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Chemokines in systemic lupus erythematosus involving the central nervous system

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1. ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ damage and neuropsychiatric complications (NPSLE) associated with increased morbidity and mortality. The pathogenesis of NPSLE is not yet fully understood, but focal symptoms are thought to most likely result from vascular lesions, whereas diffuse manifestations are more likely related to autoantibody- or cytokine-mediated impairment of neuronal function. Recent progress also has provided evidence that levels of several cytokines/chemokines are upregulated in the central nervous systems of NPSLE patients during active disease and downregulated by treatment. In particular, chemokines appear to play significant roles in both inflammatory and immunological processes in the brain. For instance, we recently showed that levels of the soluble form of the chemokine CX3CL1 are elevated in the cerebrospinal fluid of patients with active NPSLE. In this review, we will discuss the involvement of chemokines in the pathogenesis of NPSLE and their significance as a useful laboratory parameter indicative of active neuropsychiatric disease.

2. INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multi-organ damage with infiltration and sequestration of various leukocyte subpopulations and the presence of autoantibodies (1, 2). A variety of diffuse and focal neuropsychiatric symptoms are seen in patients with SLE (NPSLE), reportedly affecting 14-75% of SLE patients at any given time during the course of their disease (3). These complications are associated with increased morbidity and mortality and may include seizures, stroke, depression, psychosis and cognitive disorders (4). Although the pathogenesis of NPSLE is not well understood, the direct and indirect effects of various inflammatory mediators (e.g., cytokines) on the central nervous system (CNS) are thought to be involved (5-7). Moreover, focal symptoms are thought to more likely result from vascular lesions, while diffuse manifestations are more likely related to autoantibody- or cytokine-mediated impairment of neuronal function.

Within the CNS, chemokines regulate the migration potential of microglial cells, astrocytes and

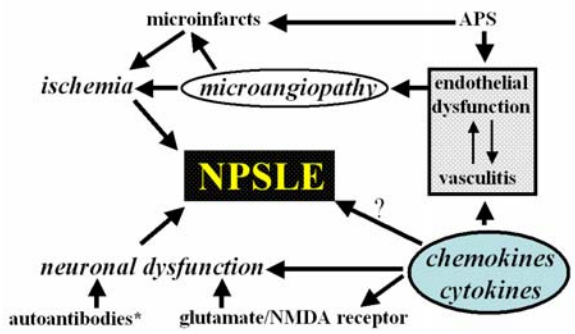

Figure 1. Simplified schematic overview of the pathogenesis of NPSLE. Ischemia, microangiopathy and/or neuronal dysfunction may contribute to NPSLE. Although the precise pathogenic mechanisms of NPSLE are not fully understood, the direct and indirect effects of various chemokines and cytokines in the CNS are thought to be likely contributors. *These autoantibodies include antineuronal antibody, antiribosomal P antibody, antineurofilament antibody, and anti-MNDA NR2 receptor antibody. APS: antiphospholipid antibody syndrome

neurons (8-11). In addition, proinflammatory stimulation of glial cells and astrocytes can lead to the elaboration of a cascade of cytokines and chemokines, several of which play crucial roles in both physiological and pathological brain functions. For instance, increases in the expression and/or presence of various chemokines have been documented in intracranial infection, multiple sclerosis (MS) and experimental allergic encephalitis (EAE). In this review, we will focus on the expression and function of chemokines within the CNS under pathological conditions and on the degree to which they are involved in NPSLE.

3. PATHOPHYSIOLOGY OF NPSLE

Small vessel angiopathies play a central role in the pathogenesis of NPSLE (6). Multifocal microinfarcts, repeated ischemia associated with inflammation of the small vessels, and the presence of antiphospholipid antibodies and increased numbers of pericapillary microglial cells are the predominant abnormalities thought to underlie the development of NPSLE (6, 12). In fact, the association of microvascular lesions with microinfarcts suggests that occlusion of the small vessels is the basis for the enduring damage to the nervous system, including damage to neurons and astrocytes, which has been demonstrated in NPSLE (13). In addition, some neurological diseases such as MS and, perhaps, NPSLE are associated with damage at the level of brain endothelial cells (ECs), which leads to altered expression of adhesion molecules, chemokine secretion, changes in the organization of tight junction proteins and lymphocyte extravasation from vessels into the CNS. While both microglia and astrocytes are thought to be responsible for chemokine secretion (11, 14), activated astrocytes contribute to the innate immune response of the brain and produce a large variety of mediators, including cytokines and chemokines, also known to be secreted by activated macrophages (15). They can also form a link between the innate and adaptive immune response by processing and presenting antigens to T cells, and mediating mononuclear leukocyte migration into the brain (16). As discussed below, these activated astrocytes are crucial for the induction of cytokine/chemokine expression in the CNS and thus play a central role in the development of NPSLE (Figure 1).

4. CHEMOKINES: OVERVIEW AND THEIR INVOLVEMENTS IN CNS PATHOLOGY

Chemokines are a family of over 40 small, secreted proteins shown to induce chemotaxis and other functional changes in subsets of leukocytes *in vitro*. They are produced by a wide variety of cell types of both hematopoietic and nonhematopoietic origin, and have been shown to play a key role in the migration and activation of leukocytes *in vivo*. Chemokines are known to belong to two major superfamilies that share substantial homology via four conserved cysteine residues (17-19). The CXC chemokine family [e.g., CXCL1 (growth related oncogene alpha; GRO-α), CXCL5 (expression of neutrophil activating protein-78; ENA-78), CXCL8 (IL-8), CXCL9 (monokine induced by interferon-gamma; MIG), CXCL10 (interferon-inducible protein 10; IP-10), CXCL11 (interferon-inducible T cell A chemoattractant; I-TAC) and CXCL16 (CXC chemokine ligand 16)] induces chemotaxis mainly in neutrophils and T cells, whereas the CC chemokine family [e.g. CCL2 (macrophage chemoattractant protein 1; MCP-1), CCL3 (macrophage inflammatory protein 1 alpha; MIP-1α) and CCL5 (regulated on activation normal T cells expressed and secreted; RANTES)] induces chemotaxis in monocytes and subpopulations of T cells. Two other minor groups, the C and CX3C chemokines, which include CX3CL1 (fractalkine), also have been identified. The members of these families show considerable structural homology and often possess overlapping chemoattractant specificities.

In addition to their roles in chemoattraction, chemokines have been implicated in the modulation of numerous biological functions, including cell adhesion, phagocytosis, cytokine secretion, T cell activation, apoptosis, angiogenesis, proliferation and viral pathogenesis (20). And it is now evident that they can aid in directing immune responses either directly by activating antigen presenting cells (APCs) and T cells or indirectly by recruiting the proper cell populations. It has been shown, for example, that the CC family chemokines CCL3 and CCL5 can effectively initiate antigen-specific responses *in vivo* when used in place of an adjuvant such as Freund's complete (21). These early studies led investigators to hypothesize that chemokines are able to skew immune responses toward either T helper (Th)1 (IFN-γ producing) or Th2 (IL-4 producing) responses (22, 23). More recent evidence indicates that the Th1 phenotype expresses certain chemokine receptors, including CXCR3, the receptor for CXCL9 and CXCL10, and CCR5, the receptor for CCL3 and CCL5 (24, 25), while the Th2 phenotype expresses CCR4, the receptor for CCL17 (TARC) and CCL22

Table 1. Detectable chemokines in NPSLE

Chemokines	other nomenclature	References
CXC families		
CXCL8	IL-8	13 37
CXCL9	MIG	42
CXCL10	IP-10	42 56
CXCL16		63
CC families		
CCL2	MCP-1	56 74
CCL5	RANTES	42
CX3C family		
CX3CL1	fractalkine/neurotactin	103

(MDC), and CCR8, the receptor for CCL1 (I-309 and TCA-3). Moreover, it has been demonstrated that polarized T cells differentially respond to CXCL10, which bind to Th1 cells, than to CCL22, which binds to Th2 cells (26, 27). It now appears, therefore, that chemokines not only have the ability to recruit specific subsets of lymphocytes, they also can aid in determining the type of immune response that occurs, which could significantly affect the development and progression of autoimmune disorders.

Chemokines are normally expressed at low levels in the CNS, but their production can be significantly upregulated by inflammatory mediators, leading to leukocyte infiltration (28). In the brain, chemokines are produced by neurons, astrocytes, microglia and ECs, as well as by infiltrating macrophages and/or activated leukocytes, including encephalitogenic T cells. In addition, astrocytes, oligodendrocytes, microglia and neurons also constitutively express functional chemokine receptors, and the networks formed among chemokines and both neurotransmitters and neuropeptides are thought to play a major role in maintaining proper brain homeostasis and function and reacting to perturbations in that homeostasis. Research on chemokines in the CNS therefore focused initially on immune and local inflammatory responses, which led to the recognition that chemokines are significantly involved in several neurological disorders, including MS, trauma, stroke, Alzheimer's disease (AD) and acquired immunodeficiency syndrome (AIDS)-associated dementia (29-31).

In the next section, we summarize the functions and activities of individual chemokines, and their involvement in NPSLE and other CNS disorders is discussed. Chemokines detectable in the CNS of NPSLE patients are listed in Table 1.

5. CXC CHEMOKINES

5.1 CXCL8

The main function of CXCL8 (IL-8) is to stimulate the migration of polymorphonuclear neutrophils during acute inflammation, though it also may induce migration of specific T cell populations during immune responses (32, 33). Indeed, CXCL8 has been implicated in lupus nephritis (34, 35). Little is known about the functional significance of CXCL8 expression in NPSLE (36); however, it is known that CXCL8 levels in CSF were elevated in a single patient with NPSLE with little correlation to the serum CXCL8 levels (13, 37). Notably, there is also no correlation between intrathecal levels of CXCL8 and pleocytosis in the CNS of NPSLE patients (37). On the other hand, CXCL8 significantly enhances neuronal survival in hippocampal cultures (38). Furthermore, expression of CXCL8 in the CNS leads to the synthesis of matrix metalloproteinase 9, which potentially culminates in an insult to the brain parenchyma, resulting in the release of neuronal and astrocyte degradation products (37). Taken together, these findings suggest that in addition to inducing chemotaxis, CXCL8 may exert protective effects against neuronal degeneration in the CNS that do not involve induction of chemotaxis.

5.2. CXCL9

CXCL9 (MIG) is a member of the CXC chemokine family and is mainly produced by activated macrophages. It induces chemotaxis in activated T cells, leading to their adhesion via CXCR3 to activated T and B cells and ECs. The fact that CXCR3 is expressed on lymphocytic cells present in virtually every perivascular inflammatory infiltrate in active MS lesions suggests CXCL9 may be constitutively expressed in brain, especially by astrocytes, and contribute to the development of CNS disorders (39, 40). Furthermore, it has been shown that human brain microvascular ECs are also able to synthesize and secrete CXCL9 after inflammatory stimulation, thereby recruiting T cells at the level of the brain ECs (41).

Fragoso-Loyo *et al.* (42) showed that expression of CXCL9 is upregulated in NPSLE, but its precise contribution to NPSLE is still unresolved, as CXCL9 stimulates CD4-T lymphocyte proliferation and effector cytokine (IFN-γ) production, in addition to its chemotactic effects (43). Increased peripheral expression of IFN-γ and a predominant Th1 response are observed in human SLE, as well as in lupus-prone NZB/W and MRL/lpr mice (44-46), and high levels of IFN-γ were found in the CSF of a patient with active lupus meningoencephalitis (47). Although IFN-γ appears to be present in the CNS under both normal physiological and pathological conditions, it likely plays a more important role in abnormal systemic immune responses such as the Th1 response seen in SLE. CXCL9 thus appears to be involved in the induction of proinflammatory cytokines such as IFN-γ and other chemokines during the progression of CNS inflammatory disorders such as NPSLE and MS.

5.3. CXCL10

CXCL10 (IP-10) is expressed and secreted by monocytes, fibroblasts and ECs after stimulation by IFN-γ (48-50) and induces migration of some subsets of T cells into inflamed sites. CXCL10 also promotes the regression of angiogenesis (51, 52).

Both CXCL10 and its receptor, CXCR3, are reportedly involved in SLE (53, 54). For instance, we recently showed that expression of CXCL10 is upregulated in lupus-prone MRL/lpr mice and that its expression parallels that of CXCR3 and is correlated with the degree of pulmonary inflammation (46). By contrast, lung expression of CCL17 and its receptor, CCR4, are suppressed in

MRL/lpr mice, which is consistent with the idea that CXCL10 acting via CXCR3 is the primary mediator of the pulmonary inflammation associated with migration of Th1 cells. In addition, CXCL10 is also reportedly involved in lupus nephritis (55). There have also been a few reports showing enhanced expression of CXCL10 in NPSLE (42, 56). And Asensio *et al.* (57) showed that CXCL10 is markedly elevated in the CSF and brain of individuals infected with HIV-1 and contributes to the pathogenesis of HIV-associated dementia (HAD) by recruiting autoreactive CD3-positive T cells to the CNS. In that report, the cellular sources of CXCL10 were primarily astrocytes and to a lesser extent microglia. Interestingly, another report has shown that CXCL10 is present in CSF of patients with AD and that levels were well correlated with the degree of cognitive impairment when it was mild (58). Although there is no significant correlation between CXCL10 expression and specific symptoms of NPSLE (56), these findings suggest that CXCL10 is significantly involved in mental disorders.

5.4. CXCL16

CXCL16 is a recently identified chemokine that exists in both membrane-bound and soluble forms. In its membrane-bound form CXCL16 functions as a scavenger receptor for oxidized low-density lipoprotein (59) and bacteria (60), and as a cell adhesion molecule. Expressed by APCs, CXCL16 also attracts activated memory type T cells. Like several other chemokines, CXCL16 has been detected in the synovial fluid in rheumatoid joints and may be involved in the progression of RA (61, 62).

CXCL16 levels are higher in the CSF of patients with NPSLE than in their serum, though two other T cell attracting chemokines, CCL18 and CCL17, are not detected in CSF (63). Levels of CXC16 in both CSF and serum are also significantly elevated in patients with MS or bacterial or viral meningitis, suggesting CXCL16 expression is not specific to NPSLE. In addition, CXCL16 appears to play an important role in EAE, a typical Th1-mediated autoimmune disease (64), and the expression of CXCR6, a specific receptor for CXCL16, is correlated with Th1-type responses (65), suggesting CXCL16 mediates the influx of activated T lymphocytes during Th1 responses in the inflamed CNS.

Because macrophages are a major source of CXCL16, microglia and/or astrocytes are the most likely sources of CXCL16 production in the CNS. Consistent with that idea, Ludwig *et al.* recently demonstrated the expression and release of CXCL16 by glial cells in both normal and malignant tissue (66), and one recent finding indicates that enhanced cleavage of the membrane-bound form by proteases can lead to elevated levels of the soluble form of CXCL16 in brain (67). Indeed, ADAM-10, a protease able to cleave membrane bound CXCL16, was recently found to be constitutively expressed in both the normal and inflamed human CNS (66).

6. CC CHEMOKINES

6.1. CCL2

CCL2 (MCP-1) acts during chronic inflammation to activate the migration of macrophages and specific T cells (68). In the CNS, CCL2 appears to orchestrate the activities of neural and inflammatory cells. For instance, findings from both transgenic mice and humans indicate that CCL2 is essential for transmigration of macrophages into the brain (69), and CCL2 is a potent chemoattractant for microglia *in vitro* (70, 71). In addition, during inflammation and in development, CCL2 recruits mononuclear phagocytes to the CNS white matter, where they act to clear myelin debris (shown to inhibit axonal growth) and enable glial progenitors to expand and differentiate (72). Substantial evidence also indicates that by mediating glomerular leukocyte infiltration, CCL2 contributes to kidney injury in the glomerulonephritis seen with SLE, and that serum CCL2 levels are significantly elevated in SLE patients and are correlated with the disease activity (SLEDAI) score, suggesting a role for CCL2 in the pathogenesis of SLE (54, 73). Furthermore, Okamoto *et al.* recently detected CCL2 in the CSF of patients with NPSLE and demonstrated its clinical relevance for diagnosis (56, 74).

6.2. CCL5

CCL5 (RANTES) is a chemoattractant for monocytes and memory T and NK cells (75), and may contribute to the pathophysiology of such immune disorders as RA (76), SLE (77) and MS (39). In EAE, CCL5 amplifies the inflammatory process, and its expression correlates with the intensity of neuroinflammation (78). In addition, CCR5, a CCL5 receptor, has been detected on lymphocytic cells, macrophages and microglia in actively demyelinating MS brain lesions (39, 79). And administration of a neutralizing monoclonal antibody specific for mouse CCL5 to a mouse model of human MS improves neurological function and reduces infiltration of T cells (80), suggesting CCL5 is very much involved in the pathogenesis of inflammation in the brain.

It appears that cell-cell interaction via CD40/CD40L is an important step toward induction of CCL5 expression in the CNS. For instance, secretion of both CCL5 and CCL2 by human brain microvessel ECs is significantly upregulated following CD40/sCD40L interactions, which offers a potential mechanism by which activated CD40L-positive T cells could regulate expression of CC chemokines by cerebral ECs (81). Despite the absence of evidence indicating CD40/CD40L interactions are involved in NPSLE, interactions between these molecules in the periphery may be important for B cell activation and the renal complications associated with SLE (82, 83). In addition, recent reports indicate that CCL5 acts during human fetal astrocyte development (84), and that it induces transcription of the chemokines CCL2 and CCL3 and the cytokine TNF-α in astrocytes (85). This effect may serve to amplify inflammatory responses within the CNS and contribute to the progression of both NPSLE (42) and MS.

7. CX3CL1

The recently cloned CX3CL1 (fractalkine) has the structure of a CX3C chemokine and is synthesized by ECs as a type I transmembrane protein (86) that is then cleaved by the metalloproteinases ADAM17 or ADAM10 (87, 88).

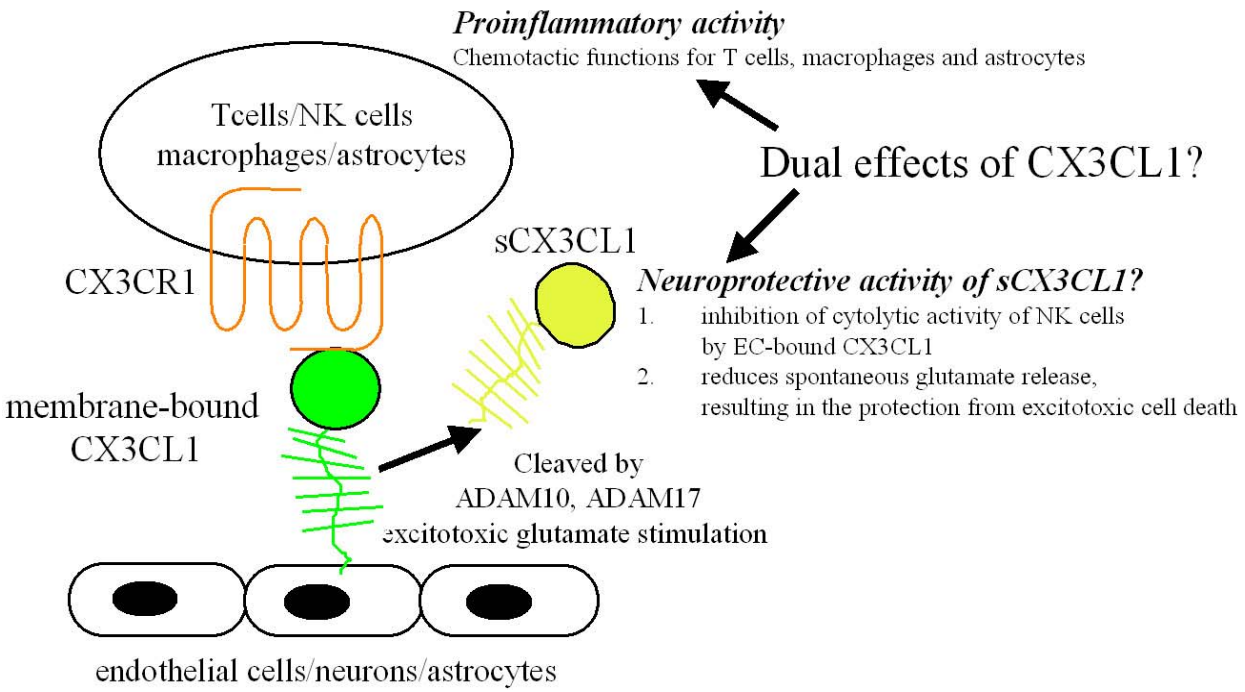

Figure 2. The dual effects of CX3CL1 in the CNS. Within the CNS, CX3CL1, and particularly sCX3CL1, appears to have dual activities. As proinflammatory mediator, CX3CL1 induces chemotaxis in T cells, NK cells, macrophages and astrocytes, and may amplify inflammatory/immune reactions. On the other hand, sCX3CL1 also appears to exert neuroprotective effects by inhibiting the otherwise enhanced cytolytic activity of NK cells interacting with EC-bound CX3CL1 and by reducing spontaneous glutamate release, thereby protecting against excitotoxic cell death.

The soluble form of CX3CL1 (sCX3CL1) was first reported to exert a chemotactic effect on monocytes, NK cells and T cells *in vitro*, and to induce cellular adhesion to ECs. In addition, CX3CL1 appears to act via its receptor, CX3CR1, as an adhesion molecule able to promote the firm adhesion of a subset of leukocytes under conditions of physiological flow (89, 90). It is noteworthy that CX3CL1 and CX3CR1 are both prominently expressed in the CNS, where CX3CL1 was previously identified as "neurotactin" (91). Within the CNS, CX3CL1 is constitutively expressed by neurons and ECs and is upregulated in neurons and astrocytes by the inflammatory stimulation that occurs with HIV encephalopathy, bacterial meningitis and Guillain-Barré syndrome (92-94). On the other hand, levels of transcription of CX3CL1 gene in the CNS appears to be unaffected by neuroinflammatory processes such as EAE or experimental cerebral ischemia (95). But once proteolytically cleaved from neurons in response to excitotoxic stimulation (87), the soluble form of CX3CL1 likely mediates subsequent migration of activated CX3CR1-bearing T cells, macrophages and/or astrocytes during the inflammatory response to brain injury. In addition, several studies have shown that sCX3CL1 can inhibit the interaction between CX3CR1-positive leukocytes and membrane-bound CX3CL1 in ECs, thereby suppressing the augmentation of cytolytic activity by NK cells (96). This suggests CX3CL1, especially its soluble form, has dual effects at sites of inflammation, and that which effects are manifested is determined by the stimulus type, the cells activated, the organ affected and/or the phase of the inflammation, among other things.

The expression and function of CX3CL1 has been observed in RA (97, 98), rheumatoid vasculitis (99), pulmonary artery hypertension (100), systemic sclerosis (101) and lupus nephritis in MRL/lpr mice (102). We recently showed that sCX3CL1 levels in the serum of SLE patients were significantly higher than in healthy individuals or RA patients, and correlated positively with disease activity, damage index scores and disease-specific autoantibodies, and correlated negatively with CH50 activity (103). In addition to sCX3CL1, a specific CX3CL1 receptor, CX3CR1, has been identified on both the $CD4^+$ and $CD8^+$ T cells from SLE patients with active disease (103). Notably, Fraticelli *et al.* showed that CX3CR1 was preferentially expressed in Th1 cells, and Th1 but not Th2 cells respond to CX3CL1. Furthermore, CX3CL1 is detected in ECs in areas affected by psoriasis, a Th1-dominated skin disorder (104). As discussed above, a pronounced Th1 response is central to the pathogenesis of SLE, which suggests that by mediating Th1 cell-EC interactions CX3CL1 may contribute significantly to the development and progression of SLE.

We also observed that levels of sCX3CL1 were elevated in the CSF of SLE patients showing neuropsychiatric manifestations and that both serum

and CSF sCX3CL1 levels declined with successful treatment (103). Recently, antibodies against glutamate receptor [N-methyl-D-aspartic acid (NMDA) receptor subunit NR2] were detected in serum from NPSLE patients (105-107). Glutamate is the major excitatory neurotransmitter of the nervous system and plays a key role in cognitive CNS functions, including learning and memory (108). NMDA receptors are also thought to mediate the neuronal injury caused by the excitotoxic effects of glutamate that occur in many neurological disorders, including stroke, dementia and neurodegenerative disorders (109, 110). In that regard, CX3CL1 is readily cleaved from neuronal membranes during excitotoxic glutamate stimulation, after which the cleaved CX3CL1 reduces spontaneous glutamate release, thereby exerting a neuroprotective effect against excitotoxic cell death (111-113).

The findings summarized above suggest sCX3CL1 could serve as a highly useful serologic marker of disease activity and organ damage in patients with SLE, and levels of sCX3CL1 in the CSF may prove to be a reliable marker for diagnosis of NPSLE and possibly for following the disease course. That CX3CL1 exerts both proinflammatory and neuroprotective effects is of particular interest in that it sheds light on the mechanisms underlying the pathogenesis of the brain damage seen in NPSLE and other CNS disorders and, perhaps, how those effects could be mitigated (Figure 2).

8. CNCLUSIONS AND PERSPECTIVE

Despite the large number of studies performed, the pathogenesis of NPSLE is still not completely understood, and a diagnosis of NPSLE continues to be difficult to make. The difficulty stems from the fact that NPSLE is a complex syndrome with a variety of symptomatic manifestations and clinical features reflecting different pathogenic processes. The critical roles played by the networks of chemokines that regulate CNS function and may even function as neurotransmitters are certainly an exciting area of promising research. During the last few years it has become apparent that chemokines not only orchestrate immune responses, but are also involved in an important way in the pathophysiology of almost every acute or chronic lesion of the nervous system (114).

What we know about the pathophysiology of chemokines during disease processes is still limited, and even in those areas where information is plentiful, it is difficult to interpret. This is because of the highly variable nature of chemokine expression, which appears to cause chemokine profiles to differ among SLE patients with different neuropsychiatric manifestations. We now recognize that it is highly important to determine as specifically as possible the correlation between each neuropsychiatric feature of SLE and the pattern of elevated chemokines in the CNS.

Although the challenge inherent in such a complex investigation is severe, additional knowledge about the biology of the cytokines and chemokines involved in NPSLE could serve as the basis for much needed improvements in the clinical management and diagnosis of NPSLE, as well as for new therapeutic strategies aimed at mitigating the mortality and morbidity associated with SLE and its attendant sequelae.

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Abbreviations: SLE; systemic lupus erythematosus, NPSLE; neuropsychiatric lupus erythematosus, CNS; central nervous system, CSF; cerebrospinal fluid, IFN; interferon, NMDA receptor; N-methyl-D-aspartic acid receptor, EC; endothelial cell, RA; rheumatoid arthritis, MS; multiple sclerosis, EAE; experimental allergic encephalitis, AD; Alzheimer's disease, AIDS; acquired immunodeficiency syndrome

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