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Review Article

Role of Advanced Glycation End Products in the Progression of Diabetes Mellitus

Abstract

Diabetes Mellitus (DM) has become a world problem that seriously affected quality of life in concerned population; however, studies concerning its etiology and therapeutics are not so satisfactory. Hyperglycemia and oxidative stress damage are two hallmarks that aggravate the progression of each other. During this process, there will generate amounts of by-products, among which advanced glycation end products (AGEs) have been demonstrated to play a pivotal role in promoting the beginning and progression of DM. AGEs may interact with its receptor named RAGE and induce a series of pathological effects, such as oxidative stress, apoptosis, and inflammation etc., and form the so-called "hyperglycemia memory". This article aims to review the pivotal role of AGEs in the progression of DM..

Introduction

Due to the population aging, urbanization and associated lifestyle changes, the incidence of diabetes worldwide is dramatically increased [1]. It is reported that the number of diabetic population has doubled over the past three decades [2] and this number will increase to 591.9 million by 2035 [3].

Diabetes is mainly composed of two types, namely type 1 and 2 diabetes mellitus (T1DM and T2DM), and T2DM shares more than 90% of diabetic population [1]. Previously, most cases of T2DM were observed in developed rather than developing countries; for instance, the prevalence of T2DM was less than 1% in China in 1980 [4]. However, this trend is completely changed at present. It is reported that 80% cases of diabetes worldwide live in developing countries or areas [5], and Asia has become a "diabetes epicenter" in the world due to its rapid economic development and western food popularization [4]. More importantly, the proportion of young cases with T2DM is higher in developing rather than in developed countries [5], strongly suggesting the association between lifestyle change and the risk of occurring with T2DM. This suggestion is supported by another fact that the global epidemic of T2DM is positively related with overweight and obesity. According to a published report, the global prevalence of overweight or obesity may reach to 57.8% in 2030 [6]. As overweight or obesity are important risk factors of T2DM [7,8], diet-associated factors may significantly exacerbate the prevalence of DM.

A range of metabolic abnormalities, in addition to hyperglycemia, are seen in the diabetes. However, it is obvious from studies in diabetic patients that glucose is the predominant metabolic abnormality and one of the major systemic risk factors in diabetes [9].

Besides hyperglycemia, Oxidative Stress (OS) is widely recognized by investigators as another hallmark and key component in the development of diabetes [10]. It is demonstrated that hyperglycemia itself can contribute to OS by forming glycation products that propagate free radicals and enlarge oxidative damage [10]. Moreover, OS itself can induce free radical damage to the DNA and finally promote cell apoptosis [11]; furthermore, OS may directly and indirectly up-regulate inflammatory proteins expression and exaggerate diabetic inflammation.

Under hyperglycemia and OS settings, a series of pro-diabetic factors will be generated, such as pro-inflammatory cytokines and advanced glycation end products (AGEs). Within this decade, more and more studies elucidated the pivotal role of AGEs in the occurrence and progression of DM. This article aims to review the role of AGEs in the development of DM.

The generation and accumulation of ages

As have been well demonstrated, level of AGEs in the body is increased during aging and may be accelerated under pathophysiological conditions such as hyperglycemia. Concerning the generation process of AGEs, there are mainly two sources responsible for the accumulation of AGEs in

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the body: one is external derived and the other is internal originated [12].

External-derived AGEs: Investigations have observed that AGEs can be directly derived from external sources such as heat-treated food [13]. It has been well demonstrated that foods high in protein and fat, such as meat, cheese, and egg yolk, are rich in AGEs [14]; while foods high in carbohydrates have the lowest amount of AGEs. In addition, increased cooking temperatures and times, like broiling and frying, will lead to increased amounts of AGEs [15]. In fact, diet-originated AGEs can be directly absorbed through the gut [16]. It is observed that diet heavy in AGEs will result in proportional elevations in serum AGEs level and increased AGEs cross-linking in diabetic patients [17]. On the contrary, strictly restriction of dietary AGEs can dramatically decrease serum AGEs level by as high as 30% ~ 40% [15].

After absorption, dietary AGEs can also mediate AGEs-related tissue injury like internal-originated AGEs. For instance, a study found that diabetic patients on a high-AGEs diet have increased expression and activity of MAPK, NF-κB, and VCAM-1 compared with diabetic subjects on a low-AGE diet [18]; while restricting dietary AGEs intake demonstrates decreased circulating AGEs and CRP levels [19] and suppressed AGEs-related tissue injury [20].

Concerning controlling the content of external-originated AGEs, investigations show a possibility to decrease the production of AGEs. By administration with aminoguanidine (an inhibitor of AGE formation) or AGE-albumin, scholars found in streptozotocin-induced diabetic rats that AGEs-promoted vascular dysfunction was ameliorated [21]. Another study from Kihara and colleagues [22] also observed that the blockade of AGE formation by aminoguanidine was help to improve neural signal transmission in diabetic rats. However, to our knowledge, there is still no satisfactory agent applied in clinic till now. It is expected that exploring such agents may open a novel market toward DM intervention.

Internal-originated AGEs: As have been well demonstrated, advanced glycation and oxidation increases during aging and these processes are accelerated under pathophysiological conditions such as hyperglycemia. McPherson and colleagues [23] found the intracellular AGE formation is significantly increased in endothelial cells after 1 week in a hyperglycemic environment. Thus, AGEs accumulated during aging may function as persistent "endogenous danger signals" that set the stage for the manifestation of various complications in older persons [24, 25].

Reducing sugars including glucose, fructose, and trioses can react non-enzymatically with the amino groups of proteins to form reversible Schiff bases and then Amadori products. These early glycation products undergo further complex reactions such as rearrangement, dehydration and condensation to become irreversibly cross-linked heterogeneous fluorescent derivatives termed advanced glycation end products (AGEs) [26], and scholars defined this AGEs formation process as "Maillard reaction".

Specifically, Maillard reaction begins from Schiff bases and the Amadori product, a 1-amino-1-deoxyketose, produced by the reaction of the carbonyl group of a reducing sugar with proteins, lipids, and nucleic acid aminos [27,28]. During Amadori reorganization, these highly reactive intermediate carbonyl groups, known as alpha-dicarbonyls or oxoaldehydes, accumulate and induce corresponding damage to the tissue [10,28,29] and this process is called "carbonyl stress." It is reported that the alpha-dicarbonyls will react with amino, sulfhydryl, guanidine, lysine and arginine functional groups in proteins and results in the denaturation and cross-linking of the involved proteins [30-32], and finally leads to the formation of stable AGE compounds [32]. Several lines of evidence indicate that accumulation of these reactive carbonyl intermediates is consequent upon hyperglycemia in diabetes. Factors responsible for the formation of AGEs include the rate of turnover of proteins for glycoxidation, the degree of hyperglycemia and oxidant stress in the environment; and if one or more of these conditions is present, both intracellular and extracellular proteins may be glycated and oxidized [28,33,34].

So far, only a few AGEs structures have been identified *in vivo*, such as Nε-(carboxymethyl) lysine (CML), pentosidine, imidazolones, and oxalic acid monolysinylamide (OMA) et al. [35]. Studies found these Maillard products will accumulate throughout the body, and vascular tissue is the most deeply affected one [36-38]. Although there is evidence that enzymes, such as glyoxalase-1, may detoxify AGE precursors thus inhibit AGE production [39], it should be noted that once AGEs are formed, they are nearly irreversible [40].

The progression of DM has been demonstrated to be closely accompanied with the generation process of AGEs. In this sense, comprehending the pathophysiological role of AGEs in DM is help to understand DM in both clinical practice and pharmacological studies. Previous studies indicate that AGE proteins prepared *in vitro* possess similar cross-reactive AGE epitopes that are common to proteins modified by AGE *in vivo* [41]. Therefore, both the endogenous formed AGEs and the exogenous derived AGEs, over-cooking foods for example, would damage the human bodies.

Role of age in DM

In the year 1980s, Brownlee and colleagues [26,42,43] firstly described the harmful consequences of AGE formation on the cardiovascular and renal systems in human and diabetic rats. Studies have confirmed that AGE cross-links accumulate in diabetic patients and animals and will cause a series of diabetic complications [44].

As discussed above, AGEs cross-links are permanent and irreversible complexes formed when glucoses bind to the target proteins. A bad news is that these target proteins are usually housekeeping proteins including collagen and elastin, which play an integral role in the maintenance of tissue integrity [45]. Therefore, once AGEs are formed, they will remain and continuously damage the tissue until the proteins involved are degraded [46]. General mechanisms through which AGEs

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contribute to diabetic complications include (1) formation of cross-links in AGEs and (2) interaction of AGEs with RAGE on cell surfaces.

Oxidative Stress-related Hyperglycemic Memory

Oxidative Stress and DM: Cells actively maintain a proper level of intracellular reactive oxygen species (ROS) through defense systems including antioxidant enzymes and low molecular weight antioxidants under physiological conditions. However, hyperglycemia-promoted over-generation of ROS will accelerate the progression of diabetic complications [9]. Several lines of evidence demonstrate that oxidative stress (OS) or ROS are involved in the pathogenesis of diabetes [10]. On the other hand, it is found that the antioxidant capacity is compromised in diabetes [47]. Altered levels of circulating antioxidants [48] and intracellular scavenging enzymes [49] provide further evidence for increased OS in diabetes. At present, OS has been widely recognized as a key component in the development of diabetes and diabetic complications [50].

Reports have shown that antioxidant therapy protects against the development of kidney disease in animal models of diabetes [47,51] and experimental evidence obtained from *in vitro* studies showed that prevention of ROS generation defends against the damaging effects of a hyperglycemic milieu on mesangial cell function [52]. Indeed, the overexpression of cellular antioxidants, such as copper- or zinc-containing superoxide disumtase, protect against end-organ damage in diabetic model [53].

Oxidative Stress and AGEs: AGEs, as the oxidative products, can induce OS, promote cell apoptosis, and finally induce both micro- and macro-vascular disease in diabetic patients [26, 54-57]. Direct cellular challenge with AGEs has been shown to cause OS in various cell types [58-60]. It is found that Schiff-base products and Amadori products themselves cause ROS production [61], while Nitric Oxide (NO) donors can scavenge free radicals and inhibit AGEs formation [62]. Moreover, there is a significant correlation between the levels of AGEs and antioxidant enzymes, such as glutathione peroxidase and Cu/Zn-superoxide dismutase, in uremic plasma [63]. Studies found AGE accumulation itself is a source of OS. In hyperglycemic environments, glucose can undergo auto-oxidation and generate OH radicals [61,64]. Besides that, Quagliaro and colleagues [65] observed that AGEs can stimulate production of superoxide within the cells, which may induce free radical damage to the DNA and finally cause cell apoptosis.

Oxidative Stress and Hyperglycemia Memory: Hyperglycemia is a hallmark of DM and hyperglycemia itself can promote formation of reactive oxygen species (ROS), which can interact with both DNA and proteins, and cause damage. It is found that the mitochondrial DNA may be an especially relevant target of hyperglycemia-promoted damage [66]. Xie et al. [66] found ROS mediated cellular damage is a form of pathologic "memory" in the microvasculature that persists even after glucose normalization, as suggested in human retinal vascular endothelial cells. Therefore, ROS may directly damage both islet beta-cells and insulin-sensitive cells thus lead to hyperglycemia. ROS may also link hyperglycemia with other pathways implicated in diabetic vascular complications, including AGEs formation, protein kinase (PK)C activation, increased polyol flux, and hexosamine formation [39,67].

It should be noted that hyperglycemia, AGEs and OS may facilitate the genesis of each other and constitute a vicious circle. This vicious circle promotes the formation and accumulation of AGEs in various tissues as well as in plasma at an extremely accelerated rate in diabetes [68]. On the other hand, hyperglycemia can activate nuclear factor-kappaB (NF-κB) [69], a key mediator that regulates multiple pro-inflammatory target genes. The genetic and non-genetic pathway serves each other and forms another vicious circle to promote the progression of diabetes and forms the so-called hyperglycemic memory.

Hyperglycemic memory is firstly demonstrated by study in dogs. It is reported in diabetic dogs that euglycemia could not inhibit the progression of diabetic microvascular dysfunction, thus scholars named this phenomenon as "hyperglycemic memory" [70-72]. In fact, this phenomenon also exists in human beings [73]. Two possible mechanisms are proposed that responsible for this phenomenon. One is AGEs and the other is OS. As discussed above, once AGEs are formed, they are hardly degraded. So AGEs may continuously damage blood vessels even blood glucose is lowered. On the other hand, the generation of AGEs will cause oxidative stress and oxidative stress will further promote AGEs-induced tissue damage [74-77].

Receptor-mediated Oxidative Stress: Besides direct damage, AGEs also enhance cell OS damage via a receptor-mediated pathway. Interaction of AGEs with the cell-associated RAGE is associated with ROS generation and NF-κB activation [59,60]. And AGEs-RAGE interaction leading to an increase in ROS production has been shown to cause cell apoptosis [78]. There is a study suggests that NADPH oxidase plays an important role in AGE-RAGE dependent ROS generation and gene activation [79]. The role of RAGE in the progression of DM will be discussed hereinafter this review.

Chronic low grade inflammation

The cytokine/adipokine profiles of Mexican Americans with diabetes suggest an association between low-grade inflammation and quality of glucose control [80]. It has been well demonstrated that diabetes as whole was strongly associated with elevated levels of IL-6, leptin, CRP and TNF-α, whereas worsening of glucose control was positively and linearly associated with high levels of IL-6, and leptin. Thus, low-grade inflammation is also believed as a hallmark of diabetes. Previous studies have demonstrated the role of AGEs in driving inflammatory response in macrophages [81].

AGEs-mediated Inflammatory Cell Infiltration: Clinical studies have found significant increase of AGEs accumulation in vascular tissues [82], which may induce monocyte migration across an endothelial cell monolayer [83] and promote expression of inflammatory cytokines such as interleukin (IL)-

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1β and TNF-α mRNA [84]. In fact, scholars have observed AGEs to be present in the plasma and to accumulate in tissues at an accelerated rate in diabetes [26,85].

AGEs also increase permeability and expression of procoagulant activity in cultured endothelium, and induce migration of mononuclear phagocytes, as well as production of platelet-derived growth factor and cytokines [86]. Schmidt et al. [87] observed that levels of AGEs and receptor for AGEs (RAGE) are increased in streptozotocin (STZ)-treated (diabetic) apolipoprotein (apo) E-null mice that have advanced atherosclerosis by 14 weeks of age. Basta and colleagues [88] further found that AGEs located on proteins, in addition to immobilized AGEs on the subendothelium, bound RAGE on the endothelium and induced hyperpermeability in diabetes. These findings are supported by another report that administration of soluble RAGE (sRAGE) inhibits vascular leakage in the intestine and skin of STZ-treated rats [34].

Adhesion Molecules in Inflammatory Cell Infiltration: Leukocyte infiltration into inflammatory lesions is mediated by sequential engagement of cell adhesion molecules and chemokines. Leukocyte influx begins with leukocyte rolling and firm attachment (sticking) to the endothelium, followed by transmigration across the endothelial surface [89]. The blockade of specific cytokines and chemokines involved in processes such as the recruitment of inflammatory cells, including monocyte MCP-1, is demonstrated to be a valid therapeutic strategy in models of diabetic nephropathy. For example, blockade of the chemokine MCP-1 could attenuate not only macrophage infiltration but also progressive renal injury in db/db mice [90].

MCP-1

Both hyperglycemia and the accumulation of AGEs can promote MCP-1 production [91, 92]. An additional influence that may induce synthesis of MCP-1 is the generation of ROS [93]. Previous reports have demonstrated that NF-κB was involved in high glucose-induced production of MCP-1 [94], it can be explained as MCP-1 promoter and enhancer regions contain NF-κB binding sequences [95]. Kislinger and colleagues investigated neuronal-associated vessels and found that RAGE is localized with its putative ligand N-epsilon-carboxymethyl lysine and NF-κB, and IL-6 [41]. It indicates the expression of MCP-1 and IL-6 is positively related with that of RAGE, and the ligation of RAGE will increase MCP-1 and IL-6 at the same time. Therefore, the expression/activation of MCP-1 and NF-κB are positively related and forms a vicious circle: the high MCP-1 contributed abundant inflammatory cells infiltration, which may release amounts of inflammatory cytokines and exacerbate inflammation status; on the other hand, inflammation status activated the intracellular NF-κB, which contributes to further production of MCP-1 and other inflammatory cytokines/proteins, such as RAGE and IL-6 *etc.*.

ICAM-1

Besides MCP-1 as discussed above, intercellular adhesion molecule (ICAM)-1, a 90-kD cell-surface protein known as CD54 which possess five immunoglobulin-like domains, is also a major molecule involves in promoting leukocyte infiltration [92, 96]. Increased ICAM-1 expression is seen in models of type 1 [97] and type 2 diabetic nephropathy [98] in parallel with disease progression [99]. In patients with diabetes, the soluble form of ICAM-1 (sICAM-1) was observed to be elevated [100], and scholars regarded it as a powerful independent predictor of T2DM and diabetic-associated cardiovascular disease [101].

It is recognized that ICAM-1 may be even more important in promoting nephropathy associated with T2DM because its expression is not only induced by factors common to both types of diabetes, such as hyperglycemia [102], AGEs [103], hyperfiltration [104], and OS [105], but it can also be increased by additional elements characteristic of T2DM, including hyperlipidemia [106], hyperinsulinemia [107], and elevated levels of circulating TNF-α [108], which are associated with obesity [109]. In fact, the up-regulation of ICAM-1 can be observed soon after the induction of diabetes in streptozotocin (STZ)-induced diabetic rats [92, 110].

Although it is still controversial whether hyperglycemia *per se* can induce the expression of ICAM-1 on vascular endothelial cells, recent studies have suggested several possible mechanisms of ICAM-1 induction in diabetes: (1) ICAM-1 is induced by inflammatory cytokines such as TNF-α, IL-1, and interferon-gamma [111]; (2) Activation of protein kinase C results in upregulation of ICAM-1 on endothelial cells [112]; (3) AGEs enhance the expression of cell adhesion molecules, including ICAM-1 on vascular endothelial cells [113,114]; (4) Shear stress could also stimulate the induction of ICAM-1 [115]. Reports indicated [97,116] that shear stress, which is increased by hyperfiltration of glomerular endothelial cells, is one of the mediators of ICAM-1 induction in glomeruli; (5) OS has been documented to increase ICAM-1 expression [117]; (6) Osmotic agents up-regulate ICAM-1 expression in HUVECs [118].

Apoptosis

Most recently, there is a research demonstrated that AGEs can directly induce glomerular mesangial cells apoptosis in a dose-dependent manner [119]. In fact, the study of cell survival, or cell death (apoptosis) control, as opposed to control of mitosis, has been a focus of research over the past decade. Much of the recent understanding concerns the molecular regulation of cell survival or death by the Bcl-2 (B cell lymphoma) multigene family [11,120]. The balance of Bcl-2 family proteins can protect cell from apoptosis by reducing cell OS [11,120]; according to the report from Hockenbery and colleagues [120] , Bcl-2 polypeptides localize to intracellular sites including membranes of the mitochondria, nuclei and endoplasmic reticulum where ROS are generated, and these polypeptides can inhibit apoptosis via an anti-oxidant pathway.

In fact, studies on the intracellular cross-talk between ROS and apoptosis are abundant and have been well demonstrated. One of these pathways involves MAP kinases (p38MAPK, extracellular signal-regulated kinase1/2 (ERK1/2), and JNK *etc.*). Reports demonstrated that the activation of p38MAPK involves AGEs-induced fibroblast apoptosis [78] and podocyte

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apoptosis [121]. And another pathway involves PI3K-Akt. Akt is a cell survival factor. Growth factors or extracellular signals lead to the activation of phosphoinositide kinase, which results in Akt phosphorylation and activation leading to cell proliferation. Therefore, Akt activation by phosphorylation is an antiapoptotic signal that may protect cells from programmed cell death and promote survival [122]. Further studies found that Forkhead transcription factors (FOXOs) may participate in Akt-mediated cell survival. FOXOs, including FOXO1, FOXO3, and FOXO4, are a family of proteins that function as sensors of signaling pathways and modulate apoptosis, cell cycle, and metabolism through regulation of gene expression [123]. Akt regulates FOXO activity by inducing a prompt and sustained nuclear exclusion. There is broad consensus on the fact that Akt-dependent phosphorylation is crucial to the regulation of FOXO function. Kops et al. [124] observed activated-Akt phosphorylates and inactivates FOXO proteins. In the absence of Akt inhibition, FOXO is translocated to the nucleus leading to gene activation. FOXO transcription factors activate three major groups of genes: anti-oxidant genes, cell cycle arrest genes, and apoptotic genes [125]. It is reported that AGEs activate FOXO4 leading to apoptosis in podocytes [121] and FOXO1 leading to apoptosis in fibroblasts [78]. Further studies found the activation of JNK also plays a role in in FOXO activity [126,127].

Receptors for age

Mechanisms involved in the pathophysiological role of AGEs in diseases mainly lies in two aspects: (1) oxidative stress damage, which is directly induced by AGEs and has been discussed above; and (2) receptor mediated injury.

Types of AGEs receptors

Amounts of studies indicate that most of AGE-modified tissue damage is via AGE receptors. AGE receptors are found in a number of different cell types [128]. To now, a series of AGEs receptors have been identified and the most important receptor type is named as "the receptor for AGE (RAGE)" [40]. The other receptor types include (1) oligosaccharyltranferase-48, also called AGE-R1 [128]; (2) 80K-H, known as AGE-R2 [128]; (3) galectin 3, known as AGE-R3 [129]; (4) lactoferrin-like AGE binding protein [130]; (4) scavenger receptors (SR) class A, type II (MSR-AII) [131] and (5) SR class B, type I (MSR-BI, also known as CD36) [132].

The AGE-receptor system can be divided into two arms: one is associated with increased OS, growth, and inflammatory effects, best represented by RAGE [103]; and the other, involved in the clearance and possible detoxification of AGEs [133], includes transduce cellular signals after engagement by AGEs [133]. In this sense, although several types of AGEs receptors exist, only RAGE is demonstrated to mediate its harmful effects [40].

Structure of RAGE

The receptor for AGEs (RAGE) is the first one that described as a receptor for the products of nonenzymatic glycation and oxidation of proteins. Thereafter, besides AGEs, amounts of natural ligands of RAGE are found, including high mobility group box 1 (HMGB1), S100/calgranulins, Mac-1, phosphatidylserine and amyloid (Aβ) can also serve as RAGE ligands [134,135]. Like AGEs, an increased level of RAGE had been found in cardiac and renal tissue in diabetes [136].

RAGE is a member of the immunoglobulin superfamily [137]. The human RAGE gene is on Chromosome 6 in the major histocompatibility complex between genes for class II and class III. RAGE has a single transmembrane domain followed by a highly charged 43–amino acid cytosolic tail [138]. Specifically, it has a 332–amino acid extracellular component, consisting of two "C"-type domains preceded by one "V"-type immunoglobulin-like domain. The V domain in the N-terminus has two Nglycosylation sites and is responsible for most (but not all) extracellular ligand binding [139], and the cytoplasmic tail is believed to be essential for intracellular signaling, possibly binding to diaphanous-1 to mediate cellular migration [140]. RAGE is expressed as both full-length, membrane-bound form (fl-RAGE or mRAGE) and various soluble forms (sRAGE) which lack the transmembrane domain. While a form of RAGE that lacks the cytosolic tail but stays embedded in the membrane where it binds AGEs functions as a dominant-negative RAGE, unable to transduce a cell signal on ligand engagement.

During homeostasis, most of the tissues express a basal level of RAGE [136]. As a member of the immunoglobulin (Ig) superfamily protein, RAGE is low expressed in normal tissue and vasculature [64] and this basal level of RAGE expression involves in embryonic growth and development [141], cellular proliferation and survival [142] and the activation of various signaling events [143].

Tissues do not express significant amounts of RAGE under physiological conditions but can be induced to express RAGE in situations where either ligand accumulate and/or various transcription factors regulating RAGE are activated [144]. AGEs activation of RAGE is found in diabetes, neurodegeneration, and aging [145]. Collison and colleagues [146] demonstrated that RAGE will bind to AGE-modified albumin but not nonglycated albumin. In the diabetic vasculature, cells expressing high levels of RAGE are often proximal to or colocalized in areas where AGEs are abundant [147].

Oxidative stress promoted RAGE expression

RAGE expression is found to be elevated in high-OS states including diabetes [147], which implies a sustained ROS and AGEs generation, resulting in RAGE activation, and so on. This cycle could conceivably alter the cell's phenotype, obscuring other receptor properties or depleting cellular antioxidant systems [148]. Furthermore, the activation of RAGE has been demonstrated to engage critical signaling pathways linked to pro-inflammatory responses, resulting in activation of various inflammatory genes [149].

Role of RAGE in diabetic-inflammation

Experimental evidence and observation strongly suggest that RAGE signaling results in profound inflammation [150].

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Engagement of RAGE by the ligands activates key signal transduction pathways, such as $p21^{ras}$, ERK1/2 kinases and NF-κB in endothelial cells (ECs), monocytes, and vascular smooth muscle cells. Activation of RAGE by its ligands results in a "feed forward" signaling mode that upregulates RAGE expression and amplifies the cell signals. This cascade of events leads to RAGE-mediated-enhanced expression of proinflammatory mediators as demonstrated by suppression of the effects of these modified adducts in the presence of blocking antibodies to RAGE, sRAGE, the extracellular ligand-binding domain of the receptor, or by transient transfection of cDNA encoding cytosolic tail-deleted RAGE into RAGE-bearing cells [41,130,151]. One mechanism underlying this observation probably is the presence of at least two functional binding elements for NF-κB in the promoter of the gene encoding RAGE [152,153]. In diabetic apolipoprotein E (apo E) deficient mice, RAGE signaling mediates prolonged vascular inflammation, and enhances the expression of vascular cell adhesion molecule (VCAM)-1 and tissue factor, leading to an exacerbation of the inflammatory state [154]. In addition, RAGE participates in diabetes associated atherosclerosis [155]. The role of RAGE as an inflammatory mediator is further demonstrated by application of RAGE antibodies or genetic knock-out methods. A report found that soluble RAGE (sRAGE) may play as a direct inhibitor of leukocyte recruitment [156].

By functioning as a co- or counter-receptor of the adhesion molecules, RAGE facilitates the recruitment of leukocytes to the injured vascular tissues. Amounts of reported studies have demonstrated that ligand-activated RAGE serves as an adhesion receptor that interacts with integrins and facilitates the recruitment of proinflammatory leukocytes to the sites of inflammation, and further enhancing the inflammatory state [157]. Some scholars also recognized RAGE plays as a counter-receptor for leukocyte integrins and directly contributs to the recruitment of inflammatory cells *in vivo* and *in vitro*. Pullerits et al. [158] reported that RAGE acts as an endothelial adhesion receptor that mediates interactions with the β2 integrin Mac-1. Evidence suggests neutrophils and myelomonocytic cells adhere to immobilized RAGE or RAGE-transfected cells, and this interaction is attributed to Mac-1 interactions [159]. Such interactions are augmented by the addition of S100B ligand. Hence, this RAGE-Mac-1-dependent leukocyte recruitment may be involved in the ICAM-1-independent leukocyte transmigration as observed in the ICAM-1 deficient mice [160]. But some scholars believe that RAGE may serve as an "indirect" promoter in inflammatory cell recruitment because RAGE mediated cellular activation and upregulation of adhesion molecules and proinflammatory factors [156]. Whatever, it seems that RAGE plays a significant role in the process of inflammatory cell adhesion and infiltration. Studies demonstrated that RAGE is highly expressed in macrophages, T lymphocytes, and B lymphocytes [161], and this expression may contribute to the inflammatory mechanisms.

Another impact of RAGE over-expression on diabetic inflammation is that the activation of RAGE by AGEs increases endothelial permeability to macromolecules [152]. Basta and colleagues [88] found that AGEs located on proteins, in addition to immobilized AGEs on the subendothelium, bind RAGE on the endothelium and induce hyperpermeability in diabetes. This finding is supported by another report than administration of sRAGE inhibits vascular leakage in the intestine and skin of streptozotocin-treated rats [34]. Reports have demonstrated that RAGE expression can be up-regulated on AGEs accumulation [64] and limiting RAGE expression can down-regulate expression of pro-inflammatory cytokines and attenuate vasculitis development [162]. Converging with the above discussions, downregulating RAGE should have significant role in protecting the organism against AGEs-induced inflammatory damage.

Due to the significant role of RAGE during the development of diabetes, blockade of RAGE ligation has been regarded as an effective way towards AGEs-induced diseases [43]. Because all soluble RAGE (sRAGE) species contain an intact N-terminal portion that encompasses the entire Ig-like domains, they maintain the full capacity of ligand binding, yet are devoid of signaling functions. These properties confer upon sRAGEs the status of a natural decoy for the plasma membrane-anchored RAGE [163]. As sRAGE blocks AGEs from binding to RAGE, as if sRAGE was a "sponge" soaking up soluble AGEs (sAGEs) [164], it becomes a potential therapeutic tool for the treatment of inflammatory diseases including diabetes and cardiovascular diseases. Reports indicated that RAGE participates in the formation of diabetes associated atherosclerosis in RAGE/apolipoprotein E double knock mice [155]. Another study observed that blockade of RAGE with anti-RAGE IgG or sRAGE inhibited NF-κB activation [34]. Furthermore, study found that the vascular inflammatory phenotypes such as accelerated expression of VCAM-1, tissue factor, or matrix metalloproteinases in mice are also prevented by sRAGE treatment [165]. Since AGEs may also form adducts with extracellular matrix (ECM), they may affect the structural integrity of the vessel in addition to signaling via RAGE [166]. Thus, sRAGE may also prevent such "non-specific" adverse effects of AGEs, especially during aging. Despite of its benefits on preventing RAGE ligation, sRAGE cannot be widely applied clinically due to its PROTEIN nature, which may induce immunogenicity *in vivo*.

Conclusion

The global prevalence of diabetes has seriously influenced the quality of life as a whole, and diabetes and diabetic dramatically increase the financial burden of the health system worldwide. Hyperglycemia and oxidative stress are two hallmarks of diabetes, and the generation of AGEs has been demonstrated to be accompanied with hyperglycemia and oxidative stress. AGEs can promote the development of diabetes via both direct and indirect pathway. On the one hand, AGEs augmented oxidative stress; on the other hand, AGEs active RAGE and induce receptor-mediated cell damage, such as apoptosis and inflammation.

The intervention of AGEs-involved damage should help to ameliorate the development of diabetes. Currently, there are mainly two strategies can be considered. Firstly, AGEs oriented strategy. Either reducing the intake of AGEs-rich foods or using AGEs formation inhibitor aminoguanidine can directly reduce

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AGEs-oriented damage to the organism. The second strategy if receptor oriented. Application of soluble RAGE (sRAGE) or inhibiting expression of RAGE has been demonstrated to possess effects on ameliorating diabetic complications. However, there is still no satisfactory agents or drugs applied in clinic that target AGEs. Investigations in this area may bring a novel strategy towards treatment of diabetes and diabetic complications.

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