Is tissue factor a mediator of fibrin deposition in glomerular pathology?

Sir,

Coagulation activation and fibrin deposition have been associated with inflammatory glomerular diseases in man and laboratory animals. Fibrin deposition has been observed within and around the glomerulus and is thought to play a major pathogenetic role in the development and the progression of the disease [1,2].

Glomerular epithelial cell proliferation has been favoured as a possible cause of local coagulation activation [3]. However, it has been suggested that the source of glomerular procoagulant activity (PCA) in glomerular pathology could either be blood or resident glomerular cells. Of the inflammatory cells that infiltrate glomeruli, lymphocytes and neutrophils exhibit no PCA [4]. On the other hand, glomerular fibrin deposition (GFD) is dependent on leukocyte accumulation [5]. When rabbits are treated with muscle-hydrochloride they develop severe leukopenia. This prevents glomerular macrophage accumulation and GFD without any functional alteration of the host coagulation factors [5].

Mononuclear cells are known to be a potent source of PCA. Increased expression of PCA by monocytes or macrophages in several inflammatory conditions is an established phenomenon [4]. Similarly, isolated glomeruli from humans and animals with some forms of glomerular disease express high levels of PCA [6]. Both mononuclear and intrinsic glomerular cells from cultured isolated glomeruli were shown to express increased PCA [6,7]. Macrophage accumulation progressively declined and eventually disappeared as the glomerulonephritis (GN) phase resolved [7]. This suggests that the PCA is mainly derived from infiltrating mononuclear leukocytes and intrinsic glomerular cells.

The generated in renal disease was initially thought to activate the extrinsic pathway of the coagulation cascade via at least three different mechanisms: (i) tissue thromboplastin or factor VIIa—neither of these components alone has any PCA [8], (ii) prothrombinase and (iii) platelet factor III. The haemostatic system has recently seen recognition of tissue factor (TF) pathway inhibitor, which has led to a revised understanding of the blood coagulation cascade. Coagulation can only significantly proceed through a TF-dependent pathway. TF is a single-chain integral plasma membrane glycoprotein. It forms a complex with factor VIIa/VIIa with the subsequent activation of both factors X and IX. Thus, TF is the primary trigger of thrombin generation and fibrin formation [8]. In glomerular disease this is supported by: (i) the exclusion of the involvement of factor VIII in GFD [9], (ii) the correlation between TF in glomerular supernatants and thromboxane B2 formation in platelets [10] and (iii) the increase in antigenic TF level in animals with induced-GN [11]. Therefore, irrespective of the source, it is reasonable to suggest that TF is the primary trigger of fibrin formation in GN-associated GFD.

In patients with GN, TF is also liberated in urine where levels are thought to be clinically important, particularly in those with immune-complex GN [12].

In conclusion, TF is implicated in glomerular pathology. Achievements in developing therapeutic measures have been modest. Manipulation of clotting activity through TF expression may have an impact in managing patients with glomerular disease. Understanding the mechanisms leading to abnormal TF expression might lead to strategies for reducing and/or preventing its induction in these conditions. It is an area, which warrants further investigation.

University Department of Haematology
Southampton University Hospitals
Tremona Road
Southampton
U.K.