Anti-SPAG16 Antibodies in Multiple Sclerosis

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INTRODUCTION

Multiple sclerosis is a chronic inflammatory disease of the central nervous system (CNS), characterized by myelin loss, axonal pathology and progressive neurodegeneration [1]. Disease starts in 85% of cases with a clinically isolated syndrome (CIS), a first (sub)acute neurological event with demyelination. Different clinical subtypes of MS exist, with 85-90% of patients experiencing relapsing-remitting (RR) disease in which clinical relapses alternate with remission [2]. About 40% of RR-MS patients develop secondary progressive (SP) MS with progressive neurological disease. In 10-20% of patients, MS manifests as a primary progressive (PP) disease with a progressive course from the onset [2].

Despite the widely held view that T cells are the main effectors in MS pathogenesis, recent studies have demonstrated that B cells and antibodies are among the major contributors to the disease process in many MS patients [3, 4]. An important hallmark of MS is the presence of oligoclonal immunoglobulin G (IgG) antibodies in the CSF of more than 90% of MS patients, which is used as a diagnostic indicator of disease [5]. During the last decade, much effort has been made to characterize the autoantibody response present in MS patients. Consensus exists on the involvement of multiple autoantibody targets. Various target antigens of these autoantibodies have been described, including myelin oligodendrocyte glycoprotein (MOG), neurofilament, neurofascin and the potassium channel KIR4.1, reflecting the disease heterogeneity [6]. Rarely, these targets showed specific antibody reactivity in MS combined with pathologic relevance in vivo. Still, studies on autoantibodies in MS contribute to a better understanding of MS pathogenesis and could help to find better disease markers and identify therapeutic targets for those MS patients with autoantibody dependent disease.

In the search for novel antigenic disease markers for MS, using a high-throughput cDNA phage display-based approach, we previously identified 8 autoantibody targets in the CSF of MS patients [7]. One of the identified targets was sperm-associated antigen 16 (SPAG16) isoform 2, which had never been linked to MS. Two SPAG16 isoforms exist; isoform 1 (SPAG16-1; 71 kDa) and isoform 2 (SPAG16-2; 20.4-kDa). In sperm cells, SPAG16-1 is part of the axoneme and plays a role in sperm motility. The function of SPAG16-2 is unknown [8, 9]. Recent data reveal the presence of SPAG16 in many tissues, including the lungs and brain ventricles but also in hematopoietic cells in the bone marrow, fibroblast-like synoviocytes in rheumatoid arthritis and in certain cancers [8, 10-12]. Since SPAG16 was a novel target of the humoral immune response in MS, with unknown function in the CNS, we further investigated SPAG16 and anti-SPAG16 antibodies in MS pathology [13]. We have
shown elevated anti-SPAG16 antibodies in the plasma of MS patients with 95% specificity and 21% sensitivity. Interestingly, the pathologic relevance of these antibodies in a subgroup of MS patients was shown by the identification of SPAG16-specific oligoclonal bands in the CSF of 5/23 MS patients. Further, in vivo experiments in myelin oligodendrocyte glycoprotein (MOG)-peptide induced experimental autoimmune encephalomyelitis (EAE) in mice demonstrated that injection with anti-SPAG16 antibodies induces disease exacerbation. Finally, we found that SPAG16 was specifically upregulated in reactive astrocytes, both in EAE and MS lesions. These results underline the involvement of SPAG16 specific autoantibodies in MS, although their exact role remains to be determined.

OBJECTIVE + METHODS

In the present study, we validated the presence of anti-SPAG16 antibodies in three novel independent cohorts of MS patients. Statistical analysis was performed to compare these cohorts.

The autoantibody reactivity to SPAG16 was tested in plasma samples using our recombinant SPAG16 protein ELISA in three different cohorts of MS patients (N=94, N=196 and N=58) recruited at three locations.

RESULTS

Elevated plasma anti-SPAG16 antibodies were detected in 20% (19/94), 23% (46/196) and 21% (12/58) of MS patients in the different cohorts. Furthermore, statistical analysis revealed that there was no overall significant difference between the three cohorts (P=0.3960). Therefore, future statistical analysis will be performed on the whole MS cohort irrespective of recruitment location and we will compare the different MS subtypes (relapsing-remitting, primary or secondary progressive). Logistic regression analysis will be performed to identify factors that are predictive of positive anti-SPAG16 antibody assay results. Pearson chi square test and Fisher’s exact test will be used for between-group comparisons.

CONCLUSIONS

Anti-SPAG16 antibody reactivity is present in a subgroup of MS patients (~22%), in three novel cohorts, which is comparable to our previous studies [7, 13]. Moreover, assessing demographic and clinical characteristics of MS patients for association with anti-SPAG16 antibody positivity will provide clues regarding prognostic and/or pathologic potential of these antibodies in MS.

Keyword(s): Multiple sclerosis, SPAG16, autoantibodies, biomarker
REFERENCES


