Chapter A17

THE CHEMOKINE SYSTEM IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Abstract: Chemokines chemoattract selected populations of inflammatory cells towards sites of inflammation in a gradient-dependent fashion, and also activate both recruited and resident inflammatory cells. Chemokines act on target cells through G-protein-coupled seven-transmembrane-domain receptors. High expression of several chemokines was found in the CNS during EAE. Cells expressing these chemokines were predominantly astrocytes and macrophages/microglia. In addition to chemokines, expression of several chemokine receptors was reported in EAE. Amelioration of EAE by anti-chemokine antibodies and studies in knock-out mice confirm the important roles of some chemokines in EAE pathogenesis. In the last several years many reports have been published addressing chemokine expression in multiple sclerosis. These results resemble results obtained earlier in EAE. Taken together, these data suggest that chemokine system may be a promising target for future treatment methods of multiple sclerosis.

Key words: Chemokines, chemokine receptors, experimental autoimmune encephalomyelitis, neuroinflammation, inflammatory cell migration

Experimental autoimmune encephalomyelitis (EAE) is a model autoimmune disease of the central nervous system (CNS) induced in susceptible strains of experimental animals with myelin, myelin proteins or peptides. The classical autoantigens used for EAE induction are myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG). This model may be induced in appropriate strains of mice, rats, guinea pigs and nonhuman primates including rhesus and marmoset species. The advances made by studying this experimental disease resulted from the observation that the pathology of EAE resembles in some
respects the pathology of the major human demyelinating disease – multiple sclerosis (MS). Typical histopathological hallmarks of the initial phase of both diseases are perivascular mononuclear inflammatory foci disseminated in the CNS. The mechanism of migration of inflammatory cells from blood to the CNS has been studied for many years and it remains incompletely understood. Our knowledge about this process has significantly grown since the observation that chemoattractant cytokines – chemokines may play an important role in inflammatory cells homing to the CNS.

CHEMOKINES AND THEIR RECEPTORS

Chemokines and their receptors are the principal determinants of leukocyte-type and organ specificity within inflammatory foci. Chemokines chemoattract selected populations of inflammatory cells towards sites of inflammation in a gradient-dependent fashion, and also activate both recruited and resident inflammatory cells. The chemokine family can be divided into four separate subfamilies (CXC, CC, C, CXXXC) according to the position of the first two cysteines near the N-terminus. Beyond these differences in structure, there are also functional differences between chemokine subfamilies. The largest subfamilies are CXC and CC chemokines. In CXC chemokines the first two cysteines are separated by one additional amino acid. The CXC subfamily can be further divided into two groups, one with ELR (glutamate-leucine-arginine) motif preceding the first cysteine and another without it. CXC chemokines with ELR are primarily chemoattractant for neutrophils, while several other non-ELR chemokines attract mainly activated lymphocytes and monocytes. SDF-1/CXCL12 is an outlier among chemokines in that it acts towards many non marrow-derived cells in addition to most leukocytes. CC chemokines have the first two cysteines adjacent to one another. They attract principally mononuclear leukocytes. The C subfamily consists of lymphotactin which is a potent T cell chemoattractant. The single member of CXXXC subfamily is fractalkine, a chemokine with three amino acids intervening between the first two cysteines. Fractalkine is the prototype tethered chemokine with a long stalk attached to the cell membrane; CXCL16 also possesses this unusual structure. After cleavage fractalkine may chemoattract mononuclear inflammatory cells [1, 2]. In the last few years several new chemokines were described by independent research teams. They have been known by different names. This complicated chemokine nomenclature. To solve this problem, a consensus meeting at the Keystone Chemokine Conference (Keystone, CO, January 18-23, 1999) proposed a new nomenclature for the chemokines (Table 1).