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Mini Review

Recent advances in understanding the biochemical and molecular mechanism of diabetic nephropathy

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ABSTRACT

Diabetic nephropathy (DN) is a chronic disease characterized by proteinuria, glomerular hypertrophy, decreased glomerular filtration and renal fibrosis with loss of renal function. DN is the leading cause of end-stage renal disease, accounting for millions of deaths worldwide. Hyperglycemia is the driving force for the development of diabetic nephropathy. The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are: hyperglycemia (causing hyperfiltration and renal injury), advanced glycosylation products, activation of cytokines. In this review article, we have discussed a number of diabetes-induced metabolites such as glucose, advanced glycation end products, protein kinase C and oxidative stress and other related factors that are implicated in the pathophysiology of the DN. An understanding of the biochemical and molecular changes especially early in the DN may lead to new and effective therapies towards prevention and amelioration of DN.

1. Introduction

Diabetic nephropathy (DN) is a serious complication of diabetes mellitus, and its prevalence has been increasing worldwide. DN is the leading cause of end stage renal diseases worldwide [1]. DN is characterized by morphological and ultrastructural changes in the kidney including expansion of the molecular matrix and loss of the charge barrier on the glomerular basement membrane [2,3]. DN is a multifactorial progressive disease where the pathogenesis of the disease is extremely complex involving many different cells, molecules, and factors [4]. The term diabetic nephropathy is used to describe the combination of lesions that often occur concurrently in the diabetic kidney. The most common kidney lesions in people with diabetes are those that affect the glomeruli. The pathogenesis of diabetic nephropathy is complex and still not fully elucidated. This review summarizes the recent advances in understanding the biochemical and molecular mechanism of DN.

2. Hyperglycemia

Hyperglycemia has generally been considered as the key initiator of kidney damage associated with DN by activation and dysregulation of several metabolic pathways. Hyperglycemia leads to an increase in oxidative stress by exacerbating glucose oxidation and mitochondrial generation of reactive oxygen species (ROS) which cause DNA damage and contributes to accelerated apoptosis [5]. Also increased ROS activate poly (ADP ribose) polymerase (PARP) as a reparative enzyme [6]. PARP inhibits glyceraldehyde phosphate dehydrogenase, diverting glucose from its glycolytic pathway and into alternative biochemical pathways that are considered to be the mediators of hyperglycemia-mediated cellular injury. Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta) in the glomeruli and of matrix proteins specifically stimulated by this cytokine. TGF-beta may contribute to the cellular hypertrophy and enhanced collagen synthesis observed in persons with diabetic nephropathy [7].

3. Advanced glycation end products (AGEs)

Increasing evidence demonstrates that AGEs play a pivotal role in the development and progression of diabetic vascular damage [8]. Further, diabetic patients with end-stage renal disease had almost twice as much AGEs in tissue as diabetic patients without renal disease [8]. Both enhanced formation and decreased clearance are responsible for the accumulation of AGEs in patients with diabetic nephropathy [9,10]. Accumulation of AGEs in the kidney may contribute to the progressive alteration in renal architecture and loss of renal function in patients and rodents via various mechanisms, including their cross-linking properties of matrix proteins and activation of the downstream signalings [11]. AGE formation on extracellular matrix proteins alters both matrix–matrix and cell–matrix interactions, being involved in diabetic glomerulosclerosis. Further,

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AGE formation on various types of matrix proteins impairs their degradation by matrix metalloproteinases, contributing to basement membrane thickening and mesangial expansion, hallmarks of diabetic nephropathy [12,13]. AGEs formed on the matrix components can trap and covalently cross-link with the extravasated plasma proteins such as lipoproteins, thereby exacerbating diabetic glomerulosclerosis [14]. AGEs including glycoxidation or lipoxidation products such as N-epsilon-carboxymethyllysine, pentosidine, malondialdehyde-lysine accumulate in the expanded mesangial matrix and thickened glomerular basement membranes of early diabetic nephropathy, and in nodular lesions of advanced disease, further suggesting the active role of AGEs for diabetic nephropathy [15].

4. Protein kinase C

Among various signaling kinases, PKC seems to be a centerpiece in the pathogenesis of diabetic nephropathy [16]. Under high glucose ambience it is activated by diacylglycerol (DAG) formed during glycolytic intermediary steps and by ROS generated following AGE: RAGE interactions [17,18]. Such interactions at the cell membrane activate PKC by increasing the activity of phospholipase C with an increase in intracellular Ca^{2+} and DAG. This cyclic generation of DAG would suggest an intimate "level and activity" relationship between DAG and PKC, and such a parallelism in their expression has been observed in various tissues in diabetes [17]. The PKC activation also leads to endothelial dysfunction with decreased nitric oxide production, increased expression of endothelin-1, and vascular endothelial growth factor [19]. At the same time, increased expression of NF-κB and plasminogen activator inhibitor-1 (PAI-1) would induce a local tissue inflammatory response and thrombotic microangiopathy, thus accentuating the vascular injury, which is further augmented by additional ROS generated by plasmalemmal nicotinamide adenine dinucleotide phosphate (NADPH) oxidoreductase [18]. The fact that PKC activation occurs by multiple routes and that the administration of PKC inhibitor, ruboxistaurin mesylate, reduces renal abnormalities in db/db mice suggests its central signaling role in hyperglycemia-induced vascular injury [18].

5. Oxidative stress

Increasing evidence in both experimental and clinical studies suggests that there is a close link between hyperglycemia, oxidative stress, and diabetic complications [20,21]. High glucose induces intracellular ROS directly via glucose metabolism and auto-oxidation and indirectly through the formation of AGEs and their receptor binding [22]. ROS mimic the stimulatory effects of high glucose and upregulate TGF-beta1, PAI-1, and ECM proteins by glomerular mesangial cells, thus leading to mesangial expansion. ROS activate other signaling molecules, such as protein kinase C and mitogen-activated protein kinases and transcription factors, such as NF-κB, activator protein-1, and specificity protein 1 leading to transcription of genes encoding cytokines, growth factors, and ECM proteins [23]. Finally, various antioxidants inhibit mesangial cell activation by HG and ameliorate features of diabetic nephropathy [23]. These findings qualify ROS as intracellular messengers and as integral glucose-signaling molecules in glomerular mesangial cells in diabetic nephropathy.

6. Inflammation

Recent evidence shows an increase in macrophage infiltration and overproduction of leukocyte adhesion molecules in kidneys from diabetic humans and in experimental animal models of diabetes [24,25]. Chronic inflammation plays an important role in the development of diabetes and its late complications [25–28]. Increasing evidence points to critical roles of pro-inflammatory cytokines in pathogenesis of diabetic nephropathy. For example, interleukin 1 (IL-1) is believed to increase vascular permeability and proliferation of mesangial cells and matrix deposition [29]. On the other hand, IL-6 reportedly upregulates mesangial cell proliferation, increases fibronectin expression and affects extracellular matrix dynamics of mesangial cells and podocytes along with increased expression of adhesion molecules on endothelial cells and vascular smooth muscle cells [30]. Still other cytokines, such as tumor necrosis factor-α (TNF-α), impair balance among vasodilator and vasoconstriction mediators, upregulate production of ROS thereby contributing to alterations in glomerular capillary permeability barrier [31]. Collectively, these effects are believed to contribute to the functional alterations associated with diabetic nephropathy such as albuminuria and dysregulation of sodium homeostasis. Importantly, chemokine-induced inflammatory cell recruitment into renal tissue is a critical feature of various forms of renal disease including diabetic nephropathy [32].

7. Poly(ADP-ribose) polymerase (PARP) activation

PPARγ (peroxisome-proliferator-activated receptor γ) modulates numerous effectors of ECM accumulation [33]. TZDs (thiazolidinediones) are synthetic ligands of PPARγ, which is involved in many important physiological processes, including adipose differentiation, lipid and glucose metabolism, energy homoeostasis, cell proliferation, inflammation, reproduction and renoprotection [34,35]. TZD prevented increase of TGF-β and increase of ECM in cultured human mesangial cells [36], and both mesangial cell and fibroblast proliferation in vitro were inhibited by PPARγ agonists [37,38]. TGF-β effects in fibroblasts were blocked by TZDs through inhibition of the downstream Smad signaling pathway [39]. PPARγ also interacts with the renin angiotensin system. In a number of studies, TZDs decreased activation of the renin angiotensin system components in both adipocytes and vascular smooth muscle cells [40,41]. Experimental knockout of PPARγ in macrophages resulted in increased expression of the angiotensin II type 1 receptor and greater migratory response to exogenous angiotensin [42].

As summarized in this review, those pathways and molecules involved in DN have been discovered, but still, the exact molecular mechanism involved in the progression of the disease is uncertain, which makes therapeutic interventions a difficult task. Therefore, it is essential to develop animal models for DN to reveal its mechanisms and to develop new therapeutic interventions.

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