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Review

Systemic lupus erythematosus and the brain: What mice are telling us

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Abstract

Neuropsychiatric symptoms occur in systemic lupus erythematosus (SLE), a complex, autoimmune disease of unknown origin. Although several pathogenic mechanisms have been suggested to play a significant role in the etiology of the disease, the exact underlying mechanisms still remain elusive. Several inbred strains of mice are used as models to study SLE, which exhibit a diversity of central nervous system (CNS) manifestations similar to that observed in patients. This review will attempt to give a brief overview of the CNS alterations observed in these models, including biochemical, structural and behavioral changes.

Keywords: Systemic lupus erythematosus; Animal models; Brain; Pathophysiology

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune disease of unknown etiology primarily affecting females of child-bearing age (Kotzin, 1996; Lawrence et al., 1998; Mills, 1994; Raptopoulou et al., 2004; Walsh et al., 1995). SLE is influenced by genetic, hormonal and environmental factors (Cooper et al., 1998; Maldonado et al., 1999). The clinical spectrum of SLE is wide and variable. While the organs primarily responsible for the morbidity and mortality observed in SLE have been the kidneys and lungs, nephritis and pneumonitis now have more favorable outcomes, which can be attributed to early and aggressive intervention (Boumpas et al., 1995; Fessler and Boumpas, 1995). Although there is increased awareness among clinicians and researchers that central nervous system (CNS) involvement is a devastating manifestation of SLE and occurs in the majority of patients at some point in their course, the etiology, natural course, and treatment for this complication remains elusive.

2. CNS involvement in human SLE

CNS involvement in SLE leading to neuropsychiatric disease (NP-SLE) is a debilitating consequence of this disease associated with substantial morbidity and occasional mortality (Sibley et al., 1992; Kaell et al., 1986; Wong et al., 1991). Between 30 and 70% of SLE patients have significant NP disturbances during the course of the disease (West, 1994; West et al., 1995; Asherson et al., 1993; Futrell et al., 1992; Rood et al., 1999). The NP syndromes exhibit a significant degree of heterogeneity and are diverse in etiology and presentation. The signs and symptoms of NP-SLE span a wide spectrum, ranging from overt findings such as seizure, stroke, psychosis, transverse myelitis, and aseptic meningitis (McCune and Golbus, 1988; West, 1994, 1996) to more subtle abnormalities of memory, concentration, intellect, and mood (Carbotte et al., 1995a,b, 1986; Denburg et al., 1987b; Fisk et al., 1993; Hanly et al., 1994; Lindal et al., 1995; Utset et al., 1994). Furthermore, such NP deficits can occur alone or in various combinations. Neurocognitive decline and depression is prevalent and has been reported in up to 60% of patients with SLE (Ginsburg et al., 1992). Cognitive dysfunction can occur in patients with no apparent history of NP disease, including abnormalities in visual, arithmetic, and writing skills (Denburg et al., 1987a; Koffler, 1987).

NP deficits in patients with SLE may not be in a steady state, but fluctuate throughout the course of the disease independent of depression or anxiety (Keenan and Conway, 1997). In

Abbreviations: SLE, systemic lupus erythematosus; CNS, central nervous system; NP-SLE, neuropsychiatric disease; MRL, medical research laboratories; NZ, New Zealand; BBB, blood–brain barrier; IC, immune complex; Cho, choline; GABA, gamma amino butyric acid; NAA, *N*-acetyl aspartate

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addition, symptoms may be compounded by medications taken for disease management, such as the common use of corticosteroids, and by other associated pathological states, such as antiphospholipid antibody syndrome. The available data suggest that NP-SLE is a complex phenomenon and may not be clinically recognizable until in an advanced phase of the disease. Furthermore, there is no specific marker or diagnostic indicator for NP-SLE. Radiologically, transient hypodensities have been noted on computerized tomography scans of SLE patients (Sibbitt et al., 1994). Magnetic resonance imaging scans of SLE patients have revealed vasculitis, arterial spasm and increased vascular permeability (Moritani et al., 2004), all of which eventually can lead to cerebral edema (Steinberg, 1994). Thus, CNS involvement in SLE is common, quite variable in presentation, with considerable overlap with other comorbid and iatrogenic NP conditions, often progressive, and remains among the most significant causes of morbidity and mortality in SLE patients.

3. Animal models of SLE

Given that our knowledge of disease pathogenesis is limited from studying humans directly, accurate animal models have been a useful adjunct to our understanding of disease mechanisms. Considerable understanding of disease pathophysiology comes from animal models *in vivo* and cell culture systems *in vitro*, which provide us with the window to study complex processes, interactions and intersecting signaling pathways. To gain insight into specific disease mechanisms in SLE, a number of murine models of SLE have been studied. Spontaneously occurring SLE as occurs in the commonly used Medical Research Laboratories (MRL), New Zealand (NZ), and BXSB strains have been incredibly informative as they share many features of their human counterparts; yet, they differ in having 100% penetrance and are progressive in contrast to the fluctuating course of flares and remissions seen in human SLE (Theofilopoulos et al., 1989; Theofilopoulos and Dixon, 1985; Andrews et al., 1978; Brey et al., 1997b; Petris, 1996).

One of the best established murine models of SLE that we have used in our studies occurs in the MRL/*Tnfrsf6*$^{lpr/lpr}$ (MRL/*lpr*) strain, that differs from the congenic MRL$^{+/+}$ strain by the nearly complete absence of the membrane apoptotic-signaling Fas protein, which is due to a retrotransposon in the *fas* gene (Adachi et al., 1993; Watanabe-Fukunaga et al., 1992). This model is heavily relied upon because of its wide spread availability, ease of use, and has disease occurring in a compressed time. Furthermore, the disease pathology is observed in both sexes. Another accurate and genetically programmed SLE model is seen in the F_1 cross between NZ black and NZ white mice (NZB/W) (Theofilopoulos and Dixon, 1985). In this model, disease occurs spontaneously in females and the pathological changes can be studied in a lupus setting without the confusing effects attributable to the absence of the Fas protein. In contrast to the NZB/W strain, the BXSB strain is a model where the males develop autoimmunity much earlier (5 months) than females (>1 year). This accelerated autoimmunity is due to the mutant *Yaa* gene on the Y chromosome (Izui et al., 1995).

Although these mouse models develop an autoimmune disease that shares immunological and histopathological features (Andrews et al., 1978), they display important differences too. Some strains have accelerated disease while others are more slowly progressive. Furthermore, in some models, females are more susceptible to disease (e.g., NZB/W), while in others it is males (e.g., BXSB). Therefore, a survey of all the models should be considered before generalizations of the findings from a single model are made.

4. SLE and the blood–brain barrier

The brain is immunologically privileged (Head and Griffin, 1985) and its microenvironment is strictly regulated for proper functioning. It is sheltered from circulating substances by the presence of the BBB, where specific transport mechanisms regulate the uptake and efflux of substances to and from the brain. The brain to blood interface is present at three locations: endothelium of the brain parenchymal vessels, arachnoid epithelium of the meninges, and the epithelium of the choroids plexus (blood–cerebrospinal fluid (CSF) interface) (Davson and Segal, 1995; Davson et al., 1993; Segal and Zlokovic', 1990). Breakdown of the BBB can result in entry of immunoglobulins and other larger molecules and blood cells into the CNS that are otherwise normally restricted at the blood–brain interface. We and others have identified immunoglobulins in brain regions close to the ventricles, in perivascular areas, surrounding microcapillaries and in granular cells of the hippocampus in MRL/*lpr*, BXSB and NZB/W mice (Alexander et al., 2003; Zameer and Hoffman, 2001; Moore, 1992). Furthermore, elevated IgG and protein levels were observed in the CSF of MRL/*lpr* mice, felt to be indicative of BBB impairment and which correlated with disease activity in patients and murine models of SLE (Sidor et al., 2005; Sakic et al., 2005). This disease is also characterized by the production of different autoAbs that may contribute to CNS manifestations (Moore, 1992; Jennekens and Kater, 2002). These autoAbs gain entry into brain when the BBB is leaky and cause neuronal death (Kowal et al., 2004) and correlate with psychosis and seizures (Tin et al., 2005) Furthermore, there is increased infiltration of lymphocytes and other blood cells into brain of all three mouse models, which are prevented in a normal setting by the BBB (Zhou et al., 2004; Kier, 1990; Rudick and Eskin, 1983; Vogelweid et al., 1991; Sakic et al., 2000). Increased homing of these cells into the CNS could also be due to the increased expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM) on CNS vessels (Brey et al., 1997a; Marshall et al., 2003; Zameer and Hoffman, 2003), which lymphocytes bind via their integrin countereceptors such as lymphocyte function-associated antigen-1 (LFA-1 or CD11a/CD18) and macrophage differentiation antigen (Mac-1 or CD11b/CD18). These results from mice are consistent with clinical evidence obtained from SLE patients, where increased