A breakthrough in diabetic nephropathy: the role of endothelial dysfunction

Takahiko Nakagawa1, Mark Segal1, Byron Croker2 and Richard J. Johnson1

1The Division of Nephrology, University of Florida, Gainesville FL 32610 and 2Pathology and Laboratory Medicine Service, North Florida/South Georgia Veterans Health System, and Department of Pathology, Immunology and Laboratory Medicine, University of Florida, Gainesville, FL 32608, USA

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Summary of key findings
Kanetsuna et al. [1] have published an important paper in the American Journal of Pathology, reporting that renal lesions resembling human diabetic nephropathy can be induced in mice made diabetic (with streptozotocin) which genetically lack endothelial nitric oxide synthase (eNOS). eNOS is a key enzyme in endothelial cells that produces nitric oxide (NO). In turn, NO has multiple functions in the vasculature, including acting as a vasodilator, anti-inflammatory, anti-thrombotic and anti-proliferative activities. In this study, diabetic eNOS knockout mice developed both renal functional (proteinuria, reduced glomerular filtration rate) and structural changes consistent with human diabetic nephropathy. Up to now, it has been difficult to develop in mice models of diabetic nephropathy that resemble human disease, so this article represents a breakthrough in the pathogenesis of diabetic nephropathy.

Review of the field
Diabetic nephropathy is currently one of the most serious complications of longstanding diabetes and has emerged as the most common cause of end-stage renal disease worldwide [2]. Despite our best efforts, 20 to 40% of subjects with type I diabetes and as many as 40% of subjects with type 2 diabetes [3] will develop this complication, typically 10 to 15 years after the onset. Numerous studies have been performed to identify why diabetic nephropathy develops in certain individuals but not in others. In this regard, the development of microalbuminuria [4] has been considered of most significance. Others have proposed that there may be a specific 'nephropathy' gene that could account for why some individuals develop diabetic nephropathy, whereas others remain free of this complication [5]. Unfortunately, the lack of a good murine model of human diabetic nephropathy has hampered progress towards an understanding of the pathophysiological changes that are required to induce the fully developed diabetic renal lesion.

Classically human diabetic nephropathy is characterized early, by thickening of the basement membrane and by mesangial expansion [6]. In more severe disease, frank mesangiolysis, microaneurysm and nodule formation can occur, often with local fibrin deposition [7]. These late changes are less commonly observed, with better blood sugar and blood pressure control, as compared with studies performed decades ago [7–9]. It has been well described that these lesions can be largely prevented when control of blood sugar, blood pressure and inhibition of the renin angiotensin system can be achieved [10]. However, if the mechanisms leading to these changes were better understood, it is possible that more targeted therapies could be developed.

Most mouse models of diabetic nephropathy can reproduce some of the changes of human diabetic nephropathy, especially the basement membrane thickening and mesangial matrix expansion. However, there are few models that develop full blown diabetic nephropathy with hypertension, proteinuria, chronic kidney disease (CKD), vascular lesions and mesangial nodule formation. Most of these latter models involve inducing diabetes in a hypertensive mouse model, and the lesions generated...
rarely resemble the full blown human diabetic nephropathy. As a consequence, the National Institutes of Health developed a multicentre consortium, to try to develop a murine model that better resembles the human disease.

Recently it has been appreciated that endothelial dysfunction is common in subjects with diabetic nephropathy [11]. Specifically, it has been shown that diabetic subjects with renal disease often have an impaired release of NO, which is a key vasodilator involved in keeping the endothelium healthy. In animal models of CKD and arteriosclerosis, blocking endothelial NO leads to an increase in microvascular disease [12,13], known to impair renal autoregulation [14]. In addition, endothelial dysfunction has also been shown to lead to an uncoupling of the vascular endothelial growth factor (VEGF)-nitric oxide axis resulting in enhanced proinflammatory and proliferative effects of VEGF (Figure 1) [15–17].

The possibility that this ‘endothelial dysfunction’ is the missing second factor in human diabetic nephropathy is now supported by the recent publication of three papers, which all report that eNOS knockout mice with diabetes (either type 1 or 2) develop lesions similar to that observed in human diabetic renal disease [1,16,18]. Mice develop not only basement membrane thickening and mesangial expansion, but also vascular lesions, mesangiolysis, microaneurysms, nodules, proteinuria and CKD (Figure 2) [1,16,18]. Interestingly, simple blood sugar control with insulin will block both the hypertension and renal injury [1,16]. Historically, scientists had not considered that blood sugar control might also prevent the development of hypertension, but there is increasing evidence that hypertension is largely mediated by subtle renal injury and inflammation [19].

**What is in it for the practicing nephrologist?**

These studies should ignite the field to determine what mechanisms account for the endothelial dysfunction in human diabetic renal disease, and whether this might represent a new target for preventing diabetic complications. For example, it has recently been shown that endothelial progenitor cells from...
diabetic subjects also have a migratory defect due to a relative absence of NO [20]. Various potential mediators need to be investigated, including the role of oxidative stress, the presence of asymmetric dimethyl arginine (an eNOS inhibitor) and uric acid. Investigation of the mechanisms of endothelial dysfunction and for means to reverse these changes might lead to new breakthroughs in this important medical condition.

**Take home message**

New studies in animal models suggest that endothelial dysfunction may represent a key risk factor for the development of nephropathy in diabetic patients. Future studies investigating the role of endothelial dysfunction in human diabetic nephropathy are needed.

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**References**


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