Controlling the receptor for advanced glycation end-products to conquer diabetic vascular complications

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Controlling the receptor for advanced glycation end-products to conquer diabetic vascular complications

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ABSTRACT

Diabetic vascular complications, such as cardiovascular disease, stroke and microangiopathy, lead to high rates of morbidity and mortality in patients with long-term diabetes. Extensive intracellular and extracellular formation of advanced glycation end-products (AGE) is considered a causative factor in vascular injuries in diabetes. Receptor-dependent mechanisms are involved in AGE-induced cellular dysfunction and tissue damage. The receptor for AGE (RAGE), originally an AGE-binding receptor, is now recognized as a member of pattern-recognition receptors and a pro-inflammatory molecular device that mediates danger signals to the body. Previous animal studies have shown RAGE dependent of diabetic vascular injuries. Prophylactic and therapeutic strategies focusing on RAGE and its ligand axis will be of great importance in conquering diabetic vascular complications. (J Diabetes Invest, doi: 10.1111/j.2040-1124.2011.00191.x, 2012)

KEY WORDS: Advanced glycation end-products, Diabetic vascular complications, Receptor for advanced glycation end-products

INTRODUCTION

Diabetes is a life-threatening disease because of its devastating vascular complications, such as cardiovascular disease, stroke and microangiopathy. In 2008, 347 million people had diabetes worldwide[1]. In proportion to the rapid increase in the diabetic population, diabetic nephropathy is now a major cause of end-stage renal disease and diabetic retinopathy is a leading cause of blindness[2]. Potential mechanisms underlying diabetic vascular diseases include activation of the polyol and hexosamine pathways, oxidative and nitrosative stress, endoplasmic reticulum stress, protein kinase C (PKC) activation, poly (adenosine diphosphate (ADP)-ribose) polymerase activation, and inflammation[3]. Extensive intracellular and extracellular formation of advanced glycation end-products (AGE) can also become a pathogenic factor in sustained hyperglycemia-induced vascular injuries in diabetes. AGE-induced cellular dysfunction and tissue damage arise from both receptor-dependent and receptor-independent mechanisms. The receptor for AGE (RAGE) is a well-characterized AGE-binding receptor, and is now known as a member of the pattern-recognition receptors (PRR) and a pro-inflammatory molecular device that mediates danger signals to the body. In the present review, the current understanding about AGE and a multiligand receptor of RAGE will be discussed from the perspective of it being a mechanism causing diabetic vascular complications and a therapeutic target of this disease.

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AGE

The formation of brown-colored substances resulting from non-enzymatic reactions between reducing sugars and proteins was first described by Maillard[4]. Exposure of the amino acid residues of proteins to reducing sugars, such as glucose, glucose 6-phosphate, fructose, ribose and intermediate aldehydes, results in non-enzymatic glycation, which forms reversible Schiff bases and subsequently Amadori compounds (Figure 1). A series of further complex molecular rearrangements including dehydration, condensation and crosslinking, yield irreversible and heterogeneous derivatives termed AGE (Figure 1)[5]. Similar reactions occur with non-glucose materials containing an aldehyde group through both enzymatic and non-enzymatic pathways. The glycolysis pathway yields the highly reactive dicarbonyls of methylglyoxal (MG), glyoxal and 3-deoxyglucosone (3DG), which can interact with protein residues to rapidly form AGE[6]. Reactive dicarbonyls can also be generated from ketones, lipids, and other metabolic pathways[7]. The major driving force for AGE formation and accumulation is a state of carbonyl stress, which can be caused by increased production of the reactive dicarbonyls or reduced detoxification by the glyoxalase system or endogenous scavengers[8]. Glyoxal is also generated by the auto-oxidation of glucose; 3DG is formed by fructosamine-3-kinase from fructoselysine,

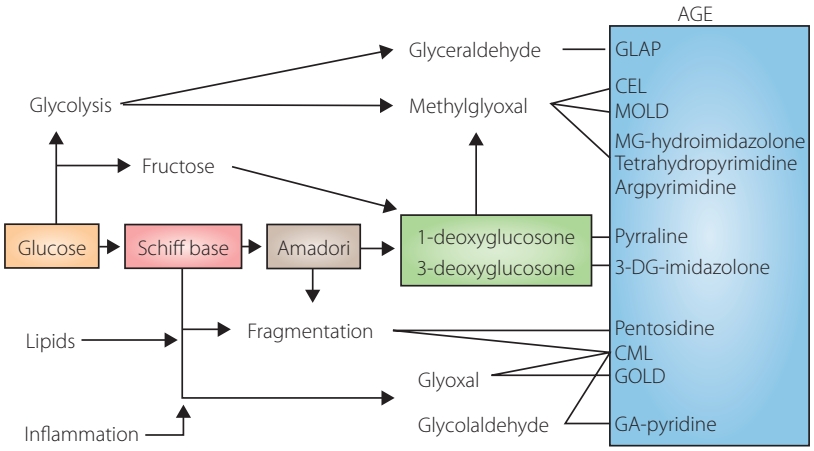

Figure 1 | Possible pathways of advanced glycation end-products (AGE) formation. This is adapted from a review paper by Monnier *et al.*[95]. The classical pathway leading to the formation of AGE involves Schiff base and Amadori products. The Amadori products can be transformed into reactive dicarbonyl products, such as glucosones, and can be fragmented by oxidation (glycoxidation) to generate pentosidine and N^{ε}-carboxymethyl-lysine (CML). Reactive dicarbonyls can also be generated from ketones, lipids, glycolysis and inflammatory pathways. Representative AGE are presented here. CEL, N^{ε}-carboxyethyl-lysine; 3-DG-imidazolone, 3-deoxyglucosone-imidazolone; GA-pyridine, glycolaldehyde-pyridine; GLAP, glyceraldehyde-related pyridinium; GOLD, glyoxal-derived lysine dimer; MG-hydroimidazolone, methylglyoxal-derived hydroimidazolone; MOLD, methylglyoxal-derived lysine dimer.

an Amadori rearrangement product[9]. Production of glycolaldehyde by myeloperoxidase from activated macrophages and neutrophils plays a pathogenic role in generating AGE and damaging tissues at inflammation foci[10].

In diabetic conditions, uncontrolled and sustained hyperglycemia drives this glycation reaction; consequently, AGE accumulate in the circulation, as well as extracellular and intracellular spaces. The hyperglycemia-induced formation of MG is reported to modify transcriptional regulators inside cells, resulting in cellular activation or dysfunction[11]. Nevertheless, AGE are also generated as a result of redox imbalances, aging and kidney dysfunction in the absence of hyperglycemia[12–14]. AGE are chemically heterogeneous groups of compounds; the structures of just 25 having been fully characterized (Figure 1). Among them, N^{ε}-carboxymethyl-lysine (CML) is the best characterized and is the main epitope for recognition by most commercially available antibodies used for the detection and quantification of AGE. Apart from endogenously formed AGE, exogenous AGE from foods are absorbed in the gastrointestinal tract and purportedly constitute ~10% of total AGE in the body[15–17]. In animal studies, the restriction of dietary AGE intake significantly improved insulin sensitivity and extended lifespan[18].

AGE RECEPTORS

The best-characterized AGE receptor is RAGE. RAGE belongs to the immunoglobulin (Ig) superfamily and is composed of an extracellular region containing one V-type and two C-type Ig domains[19]. The Ig portion of the receptor joins to a hydrophobic transmembrane-spanning domain followed by a highly charged 43-amino acid short cytoplasmic tail that is essential for post-RAGE signaling[20]. Many other AGE receptors and soluble binding proteins interacting with AGE might play important roles in AGE homeostasis. Scavenger receptors are classified as class A (scavenger receptor (SR)-A), class B (SR-B; CD36 and SR-B1), lectin-like oxidized low-densitylipoprotein receptor (LOX) 1, AGE-R1 (OST48 oligosaccharyltransferase), AGE-R2 (80K-H PKC substrate), AGE-R3 (galectin-3) or toll-like receptor (TLR)4[21–25]. Other molecules, such as lysozyme and lactoferrin-like polypeptide, play roles in the cellular uptake and degradation of AGE[26]. AGE-R1 is a type I transmembrane receptor found on the plasma membrane and in the endoplasmic reticulum[21]. Cell surface membrane-associated AGE-R1 blocks the AGE-induced cellular responses of reactive oxygen species (ROS) formation, activation of mitogen-activated protein kinase (MAPK)/Ras, and inflammation; this is mediated, in part, through RAGE[27]. The overexpression of AGE-R1 in mice is associated with decreased basal levels of circulating and tissue AGE and oxidative stress, and significant protection against wire injury-induced femoral artery intimal hyperplasia and inflammation[28]. AGE-R3 (galectin-3) is also reported to function as an AGE receptor to inhibit AGE-induced tissue injury through AGE removal or degradation[22,23].

RAGE

Experiments with vascular endothelial cells, pericytes and renal mesangial cells in culture, as well as from AGE inhibitor-treated and RAGE gene-manipulated animals, have led to the hypothesis that the AGE–RAGE axis is a crucial cause of diabetic vascular complications. The V-type domain of RAGE interacts with AGE, and deletion of its *N*-glycosylation modification enhances the binding affinity to AGE[29]. The possible mechanism of the

binding includes charge association and subsequent stabilization of the complex with hydrophobic interactions after conformational changes of the RAGE V-type domain[30]. This hypothesis is supported by the fact that low-molecular-weight heparin (LMWH; ~5 kDa, negatively charged) binds to the V-type domain of RAGE and inhibits the AGE–RAGE association, silencing the RAGE activation of nuclear factor-κ B (NF-κB)[31].

The AGE–RAGE axis in endothelial cells could induce the expressions of genes for vascular endothelial growth factor and vascular cell adhesion molecule-1[32,33], enhancing vascular permeability, angiogenesis and local inflammation. The secretion of various cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and monocyte chemotactic protein-1 are induced by the AGE–RAGE axis in monocytes and macrophages[34]. RAGE promoter assays showed that AGE–RAGE signaling promotes the transcriptional upregulation of the RAGE gene through the activation of NF-κB[35]. TNF-α and estrogen also enhance the transcription of the RAGE gene through the activation of NF-κB and the transcription factor, Sp1, respectively[35]. The mammalian homolog of the *Drosophila* gene, Diaphanous 1 (mDia1), has been identified as a direct binding molecule with the intracellular domain of RAGE and as a part of the machinery of RAGE intracellular signaling[36]. mDia1, one of the Formin homology proteins, exists widely from yeasts to mammals, and is linked to cell division, polarity formation and movement by actin polymerization[36]. Very recently, it was reported that the AGE–RAGE interaction could phosphorylate the cytoplasmic domain of RAGE at Ser391 through PKCζ[37]. TIRAP and MyD88, which are adaptor proteins for TLR 2 and 4, bind to phosphorylated RAGE and transduce the signal to downstream molecules, suggesting a functional interaction between RAGE and TLR, as well as the regulation of immune responses and inflammation in a coordinated manner[37].

RAGE LIGANDS OTHER THAN AGE

Endogenous and exogenous RAGE ligands other than AGE have been identified, including high-mobility group box protein 1 (HMGB1), calcium-binding S100 protein group, β2-integrin Mac/CD11b, amyloid β peptide, β-sheet fibrils, advanced oxidation protein products, complement C3a, lipopolysaccharides (LPS) and phosphatidylserine on the surface of apoptotic cells (Figure 2)[38–44]. RAGE is now considered to be a member of PRR like TLR; it actively participates in the interface of innate and adaptive immunity, inflammation, diabetic vascular complications and atherosclerosis (Figure 2).

HMGB1 is a nuclear protein that stabilizes nucleosome formation and facilitates transcription. HMGB1 is a strong inflammatory trigger from necrotic cells as a result of passive leakage, and can be actively secreted by activated monocytes, macrophages, dendritic cells, natural killer cells and endothelial cells, though there is no canonical signal sequence in the HMGB1 protein[45]. The association between HMGB1 and RAGE is enhanced by the presence of CpG DNA; HMGB1 directly binds LPS and IL-1β[46,47]. The formation of the complex with other

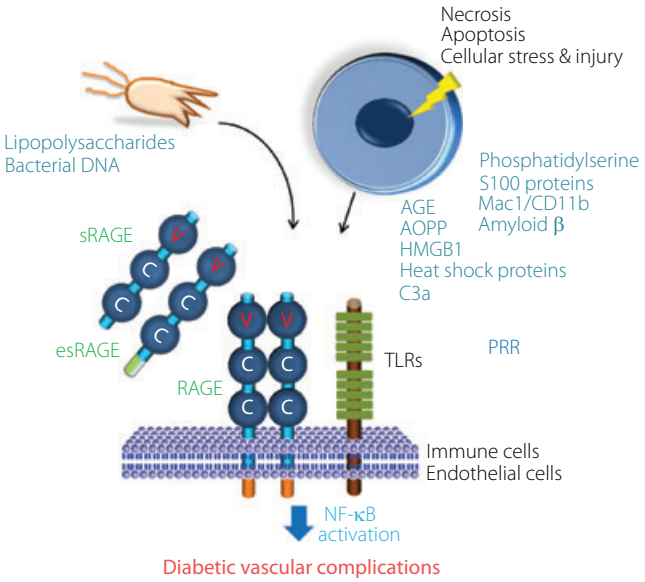

Figure 2 | Receptor for advanced glycation end-products (RAGE) and its multiple ligands in the development of diabetic vascular complications. Soluble RAGE (sRAGE) and endogenous soluble RAGE (esRAGE) might work as decoy receptors against ligand-receptor interactions. This is adapted from our review paper[96]. AGE, advanced glycation end-products; AOPP, advanced oxidation protein products; HMGB1, high-mobility group box protein 1; NF-κB, nuclear factor-κB; PRR, pattern-recognition receptors; TLR, toll-like receptors.

pro-inflammatory molecules further aggravates the activation of RAGE signaling. The lectin domain of thrombomodulin can bind HMGB1 and block the HMGB1–RAGE interaction as an anti-inflammatory mechanism[48].

S100 proteins are a family consisting of over 20 proteins sharing structural similarity with their two EF-hand Ca^{2+}-binding domains flanked by α-helices. S100A1, A2, A4, A5, A6, A7/A7A, A8/A9, A11, A12, B and P can bind RAGE[49]. Their oligomerized forms can activate RAGE signaling. CML-modified S100A8/A9 can strongly enhance intestinal inflammatory responses through RAGE, suggesting the existence of more complex varieties of RAGE ligands modified by glycation reactions[50]. While deglycosylation sensitizes RAGE to bind AGE, carboxylated *N*-glycans on RAGE increase binding affinity with S100A8/9, as well as HMGB1[51,52].

Mac-1/CD11b is a cell surface molecule expressed on neutrophils, monocytes, macrophages, dendritic cells and natural killer cells. RAGE mediates the recruitment and accumulation of these immune cells into inflammatory foci by interacting with Mac-1/CD11b and intercellular adhesion molecule 1[42].

The ligand engagement of RAGE activates the NF-κB and other signaling pathways through the stimulation of extracellular signal-regulated kinase 1/2, p38 mitogen-activated protein kinase-c-Jun N-terminal kinase, Janus kinase-signal transducer and activator of transcription and Rac-Cdc42[53]. The ligation of RAGE causes a positive feed-forward loop in which inflammatory

stimuli activate NF-κB, which induces RAGE expression, followed again by NF-κB activation[54].

ANIMAL STUDIES

To evaluate whether RAGE and the multiligand system participate in the development of diabetic vascular complications, we created transgenic mice that overexpress human RAGE proteins in endothelial cells, and crossbred them with another transgenic mouse line that develops insulin-dependent diabetes shortly after birth[55,56]. The resultant double transgenic mice showed significant increases in kidney weight, albuminuria, glomerulosclerosis and serum creatinine compared with the diabetic controls (Figure 3)[56,57]. Triple transgenic mice overexpressing RAGE, inducible nitric oxide (NO) synthase and megsin developed severe diabetic nephropathy as early as 16 weeks after birth, characterized by the development of mesangial expansion, nodule-like lesions and tubulointerstitial damage with an increase in local oxidative stress (Figure 3)[58]. In addition, indices diagnostic of diabetic retinopathy were most prominent in double transgenic mice[57]. Kaji *et al.*[59] showed blood–retinal barrier breakdown and increased leukostasis in RAGE-overexpressing mice; these were ameliorated by treatment with soluble RAGE (sRAGE). Furthermore, we generated RAGE-knockout (KO) mice and report the marked improvement in nephromegaly, albuminuria and glomerulosclerosis, as well as increased serum creatinine levels in diabetic RAGE-KO mice (Figure 3)[31]. The deletion of RAGE also attenuated the endothelial–mesenchymal transition[60]. Streptozotocin (STZ)-injected RAGE-KO mice were protected from early kidney injuries as a result of mesangial matrix expansion and thickening of the glomerular basement membrane as seen in wild-type diabetic mice[61]. Furthermore, RAGE deletion also improved diabetic nephropathy seen in OVE26 type 1 diabetic mice with progressive glomerulosclerosis and declining renal function[62].

In diabetic neuropathy models, deletion of the RAGE gene protects animals from the detrimental effects of diabetes; meanwhile, RAGE overexpression promotes diabetic neuropathy[63–65]. In addition, the loss of thermal pain perception observed in mice with diabetes could be prevented by treatment with sRAGE. Concordant with these observations, NF-κB activation and the loss of pain perception are largely blunted in RAGE-KO mice[63]. RAGE expression was observed in the perineural and endoneural endothelial cells, as well as schwann cells of peripheral nerves by *in situ* hybridization[66,67].

The inhibition of AGE formation or AGE breakers attenuates accelerated atheroma associated with diabetes[68]. Experiments on STZ-induced diabetic apolipoprotein E (ApoE)-KO mice showed that RAGE activation plays a role in the formation and progression of atherosclerotic lesions, and that the absence of RAGE is associated with a significant attenuation of atherosclerotic plaque[69]. Competitive inhibition of RAGE by exogenously administrated sRAGE decreases the mean atherosclerotic lesion area, as well as the number of complex lesions[70,71]. In addition, RAGE inactivation also inhibits atherosclerosis by blocking RAGE-mediated inflammatory reactions and oxidative stress in non-diabetic models with atherosclerosis of ApoE-KO and low-density lipoprotein receptor-KO mice[72].

SOLUBLE RAGE

RAGE is also reported to have a self-downregulation system. As an example of a pathway for the auto-downregulation of RAGE-mediated cellular activation, the binding of HMGB1 to RAGE induces an intracellular signal transduction, as well as RAGE shedding by a disintegrin and metalloproteinase domain-containing protein 10[73]. The cleavage of the membrane-bound full-length signal-transducing RAGE yields sRAGE, which could work as a decoy receptor against ligand–RAGE interactions. In the strict sense of the word, sRAGE is a heterogeneous population of total sRAGE proteins, including the soluble splice variants of RAGE, as well as the proteinase-cleaved forms of membrane-bound RAGE and the soluble splice variants (Figure 2)[74]. Endogenous secretory RAGE (esRAGE) is one of the major splice variants of RAGE (Figure 4); it exists in the circulation, and is widely distributed throughout the cell surface and cytoplasm of neurons, endothelial cells, pneumocytes, mesothelium, pancreatic β-cells, monocytes, macrophages, salivary glands, digestive tracts, renal tubules, prostate, skin, thyroid and bronchioles[75–77]. sRAGE and esRAGE are thought to act locally

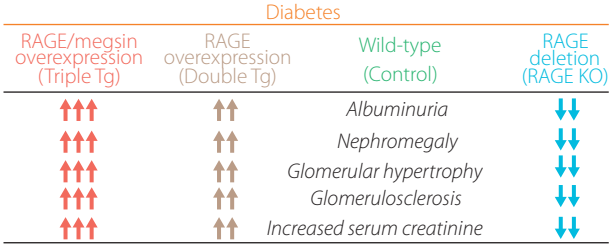

Figure 3 | Phenotypes of diabetic nephropathy in receptor for advanced glycation end-products (RAGE) gene-manipulated mice. KO, knockout mice; Tg, transgenic mice.

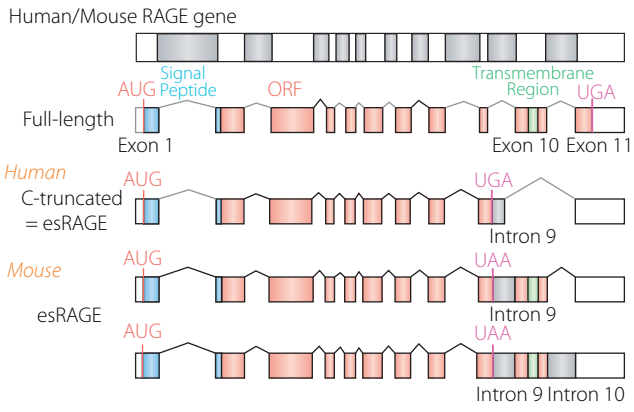

Figure 4 | Splice variants of human and mouse receptor for advanced glycation end-products (RAGE) genes. This is adapted from our original paper[97]. esRAGE, endogenous secretory RAGE; ORF, open reading frame.

and systemically as decoy receptors. Reinforcing ectodomain shedding decreases the total amount and expression of signal-transducing RAGE; this reciprocally increases the amount of decoy receptor sRAGE, which can control ligand–RAGE signaling and subsequent cellular and tissue derangement[74]. sRAGE is also reported to mediate inflammation by directly binding to monocytes under conditions with few ligands, although the mechanism of action is unknown[78]. Recent clinical studies have focused on the significance of circulating sRAGE or esRAGE in diabetic vascular complications. Findings in both type 1 and 2 diabetic patients are quite conflicting; both inverse and positive correlations are reported in diabetic retinopathy, nephropathy and incident cardiovascular disease events, as well as mortality outcomes[74,79–84]. There are several reasons why this occurs. First, sRAGE and esRAGE production is inducible; the former is sheddase-dependent, whereas the latter is original RAGE promoter- and splicing-dependent. Second, the presence of renal insufficiency can strongly and positively influence circulating sRAGE and esRAGE levels[74]. Third, medications might alter sRAGE or esRAGE level.

TARGETING RAGE FOR CONQUERING DIABETIC VASCULAR COMPLICATIONS

Suppressing RAGE action might be beneficial for preventing and retarding the development of diabetic vascular complications, atherosclerosis and inflammation. Administering inhibitors of AGE and RAGE might be prospective therapeutic approaches. Benfotiamine is a synthetic *S*-acyl derivative of thiamine, and has anti-oxidant and anti-AGE capabilities[85]. Thiazolium compounds, ALT-711 (algebrium), C36, TRC4186 and TRC4149, as well as their prototype, *N*-phenylthiazolium bromide (PTB), are known as AGE breakers that break preformed AGE or existing AGE cross-links[86–89]. TTP488 is an antagonist against RAGE[90]. LMWH can bind RAGE and act as an antagonist[31]. Thiazolidinediones, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers and statins are reported to suppress RAGE expression[91,92]. Treatment with statins and ACEI stimulates circulating sRAGE production in humans[93,94].

Future studies should focus on developing new devices and remedies for controlling RAGE ectodomain shedding. New therapeutic strategies for preventing diabetic vascular complications, and improving life expectancy and quality of life in patients with diabetes are desired.

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