

Uteroglobin deficient mice—a novel animal model for IgA nephropathy?

Zheng F, Kundu G, Zhang Z, *et al.* Uteroglobin is essential in preventing immunoglobulin A nephropathy in mice. *Nat Med* 1999;5:1018–25.

Abstract

The molecular mechanism(s) of immunoglobulin A (IgA) nephropathy, the most common primary renal glomerular disease worldwide, is unknown. Its pathologic features include hematuria, high levels of circulating IgA-fibronectin (Fn) complexes, and glomerular deposition of IgA, complement C3, Fn and collagen. We report here that two independent mouse models (gene knockout and antisense transgenic), both manifesting deficiency of an anti-inflammatory protein, uteroglobin (UG), develop almost all of the pathologic features of human IgA nephropathy. We further demonstrate that Fn-UG heteromerization, reported to prevent abnormal glomerular deposition of Fn and collagen, also abrogates both the formation of IgA-Fn complexes and their binding to glomerular cells.

Moreover, UG prevents glomerular accumulation of exogenous IgA in UG-null mice. These results define an essential role for UG in preventing mouse IgA nephropathy and warrant further studies to determine if a similar mechanism(s) underlies the human disease.

Comment

IgA nephropathy (IgAN) is the commonest form of glomerulonephritis worldwide. It is characterised by recurrent haematuria, proteinuria, and mesangial deposits of polymeric IgA1.¹ Despite extensive research its aetiology remains elusive. This arises in part from the absence of good animal models because of the significant differences between the IgA immune system in humans and animals. The structure of human IgA1 has no parallel and IgA clearance mechanisms, systemic and mucosal compartmentalisation, and handling differ across the species. Animal models have provided useful information on the role of antigen-antibody complex associated nephropathies and the progression of immune mediated glomerular damage. The pathogenesis of human IgAN however is more complex than that involved in these models. Therefore, although animal models have been informative about events after IgA deposition has occurred, lessons about the prime mechanism of mesangial IgA deposition have been largely inferred from human studies.²

Uteroglobin knockout mice represent an exciting new model for glomerulopathies.³ Uteroglobin (UG) is a steroid inducible multifunctional protein, secreted by mammalian mucosal epithelia in the bronchi, uterus, and prostate. It is detectable in blood and urine although it is not synthesised in the kidney. It is thought to be a potent endogenous immunomodulatory and anti-inflammatory protein, especially through its inhibitory effects on phospholipase A2. Scientists have used molecular biological techniques to shed light on its physiological roles.⁴ Zheng *et al* at the NIH have developed two independent mouse models: a knockout mouse where the UG gene is disrupted, and an antisense transgenic mouse where UG production is suppressed by expression of a UG antisense RNA.³ Both models produced an unexpected phenotype. The UG^{-/-}, UG^{+/-}, and AS-UG mice had nephrotic syndrome, haematuria, and glomerular fibronectin (Fn), collagen, IgA, and complement C3 deposits. This was significantly different from results in control mice with no UG deficiency. Renal histology showed hypocellular glomeruli with striking eosinophilic deposits, parenchymal fibrosis, and tubular hyperplasia.⁵ UG gene disrupted mice had high circulating IgA-Fn complexes, and addition of UG prevented mesangial deposition of IgA in vivo and IgA-Fn binding to cultured mesangial cells. UG null mice also demonstrated higher PDGF mRNA when treated with IgA and Fn compared with the wild type litter. The authors concluded that UG in mice prevents the development of a glomerulopathy characterised by Fn, collagen, and IgA deposition. They hypothesised that in health there is a balance between levels of UG, IgA, and Fn, and that the high affinity binding UG to Fn prevents IgA-Fn complex formation. If this balance is altered, UG deficiency promotes IgA-Fn complex formation and mesangial binding, which stimulates inflammatory cytokine production and renal damage.

Are the models generated by the NIH group a new breakthrough for IgAN research? The UG transgenic mice are clearly an extremely exciting and valuable model of experimental glomerulopathy involving a hitherto unexplored physiological role for UG in the prevention of renal glomerular disease. However, despite inducing IgA deposition by UG abrogation, UG transgenic mice fall short of the human IgAN model in a number of ways. Unlike UG knockout mice, patients with IgAN normally present with haematuria and nephritis, and nephrotic syndrome is an unusual presenting feature.⁶ Circulating IgA-Fn complexes which were once thought to be diagnostic of IgAN are now considered not specific to the condition and IgA binding of Fn may even be a normal process.⁷ The histological features of glomerular hypocellularity with large Fn and collagen deposits are atypical of IgAN and as such the model bears more resemblance to Fn deposition glomerulopathy.⁸ Whether similar mechanisms involving UG deficiency underlie human IgAN remains to be seen and studies investigating the role of UG in these patients will be eagerly awaited. The model nevertheless presents

researchers with an exciting new tool for exploring novel factors involved in IgA and ECM component deposition in the glomerulus and the initiation of inflammatory damage.

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