

Review Article

The MRL/lpr Mouse Strain as a Model for Neuropsychiatric Systemic Lupus Erythematosus

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To date, CNS disease and neuropsychiatric symptoms of systemic lupus erythematosus (NP-SLE) have been understudied compared to end-organ failure and peripheral pathology. In this review, we focus on a specific mouse model of lupus and the ways in which this model reflects some of the most common manifestations and potential mechanisms of human NP-SLE. The mouse MRL lymphoproliferation strain (a.k.a. MRL/lpr) spontaneously develops the hallmark serological markers and peripheral pathologies typifying lupus in addition to displaying the cognitive and affective dysfunction characteristic of NP-SLE, which may be among the earliest symptoms of lupus. We suggest that although NP-SLE may share common mechanisms with peripheral organ pathology in lupus, especially in the latter stages of the disease, the immunologically privileged nature of the CNS indicates that early manifestations of particularly mood disorders may be derived from some unique mechanisms. These include altered cytokine profiles that can activate astrocytes, microglia, and alter neuronal function before dysregulation of the blood-brain barrier and development of clinical autoantibody titres.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that is typified by multiple abnormalities of the immune system, and which results in widespread pathology of multiple organs, including skin, kidney, heart, lungs, and joints. In addition to peripheral organ dysfunction in SLE, there is a high incidence of neuropsychiatric symptoms especially headaches, cognitive dysfunction, and psychiatric disorders [1], with roughly 40–70% of SLE patients demonstrating affective disorders [2]. Brain pathology, loss of integrity of the blood-brain barrier and autoantibodies are thought to play a role in neuropsychiatric systemic lupus erythematosus (NP-SLE), although some patients with behavioral symptoms have histologically normal brain tissue and no identifiable markers in serum or CSF [3–11].

Neuropsychiatric symptoms, particularly affective disorders, may be among some of the earliest manifestations of SLE [12–14]. Approximately 40% of the NP-SLE symptoms

develop before the onset of SLE or at the time of diagnosis and about 60% within the first year of diagnosis [13, 15, 16], indicating that neuropsychiatric symptoms are reliable indicators of disease activity and are often evident even before gross peripheral organ pathology occurs (in particular kidney disease). Symptoms of NP-SLE may also be independent of active disease in other organs [17–19]. This was found to be the case also in the animal model of lupus which is the subject of this paper, the MRL/lpr mouse, where depressive-like behavior is evident in young animals before significant levels of autoantibody titers and nephritis are evident [14, 20]. There are obvious limits to the search for mechanisms of CNS disease in human patients, and furthermore the diagnosis is often made after lupus is in late stages of progression. Thus, murine models can offer many advantages to elucidate the early mechanisms of neuropsychiatric manifestations of NP-SLE and help to distinguish between CNS-specific mechanisms and nonspecific illness. In this paper we focus on a specific

murine model of lupus, the MRL/lpr strain, and the ways in which this model reflects some of the most common manifestations of human NP-SLE. In addition, we discuss experimental data pointing to viable pathogenic mechanisms that underlie CNS involvement in SLE. Excellent reviews about other aspects of this and other murine models of lupus can be found elsewhere [3, 11, 21–34].

1.1. Murine Models of NP-SLE. To best represent human disease and explore relevant translational aspects of pathogenesis and novel treatment approaches, it is crucial to identify the most appropriate animal model from among the several available mouse strains which spontaneously develop lupus-like disease. Although there are induced models of SLE in nonautoimmune mouse strains, organ involvement as a rule is less severe than that observed in genetically susceptible animals [35, 36]. Therefore, spontaneous lupus models are often preferred for modeling of lupus-associated neuropsychiatric or other target organ disease. Murine models that spontaneously develop hallmark diagnostic signs of SLE include NZB \times NZW F1, NZM2410, BXSB, and MRL/lpr mouse strains. All of these strains (to a varying degree) develop lymphoid hyperplasia, B cell hyperactivity, autoantibodies, circulating immune complexes, complement consumption, and glomerulonephritis [21]. These strains differ from human SLE in that they display a high penetrance and relatively uniform disease expression over time. However, the disease course in murine lupus models (in the absence of extraneous intervention) is progressive, in contrast to the fluctuating course of flares and remissions typical in human SLE [26, 27, 37]. Although many of the spontaneous models of SLE develop behavioral abnormalities at some point in the disease [27], the MRL mouse model has some advantages in the investigation of specific CNS dysfunction and NP-SLE.

First, NZB- and BXSB-derived strains of mice have a high incidence of inherited brain anomalies [38] which can confound the assessment of autoimmunity-induced brain damage and the links between lupus-like disease and behavioral changes. Thus the MRL/lpr model permits the examination of interrelationships between behavioral outcomes and their underlying mechanisms without the potential confound of pre-existing CNS abnormalities [38–40]. As human SLE is overwhelmingly more common in females (about a 9:1 female to male ratio), mouse models that reflect this sex bias, such as MRL/lpr [14], are also likely to be useful in elucidating the relationship of hormones, negative outcomes, and potential sex-differences in efficacy of therapeutic agents in autoimmune disease. MRL/lpr mice [41] also express cardiolipin autoantibodies [42], one of a class of antiphospholipid autoantibodies thought to be important in the development of behavioral outcomes and CNS damage [43–45]. Although the molecular defect in the *Fas* gene underlying abnormal B cell regulation in MRL/lpr mice is not believed to be a cause for human SLE [46, 47], it is clear that the B cell dysregulation that characterizes this murine model is also a critical pathological aspect of human SLE [48, 49]. Moreover, the early onset, rapid progression,

and other similarities to the human disease state in MRL/lpr mice are also useful features of this model.

The MRL lymphoproliferation strain (lpr) MRL/Tnfrsf6 lpr/lpr (a.k.a. MRL/lpr) differs from the congenic (control) MRL/+ strain by a defect in membrane apoptotic-signaling Fas protein, which is due to a retrotransposon in the *Fas* gene [50, 51]. In addition to the typical signs of peripheral SLE, including autoantibodies, skin disease, arthritis, lymphadenopathy, and nephritis, MRL/lpr mice develop a constellation of behavioral outcomes referred to as “autoimmunity-associated behavioral syndrome” [24], particularly in the behavioral domains of emotional reactivity, motivated behavior, and cognitive function [14, 20, 22, 24, 33, 52–75].

1.2. NP-SLE. Nervous system involvement in lupus can include seizures, stroke and other cerebrovascular events, psychosis, cognitive dysfunction, and notably a very high incidence of mood disorders, particularly anxiety and depression [2, 18, 76–78]. Estimations of the prevalence of NP-SLE in human lupus range from 15% to 75% (or higher), reflecting variable diagnostic methodologies, a lack of standard criteria, and the sensitivity of diagnostic instruments to assess various behavioral outcomes [1, 2, 79]. Furthermore, many clinical studies of NP-SLE address only the most severe CNS symptoms, such as seizure, psychosis, and stroke, thus both the prevalence and importance of other neuropsychiatric symptoms are often underestimated. Generally, when specific and well-validated cognitive and affective diagnostic batteries are administered, rather than simple quality of life exams, studies consistently indicate that a great majority of SLE patients have some CNS outcomes, particularly mood disorders and cognitive dysfunction. NP-SLE is a major determinant of morbidity and mortality and is associated with increased disease severity, poorer prognosis and earlier mortality [80–85]. Furthermore, NP-SLE can necessitate potent and long-term immunosuppressive treatment with attendant side effects, is a detriment to quality of life in lupus patients, may be a major factor in employment disability, and substantially increases the financial and emotional costs of SLE [86, 87]. Comprehensive reviews of NP-SLE manifestations, diagnosis, pathology, and treatment in humans are outside the scope of the paper, and can be found elsewhere [2, 4, 9, 88–94].

1.3. Neuropsychiatric Deficits in MRL/lpr Mice. As in humans, development of SLE in MRL/lpr mice is also consistently accompanied by behavioral and neurological abnormalities. The most robust and reproducible deficits in MRL/lpr mice are emotional dysfunction, particularly in assays of depressive-like behavior such as the forced swim test and anhedonia. The forced swim test [95, 96] assesses behavioral despair as the proportion of immobility when rodents are placed in a tank of water [97, 98]. Normal rodents placed in a narrow tank of water from which there is no escape will exhibit vigorous swimming and struggling activity for the duration of the test (typically 6–12 minutes) and only rarely adopt a characteristic immobile posture (floating).

In contrast, animals treated with either pharmacological agents (such as hormones or via depletion of the amino acid tryptophan necessary to make serotonin [99, 100]), environmental manipulations (unpredictable chronic stress, social isolation [101–103]), or genetic alterations (Flinders strain, SERT knockouts [104, 105]) thought to be important in the etiology of depression more rapidly become immobile and maintain this immobility for a significantly great proportion of time than control subjects [106]. This is thought to represent “behavioral despair” or helplessness. The forced swim test has been extensively validated, as immobility is reduced by a wide range of clinically active antidepressant drugs [98] and has predicted the antidepressant efficacy of novel therapeutic agents [97]. MRL/lpr mice develop depression-like behavior in the forced swim test as early as 5 weeks old, and this persists throughout the course of the disease [14, 20, 58, 65].

In addition to feelings of helplessness and despair, depressed patients report anhedonia—the inability to experience pleasure or reward from events that normally have a positive hedonic value, such as eating, social interaction, or sexual activity. In rodents, a commonly used measure of anhedonia is the failure to prefer sweet solutions [107, 108]. MRL/lpr mice exhibit this lack of normal preference for sweet solutions as early as 5–6 weeks old [59] and continue to exhibit anhedonia during the active disease phase (4–5 months old) [52, 53, 55, 109]. Further symptoms of depression-like behavior include decreased activity, fatigue, and apathy. In rodents, this can be assessed as decreased voluntary activity and exploration in a novel environment, such as an open field [110]. MRL/lpr mice exhibit reduced exploration and activity during both the nocturnal and diurnal phases [63, 65] by 8–11 weeks old [14, 33].

Despite the high prevalence of depression in lupus patients and recent evidence that antidepressants may reduce symptoms of depression, in part, by reducing inflammatory responses [111, 112], there have been few studies investigating the efficacy of antidepressant therapies in human lupus [113] or in murine models [58]. Immunosuppressive agents typically used to treat SLE, such as cyclophosphamide and steroids, do reduce measures of depression-like behavior in MRL/lpr mice [33, 55, 59, 114] and also typically reduce the other hallmarks of SLE, including autoantibody titers, proteinuria (nephritis), and the levels of proinflammatory cytokines [55, 59]. However, there have been few systematic studies to determine if these are effective at reducing measures of NP-SLE, especially cognitive and affective dysfunction, in humans. Several studies indicate that high levels of both affective and cognitive disorders are present and persistent in NP-SLE patients undergoing such therapies [115, 116], though these traditional immunosuppressive agents do seem to be effective to prevent and/or treat the more severe NP-SLE outcomes, such as seizure and cerebrovascular events [13, 117, 118].

Anxiety disorders are also common in NP-SLE [1, 119] and are often comorbid with depressive disorders. Several commonly used methods can be applied to assess anxiety in rodents, and these include the elevated plus maze and the acoustic startle test [120–127]. The elevated

plus maze (EPM) essentially assesses a preference between a comparatively safe environment (the closed arms) and a risky environment (elevated open spaces). The general principle is that the more “anxious” the subjects are, the less likely they will be to explore the open arms. The EPM has been validated pharmacologically, with other tests of anxiety-like behaviors, and physiologically [120–123]. With respect to anxiety in murine models of lupus, there have been conflicting reports. Some groups have reported increased anxiety in MRL/lpr mice assessed in the elevated plus maze [65], while others have reported that MRL/lpr mice have normal or less anxiety than MRL/+ controls [14, 20, 70]. The lack of anxiety phenotype is also supported by a generally lower startle reactivity till 11 weeks old [70].

There is also no clear consensus with respect to cognitive dysfunction in murine models of lupus. Mild spatial memory deficits have been reported in the water maze, assessed as the latency to find a new platform position after previous training in the water maze [63] and as deficits in linear maze acquisition as early as 8 weeks [68]. However, behavior in the object placement and novel object recognition tasks [128–130] is normal [14, 20].

The predominance and reproducibility of affective dysfunction in MRL/lpr mice are consistent with known pathology and/or dysfunction in several neurotransmitter systems and brain regions important in the regulation of mood [131]. These include altered responses to the dopaminergic drugs amphetamine and apomorphine [52, 109, 132] and higher levels of apoptosis in the dopaminergic neurons in the nucleus accumbens and substantia nigra (thought to be involved in response to reward and anhedonia) in MRL/lpr mice [52, 109]. There are also decreased levels of serotonin in brain regions such as the hypothalamus, which regulate stress and response to appetitive stimuli (among other things) [133], and increased levels in the hippocampus [58]. This observation is consistent with altered serotonin levels in lupus patients similar to those that occur in depressed patients [134–136], including those in which depression has been induced by cytokine therapy [137–139]. Decreased levels of noradrenaline evident in the prefrontal cortex of MRL/lpr mice would also be consistent with depressive-like behavior [58, 140–142].

1.4. Comparison of More and Less Affected Lines. There is also a fascinating “accidental” experimental difference in MRL/lpr mice. Over time, this strain of mice displayed a lessening of symptoms such as lymphoproliferation, a greatly delayed development of nephritis, and a longer lifespan. The line was eventually reconstituted and again manifests rapid development of the typical severe autoimmune profile (<http://jaxmice.jax.org/>: re-coding of stock #485-attenuated disease to stock #6825-reconstituted severe line). This serendipitous circumstance permits the differentiation between negative behavioral outcomes that may result from gross peripheral pathology and specific CNS-mediated behaviors [14, 143].

A major difference in the disease-attenuated line is the long delay to develop renal disease and profoundly decreased

proteinuria [14, 20]. The levels of autoantibodies tend to increase earlier and to a greater extent in the reconstituted severe line. Furthermore, the disease-attenuated line has normal open field activity from 8 to 18 weeks [20] while in the reconstituted severe line, the females have lower activity levels from 5 weeks, although MRL/lpr males exhibit normal open field activity until at least 18 weeks old [14, 20]. Cognitive functions assessed in novel object exploration and placement tasks were normal in mice 5–18 weeks old in both sexes and both lines [14, 20]. Motor coordination in the balance beam and anxiety in the elevated plus maze were also comparable in both lines from 5 to 18 weeks old [14, 20]. Interestingly, there was no evidence of social withdrawal assessed in the social preference test [144] in either line from 5 to 18 weeks compared to age- and sex-matched controls [14, 20]. However these results were likely due to the very low social preference evident in both MRL/+ female controls and female MRL/lpr mice [20]. It is thus not clear if social withdrawal, a typical symptom of affective disorders, is evident in the MRL/lpr females due to SLE or if there is some influence of the background strain that induces social withdrawal by some other route in females.

Depression-like behavior is robustly evident in disease-attenuated line in the forced swim test by 8 weeks [20] and in reconstituted severe line by 5 weeks [14], although earlier time points were not tested in the disease-attenuated line. Given that there is no evidence of kidney pathology in the disease-attenuated mice, these data confirm the robustness of emotional dysfunction and provide further support that such outcomes are likely a primary manifestation of autoimmunity rather than arising from nonspecific illness and peripheral organ pathology. Finally, the presence of two MRL/lpr strains that share a mutated Fas yet which differ in their autoantibody profile and neurobehavioral manifestations [14, 143] is strong evidence that the CNS manifestations in these mice are primarily immunologically mediated, rather than resulting from possible effects of abnormal Fas-mediated apoptosis on brain development or glial function.

2. CNS Mechanisms and Pathology

Several different pathogenic mechanisms are postulated to be involved in CNS manifestations of lupus. These include B cell/autoantibody-mediated nervous system compromise, immune complex deposition, vasculitis, microthrombosis and vasculopathy, aberrant MHC Class II antigen expression with T-cell mediated disease, autoactivated T-cells, and cytokine-induced brain inflammation [145, 146]. However, as there are multiple and quite disparate expressions of lupus involving the nervous system, it is unlikely that a single mechanism can account for every clinical manifestation of NP-SLE. As the most common behavioral manifestations of NP-SLE in both patients and murine models are affective and cognitive disorders, especially in the early stages of SLE, we focus on below mechanisms thought to be involved in the etiology of affective and cognitive dysfunction.

2.1. Autoantibodies. MRL/lpr mice express a range of autoantibodies [147] including antinucleosome [148], antiribosomal [149] antiphospholipid, and phosphoprotein (such as anticardiolipin [42] and antinucleolin) [150] autoantibodies [151]. A critical role of autoantibodies in the etiology of lupus-associated nephritis has been well documented. Nephritogenic lupus autoantibodies initiate immune deposit formation through direct or indirect interaction with glomerular antigens [152, 153] and result in kidney pathology that can be prevented by administration of an immunoglobulin-binding peptide [151, 154]. It has been suggested that autoantibodies reacting with brain antigens may similarly play a role in CNS pathology and negative behavioral outcomes in NP-SLE [90, 155].

Evidence supporting the role of autoantibodies in the pathogenesis of NP-SLE includes the increased titer of autoantibodies in serum of diseased MRL/lpr mice [156–158], which occurs earlier in females [156, 159], consistent with the earlier onset of depressive-like behavior in MRL/lpr females [14]. There is also evidence that some of these serum autoantibodies react with brain antigens [160, 161] and occur in serum of as early as 2–3 months old in MRL/lpr mice [61] and in CSF as early as 4–5 months [162]. Nevertheless, as further discussed below, the fact that behavioral deficits are present before major rises in serum autoantibody titers or detectable breaches in the blood-brain barrier indicates that serum antibodies alone are clearly not the sole important pathogenic factor in NP-SLE, at least early in the disease.

The relationship of serum and CSF levels of autoantibodies to the disease process is complex, but it is likely that intrathecal autoantibodies are likely to be more critically related to NP-SLE than are serum autoantibody titers. Some evidence does suggest a role for serum autoantibody levels in NP-SLE, as mice with more severe peripheral and behavioral manifestations of SLE also have more pronounced changes in hippocampal and cortical morphology and increased indices of cell death [163–166]. This can be prevented with doses of cyclophosphamide that reduce serum autoantibody titers [165], although CSF levels of autoantibodies were not assessed. However, IgG levels in serum, but not CSF, are positively correlated with spleen weight, suggesting that central autoimmune processes are relatively independent from systemic manifestations [167]. This is supported by the fact that the patterns of autoantibody expression in serum and CSF is not correlated over time in patients with NP-SLE [168]. Finally, CSF from diseased MRL/lpr mice which was treated to remove cytokines is cytotoxic to cultured cells [71, 169] and was more cytotoxic than serum derived from diseased animals [71], indicating a primary intrathecal source of cytotoxic autoantibodies. Cytotoxicity in culture was correlated with the extent of apoptosis in the brains of aged LPR mice from which the CSF was derived, thus toxic mediators produced by the CNS of diseased MRL/lpr mice are likely to be more pathogenic than those in serum. Therefore autoantibodies recognizing brain antigens are plausible candidates as neurotoxic moieties. The site of production of brain reactive antibodies in MRL-lpr mice is however not conclusively identified, although this remains a subject of intense research interest [162].

Autoantibodies recognizing brain antigens, such as the NMDA receptor subtype of the excitatory neurotransmitter, glutamate, are also present in the serum and CSF of patients with NP-SLE [168, 170]. When injected directly into the brain of otherwise healthy mice, or when injected peripherally to animals with a compromised blood-brain barrier, these are neurotoxic and result in impaired cognition and emotional behavior [171–173]. In addition, intrathecal administration of antiribosomal P antibodies induces depression-like behavior in the forced swim test [174]. There have also been reports of positive correlations between serum levels of brain reactive autoantibodies and cognitive dysfunction and depression-like behavior [90, 155, 175] although other studies have failed to find such relationships [61, 161, 176] in patients with NP-SLE. It has thus been suggested that CSF levels of brain-reactive autoantibodies may be more important factors than serum titers to the genesis of NP-SLE pathology and symptoms [90, 177]. These data further support the notion that CNS-derived specific factors and possibly intrathecal production of autoantibodies can lead to brain pathology and corresponding negative behavioral outcomes [52, 162, 169].

However, the blood-brain barrier restricts the influx of circulating factors, including lymphocytes and antibodies, from entering the brain and cerebral circulation. The brain also does not have resident antibody-producing cells. Generally, influx of antibodies or lymphocytes requires disintegration of the blood-brain barrier as general or localized lesions [27]. There is no convincing evidence to date that this occurs as early as the earliest manifestations of the negative behavioral outcomes. Therefore, while it is probable that the loss of integrity of the blood-brain barrier eventually occurs and obviously plays role in the resulting CNS pathology [9, 178–181], possibly in part by permitting the entry of autoantibodies and antibody-producing cells, negative behavioral outcomes might rather be initiated by different mechanisms than those that regulate pathology in peripheral organs and later onset, more severe symptoms of NP-SLE. Thus, autoantibodies are possibly not the sole or primarily etiology of several of the symptoms of NP-SLE, especially given the notable role of cytokines and chemokines in affective and cognitive disorders [182–186].

Indeed, several lines of evidence suggest that autoantibodies may not be sufficient to induce NP-SLE in the MRL/lpr strain. First, increased secretion of chemokines and cytokines (such as interferons) cause inflammatory pathology in kidney [187, 188], even in the absence of autoantibody deposits [189]. Furthermore, the high proinflammatory cytokine levels in MRL/lpr mice are progressive and correlated with increasing disease severity [190]. Conversely, anti-inflammatory cytokine therapy is beneficial [191]. In fact, numerous anti-inflammatory agents with a wide variety of underlying mechanisms of action increase survival, reduce peripheral organ pathology, and normalize T-cell phenotypes in mice without altering the level of autoantibodies [192–197]. However, neuropsychiatric symptoms have not been systematically assessed in most of these studies so it is not clear if there are also similar benefits to behavioral outcomes. Further evidence suggesting that autoantibodies

are not sufficient to produce NP-SLE includes the fact that DNA-binding antibodies derived from autoimmune MRL mice fail to induce SLE-like changes when administered to healthy animals [198]. Actually, all strains of mice thus far tested show some brain reactive autoantibodies in serum [199] even in the absence of abnormal behavior. Last, MRL/lpr mice that express a mutant transgene that prevents the secretion of circulating IgG still develop nephritis despite the lack of soluble autoantibody production, indicating that circulating autoantibodies are neither requisite nor sufficient to induce pathology [200].

Thus, serum antibodies could be neurotoxic, but they can only access brain tissue after a compromise of blood-brain barrier integrity. Lymphocytes can also not access the brain through an intact blood-brain barrier. Furthermore, insults to the blood-brain barrier are likely to be regional rather than global and may occur later in the disease than the onset of robust emotional disturbances. So if brain-reactive autoantibodies are not engendering such symptoms early in NP-SLE, then what is?

2.2. Chemokines and Cytokines. Cytokines and chemokines are likely to be critical early factors regulating the negative behavioral outcomes, as they need not pass the blood-brain barrier to regulate neural function [57, 183, 201]. Detection of increased secretion of peripheral inflammatory cytokines can occur across an intact blood-brain barrier, in part via the vagus nerve. This induces glia and microglia to produce cytokines and other inflammatory and cytotoxic agents (including prostaglandins and nitric oxide). These are well documented to elicit the physiological and behavioral symptoms of mood disorders, including lethargy, decreased social interaction, immobility in the forced swim test, and anhedonia [183, 184, 202–204]. Finally, cytokines have been linked to depression in humans [205–213] and to neuropsychiatric symptoms in NP-SLE patients [8, 12, 170, 185, 214, 215].

The role of cytokines in emotional disturbances in MRL/lpr mice is supported by numerous studies. In very large samples, the severity of behavioral deficits in MRL/lpr mice does not relate strictly to autoantibody titers or brain infiltration by T cells [57], which would indicate a compromised blood-brain barrier. Cytokine, chemokine, and prostaglandin dysregulation occurs as early as 1–4 weeks in MRL/lpr mice, well before disease onset and upregulation of autoantibodies [26, 30, 216–223].

Clinically, cytokine-mediated depression has certainly resulted from cytokine administration when used as treatments in cancer and viral infections [224–228]. Increased levels of IL-6 and other cytokines have been found in the cerebrospinal fluid and brains of patients with NP-SLE [229]. In MRL/lpr mice, treatment with anti-inflammatory cytokines reduces disease severity [189, 230–237] while administration of proinflammatory cytokines accelerates glomerulonephritis, vasculitis, and other disease manifestations [231, 233]. MRL/lpr mice lacking the IL-6 receptor have delayed mortality and nephritis and a reduction of autoantibody complex deposition [238], though these mice

have not been behaviorally tested, so the affect on symptoms of NP-SLE is not known.

The early dysregulation of cytokine production, especially TNF- α , IL-1, IL-2, and IL-6 [188, 223, 239, 240], corresponds to the onset of symptoms of depressive-like behavior, such as anhedonia and behavioral despair in MRL/lpr mice [59] and in other rodent strains [241, 242]. Anhedonia can be ameliorated by cyclophosphamide, which abolishes the typically early and significant rise of cytokines, particularly IL-6 [59]. Notably, anhedonia and other behavioral indices of depressive-like behavior in mice can be replicated by exogenous IL-6 [59] and are prevented by knockout of the IL-6 receptor [203]. Other proinflammatory immunomodulators, such as TNF- α , also increase behavioral indices of depressive-like behavior in mice [243] while blocking their secretion or receptors decreases depressive-like behavior [242, 243]. High levels of proinflammatory cytokines may also impair the function of the blood-brain barrier [244, 245] and may thus be permissive to the negative effects of autoantibodies and lymphocytes. Finally, cytokine dysregulation is a shared characteristic of murine lupus models with different underlying genetic mechanisms [246].

Thus, while recent and substantial evidence indicates a role for cytokines in the early mechanisms of NP-SLE, several obstacles have prevented the further studies needed to elucidate the specific underlying etiology. First, it is important to recognize that local alterations in brain cytokine levels that can be very relevant to NP-SLE pathogenesis may be present early in the disease course, yet these may not necessarily be reflected in abnormal serum levels. Second, there are numerous cytokines, and it is a gross oversimplification to assume that an individual cytokine is pro- or anti-inflammatory. Rather, the precise proportions of cytokine levels in serum and brain are likely to be more important than absolute levels of a single cytokine. However, comprehensive analysis of multiple cytokines is prohibitively expensive. Furthermore, cytokines are necessary for normal brain development and cognitive function [247–250], and thus global knock-outs of specific cytokine receptors can be problematic, as these can cause cognitive, reproductive, and other deficits [248, 251] and also require large breeding colonies to achieve appropriate genotypes. More precise timing of cytokine receptor knockdown can be accomplished by viral vectors, but these are also less than ideal in studies of SLE as they are thought to induce immune responses [252]. Other methods of receptor knockdown that are more promising include siRNA.

3. Sex Differences

There is a much higher incidence of SLE in females than in males. Moreover, females with autoimmune disease have a higher risk of psychiatric disorders, particularly depression [80]. Disease severity and rate of progression are also accelerated in female MRL/lpr mice as compared to males of this strain. Serum autoantibodies appear earlier in female MRL/lpr mice [14, 156]. Female MRL/lpr mice also have

higher levels of IgG in the CSF compared to males [253]. Symptoms of depressive-like behavior are also worse in female MRL/lpr mice [14].

One possible mediator of sex differences in the prevalence and outcomes of SLE is sex steroid hormones, such as estrogens [254–263]. Administration of exogenous estrogens can induce a lupus-like syndrome in otherwise healthy mice [258] and exacerbate symptoms in MRL/lpr mice, in which estrogens globally increase IgM levels [264] autoantibody titers [156], glomerulonephritis, lymphoproliferation, mortality [257], and cytokine levels [265]. Conversely, treatment with the estrogen receptor antagonist, tamoxifen, reduces proteinuria, serum tiers of anti-dsDNA autoantibodies and increases survival [266]. Estrogens also differentially affect B and T cell-mediated immune responses in MRL/lpr mice [255, 256]. Immune complex-mediated glomerulonephritis is significantly accelerated by estrogens whereas T cell-mediated lesions, such as renal vasculitis and periarticular inflammation, are reduced in MRL/lpr mice after estrogen treatment [255, 256]. Estrogens can also modulate blood-brain barrier permeability [267, 268] and increase cytokine levels in patients with SLE [259, 262, 269, 270]. Moreover, the myriad effects of estrogen on neuroprotection are being increasingly recognized [271–273]. While space constraints prevent going into further details about the role of sex hormones in maintaining the integrity of the blood-brain barrier and providing neuroprotection, the interested reader can find additional details in some recent comprehensive reviews [267, 271, 272, 274, 275]. These sex and hormone differences may have clinical implications for treatment of SLE, as cyclophosphamide prevents pulmonary disease in male but not female MRL/lpr mice [276]. Similarly, sex differences in the efficacy of treatment in autoimmune disorders is not uncommon [277]. Furthermore, there are notable sex differences in both humans and in animal models in the susceptibility of depression, responses to antidepressant treatments, and in underlying hormonal, immune, and neurochemical alterations in affective disorders [278, 279].

4. Conclusion

CNS disease in NP-SLE may share common mechanisms with peripheral organ pathology in SLE, especially in the latter stages of the disease, but the distinct nature of CNS-mediated immunity and the blood-brain barrier indicates that early manifestations of particularly mood disorders may be derived from some unique mechanisms. Additionally, agents critical to the pathology of NP-SLE, such as cytokines, are regulated by sex and steroid hormones, which is consistent with the predominance of SLE and mood disorders in females. Altered cytokine profiles in serum and/or CNS can result in the activation of astrocytes, microglia, and changes in neuronal function and morphology and dysregulation of the blood-brain barrier. Pathology of the blood-brain barrier could lead to altered homeostasis and play a significant role in impairment of CNS function seen in later onset of NP-SLE as well many other immune disorders.

Despite the importance of the MRL/lpr and other murine models for elucidating the underlying mechanisms of NP-SLE, there are yet many questions that have not been conclusively answered. These include relating measures of the earliest onset of negative behavioral outcomes with intrathecal levels of cytokines and native brain-reactive autoantibodies, systematic study of the efficacy of alternative therapeutics (such as traditional and novel antidepressants), and comprehensive analysis of the time course of blood-brain barrier dysfunction.

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