Letter

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Tissue distribution and biological activities of immune complexes are determined by their size and composition

Sir,

In addition to factors considered by Barratt et al. [1], the variations in size and composition of IgA1-containing immune complexes affect their properties. This characteristic may be manifested especially during flares of macroscopic haematuria in IgA nephropathy (IgAN) patients coinciding with acute mucosal infection (‘synpharyngitic’ haematuria) [2]. In IgAN patients, circulating immune complexes are composed of polymeric galactose-deficient IgA1 (Gd-IgA1; auto-antigen) and anti-glycan antibody (IgG and/or IgA1). Such complexes contain polymeric IgG1, display high molecular mass ~800–900 kDa and stimulate proliferation of cultured human mesangial cells [2]. In contrast, immune complexes with Gd-IgA1 but of smaller molecular mass do not stimulate proliferation of mesangial cells. Therefore, we hypothesize that circulating immune complexes of different sizes and/or composition are formed in flares of IgAN and in quiesence. Generally, molecular mass of immune complexes depends on the concentration ratio of the antigen and the antibody. Sera of IgAN patients contain higher levels of free IgG specific for Gd-IgA1 than do the sera of healthy individuals [3]. Therefore, in a chronic stage of IgAN, IgA1-containing immune complexes may be formed in a relative excess of antigen versus antibody. Such complexes are smaller in size and are more easily eliminated from the circulation by a predominantly physiological mechanism, i.e. hepatic clearance due to interaction with the asialoglycoprotein receptor (ASGPR) on hepatocytes [4]. However, if an increased amount of Gd-IgA1 is formed during an infection and enters the circulation, the concentration ratio between the antigen and the antibody changes. We hypothesize, based on the analogy of acute serum sickness [5], that large, nephritogenic Gd-IgA1-containing immune complexes are formed. Due to their size, they are too big to enter the space of Disse with endothelial openings ~200 Ǻ to reach the ASGPR but are able to pass through the larger fenestrae of endothelial cells in the glomerular capillaries (500–1000 Ǻ) to deposit in the mesangium. Consequently, the structure and size of the deposited complexes changes. Due to their biological activity, these large immune complexes with the ability to activate complements, attract macrophages, etc. [5] start the chain of pathogenic events to induce the acute injury of a mesangio-proliferative glomerulonephritis.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part. The authors have no conflict of interest to declare.


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Letters and Replies

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Persistent alpha-Klotho (a-Kl) expression in the parathyroid glands of patients with secondary hyperparathyroidism

To the editor:

Alpha-Klotho (a-Kl) was identified as a gene associated with premature aging-like phenotypes characterized by a short lifespan. Sugiura suggested that Klotho is involved in the pathophysiology of renal ischaemia–reperfusion injury and mitigates apoptosis in experimental ischaemic