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Letters to the Editor

Autoimmunity in primary biliary cirrhosis: An alternative view at initiation and function of anti-mitochondrial autoantibodies

To the Editor:

Primary biliary cirrhosis remains a fascinating field of research, and its possible causes have been intensively studied in the past years. Selmi and colleagues [1] provide in their review an update on recent developments in PBC, and based on their own contributions they explain that an environmental insult intervening on a genetic susceptible background precipitates PBC through molecular mimicry. However, in recent years new ideas and models have been developed that may challenge the current paradigm of autoimmunity in general and justify another view of the initiation of PBC. Schwartz and Ziv [2], for instance, present the concept of immunity to self as a maintenance mechanism to protect the integrity of tissue function. Following Matzinger's "danger model" [3], autoimmunity evoked in response to a danger signal is a by-product of a necessary immune response and as such it can be useful, neutral or harmful.

Based on these sound immunological findings, the introduction of the model of "balanced autoimmune surveillance activity" may help to explain some "inconvenient truths" [4] in PBC. Protective and organ-specific autoantibodies may be involved in its pathogenesis. An important argument that AMA fit into this concept is the fact that there is a common evolutionary origin of mitochondria. Because mitochondria are of endosymbiotic origin their proteins represent a transition from prokaryocyte foreign to essential self molecules. AMA can be, therefore, defined as natural autoantibodies of a polyreactive nature. An important feature of natural antibodies is that they contribute to maintenance of immune homeostasis and exert many functions such as clearance of apoptotic cells or selection of immune repertoire [5]. Thus, the exposure of a mitochondrial antigen such as PDC-E2 in PBC is rather supposed to initiate first at early stages an innate and not an adaptive immune response.

To get better insight into the AMA-related pathogenesis of PBC one can look at the two co-occurring diseases, Sjögren's syndrome and scleroderma that express both diagnostic and functional active anti-receptor antibodies. In patients with scleroderma different types of organ specific antibodies are associated with different clinical manifestations such as oesophageal and gastrointestinal dysmotility and tissue fibrosis [6,7]. Furthermore, there is convincing evidence that the glandular hypofunction in Sjögren's syndrome is attributed to the antagonistic action of antibodies to the muscarinic acetylcholine receptor M 3 [8].

Since proliferating bile ducts acquire all phenotypes of neuroendocrine cells [9] it seems very likely that cholangiocyte-specific anti-receptor antibodies are also induced in patients with PBC. Indeed, one even might define PBC as a neuroendocrine autoimmune disease.

The concept of the maintenance function of innate immune system would be also applicable to the different courses of PBC. This means that under normal non pathological conditions, the immune system supports the structural and functional integrity of cholangiocytes. In contrast, overactivation of the self specific immune activities would underlie the loss of bile duct maintenance leading to the eruption of autoimmune disease. Reflecting this kind of surveillance function asymptomatic, symptomatic and progressive courses become easily understandable.

Macroautophagy induction has to be also considered as a pathway in innate and adaptive immunity [10] since apoptotic stimuli target mitochondria for degradation by autophagy. Danger signals may also activate the caspase cascade via the pro- and anti-apoptotic Bcl-2 family [11]. Certainly, the question about the nature of the so called danger signals cannot be answered. Following Plotz's view [12] one could argue that the xenobiotic modified PDC-E2 antigen is especially chemoattractive for immature dendritic cells and will be readily exposed to cells of the innate and adaptive immune system. The process of apoptosis influences the presentation of the different intracellular antigens. Integrity of cholangiocytes may, therefore, depend upon the balance of

protective (proliferative) and destructive (apoptotic) mechanisms. Thus, natural occurring autoantibodies may stimulate or inhibit apoptosis by interfering with Bcl-2 proteins or with the large family of transmembrane receptors. This theoretical concept is convincingly backed up by recent findings that UDCA can prevent apoptosis by reducing the apoptotic threshold through modulation of the classical mitochondrial pathway [13].

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What is the actual role of diagnosis and how to assess it?

To the Editor:

We read with interest the paper by Mehta et al. [1] that reported that due to imperfection of liver biopsy as a reference standard it is not possible to estimate the accuracy of a non-invasive test for the diagnosis of liver fibrosis. However, we would like to challenge some points raised.

Diagnosis cannot be regarded as a primary outcome but alternatively can be represented as a decisional node.

The identification and staging of a disease (diagnosis) should support the decision to treat a patient or not. The utility of diagnosis derives from the benefits of this decision. Thus, in the context of liver disease, patients with severe fibrosis have a worse prognosis and those with significant fibrosis fare better with treatment. The identification of these subgroups is useful and allows the definition of their prognosis and initiation of effective treatment, but these differences in prognosis and benefits of treatment have widely been evaluated using exclusively histological definition, even if imperfect. Actually, no diagnostic test can be regarded as perfect and thus there are no longer "gold" but only reference standards. The limitations of liver biopsy are well known; the most important being the high percentage of false-negative results yielded in the cases of significant or severe fibrosis.

In the study by Mehta et al. there is an implicit assumption that the prognosis and the response to treatment in patients with false-negative results at histology are actually the same as in those with true-positive results. This assumption has still to be unequivocally proved. So far, it has not been possible to assume that non-invasive fibromarkers are more useful only for the merit of reducing the false- negative rate of histology. In fact, only the assessment of the prognosis of patients with discrepant results (between histology and fibromarkers) could define their actual advantage.

An unequivocal demonstration would entail a randomized controlled trial comparing hard clinical outcomes in patients in which the diagnosis of significant or severe fibrosis was obtained either by histology or by non-invasive fibromarkers.

Furthermore, the analysis by Mehta et al. is limited to the overall accuracy and AUC assessment: these are two diagnostic measures of true results, but no information can be derived on false-positive or -negative results. However, the clinical utility of a diagnostic test depends on false-negative and positive rate (i.e. on sensitivity and specificity).

Finally, Mehta et al. [1] seem to conceive possible alternatives to liver biopsy only in the form of a sin-