Reply to: Diagnostic role of anti-dsDNA antibodies: do not forget autoimmune hepatitis

David S. Pisetsky and Peter E. Lipsky

As Granito and colleagues correctly highlight in their correspondence (Granito, A., Muratori, L., Tovoli, F. & Muratori, P. Diagnostic role of anti-dsDNA antibodies: do not forget autoimmune hepatitis. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-021-00573-7 (2020))[1] on our Review (Pisetsky, D. S. & Lipsky, P. E. New insights into the role of antinuclear antibodies in systemic lupus erythematosus. *Nat. Rev. Rheumatol.* **16**, 565–579 (2020))[2], anti-DNA antibodies, among other antinuclear antibodies (ANAs), occur prominently in autoimmune hepatitis. ANAs and other serological markers enable the division of autoimmune hepatitis into two types that differ in clinical course[3–7]. ANAs and anti-SMA antibodies are markers for type 1 autoimmune hepatitis, whereas anti-LKM1 antibodies are markers for type 2 autoimmune hepatitis[8].

Patients with type 1 autoimmune hepatitis produce ANAs that recognize many nuclear antigens (including histones, centromeres and ribonucleoproteins), but the expression of anti-DNA antibodies is perhaps the most surprising. Anti-DNA antibodies are a serological criterion for classification for systemic lupus erythematosus (SLE) as well as a marker of disease activity, particularly renal disease[9]. In SLE, anti-DNA antibodies can form immune complexes that are deposited in the kidneys and induce nephritis; these complexes can also stimulate the production of cytokines, including type I interferons, that promote widespread immune abnormalities[2]. In autoimmune hepatitis, anti-DNA antibodies do not seem to have the same consequences[8].

The expression of anti-DNA antibodies in both SLE and autoimmune hepatitis raises important questions about the putative role of anti-DNA antibodies in disease manifestations. Although characterizing the fine specificity of anti-DNA antibodies is complicated because of the size and structural complexity of DNA[9], the anti-DNA antibodies in autoimmune hepatitis can be detected using the same assays as for those in SLE[3–5]. The behaviour of anti-DNA antibodies from patients with autoimmune hepatitis in these assays suggests that these antibodies are bona fide anti-DNA antibodies and have binding properties similar to those in SLE.

The expression of anti-DNA antibodies in autoimmune hepatitis and SLE provides an opportunity to consider the role of these antibodies in pathogenesis and the reasons for differing pathologies in these conditions. Unlike in SLE, the role of anti-DNA antibodies, or other ANAs, in autoimmune hepatitis is unclear. Nevertheless, it is possible that these antibodies bind to hepatocytes in some way and cause cell death or injury: a mechanism that does not seem to pertain to SLE.

The absence of certain clinical and laboratory features in autoimmune hepatitis is also notable. Activation of complement does not seem to be common in autoimmune hepatitis[10], although disturbances in complement often occur in SLE concomitant with increased anti-DNA antibody levels. Glomerulonephritis is also not a manifestation of autoimmune hepatitis, raising the question of why anti-DNA antibodies can lead to nephritis in SLE but not in autoimmune hepatitis; perhaps a relevant source of DNA to form immune complexes is lacking in autoimmune hepatitis. On the basis of these interesting considerations, we appreciate the comments of Granito and colleagues[1] because they suggest that comparative studies of anti-DNA antibodies in SLE and autoimmune hepatitis might provide novel insights into the origin of these antibodies and their role in pathogenesis.

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Competing interests
The authors declare no competing interests.