

## EDITORIAL

## A Case for Autoimmunity as the Cause of Fibromyalgia

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Unfortunately, the currently available therapies of this puzzling disorder remains modest. To go any further, we must therefore focus on its pathophysiology. Fibromyalgia syndrome (FMS), a long-known but generally neglected disease, associates widespread pain, emotional distress and moderate, mild or great tenderness [1]. It is worth emphasizing that some experts think of as a psychological disorder [2]. This is primarily a diagnosis of exclusion, so that all other causes of joint and muscle pain have first to be ruled out. However, based on the study of 293 patients with *bona fide* primary or secondary FMS and 255 controls with disorders that could have been confused with FMS, classification criteria have been proposed by 25 research groups [3]. A severity symptom scale has then been constructed [4], and the original criteria recently revised by the American College of Rheumatology [4]. Unfortunately, the currently available therapies of this puzzling disorder remains modest. To go any further, we must therefore focus on its pathophysiology. To this end, the hypothesis of a muscle disease has been intensively explored [5], and small fiber abnormalities characterized on muscle biopsies [6], but there was no advance in therapy.

To gain further insights into the pathophysiology of FMS, new informations should be obtained, not only from analysis of neurological and muscular disorders, but also on what we learn about immunological dysregulation. An exciting hypothesis has recently been put forward, speculating that the immune system contributes to the development of the disease. In this field, accumulation of clues has indeed drawn our attention. They have been gained from autoimmunity-related observations. For example, the markedly increased prevalence of FMS in patients with autoimmune rheumatological conditions, such as rheumatoid arthritis, systemic lupus erythematosus or Sjogren's syndrome [7], the demonstration that some complex regional pain syndromes are caused by antibodies (Ab) to the self [8], and the report that autoAb bind to neuronal and glial cells (NGC) surface receptors, potentially impairing signaling processes. Among them, are Ab to N-methyl-D-aspartate (NMDA) receptor, Ab to gamma-aminobutyric acid A (GABA) receptor and Ab to alpha-amino-3-hydroxy-4-isoxazolepropionic (AMPA) receptor. The discovery of these autoAb may offer an antigen (Ag)-specific model linking autoimmunity to psychopathology [9]. Worthwhile to note is that most of these recently discovered autoAb bind to surface receptors in the central nervous system. The other way round, autoimmune-associated encephalitis often encompasses psychiatric symptoms as its first manifestations. One step ahead, novel guidelines distinguish autoimmune psychosis from autoimmune encephalitis (for review see 10). Various psychiatric symptoms, including mood disorders and sleeping dysfunction, have thus been shown to be associated with synaptic and/or neuronal serum or cerebrospinal fluid (CSF) autoAb. Interestingly, the clinical pictures differ among pathologies based on Ab targets, but the heterogeneity of these autoAb improves our understanding of the variable neurological symptoms in FMS. An impaired blood-CSF barrier function might, however, be a prerequisite for autoimmune-mediated psychological symptoms. It is also most intriguing that Ag-specific cytotoxic T lymphocytes have been claimed to play a role in neuronal damages [11].

Despite the total absence of inflammation in FMS, a thus-far unknown autoimmune process may give rise to a painful disease. To help in our interpretation of this complex condition, there is a need for animal models with symptoms mimicking the human disease. They have recently been developed [12]. Before working out the models, two issues had hitherto to be addressed. The first problem was to trigger off FMS-like symptoms in rodents by transferring pathological human samples. To this end, sera from FMS patients and from healthy controls (HC) were introduced into normal mice. The ensuing pain-like behavior was examined. Its easurement in animals was precisely the second problem to be solved. The Randall-Selitto paw pressure test, the tactile and thermal sensitivities, the forelimb grip strenght and the locomotor acitivities were thus assumed to reproduce human FMS. In addition, nocireceptor excitability, intraepithelial fiber density and the tissue localization of putative autoAb and their binding to murine and human NGC after passive transfer, could also be determined. Importantly, normal mice trated with IgG from FMS patients, but neither with IgG-depleted serum from these patients, nor with IgG from HC, exhibited hypersensitivity. Patients IgG bound to NGS. Despite the resort to a proteome-wide microarray screen using 42,000 amino-acid human peptides made of 50-150 amino-acids, their target Ag has still to be identified. Taken together, these finding temtingly suggest that immune dysregulation is implicated.

The autoAb may help in the early detection of FMS, and thereby its early therapy. This improvement does not necessarily imply that they are involved in the pathophysiology. Whatever are the intimate mechanisms, therapeutic interventions would be facilitated. Conceivably, treat-ments could be effective by rituximab-induced depletion of pathogenic B lymphocytes, by reduction of the global level of IgG, using e.g. plasmapheresis, immunoabsorption through a pro-tein A column, or immunoabsorption with protein A. Even better, but requiring identification of the target Ag, should be the selective removing of pathogenic IgG by immunoabsorption. Though being a T cell-mediated autoimmune disease, FMS might benefit from B cell depletion, as was the case for multiple sclerosis.

To conclude, needless to say that, in this rerspect, we have to establish a cause and effect relationship between immunological dysregulation and the development of FMS. It is difficult to achieve, but this is a research area worthy of pursuit in the future.

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