PLA2 receptor autoantibodies, complement activation and podocyte damage

Sir,

The finding of autoantibodies to M-type phospholipase A2 receptor (PLA2R) in membranous nephropathy [1–3] still calls into question as to whether they are truly pathogenic and elucidation of downstream signalling pathways may help in further understanding of the cause(s) of podocyte damage.

Augert et al. had shown that activation of PLA2R generates arachidonic acid and reactive oxygen species (ROS) that mediate oxidative damage to DNA. PLA2R activation and subsequent DNA damage was also shown to be p53 dependent [4]. In the subset of patients with membranous nephropathy and undetectable PLA2R autoantibodies, activation of the complement pathway may be more relevant particularly as sublytic quantities (<5%) of the membrane attack complex (C5b-9) led to increased levels of p53 and DNA damage in the mouse model [5]. Immunohistochemical detection of C5b-9 complex or neoantigen deposition in membranous nephropathy and correlation with proteinuria may prove useful in future studies, as have some reports showing 71–78% positivity of anti-PLA2R antibodies with presence of proteinuria and elevated serum creatinine at baseline.

A working hypothesis based on current evidence would be that autoantibodies to PLA2R lead to ROS generation, continuous p53 activation, DNA damage and IgG1/IgG4 subclass that is capable of complement activation adds a positive feedback loop for more podocyte damage.

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