Autoimmunity Reviews 13 (2014) 963–973

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Neuropsychiatric systemic lupus erythematosus and cognitive dysfunction: The MRL-*lpr* mouse strain as a model

Hélène Jeltsch-David, Sylviane Muller *

CNRS, Immunopathologie et chimie thérapeutique/Laboratory of excellence Medalis, Institut de Biologie Moléculaire et Cellulaire, 67000 Strasbourg, France

ARTICLE INFO

Article history:
Received 1 July 2014
Accepted 10 July 2014
Available online 23 August 2014

Keywords:
Animal model
Autoimmunity
Behavioral dysfunction
Cognition
Neurodegeneration
Phosphodiesterase

ABSTRACT

Mouse models of autoimmunity, such as (NZB × NZW)F1, MRL/MpJ-Fas^{lpr} (MRL-*lpr*) and BXSB mice, spontaneously develop systemic lupus erythematosus (SLE)-like syndromes with heterogeneity and complexity that characterize human SLE. Despite their inherent limitations, such models have highly contributed to our current understanding of the pathogenesis of SLE as they provide powerful tools to approach the human disease at the genetic, cellular, molecular and environmental levels. They also allow novel treatment strategies to be evaluated in a complex integrated system, a favorable context knowing that very few murine models that adequately mimic human autoimmune diseases exist. As we move forward with more efficient medications to treat lupus patients, certain forms of the disease that requires to be better understood at the mechanistic level emerge. This is the case of neuropsychiatric (NP) events that affect 50–60% at SLE onset or within the first year after SLE diagnosis. Intense research performed at deciphering NP features in lupus mouse models has been undertaken. It is central to develop the first lead molecules aimed at specifically treating NPSLE. Here we discuss how mouse models, and most particularly MRL-*lpr* female mice, can be used for studying the pathogenesis of NPSLE in an animal setting, what are the NP symptoms that develop, and how they compare with human SLE, and, with a critical view, what are the neurobehavioral tests that are pertinent for evaluating the degree of altered functions and the progresses resulting from potentially active therapeutics.

Contents

Abbreviations: cAMP, cyclic adenosine monophosphate; CBA/J, C.C.x Bagg, strain A/Jackson; MRL, Murphy Roths Large; PDE, phosphodiesterase; Ab, antibody; CSF, cerebrospinal fluid; lpr, lymphoproliferation; NP, neuropsychiatric; SLE, systemic lupus erythematosus.

* Corresponding author. Tel.: +33 388417022; fax: +33 388610680.
E-mail addresses: H.David@ibmc-cnrs.unistra.fr (H. Jeltsch-David), S.Muller@ibmc-cnrs.unistra.fr (S. Muller).

http://dx.doi.org/10.1016/j.autrev.2014.08.015

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem relapsing–remitting autoimmune disease, primarily affecting females [1], which can be influenced by hormonal, genetic and environmental factors [2–7]. Clinical studies have shown that neurologic and neuropsychiatric (NP) symptoms occur in up to 75% of patients, a condition representing a particularly severe form of the disease known as NPSLE [8]. Some of the most frequent NP symptoms, of unknown etiology, are cognitive deficits (e.g. mood and anxiety disorders, memory impairment) [9]. Diagnosis of NPSLE remains essentially clinically defined and requires interpretation of complex criteria developed by the American College of Rheumatology (ACR), as no single laboratory test or imaging is sufficiently sensitive and specific to be diagnostic [10,11]. NP manifestations seem not to be correlated with lupus flares [12], further confounding diagnosis and emphasizing the necessity to rule out other potential etiologies such as medication-induced (corticosteroid) psychiatric symptoms, infections, or metabolic abnormalities [13,14] to establish a possible diagnosis. While lupus patients with long duration of disease hold concurrently several factors that may provoke NP manifestations, affective, cognitive and mood disorders can be found in patients with newly diagnosed disease [15]. Disruption of blood brain barrier (BBB), brain pathology, and the presence of auto-antibodies (autoAbs) are central components of NPSLE.

The lack of insight onto pathogenic mechanisms has required the development of animal models. In a special breed of lupus-prone mice, the MRL/MPJ-Fas^{lpr} (thereafter named MRL-*lpr*) substrain, the onset of systemic autoimmunity and inflammation is accompanied by various deficits in brain function comparable to that observed in SLE patients, providing a useful model to study NPSLE. Interestingly, NP manifestations can also appear early in these mice and are primarily driven by autoimmune process [16]. This review will focus on the validity of the MRL model in relation with cognition, and a particular emphasis is given to consideration of these mice as a model of choice to evaluate potential neuroprotective drugs. As regards other spontaneous models of SLE, the reader will find specific information in comprehensive reviews published elsewhere [17,18].

2. NPSLE: CNS involvement in human SLE

The manifestations of NPSLE are variable and can cover the whole spectrum of psychiatric dysfunction. Patients can experience diffuse, or focal central nervous system (CNS) disorders, as well as peripheral nervous system troubles (Table 1) [9,19–21]. These NP manifestations are not all at the same degree of severity, and are often difficult to distinguish from other conditions and etiologies.

As most NP events (50–60%) occur at SLE onset or within the first year after disease diagnosis, the NPSLE phenotype may be a presenting feature of lupus, constituting the initial patient presentation [10]. However, NPSLE phenotype may also occur outside the context of a SLE flare [22]. When compiling published data, a great variability in reported NPSLE prevalence is usually found (15–75%) [8,19,23,24]. This discrepancy results from many factors such as study design (prospective/retrospective), laboratory methodologies, lack of accepted consensus for diagnosis, selection criteria of patients [e.g. ethnic, demographic, clinical differences (disease duration and activity, duration of follow-up)], rarity of some NP syndromes, or variability in the sensitivity of diagnostic tests assessing behavioral dysfunction [23,25]. Concerning morbidity and mortality, NPSLE is associated with increased global SLE disease activity, poorer prognosis and earlier mortality [26–28]. Recently, a study conducted on a large cohort of carefully phenotyped NPSLE investigated the causes of death and the characteristics associated with mortality [29]. A 10-fold increase mortality rate was reported in this group of patients, the most common causes of death being infections and NPSLE itself.

More than 20 pathogenic brain-reactive autoAbs have been associated to NPSLE [30]. AutoAbs and cytokines found in the serum and cerebrospinal fluid (CSF) of patients have been proposed as important factors in the etiology of CNS damage [31–36]. Furthermore, a disruption of the BBB's integrity, allowing diffusion of proteins and small molecules such as

Table 1
Neuropsychiatric syndromes associated with SLE[1], as defined by ACR nomenclature [9].

Central nervous system	
Diffuse neurological manifestations	Focal neurological manifestations
Acute confusional state	Aseptic meningitis
Psychosis	Cerebrovascular disease
Depression	Seizures
Mood disorders	Movement disorder
Anxiety disorders	Myelopathy
Cognitive dysfunction	Demyelinating syndrome
Headache[2]	
Peripheral nervous system	
Cranial neuropathy	
Autonomic neuropathy	
Mononeuropathy single/multiplex)	
Myasthenia gravis	
Plexopathy	
Polyneuropathy	
Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)	

[1] Abbreviations: ACR, American College of Rheumatology; SLE, systemic lupus erythematosus.
[2] Association with SLE is still the subject of intense debates [179–181].

immunoglobulins (Igs) and cytokines into the CSF, is now considered as an important component in NPSLE development [37–39]. Increased CSF levels of Igs, Abs and proinflammatory cytokines, as well as elevated albumin concentration, are indicative of increased BBB's permeability [40–42], and have additionally been associated with NP manifestations [40,43–47].

Neuroimaging plays a substantial role in detecting neurological abnormalities in SLE patients [48–54]. Magnetic resonance imaging (MRI) is generally used but may occasionally fail in NPSLE. As an illustration, more than 40% of NPSLE patients show normal MRI scans [14,55] and even if brain imaging reveals abnormalities (e.g. cerebral atrophy, subcortical white matter lesions, regional neurometabolic dysfunctions, hypoperfusion), these findings are often nonspecific, some of them being also observed in patients without NP manifestations and in the general population after mid-adult life [55–58]. Brain atrophy, which is however quite often reported [48] has been proposed to reflect progressive neuronal injury and demyelination. Altogether, data reported so far suggest the existence of strong links between neuronal cell death, abnormal autoimmune functioning and NP manifestations [59].

Cognitive impairments and emotional disturbances are frequent in NPSLE. However, whether such dysfunctions in memory and affects are inherent to SLE or secondary (epiphenomena), resulting from infection, corticosteroid treatment, or hormonal/metabolic dysfunction, for example, remains unclear.

Studying NPSLE in humans presents obvious inherent limitations. Cause–effect relationships between immune factors and behavioral outcomes cannot easily be characterized in such paradigm and diagnosis is often made after SLE is in late stages of progression. An approach allowing to characterize the early underlying mechanisms of NPSLE in a quite systematic and more direct way includes investigation based on murine models which, then, permits to study interactions between autoimmune/inflammatory processes and cerebral functions, and to better understand the cellular and genetic mechanisms of the disease [17,60,61].

3. Murine models of SLE

3.1. Presentation

Several animal models present immune complex-mediated glomerulonephritis associated with immunological abnormalities that are comparable to those reported in human SLE. Three families of murine models have been described, namely spontaneous, induced and genetically-engineered knockout and transgenic models (Table 2). In this review, we will focus our attention on one spontaneous model of lupus, the MRL-*lpr* mouse, in relation with cognitive dysfunction. Detailed information dealing with numerous other mouse models can be found elsewhere [17,18,62–66]. In the list of relevant murine strains, it is worth noting the development of a model based on Abs cross-reacting with native, double-stranded (ds)DNA and *N*-methyl-D-aspartate (NMDA) glutamate receptor that shows cognitive impairment and emotional disturbances mediated by these autoAbs [67–70].

Generally, for modeling NP manifestations of lupus, spontaneous models are liked best. The most commonly studied spontaneous models have been made available by selective inbreeding and include BXSB, the F1 hybrid between New Zealand Black (NZB) and New Zealand White (NZW) mice called (NZB/W)F1, and the Murphy Roths large (MRL) strain. Over varying periods of time, all these mice spontaneously exhibit clinical and serological features comparable to manifestations seen in human SLE [61]. The mice not only share features such as hypergammaglobulinemia, inflammatory lesions, B cell hyperactivity, autoAbs, circulating immune complexes, and glomerulonephritis [71], but also possess unique characteristics, such as monocytosis in BXSB mice, hemolytic anemia in NZB mice, arthritis and expanded $CD4^{-}CD8^{-}$ double negative T cells and rheumatoid factors (RF) in MRL-*lpr* mice. Differences in autoimmune disease manifestations are also noticed among strains concerning sex, age of onset, symptoms' severity, and rate of development.

3.2. The MRL-lpr mouse model

The MRL-*lpr* strain is one of the best established spontaneous models of SLE and the most extensively investigated in lupus-related NP studies. These mice develop an accelerated and aggressive lupus-like disease characterized by immune-mediated damage to the kidney, skin, heart, lungs, joints, and brain, and by the presence of circulating autoAbs against dsDNA and Smith antigen, which are serological hallmarks of SLE. It has been estimated from the breeding history of MRL mice that its composite genome is derived 75.0% from LG/J, 12.6% AKR/J, 12.1% C3H/HeDi and 0.3% C57BL/6J [72]. In the 12th generation of the MRL inbreeding, a spontaneous autosomal recessive mutation divided the stock (#00486) into two substrains, one with the so-called lymphoproliferation gene (*lpr*) and the other without, leading to two groups of mice, the MRL/MpJ-Fas^{lpr} (MRL-*lpr*; stock #00485) and the MRL/$MpJ^{lpr/Fas}$ ($MRL^{+/+}$, stock #006825), with at least 89% (and more than 99.9% after several cycles of cross-intercross mating) of their genome in common.

Both congenic strains are comparable for several aspects (e.g. appearance, size, reproductive age) and develop autoimmunity accompanied by CNS involvement, although much slowly and later in life for $MRL^{+/+}$ mice, thus representing a natural and adequate control [61]. Furthermore, $MRL^{+/+}$ mice do not show evidence of CNS damage under normal conditions, unlike MRL-*lpr* mice which, as it will be discussed much further below, develop spontaneous BBB leakage. The main factor accounting for the accelerated autoimmunity in the

Table 2
Examples of some murine models of systemic lupus erythematosus.

Type of murine model	Murine model	Major autoimmune manifestations	NP manifestations
Spontaneous	MRL/MpJ-Fas^{lpr} (MRL-*lpr*)	Glomerulonephritis; arthritis; vasculitis; skin lesions; alopecia; myocardial infarcts; autoAbs (including RF)	Emotional and cognitive dysfunctions: anxiety, depression, anhedonia, decreased locomotion, impaired spatial learning
	NZB; (NZBxNZW)F1	Glomerulonephritis; hemolytic anemia; pulmonary infiltrates, autoAbs	Impairment in learning and mood-related behaviors
	BXSB	Glomerulonephritis; myocardial infarcts; monocytosis, autoAbs	Impairment in spatial abilities in old males
	Palmerston-North	Glomerulonephritis; polyarteritis nodosa; autoAbs	ND
	Motheaten	Mild glomerulonephritis; pulmonary infiltrates; hair loss; autoAbs	ND
Induced	Pristane-induced	Glomerulonephritis; autoAbs	ND
Genetically engineered			
• Knockout	$Apcs^{-/-}$	Glomerulonephritis; anti-chromatin Abs	ND
• Transgenic	*Bcl*-2 transgene	Glomerulonephritis; lymphoid hyperplasia; autoAbs; hyperIgG	ND

Abbreviations: Ab, antibody; Apcs, serum amyloid P component; *Bcl-2*, B-cell lymphoma 2 (B cell promoter); *Fas*, apoptosis stimulating fragment; F1, hybrid of the 1st generation; Ig, immunoglobulin; *lpr*, lymphoproliferation gene; MRL, Murphy Roths Large; ND, not determined; NP, neuropsychiatric; NZB, New Zealand Black; NZW, New Zealand White; RF, rheumatoid factors.

MRL-*lpr* substrain is a defect in the *Fas* gene expression, produced as related above by a spontaneous mutation of the single autosomal recessive gene *lpr* located on chromosome 19. This mutation alters transcription of the FAS receptor [73] and results in lymphadenopathy [74]. It also interferes with normal FAS-induced apoptosis, contributing to prolonged survival of activated lymphocytes and autoreactive T- and B-cell clones, and finally, in high autoAb titers [75]. MRL-*lpr* mice significantly differ from the other lupus models by the development in certain mice colonies of a rheumatoid arthritis-like polyarthritis, with a high incidence and titer of RF in their serum, and high levels of circulating immune complexes and cryoglobulins. It is important to know that over the past decade, MRL-*lpr* mice displayed "accidental" lessening of symptoms of unexplained origin [76] and that the MRL-*lpr* original stock was re-established in 2008 (http://jaxmice.jax.org/strain/006825.html). This event has been recounted in detail elsewhere [16,77].

MRL-*lpr* mice display an accelerated mortality rate, females dying approximately at 17 weeks of age and males at 22 weeks. Similarly to lupus patients, MRL-*lpr* mice spontaneously develop behavioral dysfunction concerning emotional reactivity, motivated behavior, cognition, as well as pathologic changes in the brain (i.e. degeneration of central neurons) [62,78–87]. Experimental studies showed that behavioral deficits parallel high levels of cytokines and autoAb, such as antinuclear Abs, anti-dsDNA, and RF, resulting in large amounts of immune complexes [71]. This model, as we will see below, has now become an indispensable tool in the attempt to elucidate the pathogenesis of NPSLE [16], and helped in revealing autoimmunity-induced degeneration, as well as the cytotoxic effects of IgG-rich CSF [79,88].

As in human SLE where depression and other kinds of NP manifestations can appear early in the time course of the disease [15,89], authors found that depressive-like behavior is exhibited by MRL-*lpr* mice (stock #006825) already at 8-weeks of age, at a time when there was no other apparent organ involvement [90]. Thus, these mice demonstrate increased immobility in the forced-swim test, which is usually accepted as an indicator of depression in rodents if strength, motor coordination and general locomotion are otherwise normal (mice's motor function had been evaluated and revealed no impairment in the beam-walking as well as in open field tests). Depressive symptoms significantly correlated with titers of autoAbs against dsDNA, NMDA receptor and cardiolipin. This observation indicates that lupus mice develop depression and CNS dysfunction early in the course of the disease, in the absence of substantial pathology of other organs. This observation also confirms, in the MRL-*lpr* model, the robustness of emotional dysfunction by providing further evidence that such behavioral outcomes are likely a primary manifestation of autoimmunity rather than arising from nonspecific illness or peripheral organ pathology. Finally, MRL-*lpr* mice also display anhedonia, another manifestation of murine depressive-like behavior [91], which is is a lack of response to pleasure or reward and is assessed experimentally in following the loss of the typical preference to drink sweetened fluids [92]. Anhedonia is classically considered as a hallmark diagnostic symptom of depression and, in this report, it correlates significantly with a depression-like phenotype in the forced-swim test.

An interesting finding in MRL-*lpr* mice concerns the sex bias of the disease. In human SLE, a strong gender preference (about a 9:1 female to male ratio) is generally found [93]. Recently, authors evaluated MRL-*lpr* mice, by directly comparing males and females (stock #00485) [94], and found that MRL-*lpr* females from this stock exhibited depression as early as 5 weeks as compared to MRL-*lpr* males where depression was noted only at 18 weeks. Depression scores significantly correlated with autoAbs against nuclear antigens, NMDA receptor, and ribosomal P proteins. These results are consistent with the notion of a primary role of autoAbs in the pathogenesis of early NP deficits in this lupus model, which translate into gender-based differences in clinical phenotype. In human SLE and murine MRL-*lpr* model, a different hormonal component can influence the disease progression between both sexes. Additionally, higher levels of IgG can be found in CSF of female MRL-*lpr* mice [95]. Subtle differences in the susceptibility of the male and female MRL-*lpr* brains to injury by pathogenic Abs may then lead to a more severe neurobehavioral phenotype in female lupus mice.

4. Neurobehavioral testing in MRL-*lpr* mice

As many patients with SLE, evidence suggests that MRL-*lpr* mice show changes in emotional function and cognition [82,96] in parallel with, but sometimes also before, abnormalities in the immune system. Mainly, anxiety and depressive-like behaviors have been observed [97]. This finding has raised the possibility that the characterization of behavioral modifications in autoimmune mice may help clarifying the link between autoimmunity and cognition. To examine the time course of behavioral outcomes of lupus (i.e. anxiety, feelings of helplessness or despair, anhedonia commonly described by NPSLE patients), the performances of mice, including anxiety-like behavior, depression or sickness-like behavior, cognition, as well as locomotor activity can be evaluated in a battery of tests, which are detailed below.

4.1. Anxiety tests

4.1.1. Elevated-plus maze

This maze is routinely used in pharmacology due to its sensitivity to anxiolytics. It consists of four arms, two enclosed and two open (i.e. without walls), and creates an approach-avoidance conflict between the natural tendency of rodents to explore and their aversion for open spaces (which helps preventing detection from predators). In such test, anxiety-like behavior is typically defined as the decreased exploration of open arms; the more anxious the animal is, the less it will explore them [98]. Concerning the MRL-*lpr* model, some authors reported increased anxiety levels [82] while others failed to find such effects [90,94,99].

4.1.2. Open field

This test assesses exploratory behavior in a novel, enclosed environment, which can also reflect anxiety-like behavior, as measured by the amount of time the animal avoids the central area of the arena and remains in close proximity to the walls (thigmotaxis) [100]. The degree of stress can be experimentally manipulated (i.e. by increasing enclosure's size, changing its color–white is more stressful than black–varying the intensity of the overhead lights). In this experimental situation, MRL-*lpr* mice display anxiety-like behavior as evidenced by increased thigmotaxis and impaired exploration of space [82].

4.2. Depressive, sickness-like behavior tests

4.2.1. Sucrose preference test

Reduced preference for palatable drinking solutions was first noted in one of the pioneering studies on behavior of MRL-*lpr* mice [101]. This observation was further explored using the sucrose preference paradigm summarized above. In the MRL model, this paradigm reveals impairments in motivated and goal-directed behavior, and no changes in peripheral sensory input [102]. It is noted as early as 5–6 weeks of age in female mice [103] and continues during the active disease phase (4–5 months) [104–106].

4.2.2. Forced-swim test

This test evaluates behavioral despair as the proportion of immobility when rodent is placed into a small container of room-temperature water from which escape is impossible. After a period of struggling and swimming, the animal becomes immobile, moving its limbs only when it needs to stay afloat or to rebalance itself. This immobility has been interpreted to reflect a state of "behavioral despair" or helplessness, which occurs when the animal learns that escape is impossible [107,108]. Within this interpretation, immobility is thought to reflect a depressive-like behavior and is illustrated as the percentage of time

spent immobile [109]. Increased floating is one of the most profound performance deficits observed in MRL-*lpr* mice, appearing as early as 5 weeks of age and persisting throughout the course of the disease [82,83,90,94]. However, it is equally possible that immobility is an adaptive response that allows the animal to keep its energy. Thus, it remains debatable whether the forced-swim test can be considered as a test of depression.

4.2.3. Open field locomotor activity

Further symptoms of depressive-like behavior include fatigue and apathy which can be assessed as both decreased voluntary activity and exploration in a novel environment, such as an open field. Generally, MRL-*lpr* mice are spontaneously less active [80,82,94,110].

4.3. Cognition: learning and memory tests

Parallels exist between forms of memory assessed in rodents and those evaluated in humans, all being related to hippocampal processes.

4.3.1. Novel object recognition (visual memory)

This test is based on the robust tendency of rodents to preferentially explore novel objects. It is efficient to assess non-spatial working memory, but it also reflects explorative and emotional responses in an approach-avoidance situation, where MRL-*lpr* mice usually display deficits [82,111]. The mouse is first placed into an arena containing two identical, novel objects. After a predetermined period of exploration, the animal is removed, and a delay is imposed. Following the delay, the mouse is placed back into the arena, where one of the objects is replaced by a novel object. Rodents typically explore novel objects and avoid familiar objects, so the amount of time investigating the novel object is taken as the measure of working memory. Generally, MRL-*lpr* mice are not impaired in this cognitive component of the task [90,94].

4.3.2. Morris water maze

This test assesses spatial learning and memory formation. Animals are placed into a pool of water in which a platform is hidden beneath the surface. The animal must learn to use spatial cues located in the testing room to navigate to the platform. Longer latencies indicate poorer performance. MRL-*lpr* mice present significant deficits in this test; they are dramatically impaired in their ability to learn the spatial relationships required to guide them to the hidden platform [80,81,86,112].

4.3.3. Fear-conditioning paradigm

The fear conditioning test assesses the ability of an animal to associate a conditioned stimulus (CS, neutral) with delivery of an unconditioned stimulus (aversive), usually foot-shock. Several dependent measures can be employed, although the most simple is to assess the degree of freezing that the CS elicits. The CS can be either contextual (the arena in which shock is administered), or it can be discrete (a light or tone cue that precedes the shock). Variations in the type of CS recruit neuroanatomically distinct systems; the hippocampus has been found to be crucial to supporting cued fear conditioning with a discrete CS, whereas the amygdala is essential to the acquisition and expression of contextual fear conditioning. This experimental paradigm has been used by Diamond and her group in another murine lupus model based on Abs cross-reacting with dsDNA and NMDA receptors. These authors reported disruption of emotional behavior as a consequence of a neuronal loss in the lateral amygdala [68].

4.4. Motor function tests

4.4.1. Beam-walking test

Walking on a narrow beam (diameter of 1.5 cm) is often used to test psychomotor coordination [113] and is sensitive to motor cortex damage. Motor coordination is assessed as the latency to cross the beam (100 cm-long) and the number of slips (i.e. when one of the paws is passing below the midline of the beam). Generally, there is no obvious deficit, MRL-*lpr* mice displaying normal motor coordination [90,94].

4.4.2. Climbing test

The test consists of placing mice in a wire-mesh rectangular box over 10 min; duration and frequency of climbs, rears and grooming episodes are scored. Spontaneous climbing is a behavioral pattern proposed to be controlled by the dopamine system [114]. There is evidence suggesting aberrant dopaminergic neurotransmission in MRL-*lpr* mice [83,104,105].

5. Why are MRL-*lpr* mice a good model for NPSLE?

5.1. Disruption of the BBB

The BBB, composed of a network of endothelial cells, pericytes and astrocytes, is a crucial anatomic location in the brain. It functions to limit the entry of soluble molecules and cells into the brain parenchyma, and to maintain a regulated micro-environment for reliable neuronal signaling in the CNS [115]. As mentioned above, evidence for BBB breakage or leakage in human SLE-related neuropathology is now accumulating [37–39,41]. Similarly to NPSLE patients, MRL-*lpr* mice show increased albumin concentration and IgG index, which, interestingly, are concomitant with neurodegeneration in periventricular areas [95]. Recently, experimental findings (i.e. IgG infiltration into brain parenchyma) even account for a definite loss of BBB integrity in this lupus-prone model [116]. Finally, using immunohistochemical markers and flow cytometry to assess distribution and prevalence of various cell subtypes, including plasma cells, which infiltrate the brain of MRL-*lpr* mice, other authors observed a massive penetration of $CD3^+$ T cells into the choroid plexus and brain parenchyma, as well as the presence of $CD19^+$ cells and $CD19^+IgM^+$ B cells, which increased in the brain. Severe mononuclear cell infiltration was accompanied by splenomegaly and retarded brain growth [117]. These data support the hypothesis of progressive neurodegeneration as a consequence of leukocyte infiltration and intrathecal autoAb synthesis. However, challenging questions remain as to determine when and how a loss of the BBB integrity can occur.

5.2. Evidence of pathogenic Abs

The hypothesis of a pathogenic role of certain brain-reactive Abs in mental disorders [31,118] is strengthened in MRL-*lpr* mice where analysis of serum repeatedly showed increased levels of autoAbs, noticeable earlier in females and paralleling the onset of depressive-like behavior [90,94].

After a disruption of BBB, autoreactive Abs can penetrate into the brain where they may cause neuronal death [69] and eventually psychosis and/or seizures in lupus patients [119]. In addition to be detected in the CSF following BBB break, autoreactive Abs might also be produced intrathecally [40,120,121]. Experimental studies support this last hypothesis in MRL-*lpr* model [79]. Intrathecally-generated Abs are of the IgG isotype [95] and their levels correlate with increased immobility in the forced-swim test [122]. These authors proposed that intrathecal brain-reactive Abs predict depressive-like response while anxiety-like behavior and "anhedonic" response are rather associated with circulating Abs [111].

The general observation that behavioral abnormalities appear before major increase of serum Abs titers or detectable BBB disruption indicates that serum Abs are not the unique pathogenic factor on NPSLE, at least early in the disease. The link between serum and CSF autoAbs to the disease process is complex and evidences suggest that CSF Abs are more pathogenic than serum Abs [43,79,123,124].

5.3. Cytokines

The neuromodulator role of cytokines is highly relevant in diseases characterized by inflammation, such as lupus, in which proinflammatory cytokines are involved in the pathogenesis of tissue injury and in the production of pathogenic autoAbs [125]. Cytokines play a central role in cognitive function, as well as in learning and memory in the hippocampus [126]. They have been linked to depression in humans [127] and a dysregulation of certain proinflammatory cytokines is thought to be involved in the CNS manifestations of SLE [128–130].

Cytokines affecting the brain may originate either peripherally or centrally [131]. Resident CNS cells, neurons, astrocytes, and microglia cells constitutively produce and express receptors for most of the cytokines produced in the periphery. On the other hand, cytokines are produced within the CNS by neurons and microglia, the surveillance cells of the CNS (for a review, see [132]), and take part in the regulation of neurogenesis, cell survival, proliferation and differentiation of new neurons that is crucial for hippocampal functions such as learning and memory [133,134].

In MRL-*lpr* mice, increased serum levels of proinflammatory cytokines, including tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, parallel the progress of lupus-like disease [135–137]. As well, they are known to alter emotional reactivity and motivated behavior, to provoke sickness behavior clinically and induce impairments in spatial learning experimentally [103,138–142]. To explore the relationships between cytokines and CNS disease in lupus, the expression of several proinflammatory cytokine genes in the hippocampus of autoimmune MRL-*lpr* mice was compared [143,144]. The results indicate that the proinflammatory cytokine genes for interferon (IFN)-γ, IL-1, IL-6 and IL-10, which have been shown to induce cognitive and emotional impairments, are selectively up-regulated in the hippocampi of MRL-*lpr* mice. Thus, proinflammatory cytokines may play a role in the cognitive aberrations observed in MRL-*lpr* mice and, by extension, in lupus [145]. Finally, increased expression of TNF and of its receptor TNFR1, which are moreover implicated in induction of inflammation and degeneration/apoptosis in the CNS, had been reported in the brain of MRL-*lpr* mice [146].

5.4. Neuroinflammation–neurodegeneration

Neuroinflammation and neurodegeneration represent important components of NPSLE. In MRL-*lpr* mice, the brain metabolism is dramatically altered [147], and the early onset of inflammation and autoimmunity includes pathologic events such as infiltration of mononuclear cells into the choroid plexus and parenchyma [87,112,148], increase of adhesion molecules [149], as well as deposition of complement proteins.

In MRL-*lpr* mice, the possibility of congenital brain structural defect potentially confounding disease-induced neurodegeneration is minimized as these mice do not show such inherited cerebral abnormalities, in contrast to BXSB and (NZBxNZW)F1 [150,151]. Then, the MRL model allows the study of interrelationships between systemic autoimmunity, brain changes, and behavior outcomes in a quite controlled way. From a developmental point of view, brain growth appears retarded [152] and ventricles increase in size along an early and accelerated development or autoimmune manifestations [153,154]. Furthermore, and particularly in the hippocampus (i.e. cerebral subregion crucially involved in cognitive processing), increased neurodegeneration, reduced dendritic complexity and progressive atrophy of pyramidal neurons have been commonly observed [88,155], accompany deficits in spatial learning memory [96,152], and are also consistent with the notion of an anxious/depressive-like behavioral profile [82,106,156]. Interestingly, hippocampal abnormalities also exist in human lupus [157–159]. Moreover, reports concerning reduced brain weight [84,152], and neurotoxicity of CSF [79] reinforce the notion of neuronal damage in the MRL-*lpr* substrain. Finally, in MRL-*lpr* mice, lesions of the nucleus accumbens accompany impaired motivated behavior (sucrose preference test) [104], and degeneration in the *substantia nigra* is reported with decreased locomotor activity [105]. Taken together, these data support the notion that systemic inflammation and autoimmunity induce structural damage and degeneration of central neurons (e.g. hippocampal), thus likely forming the basis of behavioral deficits in MRL-*lpr* substrain.

Progenitor cells may also degenerate in the brain of MRL-*lpr* mice. Thus, cerebral regions (e.g. subventricular zone, subgranular zone of the hippocampus) containing such progenitor cells [160] show signs of neurodegeneration [95,96,155,161]. Concerning neuronal progenitor cells, authors report that CSF from MRL-*lpr* mice, as from a deceased NPSLE patient with a history of psychosis, memory impairment, and seizures, are toxic and reduce the viability of brain cells, which proliferate in vitro (C17.2 neural stem cell line) [123]. This harmful effect was accompanied by periventricular neurodegeneration in the brain of autoimmune mice and in vivo neurotoxicity when their CSF was administered to the CNS of a rat. Proposed mechanisms of cytotoxicity involve binding of intrathecally synthesized IgG autoAbs to target(s) common to different mammalian species and neuronal populations. These results indicate also that the viability of proliferative neural cells can be compromised in systemic autoimmune diseases. Then, Ab-mediated damage of germinal layers may weaken the regenerative capacity of the brain in NPSLE, as well as in cerebral development and function in other CNS diseases in which autoimmunity has been documented [162]. Interestingly, impaired hippocampal neurogenesis could account for some of the cognitive deficits observed in MRL-*lpr* mice, as the hippocampus is well implicated in learning and memory processes [163]. Finally, hippocampal neurogenesis could also be inhibited by stress hormones, which are chronically increased in MRL-*lpr* mice [164].

Impaired neurotransmitters (i.e. dopamine, serotonin, norepinephrine, glutamate) catabolism could also be involved in the pathogenesis of CNS damage in lupus. This hypothesis was studied in MRL-*lpr* strain by evaluating the neurotransmitter/metabolite levels in several brain regions [104,105,165]. MRL-*lpr* brains showed increased dopamine levels in the paraventricular nucleus (PVN) and the median eminence, decreased serotonin concentrations in the PVN and enhanced levels in the hippocampus, and decreased norepinephrine levels in the prefrontal cortex [83]. Behavioral deficits correlated with the changes in PVN and median eminence. Concerning serotonin, data are in line with modified serotonin levels in SLE patients comparable to what occurs in depressed patients, including those in which depression has been induced by cytokine therapy [166]. Taken together, and more generally, these results are consistent with the notion that imbalanced neurotransmitter regulation of the hypothalamus–pituitary–adrenal (HPA) axis may play a significant role in the etiology of behavioral dysfunction induced by systemic autoimmune disease [83], and may induce neurotoxicity, at least for dopamine [167]. A deficit in this neurotransmitter release, moreover, may underlie impaired responsiveness to palatable stimulation during the progress of systemic autoimmune disease [104]. As such, a neurotransmitter-specific regional brain damage may account for depressive behaviors in NPSLE.

5.5. Neuroendocrine-immune interaction

The interaction between the nervous, endocrine and immune systems remains poorly understood. The HPA axis is the chief component of the stress system. The stress-induced increase serum concentration of glucocorticoids is essential for the prevention of autoreactive or uncontrolled amplification of the immune response, which results in autoimmunity and self-injury. A defective HPA axis may then confer susceptibility to autoimmune disorders, and it seems that such a deficiency is present in both murine and human lupus [110,164,168]. Nowadays, studies on the function of the HPA axis are rather limited in patients with SLE and often confounded by the effect of concomitant glucocorticoid treatment. Nevertheless, it is well documented that proinflammatory cytokines modulate the stress hormone system and alter behavior [169–171]. Such cytokines activate the HPA axis via

corticotrophin-releasing hormone, stimulating the synthesis of glucocorticoids and other neuropeptides [172,173]. In MRL-*lpr* mice, increased levels of proinflammatory cytokines, mimicking actions of glucocorticoids on the HPA axis, accompany the spontaneous onset of SLE and are associated with deficits in learning and memory function, resulting from hippocampal atrophy. Elevated cortisol levels could also cause excitatory amino acid injury to neurons via a direct decrease in synaptic reuptake of glutamate. The notion of glutamate toxicity is supported by the evidence of anti-NMDA receptor Abs resulting in neuronal apoptosis in the mouse brain [67], and a similar IgG-mediated mechanism induced by CSF from MRL-*lpr* mice [123].

Concerning the time course and the nature of CNS involvement, a report focusing on the neuroendocrine-immune characteristics of MRL-*lpr* mice recently showed that behavioral deficits are under the control of autoimmune, genetic, and endocrine factors, which interchangeably affect brain function and morphology at different phases of ontogeny [174]. Thereby, behavioral performances during the prodromal phase of NPSLE-like disease are associated with autoAbs in CSF and asymmetric activation of the HPA axis. Subsequent deterioration in behavior evolves alongside systemic autoimmunity and inflammation. Although a leaky blood-CSF barrier is a possible explanation, the authors hypothesized that, similar to neonatal lupus, maternal Abs to brain antigens might cross blood–placental barrier during embryogenesis and induce early endocrine and behavioral deficits in offspring.

The different interactions, which seem to exist in MRL-*lpr* mice between genetic, nervous, endocrine, and immune systems, and may induce abnormalities in cognitive behavior, are depicted in Fig. 1.

5.6. The MRL-lpr mouse model to evaluate potential neuroprotective drugs

We recently showed that in MRL-*lpr* mice, the cGMP-phosphodiesterase (PDE) activities are significantly increased in the kidney, spleen and liver. PDE1 activity levels were raised in their kidneys (associated with nephromegaly) and liver, and PDE2 activity was specially increased in their spleen [175]. Nearly all the PDE families are expressed in the CNS [176]. In our hands, the basal expression levels of PDE1, 2 and 5 measured in the brain of 15 week-old MRL-*lpr* mice were not significantly changed (not published). Regarding the brain cAMP-PDE activity, however, while the basal activity also appeared unchanged, that of PDE3 was found to be significantly raised (62.5 to 165.7 pmol/min/mg; $p = 0.0017$, Student's test; results obtained in three female mice of 15 weeks of age; Lugnier and Keravis, personal communication; Fig. 2). It is worth mentioning that a single intravenous administration to MRL-*lpr* mice of nimodipine (PDE1 inhibitor) but not of EHNA (PDE2 inhibitor) was able to significantly lower peripheral hypercellularity [175], which is a typical feature of this strain of lupus mice (see above). It remains to be explored if drugs known to inhibit cAMP-PDE3 activity are able to display such an effect and possibly reverse some neurological signs observed in this mouse model.

6. Limitations

Although the MRL-*lpr* strain displays many features reminding human NPSLE, there are some limitations which must be taken into account when studying NP features in this murine model.

First, several differences exist between human and rodent immune systems. Since autoimmune dysfunctions are at the root of autoimmune diseases, such particularities may limit extrapolations from animal models to autoimmune patients and precautions have to be taken for interpretations and conclusions of what it has been observed experimentally.

Thus, in contrast to the oscillating course of flares and remissions commonly reported in SLE patients, MRL-*lpr* mice show a constant disease progression [18,60], which likely reflects the fact that these mice are genetically-altered for some genes, such as *fas*, on a predisposing MRL background. We must remind here that if *FAS* mutations result in a familial autoimmune lymphoproliferative syndrome, defects in FasL have scarcely been found in lupus patients. *FAS* and *FASL* are not considered contributory genes in human SLE.

Furthermore, while affective and cognitive states of NPSLE patients can be measured by quite sophisticated tests, performances of MRL-*lpr* mice can only be evaluated using a battery of behavioral tests. Care is then required when transferring information observed in MRL-*lpr* mice to human SLE patients.

Finally, as in any reductionist approach, this murine model provides presumably a partial view only of the complex mechanisms occurring in human disease. Nonetheless, animal models are at the core of autoimmune research and numerous published studies reflect the progress brought by these animal models in terms of depicting disease mechanisms.

7. Conclusions

Clinically, NP involvement in several diseases is closely associated with, and is thought to be a consequence of, inflammation in the brain. Several studies report specific autoimmune responses to self-antigens in psychosis, affective dysregulation, and other behavioral abnormalities. Nowadays however, despite these data, no autoAbs have

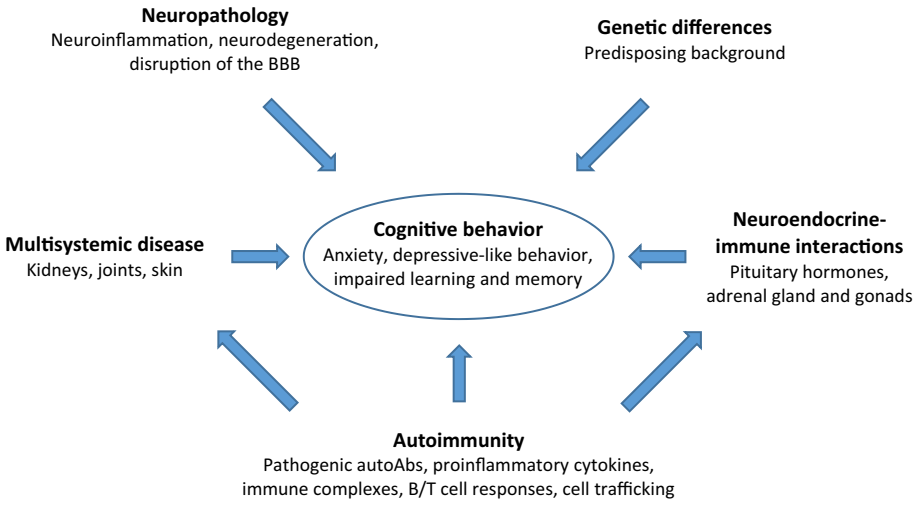

Fig. 1. Potential factors influencing cognitive behavior and abnormalities in MRL-*lpr* mice. The involvement and relative contribution of each factor may vary during different stages in the development of autoimmune disease. Abbreviations: Abs, antibodies; BBB, blood-brain barrier; MRL, Murphy Roths Large.

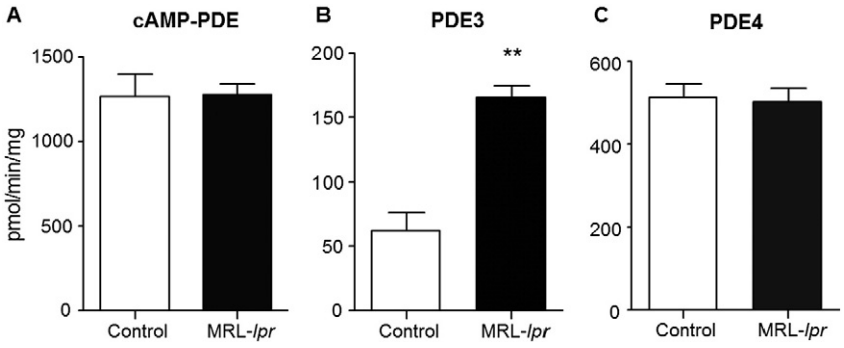

Fig. 2. Levels of basal cAMP-PDE activities in the brain of normal and lupus mice. Basal cAMP-PDE specific activities in total homogenate (A) and contribution of PDE3 (B) and PDE4 (C) were assessed on 15 week-old CBA/J and MRL-*lpr* mice as described by Yougaré and collaborators [175]. Data are expressed as pmol/min/mg of protein and are the mean ± s.e.m. of the data obtained from three individual mice. **, $p < 0.01$ (Student's test) (Lugnier and Keravis, personal communication). All experimental protocols were carried out with the approval of the local Institutional Animal Care and Use Committee (CREMEAS). Abbreviations: cAMP, cyclic adenosine monophosphate; CBA/J, C.C.x Bagg, strain A/Jackson; MRL, Murphy Roths Large; PDE, phosphodiesterase.

remained sufficiently reproducible or ubiquitous as to become a robust biomarker for disease. Experimentally, there is considerable evidence to indicate that chronic inflammation may lead to neurodegenerative disorders [177].

The MRL-*lpr* model presents several advantages as compared to other models of systemic autoimmune disease that render it an indispensable tool in studies of autoimmunity-brain interactions. Spontaneously, these mice present cerebral neuroanatomic and neurobehavioral changes similar to what is observed in human lupus, thereby indicating the validity of their use to investigate the mechanisms underlying neurobehavioral dysfunction in human SLE. An age-dependent decline in brain mass and hippocampal size are consistent with a cascade of pathogenic events, including CSF-mediated cytotoxicity, neurodegeneration and impaired neurogenesis in the limbic system, which accounts for early changes in emotional reactivity and cognitive dysfunction. Moreover, the MRL-*lpr* model is heavily relied upon because of its wide spread availability (it is commercially available), ease of use, and has disease occurring in a compressed time.

Research is still at the beginning concerning knowledge of how frequently Abs cause brain damage, which are their mechanisms of gaining access to the brain, how they potentially affect cerebral functions, and/or if other effector molecules can also display deleterious effects [178]. These questions are central in our quest to generate adapted therapeutics capable of specifically hampering the binding of brain-reactive Abs or active molecules to their targets. In this setting, availability of pertinent animal models mimicking NPSLE is crucial to elucidate precise disease factors and molecular events occurring during neuronal cell death and then to evaluate such therapeutic tools designed on the basis of acquired information.

Take-home messages

- NP symptoms of SLE (NPSLE) are dramatic complications of the disease and contribute to significant morbidity and mortality.
- Animal models are useful tools in defining the pathogenesis of human disease.
- The MRL-*lpr* strain is a murine model of lupus, which spontaneously develops specific serological (e.g., autoAbs, proinflammatory cytokines) and behavioral features (e.g. cognitive, emotional dysfunction) of human SLE.
- There is a link between autoimmune/inflammatory disease, neurodegeneration and behavioral dysfunction in MRL-*lpr* mice.
- The MRL-*lpr* substrain may constitute an excellent model to evaluate neuroprotective therapeutics.

Conflict of interest

Both authors declare no financial conflict of interest.

Author contribution

Both authors contributed in writing the article.

Acknowledgments

We gratefully acknowledge Claire Lugnier and Thérèse Keravis (CNRS-Université de Strasbourg, Biophotonique et Pharmacologie, Faculté de Pharmacie, Illkirch, France) for providing the data shown in Fig. 2.

Research in the SM's laboratory is financially supported by the French Centre National de la Recherche Scientifique, Région Alsace, the Laboratory of Excellence Medalis (ANR-10-LABX-0034) and the EquipEx program I2MC (ANR-11-EQPX-022), Initiative of Excellence (IdEx), Strasbourg University.

References

[1] Bove R. Autoimmune diseases and reproductive aging. Clin Immunol 2013;149:251–64.
[2] Koga M, Kawasaki A, Ito I, Furuya T, Ohashi J, Kyogoku C, et al. Cumulative association of eight susceptibility genes with systemic lupus erythematosus in a Japanese female population. J Hum Genet 2011;56:503–7.
[3] O'Neill S, Cervera R. Systemic lupus erythematosus. Best Pract Res Clin Rheumatol 2010;24:841–55.
[4] Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358:929–39.
[5] Rubtsov AV, Rubtsova K, Kappler JW, Marrack P. Genetic and hormonal factors in female-biased autoimmunity. Autoimmun Rev 2010;9:494–8.
[6] Tsokos GC. Systemic lupus erythematosus. N Engl J Med 2011;365:2110–21.
[7] Zandman-Goddard G, Solomon M, Rosman Z, Peeva E, Shoenfeld Y. Environment and lupus-related diseases. Lupus 2012;21:241–50.
[8] Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. Nat Rev Rheumatol 2010;6:358–67.
[9] ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
[10] Bertsias GK, Ioannidis JPA, Aringer M, Bollen E, Bombardieri S, Bruce IN, 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 2010;69:2074–82.
[11] Bertsias GK, Pamfil C, Fanouriakis A, Boumpas DT. Diagnostic criteria for systemic lupus erythematosus: has the time come? Nat Rev Rheumatol 2013;9:687–94.
[12] Aranow C, Diamond B, Mackay M. Glutamate receptor biology and its clinical significance in neuropsychiatric systemic lupus erythematosus. Rheum Dis Clin North Am 2010;36:187–201.
[13] Hanly JG. Diagnosis and management of neuropsychiatric SLE. Nat Rev Rheumatol 2014;10:338–47.

[14] Steup-Beekman GM, Zirkzee EJM, Cohen D, Gahrmann BMA, Emmer BJ, Steens SCA, et al. Neuropsychiatric manifestations in patients with systemic lupus erythematosus: epidemiology and radiology pointing to an immune-mediated cause. Ann Rheum Dis 2013;72(Suppl. 2):76–9.
[15] Petri M, Naqibuddin M, Carson KA, Wallace DJ, Weisman MH, Holliday SL, et al. Depression and cognitive impairment in newly diagnosed systemic lupus erythematosus. J Rheumatol 2010;37:2032–8.
[16] Gulinello M, Putterman C. The MRL/lpr mouse strain as a model for neuropsychiatric systemic lupus erythematosus. J Biomed Biotechnol 2011;2011:1–15.
[17] Kono DH, Theofilopoulos AN. Genetics of lupus in mice. In: Lahita RG, Tsokos G, Buyon J, Koike T, editors. Systemic lupus erythematosus. 5th ed. London: Elsevier; 2011. p. 63–105.
[18] Theofilopoulos AN, Dixon FJ. Murine models of systemic lupus erythematosus. Adv Immunol 1985;37:269–390.
[19] Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsänoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.
[20] Kozora E, Ellison MC, West S. Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. Arthritis Care Res 2004;51:810–8.
[21] Kozora E, Ellison MC, West S. Depression, fatigue, and pain in systemic lupus erythematosus (SLE): relationship to the American College of Rheumatology SLE neuropsychological battery. Arthritis Rheum 2006;55:628–35.
[22] Carbotte RM, Denburg SD, Denburg JA. Cognitive dysfunction in systemic lupus erythematosus is independent of active disease. J Rheumatol 1995;22:863–7.
[23] Borowoy AM, Pope JE, Silverman E, Fortin PR, Pineau C, Smith CD, et al. Neuropsychiatric lupus: the prevalence and autoantibody associations depend on the definition: results from the 1000 faces of lupus cohort. Semin Arthritis Rheum 2012;42:179–85.
[24] Unterman A, Nolte JES, Boaz M, Abady M, Shoenfeld Y, Zandman-Goddard G. Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. Semin Arthritis Rheum 2011;41:1–11.
[25] Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stallworth CL, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology 2002;58:1214–20.
[26] Fragoso-Loyo HE, Sánchez-Guerrero J. Effect of severe neuropsychiatric manifestations on short-term damage in systemic lupus erythematosus. J Rheumatol 2007; 34:76–80.
[27] Morrison E, Carpentier S, Shaw E, Doucette S, Hanly J. Neuropsychiatric systemic lupus erythematosus: association with global disease activity. Lupus 2014:370–7.
[28] Zhou HQ, Zhang FC, Tian XP, Leng XM, Lu JJ, Zhao Y, et al. Clinical features and outcome of neuropsychiatric lupus in Chinese: analysis of 240 hospitalized patients. Lupus 2008;17:93–9.
[29] Zirkzee E, Huizinga T, Bollen E, van Buchem M, Middelkoop H, van der Wee N, et al. Mortality in neuropsychiatric systemic lupus erythematosus (NPSLE). Lupus 2014; 23:31–8.
[30] Zandman-Goddard G, Chapman J, Shoenfeld Y. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. Semin Arthritis Rheum 2007;36: 297–315.
[31] Diamond B. Antibodies and the brain: lessons from lupus. J Immunol 2010;185: 2637–40.
[32] Diamond B, Kowal C, Huerta PT, Aranow C, Mackay M, DeGiorgio LA, et al. Immunity and acquired alterations in cognition and emotion: lessons from SLE. Adv Immunol 2006;89:289–320.
[33] Gono T, Kawaguchi Y, Yamanaka H. Discoveries in the pathophysiology of neuropsychiatric lupus erythematosus: consequences for therapy. BMC Med 2013;11:91.
[34] Hirohata S, Kanai Y, Mitsuo A, Tokano Y, Hashimoto H, NPSLE Research Subcommittee. Accuracy of cerebrospinal fluid IL-6 testing for diagnosis of lupus psychosis. A multicenter retrospective study. Clin Rheumatol 2009;28:1319–23.
[35] Yokoyama T, Fujii T, Kondo-Ishikawa S, Yamakawa N, Nakano M, Yukawa N, et al. Association between anti-U1 ribonucleoprotein antibodies and inflammatory mediators in cerebrospinal fluid of patients with neuropsychiatric systemic lupus erythematosus. Lupus 2014;23:635–42.
[36] Yoshio T, Okamoto H, Hirohata S, Minota S. IgG anti-NR2 glutamate receptor autoantibodies from patients with systemic lupus erythematosus activate endothelial cells. Arthritis Rheum 2013;65:457–63.
[37] Abbott NJ, Mendonça LLF, Dolman DEM. The blood–brain barrier in systemic lupus erythematosus. Lupus 2003;12:908–15.
[38] Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? Maybe it's the antibodies. Nat Rev Immunol 2009;9:449–56.
[39] Stock AD, Wen J, Putterman C. Neuropsychiatric lupus, the blood brain barrier, and the TWEAK/Fn14 pathway. Front Inflamm 2013;4:484.
[40] McLean BN, Miller D, Thompson EJ. Oligoclonal banding of IgG in CSF, blood-brain barrier function, and MRI findings in patients with sarcoidosis, systemic lupus erythematosus, and Behçet's disease involving the nervous system. J Neurol Neurosurg Psychiatry 1995;58:548–54.
[41] Nishimura K, Harigai M, Omori M, Sato E, Hara M. Blood-brain barrier damage as a risk factor for corticosteroid-induced psychiatric disorders in systemic lupus erythematosus. Psychoneuroendocrinology 2008;33:395–403.
[42] Sato T, Fujii T, Yokoyama T, Fujita Y, Imura Y, Yukawa N, et al. Anti-U1 RNP antibodies in cerebrospinal fluid are associated with central neuropsychiatric manifestations in systemic lupus erythematosus and mixed connective tissue disease. Arthritis Rheum 2010;62:3730–40.
[43] Arinuma Y, Yanagida T, Hirohata S. Association of cerebrospinal fluid anti-NR2 glutamate receptor antibodies with diffuse neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 2008;58:1130–5.
[44] Fragoso-Loyo H, Cabiedes J, Orozco-Narváez A, Dávila-Maldonado L, Atisha-Fregoso Y, Diamond B, et al. Serum and cerebrospinal fluid autoantibodies in patients with neuropsychiatric lupus erythematosus. Implications for diagnosis and pathogenesis. PLoS One 2008;3:e3347.
[45] Greenwood DLV, Gitlits VM, Alderuccio F, Sentry JW, Toh B-H. Autoantibodies in neuropsychiatric lupus. Autoimmunity 2002;35:79–86.
[46] Katsumata Y, Harigai M, Kawaguchi Y, Fukasawa C, Soejima M, Takagi K, et al. Diagnostic reliability of cerebral spinal fluid tests for acute confusional state (delirium) in patients with systemic lupus erythematosus: interleukin 6 (IL-6), IL-8, interferon-alpha, IgG index, and Q-albumin. J Rheumatol 2007; 34:2010–7.
[47] Yoshio T, Hirata D, Onda K, Nara H, Minota S. Antiribosomal P protein antibodies in cerebrospinal fluid are associated with neuropsychiatric systemic lupus erythematosus. J Rheumatol 2005;32:34–9.
[48] Ainiala H, Dastidar P, Loukkola J, Lehtimäki T, Korpela M, Peltola J, et al. Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: a population-based study. Scand J Rheumatol 2005;34:376–82.
[49] Fitzgibbon BM, Fairhall SL, Kirk IJ, Kalev-Zylinska M, Pui K, Dalbeth N, et al. Functional MRI in NPSLE patients reveals increased parietal and frontal brain activation during a working memory task compared with controls. Rheumatology 2008;47:50–3.
[50] Peterson PL, Axford JS, Isenberg D. Imaging in CNS lupus. Best Pract Res Clin Rheumatol 2005;19:727–39.
[51] Sibbitt Jr WL, Brooks WM, Kornfeld M, Hart BL, Bankhurst AD, Roldan CA. Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. Semin Arthritis Rheum 2010;40:32–52.
[52] Toledano P, Sarbu N, Espinosa G, Bargalló N, Cervera R. Neuropsychiatric systemic lupus erythematosus: magnetic resonance imaging findings and correlation with clinical and immunological features. Autoimmun Rev 2013;12: 1166–70.
[53] Zardi EM, Taccone A, Marigliano B, Margiotta DPE, Afeltra A. Neuropsychiatric systemic lupus erythematosus: tools for the diagnosis. Autoimmun Rev 2014;13: 831–939.
[54] Zimny A, Szmyrka-Kaczmarek M, Szewczyk P, Bladowska J, Pokryszko-Dragan A, Gruszka E, et al. In vivo evaluation of brain damage in the course of systemic lupus erythematosus using magnetic resonance spectroscopy, perfusion-weighted and diffusion-tensor imaging. Lupus 2014;23:10–9.
[55] Luyendijk J, Steens SCA, Ouwendijk WJN, Steup-Beekman GM, Bollen ELEM, van der Grond J, et al. Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging. Arthritis Rheum 2011;63:722–32.
[56] Curiel R, Akin EA, Beaulieu G, DePalma L, Hashefi M. PET/CT imaging in systemic lupus erythematosus. Ann N Y Acad Sci 2011;1228:71–80.
[57] Mak A, Ren T, Fu EH, Cheak AA, Ho RC. A prospective functional MRI study for executive function in patients with systemic lupus erythematosus without neuropsychiatric symptoms. Semin Arthritis Rheum 2012;41:849–58.
[58] Sachdev P, Chen X, Wen W. White matter hyperintensities in mid-adult life. Curr Opin Psychiatry 2008;21:268–74.
[59] Kayser MS, Dalmau J. The emerging link between autoimmune disorders and neuropsychiatric disease. J Neuropsychiatry Clin Neurosci 2011;23:90–7.
[60] Alexander JJ, Quigg RJ. Systemic lupus erythematosus and the brain: what mice are telling us. Neurochem Int 2007;50:5–11.
[61] Theofilopoulos AN. Murine models of lupus. In: Lahita RG, editor. Systemic lupus erythematosus. New York: Churchill Livingstone; 1992. p. 121–94.
[62] Brey RL, Sakic B, Szechtman H, Denburg JA. Animal models for nervous system disease in systemic lupus erythematosus. Ann N Y Acad Sci 1997;823:97–106.
[63] Morel L. Genetics of SLE: evidence from mouse models. Nat Rev Rheumatol 2010;6: 348–57.
[64] Perry D, Sang A, Yin Y, Zheng Y-Y, Morel L. Murine models of systemic lupus erythematosus. J Biomed Biotechnol 2011;2011.
[65] Putterman C, Naparstek Y. Murine models of spontaneous systemic lupus erythematosus. In: Cohen IR, Miller A, editors. Autoimmune disease models — a guidebook. San Diego: Academic Press; 1994. p. 245–55.
[66] Xu Y, Zeumer L, Reeves WH, Morel L. Induced murine models of systemic lupus erythematosus. In: Eggleton P, Ward FJ, editors. Systemic Lupus Erythematosus: Methods and Protocols, vol. 1134. New York: Springer Science + Business Media; 2014. p. 103–30.
[67] DeGiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nat Med 2001;7:1189–93.
[68] Huerta PT, Kowal C, DeGiorgio LA, Volpe BT, Diamond B. Immunity and behavior: antibodies alter emotion. Proc Natl Acad Sci U S A 2006;103:678–83.
[69] Kowal C, DeGiorgio LA, Nakaoka T, Hetherington H, Huerta PT, Diamond B, et al. Cognition and immunity: antibody impairs memory. Immunity 2004; 21:179–88.
[70] Kowal C, DeGiorgio LA, Lee JY, Edgar MA, Huerta PT, Volpe BT, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. Proc Natl Acad Sci 2006;103:19854–9.
[71] Andrews BS, Eisenberg RA, Theofilopoulos AN, Izui S, Wilson CB, McConahey PJ, et al. Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. J Exp Med 1978;148:1198–215.
[72] Murphy ED, Roths JB. A Y chromosome associated factor in strain BXSB producing accelerated autoimmunity and lymphoproliferation. Arthritis Rheum 1979;22: 1188–94.
[73] Watson ML, Rao JK, Gilkeson GS, Ruiz P, Eicher EM, Pisetsky DS, et al. Genetic analysis of MRL-lpr mice: relationship of the Fas apoptosis gene to disease manifestations and renal disease-modifying loci. J Exp Med 1992;176:1645–56.

[74] Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. Nature 1992;356:314–7.
[75] Chu JL, Drappa J, Parnassa A, Elkon KB. The defect in Fas mRNA expression in MRL/lpr mice is associated with insertion of the retrotransposon, ETn. J Exp Med 1993;178:723–30.
[76] Williams S, Sakic B, Hoffman SA. Circulating brain-reactive autoantibodies and behavioral deficits in the MRL model of CNS lupus. J Neuroimmunol 2010;218:73–82.
[77] Sakić B. The MRL model: an invaluable tool in studies of autoimmunity–brain interactions. In: Yan Q, editor. Psychoneuroimmunology: methods and protocols. New York: Springer Science + Business Media; 2012. p. 277–99.
[78] Ballok DA. Neuroimmunopathology in a murine model of neuropsychiatric lupus. Brain Res Rev 2007;54:67–79.
[79] Maric D, Millward JM, Ballok DA, Szechtman H, Denburg JA, Barker JL, et al. Neurotoxic properties of cerebrospinal fluid from behaviorally impaired autoimmune mice. Brain Res 2001;920:183–93.
[80] Sakić B, Szechtman H, Keffer M, Talangbayan H, Stead R, Denburg JA. A behavioral profile of autoimmune lupus-prone MRL mice. Brain Behav Immun 1992;6:265–85.
[81] Sakić B, Szechtman H, Denburg S, Carbotte R, Denburg JA. Spatial learning during the course of autoimmune disease in MRL mice. Behav Brain Res 1993;54:57–66.
[82] Sakić B, Szechtman H, Talangbayan H, Denburg SD, Carbotte RM, Denburg JA. Disturbed emotionality in autoimmune MRL-lpr mice. Physiol Behav 1994;56:609–17.
[83] Sakic B, Lacosta S, Denburg JA, Szechtman H. Altered neurotransmission in brains of autoimmune mice: pharmacological and neurochemical evidence. J Neuroimmunol 2002;129:84–96.
[84] Sakić B, Hanna SE, Millward JM. Behavioral heterogeneity in an animal model of neuropsychiatric lupus. Biol Psychiatry 2005;57:679–87.
[85] Szechtman H, Sakić B, Denburg JA. Behaviour of MRL mice: an animal model of disturbed behaviour in systemic autoimmune disease. Lupus 1997;6:223–9.
[86] Vogelweid CM, Wright DC, Johnson JC, Hewett JE, Walker SE. Evaluation of memory, learning ability, and clinical neurologic function in pathogen-free mice with systemic lupus erythematosus. Arthritis Rheum 1994;37:889–97.
[87] Vogelweid CM, Johnson GC, Besch-Williford CL, Basler J, Walker SE. Inflammatory central nervous system disease in lupus-prone MRL/lpr mice: comparative histologic and immunohistochemical findings. J Neuroimmunol 1991;35:89–99.
[88] Sakić B, Kolb B, Whishaw IQ, Gorny G, Szechtman H, Denburg JA. Immunosuppression prevents neuronal atrophy in lupus-prone mice: evidence for brain damage induced by autoimmune disease? J Neuroimmunol 2000;111:93–101.
[89] Meszaros ZS, Perl A, Faraone SV. Psychiatric symptoms in systemic lupus erythematosus. J Clin Psychiatry 2012;73:993–1001.
[90] Gao H-X, Campbell SR, Cui M-H, Zong P, Hwang J-H, Gulinello M, et al. Depression is an early disease manifestation in lupus-prone MRL/lpr mice. J Neuroimmunol 2009;207:45–56.
[91] Malatynska E, Steinbusch HWM, Redkozubova O, Bolkunov A, Kubatiev A, Yeritsyan NB, et al. Anhedonic-like traits and lack of affective deficits in 18-month-old C57BL/6 mice: Implications for modeling elderly depression. Exp Gerontol 2012;47:552–64.
[92] Wen J, Xia Y, Stock A, Michaelson JS, Burkly LC, Gulinello M, et al. Neuropsychiatric disease in murine lupus is dependent on the TWEAK/Fn14 pathway. J Autoimmun 2013;43:44–54.
[93] Ward MM. Prevalence of physician-diagnosed systemic lupus erythematosus in the United States: results from the third national health and nutrition examination survey. J Womens Health 2004;13:713–8.
[94] Gao H-X, Sanders E, Tieng AT, Putterman C. Sex and autoantibody titers determine the development of neuropsychiatric manifestations in lupus-prone mice. J Neuroimmunol 2010;229:112–22.
[95] Sidor MM, Sakic B, Malinowski PM, Ballok DA, Oleschuk CJ, Macri J. Elevated immunoglobulin levels in the cerebrospinal fluid from lupus-prone mice. J Neuroimmunol 2005;165:104–13.
[96] Ballok DA, Woulfe J, Sur M, Cyr M, Sakic B. Hippocampal damage in mouse and human forms of systemic autoimmune disease. Hippocampus 2004;14:649–61.
[97] Sakić B, Szechtman H, Denburg JA. Neurobehavioral alterations in autoimmune mice. Neurosci Biobehav Rev 1997;21:327–40.
[98] Pellow S, Chopin P, File SE, Briley M. Validation of open:closed arm entries in an elevated plus-maze as a measure of anxiety in the rat. J Neurosci Methods 1985;14:149–67.
[99] Nielsen DM, Crnic LS. Elevated plus maze behavior, auditory startle response, and shock sensitivity in predisease and in early stage autoimmune disease MRL/lpr mice. Brain Behav Immun 2002;16:46–61.
[100] Simon P, Dupuis R, Costentin J. Thigmotaxis as an index of anxiety in mice. Influence of dopaminergic transmissions. Behav Brain Res 1994;61:59–64.
[101] Grota LJ, Ader R, Cohen N. Taste aversion learning in autoimmune Mrl-lpr/lpr and Mrl +/+ mice. Brain Behav Immun 1987;1:238–50.
[102] Ballok DA, Szechtman H, Sakic B. Taste responsiveness and diet preference in autoimmune MRL mice. Behav Brain Res 2003;140:119–30.
[103] Sakić B, Szechtman H, Braciak T, Richards C, Gauldie J, Denburg JA. Reduced preference for sucrose in autoimmune mice: a possible role of interleukin-6. Brain Res Bull 1997;44:155–65.
[104] Anderson KK, Ballok DA, Prasad N, Szechtman H, Sakic B. Impaired response to amphetamine and neuronal degeneration in the nucleus accumbens of autoimmune MRL-lpr mice. Behav Brain Res 2006;166:32–8.
[105] Ballok DA, Earls AM, Krasnik C, Hoffman SA, Sakic B. Autoimmune-induced damage of the midbrain dopaminergic system in lupus-prone mice. J Neuroimmunol 2004;152:83–97.
[106] Sakić B, Denburg JA, Denburg SD, Szechtman H. Blunted sensitivity to sucrose in autoimmune MRL-lpr mice: a curve-shift study. Brain Res Bull 1996;41:305–11.
[107] Katzav A, Solodeev I, Brodsky O, Chapman J, Pick CG, Blank M, et al. Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. Arthritis Rheum 2007;56:938–48.
[108] Porsolt RD, Bertin A, Jalfre M. "Behavioural despair" in rats and mice: strain differences and the effects of imipramine. Eur J Pharmacol 1978;51:291–4.
[109] Porsolt RD. Animal model of depression. Biomedicine 1979;30:139–40.
[110] Sakić B, Laflamme N, Crnic LS, Szechtman H, Denburg JA, Rivest S. Reduced corticotropin-releasing factor and enhanced vasopressin gene expression in brains of mice with autoimmunity-induced behavioral dysfunction. J Neuroimmunol 1999;96:80–91.
[111] Sakić B, Szechtman H, Denburg SD, Denburg JA. Immunosuppressive treatment prevents behavioral deficit in autoimmune MRL-lpr mice. Physiol Behav 1995;58:797–802.
[112] Hess DC, Taormina M, Thompson J, Sethi KD, Diamond B, Rao R, et al. Cognitive and neurologic deficits in the MRL/lpr mouse: a clinicopathologic study. J Rheumatol 1993;20:610–7.
[113] Feeney DM, Gonzalez A, Law WA. Amphetamine, haloperidol, and experience interact to affect rate of recovery after motor cortex injury. Science 1982;217:855–7.
[114] Costall B, Eniojukan JF, Naylor RJ. Dopamine agonist action in mesolimbic, cortical and extrapyramidal areas to modify spontaneous climbing behaviour of the mouse. Psychopharmacology (Berl) 1985;86:452–7.
[115] Abbott NJ, Patabendige AAK, Dolman DEM, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. Neurobiol Dis 2010;37:13–25.
[116] Jacob A, Hack B, Chiang E, Garcia JGN, Quigg RJ, Alexander JJ. C5a alters blood–brain barrier integrity in experimental lupus. FASEB J 2010;24:1682–8.
[117] Ma X, Foster J, Sakic B. Distribution and prevalence of leukocyte phenotypes in brains of lupus-prone mice. J Neuroimmunol 2006;179:26–36.
[118] Lapteva L, Nowak M, Yarboro CH, Takada K, Roebuck-Spencer T, Weickert T, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. Arthritis Rheum 2006;54:2505–14.
[119] Tin SK, Xu Q, Thumboo J, Lee LY, Tse C, Fong KY. Novel brain reactive autoantibodies: prevalence in systemic lupus erythematosus and association with psychoses and seizures. J Neuroimmunol 2005;169:153–60.
[120] Hirohata S, Hirose S, Miyamoto T. Cerebrospinal fluid IgM, IgA, and IgG indexes in systemic lupus erythematosus. Their use as estimates of central nervous system disease activity. Arch Intern Med 1985;145:1843–6.
[121] Winfield JB, Shaw M, Silverman LM, Eisenberg RA, Wilson III HA, Koffler D. Intrathecal IgG synthesis and blood-brain barrier impairment in patients with systemic lupus erythematosus and central nervous system dysfunction. Am J Med 1983;74:837–44.
[122] Stanojcic M, Loheswaran G, Xu L, Hoffman SA, Sakic B. Intrathecal antibodies and brain damage in autoimmune MRL mice. Brain Behav Immun 2010;24:289–97.
[123] Sakić B, Kirkham DL, Ballok DA, Mwanjewe J, Fearon IM, Macri J, et al. Proliferating brain cells are a target of neurotoxic CSF in systemic autoimmune disease. J Neuroimmunol 2005;169:68–85.
[124] Yoshio T, Onda K, Nara H, Minota S. Association of IgG anti-NR2 glutamate receptor antibodies in cerebrospinal fluid with neuropsychiatric systemic lupus erythematosus. Arthritis Rheum 2006;54:675–8.
[125] Dean GS, Tyrrell-Price J, Crawley E, Isenberg DA. Cytokines and systemic lupus erythematosus. Ann Rheum Dis 2000;59:243–51.
[126] Arisi GM. Nervous and immune systems signals and connections: cytokines in hippocampus physiology and pathology. Epilepsy Behav 2014 http://dx.doi.org/101016/J.yebeh.2014.01.17 [in press].
[127] Dinan TG. Inflammatory markers in depression. Curr Opin Psychiatry 2009;22:32–6.
[128] Fragoso-Loyo H, Richaud-Patin Y, Orozco-Narváez A, Dávila-Maldonado L, Atisha-Fregoso Y, Llorente L, et al. Interleukin-6 and chemokines in the neuropsychiatric manifestations of systemic lupus erythematosus. Arthritis Rheum 2007;56:1242–50.
[129] Fragoso-Loyo H, Cabiedes J, Richaud-Patin Y, Orozco-Narváez A, Diamond B, Llorente L, et al. Inflammatory profile in the cerebrospinal fluid of patients with central neuropsychiatric lupus, with and without associated factors. Rheumatology 2009;48:1615–6.
[130] Svenungsson E, Andersson M, Brundin L, van Vollenhoven R, Khademi M, Tarkowski A, et al. Increased levels of proinflammatory cytokines and nitric oxide metabolites in neuropsychiatric lupus erythematosus. Ann Rheum Dis 2001;60:372–9.
[131] Szelényi J. Cytokines and the central nervous system. Brain Res Bull 2001;54:329–38.
[132] Yang I, Han SJ, Kaur G, Crane C, Parsa AT. The role of microglia in central nervous system immunity and glioma immunology. J Clin Neurosci 2010;17:6–10.
[133] Johansson S, Price J, Modo M. Effect of inflammatory cytokines on major histocompatibility complex expression and differentiation of human neural stem/progenitor cells. Stem Cells 2008;26:2444–54.
[134] Patterson PH, Nawa H. Neuronal differentiation factors/cytokines and synaptic plasticity. Cell 1993;72:123–37 [Suppl.].
[135] Li P, Lin W, Zheng X. IL-33 neutralization suppresses lupus disease in lupus-prone mice. Inflammation 2014:1–9.
[136] Tang B, Matsuda T, Akira S, Nagata N, Ikehara S, Hirano T, et al. Age-associated increase in interleukin 6 in MRL/lpr mice. Int Immunol 1991;3:273–8.
[137] Tsai CY, Wu TH, Huang SF, Sun KH, Hsieh SC, Han SH, et al. Abnormal splenic and thymic IL-4 and TNF-alpha expression in MRL-lpr/lpr mice. Scand J Immunol 1995;41:157–63.
[138] Anisman H, Hayley S. Inflammatory factors contribute to depression and its comorbid conditions. Sci Signal 2012;5:pe45.

[139] Dantzer R. Cytokine, sickness behavior, and depression. Immunol Allergy Clin North Am 2009;29:247–64.
[140] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–56.
[141] Oitzl MS, van Oers H, Schöbitz B, de Kloet ER. Interleukin-1 beta, but not interleukin-6, impairs spatial navigation learning. Brain Res 1993;613:160–3.
[142] Santoro TJ, Tomita M, Larson SJ. The potential impact of sickness-motivated behavior on the expression of neuropsychiatric disturbances in systemic lupus erythematosus. Med Hypotheses 2007;69:502–7.
[143] Tomita M, Holman BJ, Santoro TJ. Aberrant cytokine gene expression in the hippocampus in murine systemic lupus erythematosus. Neurosci Lett 2001;302:129–32.
[144] Tomita M, Holman BJ, Williams LS, Pang KC, Santoro TJ. Cerebellar dysfunction is associated with overexpression of proinflammatory cytokine genes in lupus. J Neurosci Res 2001;64:26–33.
[145] Tomita M, Khan RL, Blehm BH, Santoro TJ. The potential pathogenetic link between peripheral immune activation and the central innate immune response in neuropsychiatric systemic lupus erythematosus. Med Hypotheses 2004;62:325–35.
[146] Alexander JJ, Jacob A, Bao L, Macdonald RL, Quigg RJ. Complement-dependent apoptosis and inflammatory gene changes in murine lupus cerebritis. J Immunol 2005; 175:8312–9.
[147] Alexander JJ, Zwingmann C, Quigg R. MRL/lpr mice have alterations in brain metabolism as shown with [1H-13C] NMR spectroscopy. Neurochem Int 2005;47: 143–51.
[148] Zameer A, Hoffman SA. B and T cells in the brains of autoimmune mice. J Neuroimmunol 2004;146:133–9.
[149] Zameer A, Hoffman SA. Increased ICAM-1 and VCAM-1 expression in the brains of autoimmune mice. J Neuroimmunol 2003;142:67–74.
[150] Sherman GF, Galaburda AM, Behan PO, Rosen GD. Neuroanatomical anomalies in autoimmune mice. Acta Neuropathol 1987;74:239–42.
[151] Sherman GF, Morrison L, Rosen GD, Behan PO, Galaburda AM. Brain abnormalities in immune defective mice. Brain Res 1990;532:25–33.
[152] Sakić B, Szechtman H, Denburg JA, Gorny G, Kolb B, Whishaw IQ. Progressive atrophy of pyramidal neuron dendrites in autoimmune MRL-lpr mice. J Neuroimmunol 1998; 87:162–70.
[153] Denenberg VH, Sherman GF, Rosen GD, Morrison L, Behan PO, Galaburda AM. A behavior profile of the MRL/Mp lpr/lpr mouse and its association with hydrocephalus. Brain Behav Immun 1992;6:40–9.
[154] Sled JG, Spring S, van Eede M, Lerch JP, Ullal S, Sakic B. Time course and nature of brain atrophy in the MRL mouse model of central nervous system lupus. Arthritis Rheum 2009;60:1764–74.
[155] Ballok DA, Millward JM, Sakic B. Neurodegeneration in autoimmune MRL-lpr mice as revealed by Fluoro Jade B staining. Brain Res 2003;964:200–10.
[156] Sakić B, Gurunlian L, Denburg SD. Reduced aggressiveness and low testosterone levels in autoimmune MRL-lpr males. Physiol Behav 1998;63:305–9.
[157] Kozora E, Brown MS, Filley CM, Zhang L, Miller DE, West SG, et al. Memory impairment associated with neurometabolic abnormalities of the hippocampus in patients with non-neuropsychiatric systemic lupus erythematosus. Lupus 2011;20:598–606.
[158] Schnider A, Bassetti C, Schnider A, Gutbrod K, Ozdoba C. Very severe amnesia with acute onset after isolated hippocampal damage due to systemic lupus erythematosus. J Neurol Neurosurg Psychiatry 1995;59:644–6.
[159] Shapira-Lichter I, Vakil E, Litinsky I, Oren N, Glikmann-Johnston Y, Caspi D, et al. Learning and memory-related brain activity dynamics are altered in systemic lupus erythematosus: a functional magnetic resonance imaging study. Lupus 2013;22:562–73.
[160] Yamashita T, Ninomiya M, Hernández Acosta P, García-Verdugo JM, Sunabori T, Sakaguchi M, et al. Subventricular zone-derived neuroblasts migrate and differentiate into mature neurons in the post-stroke adult striatum. J Neurosci 2006;26:6627–36.
[161] Sakić B, Maric I, Koeberle PD, Millward JM, Szechtman H, Maric D, et al. Increased TUNEL staining in brains of autoimmune Fas-deficient mice. J Neuroimmunol 2000;104:147–54.
[162] Stanojcic M, Burstyn-Cohen T, Nashi N, Lemke G, Sakic B. Disturbed distribution of proliferative brain cells during lupus-like disease. Brain Behav Immun 2009;23: 1003–13.
[163] Zola-Morgan S, Squire LR. The neuropsychology of memory. Parallel findings in humans and nonhuman primates. Ann N Y Acad Sci 1990;608:434–56.
[164] Lechner O, Dietrich H, Oliveira dos Santos A, Wiegers GJ, Schwarz S, Harbutz M, et al. Altered circadian rhythms of the stress hormone and melatonin response in lupus-prone MRL/MP-fas(lpr) mice. J Autoimmun 2000;14:325–33.
[165] Chun S, McEvilly R, Foster JA, Sakic B. Proclivity to self-injurious behavior in MRL-lpr mice: implications for autoimmunity-induced damage in the dopaminergic system. Mol Psychiatry 2008;13:1043–53.
[166] Schäfer A, Scheurlen M, Seufert J, Keicher C, Weißbrich B, Rieger P, et al. Platelet serotonin (5-HT) levels in interferon-treated patients with hepatitis C and its possible association with interferon-induced depression. J Hepatol 2010;52:10–5.
[167] Asanuma M, Miyazaki I, Ogawa N. Dopamine- or L-DOPA-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson's disease. Neurotox Res 2003;5:165–76.
[168] Shanks N, Moore PM, Perks P, Lightman SL. Alterations in hypothalamic–pituitary–adrenal function correlated with the onset of murine SLE in MRL +/+ and lpr/lpr mice. Brain Behav Immun 1999;13:348–60.
[169] Hayley S, Merali Z, Anisman H. Stress and cytokine-elicited neuroendocrine and neurotransmitter sensitization: implications for depressive illness. Stress 2003;6: 19–32.
[170] Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol Psychiatry 2009;65:732–41.
[171] Raison CL, Miller AH. Is depression an inflammatory disorder? Curr Psychiatry Rep 2011;13:467–75.
[172] Del Rey A, Besedovsky HO. The cytokine-HPA axis circuit contributes to prevent or moderate autoimmune processes. Z Rheumatol 2000;59(Suppl. 2):31–5.
[173] Spangelo BL, Judd AM, Call GB, Zumwalt J, Gorospe WC. Role of the cytokines in the hypothalamic–pituitary–adrenal and gonadal axes. Neuroimmunomodulation 1995;2:299–312.
[174] Loheswaran G, Kapadia M, Gladman M, Pulapaka S, Xu L, Stanojcic M, et al. Altered neuroendocrine status at the onset of CNS lupus-like disease. Brain Behav Immun 2013;32:86–93.
[175] Yougbaré I, Keravis T, Abusnina A, Decossas M, Schall N, Muller S, et al. Cyclic GMP catabolism up-regulation in MRL/lpr lupus-prone mice is associated with organ remodeling. Biochim Biophys Acta 2014;1842:916–26.
[176] Menniti FS, Faraci WS, Schmidt CJ. Phosphodiesterases in the CNS: targets for drug development. Nat Rev Drug Discov 2006;5:660–70.
[177] Owens T, Wekerle H, Antel J. Genetic models for CNS inflammation. Nat Med 2001; 7:161–6.
[178] Jeltsh-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: pathogenesis and biomarkers. Nat Rev Neurol 2014 [in press].
[179] Hanly JG. Reply. Arthritis Rheumatol 2014;66:1059–60.
[180] Hanly JG, Urowitz MB, O'Keeffe AG, Gordon C, Bae S-C, Sanchez-Guerrero J, et al. Headache in systemic lupus erythematosus: results from a prospective, international inception cohort study. Arthritis Rheum 2013;65:2887–97.
[181] Mitsikostas DD, Katsiari C, Sfikakis PP. "Lupus headache" may not exist: comment on the article of Hanly et al. Arthritis Rheumatol 2014;66:1058. http://dx.doi.org/10.10002/art38333.