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The pathogenic role of the renal proximal tubular cell in diabetic nephropathy

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Abstract

A growing body of evidence indicates that the renal proximal tubular epithelial cell (PTEC) plays an important role in the pathogenesis of diabetic nephropathy (DN). Microalbuminuria that intensifies over time to overt proteinuria, a hallmark of DN, is already known to activate the PTEC to induce tubulointerstitial inflammation. In addition to proteins, a number of diabetic substrates including high glucose *per se*, advanced glycation end-products and their carbonyl intermediates, angiotensin II, and ultrafiltered growth factors activate a number of signaling pathways including nuclear factor kappa B, protein kinase C, extracellular signal-regulated kinase 1/2, p38, signal transducer and activator of transcription-1 and the generation of reactive oxygen species, to culminate in tubular cell hypertrophy and the accumulation in the interstitium of a repertoire of chemokines, cytokines, growth factors and adhesion molecules capable of orchestrating further inflammation and fibrosis. More recently, the kallikrein-kinin system (KKS) and toll-like receptors (TLRs) in PTECs have been implicated in this process. While *in vitro* data suggest that the KKS contributes to the progression of DN, there are conflicting *in vivo* results on its precise role, which may in part be strain-dependent. On the other hand, there are both *in vitro* and *in vivo* data to suggest a role for both TLR2 and TLR4 in DN. In this review, we offer a critical appraisal of the events linking the participation of the PTEC to the pathogenesis of DN, which we believe may be collectively termed diabetic tubulopathy.

Keywords: *db/db* mice; diabetic nephropathy; fibrosis; inflammation; kallikrein-kinin system; proximal tubular epithelial cell; TLR4 KO mice; toll-like receptor

Introduction

It is estimated that over 285 million people worldwide have diabetes mellitus, and that this figure will reach 439 million by 2030 [1]. This epidemic is predominantly of Type 2 diabetes, which is a leading cause of end-stage renal disease (ESRD) in developed countries. In the USA, around 8.3% of the population has diabetes of which over 90% are Type 2 diabetics, and kidney failure arising from diabetes now accounts for 44% of incident cases, according to statistics from the American Diabetes Association. Despite this global epidemic of Type 2 diabetes mellitus (T2DM) and the escalating cost of treating patients with ESRD, advances in preventing or retarding the progression of diabetic nephropathy (DN) to ESRD have been rather modest. The danger of DN leading to albuminuria and chronic kidney disease (CKD) is further compounded by evidence linking proteinuria, endothelial dysfunction, accelerated atherosclerosis and cardiovascular morbidity. Yet, despite current recommendations of full renin-angiotensin system blockade [2] and stringent glycemic, lipid and blood pressure control, the number of DN patients who progress to ESRD or must undergo renal replacement therapy has continued to increase year on year, imposing enormous medical and socioeconomic burdens. One major reason for this relentless progression is related to our incomplete understanding of the pathogenetic mechanisms of DN, which is fundamental to the development of a more effective preventive or therapeutic strategy.

Although glomerulosclerosis is a cardinal feature of DN, it is the extent of tubulointerstitial injury that ultimately determines the rate of attrition of renal function [3]. To this end, the renal proximal tubular epithelial cell (PTEC) is increasingly implicated in the pathogenesis of DN and its progression. In this review, we will summarize the currently available evidence linking the PTEC and intrarenal inflammation and fibrogenesis in DN.

PTEC as a pro-inflammatory/pro-fibrotic effector

Progression from microalbuminuria to macroalbuminuria to heavy proteinuria is the hallmark of disease progression in DN. The onset of abnormal protein trafficking through the glomerulus that marks the development of DN is also a common feature in many forms of CKD. Indeed, progression of CKD to ESRD is characterized by pathogenic mechanisms that converge upon a common pathway leading to progressive interstitial fibrosis, peritubular capillary loss and destruction of functioning nephrons due to tubular atrophy [4]. These processes are invariably

heralded by the interstitial recruitment of inflammatory leukocytes and myofibroblasts. The past 20 years of research have indicated that abnormal protein trafficking through the glomerulus in CKD plays a pivotal mechanistic role in inducing tubulointerstitial lesions through PTEC activation [5–10].

Several *in vitro* studies have demonstrated that urinary proteins, mainly albumin, transferrin and immunoglobulin G, can stimulate PTECs to synthesize a repertoire of inflammatory molecules and chemokines [11, 12]. The molecular mechanisms underlying chemokine upregulation in PTECs upon protein challenge have been shown to involve an array of tightly regulated signaling cascade. For instance, superinduction of tubular interleukin (IL)-8 involved a succession of receptor-mediated uptake of protein, followed by protein kinase C (PKC) activation, reactive oxygen species (ROS) generation, nuclear factor kappa B (NF-κB) signaling and finally, transcription of the candidate chemokine [10]. Besides the NF-κB activation, other signal transduction pathways are also heavily involved and these include extracellular signal-regulated kinase (ERK1/2) [13], p38 mitogen-activated protein kinases [14] and signal transducer and activator of transcription (STAT) [15].

In addition to inflammation, interstitial fibrosis is another hallmark of progressive renal disease. Locally recruited macrophages regulate matrix accumulation via the release of growth factors, most notably transforming growth factor (TGF)-β which remains the most potent cytokine for renal fibrogenesis and stimulus for epithelial-myofibroblast transdifferentiation (EMT) of PTECs [16]. Besides, albumin stimulated PTECs secrete TGF-β [17] and extracellular matrix (ECM) materials [18]. For over 15 years, EMT has been viewed as a principal source of fibroblasts in tissue fibrosis. This concept is rigorously challenged by anecdotal and recent scientific evidence using genetic labeling techniques [19, 20]. Kriz *et al.* [21] recently reviewed this subject and suggested that unequivocal evidence supporting EMT as an *in vivo* process in kidney fibrosis is lacking. Whereas EMT from a fibroblast-centric view is a highly efficient way to recruit fibroblasts rapidly to local sites of tubulointerstitial injury [22], its authenticity probably requires further scrutiny.

Collectively, these data highlight the proteinuria–interstitial inflammation–fibrosis connections, and suggest that proteinuria is not merely a marker of glomerular injury, but also a direct tubulotoxic agent. This is reflected clinically by the observation of a more favorable renal outcome among diabetic and non-diabetic CKD subjects who achieved significant proteinuria reduction after the initiation of anti-proteinuric therapy versus those who did not [23–25]. An alternative explanation for the development of proteinuria which involves primarily an abnormality in tubular handling of ultrafiltered proteins, the albumin retrieval hypothesis [26], has also been put forward. This observation, however, was questioned by several investigators [27], and reports using similar techniques suggested that the albumin retrieval hypothesis probably arose from an artifact [28]. Further deliberation on this debate is outside the scope of this review.

Impact of different diabetic substrates on the PTEC

The occurrence of proteinuria is but one of many stimuli to PTECs in the diabetic kidney. Although an alternative theory for the development of albuminuria (dysfunction in lysosomal degradation) in DN exists [29], the changes are not necessarily exclusive to the altered properties of the glomerular ultrafiltration barrier. *In vitro* studies have demonstrated the pathogenic role of different diabetic substrates in inducing an inflammatory and profibrotic phenotype in PTECs. Components of the diabetic milieu include high glucose (HG), accumulation of glycated proteins, elevated intrarenal angiotensin II, oxidative stress and hypertension-induced mechanical stress. Some of these elements have been shown to impact on the PTEC. Hyperglycemia is the key metabolic manifestation of diabetes. The first *in vitro* model of diabetic renal disease was pioneered by Ziyadeh *et al.* [30, 31] who observed that culturing PTECs in HG promotes cellular hypertrophy and stimulates ECM production. These HG effects act through a TGF-β-dependent mechanism as HG stimulates TGF-β expression and bioactivity in the proximal tubule [32], and antisense TGF-β1 oligodeoxynucleotides attenuate HG-induced PTEC hypertrophy and partially prevents the increase in kidney weight and ECM expression in streptozotocin (STZ)-induced diabetic mice [33]. Moreover, cultured PTECs from TGF-β1 null mice exhibit impaired hypertrophy and fibronectin expression in HG [34]. In addition, the polyol pathway, triggered from intracellular glucose accumulation, mediates HG-induced collagen synthesis in PTECs [35]. More recently, HG has also been shown to induce IL-6 and CC chemokine ligand (CCL)-2, TGF-β and vascular endothelial growth factor (VEGF) expression in PTECs via ERK1/2 and PKC activation [36]. The peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists rosiglitazone or pioglitazone have been shown to partially block HG-induced PKC activation [36] and profibrotic phenotypes in PTECs [37]. HG also stimulates EMT in PTECs via p38 signaling and activator protein-1 activation [38]. All of these factors play complementary roles: IL-6 and CCL-2 induce intrarenal inflammation and coordinate leukocyte chemotaxis during diabetes [39, 40]; TGF-β is heavily implicated in tubular EMT which is conducive to interstitial fibrosis [41] and VEGF stimulates endothelial proliferation, neoangiogenesis and influx of macrophages, particularly in the absence of nitric oxide, the so-called VEGF–NO uncoupling phenomenon [42].

In addition to their direct tubulotoxic effects, reducing sugars may react non-enzymatically with amino groups in proteins or lipids, which involve a series of complex biochemical events with oxidative and non-oxidative molecular rearrangements termed the Maillard reaction which ultimately leads to stable covalent adducts known as advanced glycation end-products (AGEs). In human, irreversible advanced glycation of proteins is a part of the aging process, which is markedly amplified and accelerated in diabetes as a consequence of hyperglycemia. AGEs upregulate tubular IL-8 and intracellular adhesion

molecule (ICAM)-1 expression through NF-κB, ERK1/2 and STAT-1 signaling, and the PPAR-γ agonist rosiglitazone could completely abolish glycated albumin-induced STAT-1 signals [43]. These observations were supported *in vivo* by the renoprotective effect of rosiglitazone and glycated albumin antagonists in *db/db* mice independent of blood glucose levels [44, 45]. AGEs also induce tubular connective tissue growth factor (CTGF) via TGF-β-independent Smad3 signaling [46], and upregulate heparanase expression in PTECs, thus affecting ECM remodeling and degradation [47]. Finally, AGE rapidly activates Smad2/3 to induce tubular EMT and fibrosis independent of TGF-β via ERK/p38-Smad signaling crosstalk pathways [48].

The carbonyl intermediates of AGE formation are not entirely inert and also participate in triggering tubular inflammatory signals. For instance, carboxymethyllysine (CML), methyglyoxal-bovine serum albumin (BSA)-AGE and CML-BSA activates NF-κB in cultured PTECs and perpetuates an increase in pro-inflammtory gene products, such as IL-6, CCL2 and CTGF, and play a role in inducing renal tubular damage [49, 50].

Many of the renal actions of AGEs appear to be mediated by interactions with specific AGE receptors and binding proteins in the kidney, of which the receptor for AGEs (RAGE) is the best characterized [51]. RAGE is a multiligand receptor and may be activated not only by AGEs but also high mobility group box 1 (HMGB1), S-100 calgranulins, Mac-1, amyloid-b peptide and advanced oxidation protein products (AOPPs). Activation of RAGE triggers the activation of key secondary messenger pathways in renal cells such as PKC, NF-κB and increases production of inflammatory and fibrogenic growth factors and cytokines, including TGF-β and CTGF. With regard to the PTEC, RAGE activation promotes tubular EMT through the induction of TGF and CTGF, thus contributing to interstitial fibrogenesis [52].

An increase in plasma levels of AOPPs has been found in obesity and in Type 2 diabetes [53]. Oxidative stress defined as an excessive production of ROS surpassing existing antioxidative defense mechanisms plays a critical role in the development and progression of diabetic vascular complications including nephropathy. Overproduction of ROS in the diabetic milieu is both a direct consequence of hyperglycemia and an indirect consequence of AGEs or mediators of glucotoxicity such as cytokines and growth factors. Nicotinamide adenosine dinucleotide phosphate oxidase and mitochondrial dysfunction have been recognized as two major sources of ROS generation in diabetic kidneys. An increase in ROS generation has been observed in PTECs from *db/db* mice when compared with *db/m* control [54], and increased urinary 8-hydroxy-2′-deoxyguanosine and decreased NO have been shown in obese ZSF1 rats, a new experimental model for Type 2 diabetes [55]. Chronic therapy with ebselen, a glutathione mimicking agent, has demonstrated a scavenging effect of peroxynitrite associated with an improvement of tubulointerstitial pathology and inflammation in early DN [56]. Furthermore, overexpression of catalase in *db/db* mice has been demonstrated to attenuate interstitial fibrosis and tubular apoptosis [57].

Heightened bioactivation of the intrarenal angiotensin II system resulting from HG, mechanical stretch and proteinuria gives rise to non-hemodynamic disturbances and results in hypertrophy of PTECs via activation of endogenous TGF-β [58]. Interestingly, the hypertrophic response of PTECs to angiotensin II is greater in HG medium [59]. Angiotensin II stimulates uptake of filtered proteins into tubular cells and enhances the production of pro-inflammatory and profibrotic cytokines within these cells [60]. Increased synthesis and decreased turnover of ECM proteins in tubular cells and interstitial fibroblasts contribute to interstitial fibrosis [60]. In addition, under high local concentrations of angiotensin II and TGF-β1, PTECs may undergo EMT which contributes to interstitial fibrosis and tubular atrophy due to vanishing epithelial cells. Regardless of whether EMT contributes to intrarenal fibrosis, these observations are in line with the clinical observations of the renoprotective effects of antagonizing the angiotensin converting enzyme or the AT_1 receptor even in the absence of systemic hypertension.

Apart from the diabetic substrates, other biologically active growth factors ultrafiltered through the glomerulus in DN, such as hepatocyte growth factor, insulin-like growth factor-1 and TGF-β, may also activate PTECs apically, leading to basolateral secretion of chemokines (CCL2 and CCL5) and peptides (platelet-derived growth factor-B) into the peritubular interstitium that may culminate in progressive interstitial fibrosis [61].

The role of glucose transport in the proximal tubule

At least two sodium-coupled glucose transporters, SGLT1 and SGLT2, play an important role in the apical membrane of PTECs. SGLT2 plays a major role in renal glucose reabsorption [62]. According to the tubulo-centric nature of renal function in diabetes, the underlying mechanism of early diabetic hyperfiltration includes a primary increase in proximal tubular reabsorption of glucose by SGLT2 along with sodium, which reduces delivery of NaCl to the macula densa [63]. The macula densa then senses this decline in salt delivery as an error signal and elicits an increase in glomerular filtration rate (GFR) through tubuloglomerular feedback physiology. Enhanced tubular growth and glucose reabsorption have been implicated in proximal hyper-reabsorption and glomerular hyperfiltration in early diabetes. This growth phenotype explains unusual responses like the salt paradox of the early diabetic kidney in which low-salt diets lead to a paradoxical reduction of GFR [64].

Increased glucose uptake may regulate renal SGLT activities through the ROS-NF-κB pathways. Thus, the diabetic milieu triggers early tubular cell proliferation. The induction of angiotensin II, TGF-β and cyclin-dependent kinase inhibitors such as p16INK4 and p27KiP1 causes a cell cycle arrest and a switch to tubular hypertrophy and a senescence-like phenotype [65]. Cell cycle proteins may also be involved in these molecular events, leading to a limited degree of tubular apoptosis [65]. The activated

molecular pathways may set the stage for tubulointerstitial injury and DN.

Participation of the kallikrein-kinin system: the jury is still out

The kallikrein-kinin system (KKS) has traditionally been considered to play a physiological role in controlling blood pressure. A growing body of evidence, however, has implicated the KKS in the pathogenesis of DN.

The actions of the KKS are primarily mediated by bradykinin (BK), a peptide that triggers vasodilatation, vascular leakage and secretion of pro-inflammatory mediators [66]. The generation of BK is mediated by both plasma and tissue kallikreins, which are serine protease enzymes. Tissue kallikrein 1 (KLK1) acts through two cell surface G-protein-coupled receptors: the widely expressed B2R and the inducible B1R [66]. The intracellular signals that follow stimulation of B1R and B2R are reviewed elsewhere [67].

All components of the KKS are expressed in the kidney and are regulators of intrarenal hemodynamics and tubular function. In the kidney, B2R mRNA is expressed in all segments under physiological conditions, whereas B1R is almost absent [67]. The involvement of the KKS in the diabetic kidney is suggested by increased urinary excretion of active KLK kinins with reduced vascular resistance in STZ-induced diabetic rats [68], and by the influence of kinins on inflammation and cell proliferation under diabetic conditions [69].

Emerging evidence suggests that PTECs also produce KLK1 [36]. There are both *in vitro* and *in vivo* data to support the notion that the KKS participates in DN involving the PTEC. *In vitro*, HG stimulates the expression of renal tubular kallikrein (KLK1) and low molecular weight kininogen, and this inevitably leads to generation of BK. Indeed, HG also upregulates B2R expression in PTECs. These downstream effects were attenuated by aprotinin (a tissue kallikrein inhibitor). Stimulation of B2R with its ligand, BK, resulted in pro-inflammatory and profibrotic, but not angiogenic responses in PTECs. Blockade of B2R using a specific blocker icatibant partially attenuated HG and BK stimulation of these responses. The inhibitory effect of icatibant further suggests that HG may be coupled to generation of kininogen and kallikrein in PTECs.

In vivo, there is tubular expression of both KLK1 and B2R in the human diabetic kidney [36]. In uninephrectomized *db/db* mice that demonstrate pathologic lesions resembling Type 2 DN, application of icatibant decreases B2R but increases B1R expression, together with reduced serum creatinine and albuminuria [70]. In addition, the severity of reactive glomerular and proximal tubular hypertrophy, glomerulosclerosis, interstitial injury, cortical F4/80 and α-smooth muscle actin immunostaining, and tubular CCL-2, ICAM-1 and TGF-β overexpression are all attenuated by icatibant. On the other hand, there are conflicting *in vitro* and animal data as to whether KKS overactivation is good (protective) or bad (destructive) in DN. These reports, which do not necessarily involve PTECs, are reviewed elsewhere [71]. The discrepancies in these results may be related to the different cell types used and genetic backgrounds of the studied animals. But more importantly, these animal models directly exploring the effects of the KKS in DN are mostly restricted to type 1 diabetes mellitus (T1DM), such as via STZ induction or in Akita mice. Hence, the jury is still out to determine whether the KKS is a friend or foe in T2DN. In addition, the exact role of the compensatory B1R elevation during B2R blockade in the diabetic kidney warrants further studies.

In addition to BK generation, KLK1 signaling may also act on protease-activated receptors (PARs) [72]. PARs are potent mediators of inflammation and fibrosis after being cleaved and activated by serine proteases. Overexpression of PARs in several kidney diseases suggests a possible role in the progression of kidney damage. Our preliminary data showed that PARs are expressed in PTECs [73]. PAR-2 is the most abundant receptor in PTECs compared with PAR-1 and PAR-4, whereas PAR-4 has the lowest expression among the receptor family. HG selectively enhanced PAR-4, but not PAR-1 and PAR-2 mRNA expression in PTECs. In addition, HG stimulates a time-dependent increase in CTGF mRNA and protein levels, and the expression is significantly inhibited by pre-incubation with PAR-1, PAR-2 and PAR-4 antagonists. Whether PAR-4 and other PARs possibly contribute to the progression of fibrosis in the diabetic kidney requires further investigation.

The emerging role of toll-like receptors

Emerging data indicate that toll-like receptors (TLRs) participate in the pathogenesis of acute and chronic renal disorders, including DN. TLRs are a conserved family of pattern recognition receptors that play a fundamental role in the innate immune system, and are activated by both microbial pathogens and endogenous agonists of non-infectious inflammatory conditions. As discussed above, inflammatory mechanisms play a key role in the development of DN. Therefore, TLR4 might be an important molecular link between inflammation and the metabolic syndrome-associated disorders such as hyperglycemia [74], dyslipidemia [75] and hemodynamic abnormalities [76]. Moreover, TLR4 expression by intrinsic renal cells and leukocytes has been reported to contribute to various acute and CKD diseases [77–79]. Besides, it has been demonstrated that TLR2 and TLR4 expression is elevated in adipose tissue [75] and muscle [80] of human subjects and/or animal models of insulin resistance. In Type 1 and Type 2 diabetic patients, increased TLR2 and TLR4 expression in monocytes is positively correlated with HbA1c levels [81] and homeostasis model assessment-insulin resistance [82].

In support of the pro-inflammatory role of TLRs in diabetes, Dasu *et al.* [82] observed an upregulation and the activation of TLR2 and TLR4 and their ligands in circulating monocytes of recently diagnosed Type 2 diabetic subjects. Our group observed that tubular TLR4 is the main mediator of DN. There are three lines of evidence:

(i) in human DN, TLR4 but not TLR2 was highly expressed in the renal tubules, which correlated positively with interstitial macrophage infiltration and HbA1c level, and negatively with estimated GFR at the time of biopsy. Tubular expression of HMGB1 was increased in DN biopsies. As HMGB1 has been identified as a TLR4 endogenous ligand activated by the diabetic state [82], such a finding supports its role in TLR4 activation in DN; (ii) in cultured PTECs, HG induced TLR4 but not TLR2 expression via PKC activation, resulting in upregulation of IL-6 and CCL-2 expression via inhibitory kappa B (IκB)/NF-κB activation. Molecular silencing of TLR4 in PTECs with siRNA attenuated HG-induced IκB/NF-κB activation, the associated downstream IL-6 and CCL-2 synthesis and impaired the ability of PBMC/U937 mononuclear cell transmigration induced by HG-treated PTEC conditioned media; (iii) STZ-induced diabetic and uninephrectomized TLR4$^{-/-}$ mice displayed significantly reduced albuminuria, renal dysfunction, renal cortical NF-κB activation, tubular CCL-2 expression and interstitial macrophage infiltrates than wild-type animals. Whereas in sham-operated wild-type animals, tubular TLR4 expression was upregulated after STZ induction. A similar degree of renoprotection was also observed in STZ-induced eNOS$^{-/-}$ mice, a model of advanced DN [83], treated with a systemic TLR4 inhibitor versus untreated mice (unpublished observation).

In addition to TLR4, TLR2 has been observed by other groups to be important in DN. In STZ-induced rats, renal tubular TLR2 expression was significantly upregulated, which was associated with increased renal expression of myeloid differentiation factor MyD88 and monocyte chemoattractant protein-1, the activation of NF-κB, infiltration of macrophages and the endogenous ligands of TLRs, namely HSP70 and HMGB1. These findings were reproduced in rat tubular cell line (NRK-52E cells) in which HG induced the expression of TLR2 mRNA [84]. More recently, in a model of STZ-induced TLR2$^{-/-}$ mice, there was less intense macrophage TLR2 expression and MyD88-dependent signaling, decreased TGF-β and laminin levels and restoration of nephrin, podocin, podocyte number and effacement compared with STZ-induced wild-type animals [85]. The study underscores that genetic deficiency of TLR2 (i) significantly abrogates the pro-inflammatory state of T1DM up to 14 weeks, despite the other TLRs, including TLR4, being intact; and (ii)

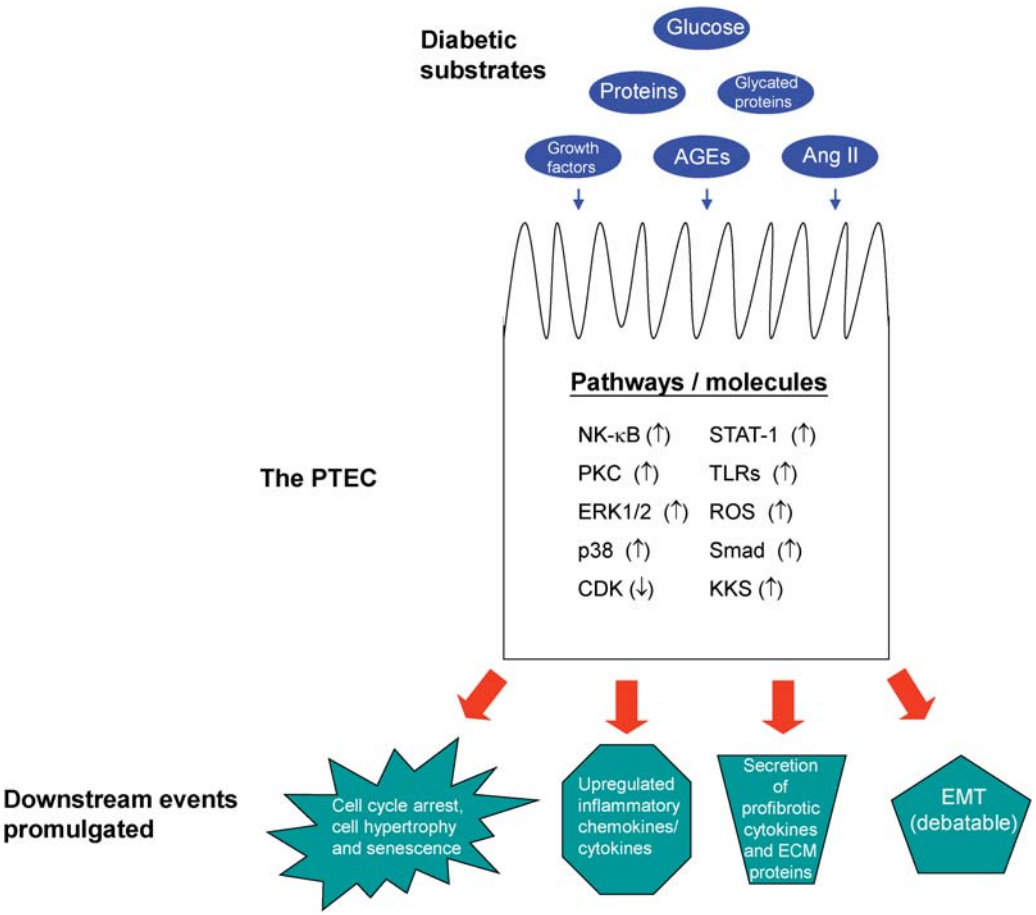

Fig. 1. Simplistic overview illustrating the activation of the PTEC by the possible diabetic substrates and the downstream signaling and biologic events. ↑ denotes activation; ↓ denotes inhibition; AGEs, advanced glycation end-products and their intermediates; Ang II, angiotensin II; CDK, cyclin-dependent kinases of cell cycle; EMT, epithelial-myofibroblast transdifferentiation; ERK, extracellular signal-regulated kinase; KKS, kallikrein-kinin system; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TLRs, toll-like receptors.

attenuates incipient DN at the cellular level, with normalization of microalbuminuria and podocyte number. However, it is not clear from this study whether it is tubular or macrophage TLR2, or both, that orchestrates the nephropathy.

Several factors may contribute to the divergent findings of TLR4 versus TLR2, including a generic difference between human and rodent DN pathologies, the disease duration in human versus animal models, Type 2 DN in human versus Type 1 DN in STZ-induced rats, and use of primary culture versus cell lines in *in vitro* studies. Further studies are required to pinpoint the precise role of TLR2 in the pathogenesis of DN.

Conclusion

Collectively, the published data support a pivotal role of the PTEC in orchestrating kidney injury in the progression of DN through the action of several key substrates of diabetes that activate major pro-inflammatory and fibrogenic signaling pathways via a number of receptors to result in a phenotype that favors tubulointerstitial inflammation, fibrosis and renal function attrition. This cascade of events is simplistically depicted in Figure 1. Therapeutic strategies targeted at the various steps of this cascade to abrogate inflammation in diabetes may eventually result in a promising protocol for the treatment of DN. It must be emphasized that in addition to PTECs, other cell types, such as the podocyte, also mediate renal injury during DN. Their inclusion is beyond the scope of the present review.

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Conflict of interest statement. None declared.

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Metabolic acidosis and kidney disease: does bicarbonate therapy slow the progression of CKD?

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Abstract

Metabolic acidosis is a common complication associated with progressive loss of kidney function. The diminishing ability of the kidneys to maintain acid–base homeostasis results in acid accumulation, leading to various complications such as impairment in nutritional status, worsened uremic bone disease and an association with increased mortality. In addition to these adverse effects which are related to acid retention, metabolic acidosis may also cause kidney damage, possibly through the stimulation of adaptive mechanisms aimed at maintaining acid–base homeostasis in the face of decreasing kidney function. Recent clinical trials have suggested that correction or prevention of metabolic acidosis by alkali administration is able to attenuate kidney damage and to slow progression of chronic kidney disease (CKD), and may hence offer an effective, safe and affordable renoprotective strategy. We review the physiology and pathophysiology of acid–base homeostasis in CKD, the mechanisms whereby metabolic acidosis may be deleterious to kidney function, and the results of clinical trials suggesting a benefit of alkali therapy, with special attention to details related to the practical implementation of the results of these trials.

Keywords: bicarbonate; chronic kidney disease; metabolic acidosis; therapy

Introduction

Metabolic acidosis is one of the many complex changes associated with the development of chronic kidney disease (CKD) [1, 2]. Decreasing kidney function causes progressively increased retention of acids, resulting in numerous deleterious consequences, such as protein catabolism and protein-energy wasting [3–18], worsening uremic bone disease [19–22] and an association with decreased functional capacity [23] and with increased mortality in patients with end-stage renal