



Autoantibodies in autoimmune liver disease: biomarkers versus epiphenomena

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histopathology obtained in HCV-infected chimpanzees administered with a miR-122-locked antisense oligonucleotide (SPC3649) holds promise for upcoming miRNA-based interventions.²¹

In the infancy of miRNA research in IBS, the pioneering nature of the work now published in *Gut*¹⁹ is acknowledged. Concurrently, and without lessening the merit of the authors, caution is advised when interpreting the significance and applicability of their results. Because this investigation, like the majority of studies in the field, has been conducted in rather small and limited patient populations, the results will have to be replicated in multiple, independent patient populations before being translated into clinical strategies. Therefore, a major challenge lies ahead to determine the true biological importance of miRNAs in human gastrointestinal disorders.

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Autoantibodies in autoimmune liver disease: biomarkers versus epiphenomena

Carlo Selmi,¹ M Eric Gershwin²

Serum autoantibodies have steadily established themselves as critical biomarkers for the diagnosis of autoimmune diseases. This is well illustrated in the case of

primary biliary cirrhosis (PBC) in which antimitochondrial antibodies (AMAs) are a major diagnostic criterion, being both sensitive and specific, despite lacking prognostic significance. The mitochondrial autoantigen was identified >20 years ago¹ and rigorous dissection of the immune response subsequently led to the development of molecular methods to increase the test specificity and sensitivity, and the identification of autoreactive CD4 and CD8 cells. This example of AMAs reminds us that the recognition of an autoantigen can become a milestone in understanding

the disease. This paradigm may well be illustrated in data described in this issue of *Gut* by Terjung and colleagues (*see page 808*). In this report, the authors demonstrate that β tubulin isotype 5 (TBB-5), the atypical pANCA autoantigen, further suggesting that the TBB-5 bacterial precursor FtsZ leads to tolerance breakdown and chronic inflammation.²

The history of autoantibodies reactive with the cytoplasm of neutrophils (ANCAs) has been a difficult and conflicting field. Similar to antinuclear antibodies, ANCAs are a non-uniform family of antibodies recognising diverse cytoplasmic constituents of human neutrophilic granulocytes. Such autoantibodies produce either a cytoplasmic (cANCAs) or a perinuclear (pANCAs) pattern by indirect immunofluorescence.³ Classical pANCAs react with myeloperoxidase and are frequently detected in microscopic polyangiitis, while cANCAs are more specific to patients with Wegener granulomatosis and react with proteinase 3. Classical

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pANCA staining was later demonstrated to be the result of an artefact secondary to ethanol fixation.³ On the other hand, atypical pANCAs are quite unique in their being shared by patients with different autoimmune liver disease (including primary sclerosing cholangitis (PSC) and autoimmune hepatitis type 1 (AIH-1)) or inflammatory bowel disease (IBD), particularly ulcerative colitis, thus proving of limited specificity in the diagnostic process. In the past decade, the atypical pANCA autoantigen was reported to be a 50 kDa neutrophil-specific nuclear protein of the nuclear pore complex,⁴ thus leading to the new nomenclature of perinuclear antinuclear neutrophil antibodies (pANNAs). However, this designation failed to become accepted and only increased the confusion related to this family of autoantibodies. Thus, the data reported in this issue *Gut* by Terjung *et al* prompt the scientific community to find an agreement in defining new terms for these serum biomarkers in liver autoimmunity.³

The implications of the findings of Terjung and colleagues impact on our knowledge of the aetiopathogenesis of IBD and the commonly associated liver phenotype PSC. Indeed, the demonstration of a common autoantigen for this shared biomarker further supports the hypothesis that the primary derangement in IBD-associated PSC occurs within the digestive tract, as well represented by the lack of pANCAs in animal models in a germ-free environment.² However, a puzzling observation is the fact that antibodies directed against TBB-5 and FtsZ are not primarily of the immunoglobulin A (IgA) isotype, as would be expected based on the hypothesis that mucosal immunity is key to the disease pathogenesis. Similarly, one would expect that the innate immunity compartment would play a crucial role in this disease, but data are scanty.

We may infer that changes in intestinal flora secondary to diet and/or nanoparticles may be responsible for the increased incidence of IBD and PSC (but not AIH-1). The working hypothesis illustrated by this study is vigorously supported by evidence that gut-primed lymphocytes constitute liver-infiltrating

mononuclear cells observed in the PSC liver.⁵ However, whether anti-TBB-5 antibodies have a direct impact on the pathogenesis of PSC remains to be determined, and there are several voids. Among these, a major issue remains as to whether PSC and IBD should be considered as autoimmune diseases; autoantibody transfer and/or simulation in animal models is awaited. Similarly, there should be evidence of T cell reactivity against these novel autoantigens and thus evidence for true loss of tolerance. The possible usefulness of these data is based on tubulin-directed treatments that are becoming common in oncology⁶; in this regard it is intriguing that both ulcerative colitis and PSC manifest a significant oncogenic potential and are major risk factors for colorectal and cholangiocellular carcinoma, respectively. The recent discoveries in the growing field of microRNA and autoimmunity⁷ are also expected to provide exciting new developments in the pathogenesis and treatment options for the chronic inflammation observed in IBD and autoimmune liver disease.

At the end of the day, what should we expect as further developments of these data? Should we foresee new practical implications in real-life clinical practice? Some scepticism may prevail, based on the previous negative examples of other liver-specific autoantibodies such as those directed against soluble liver antigens that failed to prove efficient or helpful in the management of patients.⁸ Secondly, the reported similarities in low-titre serum autoantibodies only in subgroups of patients with clinically unrelated conditions such as AIH-1 and PSC/IBD (with the exception of overlap syndromes)⁹ may cast some doubts on the practical use of atypical pANCAs determined with recombinant TBB-5. To determine whether this is related to a limited assay sensitivity or suggests that autoantibodies are mere epiphenomena of chronic inflammation per se constitutes a priority for future studies. Thirdly and similarly, the limited specificity of anti-FtsZ reactivity does not fully support the aetiopathogenetic role of bacteria in determining autoimmune liver diseases or IBD. Fourthly, solid case-

finding and validation studies in a large number of patients are encouraged and the relative rarity of these conditions may warrant multicentre collaborations. We do note a recent genome-wide genetic association study¹⁰ that involved multiple centres, and we suggest that the resources from this multidiscipline approach should continue and provide the large numbers of serum samples required to validate the current observation and future mechanistic studies.

Competing interests None.

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