Multiple sclerosis (MS) is a chronic inflammatory disease of the human central nervous system which causes severe morbidity in the majority of cases. It is the leading cause of non-traumatic neurological disability in young adults. In most patients, MS starts as relapsing remitting MS (RR-MS), which is characterised by episodes of neurological dysfunction followed by substantial improvement. These patients may go on to develop secondary progressive MS, suffering increasing disability as the disease progresses. 10-15% of patients experience a primary progressive form of MS. The aetiology of the ongoing demyelination and inflammation with tissue injury in MS is unknown. Many immune abnormalities have been described in MS, which may emphasise the role of the immune system in the pathogenesis of this disease. In individuals with a genetically determined susceptibility, exposure to certain environmental factors (e.g., a viral infection) may trigger a cascade that enables T-cells to migrate through the blood-brain barrier (BBB) into the brain and spinal cord. This process may be facilitated by cell adhesion molecules, particularly ICAM-1 [1]. T-cells become activated in the peripheral blood (PB) and then reactivated in the CNS. The subsequent release of proinflammatory Th1 cytokines sets the destructive pathway in motion. The destruction can be either a T-cell and macrophage-mediated demyelination, an antibody-mediated demyelination, a distal oligodendrogliopathy or a primary oligodendrocyte degeneration.

Chemokines and chemokine receptors

Chemokines are small (8-14kDa) structurally related molecules released by various cells. In humans more than 40 different chemokines have been identified. The interaction of chemokines with their respective cell surface receptors leads to the recruitment of specific leukocyte subpopulations to the sites of inflammation. CNS inflammation differs from that of other organs because of the presence of the BBB. Chemokines are involved in the process of leukocyte recruitment into the CNS, including induction and activation of leukocyte adhesion molecules, establishment of a chemotactic concentration gradient and induction of proteolytic enzymes. In addition, chemokines have many different effects on many different cell types beyond the immune system.

Chemokines can be divided into two major families and two additional subfamilies: CXC (the α family), CC (the β family), C (lymphotactin) and CX3C (fractalkine). In the CXC subgroup the cysteine residues are separated by an additional amino acid. A further division in this subgroup is made by a glutamic acid-leucine-arginine sequence, known as the ELR motif. ELR-positive CXC chemokines are chemoattractants for neutrophils, while ELR-negative CXC chemokines are inert to neutrophils but potent chemotractants for activated T lymphocytes. Examples of non-ELR-motif CXC chemokines are CXCL8 (old name IL-8) and CXCL10 (old name IP-10). The first two cysteine residues of the CC chemokines are adjacent to each other and close to the N-terminus. Most CC chemokines are chemotactic for monocytes/macrophages, T-lymphocytes, eosinophils and basophils. Typical examples of this group are CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES). C and CX3C chemokines stimulate the migration of mononuclear inflammatory cells.

In order to function, chemokines need to interact with their receptors. These receptors are seven-transmembrane G protein-coupled receptors which mediate leukocyte responses such as chemotaxis and immune interaction. The chemokine receptor nomenclature uses the name of the chemokine followed by R (for receptor) and then a number. Some chemokine receptors are expressed on T-cells in association with the Th1 phenotype, such as CCR5 and CXCR3, or the Th2 phenotype, such as CCR3, CCR4 and CCR8. No chemokine receptor is uniquely expressed on one leukocyte population. Usually one leukocyte subset has multiple chemokine receptors [Table 1]. For example, it has been reported that human CCR1 is expressed on several leukocyte populations including monocytes, T-lymphocytes, basophils, eosinophils, neutrophils, NK cells and mast cells [2].

Table 1. Expression of CC-chemokine receptors in different leukocyte populations.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>T-lymphocytes</th>
<th>B-lymphocytes</th>
<th>Macrophages</th>
<th>Eosinophils</th>
<th>Basophils</th>
<th>Neutrophils</th>
<th>Mast cells</th>
<th>NK cells</th>
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<tr>
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<td>+</td>
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</table>

Multiple sclerosis (MS) is an autoimmune disease of the human central nervous system that leads to demyelination and tissue injury. Migration of inflammatory T-cells via the blood-brain barrier (BBB) into the CNS is a crucial event in the pathogenesis of MS. Chemokines are key mediators of inflammation and have major effects on the migration of cells to sites of inflammation as well as activation of cells, either recruited or resident. It has therefore been hypothesised that chemokines and their receptors may not only play a key role in the pathogenesis of MS, but could also provide the basis of future immune-based therapies for MS. In both cases, a deeper understanding of chemokines and their receptors is needed.

Chemokines in experimental allergic encephalomyelitis and patients with MS

Experimental allergic encephalomyelitis (EAE), a T-cell-mediated demyelinating disorder of the CNS, is used as an animal model for MS. Data generated in this model are of great use in directing research into MS. In EAE an upregulation of CCL5, CCL4, CCL3, CCL1, CCL10 and CCL2 expression occurs shortly before the onset of clinical symptoms.

Chemokines influence T-cell differentiation and the regulation of the Th1/Th2 cytokine profile. CCL3 (MIP-1α) stimulates the production of IFNγ (a Th1 cytokine) and drives Th0 cells to differentiate into Th1 cells, whereas CCL2 (MCP-1) stimulates IL-4 production (a Th2 cytokine) and promotes cell differentiation into Th2 cells. Since it is known that Th1 cytokines promote EAE and MS, while Th2 cytokines reverse EAE and MS, the effect of chemokines on the cytokine profile is of essential importance in the clinical manifestation of the diseases.

Immunohistochemical studies of autopsy brain sections from patients with MS showed CXCR3 expression on most of the perivascular lymphocytes. These CXCR3 positive cell infiltrates are hardly ever found in control brain sections from patients without MS. The ligand of CXCR3 is CXCL10 (IP-10). It was assumed that CXCR3-cells form perivascular cell infiltrates whenever CXCL10 is present, whereas in the absence of CXCL10, CXCR3 recirculates. In the later stages of MS,
In a study from Trebst, et al., the expression of CCR1 and CCR5 on mononuclear phagocytes was examined in relation to demyelinating activity. It was proposed that CCR5+ monocytes are only retained in the CNS perivascular space in the presence of appropriate ligands, such as CCL3, CCL4, and CCL5. CCL3 and CCL4 expression was associated with macrophages and microglia, whereas CCL5 expression was due to perivascular inflammatory cells and astrocytes [3,4].

To study the pathogenesis of acute relapses in vivo, flow cytometric measurements of CSF and peripheral blood (PB) were carried out. CXCR3+ T-cells were enriched in the CSF compared with the PB; over three quarters of the T-cells in the CSF expressed the CXCR3 receptor. In addition, CXCL10 levels in the CSF of patients with RR-MS were significantly higher compared with PB. In these patients the BBB was mainly intact, so the elevated CXCL10 concentrations reflect an intrathecal release. CXCR3 receptor expression on CSF T-cells was significantly higher in patients suffering from acute attacks and shown to have Gd-enhancing lesions by MRI, compared to patients without these enhanced MRI lesions [5].

In contrast to CXCL10, the CCL2 level in the CSF of MS patients is reduced. In MS patients treated with methylprednisolone, the CCL2 concentration in the CSF is significantly reduced. It can therefore be assumed that MS relapses are triggered by a predominance of Th1 cytokines and depression of Th2 cytokines.

Therapeutic strategies

The role chemokines and their receptors play in the pathogenesis of MS is only just being elucidated. During the inflammatory process, chemokine production increases as T-lymphocytes and macrophages invade the CNS. Chemokines are also produced by the resident glia. These chemokines can attract leukocytes into the CNS, thereby influencing Th1/Th2 differentiation. In this way, chemokines are actively involved in the pathogenesis of EAE and MS. Any immune-based MS therapy should therefore target the chemokines and their receptors.

Human CCR1 is able to specifically bind multiple CC chemokines, including CCL3, CCL5, CCL7, CCL8, CCL14, CCL15 and CCL23 with high affinity and CCL2, CCL7 and CCL11 with poor binding affinity. In the EAE model, CCR1-deficient mice have a significantly reduced incidence of disease compared to wild-type mice. A CCR1 antagonist (BX-471), which showed a high affinity to its receptor, has been identified and found to reduce the clinical score in the EAE model. BX-471 is now undergoing phase II clinical trials in MS patients [2]. Another therapeutic approach involves a vaccination composed of naked DNA encoding CC chemokines [6]. Specific monoclonal antibodies which block chemokine activity might be another interesting approach. Overall a greater understanding about the role of chemokines and their receptors in the pathogenesis of MS is required.

References


The authors

Kerstin Haegle, MD, and Eckhart Sindern, MD.
Department of Neurology, BG-Kliniken Bergmannsheil Ruhr-University Bochum
Buerkle-de-la-Camp Platz 1, 44789 Bochum, Germany
E-mail: khaegle@tiscali.de