

Is Heparan Sulfate in the Glomerular Basement Membrane Necessary for the Etiology of Diabetic Nephropathy?

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Heparan sulphate (HS) is a negatively charged glycosaminoglycan covalently attached to a core protein to form a heparan sulfate proteoglycan (HSPG). HSPG is widely expressed on the cell surfaces as well as in the extracellular matrix, and interacts with variety of proteins to perform many biologically important processes. We recently generated systemic knockout mice of *Extl3*, which encodes N-acetylglucosamine transferases involved in the HS chain initiation/elongation, and observed that the mice were embryonic lethal at around 9 days postcoitum [1], indicating the necessity of HS for the embryonic development and survival. We also observed that pancreatic β -cell specific *Extl3* knockout mice demonstrated abnormal islet morphology, impairment of β -cell proliferation, and impaired glucose-induced insulin secretion [1], suggesting the involvement of HS in the etiology of diabetes mellitus.

Diabetic nephropathy (DN), a major complication of diabetes mellitus, is the leading cause of end-stage renal disease throughout the world, and the elucidation of its etiology is urgently necessary. In patients with DN, loss of HSPG in glomerular extracellular matrices has been reported [2]. Additionally, both the urinary and plasma levels of heparanase, an endoglycosidase that specifically cleaves HS side chains of HSPG, have been reported to be elevated in type 2 diabetic patients [3]. Moreover, an increased urinary heparanase activity was observed in both type 1 and type 2 diabetic patients with proteinuria [4]. Consistent to these clinical observations, gene disruption of heparanase protected the streptozotocin-induced diabetic mice from DN [5], while overexpression of heparanase resulted in the increase of urinary protein [6]. Therefore, the decrease of the anionic charge barrier due to the loss of HS in the glomerular basement membrane (GBM) may possibly be one of the major causes of albuminuria in DN [7].

However, several reports have demonstrated controversial observations. Agrin is reported to be the pre-dominant HSPG in the GBM, and is recognized as the main source of the anionic charge barrier [8]. Although podocyte-specific knockout mice of agrin resulted in the significant loss of HS in the GBM, their urinary protein levels were demonstrated to be almost equivalent to those of control mice [9]. Additionally, podocyte-specific knockout mice of *Ext1* gene, that encodes the polymerase responsible for HS biosynthesis, did not result in a significant increase of urinary protein comparing with control mice [10]. However, although not significant, the urinary albumin level in *Ext1* knockout mice was observed to be much higher than that in control mice [10], suggesting the involvement of GBM HS in the etiology of albuminuria. Additionally, since these experiments using agrin and *Ext1* knockout mice were performed in the absence of diabetes, they may possibly be inadequate to examine the etiology of DN. Further studies are needed to elucidate the significance of GBM HS in the etiology and progression of DN.

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