Hunting for autoantibodies in multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the CNS. Many findings support the assumption that the immune system plays a key role in the pathogenesis of MS, at least during the relapsing-remitting phase of disease.[1,2] Both arms of the adapted immune response seem to be crucial for the induction and maintenance of the autoimmune response as suggested by the success of therapies targeting T cells, B cells, or both. While genes and pathways involved in the pathogenesis of MS have emerged from recent studies, the molecular targets of the autoimmune response in MS are still largely uncertain. The identification of these targets, to better understand the pathogenesis and develop specific immune therapies, has been the focus of MS research during the last decades.

Similar to other autoimmune diseases, researchers have been trying to identify MS autoantigens via the specificity of the adapted immune response. It can be assumed that patients with MS harbor autoreactive T cells and B cells in their repertoire that are responsible for the highly organ-specific immune response in MS. Both lymphocyte subsets express surface receptors that ensure specific recognition of antigens. While T cells are difficult to study with respect to their antigen specificity, antibodies, the soluble antigen receptor of B cells, provide excellent tools to hunt for MS autoantigens. However, this hunt has been more difficult than initially anticipated.

It remains uncertain which compartment is best suited to screen for autoantibody reactivities. The occurrence of intrathecal immunoglobulin G (IgG) synthesis and oligoclonal IgG bands in the CSF of patients with MS suggests CSF IgG as ideal bait to search for autoantibody reactivity. However, studies with CSF IgG are challenging; the overall IgG concentration in the CSF is low and it is well-known that CSF IgG from patients with MS binds with low affinity to different antigens that are most likely unrelated to the disease (e.g., against common viruses).[3] Moreover, recent progress in the discovery of autoantibodies in inflammatory CNS diseases has primarily emerged from studying serum instead of CSF IgG.[4–7]

Several strategies have been applied to identify possible targets of autoantibodies in MS. Initial studies focused on candidate autoantigens that are highly expressed in CNS white matter. The proteins used in the assays were either isolated from brain tissue or recombinantly expressed in bacteria. Over time it became clear that antibodies, especially those that are biologically active, target conformational epitopes that require proper folding and cell-specific posttranslational modifications.[5,7,8] Therefore, more sophisticated technologies have been developed that aim to fully reflect the native conformation of the protein in vivo. These include expression systems that allowed protein expression in human cell lines derived from the CNS. In parallel, large-scale screening assays were developed based on cDNA expression libraries, phage display libraries, and protein and peptide arrays, to systematically screen for autoantibody binding. Moreover, unbiased screening approaches by immunohistochemistry and proteomic analysis of antibody:antigen complexes have been applied.[6] These approaches have yielded a number of candidate autoantibody targets in MS.

In this issue of *Neurology*®, Querol and colleagues[9] applied a protein array to investigate the specificity of CSF IgG. The protein microarray comprises almost 10,000 unique human proteins. CSF samples from 8 patients with MS and 7 patients with other neurologic diseases were used to screen the arrays for MS-specific autoantibodies. Although the protein array does not display most proteins with proper conformation and posttranslational modifications and will therefore miss many autoantibody reactivities, it is currently the best approach to perform large-scale target screening with antibodies.

In their elegant study, the authors identified a new target antigen called recombination signal binding protein for immunoglobulin kappa J region (RBPJ) that was bound by IgG from patients with MS but to a much lesser extent by IgG from controls. In a second set of experiments, they confirmed this finding in an independent cohort of patients with MS and controls using an ELISA assay. Also, binding of CSF

See page 956

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from patients with MS to cells expressing the protein was shown, confirming that the antibodies can bind the protein when expressed in mammalian cells. RBPJ is a nuclear protein involved in development and differentiation of various cells. Antibodies to RBPJ have been described in different diseases such as breast cancer and leukemia. Therefore, it is rather unlikely that the antibody response to the intracellular protein itself reflects a primary and pathogenic immune response in MS. The generation of RBPJ antibodies is more likely a secondary event, when the protein is released from damaged cells. Therefore, this antibody might instead be related to CNS damage and may allow the stratification of patients with respect to their disease activity and progression, rather than becoming a diagnostic tool. The 12.5% of patients testing positive by ELISA could possibly represent a group of patients with more extensive tissue damage. However, additional studies are needed to address the relation of RBPJ to tissue damage and establish it as a useful biomarker for clinical practice.

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B. Hemmer has served on scientific advisory boards for Roche, Novartis, Bayer Schering, Merck Serono, Biogen Idec, GSK, Chugai Pharmaceuticals, Micormet, and Genzyme Corporation; serves on the international advisory board of *Archives of Neurology* and *Experimental Neurology*; is author on patents re: KIR4.1 antibody testing in MS and Genetic determinant of neutralizing antibody development in interferon-beta–treated patients; has received speaker honoraria from Bayer Schering, Novartis, Biogen Idec, Merck Serono, Roche, and Teva Pharmaceutical Industries Ltd.; and has received research support from Biogen Idec, Bayer Schering, Merck Serono, Five prime, Metanomics, and Novartis. R. Srivastava is author on a patent re: KIR4.1 antibody testing in MS. Go to Neurology.org for full disclosures.

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