The Proximal Tubule in Progressive Diabetic Nephropathy: Are Tubular Polyamines a New Paradigm for Developing Therapies?

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The World Health Organization estimates that by 2030, 350 million people will have diabetes. Type 1 Diabetes (T1D) usually strikes children and young adults, but disease onset can occur at any age.

Diabetes is the leading cause of End-Stage Renal Disease (ESRD), a life-threatening condition that requires patients to undergo dialysis or transplantation to survive. Even though a declining incidence rate of ESRD has been reported [1], some epidemiological issues have been raised by others [2] to question this assumption. In any case, the long-term prognosis of T1D patients with ESRD is still considerably worse than for individuals without diabetes.

The development of new treatment options for diabetes-related comorbidities which include ESRD is in increasing need. Trials have focused on the importance of glycemic or hypertensive control, in order to obtain positive outcomes. However, spikes of hyperglycemia or large fluctuations of blood glucose levels in diabetic patients are common. Thus, it is more difficult to evaluate benefits of conventional or new therapies in the context of poor or unpredicted glycemic control.

What are the targets to accomplish an effective therapy? Among all cell populations in the kidney, the glomerular endothelium on the one hand and the tubular epithelium on the other hand represent the main components of diabetic renal injury and both are involved in the progression of Diabetic Nephropathy (DN). As such this gave rise to a vascular and a tubular hypothesis of disease progression, as pointed out below.

Vascular Hypothesis

Endothelial Dysfunction (ED) represents a key mechanism in the onset and progression of cardiovascular and renal complications of T1D patients. The hallmark of hyperglycemia-induced ED is the impairment of endothelial Nitric Oxide Synthase (eNOS), causing reduction of NO levels and an exaggerated generation of Reactive Oxygen Species (ROS). The disruption of the glomerular barrier is considered a major determinant of diabetic urinary albumin leakage [3]. The relevance of the glomerular endothelium for the maintenance of barrier function has only been recently recognized [4]. Moreover, NO generation has been proposed to contribute to glyocalyx and endothelial barrier preservation and prevention of albumin permeability [3-8].

Since the 1980s, many studies have linked the occurrence of albuminuria with a higher risk for cardiovascular morbidity and mortality [9-12], which has been confirmed by recent reports [13-14]. This evidence points toward the importance of the glomerular endothelium as a primary target for therapies limiting progression of ESRD and mortality.

Are conventional therapies such as ACE inhibitors, angiotensin-receptor blockers and PKC inhibitors conferring protection to the kidney through effectively preserving glomerular endothelial integrity? What are the advantages of these therapies over the pleiotropic actions of statins? Studies in subjects with kidney disease suggest that the progression of kidney dysfunction may be halted with statin therapy, at least in early stages of chronic kidney disease [15].

Recently, an emerging role of endothelial arginase has been associated with a high catabolic state of L-arginine in diabetes, indicating that therapeutic strategies limiting up-regulation of this enzyme would be beneficial in reducing diabetes-induced endothelial dysfunction [16-18]. However, the clinical usefulness of specific arginase inhibitors, which are not yet available, to control endothelial arginase activity remains to be demonstrated. In spite of promising results with inhibition of arginase activity in rodent models of diabetes [17,18], the use of arginase inhibitors may be somewhat limited due to the possible disruption of the hepatic urea cycle [19] and the suppression of renal arginase 2 function, essential for polyamine homeostasis and PT cell integrity and function [20,21].

Tubular Hypothesis

Diabetes-induced tubular hypertrophy is also thought to be responsible for early harmful hyperfiltration that initiates kidney damage and albuminuria, progression of kidney fibrosis and decline in kidney function. These are indications that, in early diabetes, hyperfiltration occurs independently of any primary malfunction of the glomerular microvasculature and that renal tubular hypertrophy is linked to hemodynamic adaptation of the diabetic kidney [22-24].

Emerging evidence indicates an important role of PT cells in progression of kidney damage. Grig et al. [25] have identified that selective PT epithelial injury can drive the formation of interstitial fibrosis, capillary rarefaction, and potentially glomerulosclerosis, substantiating a direct role for damaged tubule epithelium in the pathogenesis of chronic kidney disease. This is an interesting observation which may potentially pertain to DN. The PTs are at high risk of damage under the constant insult maintained in the diabetic milieu, especially in patients with poor glycemic control. Damaged PTs undergo an extensive repair process, either by regeneration of dedifferentiated surviving cells [25-28] or by proliferation and differentiation of stem cells [29]. Polyamines (PA) may be important for this repair process. Despite some reports that link PA to kidney hypertrophy [23,24], depletion of PA has been shown to cause disruption of epithelial adherens junctions and to enhance TGFβ-induced epithelial-to-mesenchymal transition, substantiating

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the beneficial involvement of PA in epithelial PT cell regeneration and function [20,30-32].

In conclusion, it is extremely important to understand the molecular mechanisms regulating tubular epithelial homeostasis and repair in diabetes, and other kidney injuries. This information is necessary to identify molecular targets and to develop new therapies toward preservation of PT function.

The hope of the majority of T1D patients resides on cell-based treatment, however there are still significant challenges to overcome before this therapy is available.

References


