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PODOCYTES IN DIABETIC NEPHROPATHY

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ABSTRACT

Diabetic Kidney Disease (DKD) is a major public health problem. Diabetes is on the rise and is the leading cause of end-stage kidney disease in the United States. Diabetic nephropathy involves glomerular proteinuria. Podocytes are ultimately differentiated, specializing in blood cells that are essential for maintaining glomerular filtration. Podocyte deficiency has been identified as a major cause of kidney disease, glomerulosclerosis, and loss of kidney function. This review describes the weakening of podocytes due to cell loss and cell death. Many mediators, such as TGF-b and angiotensin-II, have profound effects on diabetic nephropathy podocytes and also focus on the role of podocytes in kidney disease.

Keywords: Diabetic Kidney Disease, Podocyte, Glomerulosclerosis, Mediators

INTRODUCTION

Diabetic kidney disease (DKD) is a degenerative disease caused by diabetes and causes more than 40% of new end-stage renal disease (ESKD). It is the leading cause of renal disease in the United States [1]. A 30% to 40% of diabetics develop DKD, and most cases associated with type 2 diabetes are the most common type of diabetes [2]. Due to the prevalence of T2DM, these patients are the most common cause of DKD and make up the majority of diabetics undergoing dialysis [3]. Glycemic control, high blood pressure, smoking, and family history increase the risk of nephropathy [4-7]. Diabetes causes a change in kidney function, including hyperfiltration, albuminuria, and decreased glomerular filtration rate (GFR). At the hospital, DKD was diagnosed with albuminuria in patients with a history of diabetes [8-10].

Albuminuria is not only the first symptom of diabetic nephropathy, but it is also associated with an increased risk of heart disease and stroke and is the best vision for reducing GFR [11-12]. However, approximately 30% of patients with DKD do not develop albuminuria [13]. The risk of developing DKD is strongly correlated with the duration of diabetes [14]. Historical changes in the glomerulus were specific to diabetes and could be used to diagnose DKD. Primary glomerular changes are associated with the thickness of the underlying membrane that accompanies vascular disease and sickle cell disease [15,16]. Glomerulosclerosis is associated with central fibrosis, vascular disease, and progressive degeneration in GFR [17, 18].

PODOCYTES

Podocytes are highly specialized biological organisms that comprise the major cellular pathways and the movement of the limbs. Podocytes contain a large number of vesicle membranes, as shown by the multi-layered vesicles and the perforated holes along with the region of origin of these cells. Podocytes have a high potential for protein synthesis and modification after translation due to the enhanced endoplasmic reticulum and high Golgi function [19]. The role of podocytes in the pathology of DKD has become prominent after careful study by Pagtalunan et al. Podocyte deficiency has been shown to be strongly associated with albuminuria and GFR loss in Pima, India, with type 2 diabetes [20]. Since then, several clinical studies have confirmed a correlation between podocyte loss, proteinuria, and glomerulosclerosis, and podocyte loss may be an important contributing factor to the development of DKD [21-23]. Podocyte integrity is essential for the maintenance and operation of a transparent filter wall. It is a major source of GBM Laminin Beta 2 and Collagen IV compounds. It initiates the formation of a clear water window containing endothelial cells, albumin, and immunoglobulins. It suppresses vascular endothelial growth factor VEGFA, angiopoietin-1, and the cells necessary for endothelial cell life. Although differentiated in the end, the cells are very strong, interacting with the base membrane of the eyeball and communicating by turning signals from the diaphragm gap [24 - 26].

LOSS OF PODOCYTE

Foot process effacement results in contraction, enlargement, and deterioration of the function of each podocyte. This is not a disease-specific pathological study, but it is not limited to many forms of glomerular disease, with or without protein [27]. Live and dead podocytes can be recovered from urine. This indicates that the loss of podocytes is the result of segregation and death [28]. Podocytes track GBM via β3β1 integrins and dystroglycan (DG) [29]. Recent studies have also shown reduced renal expression and altered renal localization in biopsies of patients with type I and type II diabetic nephropathy [30]. This change in nephrine expression is enhanced by the elimination of the signaling Ca^{+} kinase protein [31] and the blockage of the renin-angiotensin system [32]. In addition, a similar change has been observed in nephrine expression in podocytes culture expressing glycated albumin and angiotensin II [33]. In 2006, Susztaketal suggests that normal podocytes in high glucose conditions die due to apoptosis. By mechanism, they showed that the release of membrane plasma mitochondrial and ROS play an important role in the function of p38 MAPK

[34]. Subsequent studies have shown that the plasma filter NADPH oxidase (NOX) is also involved. This study found that podocyte apoptosis induces the development of DKD, which in turn leads to podocyte degradation, increased urinary albumin secretion, and expansion of the matrix in type I and type II diabetic animal models [35,36]. Recent studies have shown that the inflammatory pathway to cell death also contributes to the loss of podocytes in diabetes [37].

GLOMERULOSCLEROSIS

The onset of glomerulosclerosis is widely reviewed. The first factor that causes the development of glomerulosclerosis is the loss of podocytes. Persistent deficiency of other podocytes covering the lesion causes the excess protein to develop through the low-density Glomerular Basement Membrane (GBM), causing endosubcutaneous hyaline disease of the affected ligament and causing lumps in the Bowman's ligament [38]. In 2005, Ichikawa et al. has shown that podocytes not only transmit damage to other glomerular cells, but also transmit damage from podocytes to podocytes. Recombinant immunotoxin injection using chimeric rats containing NEP25 podocytes that require Pseudomonas immunotoxin or cancer cells that do not respond to the immunotoxin caused damage to both NEP25 podocytes and wild-type podocytes. [39]. Severe damage to podocytes results in the loss of intercellular networks. VEGF is a common example of this concept. Although VEGF is produced by podocytes, it plays an important role in the regulation of endothelial cells [40].

PODOCYTOPENIA

The number of podocytes decreases in glomeruli in type I diabetics of any age, even in short-term diabetics [41]. Podocyte mass usually indicates a correlation between podocyte loss and proliferation. Two major factors are involved in the process of podocyte loss, proliferation, and apoptosis, while DNA deterioration and hypertension contribute to its proliferation [42]. Previous studies have shown that a3b1 expression decreases in patients with diabetic nephropathy and streptozotocin-induced diabetic rats, resulting in the release of local GBM podocytes [43,44].

EFFECT OF VARIOUS MEDIATORS ON PODOCYTE

Further research designed to identify the mechanisms underlying these end-to end statements provides important insights. The importance of this area to the nephrology research team comes from several studies conducted in recent years, including discussing the effects of vascular endothelial growth factor (VEGF) [45], mechanical stress [46], NOTCH pathway [47], and TGF-β [48], as shown in Table 1. [49].

S.No.	Mediators	Effects on Podocytes
1.	High glucose	Induction of hypertrophy, Increased production of collagen a1(IV), a3(IV), and a5(IV), Activation of p38 MAPK pathway, Increased production of VEGF and angiotensin II, Reduced expression of P-cadherin, Reduced expression of integrin a3 subunit, Increased C-type NP-induced production of cGMP, Enhancement of mechanical stress-induced glucose uptake
2.	TGF-b	Modulation of CTGF expression, Increased production of collagen a3(IV), Involvement of Ang II-mediated collagen a3(IV) production, Decreased production of collagen a1(IV) and a5(IV), Increased activities of MMP-2 and -9, Enhanced secretion of cystatin C, Induction of apoptosis, Increased production of VEGF
3.	Mechanical stress	Increased glucose uptake, Induction of hypertrophy, Reduced proliferation, Activation of the intracellular renin-angiotensin system, Increased osteopontin expression, Induction of reversible reorganization of the actin cytoskeleton
4.	Angiotensin II	Induction of hypertrophy, Increased production of collagen a3(IV), Modulation of the expression of SD complex and induction of proteinuria, Induction of apoptosis, Increased excretion of podocytes in urine, Increased intracellular calcium activity and induction of depolarization, Release of various growth factors (7)

Table 1. ANP, atrial natriuretic peptide; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NP, nitroprusside; SD, slit diaphragm; TGF-b, transforming growth factor-b; VEGF, vascular endothelial growth factor.

PATHOLOGY OF PODOCYTES:

Chronic renal disease assumes a predictable pattern of development. There is a constant loss of renal activity, marked by a decrease in the glomerular filtration rate, regardless of the type of underlying disease. Progressive nephron deficiency induces this deterioration in renal activity. The absence of nephrons fits a pattern of degeneration known as focal segmental glomerulosclerosis, and is consistent with tubular degeneration and interstitial fibrosis when observed histologically. So far, no commonly accepted explanation has been proposed to describe this stereotyped degenerative method. The degeneration phase in a variety of animal models, including subtotal renal ablation [50-51], desoxycorticosterone-trimethylacetate (DOCA)-hypertension [52], chronic Masugi nephritis [53], experimental membranous nephropathy [54], in the Milan normotensive rat [55], in the fawn-hooded rat [56], and after long-term mitogenic stimulation of the glomerulus by exogenous fibroblast growth factor [57].

FUNCTION OF PODOCYTES IN DIABETIC NEPHROPATHY

Therefore, the main function of podocytes, along with GBM and endothelium, is to be involved in the formation of filter barriers and the regulation of overall filtration. Podocytes also support bipolar disorder and bipolar disorder that participate in GBM mutations, and are involved in the overall immune response. DN growth is manifested by virus collection, virus growth, and GBM damage. Following these changes, the small intestine, interstitium, and arterioles change. Recent changes include elevated glomerular pressure and interstitial fibrosis [58]. Type 1 diabetes has been shown to reduce the amount of visceral epithelial glomerular tissue, even after a short period of illness [59]. In the biological study by Dalla Vestra et al. among patients with type 2 diabetes, they determined that a decrease in podocyte deficiency was more likely than albuminuria than a decrease in total podocyte count [60]. Mature podocytes have proliferative limits. Bacterial growth occurs when up to 20% of podocytes are lost and GBM is depleted when a further loss occurs, resulting in increased glomerular fibrosis and proteinuria [61-62]. Podocytes are excreted in the urine of patients with glomerulopathy, and podocyte size corresponds to disease function [63, 64].

TARGETING PODOCYTES AS RENAL SPECIFIC THERAPY:

Medical nephrologists and renal researchers should work to define the renal defense system and establish therapeutic plans for the kidney or the different renal compartments that make up the kidney. Podocytes are probably the most possible candidate cell population to be studied on a molecular basis since they are the most delicate component of the glomerular filtration network even during early stages of injury and serve as hallmarks of a condition of glomerular disease [65].

Podocytes have a small ability for cell division and do not regenerate in response to damage or destruction due to their post-mitotic disposition [66]. If left untreated, glomerular diseases will progress quickly. Podocytes, regardless of their source, are essential determinants of outcome for all glomerular diseases, making podocytes a specific paradigm for monitoring and studying disease progression [67]. As a result, in the last decade, there has been a significant change toward podocyte proteins as therapeutic targets [68]. Sialic acid and its precursors are effective in the treatment of MCD32 and diabetic nephropathy [69].

In FSGS and diabetic nephropathy, mutated variants of human ANGPTL4 reduce proteinuria without inducing hypertriglyceridemia [70]. By specifically attacking the upregulated integrin αvβ3 on podocytes, a particular inhibitor of integrin αvβ3, cyclo-RGDfV, alleviates proteinuria in mouse models of nephrotic syndrome [71]. Rituximab, a CD20 antibody, attaches to sphingomyelin phosphodiesterase acid-like 3b (SMPDL-3b) and stabilizes the structure and function of podocytes treated with repeated FSGS sera [72].

CONCLUSION: Numerous factors considered to be mediators in the pathogenesis of diabetic nephropathy are known to induce podocyte injury, resulting in proteinuria and some characteristic pathologic changes, such as glomerular hypertrophy, podocytopenia, glomerulosclerosis, and foot process effacement. Various functions of podocytes are also involved in the formation of filters.

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