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Neuroimmunopathology in a murine model of neuropsychiatric lupus

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Abstract

Animal models are extremely useful tools in defining pathogenesis and treatment of human disease. For many years researchers believed that structural damage to the brain of neuropsychiatric (NP) patients lead to abnormal mental function, but this possibility was not extensively explored until recently. Imaging studies of NP-systemic lupus erythematosus (SLE) support the notion that brain cell death accounts for the emergence of neurologic and psychiatric symptoms, and evidence suggests that it is an autoimmunity-induced brain disorder characterized by profound metabolic alterations and progressive neuronal loss. While there are a number of murine models of SLE, this article reviews recent literature on the immunological connections to neurodegeneration and behavioral dysfunction in the Fas-deficient MRL model of NP-SLE. Probable links between spontaneous peripheral immune activation, the subsequent central autoimmune/inflammatory responses in MRL/MpJ-Tnfrsf6^{lpr} (MRL–lpr) mice and the sequential mode of events leading to Fas-independent neurodegenerative autoimmune-induced encephalitis will be reviewed. The role of hormones, alternative mechanisms of cell death, the impact of central dopaminergic degeneration on behavior, and germinal layer lesions on developmental/regenerative capacity of MRL–lpr brains will also be explored. This model can provide direction for future therapeutic interventions in patients with this complex neuroimmunological syndrome.

Keywords

MRL mice; Autoimmunity; Neuroinflammation; Neurodegeneration; Impaired neurogenesis; Dopamine; Corticosteroids; Behavioral dysfunction

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune/inflammatory disease with a broad spectrum of clinical and immunological manifestations (Isenberg et al., 1989). Neurologic and psychiatric (NP) manifestations of unknown etiology are common in SLE and have been proposed to represent a more severe form of the disease, occurring in up to 75% of patients (Scolding and Joseph, 2002; Navarrete and Brey, 2000; Hanly, 2001; Bluestein, 1992; Adelman et al., 1986; Mcnicholl et al., 1994). The manifestations of NP-SLE range from diffuse CNS disorders (i.e. acute confusional state, psychosis, anxiety and depressive disorders, clinical to subclinical cognitive disorder of variable functional significance) to CNS syndromes

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(i.e. seizures, cerebrovascular disease, chorea and myelopathy, transverse myelitis, demyelinating syndrome and aseptic meningitis, headaches) and PNS disorders (i.e. polyneuropathies and mononeuropathies, autonomic disorders, plexopathy, myasthenia gravis) (Tincani et al., 1996). Approximately 40% of the NP-SLE manifestations develop before the onset of SLE or at the time of diagnosis and about 60% within the first year after diagnosis (van Dam, 1991). While a histologically normal brain with no specific pathognomonic brain lesions is a possible finding in NP-SLE, various abnormalities include hypoperfusion (Colamussi et al., 1995; Handa et al., 2003; Huang et al., 2002; Lopez-Longo et al., 2003) and regional metabolic abnormalities (Komatsu et al., 1999; Sibbitt and Sibbitt, 1993; Brooks et al., 1997; Volkow et al., 1988). Brain atrophy, however, is the most frequent observation on CT scans (Gonzalez-Scarano et al., 1979; Kaell et al., 1986; Miguel et al., 1994; Omdal et al., 1989; Ainiala et al., 2005; Waterloo et al., 1999) and is proposed to reflect widespread and progressive neuronal loss (Sibbitt and Sibbitt, 1993; Sibbitt et al., 1994).

Research has helped to distinguish the role of autoimmune disease as the primary factor inducing NP-SLE, apart from complications of kidney damage, infections, and steroid therapy. Autoantibodies in the serum and cerebrospinal fluid (CSF) of lupus patients have been proposed as an important factor in the etiology of CNS damage (Jennekens and Kater, 2002). Increased intrathecal synthesis (as revealed by an elevated IgG index and oligoclonal banding) in patients with CNS dysfunction (McLean et al., 1995; Hirohata et al., 1985; Winfield et al., 1983) and antigen-specific autoantibodies in the CSF (Yoshio et al., 2005) are associated with NP manifestations (Greenwood et al., 2002). For example, evidence suggests that neuronal antibodies are involved in the pathogenesis of psychiatric disease (Quismorio and Friou, 1972; Vincent et al., 2003; Diederichsen and Pyndt, 1970; Bluestein and Zvaifler, 1983), and parenchymal lesions associated with movement disorder have recently been documented in these patients (Rocca et al., 2006), supporting the link between autoimmunity, neuronal death, and neurologic manifestations. In many cases however, the correlational nature of clinical data has lead to the necessity for animal models. Using animal models, interactions between autoimmune/inflammatory phenomena and brain function can be examined in a more systematic and direct way. Several animal models develop a fatal immune complex-mediated glomerulonephritis associated with immunological abnormalities (i.e. autoantibody production) very similar to the salient features of human SLE (Theofilopoulos, 1992). The existence of murine models for this disease (both induced and spontaneous) have been extremely valuable to researchers in evaluating the various behavioral manifestations and autoimmune abnormalities which present in this syndrome.

The most commonly studied spontaneous models of lupus include the (NZB×NZW)F1(BWF1) hybrid, BXSB, and MRL mice. These strains are characterized by a wide spectrum of autoimmune manifestations (Dixon et al., 1978) and share common characteristics such as hypergammaglobulinemia and antinuclear antibodies (ANA). However, no animal model is a pure representation of an entire clinical syndrome, and each strain has distinct features which make them beneficial for examining certain aspects of disease (Dixon et al., 1978; Andrews et al., 1978). Considering that the NZB and BXSB strains of mice have a high incidence of inherited brain anomalies (Sherman et al., 1990) which can confound the assessment of autoimmunity-induced brain damage and the links between lupus-like disease and behavioral changes, the MRL model permits the examination of interrelationships between systemic autoimmunity, brain pathology, and aberrant behavior in a more controlled manner. Due to profound deficits in behavior, which appear at a high frequency during the onset of spontaneous CNS-lupus-like disease in MRL/MpJ-Tnfrsf6^{lpr} (MRL–lpr) mice (Szechtman et al., 1997; Sakic et al., 1997), this review focuses on the validity of the MRL model in exploring organic causes of NP manifestations in SLE.

When studied together, MRL–lpr and MRL/MpJ+/+ (MRL+/+) congenic mice (sharing >99.9% of their genome) are considered to be a natural, well controlled model of NP-SLE (Sakic et al., 1997). These substrains are comparable in many respects (appearance, size and reproductive age), except in the onset of autoimmunity and neurobehavioral dysfunctions. While MRL–lpr mice have rapid onset of disease beginning around 7 weeks of age, MRL+/+ controls develop milder symptoms much later in life (Theofilopoulos, 1992). A mutation of a single autosomal recessive gene, designated *lymphopoliferation* (*lpr*), on chromosome 19 results in massive lymphoadenopathy, induced by the accumulation of abnormal T-lymphocytes in the MRL–lpr strain (Theofilopoulos, 1992). There is also a spontaneous loss-of-function mutation in Fas (Nagata, 1994) which leads to a deficit in apoptotic Fas receptor expression in MRL–lpr animals (Nagata, 1994; Singer et al., 1994). The main function of Fas is to bind to its ligand (FasL), and transduce signals leading to cell death (Nagata and Suda, 1995). Similar to various CNS cell death mechanisms and compensatory processes, the pathogenic etiology of behavioral deficits in this model of NP-SLE appears to be multi-factorial. Therefore, this review article examines the interplay between underlying genetics, autoimmunity and inflammation, hormones, and a number of secondary factors leading to nervous tissue injury, death and behavioral dysfunction in MRL–lpr mice.

2. Prelude to CNS damage: disruption of the blood–brain barrier

The blood–brain barrier (BBB) is formed by brain capillary endothelial cells that line cerebral microvessels and has an important role in maintaining a precisely regulated micro-environment for reliable neuronal signalling in the CNS (Abbott et al., 2006). Some chronic neuropathologies may involve an early phase of BBB disturbance preceding neuron damage, which suggests that vascular damage can lead to secondary neuronal disorder (Minagar and Alexander, 2003). For example, autoantibodies may have a pathogenic role should they penetrate the compromised BBB and gain access to neuronal tissues. In the case of NP-SLE, it is hypothesized that disruption of the BBB and anti-neuronal autoantibodies account for CNS manifestations of disease (Rice et al., 2005; Hanly et al., 2006). Indeed, antibodies which react with neuronal cell lines and brain tissue have been reported in the sera and CSF of patients with CNS-lupus, but they are also found in lupus patients with no clinical evidence of CNS involvement (Long et al., 1990; Denburg et al., 1988; Bluestein et al., 1981; Kelly and Denburg, 1987).

Similar to humans, evidence of this same phenomena has been found in murine models of CNS lupus (Narendran and Hoffman, 1989; Hoffman and Madsen, 1990). When the BBB is disrupted in lupus-prone mice, large molecules and cells (normally blocked from entry into the CNS), can infiltrate into the brain and lead to CNS damage. Correlational evidence in aged MRL–lpr animals (i.e. associations between ANA, dsDNA, splenomegaly, brain atrophy, and neurodegeneration) supports this notion (Sakic et al., 2000a; Ballok et al., 2003, 2006). Binding of brain-reactive autoantibodies (BRAs) to CNS tissue also appears to have detrimental consequences (Harbeck et al., 1978; Hoffman et al., 1978, 1988; Narendran and Hoffman, 1988; Sidor et al., 2005). While the mechanism by which circulating BRAs access the brain is not well understood (Hoffman and Harbeck, 1989), aberrant behavioral and emotional manifestations in human and murine forms of lupus does suggest that multiple CNS antigens and sites are targeted (Hoffman and Madsen, 1990; Hoffman et al., 1987; Crimando and Hoffman, 1992; Sakic et al., 1994; Huerta et al., 2006; DeGiorgio et al., 2001; Kowal et al., 2004). For example, autoantibody-mediated compromise of central neurotransmission is one pathogenic mechanism proposed in the etiology of NP-SLE (Bluestein and Zvaifler, 1983). Taken together, alterations in BBB permeability and BRAs appear to contribute to and mediate CNS disease in some forms of SLE (Bresnihan et al., 1979).

A dysregulated cytokine network is also thought to play a key role in NP-SLE disease pathogenesis. In general, pro-inflammatory cytokines appear to be instrumental in expanding peripheral autoimmunity to the CNS by inducing dysfunctional endothelial activation (Meroni et al., 2003; Abbott et al., 2003). For example, these cytokines have been shown to cause exaggerated intracellular adhesion molecule (ICAM)-dependent leukocyte-endothelial interactions in MRL–lpr brains (Marshall et al., 2003), which can be prevented by antibody treatment directed against pro-inflammatory cytokines or ICAM (McHale et al., 1999; Brey et al., 1997a). In addition, they can cross the BBB by specific transport systems, and can bind receptors on endothelial cells of brain vasculature to release other mediators (e.g. cytokines, nitric oxide, prostaglandins) into the CSF and brain parenchyma (Tsai et al., 1994; Svenungsson et al., 2001). Pro-inflammatory cytokines can also alter the stress hormone axis (Hayley et al., 2003; Hu et al., 1993; Rivest et al., 1992; Spangelo and Gorospe, 1995; Hansen and Krueger, 1997; Rivier and Rivest, 1993). More specifically, these cytokines are known to modulate immune responses and regulate corticosteroid levels through targeting glucocorticoid receptors in adrenal and the hypothalamic–pituitary glands (Del and Besedovsky, 2000; Lorton et al., 2003). This may ultimately contribute to the neurodegeneration and neurological dysfunction seen in NP lupus (Fig. 1) (Svenungsson et al., 2001; Jongen et al., 1990; Hafler and Weiner, 1989; Brey et al., 1997a; Shanks et al., 1999; Sakic et al., 1999; Ballok et al., 2003; Kyttaris et al., 2005). The precise regulatory mechanisms of cytokines in this dynamic autoimmune disease, however, remain unresolved.

Abnormal cytokine production also modulates systemic autoimmunity by overactivating B-cells that differentiate into pathogenic autoantibody-forming cells. These pathogenic autoantibodies are a prelude to immune complex disease, a common feature of lupus (Peress et al., 1981). Indeed, deposition of antigen–antibody complexes (immune aggregates) in choroidal blood vessels have been associated with neuropsychiatric dysfunction, and vascular deposits within the choroid plexus (CP) are accompanied by histopathologic evidence of inflammation (Schwartz and Roberts, 1983). Therefore, autoantibodies to endothelial cells, as well as the pathogenic action of circulating–immune complexes (CIC) on microvessels, likely contribute to, if not cause, endothelial cell damage and breakdown of the BBB in lupus patients and mice (Valesini et al., 2006; Hoffman et al., 1983; Ma et al., 2006).

3. Evidence of neuroinflammation in CNS disease

Recently, the role of neuroinflammation is emerging as an important component in lupus-like disease. It has been documented that there is an age-related increase in the frequency of T-cells and perivascular leakage of IgG around brain vessels (Vogelweid et al., 1991), upregulation of adhesion molecules (McHale et al., 1999; Zameer and Hoffman, 2003), the expression of mRNA for pro-inflammatory cytokines (Tomita et al., 2001a,b), and deposition of complement proteins (Alexander et al., 2005a) within brains of MRL–lpr mice. Major histocompatibility complex (MHC) upregulation (McIntyre et al., 1990) and F4/80 microglia staining provides additional evidence for microglia-induced neuronal excitotoxicity in these animals (Ballok et al., 2006). When evaluating the global pattern of neuronal damage in diseased MRL–lpr brains (Ballok et al., 2003), the same pattern of degeneration is similarly seen in cases of hydrocephalus, meningoencephalitis, and hypoglycemic encephalopathy (Weller et al., 1978; Del Bigio, 1993; Gerber et al., 2001; Alexander and Alexander, 1983; Auer et al., 1984; Fujioka et al., 1997), all resulting in cerebritis. Supporting this notion, others have reported manifestations of hydrocephalus (Denenberg et al., 1992), meningoencephalitis (Alexander et al., 1983) and altered glucose metabolism (Alexander et al., 2005b) in the brains of these mice, with complement activation as a likely precursor to cerebral edema (Alexander et al., 2003).

In a recent study, congenic MRL+/+ animals were found to have greater cell loss, and a more aggressive, sustained microglial inflammatory response following mechanical injury and

breakdown of their BBB (Hampton et al., 2004). Unlike MRL–lpr animals which develop spontaneous BBB disruption, MRL+/+ mice do not show evidence of CNS damage under normal conditions, but the MRL strain may have an inherent propensity toward exaggerated CNS inflammatory responses. For example, considering the substantia nigra of mice have more microglia than other areas (Lawson et al., 1990), one may assume that this neuroanatomical trait reflects the region-specific susceptibility of the substantia nigra in lupus mice (Ballok et al., 2004a) to inflammatory and excitotoxic metabolites produced by activated microglia.

While neuroinflammation appears to be a contributing factor to disease in MRL–lpr animals, a distinct inflammatory response is not commonly seen in brains of lupus patients. Some of the most common neuropathological findings in SLE, however, are small vessel cerebral vasculopathy and micro-infarcts. These observed features likely reflect the end result of repeated episodes of acute inflammation in the small vessels of the brain (Hess, 1997). Soluble adhesion molecules found in serum and CSF of patients with central nervous involvement (Baraczka et al., 2001) also suggests that neuroinflammatory conditions may play an understated role in some NP manifestations.

4. Evidence of neuronal death and impaired brain growth/atrophy

The MRL strain does not show a high incidence of inherited neuroanatomical abnormalities (Sherman et al., 1987) which minimize the possibility of congenital defects confounding the study of disease-induced neurodegeneration. At the onset of autoimmune symptoms in MRL–lpr mice, reports of reduced complexity of pyramidal neurons, reduced brain weights (Sakic et al., 1998b), and selectively neurotoxic CSF (Maric et al., 2001) provided indirect evidence of neuronal damage in diseased animals. Direct evidence of neuronal death, however, was first confirmed in MRL–lpr brains using the Fluoro Jade B (FJB) cytochemical stain (specific for dying neurons). A small percentage of these neurons where subsequently found to contain TdT-labeled apoptotic nuclei, and co-localized with FJB (Ballok et al., 2003) and anti-neurofilament staining (Alexander et al., 2005a). Providing further evidence of neurodegeneration, while the size of hippocampal fields and neuronal density are not reduced in young Fas-deficient *lpr* mice (Kovac et al., 2002), cell densities are reduced within the hippocampus, cortex (Ballok et al., 2004b) and midbrain (Ballok et al., 2004a) of aged/diseased lupus mice.

In addition to mature neurons, recent findings suggest that progenitor cells also degenerate in MRL–lpr brains. More specifically, the subventricular zone (Sakic et al., 2000b; Sidor et al., 2005), subgranual zone (Ballok et al., 2003, 2006), and substantia nigra (Ballok et al., 2004a), known to contain proliferative progenitor cells capable of neurogenesis (Yamashita et al., 2006; Suh et al., 2005; McGuire et al., 2001; Zhao et al., 2003), show signs of damage in these animals. CSF from diseased lupus mice is also cytotoxic to neurons and neuronal progenitor cells *in vitro* (Maric et al., 2001; Ballok et al., 2004a) supporting a link between toxic CSF IgG and neuronal/progenitor cell damage (Sidor et al., 2005; Sakic et al., 2005b). If *in vitro* findings are predictive of *in vivo* events, then autoimmune-induced lesions of germinal layers may reduce the developmental and regenerative capacity of MRL–lpr brains. An impairment in this process would likely exacerbate subsequent autoimmune/inflammatory-mediated neuronal death and behavioral deficits. For example, an impaired capacity for hippocampal neurogenesis could account for the cognitive impairments observed in these animals (Ballok et al., 2004b). Stress hormones, chronically elevated in lupus mice (Lechner et al., 2000), have also been shown to inhibit cell proliferation and neurogenesis (Mirescu and Gould, 2006), and may additionally account for impaired brain growth and regeneration along the progression of autoimmune disease.

5. Stress-like behavior is associated with autoimmune disease

The onset and progression of disease in MRL–lpr mice parallels the emergence of aberrant stress-like behaviors (Szechtman et al., 1997). The nature of this autoimmune-associated behavioral syndrome (AABS) suggests a progressive anxious- and depressive-like state (and differences in emotionality), as indicated by increased thigmotaxic behavior, impaired exploration of novel objects and spaces, performance deficits in the plus-maze and step-down tests, excessive floating in the forced swim test (FST) (Sakic et al., 1992, 1993a, 1994), reduced responsiveness to a palatable stimulus (Sakic et al., 1996a), and reduced isolation-induced inter-male fighting (Sakic et al., 1998a). Moreover, impaired “cognitive flexibility” and poor spatial learning was revealed through the Morris water maze (Sakic et al., 1993b), and spontaneous alternation behavioral test (Ballok et al., 2004b). In addition, diseased MRL–lpr animals display lower nocturnal and open-field activity, and significant deficiencies in neurological (Hess et al., 1993; Brey et al., 1997b) and psychomotor (beam-walking) tests (Sakic et al., 1993a, 1996b). Chronic social isolation stress has also been shown to exacerbate autoimmunity and reduce survival of MRL–lpr mice (Chida et al., 2005).

The causative role of autoimmunity and inflammation in the pathogenesis of AABS has been supported by studies employing the immunosuppressive drug cyclophosphamide (CY), which prevented some behavioral deficits in lupus animals (Sakic et al., 1995, 1996a; Farrell et al., 1997). More specifically, CY prevented anxiety- and depressive-like behaviors as indicated by the restoration of novel object exploration, increased responsiveness to a sweet palatable solution, and reduced floating in the FST. In addition to autoimmunity, other factors have been suggested to be involved in the emergence of AABS such as genetics (e.g. the Fas mutation), endocrine factors (e.g. corticosterone-releasing factor, glucocorticoid, prolactin), and multi-system disease (e.g. kidneys, joints, skin, eyes). Taken together, the inherited lack of anti-inflammatory-Fas-dependent mechanisms leading to unsuppressed peripheral immune activation, coincides with elevated levels of corticosteroids (Lechner et al., 2000) and the appearance of stress-like behaviors in MRL–lpr mice (Sakic et al., 1994).

6. Corticosteroids: the permissive factor for cell death?

Similar to chronic cerebral ischemia, corticosteroid therapy has been linked to cerebral atrophy (Ainiala et al., 2005) and cognitive decline often documented in NP-SLE patients (Yamauchi et al., 1994; Chinn et al., 1997). Similar to the effects of chronic stress, NP-lupus mice show brain atrophy and deficits in cognition at the onset of disease (Sakic et al., 1993b, 1998b; Ballok et al., 2004b). In addition to the peripheral dysregulation of glucocorticoids, studies have also revealed a dysfunctional hypothalamic–pituitary axis in these animals (Shanks et al., 1999; Sakic et al., 1999). Although an imbalanced neuro-immuno-endocrine network is proposed to play a key role in the etiology of brain damage, it is still not clear whether central neurons are initially damaged by an autoimmune-driven upregulation in corticosterone production.

Corticosterone-induced atrophy of neurons may be reversible, but it can also be indicative of an early stage of neurodegeneration (McEwen, 1999; Woolley et al., 1990). MRL–lpr mice normally show profound neuronal spine loss relative to asymptomatic MRL+/+ controls (Sakic et al., 1998b), but chronic corticosterone treatment further exacerbated this spontaneous process. In a recent study, while prolonged treatment with corticosterone attenuated signs of autoimmune disease, it lead to profound dendritic spine deterioration (revealed by the Golgi method) in both MRL substrains (unpublished results). Therefore, based on evidence of chronically elevated serum corticosterone levels in MRL–lpr mice (Lechner et al., 2000), sustained endogenous immunosuppression may be a precursor predisposing neurons to the degenerative autoimmune/inflammatory cascade seen at later stages of disease (i.e. following a breach in the BBB). Indeed, studies have revealed that changes in the morphology of neuronal

dendrites, cerebral atrophy, and immunoreactive ubiquitin particles (denoting axon terminal degeneration) occur by 14 weeks of age in MRL–lpr brains, but progressive neurodegeneration and microglial activation does not become pronounced until terminal stages of disease (e.g. by 5 months). Few MRL–lpr mice survive beyond 6 months of age (Dixon et al., 1978), which may be attributed to profound CNS damage (Ballok et al., 2003) and brain edema (Alexander et al., 2003). Future studies examining the possibility that adrenalectomy can prevent or delay the degeneration and death of cells in these animals should be explored.

7. Behavioral consequences of CNS damage

Clinical studies have reported that NP manifestations are accompanied by cerebral atrophy (Chinn et al., 1997), progressive neuronal loss (Brooks et al., 1997; Sibbitt and Sibbitt, 1993), and parenchymal lesions associated with movement disorder (Rocca et al., 2006). In MRL–lpr mice, despite parallels between the emergence of behavioral dysfunction and systemic autoimmunity, there has been no direct evidence that brain pathology can account for aberrant behavior. Recently, the phenomena and extent of neurodegeneration in MRL–lpr brains, and the connections between brain morphology and functional damage has been explored more systematically. While it is not possible to verify causation, correlations suggest links between structural brain damage and functional/behavioral impairments in lupus animals. For example, deficits in spatial learning/memory emerged concomitant with hippocampal damage (Ballok et al., 2004b), aberrant performance in the sucrose preference test (i.e. impaired motivated behavior) coincided with lesions of the nucleus accumbens (Anderson et al., 2006), and hypoactivity (i.e. decreased locomotor capacity) accompanied the appearance of degeneration in the substantia nigra (Ballok et al., 2004a) of autoimmune mice. Although the causes and mechanisms underlying these neurological deficits are poorly understood (Hess et al., 1993; Brey et al., 1995), recent pharmacological evidence supports a link between dopaminergic circuit damage and AABS in diseased MRL–lpr animals.

In comparison to other neurotransmitters, central dopamine system activity (implicated in reward, movement, and cognitive processes) is most profoundly altered in MRL brains (Sakic et al., 2002). There is now evidence that damage to central dopaminergic circuits in MRL–lpr brains account for some behavioral deficits. For example, chronic injection with the selective D_2/D_3 agonist quinpirole induced self-injurious behavior in lupus mice (Sakic et al., 2002). Similarly, rotational behavior increased in MRL–lpr mice following acute injection with the selective D_1/D_2 dopamine agonist apomorphine (Ballok et al., 2004a). In the sucrose preference paradigm, acute injection with the indirect dopamine agonist D-amphetamine failed to alter the response rates of diseased animals to sucrose solutions (Anderson et al., 2006), while chronic treatment increased their mobility in the FST (unpublished data). Immunosuppressive treatment, suppressing autoimmunity and preventing hippocampal damage, circumvented an age-related decline in spatial memory and retrieval (Rolls and Kesner, 2006; Ballok et al., 2004b). Taken together, these results link neuropathological findings of dopaminergic cell death in nigrostriatal, mesolimbic, and mesocortical pathways to certain behavioral deficits (e.g. locomotor, motivated, and learning behaviors) in lupus-prone animals (Table 1). Although the contribution of peripheral disease manifestations on behavioral performance cannot be excluded, these pharmacological results do indicate that anhedonic- and depressive-like behaviors are a consequence of disease-driven damage to several dopamine systems in MRL–lpr brains.

8. Possible mechanisms and targets of brain cell death

The well-characterized apoptotic pathway defect in MRL–lpr mice has lead to much speculation as to which compensatory processes most likely predominate in CNS disease. One consequence of impaired apoptotic mechanisms may be the accumulation of unwanted proteins

which often underlie the pathogenesis of several major human neurodegenerative diseases. For example, as a result of defective ubiquitin-dependent proteolysis, neurodegeneration can occur (Layfield et al., 2001). Indeed, the ubiquitin–proteasome system appears to be overactive in MRL–lpr brains (Ballok et al., 2004b), and it is possible that autoantibodies reactive to ubiquitin in peripheral tissue of MRL–lpr mice (Elouaai et al., 1994) target these antigens in the brain. Impaired dopamine catabolism has also been suggested in the pathogenicity of CNS damage in lupus mice. Increased levels of this neurotransmitter have been reported in the tuberoinfundibular pathway of animals (Sakic et al., 2002), and may induce neurotoxicity (Blum et al., 2001; Asanuma et al., 2003) at a later stage of disease. More specifically, if impaired dopamine catabolism is a feature of other pathways (i.e. nigrostriatal, mesolimbic, and mesocortical circuits) it is possible that over time, accumulated metabolites induce the dopaminergic cell damage observed in MRL–lpr brains. Overall, impaired protein processing may be a factor contributing to progressive Fas-independent neurodegenerative autoimmune-induced encephalitis in MRL–lpr mice.

Although the Fas antigen/surface receptor (Fas/Apo-1/CD95) is not expressed in brains of MRL–lpr animals, an apoptotic mode of neuronal demise may still be mediated by mechanisms such as TNF-alpha or granzyme B receptors. Considering the massive lymphocytosis of CD8 cytotoxic T-cells (known to release granzyme B) into the third ventricles and brain parenchyma of MRL–lpr mice (Sakic et al., 2000b; Ballok et al., 2003), and TNF-alpha detected in CSF and brains of these animals (Ballok et al., 2004a; Ma et al., 2006), it is likely that both mechanisms activate terminal caspase cascades (Alexander et al., 2005a). Alternatively, lymphocytes which infiltrate MRL–lpr brains (Sakic et al., 2000b) are likely polyclonally activated and will cause substantial neuronal death in an allogeneic and syngeneic manner. More specifically, neurons have a high and selective vulnerability to T-cells in contrast to other CNS cell types (e.g. oligodendrocytes and astrocytes) which are not killed by T lymphocytes (Giuliani et al., 2003). When enough activated T-cells accumulate in the CNS of lupus mice, neuronal cytotoxicity could be mediated through cell contact-dependent mechanisms involving LFA-1 and CD40, but not FasL (due to the fas receptor deficiency).

Another pathway which could play an important role in neuronal death in MRL–lpr mice involves p53. As a well-characterized transcription factor, p53 is known to respond to DNA damage and other genotoxic stresses by the activation of downstream targets involved in repair, differentiation, senescence, growth arrest, and apoptosis (Resnick-Silverman and Manfredi, 2006). In a recent pilot study, densities of p53 dot-like particles were examined in the brain parenchyma of MRL mice. Unexpectedly, significantly reduced anti-p53 immunohistochemical staining was observed in MRL–lpr brains, relative to congenic controls (unpublished results). Consistent with this finding, cellular entry of anti-DNA antibodies into glomerular tissue of MRL–lpr mice resulted in an inhibition/reduction of p53, and suppression of apoptosis (Yanase and Madaio, 2005). When considering that elevated immunoglobulin levels are seen in the CSF and brain of lupus animals (Sidor et al., 2005; Zameer and Hoffman, 2001) one may assume that a similar autoantibody-mediated process is occurring within neurons and accessory cells of the CNS. Therefore, disrupted p53 functions may account for the morphological features and “intermediate form” of cell demise seen in MRL–lpr brains (Ballok et al., 2006), leading to cytoskeletal collapse. Future studies should examine the role of antibodies to p53 in delaying degeneration and cell death processes more closely.

There are numerous factors that can induce excitotoxic damage, and in an injured or immunologically challenged brain, cytokine-producing microglia appear to play an important role (Gwag et al., 1997). Microglia readily activate by transforming from a ramified, resting state into amoeboid cells to express MHC molecules (Lawson et al., 1990), as seen in MRL–lpr brains (McIntyre et al., 1990). Inflammatory responses are then perpetuated by both cyclooxygenase (COX) and nitric oxide (NO). In lupus mice, however, prostaglandin

production abnormalities have been observed (Reilly et al., 2000), and COX inhibition is not effective in ameliorating CNS disease (Ballok et al., 2006) suggesting that inducible NO synthase (Alexander et al., 2005a) is likely the mediator of neuroinflammation in these animals. Recent ultrastructural evidence obtained from electron microscopy (Ballok et al., 2006) and a study which found significant increases in glutamine, glutamate and lactate concentrations in MRL–lpr brains (Alexander et al., 2005b) supports the notion of excitotoxic cell death in these animals. In the case of glutamate toxicity, anti-DNA antibodies may play an important role. These autoantibodies have recently been found to cross-react with central NMDA receptors in mice, producing neuronal apoptosis (DeGiorgio et al., 2001), and a similar IgG-mediated neurodegenerative event is proposed to occur in MRL–lpr brains (Sakic et al., 2005b). This causal relationship between NR2 receptor-reactive autoantibodies and brain damage has also been reported in NP-SLE patients (Omdal et al., 2005). Interestingly, the immunosuppressive drug CY has been found to abolish the infiltration of cells of the monocyte–macrophage lineage into the CP of the MRL–lpr substrain (Farrell et al., 1997) and successfully prevented atrophy of dendritic spines (Sakic et al., 2000a), and neuronal death (Ballok et al., 2004b). However, since CY affects a broad population of cells, the factors which play a predominant role in the etiology of brain damage in lupus animals is still unknown. Considering that anti-CD4 treatment (O'Sullivan et al., 1995) and a potent complement inhibitor (Alexander et al., 2005a) both ameliorated CNS disease manifestations in MRL–lpr mice, one may assume that autoimmune and inflammatory factors are both requisites for brain pathology.

9. Conclusions and future perspectives

Neurodegenerative disorders are characterized by a gradual and relentlessly progressive neuronal loss that is often selective in that it occurs in anatomically and physiologically related brain areas. Progressive neuronal death and microglial activation are concomitant with the onset and development of systemic autoimmune/inflammatory disease and behavioral deficits in the MRL–lpr model of NP-SLE. The initial role of corticosterone appears to be important in SLE-like disease given that glucocorticoids are innately elevated in MRL–lpr mice (Lechner et al., 2000), and may act similar to the iatrogenic effects of sustained corticosteroid therapy on brains of NP-SLE patients (Ainiala et al., 2005). At a later stage of disease, dopamine neurons and their progenitor cells appear to be a target of the disease process, possibly accounting for some aberrant behaviors in lupus mice. An interplay among numerous factors (i.e. activated microglia, neuroactive cytokines, autoantibodies, cytotoxic T-cells) likely leads to edema and neurodegeneration in MRL–lpr brains. Many years of clinical evidence support the therapeutic use of immunosuppressive drugs in treating SLE, with some undesirable effects (Miller, 1997). Further work elucidating precise disease factors and molecular events during neuronal death is needed to devise more effective and less toxic treatments for patients diagnosed with this complex immunological syndrome. Knowledge of the precise immune components and the biochemical profile of neurotoxic mediators in lupus mice may help identify pathogenic circuits in NP-SLE, and be beneficial when designing protocols which foster both neuroprotection and immunosuppression.

A better understanding of neuroendocrine hormones in the progression of NP-SLE may lead to novel therapeutic approaches. One hormone of recent interest is prolactin, a pituitary hormone under the control of dopamine. Elevated secretion of prolactin is commonly seen in SLE (Jara et al., 2001), and given recent results of dysfunctional dopaminergic circuits in lupus mice, one may wonder whether this endocrine imbalance is a consequence of impaired dopamine regulation in the hypothalamus (Freeman et al., 2000; Walker, 2006). Consistent with this notion, the dopamine agonist bromocriptine suppressed secretion of prolactin and ameliorated affect in SLE patients (Walker et al., 2000) and disease activity in autoimmune mice (McMurray et al., 1991; Walker, 2001). Interestingly, a recent post-mortem analysis of a NP-SLE patient's brain found evidence of hypothalamic and basal ganglia damage (Ballok

et al., 2004b), suggesting that these regions may be more susceptible to disease. Additional studies, however, are needed to determine whether dopaminergic neurons die excessively in a subset of SLE patients, as seen in lupus animals. Another hormone which may be of interest in the treatment of NP-SLE is progesterone. Considering that progesterone and its precursors/metabolites have been shown to reconstitute the BBB and enhance functional and structural recovery in rodents and patients with brain edema (Shear et al., 2002; Guo et al., 2006; Sayeed et al., 2006), this hormone may prove to be an effective treatment for the edema seen in NP-SLE patients and MRL–lpr mice (van Dam, 1991; Alexander et al., 2003).

Although progenitor cells are a target in aged MRL–lpr animals (Ballok et al., 2004a), the possible effect of autoimmunity on neural stem cells may be extended into pre-natal life. For example, multipotent brain cells may be the target of an attack mounted by the immune system of autoimmune mothers. Indeed, ova-transfer experiments in mice have shown that profound deficiencies in offspring behavior are produced if embryos were reared in an autoimmune uterine environment and conversely, that the severity of behavioral dysfunction in autoimmunity-prone mice is reduced if they were transferred as embryos into a non-autoimmune uterine environment (Denenberg et al., 1991). Consistent with the possibility that the blood–placental barrier does not provide sufficient protection from mother's autoimmunity is the fact that neonatal lupus is a well-documented phenomenon in humans (Cabanas et al., 1996; Prendiville et al., 2003). Therefore, more work needs to be done to determine if conditions for progressive neurodegenerative events later in life are antedated by early neural precursor cell damage.

While the MRL–lpr strain displays many characteristics that resemble human NP-SLE, there are a number of limitations which must be considered when studying this murine model. First, human NP-SLE often has oscillating relapsing–remitting presentations of symptoms, while MRL–lpr mice show a progressive and unrelenting course of disease. This difference appears to be the most fundamental difference between human and murine SLE. Secondly, human SLE shows a strong gender preference (i.e. about nine to ten times more female patients than male). The MRL–lpr strain, however, has no gender bias, possibly suggesting a different hormonal differentiation between two sexes in human and murine lupus. Lastly, while more sophisticated and systematic assessments are administered in human SLE, affective states of MRL–lpr mice can only be assessed by behavioral tests (Scolding and Joseph, 2002; Sakic et al., 2005a), and care is required when transferring information obtained from an animal model to human disease. Despite these limitations, the MRL model of NP-SLE remains a critical tool toward understanding the complex etiopathogenesis of this neuroimmunological syndrome.

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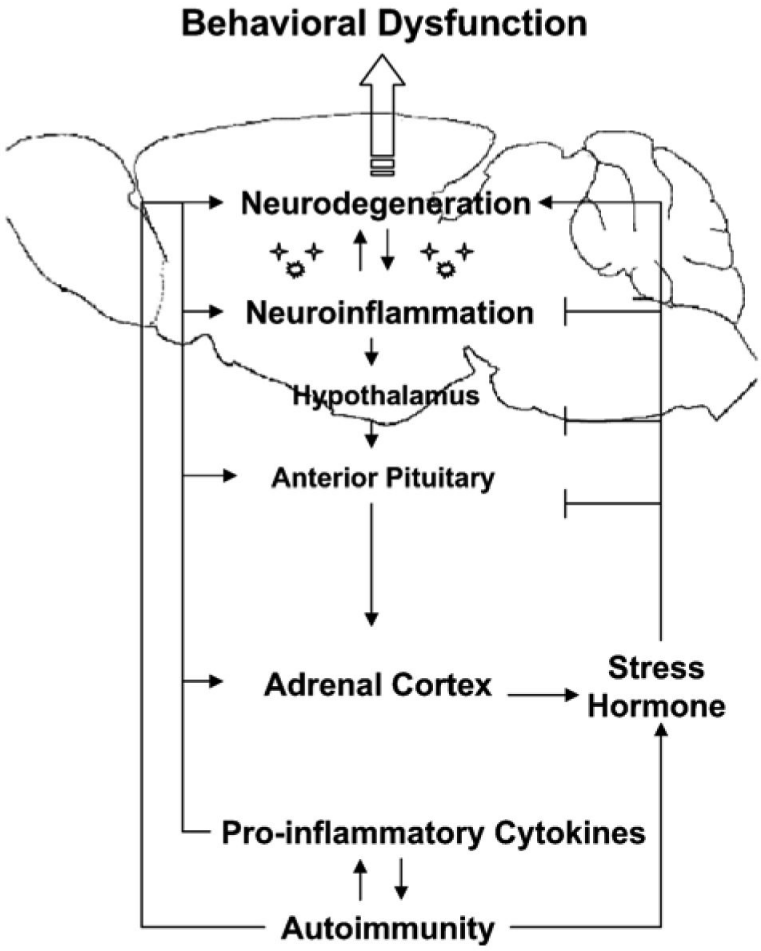

Fig. 1.

– Behavioral disorders may represent a consequence of chronic autoimmune disease-induced ‘stress’ and brain damage in neuropsychiatric lupus-like disease. The spontaneous onset of systemic autoimmunity in MRL–lpr mice includes increased levels of pro-inflammatory cytokines which mimic actions of glucocorticoids on the hypothalamic–pituitary–adrenal (HPA) axis. While these cytokines stimulate the HPA axis, glucocorticoids feedback to suppress the system at multiple levels. Due to the chronic nature of disease, however, glucocorticoids, cytokines and other autoimmune components remain elevated in lupus animals, contributing to neuronal damage and aberrant behaviors. The precise regulatory mechanisms of the dynamic interrelated systems remain largely unknown.

Table 1

Correlations between brain region, functional damage and dopaminergic system deficits in aged MRL–lpr mice

Brain lesion	Behavioral task	Dopamine agonist	Behavioral consequence	Dopamine pathway
Hippocampus	Spontaneous alternation	n/a	Deficits in spatial learning	Mesocortical
Nucleus accumbens	Sucrose preference test	Amphetamine *acute*	Impaired motivation	Mesolimbic
n/a	Forced swim test	Amphetamine *chronic*	Increased mobility	Nigrostriatal
Ventral tegmental area	Activity in novel environment	n/a	Decreased exploration	Mesolimbic
Substantia nigra	Rotation test	Apomorphine *acute*	Increased movement	Nigrostriatal
n/a	Grooming behavior	Quinpirole *chronic*	Self-injurious behavior	Mesolimbic

Major neural systems of the brain use dopamine as a principal neurotransmitter to mediate learning and memory (mesocortical system), motivated behavior (mesolimbic system), and locomotor behavior (nigrostriatal system). While young asymptomatic MRL–lpr animals do not show brain abnormalities or behavioral deficits, aged autoimmune MRL–lpr mice exhibit behavioral dysfunctions concomitant with brain damage. These behavioral impairments can be linked to specific brain structures and/or are modulated by dopamine agonists, providing pharmacological evidence that brain cell death is selective (e.g. a target of neuroactive antibodies) and accounts for some functional abnormalities in these animals. *Note*: ‘acute’ denotes a single injection while ‘chronic’ denotes at least 5 successive treatments with a given drug; ‘n/a’ indicates data is not available.