

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 worldwide¹. 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 blindness². 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 inflammation³. 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.

AGE

The formation of brown-colored substances resulting from non-enzymatic reactions between reducing sugars and proteins was first described by Maillard⁴. 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 AGE⁶. Reactive dicarbonyls can also be generated from ketones, lipids, and other metabolic pathways⁷. 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 scavengers⁸. Glyoxal is also generated by the auto-oxidation of glucose; 3DG is formed by fructosamine-3-kinase from fructoselysine,

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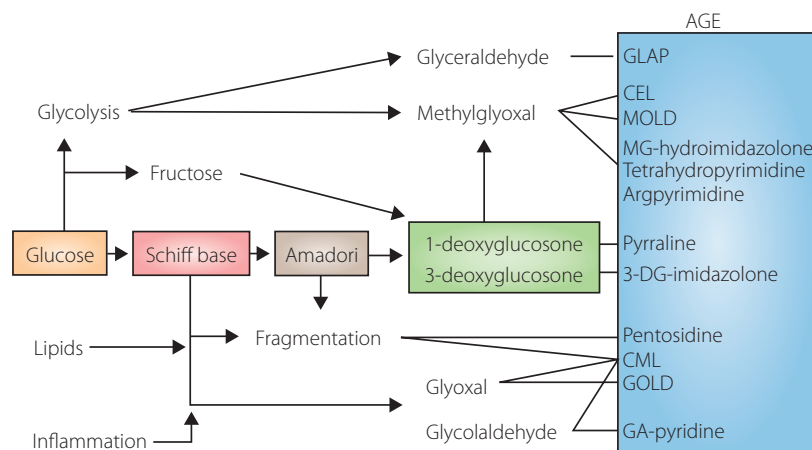


Figure 1 | Possible pathways of advanced glycation end-products (AGE) formation. This is adapted from a review paper by Monnier *et al.*⁹⁵. The classical pathway leading to the formation of AGE involves Schiff base and Amadori products. The Amadori products can be transformed into reactive dicarbonyl products, such as glucosones, and can be fragmented by oxidation (glycooxidation) 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 product⁹. Production of glycolaldehyde by myeloperoxidase from activated macrophages and neutrophils plays a pathogenic role in generating AGE and damaging tissues at inflammation foci¹⁰.

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 dysfunction¹¹. 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 lifespan¹⁸.

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 domains¹⁹. 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 signaling²⁰. 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-density lipoprotein 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 AGE²⁶. AGE-R1 is a type I transmembrane receptor found on the plasma membrane and in the endoplasmic reticulum²¹. 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 RAGE²⁷. 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 inflammation²⁸. 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 AGE²⁹. 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 domain³⁰. 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- κ B)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-1 β (IL-1 β), IL-6 and monocyte chemoattractant protein-1 are induced by the AGE-RAGE axis in monocytes and macrophages³⁴. RAGE promoter assays showed that AGE-RAGE signaling promotes the transcriptional upregulation of the RAGE gene through the activation of NF- κ B³⁵. TNF- α and estrogen also enhance the transcription of the RAGE gene through the activation of NF- κ B and the transcription factor, Sp1, respectively³⁵. 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 signaling³⁶. 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 polymerization³⁶. Very recently, it was reported that the AGE-RAGE interaction could phosphorylate the cytoplasmic domain of RAGE at Ser391 through PKC ζ 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 manner³⁷.

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, β 2-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 protein⁴⁵. The association between HMGB1 and RAGE is enhanced by the presence of CpG DNA; HMGB1 directly binds LPS and IL-1 β ^{46,47}. The formation of the complex with other

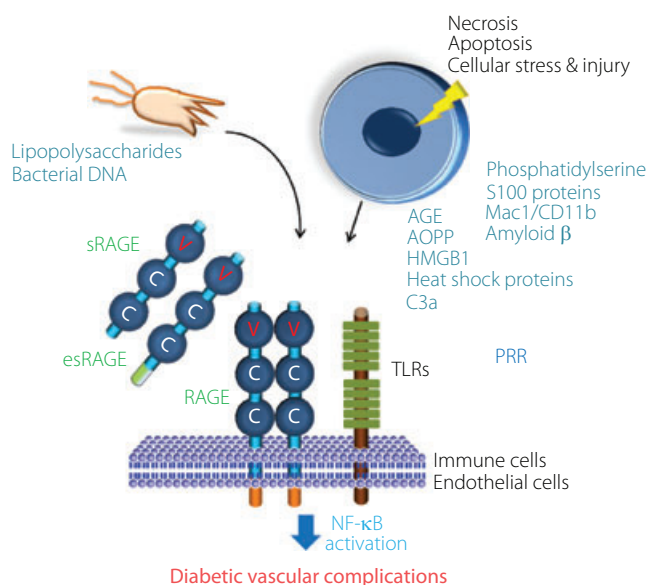


Figure 2 | Receptor for advanced glycation end-products (RAGE) and its multiple ligands in the development of diabetic vascular complications. Soluble RAGE (sRAGE) and endogenous soluble RAGE (esRAGE) might work as decoy receptors against ligand-receptor interactions. This is adapted from our review paper³⁶. AGE, advanced glycation end-products; AOPP, advanced oxidation protein products; HMGB1, high-mobility group box protein 1; NF- κ B, nuclear factor- κ B; 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 mechanism⁴⁸.

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 RAGE⁴⁹. 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 reactions⁵⁰. 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 1⁴².

The ligand engagement of RAGE activates the NF- κ B 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-Cdc42⁵³. 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 activation⁵⁴.

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 mice⁵⁷. 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 transition⁶⁰. 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 mice⁶¹. Furthermore, RAGE deletion also improved diabetic nephropathy seen in OVE26 type 1 diabetic mice with progressive glomerulosclerosis and declining renal function⁶².

In diabetic neuropathy models, deletion of the RAGE gene protects animals from the detrimental effects of diabetes; meanwhile, RAGE overexpression promotes diabetic neuropathy⁶³⁻⁶⁵. 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 mice⁶³. 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 diabetes⁶⁸. 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 plaque⁶⁹. 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 mice⁷².

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 10⁷³. 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 bronchioles⁷⁵⁻⁷⁷. sRAGE and esRAGE are thought to act locally

Diabetes			
RAGE/megsin overexpression (Triple Tg)	RAGE overexpression (Double Tg)	Wild-type (Control)	RAGE deletion (RAGE KO)
↑↑↑	↑↑	Albuminuria	↓↓
↑↑↑	↑↑	Nephromegaly	↓↓
↑↑↑	↑↑	Glomerular hypertrophy	↓↓
↑↑↑	↑↑	Glomerulosclerosis	↓↓
↑↑↑	↑↑	Increased serum creatinine	↓↓

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

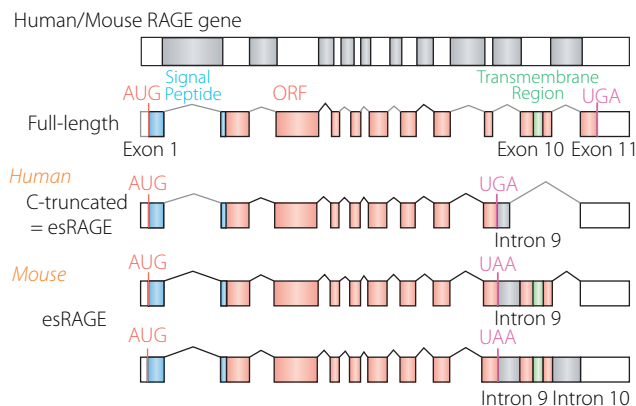


Figure 4 | Splice variants of human and mouse receptor for advanced glycation end-products (RAGE) genes. This is adapted from our original paper⁹⁷. esRAGE, endogenous secretory RAGE; ORF, open reading frame.

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 derangement⁷⁴. sRAGE is also reported to mediate inflammation by directly binding to monocytes under conditions with few ligands, although the mechanism of action is unknown⁷⁸. 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 levels⁷⁴. 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 capabilities⁸⁵. Thiazolium compounds, ALT-711 (algebraium), 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 RAGE⁹⁰. LMWH can bind RAGE and act as an antagonist³¹. 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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REFERENCES

1. Danaei G, Finucane MM, Lu Y, *et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011; 378: 31–40.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87: 4–14.
3. Pacher P, Szabó C. Role of poly(ADP-ribose) polymerase-1 activation in the pathogenesis of diabetic complications: endothelial dysfunction, as a common underlying theme. *Antioxid Redox Signal* 2005; 7: 1568–1580.
4. Maillard LC. Action des acides amine's sur les sucres: formation des melanoïdes par voie methodique. *C R Acad Sci* 1912; 154: 66–68.
5. Yamamoto H, Watanabe T, Yamamoto Y, *et al.* RAGE in diabetic nephropathy. *Curr Mol Med* 2007; 7: 752–757.
6. Rabbani N, Thornalley PJ. Dicarbonyls linked to damage in the powerhouse: glycation of mitochondrial proteins and oxidative stress. *Biochem Soc Trans* 2008; 36: 1045–1050.
7. Victor R, Lorenz FW. Nonenzymic, polyvalent anion-catalyzed formation of methylglyoxal as an explanation of its presence in physiological systems. *J Biol Chem* 1968; 243: 2718–2724.
8. Thornalley PJ. The glyoxalase system: new developments towards functional characterization of a metabolic pathway fundamental to biological life. *Biochem J* 1990; 269: 1–11.
9. Nagai R, Hayashi CM, Xia L, *et al.* Identification in human atherosclerotic lesions of GA-pyridine, a novel structure derived from glycolaldehyde-modified proteins. *J Biol Chem* 2002; 277: 48905–48912.
10. Nagai R, Matsumoto K, Ling X, *et al.* Glycolaldehyde, a reactive intermediate for advanced glycation endproducts, plays an important role in the generation of an active ligand for the macrophage scavenger receptor. *Diabetes* 2000; 49: 1714–1723.
11. Yao D, Taguchi T, Matsumura T, *et al.* High glucose increases angiotensin-2 transcription in microvascular endothelial cells through methylglyoxal modification of mSin3A. *J Biol Chem* 2007; 282: 31038–31045.
12. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. *Diabetes* 1999; 48: 1–9.
13. Sell DR, Monnier VM. Structure elucidation of a senescence cross-link from human extracellular matrix. Implication of pentoses in the aging process. *J Biol Chem* 1989; 264: 21597–21602.
14. Miyata T, Wada Y, Cai Z, *et al.* Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. *Kidney Int* 1997; 51: 1170–1181.
15. Koschinsky T, He CJ, Mitsuhashi T, *et al.* Orally absorbed reactive advanced glycation end products (glycotoxins): an environmental risk factor in diabetic nephropathy. *Proc Natl Acad Sci USA* 1997; 94: 6474–6479.
16. Vlassara H, Cai W, Crandall J, *et al.* Inflammatory mediators are induced by dietary glycotoxins, a major risk factor for

- diabetic angiopathy. *Proc Natl Acad Sci USA* 2002; 99: 15596–15601.
17. Cai WJ, Cao QD, Zhu L, *et al.* Oxidative stress-inducing carbonyl compounds from common foods: novel mediators of cellular dysfunction. *Mol Med* 2002; 8: 337–346.
 18. Vlassara H, Striker GE. AGE restriction in diabetes mellitus: a paradigm shift. *Nat Rev Endocrinol* 2011; 7: 526–539.
 19. Neeper M, Schmidt AM, Brett J, *et al.* Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. *J Biol Chem* 1992; 267: 14998–15004.
 20. Huttunen HJ, FAGE C, Rauvala H. Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF- κ B require the cytoplasmic domain of the receptor but different downstream signaling pathways. *J Biol Chem* 1999; 274: 19919–19924.
 21. Yang Z, Makita Z, Horii Y, *et al.* Two novel rat liver membrane proteins that bind advanced glycosylation endproducts: relationship to macrophage receptor for glucose-modified proteins. *J Exp Med* 1991; 174: 515–524.
 22. Vlassara H, Li YM, Imani Y, *et al.* Identification of galectin-3 as a high-affinity binding protein for advanced glycation end products (AGE): a new member of the AGE-receptor complex. *Mol Med* 1995; 1: 634–646.
 23. Zhu W, Sano H, Nagai R, *et al.* The role of galectin-3 in endocytosis of advanced glycation end products and modified low density lipoproteins. *Biochem Biophys Res Commun* 2001; 280: 1183–1188.
 24. Suzuki H, Kurihara Y, Takeya M, *et al.* A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. *Nature* 1997; 386: 292–296.
 25. Hodgkinson CP, Laxton RC, Patel K, *et al.* Advanced glycation end-product of low density lipoprotein activates the toll-like 4 receptor pathway implications for diabetic atherosclerosis. *Arterioscler Thromb Vasc Biol* 2008; 28: 2275–2281.
 26. Mitsuhashi T, Li YM, Fishbane S, *et al.* Depletion of reactive advanced glycation endproducts from diabetic uremic sera using a lysozyme-linked matrix. *J Clin Invest* 1997; 100: 847–854.
 27. Lu C, He JC, Cai W, *et al.* Advanced glycation endproduct (AGE) receptor 1 is a negative regulator of the inflammatory response to AGE in mesangial cells. *Proc Natl Acad Sci USA* 2004; 101: 11767–11772.
 28. Torreggiani M, Liu H, Wu J, *et al.* Advanced glycation end product receptor-1 transgenic mice are resistant to inflammation, oxidative stress, and post-injury intimal hyperplasia. *Am J Pathol* 2009; 175: 1722–1732.
 29. Osawa M, Yamamoto Y, Munesue S, *et al.* De-N-glycosylation or G82S mutation of RAGE sensitizes its interaction with advanced glycation endproducts. *Biochim Biophys Acta* 2007; 1770: 1468–1474.
 30. Matsumoto S, Yoshida T, Murata H, *et al.* Solution structure of the variable-type domain of the receptor for advanced glycation end products: new insight into AGE-RAGE interaction. *Biochemistry* 2008; 47: 12299–12311.
 31. Myint KM, Yamamoto Y, Doi T, *et al.* RAGE control of diabetic nephropathy in a mouse model: effects of RAGE gene disruption and administration of low-molecular weight heparin. *Diabetes* 2006; 55: 2510–2522.
 32. Yamagishi S, Yonekura H, Yamamoto Y, *et al.* Advanced glycation end products-driven angiogenesis in vitro. Induction of the growth and tube formation of human microvascular endothelial cells through autocrine vascular endothelial growth factor. *J Biol Chem* 1997; 272: 8723–8730.
 33. Yamamoto Y, Yonekura H, Watanabe T, *et al.* Short-chain aldehyde-derived ligands for RAGE and their actions on endothelial cells. *Diabetes Res Clin Pract* 2007; 77: 30–40.
 34. Hou FF, Miyata T, Boyce J, *et al.* Beta(2)-microglobulin modified with advanced glycation end products delays monocyte apoptosis. *Kidney Int* 2001; 59: 990–1002.
 35. Tanaka N, Yonekura H, Yamagishi S, *et al.* The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-alpha through nuclear factor-kappa B, and by 17beta-estradiol through Sp-1 in human vascular endothelial cells. *J Biol Chem* 2000; 275: 25781–25790.
 36. Hudson BI, Kalea AZ, Arriero MDM, *et al.* Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42. *J Biol Chem* 2008; 283: 34457–34468.
 37. Sakaguchi M, Murata H, Yamamoto K, *et al.* TIRAP, an adaptor protein for TLR2/4, transduces a signal from RAGE phosphorylated upon ligand binding. *PLoS ONE* 2011; 6: e23132.
 38. Kislinger T, Fu C, Huber B, *et al.* N ϵ -(carboxymethyl) lysine adducts of proteins are ligands for receptor for advanced glycation end products that activate cell signaling pathways and modulate gene expression. *J Biol Chem* 1999; 274: 31740–31749.
 39. Hori O, Brett J, Slattery T, *et al.* The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphotericin. Mediation of neurite outgrowth and co-expression of rage and amphotericin in the developing nervous system. *J Biol Chem* 1995; 270: 25752–25761.
 40. Hofmann MA, Drury S, Fu C, *et al.* RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell* 1999; 97: 889–901.
 41. Yan SD, Chen X, Fu J, *et al.* RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996; 382: 685–691.
 42. Chavakis T, Bierhaus A, Al-Fakhri N, *et al.* The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. *J Exp Med* 2003; 198: 1507–1515.
 43. Yamamoto Y, Harashima A, Saito H, *et al.* Septic shock is associated with receptor for advanced glycation end products ligation of LPS. *J Immunol* 2011; 186: 3248–3257.
 44. He M, Kubo H, Morimoto K, *et al.* Receptor for advanced glycation end products binds to phosphatidylserine and assists

- in the clearance of apoptotic cells. *EMBO Rep* 2011; 12: 358–364.
45. Gardella S, Andrei C, Ferrera D, *et al.* The nuclear protein HMGB1 is secreted by monocytes via a non-classical, vesicle-mediated secretory pathway. *EMBO Rep* 2002; 3: 995–1001.
 46. Tian J, Avalos AM, Mao SY, *et al.* Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. *Nat Immunol* 2007; 8: 487–496.
 47. Qin YH, Dai SM, Tang GS, *et al.* HMGB1 enhances the pro-inflammatory activity of lipopolysaccharide by promoting the phosphorylation of MAPK p38 through receptor for advanced glycation end products. *J Immunol* 2009; 183: 6244–6250.
 48. Abeyama K, Stern DM, Ito Y, *et al.* The N-terminal domain of thrombomodulin sequesters high-mobility group-B1 protein, a novel antiinflammatory mechanism. *J Clin Invest* 2005; 115: 1267–1274.
 49. Sims GP, Rowe DC, Rietdijk ST, *et al.* HMGB1 and RAGE in inflammation and cancer. *Annu Rev Immunol* 2010; 28: 367–388.
 50. Andrassy M, Igwe J, Autschbach F, *et al.* Posttranslationally modified proteins as mediators of sustained intestinal inflammation. *Am J Pathol* 2006; 169: 1223–1237.
 51. Srikrishna G, Huttunen HJ, Johansson L, *et al.* N-glycans on the receptor for advanced glycation end products influence amphotericin binding and neurite outgrowth. *J Neurochem* 2002; 80: 998–1008.
 52. Srikrishna G, Nayak J, Weigle B, *et al.* Carboxylated N-glycans on RAGE promote S100A12 binding and signaling. *J Cell Biochem* 2010; 110: 645–659.
 53. Barlovic DP, Soro-Paavonen A, Jandeleit-Dahm KA. RAGE biology, atherosclerosis and diabetes. *Clin Sci (Lond)* 2011; 121: 43–55.
 54. Bierhaus A, Schiekofer S, Schwaninger M, *et al.* Diabetes-associated sustained activation of the transcription factor nuclear factor- κ B. *Diabetes* 2001; 50: 2792–2808.
 55. Takamura T, Kato I, Kimura N, *et al.* Transgenic mice overexpressing type 2 nitric-oxide synthase in pancreatic beta cells develop insulin-dependent diabetes without insulinitis. *J Biol Chem* 1998; 273: 2493–2496.
 56. Yamamoto Y, Kato I, Doi T, *et al.* Development and prevention of advanced diabetic nephropathy in RAGE-overexpressing mice. *J Clin Invest* 2001; 108: 261–268.
 57. Yamamoto Y, Yamagishi S, Yonekura H, *et al.* Roles of the AGE-RAGE system in vascular injury in diabetes. *Ann N Y Acad Sci* 2000; 902: 163–172.
 58. Inagi R, Yamamoto Y, Nangaku M, *et al.* A severe diabetic nephropathy model with early development of nodule-like lesions induced by meginin overexpression in RAGE/iNOS transgenic mice. *Diabetes* 2006; 55: 356–366.
 59. Kaji Y, Usui T, Ishida S, *et al.* Inhibition of diabetic leukostasis and blood-retinal barrier breakdown with a soluble form of a receptor for advanced glycation end products. *Invest Ophthalmol Vis Sci* 2007; 48: 2858–2865.
 60. Li L, Qu X, Yao J, *et al.* Blockade of endothelial-mesenchymal transition by a Smad 3 inhibitor delays the early development of streptozotocin-induced diabetic nephropathy. *Diabetes* 2010; 59: 2612–2624.
 61. Wendt TM, Tanji N, Guo J, *et al.* RAGE drives the development of glomerulosclerosis and implicates podocyte activation in the pathogenesis of diabetic nephropathy. *Am J Pathol* 2003; 162: 1123–1137.
 62. Reinger N, Lau K, McCalla D, *et al.* Deletion of the receptor for advanced glycation end products reduces glomerulosclerosis and preserves renal function in the diabetic OVE26 mouse. *Diabetes* 2010; 59: 2043–2054.
 63. Bierhaus A, Haslbeck KM, Humpert PM, *et al.* Loss of pain perception in diabetes is dependent on a receptor of the immunoglobulin superfamily. *J Clin Invest* 2004; 114: 1741–1751.
 64. Vincent AM, Perrone L, Sullivan KA, *et al.* Receptor for advanced glycation end products activation injures primary sensory neurons via oxidative stress. *Endocrinology* 2007; 148: 548–558.
 65. Toth C, Rong LL, Yang C, *et al.* Receptor for advanced glycation end products (RAGE) and experimental diabetic neuropathy. *Diabetes* 2008; 57: 1002–1017.
 66. Wada R, Yagihashi S. Role of advanced glycation end products and their receptors in development of diabetic neuropathy. *Ann N Y Acad Sci* 2005; 1043: 598–604.
 67. Yagihashi S, Mizukami H, Sugimoto K. Mechanism of diabetic neuropathy: where are we now and where to go? *J Diabetes Invest* 2011; 2: 18–32.
 68. Forbes JM, Yee LT, Thallas V, *et al.* Advanced glycation end product interventions reduce diabetes-accelerated atherosclerosis. *Diabetes* 2004; 53: 1813–1823.
 69. Soro-Paavonen A, Watson AM, Li J, *et al.* Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes. *Diabetes* 2008; 57: 2461–2469.
 70. Park L, Raman KG, Lee KJ, *et al.* Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. *Nat Med* 1998; 4: 1025–1031.
 71. Wendt T, Harja E, Bucciarelli L, *et al.* RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. *Atherosclerosis* 2006; 185: 70–77.
 72. Sun L, Ishida T, Yasuda T, *et al.* RAGE mediates oxidized LDL-induced pro-inflammatory effects and atherosclerosis in non-diabetic LDL receptor-deficient mice. *Cardiovasc Res* 2009; 82: 371–381.
 73. Raucci A, Cugusi S, Antonelli A, *et al.* A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase a disintegrin and metalloprotease 10 (ADAM10). *FASEB J* 2008; 22: 3716–3727.
 74. Yamamoto Y, Miura J, Sakurai S, *et al.* Assaying soluble forms of receptor for advanced glycation endproducts. *Atheroscler Thromb Vasc Biol* 2007; 27: 33–34.

75. Yonekura H, Yamamoto Y, Sakurai S, *et al.* Expression and function of novel splice variants of RAGE in human vascular endothelial cells and pericytes. *Biochem J* 2003; 370: 1097–1109.
76. Chunmei CM, Tsuneyama K, Kominami R, *et al.* Expression profiling of endogenous secretory receptor for advanced glycation endproducts in human organs. *Mod Pathol* 2005; 18: 1385–1396.
77. Nagai R, Mori T, Yamamoto Y, *et al.* Significance of advanced glycation endproducts (AGE) in aging-related disease. *Anti-aging Med* 2010; 7: 112–119.
78. Wang Y, Wang H, Piper MG, *et al.* sRAGE induces human monocyte survival and differentiation. *J Immunol* 2010; 185: 1822–1835.
79. Sakurai S, Yamamoto Y, Tamei H, *et al.* Development of an ELISA for eRAGE and its application to type 1 diabetic patients. *Diabetes Res Clin Pract* 2006; 73: 158–165.
80. Koyama H, Shoji T, Fukumoto S, *et al.* Low circulating endogenous secretory receptor for AGE predicts cardiovascular mortality in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 2007; 27: 147–153.
81. Katakami N, Matsuhisa M, Kaneto H, *et al.* Serum endogenous secretory RAGE level is an independent risk factor for the progression of carotid atherosclerosis in type 1 diabetes. *Atherosclerosis* 2009; 204: 288–292.
82. Tam XH, Shiu SW, Leng L, *et al.* Enhanced expression of receptor for advanced glycation end-products is associated with low circulating soluble isoforms of the receptor in type 2 diabetes. *Clin Sci (Lond)* 2011; 120: 81–89.
83. Thomas MC, Söderlund J, Lehto M, *et al.* Soluble receptor for AGE (RAGE) is a novel independent predictor of all-cause and cardiovascular mortality in type 1 diabetes. *Diabetologia* 2011; 54: 2669–2677.
84. Colhoun HM, Betteridge DJ, Durrington P, *et al.* Total soluble and endogenous secretory receptor for advanced glycation endproducts as predictive biomarkers of coronary heart disease risk in patients with type 2 diabetes: an analysis from the CARDS Trial. *Diabetes* 2011; 60: 2379–2385.
85. Stirban A, Negrean M, Stratmann B, *et al.* Benfotiamine prevents macro- and microvascular endothelial dysfunction and oxidative stress following a meal rich in advanced glycation end products in individuals with type 2 diabetes. *Diabetes Care* 2006; 29: 2064–2071.
86. Schwedler SB, Verbeke P, Bakala H, *et al.* N-phenacylthiazolium bromide decreases renal and increases urinary advanced glycation end products excretion without ameliorating diabetic nephropathy in C57BL/6 mice. *Diabetes Obes Metab* 2001; 3: 230–239.
87. Joshi D, Gupta R, Dubey A, *et al.* TRC4186, a novel AGE-breaker, improves diabetic cardiomyopathy and nephropathy in Ob-ZsF1 model of type 2 diabetes. *J Cardiovasc Pharm* 2009; 54: 72–81.
88. Wolffenbittel BH, Bouanger CM, Crijns FR, *et al.* Breakers of advanced glycation endproducts restore large artery properties in experimental diabetes. *Proc Natl Acad Sci USA* 1998; 95: 4630–4634.
89. Cheng G, Wang LL, Long L, *et al.* Beneficial effects of C36, a novel breaker of advanced glycation endproducts cross-links, on the cardiovascular system of diabetic rats. *Br J Pharmacol* 2007; 152: 1196–1206.
90. Chen Y, Akirav EM, Chen W, *et al.* RAGE ligation affects T cell activation and controls T cell differentiation. *J Immunol* 2008; 181: 4272–4278.
91. Marx N, Walcher D, Ivanova N, *et al.* Thiazolidinediones reduce endothelial expression of receptors for advanced glycation end products. *Diabetes* 2004; 53: 2662–2668.
92. Yamagishi S, Takeuchi M. Nifedipine inhibits gene expression of receptor for advanced glycation end products (RAGE) in endothelial cells by suppressing reactive oxygen species generation. *Drugs Exp Clin Res* 2004; 30: 169–175.
93. Cuccurullo C, Lezzi A, Fazia ML, *et al.* Suppression of RAGE as a basis of simvastatin-dependent plaque stabilization in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 2006; 26: 2716–2723.
94. Santilli F, Bucciarelli L, Noto D, *et al.* Decreased plasma soluble RAGE in patients with hypercholesterolemia: effects of statins. *Free Radic Biol Med* 2007; 43: 1255–1262.
95. Monnier VM, Mustata GT, Biemel KL, *et al.* Cross-linking of the extracellular matrix by the maillard reaction in aging and diabetes: an update on “a puzzle nearing resolution”. *Ann N Y Acad Sci* 2005; 1043: 533–544.
96. Win MTT, Yamamoto Y, Munesue S, *et al.* Regulation of RAGE for attenuating progression of diabetic vascular complications. *Exp Diabetes Res* 2012; 2012: 894605.
97. Harashima A, Yamamoto Y, Cheng C, *et al.* Identification of mouse orthologue of endogenous secretory receptor for advanced glycation end-products: structure, function and expression. *Biochem J* 2006; 396: 109–115.