Letters to the Editor

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4-Hydroxynonenal-modified Ro 60 autoantigen accelerates autoimmunity in experimental animals

SIR, We read with interest the review article entitled ‘Consequence of neo-antigenicity of the ‘altered self’’ [1], where the authors discuss the importance of oxidation-specific protein adducts in plasma membranes. We would like to point out that we have also shown the importance of 4-hydroxynonenal (HNE), a lipid peroxidation by-product, modified Ro 60 (SS-A) autoantigen in the rapid development of autoimmunity in an animal model of SLE [2] and the role of oxidatively modified proteins in autoimmune diseases [3]. Ro 60 RNP is a common target of autoantibodies in both SLE and SS. This structure is made up of a 60 kDa protein non-covalently associated with at least one of four short uridine-rich RNAs (the hY RNAs) [3, 4]. These hY RNAs are also associated with the 48 000 molecular weight La (or SS-B) autoantigen. Anti-Ro is found in 25–40% of patients with SLE, while anti-La is found in substantially fewer patients [3, 4].

Tolerance against Ro 60 and other autoantigens was abrogated faster and more strongly in the HNE-Ro 60-immunized animals compared with the Ro 60-immunized animals. Immunization with HNE-modified Ro 60 induced a rapid intramolecular epitope spreading (within the Ro 60 molecule) and a rapid inter-molecular epitope spreading to other autoantigens. Such a scenario envisages developing antibodies to 60 kDa Ro and thus autoimmunity to the entire Ro RNP particle after an initial immune response to oxidized Ro 60.

We studied oxidative modification of Ro 60 since we and others observed free radical mediated peroxidative damage in SLE and other diseases [5–9]. Significantly higher HNE-modified protein levels have been found to occur in children with SLE [7].

Thus, we believe that oxidative modification of proteins is important in the generation of autoantibodies and thus brings about autoimmunity.

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Rheumatology key message

• Oxidatively modified proteins, in their capacity as neoantigens, may play an important role in initiating autoimmunity.

Disclosure statement: The authors have declared no conflicts of interest.

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Rheumatology key message

• SSZ should be monitored every 2 weeks during the first 6 weeks of therapy.

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SIR, A 49-yr-old nulliparous Caucasoid lady presented with a several week history of florid oral ulceration, malaise, weight loss and fever. There was no rash, photosensitivity, arthralgia, alopecia, RP, headache, ocular disturbance or recent foreign travel. Past medical history included hypothyroidism associated with thyroxine, bacterial meningitis at the age of 21 and 27 yrs and anti-thyroid microsomal antibodies for which she was taking thyroxine.

Mean cell volume 92.1 fl, white cell count 5 × 10⁹/l, platelet count 248 × 10⁹/l. Renal function, creatinine phosphokinase and immunoglobulin levels were normal. Liver function tests were abnormal: aspartate transaminase 219 IU/l (0–31), alanine transaminase 117 IU/l (0–31), γGT 331 IU/l (2–30), alkaline phosphatase 177 IU/l (30–130), bilirubin 6 µmol/l (0–17) and albumin 27 g/l (33–47). Hepatitis B surface antigen, hepatitis C antibody, HIV serology were negative and viral studies for CMV, Epstein–Barr virus, Herpes simplex virus and parvovirus did not indicate acute infection. ANAs (1 : 320), anti-Ro antibodies (>100 u/ml, normal range 0–20) and anti-thyroid microsomal antibodies were positive. Anti-double-stranded DNA, aCLs, ANCA, anti-mitochondrial and anti-liver/kidney microsomal antibodies were negative. Percutaneous liver core biopsy showed mild mononuclear cell infiltrate in the portal tracts, moderate interface hepatitis and focal necrosis and hepatocyte apoptosis within parenchymal areas, features consistent with autoimmune hepatitis.

Whilst C3 and C4 levels were normal, total complement haemolytic activity (CH50) was repeatedly absent indicating possible complement deficiency state. Reconstitution assays were performed in which sera with selective defects of complement components or subunits were mixed with the patient sera and the haemolytic activity of the resultant mixture measured (Table 1). Serum deficient in either the C8β subunit of the C8 protein or the classical pathway component C1q did not restore haemolytic activity to the patient’s sera. Normal CH50 was only restored following the addition of both C8 and C1q to the patient’s sera. Antigenic assays confirmed complete absence of both C8β and C1q in our patient (Table 1). The genetic basis of the C8β...