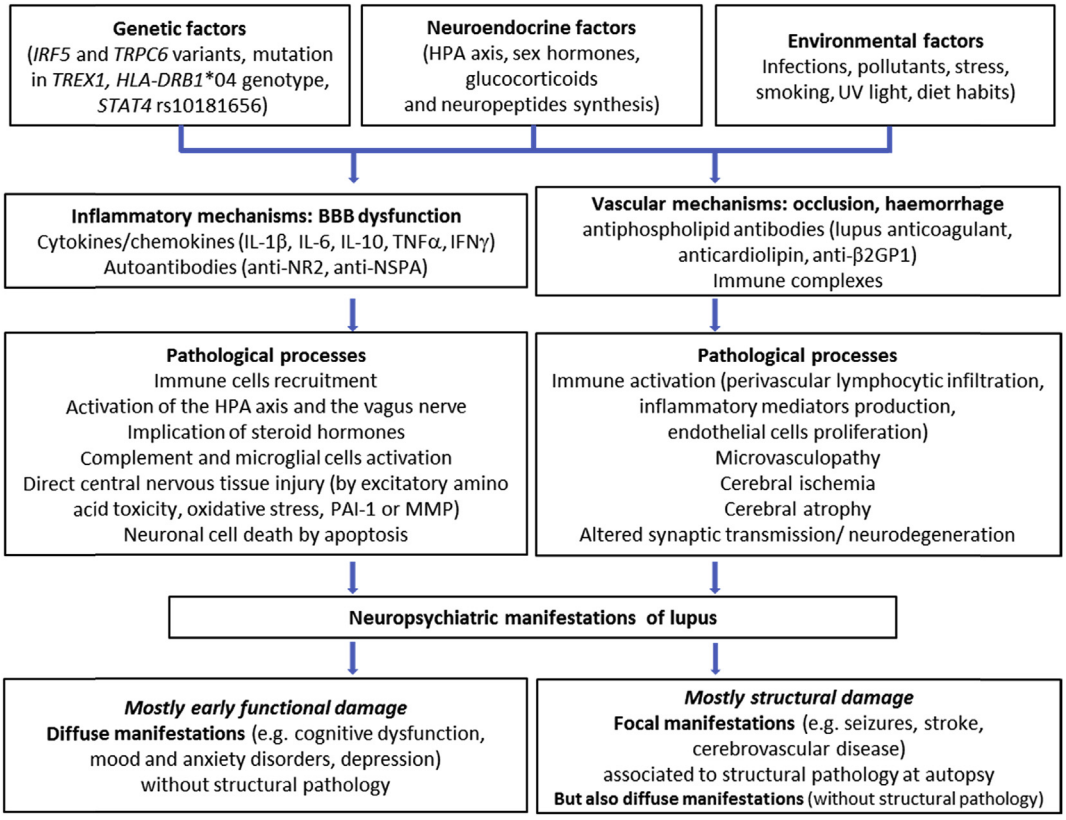

Fig. 1. Schematic view of pathogenic mechanisms of NPSLE. Genetic, neuroendocrine and environmental components participate to immune dysfunction and emergence of neuropsychiatric manifestations in lupus. Inflammatory mechanisms involve autoimmune damage, with upregulation of circulating proinflammatory cytokines, activation of the HPA axis, penetration of autoantibodies into the cerebral parenchyma and increased BBB permeability, which is possibly linked to infection; these mechanisms mainly contribute to diffuse manifestations encountered in neurolupus. Vascular mechanisms, mostly mediated by antiphospholipid antibodies and immune complexes, contribute rather to focal neuropsychiatric manifestations, and to a lesser extent, to diffuse neuropsychiatric events. In generic terms, neuropsychiatric manifestations occur after environmental factors generate immunological defects in susceptible subjects, inducing loss of tolerance towards native proteins. Infections play determinant roles in this scheme. Abbreviations: β2GP1, β2-glycoprotein 1; BBB, blood-brain barrier; HPA, hypothalamic-pituitary axis; IFN, interferon; IL, interleukin; IRF5, interferon regulatory factor 5; MMP, matrix metalloproteinase; NPSLE, neuropsychiatric systemic lupus erythematosus; NR2, *N*-methyl-D-aspartate receptor subtype 2; NSPA, neuronal surface P antigen; PAI-1, plasminogen activator inhibitor 1; STAT4, signal transducer and activator of transcription 4; TNF, tumour necrosis factor; TREX 1, three prime repair exonuclease 1; TRPC, transient receptor potential canonical; UV, ultraviolet.

autoAbs) and non-SLE factors (e.g. LPS, viral proteins, UV, stress, hormones, smoking, certain addictive drugs) (Table 2) [34]. In NPSLE, leakage in the BBB might be induced by the binding of glutamate to NMDARs localised on brain ECs. NSPA participates to NMDAR function, glutamatergic transmission and hippocampal memory by moderating the detrimental action of anti-ribosomal P protein Abs. Diffuse NPSLE symptoms may arise after these autoAbs gain access to cerebral areas co-expressing both NMDAR and NSPA. Importantly, these two SLE-related autoAbs recognizing NSPA influence glutamatergic transmission, albeit *via* distinctive processes [35].

Increased intrathecal production of several cytokines (Fig. 1) by neuronal and glial cells, presumably following intrathecal presence of autoAbs, is also linked to NP manifestations in lupus [36–38]. As suggested from *in vitro* studies, cytokines are produced after binding of ICs to FcβRII on plasmacytoid dendritic cells (DCs; which are major antigen-presenting cells of the immune system) and stimulation of TLR7. This mechanism is substantiated by the presence, in the CSF of NPSLE patients, of degraded neuronal and glial material (potential antigens source), and increased matrix metalloproteinase-9 levels [39], which augment BBB permeability, thus providing intrathecal access to circulating autoAbs [22,40]. It is worth mentioning that high levels of oxidative and nitrosative stress (O&NS) are significantly associated to neurodegeneration and might be an important component of NPSLE [41]. Whether neurological dysfunction progresses independently, results from systemic disorder, or both, remains unclear. In fact, CNS dysfunction and NP manifestations could be part of existing disease or they could be consecutive to treatment, infection, and metabolic dysfunctions.

2.3. Sickness behaviour

Depression, fatigue, anhedonia and defects in cognition are frequently noted in clinical conditions where inflammation is always reported, which could then be considered as a pivotal contributor to the expression of such symptoms [42,43]. In rodents, alteration in cognition, emotionality and sleep-wake cycle is detected after peripheral immune activation [44]. These modifications coexisting with activation of the peripheral immune system are known as “sickness behaviour” [45,46], which is well-documented in SLE and in spontaneous murine models, notably in MRL/lpr lupus-prone mice. As compared to $MRL^{+/+}$ mice counterparts, MRL/lpr mice display deficient cognitive performances in spontaneous alternation (Fig. 2; Jeltsch-David and Muller, unpublished observations) and water maze tasks, suggestive of hippocampal dysfunction and consequences on the neural processing of learning and memory [47,48]. It is worth noting that SLE patients displaying cognitive difficulties may also present structural hippocampal anomalies [46,49].

3. Immunity, infection and central inflammation

3.1. The immune system: its basics

The immune system includes the innate and the adaptive systems, and is composed by cells adjusted to protect the organism against foreign agents, while being nonreactive towards self [50]. The body responds to pathogenic exogenous and endogenous signals with comparable reactions *via* sentinel cells (e.g. monocytes, macrophages, DCs, microglia), which initiate an inflammatory response followed by a “mirrored” immune reaction within the CNS (neuroinflammation), possibly resulting in behavioural symptoms. Pathogenic agents exhibit pathogen-associated molecular patterns (PAMPs) that activate pattern-recognition receptors (PRRs). The latter recognise PAMPs as non-self-molecules and damage-associated molecular patterns (DAMPs) as self-molecules. Both give rise to innate response, one to eradicate invading elements and the other to eliminate injured tissue. Among the most widely studied PRRs are TLRs, which, for some, recognise extracellular pathogens (primarily bacteria) and for others, present within endosomes and lysosomes, interact with intracellular pathogens (Table 3). The activation of TLRs promotes inflammatory responses by generating intracellular signalling cascades *via* two main pathways, namely myeloid differentiation primary response 88 (MyD88) and Tir-domain-containing adaptor inducing interferon-β (TRIF) pathways. Almost all TLRs combine MyD88 inaugurating a series of events to finally initiate NF_KB, whose translocation directly stimulates gene transcription of TNFα, IL-1β and IFNγ. Only TLR3 strictly associates with TRIF signalling to induce IFNα and IFNβ. TRIF pathway seems to mainly play a role against viral infections, and Myd88 against bacterial ones. Concerning Nod-like receptors, they act similarly as TLRs by initiating inflammatory reactions after recognition of bacteria's peptidoglycans.

Table 2
Examples of factors modulating the BBB's[a] permeability (data adapted from Ref. [34]).

Conditions	Substances	Action
Infections	LPS	ECs activation P-glycoprotein regulation Cytokines secretion
	Viral proteins (e.g. HIV)	Tight junction dysfunction Perivascular macrophages and microglia activation
Inflammation	Cytokines (e.g. TNFα, IL-1β, IL-6, Type 1 IFN)	ECs activation Tight junction dysfunction
	Circulating Abs (e.g. anti-NR2 Abs, anti-P autoAbs)	Recognition of neuronal cell surface antigens, and enhancement of glutamatergic transmission through two different mechanisms (when Mg^{2+} is removed and in the presence of Mg^{2+}, respectively); the mechanism mediated by NSPA involves NMDAR activation
Stress, stroke	Glutamate	Vasodilatation ECs activation
Hormonal dysfunctions	Œstrogens (e.g. 17β-œstradiol)	Inhibition of MMP2 and MMP9
	Glucocorticoids (e.g. dexamethasone)	VEGF and angiopoietin regulation
Addictive agents	Tobacco (e.g. nicotine)	Tight junction modulation
	Coffee (e.g. caffeine)	Action on junctional proteins by neurotoxins and other agents
	Alcohol (e.g. ethanol)	Choroid plexus dysfunction

[a] Abbreviations: Ab, antibody; BBB, blood-brain barrier; ECs: endothelial cells; HIV, human deficiency virus; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; Mg^{2+}: magnesium; MMP, matrix metalloprotease; NMDAR: *N*-methyl-D-aspartate receptor; NR2: NMDAR subtype 2; NSPA: neuronal surface P antigen; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

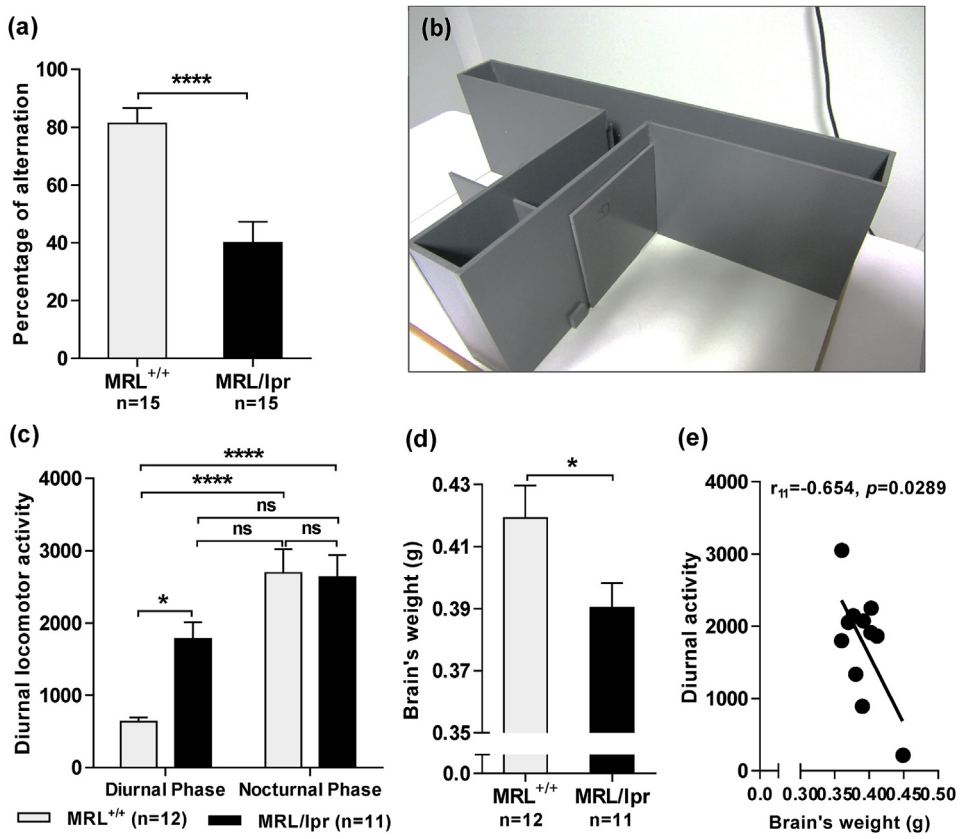

Fig. 2. Behavioural deficits in MRL/lpr mice as compared to control MRL$^{+/+}$ mice. **a**| As compared to age-matched counterparts, 17 week-old MRL/lpr mice display T-maze alternation deficit ($t_{28} = 4.573$, $p < 0.0001$). **b**| The maze included three Plexiglas arms (24 × 17 × 5 cm). Mice were tested over 5 days; a daily session consists of trial#1 (5 s in the start position, and entry into the unblocked arm), 20-s inter-trial period (restraining in the arm), and trial#2 where both arms are open and the mouse is expected to choose the unvisited arm. **c**| Concerning circadian activity, MRL/lpr mice showed, at the same age, a marked hyperactivity as compared to MRL$^{+/+}$ control mice ("Substrain": $F_{(1,42)} = 4.759$, $p = 0.034$, "Phase": $F_{(1,42)} = 33.96$, $p < 0.0001$, "Substrain" × "Phase": $F_{(1,42)} = 5.786$, $p = 0.021$), particularly during the diurnal phase of the cycle ($p < 0.05$). Circadian activity was continuously recorded over one week using infrared captors mounted on the top of the cages. **d**| Finally, a significant reduction of brain weight was noticed in 17 week-old diseased MRL/lpr mice ($t_{21} = 2.188$, $p = 0.040$), observation that is in line with the cerebral atrophy classically reported in some NPSLE patients. **e**| Furthermore, we found a significant negative correlation ($r_{11} = -0.654$; Pearson's test) between brain's weight and diurnal activity in MRL/lpr mice ($p = 0.028$) (Jeltsch-David and Muller, unpublished observations). Statistics: Alternation scores and brain's weight data were analysed with unpaired *t*-test (two-tailed). Circadian activity was analysed with a two-way ANOVA ("Substrain" and "Phase" as between factors) with Bonferroni post-hoc tests. Significance was defined as $p < 0.05$: $^{*}p < 0.05$, $^{****}p < 0.0001$, ns, not significant. Errors bars are mean standard deviation. Sample size is indicated as n. The experimental protocol and animal care were carried out in strict accordance with EU regulations (European Community Council Directive 2013-118 of February 1, 2013) and with the recommendations of the French national chart for ethics of animal experiments (articles R 214-87 to 126 of the "Code rural et de la pêche maritime"; authorization no. 04436.02). The protocol was also approved by the local committee on the ethics of animal experiments (CEEA 35). All efforts were made to minimize animal suffering and to respect the concept of the 3Rs (Reduce, Refine, Replace).

Table 3
Central receptors and molecules of innate immunity and their effects (data adapted from Ref. [4]).

PRRs[a]	Neuron	Microglia	Astrocyte	Infectious agent	Signalling pathways	Secreted cytokines
TLR1	–	+	–	Bacteria	Myd88	TNFα,IL-1β, IFNγ
TLR2	–	+	+	Bacteria	Myd88	TNFα,IL-1β, IFNγ
TLR3	+	+	+	Bacteria-virus	TRIF	IFNα,IFNβ,TNFα,IL-6
TLR4	–	+	–	Bacteria-virus	Myd88	TNFα,IL-1β,IFNγ
TLR5	–	+	–	Bacteria	Myd88	TNFα,IL-1β,IFNγ
TLR6	–	+	–	Bacteria-fungi	Myd88	TNFα,IL-1β,IFNγ
TLR7	+	+	–	Bacteria-virus	Myd88	IFNα,IFNβ,TNFα,IL-1β
TLR8	+	+	–	Bacteria-virus	Myd88	TNFα,IL-1β,IFNγ
TLR9	+	+	+	Bacteria-virus	Myd88	IFNα,IFNβ,TNFα,IL-1β
Nod2	+	+		Bacteria	RIPK or RICK	TNFα,IL-1β,IL-6
TNFαR	+	low	low	/	/	/
IL-1R	+	+	+	/	/	/
IL-6R	low	low	low	/	/	/
IFNαR	+	+	+	/	/	/
IFNγR	+	+	+	/	/	/

[a] Abbreviations: IFN, interferon; IL, interleukin; MyD88, myeloid differentiation primary response 88; Nod, nucleotide-binding oligomerization domain 2; PRR, pattern recognition receptor; R, receptor; RIPK, receptor-interacting serine-threonine kinase 2, aka RICK; TLR, Toll-like receptor; TNF, tumour necrosis factor; TRIF, TIR (Toll/interleukine-1 receptor-like) domain-containing adaptor-inducing interferon-β.

3.2. Inflammation mechanism

Inflammation is not synonymous to infection; its understanding requires distinction between innate and adaptive immune reactions, which are functionally intertwined [51]. Inflammation is the innate system's response to fight infection. It is boosted by cytokines released by sentinel cells. This secretion and the resulting activation of NF_KB upregulate cytokines and O&NS pathways, which in turn upregulate NF_KB, perpetuating chronic inflammation process and immune activation *via* TLRs. As aggravating factors, O&NS may generate redox-derived DAMPs, further leading to activation of NF_KB and cytokines. Thus, chronic inflammation and immune activation can be prolonged and even heighten by engagement of TLRs and DAMPs [52].

Bacterial, viral, parasitic and fungal infectious agents are able to trigger autoimmunity (the pathogen must be present to initiate the disease), activate autoimmunity in genetically-predisposed subjects (the pathogen is not essential but its presence precipitates or aggravates the pathology), or even they can impede autoimmunity [53]. Hypotheses linking infection and autoimmunity have been formulated, and five major mechanistic lines have emerged. They include molecular mimicry, 'epitope spreading' [i.e. diversification of the immune response (e.g. B- and T-cells, Abs) following initiation of immunity to a single or few foreign or self-components], bystander activation, polyclonal activation of lymphocytes, and a mechanism in which bacteria and viruses produce super-antigens (Table 4) [54]. Viruses may also activate intracellular TLRs through intracellular signalling pathways, inducing expression of type 1 IFN genes, leading to the typical 'interferon signature' described in lupus [55].

Viral or bacterial infections take part in lupus disease development by inducing cellular debris, which activate B-cells, or promoting autoAbs production. Thus, infections by cytomegalovirus, Parvovirus B19 and Epstein-Barr virus (EBV) are frequently cited in the production of favourable immune conditions allowing autoimmune phenomena, or as breakers of immune tolerance to self-molecules. Molecular mimicry could be one mechanism responsible for the generation of lupus autoAbs and data obtained with EBV are particularly relevant [56]. Interestingly, an association between high titres of EBV Abs and skin and joint symptoms, but not with NP manifestations, have been found in lupus patients [57].

3.3. At the CNS level: cells in the brain parenchyma

In the CNS, the main cell types are neurons and glial cells (monocyte origin), which are further distinguished between microglial and macroglial cells (e.g. astrocytes, oligodendrocytes). Astrocytes are star-shaped glial cells providing mechanical and metabolic support for neurons, thereby regulating the external chemical environment by removing excess ions and recycling neurotransmitters. They respond to pathological changes with hypertrophy and hyperplasia, and are also essential for the integrity of the BBB, acting as filtres. With microglial cells, they are the brain-resident macrophages, being actively involved in immune defence [58]. They regulate and limit inflammatory processes [59] through different mechanisms [e.g. production of anti-inflammatory molecules, expression of receptors (e.g. PRRs, receptors for cytokines and growth factors that are released by damaged neurons, receptors critical for antigen presentation)]. Microglial cells migrate into CNS during development, where they continue to expand specifically after trauma (being able to be directly activated by PAMPS and DAMPS) in which case they react by displaying morphological and functional changes (Fig. 3) with central proinflammatory cytokine expression (Table 3). Microglial cells are critical in both neuronal protection and pathology [60]. They notably produce neurotrophic substances crucial for cellular repair and recruitment of immune cells capable of eliminating pathogens or cell debris from the CNS. Increased microglial activation is related to both exaggerate production of proinflammatory molecules and neurodegenerative process [61]. According to the classification of microglia, M1-polarised microglia are prone to produce proinflammatory cytokines, reactive oxygen species (ROS) and nitric oxide (NO), whereas M2 cells rather inhibit inflammation and reinstate homeostasis [62]. Microglia would be polarised to M1 type in high-anxiety inbred mice, especially after a peripheral innate immune challenge, revealing thus potential molecular mechanisms of how anxiety might regulate microglial activation and polarization [63]. In SLE, even if reactive microglia has been observed in patients suffering from CNS troubles [64], the role of microglia remains to be deeply characterised. In lupus-prone mice, microglia activation and cytoplasm condensation suggest metabolic perturbations, which lead to dysfunction as well as early neuronal death [65]. In this complex scenario, infections seem to play a major, possibly triggering, role. Microglia is also an essential element of a competent BBB, which permit crosstalk between peripheral and CNS immune activities [66]. Centrally, neurons and astrocytes are generally not activated by PAMPs. The lack of most of the bacterial TLRs on neurons suggests that the consequences of a bacterial infection on behaviour are secondary to activation of other CNS cells, primary microglia (Table 3) [4].

4. Inflammation-induced behaviour

Circulating cytokines and proinflammatory molecules affect the CNS through neural and humoral circuits [67]; the neural circuit is related to afferent nerves, while the humoral pathway is mostly

Table 4
Main mechanisms used by pathogens for the activation of autoreactive T and B-cells (adapted from Refs. [54,147]).

Mechanism	Actions
Molecular mimicry	Microbial pathogens displaying structural resemblance with self-peptides activate autoreactive T and B-cells
Epitope spreading	Microorganisms specific to TH1 cells[a] are activated, leading to release of self-peptides, which are further engulfed by APCs and exposed to self-reactive TH1 cells
Bystander activation	The production of cytokines is amplified, which induces expansion of autoreactive T-cells at an inflammatory site
Polyclonal activation	Lymphotropic viruses stimulate lymphocytes, resulting in increased Abs production and ICs in the circulation
Bacterial and viral super-antigens	Microorganisms produce proteins, which through binding to TCR and MHCII, activate numerous T-cells of different antigenic specificity
Alteration of apoptosis	Non-ingested nuclear elements supply survival cues for autoreactive B-cells, this resulting to Abs production against exposed nuclear features
Deficits of the immunity	Defect of the complement leads to decreased and inadequate clearance of infectious substances
IFN signature	Activation of intracellular receptors (TLRs) via intracellular pathways leads to expression of type 1 IFN genes

[a] Abbreviations: Abs, antibodies; APCs: antigen-presenting cell; ICs: immune complexes; IFN, interferon; MHCII: major histocompatibility complex Classe II; T_H cell: T helper cell; TLRs, Toll-like receptors; TCR, T-cell receptor.

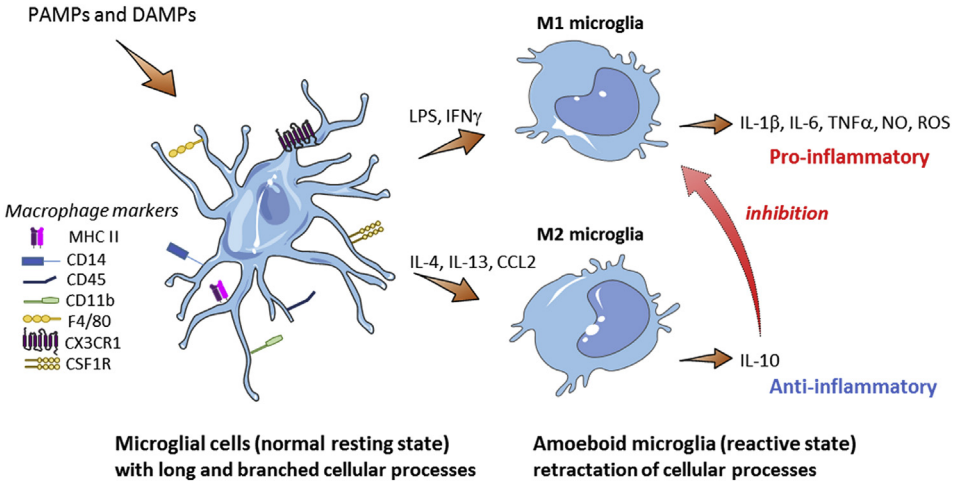

Fig. 3. Immune profile, activation and polarization of microglial cells Microglial cells express MHC molecules and macrophage markers. In the central nervous system, these cells are sentinels and preserve homeostasis. When pathological changes occur, resting microglial retract their long cellular processes, thus developing an amoeboid appearance. In the presence of LPS or IFNγ, microglial cells differentiate to M1 phenotype and secrete proinflammatory factors. In the presence of IL-4, IL-13 or CCL2, they polarise to M2 phenotype, which inhibits M1 microglia functions via IL-10 secretion. It is likely that the balance between exacerbation and recovery of central inflammation is highly regulated by microglia M1/M2 polarization. Abbreviations: CCL2, monocyte chemoattractant protein 1; CD, cluster of differentiation; CSF1R, colony-stimulating factor 1 receptor; CX3CR1, CX3 chemokine receptor 1 (also known as fractalkine receptor); DAMP, damage-associated molecular pattern; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NO, nitric oxide; PAMP, pathogen-associated molecular pattern; ROS: reactive oxygen species. Figure realised thanks to material provided by Servier Medical Art (www.servier.fr) under the CC 3.0 FR license.

related to the BBB, which regulates efflux of elements from the blood to the CNS, and then protects the brain from blood-borne pathogens [68].

4.1. BBB: its compromise in neuroinflammation

The BBB is a selectively permeable barrier formed by astrocytes and capillary endothelial cells connected by tight junctions, which restricts passage of small molecules into the brain. Part of the innate immune defence against pathogens entering the CNS is achieved by the BBB. When systemic inflammation occurs, as in SLE-related neuropathology, the permeability of the BBB increases [68,69]. Different cases of blood-to-brain signalling have been reported [70]. For example, peripheral inflammation induced by LPS directly provokes release of proinflammatory factors, activation of brain ECs, which further leads to upregulation of cell adhesion molecules, destabilization of tight junctions, thereby weakening BBB integrity [71]. After sepsis induction in mice, the BBB becomes rapidly leaky (24 h) with dramatic neuronal degeneration [72]. Following peripheral LPS challenge, brain region-specific upregulation of gene coding for several cytokines (IL-1β, IL-6), glial fibrillary acidic protein and immune cell markers are also observed, demonstrating that cortical inflammation and glial stimulation arise in the context of peripheral inflammation [73,74]. In mice, even a single injection of a low LPS dose (5 mg/kg) generates long-lasting affective modifications as diminution of exploratory ambulation and increase in depressive- and anxiety-like behaviours [75]. Similarly, in rats, LPS administered once is followed by prolonged neuroinflammation [76].

4.2. Cytokines and NP manifestations

Abnormal levels of circulating cytokines evidence chronic inflammation and immune activation, and is commonly observed in lupus [77]. In human and murine lupus, cytokines play an active role in the pathophysiology of the disease, contributing to the production of pathogenic autoAbs and to depression and sickness behaviour [78]. Furthermore, *via* their action on TLRs, cytokines are thought to impair hippocampal neurogenesis [79], which is an important mechanism in depression [80].

Cytokines acting on the brain proceed either peripherally or centrally [47]. From the periphery, cytokines enter the brain by different ways, including (i) cytokine passage through leaky BBB regions, (ii) active transport *via* transport molecules, (iii) activation of ECs and perivascular macrophages, and (iv) binding to cytokine receptors present on afferent fibres (the vagus nerve) [81]. At the BBB interface, NF_KB is pivotal to transmit signals. In rodent, it was demonstrated that inhibiting central NF_KB activity prevents activation of c-fos in different cerebral areas and accelerates recovery from LPS- and IL-1β-induced sickness [82,83].

Cytokines produced centrally by astrocytes and microglia directly contribute to vasculopathy of focal ischemic and haemorrhagic brain disease. In lupus, several reports demonstrated that deregulated secretion of cytokines happens within the CNS, as IL-1, IL-6, IL-8, IFNα, APRIL or BAFF, are found in the CSF of NPSLE patients [84,85]. IL-6 is commonly associated with SLE, inflammatory and neurological states, cerebrovascular disease, as well as depressive events [86]. Thus, activation of IL-6 and NF_KB pathway is linked to deregulated sleep in depressed patients [87]. The BBB integrity and intrathecal IgG synthesis levels are classically evaluated by IgG index and Q-albumin test, respectively [70]. As such, the fact that IL-6 CSF levels are associated with IgG index implies that increased intrathecal IL-6 may enhance B-cell responses within the CNS [88]. In addition to IL-6, IFNα is another cytokine that is associated with several NP symptoms in SLE and whose secretion is stimulated by ICs resulting from the binding of CSF autoAbs to antigens released by neurocytotoxic Abs [89].

Cytokine inducers (e.g. LPS, vaccination) can also cause behavioural manifestations overlapping those reported in depression. Then, LPS-administered healthy volunteers display acute anxiety and depressive behaviour and, as well, injection of a *Salmonella typhi* vaccine to healthy persons results in fatigue, depression, cognitive difficulty and psychomotor slowing [90,91]. The complex molecular and mechanistic interplay between neuroinflammation and infection in a context of autoimmunity has immediate consequences in clinical terms.

5. Link with neurodegeneration

Under systemic inflammatory conditions, as those occurring during NPSLE, several mechanisms may activate neuro-inflammation and neurodegeneration. Thus, due to increased permeability of the BBB, peripheral immune cells and inflammatory factors penetrate in the CNS where they provoke several reactive phenomena, including (i) astrogliosis (also known as reactive astrocytosis), which is an aberrant augmentation of the astrocytes density inducing diminution of synaptic maintenance, (ii) damages of myelin sheaths, which cause demyelination and axonal degeneration, and (iii) microgliosis, which usually involves hypertrophy and proliferation, and generates a proinflammatory phenotype of microglial cells with diminution of phagocytic and tissue homeostasis function (Fig. 4).

Cerebral perturbations can be direct effects of soluble factors or may be indirectly linked to reactive astrocytic and microglial responses. Data demonstrated that LPS activates microglial cells and contributes to cognitive dysfunction *via* an IL-1-dependent process; thus, the blockage of IL-1 signalling weakens the LPS inflammatory cascade, thereby attenuating microglial activation and hampering behavioural abnormalities [92].

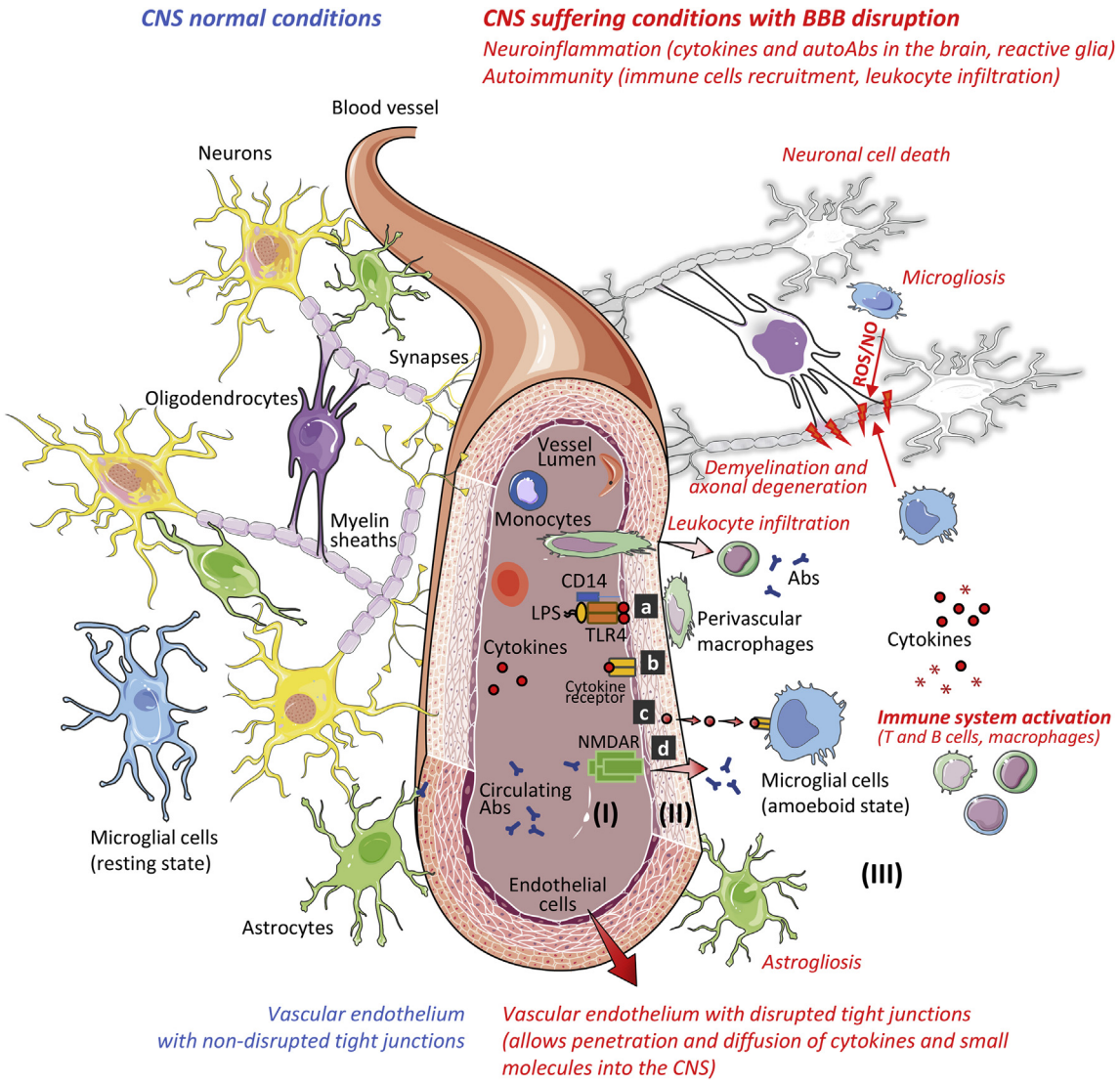

Fig. 4. Cerebral milieu and BBB modifications following systemic inflammation in NPSLE. Neurons are connected by axons (isolated by myelin sheaths provided by oligodendrocytes) and synapses. Astrocytes combine with blood vessels and constitute the BBB. Microglia survey the CNS, eliminating apoptotic cells. When inflammation, neuroinflammation and autoimmunity features appear: peripheral immune cells and proinflammatory mediators target ECs and cross the BBB, exerting direct and indirect damages. NO and ROS injure myelin sheaths, leading to demyelination and axonal degeneration. Density of astrocytes increases, leading to damage of BBB. Lastly, microglia adopts proinflammatory phenotype with diminution of phagocytic function and release of neurotoxic mediators generating ROS [101]. Circulating inflammatory factors may affect cerebral function by several ways. **a**| When infection occurs, pathogens (e.g. LPS) bind TLR4s ($NF_{K}B$ activation) on ECs, inducing leakage of the BBB and activation of perivascular macrophages at circumventricular zones. **b**| Cytokines secreted systemically in response to LPS act on cytokine receptors present on ECs, thus altering the architecture of tight junctions. **c**| Cytokines may also cross the BBB using specific transporters, and then activate immune cells *in situ*, further amplifying BBB dysfunction. **d**|Circulating Abs recognizing NMDAR are transported into the brain by receptor-mediated endocytosis. In short: **(I)** Firstly, presence of proinflammatory circulating factors (e.g. microbial substances, Abs, cytokines); **(II)** Secondly, cascade of endothelial inflammatory events (production and release of NO, ROS, cytokines, upregulation of adhesion molecules); **(III)** Lastly, parenchyma inflammatory cascades (macrophages infiltration, astrocytes and microglia activation; unregulated inflammation leading to neuronal injury and brain disease). Abbreviations: Abs, antibodies; BBB, blood-brain barrier; CD, cluster of differentiation; CNS, central nervous system; ECs, endothelial cells; LPS, lipopolysaccharide; NMDAR, *N*-methyl-D-aspartate receptor; NO, nitric oxide; NPSLE, neuropsychiatric systemic lupus erythematosus; ROS, reactive oxygen species; TLR4, Toll-like receptor 4. Figure adapted from Ref. [101] and realised thanks to material provided by Servier Medical Art (www.servier.fr) under the CC 3.0 FR license.

Immune control of the CNS and regulation of neuroinflammation are provided by brain microglia and peripheral immune cells [93–95]. The total elimination of infectious agents during cerebral infection generally entails irreversible cerebral tissue shrinkage, which however may be counteracted by processes of pathogen tolerance, as exemplified with HSV [96].

5.1. Caspases in neurodegeneration and inflammation

An important trigger for neurodegenerative processes is apoptosis. Under physiological conditions, apoptosis constantly occurs and cell fragments are removed without release of inflammatory mediators [97]. During systemic inflammation, such as lupus-related neuropathology, apoptosis of stressed cells but also pyroptosis, which is a form of programmed cellular death linked to antimicrobial response, might further exacerbate the underlying pathology [98]. Directly and indirectly, apoptosis stimulates caspases, which are effectors of apoptosis but are also important for initiating innate immune response through inflammasome [99], a multiprotein complex expressed in myeloid cells, thereby constituting essential element of the innate immune system, which cleaves pro-interleukin into proinflammatory cytokines (Il-1β, IL-18) and induces pyroptosis. Nowadays, data extend the role of caspases relating neuroinflammation to neurodegenerative processes [100,101]. Caspases activation has also a crucial role in lupus, as they can cleave self-proteins leading to fragments (some of which encompass apoptosis-specific post-translational modifications) that can be potent immunogens [102].

5.2. Immune cells, AutoAbs, and neuroimmunology

Proinflammatory cytokines, reactive oxygen species (ROS) and activated immune cells directly trigger apoptosis of central neurons [103]. Similarly, anti-brain Abs, such as anti-NMDAR Abs, can drive cerebral pathology further affecting behaviour and cognition, as described in SLE [104,105].

In NPSLE patients, the pathogenicity of CSF IgG Abs to NR2 subunit has been published both *in vitro* and *in vivo* [26,33]. Patient-derived NMDAR Abs mediate persistent cognitive impairment as well as neuronal damage the hippocampus, which in one cerebral area crucially implicated in learning and memory process, of mice [27]. Structural abnormalities and hypermetabolism have also been similarly evidenced in the hippocampus of NPSLE patients [49,105]. All these findings, and others published more recently in NPSLE patients, suggest that NMDAR Abs are directly implicated in neurodegeneration [34,105]. Recently, authors proposed that anti-NR2 Abs and NF_KB activation may generate NPSLE pathogenesis [28]. An observation that may be highly relevant concerning reversibility of symptoms is that depending on their concentration, NMDAR Abs may either induce neuronal perturbation by transitory increment of excitatory postsynaptic potentials, or provoke neuronal death [101,106].

Synaptic autoimmunity is currently an exciting burgeoning field of research. The identification of neurological syndromes, particularly encephalitis, associated with autoAbs reacting with extracellular epitopes of synaptic receptors and constituents of trans-synaptic protein complexes [107,108] displays determinant interest, extending and re-questioning classical concepts of neuroscience, neurology and psychiatry [109,110]. Targeted antigens that include NMDAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), inhibitory gamma-aminobutyric acid B receptor ($GABA_BR$) or the glycine receptor (GlyR) are all essential actors of synaptic transmission, plasticity and nerve excitability. Other autoantigens are also implicated in mechanisms such as the secreted neuronal protein leucine-rich glioma-inactivated-1 (LGl1), contactin-associated protein-like 2 (Caspr2) and the intracellular enzyme glutamate decarboxylase (GAD). Clinical expression of these immune reactions is described in Table 5. In the past, these syndromes were considered as idiopathic or of unknown viral cause, and were designated with descriptive terms (i.e. dyskinetic encephalitis lethargica) [111]. The most extensively described neuronal cell surface Abs are here again NMDAR-Abs of individuals suffering from anti-NMDAR encephalitis. At the beginning, and due to its high relation with teratoma, anti-NMDAR encephalitis was categorised as a paraneoplastic syndrome [112]. However, a growing set of clinical evidence proposes that it may be rather considered as a neuroimmune disorder, where Abs are expressed following several signals (infection, tumour) and bind to synaptic proteins and NMDAR [113]. These Abs recognise NR1 subunit of the NMDAR, cross-react and internalise the receptor, thus decreasing the receptor density, and impairing neuronal functioning [109,114]. Autophagy may be another mechanism of action of these autoAbs; in this case, the process of degradation of NMDAR is comparable to that described in the case of acetylcholine receptors in myasthenia gravis [115]. It is important not to confuse NMDAR-Abs, which are greatly specific for anti-NMDAR encephalitis, with NMDAR autoAbs detected in SLE individuals that recognise a linear epitope of the NR2A and B subunits of the NMDAR [109].

6. Implication for the treatment

For the last few decades, SLE patients are living significantly longer in developing countries thanks to both earlier diagnosis and administration of high doses of glucocorticoids or other cytotoxic/immunosuppressive agents [116]. However, although such drastic treatments have lowered the mortality rate, we noticed that drug side effects, especially infections (e.g. bacterial sepsis, mycobacterial infection recrudescence, fungal and viral infection and/or reactivation, in some cases with dramatic consequences such as virus-induced malignancies) have been described in lupus patients [117–119]. This increased risk is linked to the disease itself (Table 6), but also to immunosuppressive treatment the patients receive to reduce some of their inflammatory symptoms and pain. Potentially, immunosuppressive therapy could also affect the ability of treated patients to behave appropriately to preventive vaccination. At least in part, this legitimate concern can be discarded, as there is no objective evidence, in large case reports, that vaccination causes lupus flares when killed vaccines are used [e.g. influenza, pneumococcal and hepatitis B (HBV) vaccines]. In general, however, live vaccines (e.g. varicella, measles, and rubella) are not recommended due to the potentiated infection risk from the vaccine, and should be preferably replaced by killed vaccines since the latter are available. It is also recommended that patients with lupus get vaccination outside active episodes of their disease and following careful consideration of their individual medication usage [120–122]. Some cases of flares have been described after vaccination against HBV, papillomavirus and norovirus. In summary, however, only few vaccines are unsafe in lupus patients. When carefully managed, vaccination is even particularly encouraged as it may significantly decrease the mortality in SLE population.

Nowadays, as infections are the main causes of morbidity and mortality in SLE [123–125], management and prevention of infections arise of greater importance [126]. In addition to adapted strategies of vaccination described above, there is an urgent need to replace immunosuppressive drugs by molecules that will modulate the autoimmune response without affecting the whole immune system [127,128]. This challenge appears set to be successful with the P140 synthetic peptide (also known as Lupuzor™), which corresponds to a sequence of the U1-70K spliceosomal protein. This

Table 5
Encephalitis related to major Abs[a] to neuronal cell surface antigens and their clinical characteristics (adapted from Refs. [3,107,109,148–151]).

	NMDAR	AMPAR	$GABA_BR$	GlyR	LGI1	Caspr2
Gender	Female (80%)	Female (90%)	Female (50%)	Male (60%)	Male (65%)	Male (85%)
Age (median)	21 yrs	60 yrs	62 yrs	46 yrs	60 yrs	60 yrs
Symptoms	Seizures; psychosis; abnormal movements; language and memory dysfunction; defect of consciousness; hypoventilation; breathing and autonomic instability	Seizures; agitation; confusion; disorientation; mood disorder; irritability; short-term memory dysfunction; psychosis; limbic encephalitis	Prominent seizures; memory dysfunction; confusion; disorientation; hallucination; mood disorder; ataxia; irritability; psychosis; limbic encephalitis	Progressive encephalo-myelitis with rigidity and myoclonus; Stiffman syndrome	Tonic-myoclonic seizures; limbic encephalitis; amnesia; apathy; irritability; confusion; disorientation	Encephalitis, neuromyotonia, or both (Morvan syndrome); seizures; confusion; amnesia; insomnia; weight loss
MRI	Transient increase of FLAIR signal in the cerebellar cortex or in medial temporal lobes; intracranial hypertension; demyelination	Increase of FLAIR signal in medial temporal lobes	Increase of FLAIR signal in medial temporal lobes	Normal	Increase of FLAIR signal in medial temporal lobes	Increase of FLAIR signal in medial temporal lobes when encephalitis; spontaneous muscular hyperactivity (EMG) when neuromyotonia
Tumour	Ovarian teratoma in most cases	Small cell lung carcinoma, thymoma, breast cancer	Small cell lung carcinoma	Thymoma; Hodgkin lymphoma	Thymoma (rare)	Limited data: probably thymoma
CSF	Lymphocytosis; increased protein level; CSF-specific oligoclonal bands; frequent intrathecal Abs synthesis	Lymphocytosis; increased protein level; CSF-specific oligoclonal bands; frequent intrathecal Abs synthesis	Lymphocytosis; increased protein level; CSF-specific oligoclonal bands; constant intrathecal Abs synthesis	Usually normal; occasional mild lymphocytosis	Infrequent intrathecal Abs synthesis	Limited data concerning intrathecal Abs synthesis
Other Abs	~10% (ANA, TPO)	~60% (ANA, TPO, GAD_{65}, VGCC, SOX1, cardiolipin)	~50% (VGCC, GAD_{65}, TPO, SOX1)	Unknown	~10% (ANA, TPO, GAD_{65})	~20% MuSK; AChR, GAD_{65}
Outcomes	Good when immunotherapy; possible cognitive sequelae	Tendency to relapse	Good, with rare relapses	Good	Good, or mild sequelae	Limited data

[a] Abbreviations: Abs, antibodies; AChR, acetylcholine receptor; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANA, antinuclear Ab; Caspr2, contactin-associated protein-like 2; CSF, cerebrospinal fluid; EMG, electromyogram; FLAIR, fluid-attenuated inversion recovery; $GABA_BR$, gamma-aminobutyric acid B receptor; GAD_{65}, glutamic acid decarboxylase 65; GlyR, glycine receptor; LGI1, leucine-rich glioma-inactivated 1; MRI, magnetic resonance imaging; MuSK, muscle-specific kinase; NMDAR, *N*-methyl-D-aspartate receptor; SOX1, sex determining region Y-box 1; TPO, thyroid peroxidase; VGCC, voltage-gated calcium channel; yrs, years.

peptide was chemically modified by inserting a phosphoserine residue at the position 140, and only the modified peptide displays protective properties in a murine model of lupus [129]. In patients, P140/Lupuzor™ is well tolerated [130], non immunogenic [129], and a phase III-clinical study is currently in progress. In MRL/lpr lupus-prone mice, P140 binds HSPA8/HSC70 chaperone protein, decreases its expression and reduces autophagic flux in B lymphocytes of peptide-treated mice [131]. P140 interferes with chaperone-mediated autophagy (CMA) [132]. It induces lower expression of MHC-II molecules and alteration of peptides presentation to autoreactive T-cells, leading to a reduction of T and B-cells activation and a drop of potentially pathogenic autoAbs production. This process is without effect on the resistance of mice to infection by Flu virus, meaning that after P140 treatment, the overall immune system remains intact. Based on this unique selective inhibitory effect of P140 peptide on CMA, we anticipate that P140/Lupuzor may be efficient in several other pathological conditions in which activity of CMA is abnormally raised as is the case, particularly, in several neuroinflammatory diseases [132,133].

7. Outstanding questions and future research

Research is still at the beginning concerning how infectious pathogens are able to trigger, sustain, or exacerbate neuroinflammation and neurodegeneration, as well as concerning the precise role of T-cells in CNS homeostasis. Are these cells only pathogenic in being involved in CNS injury following infection and neurodegeneration? Or could certain T-cells subsets also be implicated in limiting neuroinflammation? A breakthrough would be to identify these T cell subsets.

Other questions remain open concerning CNS inflammatory responses in general, and NPSLE in particular; what about the precise role played by microglia? And what about “glial autophagy”, as this mechanism may be essential to preserve cellular vesicles and proteins, notably mitochondrial architecture during inflammation in astrocytes, and as such, neuronal homeostasis? Is glial autophagy a target for specific therapy? Concerning therapy, which immune-based treatment should be investigated in neuropsychiatric autoimmune diseases to foster CNS repair? Are small

Table 6
Susceptibility factors for infections in lupus patients.

Genetically predisposing factors	Risk factors
Genetic complement deficiency	Leucopenia
MBL[a] deficiency	Functional hyposplenism
CRP deficiency	Hypogammaglobulinaemia
	Complement deficiency
	Corticosteroid use (prednisolone doses over 7.5–10 mg/day)[b]
	Immunosuppressive medication (e.g. cyclophosphamide[b], azathioprine, mycophenolate mofetil)
	Biologics (e.g., rituximab)
	High-dose chemotherapy
	Splenectomy

[a] Abbreviations: CRP, C reactive protein; MBL, mannose-binding lectin.
[b] The risk for developing infection is dose-dependent.

molecules/peptides that target autophagy processes promising tools for treating patients with NPSLE and other NP autoimmune/inflammatory diseases? Finally, how are autoimmunity, neurology, and psychiatry intertwined?

8. Conclusions

The etiology of autoimmune and NP diseases, especially NPSLE, is still fragmented and incomplete. Immunological, hormonal and environmental factors undoubtedly interact to induce disease in genetically-predisposed individuals. A disruption of BBB integrity caused by external factors, including infections, is a pivotal factor in the etiopathology of NPSLE in allowing the penetration of Abs into the brain and binding to cross-reactive epitopes.

There is much current interest in the idea that gut microbiota contributes to the autoimmune status of individuals and therefore to behavioural defect. This idea remains however difficult to analyze deeply in humans since the commensal microbiota can either be altered due to the disease itself or treatment. The use of animal models where the intestinal flora can be manipulated represents an experimental strategy of choice to investigate this central mechanistic question. Some studies have shown that, in patients suffering from myalgic encephalomyelitis/Chronic fatigue syndrome, translocation of bacterial LPS from the gut and engagement with TLRs (further acting as PAMPs) due to modification of intestinal permeability generated by molecules of chronic inflammation (cytokines, NF_KB, O&NS), may be source for fatigue and depression [43,134,135].

The theory of “early-life programming of adult disease”, which supposes that prenatally or early postnatally environmental factors lead to permanent modifications in physiology throughout life is now well accepted [136], and happens also for the immune system [137]. Then, prenatal maternal exposure of rats to LPS or IL-6 significantly increases central and peripheral proinflammatory mediators amounts, along with an increase of the microglial density in the progeny, which persist until adulthood [138,139]. Contact with infectious pathogens and/or immune activation early in life, may also raise the risk of developing NP disorders later. From a molecular point of view, data emphasise the role of prenatal cytokine-related inflammatory mechanisms in the mediation of maternal infection effects on the offspring; thus, both genetic and pharmacological blockage of IL-6 in murine pregnant maternal host, or a genetically-induced over-expression of IL-10, prevent the long-term deleterious effects of prenatal viral-like immune activation, both at the cerebral and behavioural levels [140].

Finally, historically considered as an immune-privilege site, the brain is presently viewed as being able to display immune reactions [141–144]. Indeed, the brain presents functional lymphatic vessels, located in the meninges, which remove fluid and immune cells. Then, dysfunction of this meningeal lymphatic system may drive numerous neurological and neuroinflammatory conditions (including NPSLE), in which modified immunity plays crucial role.

Conflict of interest

Both authors declare no financial conflict of interest.

Author contribution

Both authors wrote the article.

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