The Role of the Complement System in the Pathogenesis of Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis

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1. INTRODUCTION

The central nervous system (CNS) has long been known as an immunologically privileged site, isolated from systemic circulation by the so-called blood–brain barrier (BBB): a special anatomical structure formed by endothelial cells and astrocytes. However, increasing evidence is available now that there is immune surveillance in the healthy brain, as a wide variety of leukocytes have the ability to enter the CNS. Activated immune cells gain further capabilities to cross the BBB, while inflammatory mediators can adversely affect the barrier function of endothelial cells. Hence, under conditions of CNS-directed immune activity, the stage is set for initiation of the complement cascade, utilizing systemic or locally produced complement components and regulated by both the infiltrating leukocytes and proper cells of the CNS.

Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the CNS, affecting approximately 1 in 700 people in the United Kingdom.
Demyelination in MS is caused by activated immune effectors, like T_h1 and T_c cells, macrophages, and the complement system. The clinical course of MS is highly variable both within and between patients. Differences in the pathological character are also so wide that it raised the assumption about diverse causes of demyelination. Investigating biopsies and autopsies, Lucchinetti et al. have described four main types of pattern based on the structure of lesions. In patterns I and II active demyelination was associated with a T-lymphocyte- and macrophage-dominated inflammation. Prominent deposition of Igs and C9neo antigen at lesions was found exclusively in pattern II. Sharply demarcated plaques were typically centered on small veins or venules in both types, with a high incidence of remyelinated shadow plaques. Pattern III inflammatory infiltrates contain T lymphocytes, macrophages and microglia, while Ig and complement deposition is absent. The striking feature in these cases was a preferential loss of Myelin Associated Glycoprotein (MAG), while other myelin proteins, including Proteolipid Protein (PLP), Myelin Basic Protein (MBP) and Myelin Oligodendrocyte Glycoprotein (MOG) were still present. In pattern IV, inflammatory infiltrates were also dominated by T lymphocytes and macrophages, but neither immune complex deposition nor a difference in staining patterns of myelin-specific proteins (such as MAG, MBP, PLP, MOG) was observed. Overall, the most frequently observed pattern was type II, followed by patterns III, IV and I. Thus, pathological evidence supports that the complement system is activated at the most frequently found type II lesions.

Experimental Autoimmune Encephalomyelitis (EAE) is a widely used animal model of MS. EAE, too, has many types depending on the species, strains, quality of antigen and adjuvants, and method of antigen administration used. Basically, EAE can be induced by active immunization with proteins or peptides derived from the myelin sheath of neurons, or by passive transfer of myelin antigen-stimulated lymphocytes. Both treatments result in an immune-mediated attack on the myelin sheath of neurons, demyelination, and MS-like symptoms. Pathological assessment of disease severity relies on quantification and qualification of infiltrating cells in the CNS and measurement of the extent of demyelination. Clinical assessment relies on motoneuron involvement in CNS damage and is carried out by scoring the degree of paralysis, ranging from tail weakness to tetraplegia. The most susceptible and very extensively studied mouse strains are SJL/J, and B10.PL. EAE in B10.PL mice is a chronic disease characterized by MBP epitope specificity, while in SJL/J mice it manifests as a relapsing-remitting disease with PLP as the predominant antigen. Although less frequently used, EAE has been worked out for many other inbred, less susceptible mouse strains (A.SW, B10.S, PL/J, B10RIII, SWR, 129/J, C3H, Balb/c, Biozzi AB/H, NOD/Lt) as well. While C57BL/6 is presumed to be a less susceptible strain, these mice are also widely used in EAE experiments because of the availability of numerous genetically modified mice on this background. MOG 35-55 peptide has been successfully used in C57BL/6 to induce active EAE.