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Significance of Advanced Glycation End-Products (AGE) and the Receptor for AGE (RAGE) in Diabetic Nephropathy

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1. Introduction

Diabetic nephropathy is a life-threatening complication of *diabetes mellitus* and the leading cause of end-stage renal disease (ESRD) in developed countries. Diabetes is responsible for over 40% of all new cases with ESRD in the United States and Japan, eventually undergoing renal dialysis or transplantation. Diabetic nephropathy is characterized by glomerular hyperfiltration and thickening of glomerular basement membranes, followed by expansion of extracellular matrix in mesangial area. There are many factors and pathways that are involved in the pathogenesis of diabetic nephropathy. In this chapter, we will focus on advanced glycation end-products (AGE) and the receptor for AGE (RAGE) in the development and prevention of diabetic nephropathy.

2. Possible molecular mechanisms for the development of diabetic nephropathy

Diabetic nephropathy occurs in 20-40% of patients with diabetes and accounts for disabilities and the high mortality rate in patients with diabetes (1). In proportion to the rapid increase of diabetic population, diabetic nephropathy is now the major cause of ESRD in developed countries. There are many factors influencing the development of diabetic nephropathy, this including genetic, hemodynamic, environmental, and metabolic factors. The epidemiological studies have revealed that hyperglycemia *per se* is the most important factor in the onset and progression of diabetic vascular complications (2). Potential mechanisms underlying diabetic nephropathy include activations of polyol and hexosamine pathways, oxidative and nitrosative stress, ER stress, protein kinase C activation, poly(ADP-ribose) polymerase activation, and inflammation (3). Extensive intracellular and extracellular formation of AGE can also become a pathogenic factor in sustained hyperglycemia-induced kidney injuries. Both receptor-dependent and -independent mechanisms are involved in AGE-induced cellular dysfunction and tissue damage.

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3. AGE

Reducing sugars like glucose can react nonenzymatically with amino groups of proteins, and a series of further complex molecular rearrangements of dehydration, condensation and crosslinking yield irreversible and heterogeneous derivatives termed AGE (4). AGE are also generated by the reaction of aldehydes and metabolites from glycolysis pathway such as dicarbonyls of methylglyoxal (MG), glyoxal and 3-deoxyglucosone (3DG) with amino acids, lipids and nucleic acids, and through lipid peroxidation (5,6). Although this process takes place continuously within the body during aging, it is extremely accelerated in diabetes (7). There are a large portion of these agents can be exogenous. Tobacco smoke has already been recognized as an important exogenous source of AGE (8). The diet, especially the modern western diet, also provides a relatively large portion of formed AGE and AGE-precursors; e.g. ϵ N-carboxymethyl-lysine (CML) and MG (9). However, the exact nature of various diet-derived AGE derivatives has not yet been fully elucidated.

In vitro, AGE stimulate the generation of reactive oxygen species (ROS), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor- β (TGF- β) in mesangial cells (10, 11), the features characteristic of glomerulosclerosis. AGE also induce TGF- β production in tubular cells, which links to the pathogenesis of tubulointerstitial fibrosis (12). Podocytes undergo apoptosis when exposed to AGE (13), this being implicated in podocyte injuries in diabetes (Fig. 1).

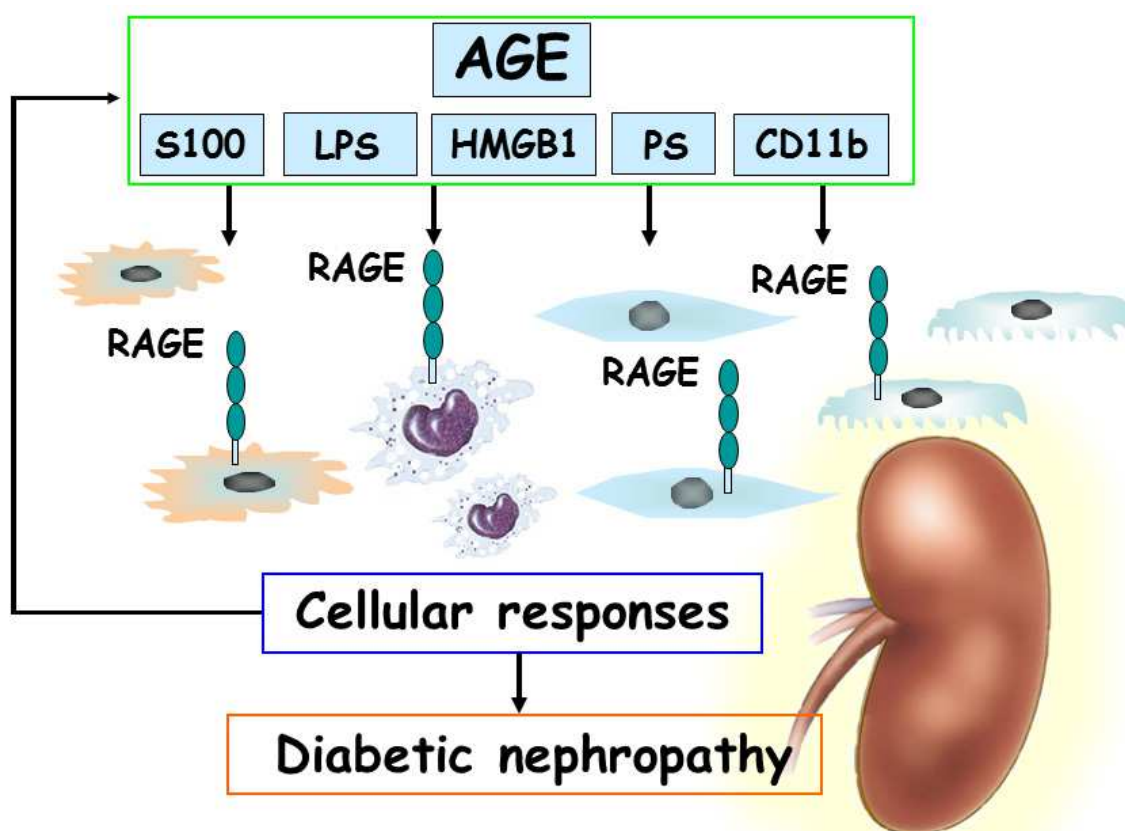


Fig. 1. AGE-RAGE axis and the interaction of other ligands with RAGE contribute to cellular responses and development of diabetic nephropathy. LPS, lipopolysaccharides; PS, phosphatidylserine.

There are three lines of evidence for the role of AGE in diabetic nephropathy. The first line concerns the association between the accumulation of AGE-modified proteins and severity of diabetic nephropathy in both diabetic animals and man (14-17). The second comes from the fact that kidney injuries develop following injection of AGE-modified proteins in non-diabetic animals (18). The third kind of evidence is that the development and progression of diabetic nephropathy is attenuated by the treatment with inhibitors of AGE formation and AGE breakers such as aminoguanidine, pyridoxamine and ALT-711 (19-22).

4. AGE receptors

Accumulating evidence indicates that the interaction of AGE with their receptor can play an important role in the pathogenesis of diabetic nephropathy (23). The best characterized AGE receptor is RAGE. Many other AGE receptors and soluble binding proteins interacting with AGE may also participate in the AGE homeostasis: scavenger receptors class A (MSR-A), class B (MSR-B) (CD36 and LOX1), AGE-R1 (OST48 oligosaccharyltransferase), AGE-R2 (80K-H protein kinase C substrate), AGE-R3 (galectin-3), and toll-like receptor (TLR) 4 (24-28). There are also other molecules like lysozyme and lactoferrin-like polypeptide that play a role in cellular uptake and degradation of AGE (29).

RAGE is a member of the immunoglobulin superfamily, having a total of 394 amino acid residues in the case with human ortholog with a single hydrophobic transmembrane domain (19 amino acids) and a highly charged C-terminal cytosolic tail (43 amino acids) that mediates intracellular signaling pathways (30). Extracellularly, RAGE has an N-terminal immunoglobulin (Ig) V-type ligand binding domain and two Ig C-type domains (V-C-C') (Fig. 2).

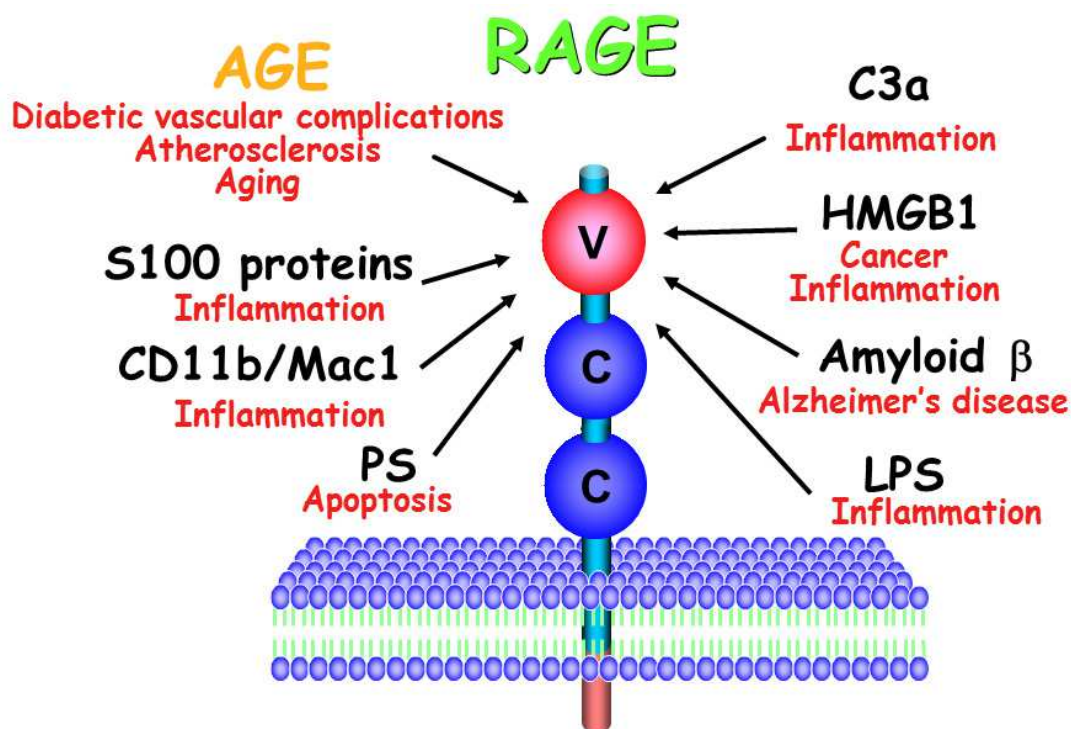


Fig. 2. RAGE belongs to an immunoglobulin superfamily and functions as a member of PRRs. LPS, lipopolysaccharides; PS, phosphatidylserine.

AGE-RAGE interaction can induce expressions of genes for vascular endothelial growth factor (VEGF) and for vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells (EC) (31, 32), leading to enhancement of vascular permeability and local inflammation. Secretion of various cytokines such as tumor necrosis factor α (TNF α), interleukin 1 β (IL1 β), IL6, and monocyte chemotactic protein-1 (MCP-1) were induced by the AGE-RAGE system in monocytes and macrophages (33) (Fig. 1). Mammalian homologue of *Drosophila* gene Diaphanous 1 (mDia1) has been identified as a directly binding molecule with an intracellular domain of RAGE and subsequently proven to act as a part of the machinery of RAGE intracellular signaling (34). It is very recently reported that AGE-RAGE interaction can cause phosphorylation of cytoplasmic domain at Ser391 of RAGE by PKC ζ (35) (Fig. 3).

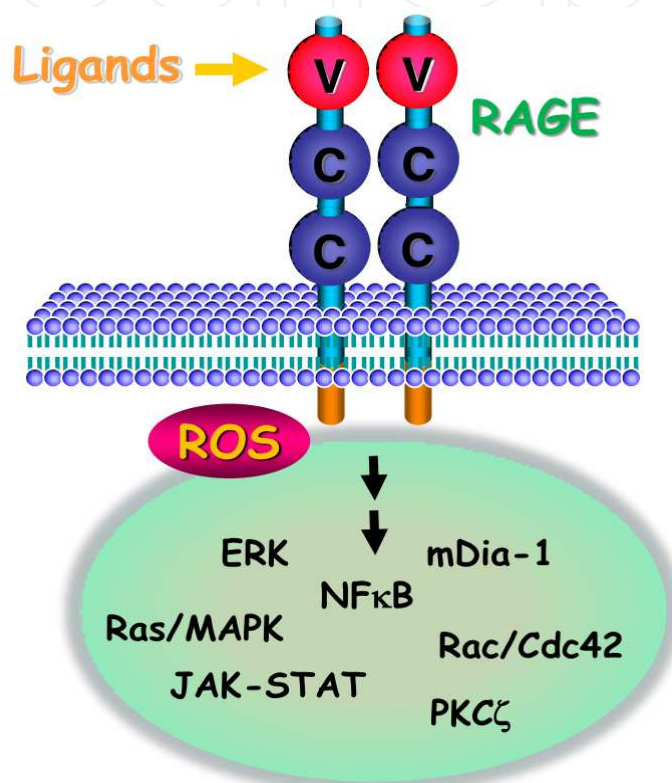


Fig. 3. RAGE intracellular signaling pathways. ERK, extracellular signal-regulated kinase; mDia-1, mammalian Diaphanous-related formin-1; NFκB, nuclear factor κB; PKC ζ , protein kinase C ζ ; JAK-STAT, The Janus kinase-signal transducers and activators of transcription; Ras/MAPK, Ras/mitogen-activated protein kinase; Rac/Cdc42, Rac/Cell division control protein 42 homolog.

RAGE ligands other than AGE have been identified, including high-mobility group box protein 1 (HMGB1), calcium-binding S100 protein group, β 2-integrin Mac/CD11b, amyloid β peptide, β -sheet fibrils, advanced oxidation protein products (AOPP), complement C3a, lipopolysaccharides (LPS), and phosphatidylserine on the surface of apoptotic cells (36-41) (Fig. 2). RAGE is thus considered a member of pattern-recognition receptors like TLRs, actively participating not only in diabetic vascular complications but in the interface of innate and adaptive immunity and in inflammation.

Ligand engagement of RAGE activates the nuclear factor-κB (NF-κB) and other signaling pathways through stimulation of ERK (extracellular signal-regulated kinase)1/2, p38 MAPK

(mitogen-activated protein kinase)-JNK (c-Jun N-terminal kinases), JAK (Janus kinase)-STAT (signal transducer and activator of transcription), and Rac-Cdc42 (42) (Fig. 3). Expression of RAGE is basically low in vascular cells but apparently constitutively induced during diabetes and inflammation. This is explained by the fact that the gene for RAGE *per se* is under the control of NF- κ B, which thus constitutes a positive loop of regulation (43), thereby resulting in the superdrive of the AGE-RAGE system during prolonged hyperglycemic exposure.

5. RAGE and diabetic nephropathy in mice

Development of diabetic nephropathy is characterized by glomerular hyperfiltration and thickening of glomerular basement membranes, followed by an expansion of extracellular matrix in mesangial areas and increased albuminuria. Diabetic nephropathy ultimately proceeds to glomerular sclerosis associated with renal dysfunction.

Because diabetic nephropathy is the major cause of ESRD, the development of effective remedies to retard the progression of diabetic nephropathy has become a pharmaceutical goal. However, it has been hampered by the lack of adequate experimental models to test them (44). We created transgenic (Tg) mice that overexpressed human RAGE in vascular cells by introducing fertilized ovum a transgene carrying human RAGE gene under the control of the murine *flk-1* promoter which works in EC (45). The Tg mice were made

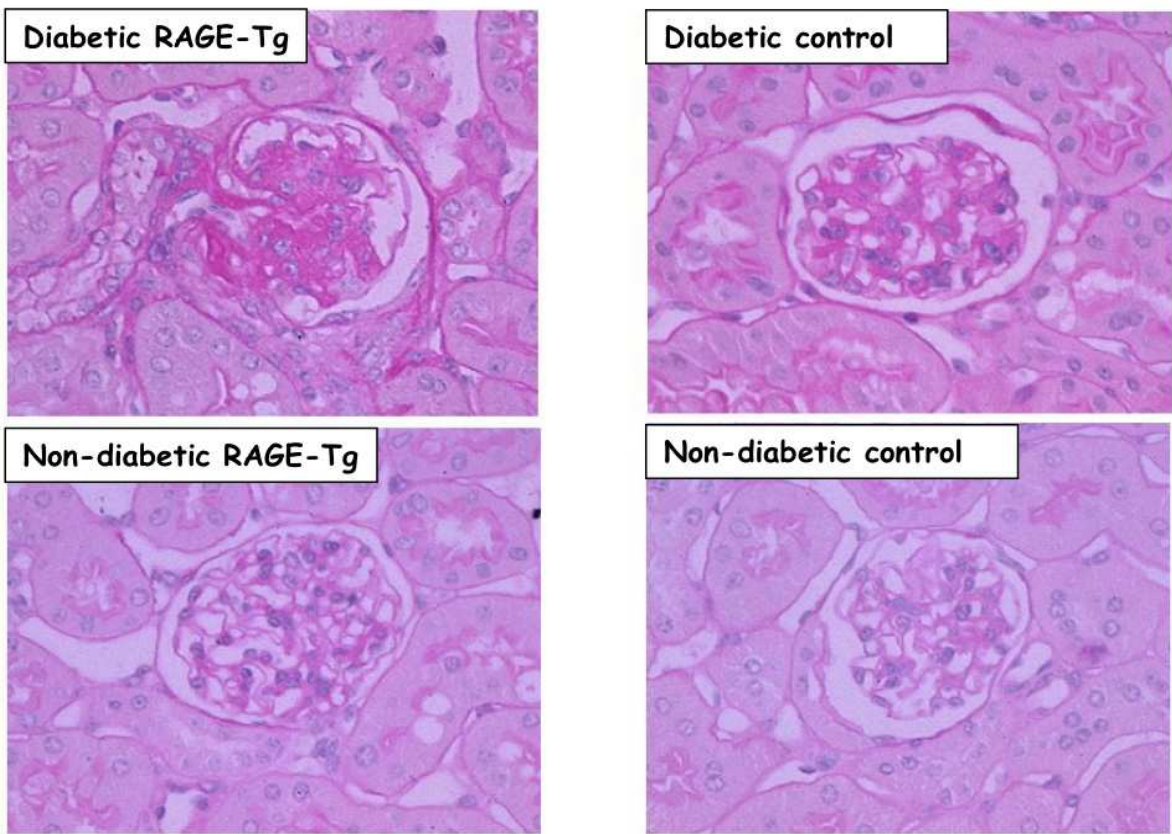


Fig. 4. Periodic acid-Schiff (PAS) stain of the mouse kidneys at 16 weeks of age (ref. 45). Diabetic RAGE-Tg, diabetes-induced RAGE-overexpressing transgenic mice; Diabetic control, diabetes-induced non-transgenic mice; Non-diabetic RAGE-Tg, non-diabetic RAGE-overexpressing transgenic mice; Non-diabetic control, non-diabetic non-transgenic mice.

diabetic by crossbreeding with another Tg line carrying inducible nitric oxide synthase (iNOS) cDNA under the control of insulin promoter (46). The resultant double Tg mice showed significant increases in kidney weight, albuminuria, glomerulosclerosis, and serum creatinine compared with the diabetic iNOS Tg controls (45) (Fig. 4). The sole iNOS Tg mice also showed progression of diabetic nephropathy accompanied by expression of TGF- β in glomeruli (47). Inagi and our group introduced megin (mesangial cell-specific gene with homology to serine protease inhibitor) as the third transgene into RAGE-iNOS double Tg mice, this resulting in further acceleration of the development of nephropathy signs such as mesangial expansion, nodule-like lesion, and tubulointerstitial damage with an increase in local oxidative stress (48). Our group also generated homozygous RAGE knockout (KO) mice and found that the RAGE KO mice displayed suppression of all of the following features of advanced glomerular disease: kidney enlargement, increase in glomerular cell number, mesangial expansion, advanced glomerulosclerosis, albuminuria and the increase in serum creatinine (49). The endothelial-mesenchymal-transition (EndoMT) was also attenuated by the deletion of RAGE (50). That RAGE axis is a crucial cause of diabetic nephropathy has thus clearly emerged from experiments with RAGE-gene manipulated animals. Another model is the OVE26 mouse, in which diabetes is induced by transgene-mediated introduction of calmodulin in pancreatic β -cells (51). RAGE deletion was also beneficial to diabetic nephropathy in the OVE26 diabetic mice (52).

6. Inhibition of AGE and RAGE for the treatment of diabetic nephropathy

A key aim of therapy in diabetic patients is to reduce hyperglycemia by modification of the diet. However, dietary compliance is often difficult, and the alternative is to use pharmacological compounds that can reduce AGE and inhibit RAGE action. There are several endogenous molecular devices that can serve to protect the body from glycation and AGE such as α -ketoglutaraldehyde dehydrogenase, glyoxalase and scavengers (53, 54). Hyperglycemia and RAGE activation are suggested to down-regulate glyoxalase I production and the enzyme activity (55). It is, therefore, rational to take pharmacologic strategies against the down-regulation of those endogenous detoxication enzymes.

Applications of inhibitors for AGE and RAGE may be promising therapeutic approaches for diabetic nephropathy (Table 1). Antioxidants may protect against free radicals derived from autooxidative glycation and AGE. Benfotiamine is a synthetic S-acyl derivative of thiamine and has anti-oxidant and anti-AGE formation (56). Amadoriases may be used to deglycate Amadori products or to inactivate intermediates such as 3DG. AGE-crosslink breakers such as ALT-711 (algebrium) and *N*-phenylthiazolium bromide (PTB) offer the potential of reversing diabetic nephropathy, although their precise mechanism of action is still unclear (57, 58). TTP488 is an antagonist against RAGE, which is under clinical studies, and neutralizing anti-RAGE antibody may also be useful (59). Low-molecular weight heparin (LMWH) can bind RAGE and act as an antagonist to RAGE [31]. LMWH treatment of the mouse model of diabetic nephropathy showed both the preventive and therapeutic effects on albuminuria and glomerulosclerosis in a dose-dependent manner (49). Thiazolidinediones, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and statins are reported to suppress RAGE expression (60, 61). There are numerous compounds that have been investigated for the anti-glycation activity but their use in humans is still debatable (62). Decoy type receptors of

RAGE, namely soluble RAGE (sRAGE), is also applicable for the treatment of diabetic nephropathy. sRAGE corresponds to the extracellular domain of RAGE lacking the transmembrane and cytosolic domains. As the N-terminal V-type domain is included, sRAGE has the same ligand-binding ability as membrane RAGE and thus is able to act as a decoy by preventing the ligands to reach the membrane-bound counterpart. In *db/db* mice, treatment with murine sRAGE (50 mg/day for 19 weeks) decreased albuminuria, glomerulosclerosis and GBM thickening (63); the sRAGE employed in that study was the truncated form of RAGE artificially produced by recombinant gene technology. Endogenous sRAGE exists in the circulation of humans. To generate sRAGE endogenously, two mechanisms are considered: (1) the alternative splicing to remove the transmembrane region and (2) the proteolytic cleavage from the cell surface. We identified and reported a splice variant form of soluble RAGE and named it endogenous secretory RAGE (esRAGE) (64, 65). Reinforcing sRAGE genesis by ectodomain shedding will decrease an amount of signal-transducing RAGE and will in turn reciprocally increase an amount of decoy receptor sRAGE; this can control ligand-RAGE signaling and subsequent cellular derangement in the kidney. Treatment with statins and ACEI is reported to stimulate circulating sRAGE production in human studies (66, 67). Further investigations are needed for better understanding of the regulation of sRAGE production and for developing drugs that can simultaneously upregulate sRAGE and downregulate mRAGE.

AGE inhibitors	Pyridoxamine Benfotiamine GLY-230
AGE-crosslink brakers	PTB ALT-711 (Algebrium) C36 TRC4186
RAGE inhibitors	LMWH TTP488/PF04494700 TTP3000, TTP4000
sRAGE	ACEI ARB TZD

PTB, N-phenacylthiazolium bromide; LMWH, low-molecular weight heparin; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; TZD, thiazolidinedione; sRAGE, soluble RAGE.

Table 1. Inhibitors of AGE and RAGE

7. Conclusions

Accumulating evidence has supported the concept that AGE and RAGE play an active role in the development and progression of diabetic nephropathy. Prophylactic and therapeutic strategies focusing on RAGE and its ligand axis will be of great importance in conquering diabetic kidney injuries.

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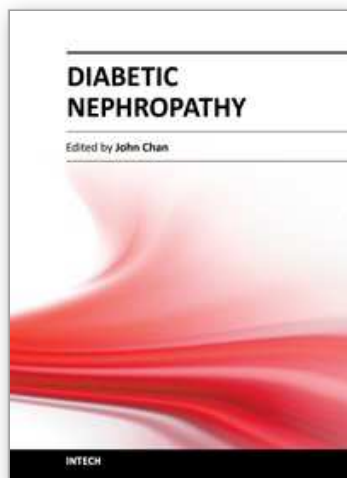
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Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

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