Are current immunological concepts of multiple sclerosis reflected by the immunopathology of its lesions?

H. Lassmann¹, K. Vass²

¹ Neurological Institute, University of Vienna, Schwarzspanierstrasse 17, A-1090 Wien, Austria
² Department of Neurorehabilitation, University of Vienna, Austria

Abstract. Immunopathological studies on multiple sclerosis (MS) brain clearly indicate that a T cell-mediated immune response is the driving force in the induction of the lesions. This T cell-mediated response alone, however, is not sufficient to explain the widespread and selective destruction of myelin sheaths. According to present evidence, it is likely that antibodies directed against surface components of myelin sheaths are at least one factor involved in the demyelinating process. The patterns of inflammation, demyelination and oligodendrocyte destruction, however, suggest that the pathogenesis of the lesions may be fundamentally different in individual MS patients and that autoimmunity may not be the sole cause. In the case of autoimmune reactions various different proteins of the nervous system may become targets and it appears unlikely, that myelin basic protein is a major candidate for a pathogenetic role in MS.

Introduction

The pathology of multiple sclerosis (MS) was defined more than a hundred years ago [3, 6, 29]. The disease is characterized by plaques of demyelination and sclerosis, randomly distributed throughout the central nervous system (CNS). The nature of these lesions is thought to be selective, involving mainly myelin and its supporting cells, the oligodendrocytes, but sparing other tissue elements of the nervous system, such as axons, neurons or astrocytes. During active disease, demyelination is associated with an inflammatory reaction, which is predominantly accomplished by lymphocytes and macrophages. It is generally believed, although not formally proven, that the chronic inflammatory process in the nervous system is responsible for the destruction of myelin sheaths. Infectious agents have not been reproducibly isolated from MS lesions and immunosuppression has a significant beneficial effect on the development...
of the disease. Furthermore, autosensitization in humans may lead to a disease which, at least on the basis of the pathology of its lesions, is indistinguishable from MS [47, 57].

For these reasons MS is believed to be an autoimmune disease, triggered in genetically susceptible individuals by an exogenous factor, possibly a virus infection during childhood. However, the nature of the autoantigen, and the mechanism by which the immune system exerts its deleterious effects on the nervous system, are still subjects of controversy. In the present review, recent observations on the immunopathology of MS will be summarized and critically discussed in the light of current immunopathogenetic concepts of the disease.

**Immunopathology of brain inflammation in MS**

The inflammatory reaction in MS is dominated by lymphocytes and macrophages. More detailed characterization of lymphocytes in MS lesions revealed controversial data on the relative numbers of CD4\(^+\) and CD8\(^+\) cells and their subsets [9, 12, 53]. This, however, is not surprising due to the extensive recruitment of secondary, antigen-nonspecific inflammatory cells into established inflammatory foci [5, 51]. Yet the bulk of evidence suggests that in early active lesions CD4\(^+\) cells of the "helper/inducer" phenotype dominate, whereas there may be a significantly lower incidence of CD45R\(^+\) putative "suppressor/inducer" cells compared to other inflammatory diseases of the CNS [12, 53]. T cell receptor analysis suggests oligoclonal expansion of both \(\alpha/\beta\) [33] and \(\gamma/\delta\) T lymphocytes [63] within MS lesions.

Although much fewer in numbers, B lymphocytes and plasma cells contribute to the inflammatory reaction [8, 32]. Interestingly, the relative frequency of immunoglobulin-producing B cells and plasma cells is significantly higher in the lesions of MS patients in the late chronic stage of the disease, compared to lesions formed in Marburg's type of acute MS or during the first or second bout of chronic MS [22, 35]. A considerable proportion of plasma cells within chronic MS lesions have been shown to locally produce antibodies against myelin basic protein (MBP) [11].

The dominant leukocyte population in MS lesions are macrophages. Macrophage activation and phagocytosis of myelin proteins in the lesions are reliable indicators of ongoing demyelinating activity [18, 23, 35, 46].

The inflammatory reaction in MS brains is associated with the up-regulation of immune-associated molecules and cytokines on infiltrating leukocytes as well as on resident cells of the nervous system. As an example, activated endothelial cells in active lesions may express adhesion molecules [7, 54], fibronectin [52], urokinase plasmin activator receptor [7], major histocompatibility complex molecules [7, 55], and stress proteins, and may be dressed with activated complement [4]. Undoubtedly, these molecules are important for the passage of inflammatory cells through the blood-brain-barrier.

Data on the expression of cytokines in MS lesions are incomplete and controversial. By polymerase chain reaction (PCR) amplification interleukin (IL)-1 mRNA has consistently been found in active lesions [64], whereas mRNAs for IL-2, IL-4 and IL-10 were present only in a small minority of plaques or completely absent [43, 64]. In addition, mRNAs for certain intercines (IL-8 and membrane cofactor protein) were detected. In situ hybridization revealed mRNAs for a variety of cytokines [IL-1, 2, 4, 6, 10, interferon-\(\gamma\) (IFN-\(\gamma\)), tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) and