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Untapped targets in multiple sclerosis

Edgar Meinl*

Institute of Clinical Neuroimmunology, Ludwig-Maximilians University, Munich and Department of Neuroimmunology, Max-Planck-Institute of Neurobiology, Martinsried, Germany

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SUMMARY

Multiple sclerosis is a chronic inflammatory disease of the white and grey matter which results in irrevocable axonal and neuronal damage. Grey matter injury is widespread and reflects disability to a greater extent than do white matter lesions. Growing understanding of the immunopathology of multiple sclerosis is leading the way to the identification and testing of untapped targets that may offer new and more specific ways to treat the disease. For example, data from animal models support a two-step pathological process in multiple sclerosis, whereby T cells initially induce inflammation and open up the blood–brain barrier, which then allows access to antibodies which aggravate tissue damage. Determination of the specificity of the invading T cells and the autoantibodies that cause disease is a major focus of current research. The discovery of anti-aquaporin-4 autoantibodies in patients with neuromyelitis optica and of anti-MOG antibodies in a subset of children with paediatric autoimmune demyelinating disease are promising steps in this direction. Recently, the axoglial antigens neurofascin and contactin-2/TAG-1, which are localised around the node of Ranvier, were identified as targets of an autoimmune response in multiple sclerosis. Such an autoimmune response might induce axonal injury and direct the immunopathological response to the grey matter. It is to be hoped that the outcome of such investigations will lead to the identification of patient subgroups based on their autoreactivity and new ways to treat them safely and effectively.

Introduction

Multiple sclerosis (MS) is a disease which has multiple facets, both in terms of its clinical presentation and in terms of pathological stigmata. It is characterised by chronic inflammatory activity in the central nervous system (CNS), demyelination, injury to grey matter and axonal loss. Over the last decade a consensus has emerged that damage to grey matter and axonal injury reflect disability to a greater extent than do lesions in white matter. Current immune-directed disease-modifying therapies all target primarily the inflammatory process that underlies loss of myelin and the formation of white matter lesions. It would therefore be of interest to develop new therapies that target pathology in the grey matter or neurodegenerative processes in order to have treatments at our disposal which may be more effective at preventing long-term disability than current therapies. In this respect, it is important to identify the biological mechanisms implicated in these processes, which could be targets for new treatments.

Autoantibodies in autoimmune demyelinating diseases

Clues to the disease mechanisms in autoimmune demyelinating diseases may come from the identification and characterisation of autoantibodies that appear in certain patient subgroups and may trigger or maintain the disease process [1]. An example of this situation is the case of anti-aquaporin-4 antibodies in *neuromyelitis optica* (NMO; Devic's disease). The discovery that these antibodies can be identified in the serum of many (60–90%) patients with NMO [2,3] was a major breakthrough. A role for autoantibodies against myelin oligodendrocyte glycoprotein (MOG) in multiple sclerosis has been under investigation for several decades. While their presence in adult-onset multiple sclerosis still remains controversial (reviewed in [1]), the occurrence of anti-MOG Ig in a proportion of children with MS or acute disseminated encephalomyelitis (ADEM) now seems fairly well established [4,5]. Autoantibodies against glycolipids have been well characterised in Guillain–Barré syndrome [6] and may also be relevant to some patients with multiple sclerosis. However, for the majority of patients, autoimmune demyelinating diseases in general and multiple sclerosis in particular, the specificity of the suspected pathogenic autoantibodies is unknown.

Autoantibodies to myelin oligodendrocyte glycoprotein (MOG)

MOG is a transmembrane glycoprotein of unknown function related to immunoglobulins which is synthesised in oligodendrocytes and expressed on the outer surface of myelin. In contrast to many other myelin proteins, it is localised exclusively to the CNS and is not a component of the myelin sheath of peripheral nerves. Since it is expressed on the outer surface, it can be recognised by antibodies in the extracellular milieu, if these have access to the CNS. These characteristics make it an attractive candidate for an autoimmune target in multiple sclerosis [7]. Indeed, in the

* Correspondence: Prof. Dr. Edgar Meinl, Institut für Klinische Neuroimmunologie, Marchioninistr. 15, 81377 München, Germany.
Fax: +49 89 8578 3790
E-mail address: meinl@neuro.mpg.de (E. Meinl).

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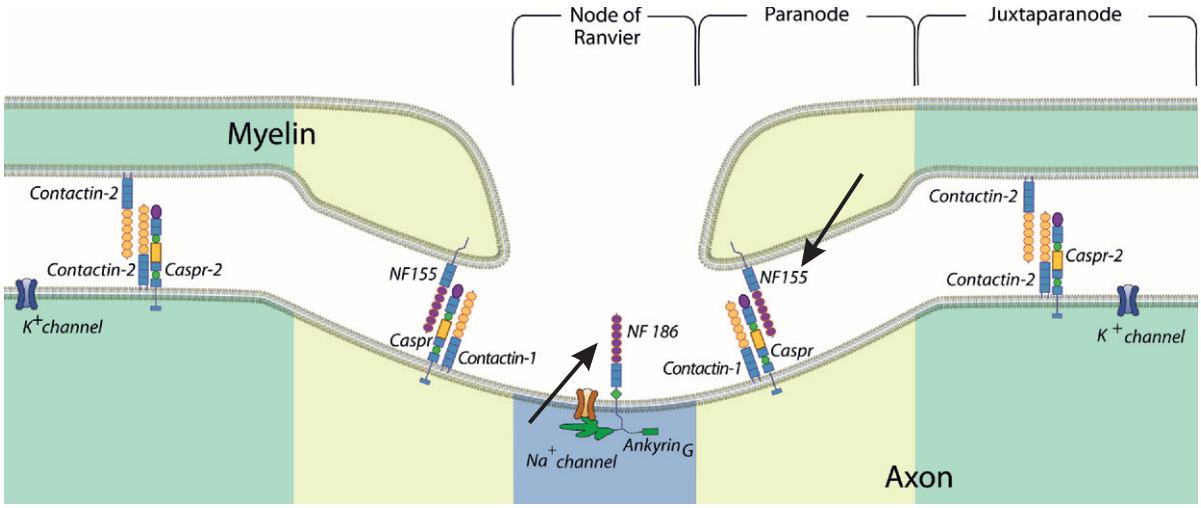

Fig. 1. Architecture of the node of Ranvier, illustrating the localisation of different proteins important in maintaining structural integrity. The arrows point to two isoforms of neurofascin which are expressed by axons and oligodendrocytes. Reproduced from reference [1] with permission.

experimental autoimmune encephalomyelitis (EAE) animal model of multiple sclerosis, anti-MOG Ig can enhance disease induced by encephalitogenic T cells and induce demyelination.

Using a sensitive radioimmunoassay for conformationally intact MOG oligomers, O'Connor et al. [8] were able to detect anti-MOG autoantibodies in a subset of children with ADEM, and some children with relapsing inflammatory demyelinating disease, but only rarely in patients with adult-onset multiple sclerosis. Similar results were obtained with MOG-transfected cells [4,5]. Some of the contradictions in the literature concerning the presence of anti-MOG antibodies in multiple sclerosis may be due to differences in the types of assay system used to detect them. We have developed a flow cytometry assay with a MOG-transfected cell line to detect antibodies to conformationally intact MOG. This assay, but not a Western blot with purified myelin glycoproteins, identifies a proportion of some 30% children with acute demyelination [9]. These autoantibodies to MOG disappeared in monophasic acute disseminated encephalomyelitis, but tended to persist in childhood MS. Anti-MOG antibodies detected in these children share epitopes with pathogenic anti-MOG antibodies that appear in a spontaneous EAE model [10] and are of the IgG1 complement-activating subtype [9]. The reason why there are more anti-MOG autoantibodies in childhood MS than adult MS is unclear.

Autoimmunity to neurofascin

In adult multiple sclerosis, anti-MOG antibodies appear to play a limited role, but it is possible that other myelin components may be antigenic and generate autoantibodies that play a role in adult-onset disease. For this reason we have purified myelin glycoproteins and screened them for their affinity for immunoglobulins present in the serum of multiple sclerosis patients, which could be pathologically relevant. Using two-dimensional electrophoresis, we identified one such protein with a molecular weight of about 150 KDa which turned out to be neurofascin [11]. Neurofascin, which is expressed by both oligodendrocytes and axons, is localised at and around the node of Ranvier (Fig. 1). The node of Ranvier corresponds to the gap in the myelin sheath where fast saltatory action potential propagation takes place. The integrity of the node of Ranvier is essential for efficient propagation of nerve impulses, and is maintained by specialised proteins that anchor the myelin sheath to the underlying axon [12]. The oligodendrocyte form of neurofascin (NF155) is one of these proteins that maintain the cytoarchitecture of the node of Ranvier. Another larger isoform of neurofascin is expressed by neurons (NF186) and is responsible for maintaining

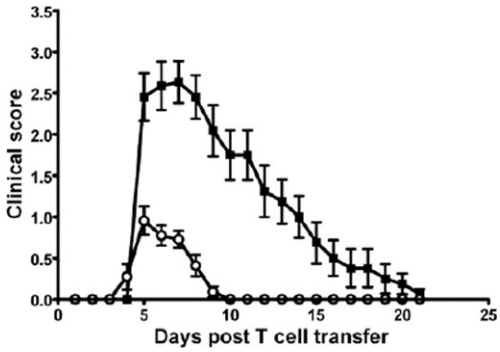

Fig. 2. Anti-neurofascin mAb enhances T cell mediated experimental autoimmune encephalomyelitis (EAE) in rats. EAE was induced by inoculation of MOG-specific T cells. At the beginning of the disease an anti-neurofascin mAb (solid symbols) or a control antibody (open symbols) was injected. Reproduced from reference [11] with permission.

the clustering of voltage-dependent sodium channels, responsible for propagation of the action potential, at the node of Ranvier.

To assess whether autoantibodies to neurofascin may be pathogenic, we have injected a mAb that recognizes both NF155 and NF186 into rats in whom EAE has been induced by inoculation of MOG-specific T cells [11]. If anti-neurofascin antibodies are administered during the time window when the blood–brain barrier is open, then the clinical symptoms are enhanced and the duration of disability prolonged (Fig. 2). Histopathological studies in these mice indicate that this mAb selectively targets the nodes of Ranvier, resulting in deposition of complement and axonal injury visualised by β-amyloid precursor protein staining (Fig. 3).

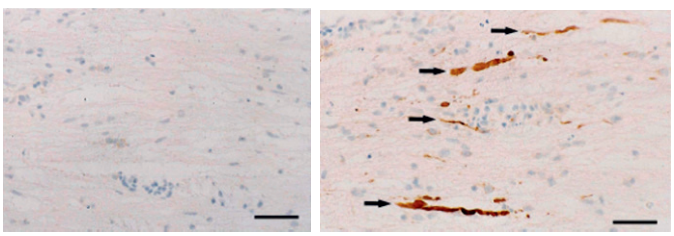

Fig. 3. Anti-neurofascin mAb induces axonal injury. EAE was induced by inoculation of MOG-specific T cells. At the beginning of the disease an anti-neurofascin mAb (right) or a control antibody (left) was injected. Longitudinal sections of the spinal cord were stained for β-amyloid precursor protein and the brown color indicates axonal injury. Scale bar: 30 μm. Reproduced from reference [11] with permission.