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AGE/RAGE as a Mediator of Insulin Resistance or Metabolic Syndrome: Another Aspect of Metabolic Memory?

Hidenori Koyama and Tetsuya Yamamoto
Department of Internal Medicine, Division of Endocrinology and Metabolism,
Hyogo College of Medicine,
Japan

1. Introduction

Large randomized studies in diabetes have established that early intensive glycemic control reduces the risk of diabetic microvascular complications, with less impact on macrovascular complications [1, 2]. In type 2 diabetic patients, further intensive therapy to target normal glycated hemoglobin levels also failed to reduce mortality and major cardiovascular events [3, 4], while it may be rather harmful [5]. However, follow-up data of these trials reveal a long-term influence of early metabolic control on longer cardiovascular outcomes, even though the influence on glycemic control has been immediately disappeared after the trials [6, 7]. This phenomenon has recently been defined as "metabolic memory". In at-risk patients with type 2 diabetes, intensive intervention with multiple drug combinations and behavior modification had similar sustained beneficial effects with respect to vascular complications and on rates of death from any cause and from cardiovascular causes [8]. Similarly in patients with end-stage renal disease (ESRD), intensive interventions to the general risk factors, such as high LDL-cholesterol or C-reactive protein, have not been successful in improving their cardiovascular outcomes [9, 10], suggesting that the beneficial effect of risk reduction may be overwhelmed by accumulated “metabolic memory” by long-term exposure to oxidative stress during the progression of renal failure.

Potential mechanisms for propagating this "memory" are the non-enzymatic glycation of cellular and tissue proteins which are conceptualized as advanced glycation end-products (AGEs), the generation of which has been implicated to be deeply associated with increased oxidative stress as well as hyperglycemia. AGEs, with their receptor (receptor for AGEs, RAGE), potentially mediate molecular and cellular pathway leading to metabolic memory. Moreover, interaction of the RAGE with AGEs leads to crucial biomedical pathway generating intracellular oxidative stress and inflammatory mediators, which could result in further amplification of the pathway involved in AGE generation.

By utilizing genetically engineered mouse models, emerging evidence suggests that AGE/RAGE axis is also found to be profoundly associated with non-diabetic, non-uremic pathophysiological conditions including 1) atherogenesis, 2) angiogenic response, 3) vascular injury, and 4) inflammatory response (see review in [11]), many of which are now implicated in metabolic syndrome. Numerous truncated forms of RAGE have also been described, and the

C-terminally truncated soluble form of RAGE has received much attention. Soluble RAGE consists of several forms including endogenous secretory RAGE (esRAGE) which is a spliced variant of RAGE [12], and a shedded form derived from cell surface RAGE [13, 14]. These heterogeneous forms of soluble RAGE, carrying all of the extracellular domains but devoid of the transmembrane and intracytoplasmic domains, bind ligands including AGEs, and may antagonize RAGE signaling in vitro and in vivo. ELISA systems to measure plasma esRAGE and total soluble RAGE have been developed, and decreased plasma esRAGE is found to be associated with insulin resistance, obesity and metabolic syndrome [15]. Moreover, our recent observation highlights the direct role of RAGE in adiposity; RAGE deficiency is associated with less weight gain, less abdominal fat mass, less adipocyte size, less atherosclerotic lesion formation and higher plasma adiponectin than wild type control [16].

Insulin resistance is the primary mechanism underlying the development of type 2 diabetes and is a central component defining the metabolic syndrome, a constellation of abnormalities including obesity, hypertension, glucose intolerance, and dyslipidemia. Insulin resistance or metabolic syndrome has been defined to be associated with low-grade inflammation, and therefore inflammation could contribute in large part to its development [17], implicating an intriguing possibility that this pathophysiological condition is also an additional face of metabolic memory driven by RAGE axis. Although insulin resistance has been characterized by complex factors including genetic determinants, nutritional factors, and lifestyle, growing evidence suggests that mediators synthesized from inflammatory cells are critically involved in the regulation of insulin action. In brief, insulin binding to its specific receptor stimulates tyrosine phosphorylation of insulin receptor substrate (IRS) proteins, which is a crucial step for insulin signaling system. Many inflammatory signals appear to induce serine phosphorylation of IRS, which could be involved in disruption of insulin-receptor signaling [17]. In this chapter, we would like to summarize the recent findings regarding pathophysiological roles of RAGE and soluble RAGE in insulin resistance and metabolic syndrome.

2. AGEs

2.1 AGE formation by glucose and its derivatives

AGEs are proteins generated by a series of reactions termed the Maillard Reaction. Classically, AGE formation has been described by a nonenzymatic reaction between proteins and glucose [18, 19]. AGEs derive from the spontaneous reaction of carbohydrates with amino group of proteins, which undergo from the formation of reversible products (Schiff base adducts) to the generation of more stable products (Amadori products). Subsequently, complex reactions occur including intermolecular crosslink formation, and cleavage through oxidation, dehydration, condensation, cyclization, and other reactions follows, with generation of AGEs through a late reaction characterized by fluorescent and brown coloration and molecular crosslinkage. Recently, it was confirmed that AGEs are also formed by non-enzymatic reaction of reactive carbonyl compounds such as 3-deoxyglucosone, methylglyoxal resulting from persisting high blood glucose level, and oxidative stress associated with the amino residues of proteins.

2.2 AGEs formation independent of hyperglycemia

There is also increasing evidence that AGEs are also formed through lipid-derived intermediates, resulting in advanced lipoxidation products [20]. AGEs might be formed directly by autoxidation of free glucose [21, 22]. In this pathway, known as autoxidative

glycosylation, such reactive oxygen species as hydrogen peroxide were identified as both products and catalysts of autoxidation of sugars. Other than diabetes mellitus patients, high plasma and tissue levels of AGEs are observed in patients with ESRD. It has been reported that no difference was noted in blood AGEs levels between those with and without diabetes mellitus among chronic renal failure patients on hemodialysis, which is believed to enhance production and accumulation of AGEs in conditions other than hyperglycemia. Local accumulation of AGEs is also observed in patients with Alzheimer disease, rheumatoid arthritis, arteriosclerosis, cancer, and other diseases, suggesting the involvement of inflammation and oxidative stress in the formation of AGEs.

2.3 Orally absorbed AGEs

In addition to the endogenously formed, AGEs are abundant in exogenous sources such as foods, especially when prepared under elevated temperatures [23]. Vlassara's group has extensively examined the role of the exogenous AGEs in several pathological conditions (see review in [24]). After ingestion, 10% of orally-administered AGEs are absorbed into the circulation [25-27], majorities of which are shown to be accumulated in tissues. Among them are tissue-reactive α, β-dicarbonyl-containing intermediate products, such as methylglyoxal, which has been linked to cellular oxidant stress and apoptosis [28], and terminal products, such as ε *N*-carboxymethyllysine (CML), which is formed by glycoxidation as well as by lipoxidation [29-31]. Both methylglyoxal and CML have been identified in vivo and are shown to be associated with oxidant stress and tissue damage [31-33].

3. AGEs and endogenous RAGE ligand in insulin resistance or metabolic syndrome

3.1 AGEs in insulin producing and acting tissues

Importantly, among the multiple targets of bioactive AGEs are also such diverse tissues as the pancreatic islet [34, 35], the adipose tissue (adipocyte) [36] and skeletal muscle cells [37], major tissues involved in insulin secretion and its actions. Pharmacological inhibition of glycoxidation protects against damage to either tissue [33, 38]. AGEs are shown to inhibit glucose-stimulated insulin secretion from islet through iNOS-dependent nitric oxide production [35]. Reduced intake of dietary AGEs has also been shown to decrease the incidence of type 1 diabetes in NOD mice [39] as well as the formation of atherosclerotic lesions in diabetic apolipoprotein E-deficient mice [40].

3.2 AGEs and insulin resistance in vivo

AGEs burden is also shown to be associated with impaired endothelial function [41-44]. Endothelial dysfunction could be profoundly associated with less insulin delivery to the skeletal muscle interstitium, leading to decreased insulin-stimulated glucose uptake by the skeletal muscle [45-49], which is implicated in the pathogenesis of insulin resistance. More directly, the restriction of the AGE content in standard mouse diets was found to markedly improve insulin resistance in obese *db/db*$^{(++)}$ mice [50]. More recent observation shows targeted reduction of the advanced glycation pathway improved renal function in obesity [51]. This interesting observation was further supported by the findings that the development of insulin resistance and type 2 diabetes during prolonged high-fat feeding are linked to the excess AGEs/advanced lipoxidation end products inherent in fatty diets [52].

3.3 AGEs and insulin resistance in vitro

Several evidences also suggest that AGEs affect the function of insulin-target cells in vitro. AGEs interact with CD36 in mouse 3T3 and human subcutaneous adipocytes, which is associated with down-regulation of leptin expression in adipocyte through reactive oxygen species (ROS) system [53]. Miele et al showed in L6 skeletal muscle cells that AGEs affect glucose metabolism by impairing insulin-induced insulin receptor substrate (IRS) signaling through protein kinase Cα-mediated mechanism [37]. The same research group also showed in the muscle cells that methylglyoxal, an essential source of intracellular AGEs, hampers a key insulin signaling molecule [54]. Recent observations by Unoki et al also showed that AGEs impair insulin signaling in adipocytes by increasing generation of intracellular ROS [55]. Thus, AGEs may not only induce the debilitating complications of diabetes, but may also contribute to the impairment of insulin signaling in insulin-target tissues which could be involved in pathophysiology of insulin resistance, metabolic syndrome and diabetes.

3.4 Endogenous RAGE ligands, insulin resistance and metabolic syndrome

RAGE also interacts with other endogenous non-glycated peptide ligands including S100/calgranulin [56], amphoterin (also termed as high mobility group box 1 protein, HMGB1) [57, 58], amyloid fibrills [59], transthyretin [60], and a leukocyte integrin, Mac-1 [61], many of which are important inflammatory regulators. Some of these inflammatory ligands for RAGE may be involved in pathogenesis of obesity and metabolic syndrome. Early studies show expression of S100B protein in pre- and mature- adipocyte and is induced during adipogenesis [62, 63]. Physiological S100B levels appear to closely reflect adipose tissue mass or insulin resistance in humans [64-66]. HMGB1 is also found to be expressed in human adipose tissue with the expression level associated with the fat mass and obesity-associated gene [67]. Moreover, growing evidences suggest that infiltration of inflammatory cells, including macrophages, play fundamental roles in adiposity and metabolic syndrome [68-70]. MAC-1, an integrin expressed in macrophage, can act as a RAGE ligand [61], and may be involved in adipogenesis through interaction with RAGE.

4. RAGE and its potential link with insulin resistance and metabolic syndrome

4.1 Structure and function of RAGE

RAGE is a multiligand cell-surface protein that was isolated from bovine lung in 1992 by the group of Schmidt and Stern [71, 72]. RAGE belongs to the immunoglobulin superfamily of cell surface molecules and has an extracellular region containing one "V"-type immunoglobulin domain and two "C"-type immunoglobulin domains [71, 72] (Figure 1). The extracellular portion of the receptor is followed by a hydrophobic trans-membrane-spanning and then by a highly charged, short cytoplasmic domain which is essential for intracellular RAGE signaling. RAGE is initially identified as a receptor for CML-modified proteins [73], a major AGE in vivo [74]. Three-dimensional structure of the recombinant AGE-binding domain by using multidimensional heteronuclear NMR spectroscopy revealed that the domain assumes a structure similar to those of other immunoglobulin V-type domains [75, 76]. Three distinct surfaces of the V domain were identified to mediate AGE-V domain interactions [75]. The site-directed mutagenesis studies identified the basic amino acids which play a key role in the AGE binding activities [76]. As mentioned in the previous sentence, RAGE also interacts with other endogenous non-glycated peptide ligands, many of which are important

inflammatory regulators. The common characteristics of these ligands are the presence of multiple β-sheets [61, 77, 78]. RAGE is thought to interact with these ligands through their shared three-dimensional structure.

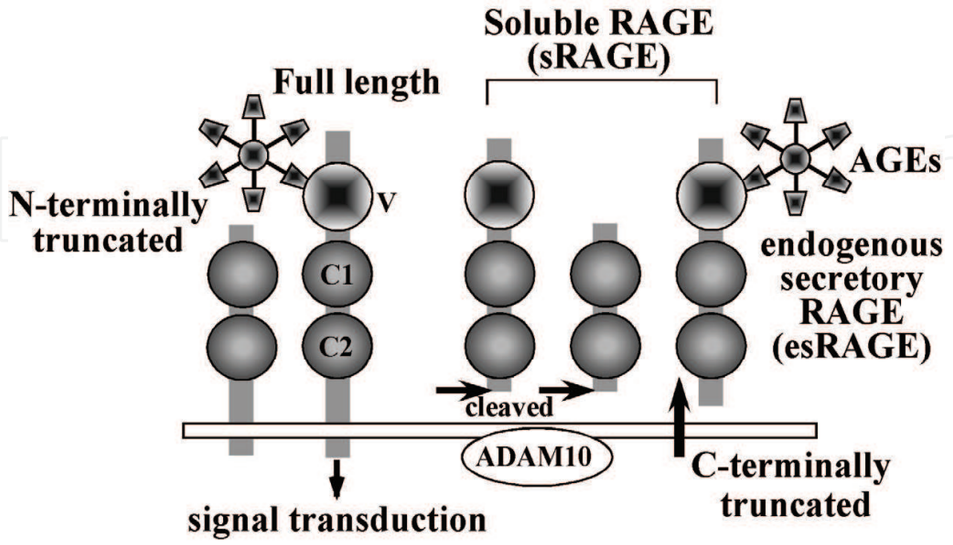

Fig. 1. Numerous truncated forms of RAGE. There are three major spliced variants of RAGE: full length, N-terminally truncated, and C-terminally truncated. The C-terminally truncated form of RAGE is secreted from the cell and is named endogenously secreted RAGE (esRAGE). esRAGE has a V-domain, which is essential for binding with ligands, and is capable of competing with RAGE signaling as a decoy receptor. There are other forms of soluble RAGE (sRAGE) that are cleaved from cell-surface RAGE by matrix metalloproteinases. The ELISA assay for sRAGE measures all soluble forms including esRAGE in human plasma, while the ELISA for esRAGE measures only esRAGE, using polyclonal antibody raised against the unique C-terminus of the esRAGE sequence.

4.2 Inflammatory signaling mediated by RAGE

Ligand engagement of RAGE leads to prolonged inflammation, resulting in a RAGE-dependent expression of proinflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) [79, 80]. RAGE-mediated proinflammatory signals could potentially converge with insulin signaling system (Figure 2). The engagement of RAGE has been reported to induce activation of the transcription factor nuclear factor-κB (NF-κB). Recent reports by Harja et al demonstrate that RAGE mediates upregulation of VCAM-1 in response to S100b and oxLDL and JNK MAP kinase underlies the RAGE ligand-stimulated molecular events [81]. It is not known at present whether this is also the case in classical insulin target cells. JNK activity is strikingly increased in critical metabolic sites (eg. adipose and liver tissues) [82], and is shown to be crucial in IRS-1 phosphorylation and consequently insulin resistance [82, 83]. Moreover, the main pathological consequence of RAGE ligation is the induction of intracellular reactive oxygen species (ROS) via NAD(P)H oxidases and other identified mechanisms such as mitochondrial electron transport chain [84], which consequently results in oxidative stress in the cells [85]. Oxidative stress is emerging as a feature of obesity and an important factor in the development of insulin resistance [86, 87]. Both the NF-kB and JNK pathways can be activated

under the conditions of oxidative stress, and this may be important for the ability of ROS to mediate insulin resistance. RAGE has a short cytosolic portion that contains 43 amino acids [72]. So far, adaptors and/or scaffold proteins that interact with the cytosolic tail of RAGE has barely been identified. The RAGE mutant lacking the 43-residue C-terminal tail fails to activate NF-κB, and expression of the mutant receptor results in a dominant negative effect against RAGE-mediated production of proinflammatory cytokines from macrophages [56, 57].

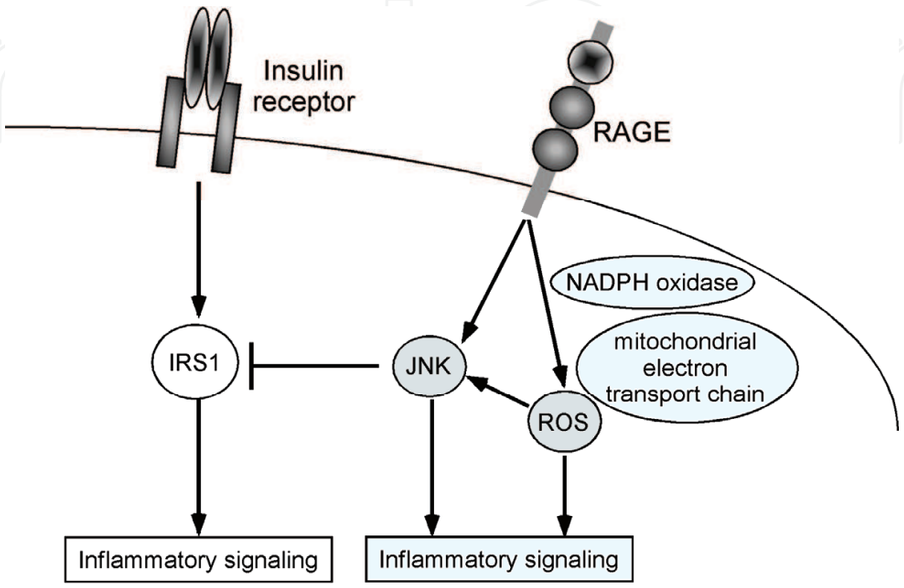

Fig. 2. RAGE and insulin signaling. RAGE is known to activate JNK pathway, which could phosphorylate serine-residue of insulin receptor substrate (IRS) and inhibit its activity. RAGE mediated generation of reactive oxygen spices (ROS) may alternatively influence insulin signaing.

4.3 RAGE and obesity

A. RAGE, adiposity and atherosclerosis in mouse model

Recent reports suggest that RAGE could be involved in progression of obesity. Recent study in humans shows RAGE mRNA expression in subcutaneous adipose tissues [88]. Although this study does not delineate which cells in adipose tissue express RAGE, our current animal study shows RAGE expression in adipocyte as wells as endothelial cells in adipose tissues [16]. We have shown by using apo E/RAGE double knockout mice that progression of atherosclerosis is closely associated with RAGE-regulated adiposity in non-diabetic conditions [16]. As shown in Figure 3, apoE$^{-/-}$RAGE$^{-/-}$ mice fed either with standard or atherogenic diet exhibited significantly decreased atherosclerotic plaque area in aorta as compared with apoE$^{-/-}$RAGE$^{+/+}$ mice. Importantly, apoE$^{-/-}$RAGE$^{-/-}$ mice also exhibited significantly less body weight, epididymal fat weight and epididymal adipocyte size than apoE$^{-/-}$RAGE$^{+/+}$ mice at 20-weeks of age (Figure 4). Decreased body weight, epididymal fat weight, and adipocyte size are associated with higher plasma adiponectin levels and decreased atherosclerosis progression. RAGE is involved in adiposity even in apo E$^{+/+}$ genetic background. At 20-weeks of age, epididymal adipocyte size of RAGE$^{-/-}$ mice was significantly smaller than that of RAGE$^{+/+}$ mice (data not shown).

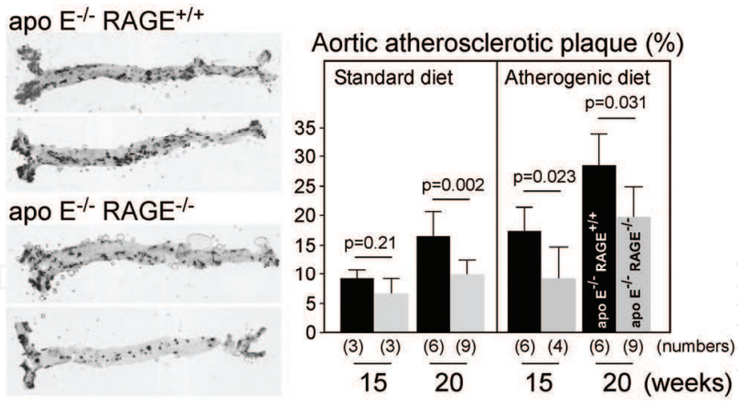

Fig. 3. RAGE deficiency suppresses atherosclerotic progression in apoE deficient mice. Representative aortas from apoE$^{-/-}$RAGE$^{+/+}$ and apoE$^{-/-}$RAGE$^{-/-}$ mice (20-weeks old) fed with atherogenic diet were shown in left panel. Right panel summarizes the quantitative analyses. Plaque area was represented as percentages of the total plaque area. Columns represent mean ± standard deviation. Black columns represent apoE$^{-/-}$RAGE$^{+/+}$ mice, and grey columns, apoE$^{-/-}$RAGE$^{-/-}$ mice. P values were analyzed by Student's unpaired t-test. Reproduced from ref [16].

B. Roles of inflammatory cells?

RAGE is also known to play fundamental role in functions of inflammatory cells [61, 89, 90], raising an intriguing possibility that RAGE's function on adiposity may be mediated through its function in inflammatory cells infiltrated in adipose tissues. In our study in apoE$^{-/-}$ genetic background fed with atherogenic diet, numbers of Mac-3-positive inflammatory cells infiltrated in the epididymal adipose tissues of RAGE$^{+/+}$apoE$^{-/-}$ mice and RAGE$^{-/-}$apoE$^{-/-}$ did not show significant differences, and crown-like structure were barely detected in epididymal adipose tissue in both groups even at 20-week of age. In standard diet-fed mice, even though the adiposity was significantly different between RAGE$^{+/+}$apoE$^{-/-}$ and RAGE$^{-/-}$apoE$^{-/-}$ mice, crown-like structure were not detected in epididymal adipose tissues in both groups even at 20-week of age. Further in apoE$^{+/+}$ genetic background at 10 week of age when significantly different pattern of gene expression was observed between WT and RAGE$^{-/-}$ mice, no marked differences in expressions of macrophage markers were observed as analyzed by gene microarray. At that age, macrophage infiltration in adipose tissues is also reported to be scant [91]. Thus, it appears infeasible to RAGE acting primarily at inflammatory cells at least in early phase of adiposity, while RAGE expressed in endothelial cells or adipocyte might play fundamental roles.

C. RAGE-regulated genes in adipose tissue: gene chip analysis

To explore potential mechanisms underlying RAGE-regulation of adiposity, mRNA expression profile in epididymal adipose tissue was compared between RAGE$^{+/+}$ and RAGE$^{-/-}$ mice using Affymetrix GeneChip Mouse Genome 430 2.0. We isolated total RNA from epididymal adipose tissue at 10-weeks of age, at which phenotypic change in adipocyte size was not observed. Using 3 μg of total RNA, 59.8% and 61.4% of 45,037 genes were revealed to be present in RAGE$^{+/+}$ and RAGE$^{-/-}$ adipose tissue, respectively. Comparison analysis of the genes (RAGE$^{+/+}$ adipose tissue as base line) revealed that 10.3% of the total genes were decreased, while 11.7% increased in RAGE$^{-/-}$ adipose tissue. As compared with RAGE$^{+/+}$ adipose tissue, 623 genes were downregulated to less than a half, and 2,470 genes upregulated more than 2 fold in RAGE$^{-/-}$ adipose tissue.

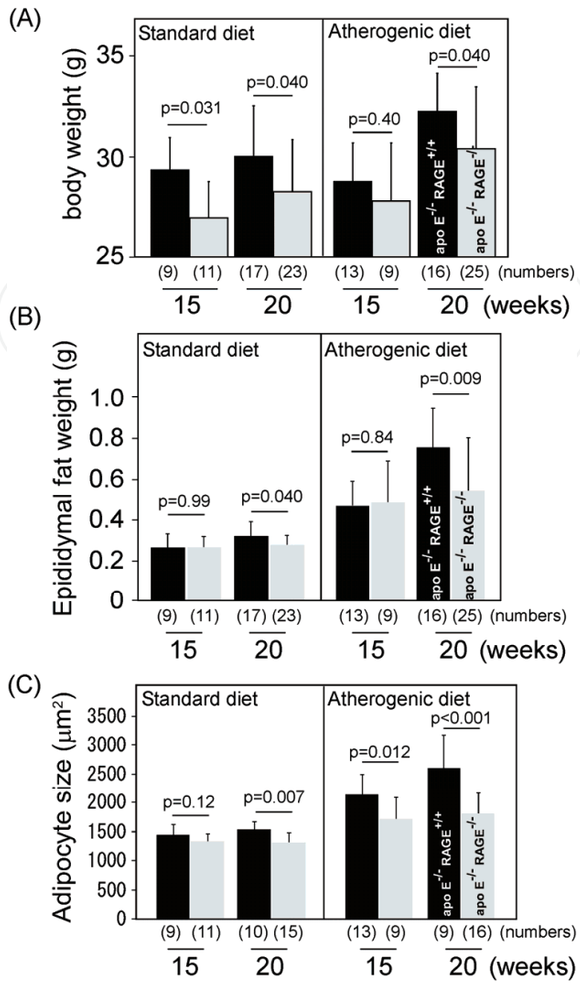

Fig. 4. RAGE deficiency is associated with decreased body weight, epididymal fat weight and adipocyte size in apolipoprotein E (apoE)-deficient genetic background. (A) Comparisons of body weight between apoE$^{-/-}$RAGE$^{+/+}$ and apoE$^{-/-}$RAGE$^{-/-}$ mice fed with standard or atherogenic diet. (B) Comparisons of epididymal fat weight between apoE$^{-/-}$RAGE$^{+/+}$ and apoE$^{-/-}$RAGE$^{-/-}$ mice fed with standard or atherogenic diet. (C) Comparisons of adipocyte size in epididymal adipose tissues. Columns represent mean ± standard deviation. P values were analyzed by Student's t-test. Modified from ref [16].

D. RAGE-regulated genes in adipose tissue: ontology analysis

To mine specific group of genes involved in adiposity regulated by RAGE, gene ontology analyses were performed. Downregulated genes in RAGE$^{-/-}$ adipose tissue were significantly accumulated in the ontology terms of metabolic process including acetyl-CoA biosynthetic process, neutral lipid biosynthetic process, pyruvate metabolic process, gluconeogenesis, glycogen biosynthetic process, and NADPH regeneration. Interestingly, genes involved in fat cell differentiation were also identified to be accumulated as down-regulated in RAGE$^{-/-}$ adipose tissue. Ontology terms of glucose transport and neutral amino acid transport were also significantly extracted as downregulated in RAGE$^{-/-}$ adipose tissue. Insulin receptor signaling pathway was a highly significant ontology term downregulated in RAGE$^{-/-}$ adipose tissue. On the contrary, many of the genes upregulated in RAGE$^{-/-}$ adipose tissue were

accumulated in ontology terms including cell adhesion, endocytosis, T cell activation, prostaglandin biosynthesis, protein binding, protein folding, processing and glycoprotein biosynthetic process, many of which are known be associated with cellular mechanisms for inflammation and defensive process. Nitrogen compound metabolic process, including amino acid metabolic process, was also identified to be a significant ontology term upregulated in RAGE$^{-/-}$. Interestingly, upregulated genes in RAGE$^{-/-}$ tissue were also significantly accumulated in ontology term for cell redox homeostasis process.

E. RAGE-regulated genes in adipose tissue: pathway analysis

To further identify potential pathways involved in RAGE-regulation of adiposity, KEGG pathway analyses were performed (Table 1). In accordance with the ontology analyses, insulin signaling pathway, pyruvate metabolism, fatty acid biosynthesis and gluconeogenesis were identified to be downregulated pathways in RAGE$^{-/-}$ adipose tissue. PPAR signaling and adipocytokine signaling were also identified to be downregulated in RAGE$^{-/-}$ adipose tissue. Similar to gene ontology analyses, inflammatory pathways including cell adhesion molecules and leukocyte transendothelial migration were the significant pathways upregulated in RAGE$^{-/-}$ mice. Pathways including amino acid metabolic pathways, nitrogen metabolism, glycan biosynthesis, structure and degradation were the pathways significantly upregulated in RAGE$^{-/-}$ adipose tissues.

WT>RAGE-/- (>= 3 fold)	count	P value
Insulin signaling pathway	4/137	0.0002
Fatty acid biosynthesis	1/6	0.0146
ErbB signaling pathway	2/87	0.0179
Ethylbenzene degradation	1/10	0.0242
1- and 2-methylnaphthalene degradation	1/20	0.0478
Jak-STAT signaling pathway	2/151	0.0500
WT>RAGE (>= 2 fold)		
Alanine and aspartate metabolism	7/33	<0.0001
Pyruvate metabolism	7/41	<0.0001
Insulin signaling pathway	12/137	0.0001
Adipocytokine signaling pathway	6/71	0.0059
Fatty acid biosynthesis	2/6	0.0077
Glycerophospholipid metabolism	5/61	0.0134
Glycerolipid metabolism	4/41	0.0148
Glutathione metabolism	4/42	0.0160
Ethylbenzene degradation	2/10	0.0216
Valine, leucine and isoleucine biosynthesis	2/10	0.0216
Type II diabetes mellitus	4/46	0.0218
Metabolism of xenobiotics by cytochrome P450	5/71	0.0245
Sulfur metabolism	2/11	0.0260
PPAR signaling pathway	5/74	0.0287
Propanoate metabolism	3/30	0.0320
Glycolysis / Gluconeogenesis	4/53	0.0345
Circadian rhythm	2/13	0.0358

Table 1. Pathway analyses of the genes differentially expressed in WT vs. RAGE-/- epididymal adipose tissue.

WT<RAGE-/- (>= 2 fold)		
Arginine and proline metabolism	6/33	0.0008
Glycine, serine and threonine metabolism	7/47	0.0010
Glycerolipid metabolism	5/41	0.0128
N-Glycan degradation	3/15	0.0136
Cyanoamino acid metabolism	2/6	0.0163
One carbon pool by folate	3/16	0.0164
Glycosphingolipid biosynthesis - ganglioseries	3/16	0.0164
Polyunsaturated fatty acid biosynthesis	3/17	0.0194
Ether lipid metabolism	4/32	0.0234
Cell adhesion molecules (CAMs)	10/147	0.0301
Prostate cancer	7/88	0.0317
Nitrogen metabolism	3/21	0.0343
Glycosylphosphatidylinositol(GPI)-anchor biosynthesis	3/21	0.0343
Glycan structures - biosynthesis 1	8/114	0.0428
WT<RAGE-/- (>= 3 fold)		
Arginine and proline metabolism	4/33	0.0053
Polyunsaturated fatty acid biosynthesis	3/17	0.0054
Glycerolipid metabolism	4/41	0.0114
Leukocyte transendothelial migration	7/115	0.0118
Glutathione metabolism	4/42	0.0124
Cell adhesion molecules (CAMs)	8/147	0.0137
O-Glycan biosynthesis	3/27	0.0199
Thyroid cancer	3/28	0.0219
Glyoxylate and dicarboxylate metabolism	2/14	0.0358
Glycan structures - biosynthesis 1	6/114	0.0364
One carbon pool by folate	2/16	0.0459
Pantothenate and CoA biosynthesis	2/16	0.0459

Table 1. Pathway analyses of the genes differentially expressed in WT vs. RAGE-/- epididymal adipose tissue (continuation).

F. RAGE-regulated genes in adipose tissue: real time RT-PCR confirmation

Adipogenesis related genes including, lipin 1, peroxisome proliferator-activated receptor (PPAR)-γ, adipose differentiation related protein, were shown to be downregulated in RAGE$^{-/-}$ mice. Fatty acid binding protein 5, 1-acylglycerol-3-phosphate O-acyltransferase 2, diacylglycerol O-acyltransferase 2, monoacylglycerol O-acyltransferase 1, acetoacetyl-CoA synthetase, acetyl-coenzyme A carboxylase α were downregulated in RAGE$^{-/-}$ adipose tissue, which could be an essential mechanisms for decreased adiposity in RAGE$^{-/-}$ mice. In insulin signaling, phosphatidylinositol 3-kinase (p85α), adaptor protein with pleckstrin homology and src (APS), sorbin and SH3 domain containing 1 (CAP), insulin receptor substrate (IRS) 1 and 3, thymoma viral proto-oncogene 2 / similar to serine/threonine kinase (Akt), Protein phosphatase 1 regulatory (inhibitor) subunit 3C, facilitated glucose

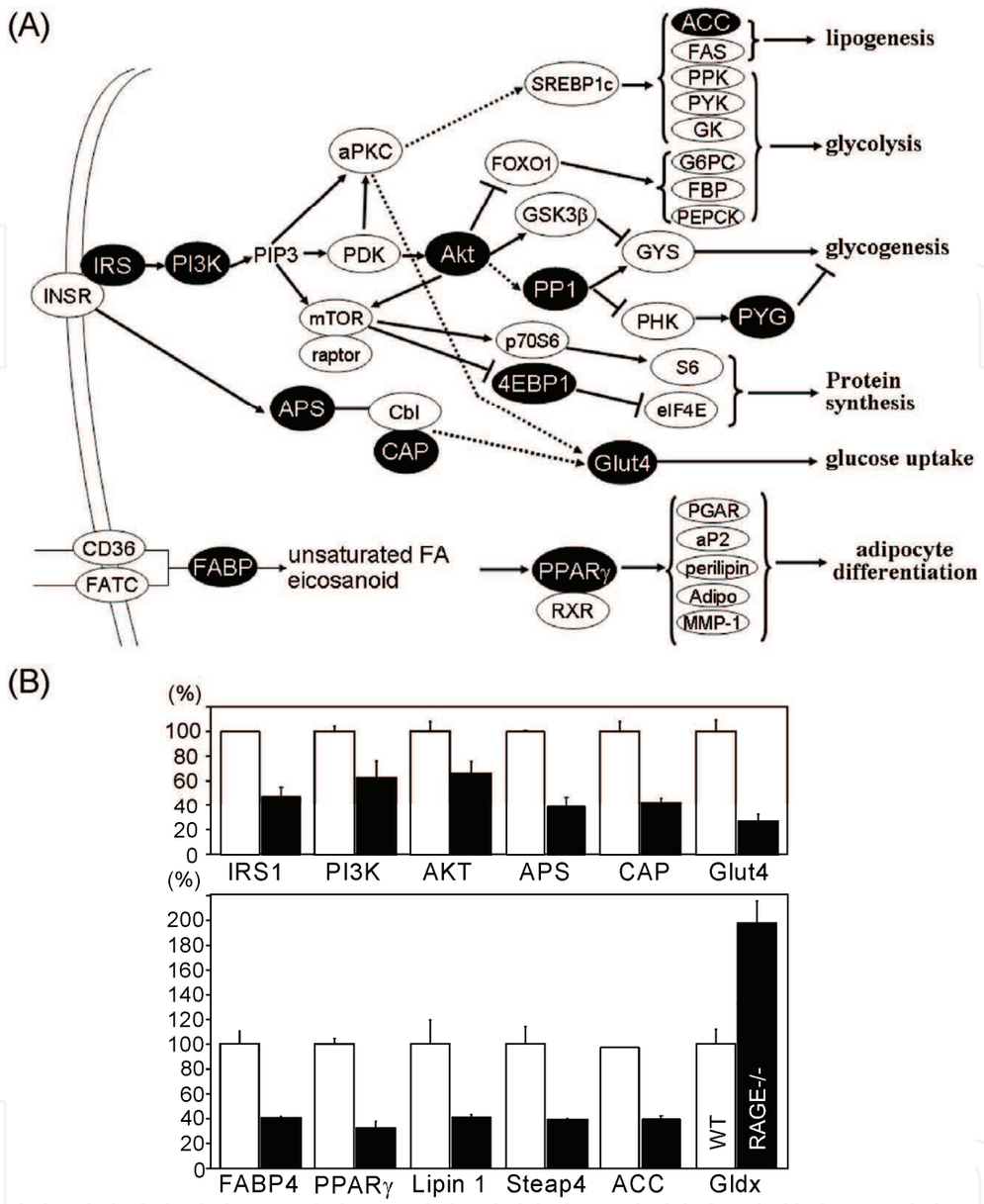

Fig. 5. Gene microarray, Ontology and KEGG pathway analyses suggest that insulin signaling and adipocyte differentiation are the potential pathways regulated by RAGE. (A) Figure summarizes the results of Ontology and KEGG pathway analyses. Genes suppressed in RAGE$^{-/-}$ adipose tissue were described in black circles. (B) Changes in mRNA expression obtained by gene microarray analyses were confirmed by real-time quantitative RT-PCR analyses. All changes in gene expression were statistically significance ($p<0.05$, Student's t-test). IRS-1: insulin receptor substrate 1, PI3K: phosphatidylinositol 3-kinase (p85α), AKT: thymoma viral proto-oncogene 2 / similar to serine/threonine kinase, APS: adaptor protein with pleckstrin homology and src, CAP: sorbin and SH3 domain containing 1, Glut4: facilitated glucose transporter member 4, FABP4: fatty acid binding protein 4, PPAR-γ: peroxisome proliferator-activated receptor, Steap4: six-transmembrane epithelial antigen of prostate 4, ACC: acetyl-coenzyme A carboxylase α, Gldx: glutaredoxin.

transporter member 4 (Glut 4) were identified to be downregulated in RAGE$^{-/-}$ adipose tissue. Figure 5A shows genes specifically suppressed in RAGE$^{-/-}$ adipose tissue (closed circles) in insulin signaling and adipocyte differentiation pathways. Real-time quantitative RT-PCR analyses confirmed the genes in the pathways were indeed down-regulated in RAGE$^{-/-}$ adipose tissue (Figure 5B). These results altogether suggest direct role of RAGE in adiposity. Although in which cell types RAGE is principally working, insulin signaling and adipocyte signaling pathway in adipose tissue appear to play important part in RAGE regulation of adiposity.

4.4 RAGE, endothelial dysfunction and insulin resistance

Impaired insulin action, when assessed by fasting serum insulin levels or the homeostasis model assessment of insulin resistance (HOMA-IR) [92], is associated with atherosclerosis and an increased risk of myocardial infarction. Insulin resistance is associated with endothelial dysfunction [93] and may serve as a link between insulin resistance and atherosclerosis. Recent findings by Harja et al highlighted the involvement of RAGE in endothelial dysfunction [81]. Endothelium-dependent vasorelaxation was tested in isolated mouse aortic rings from *apoE*$^{-/-}$ and *apoE*$^{-/-}$*RAGE*$^{-/-}$ mice, and relaxation response to acetylcholine was significantly improved in the RAGE deficient mouse. Similarly, impaired endothelial function in diabetic obese mice was also shown to be mediated by AGEs/RAGE system, since blockade of AGE-RAGE interaction by soluble RAGE significantly improved endothelial function [94]. Recent clinical observations by Linden et al [44] also implies AGEs/RAGE system is involved in impaired endothelial function in patients with chronic kidney diseases. Thus, not only by the interaction at the cellular signaling level, but RAGE appears to impair endothelial function and potentially blood flow in insulin target tissues, leading to insulin resistance in vivo.

5. C-terminally truncated form of RAGE (soluble RAGE, sRAGE) as potential biomarkers for cardiovascular diseases, metabolic syndrome and insulin resistance

5.1 Truncated form of RAGE

Numerous truncated forms of RAGE have recently been described [12, 95-98] (Figure 1). Two major spliced variants of RAGE mRNA, N-terminal and C-terminal truncated forms, have been most extensively characterized [12]. The N-truncated isoform of RAGE mRNA codes for a 303-amino-acid protein lacking the N-terminal signal sequence and the first V-like extracellular domain. The N-truncated form is incapable of binding with AGEs, since the V-domain is critical for binding of the ligand [71]. The N-truncated form of RAGE appears to be expressed on the cell surface similar to the full-length RAGE, although its biological roles remain to be elucidated [99]. It has been suggested that this form of RAGE could be involved in angiogenic regulation in a fashion independent of the classical RAGE signaling pathway [99].

5.2 Endogenous secretory RAGE (esRAGE)

The C-terminal truncated form of RAGE lacks the exon 10 sequences encoding the transmembrane and intracytoplasmic domains [12]. This spliced variant mRNA of RAGE

encodes a protein consisting of 347 amino acids with a 22-amino-acid signal sequence, and is released from cells. This C-truncated form is now known to be present in human circulation and is named endogenous secretory RAGE (esRAGE) [12]. Regulation of alternative splicing of the RAGE is recently shown to be regulated through G-rich cis-elements and heterogenous nuclear ribonucleoprotein H [100]. esRAGE was found to be capable of neutralizing the effects of AGEs on endothelial cells in culture [12]. Adenoviral overexpression of esRAGE in vivo in mice reverses diabetic impairment of vascular dysfunction [101]. Thus, the decoy function of esRAGE may exhibit a feedback mechanism by which esRAGE prevents the activation of RAGE signaling.

5.3 Soluble RAGE generated by shedding

It has also been suggested that some sRAGE isoforms that could act as decoy receptors may be cleaved proteolytically from the native RAGE expressed on the cell surface [102], suggesting heterogeneity of the origin and nature of sRAGE. This proteolytic generation of sRAGE was initially described as occurring in mice [103]. Recent studies suggest that ADAM10 and MMP9 to be involved in RAGE shedding [13, 14]. ADAM is known as a shedase to shed several inflammatory receptors and can be involved in regulation of RAGE/sRAGE balance. A RAGE gene polymorphism is shown to be strongly associated with higher sRAGE levels, although the mechanism by which the polymorphism alters the sRAGE levels remains to be elucidated [104]. Thus, the molecular heterogeneity of the diverse types of sRAGE in human plasma could exert significant protective effects against RAGE-mediated toxicity. However, the endogenous action of sRAGE may not be confined to a decoy function against RAGE-signaling. In HMGB1-induced arthritis model, for example, sRAGE is found to interact with Mac-1, and act as an important proinflammatory and chemotactic molecule [105]. Further analyses are warranted to understand more about the endogenous activity of sRAGE.

5.4 Circulating sRAGE and esRAGE in diseases

A. Circulating sRAGE and cardiovascular diseases

Since sRAGE and esRAGE may be involved in feedback regulation of the toxic effects of RAGE-mediated signaling, recent clinical studies have focused on the potential significance of circulating sRAGE and esRAGE in a variety of pathophysiological conditions, including atherosclerotic disorders, diabetes, hypertension, Alzheimer's dieases and chronic kidney diseases (Table 2). First, Falcone et al [106] reported that total sRAGE levels are significantly lower in patients with angiographically proven coronary artery disease (CAD) than in age-matched healthy controls. The association between circulating sRAGE and angiographic observations was shown to be dose-dependent, with individuals in the lowest quartile of sRAGE exhibiting the highest risk for CAD. Importantly, this cohort consisted of a non-diabetic population, suggesting that the potential significance of sRAGE is not confined to diabetes. Falcone et al also showed that the association between sRAGE and the risk of CAD was independent of other classical risk factors. Their findings are reproduced later by several research groups in larger numbers of subjects, and are also extended to other atherosclerotic diseases, such as carotid atherosclerosis, cerebral ischemia, and aortic valve stenosis (Table 2). Patients with

Alzheimer disease have also lower levels of sRAGE in plasma than patients with vascular dementia and controls, suggesting a role for the RAGE axis in this clinical entity as well [107].

sRAGE		references
CAD (non-DM)	decreased	106, 153, 154
	increased	124
Calcified aortic valve stenosis	decreased	155
Carotid atherosclerosis	decreased	156
Cerebral ischemia	decreased	157 158 127
Alzheimer's disease	decreased	107 159
Endothelial dysfunction	decreased	160
Diabetes (type 1)	increased	122
Diabetes (type 2)	increased	123, 124
	decreased	120, 121
Hypertension	decreased	117
NASH	decreased	118 119
Chronic kidney disease	increased	109, 123, 129, 161 162
Oxidative stress and inflammatory markers	positively associated	163, 164
	inversely associated	121
esRAGE		
Insulin resistance	inversely associated	15
Metabolic syndrome	decreased	15
Diabetes (type 1)	decreased	108, 110
Diabetes (type 2)	decreased	15, 113
Hypertension	decreased	15
NASH	decreased	119
Carotid atherosclerosis	decreased	15, 110-112
	no association	109
CAD	decreased	113, 153
Altzheimer's disease	decreased	165
Chronic kidney disease	increased	114, 161 162

Table 2. Levels of circulating soluble RAGE in cardiovascular and metabolic diseases.

B. Circulating esRAGE and cardiovascular diseases

Following development of an ELISA system to specifically measure human esRAGE [108], we measured plasma esRAGE level and cross-sectionally examined its association with atherosclerosis in 203 type 2 diabetic and 134 non-diabetic age- and gender-matched subjects [15]. esRAGE levels were inversely correlated with carotid and femoral atherosclerosis, as measured as intimal-medial thickness (IMT) by arterial ultrasound. Stepwise regression analyses revealed that plasma esRAGE was the third strongest and an independent factor associated with carotid IMT, following age and systolic blood pressure[15]. Importantly however, when non-diabetic and diabetic groups were separately

analyzed, inverse correlation between plasma esRAGE level and IMT was significant in non-diabetic population only, suggesting a potential significance of esRAGE in non-diabetic condition. No association of plasma esRAGE with IMT in diabetes was also reported in other study with 110 Caucasian type 2 diabetic subjects [109]. Another Japanese research group found an inverse correlation between plasma esRAGE and carotid atherosclerosis in type 1 [110] and type 2 diabetic subjects [111]. Recently, the same research group also longitudinally examined the predictive significance of plasma esRAGE and sRAGE on progression of carotid atherosclerosis, and found that low circulating esRAGE level as well as sRAGE level was an independent risk factor for the progression of carotid IMT in type 1 diabetic subjects [112]. In Chinese type 2 diabetic patients, plasma esRAGE is recently shown to be decreased in angiographically-proved patients with coronary artery disease than those without it [113].

C. Low circulating sRAGE as a predictor of cardiovascular diseases

We also reported an observational cohort study in patients with end-stage renal disease (ESRD) and longitudinally evaluated the effect of plasma esRAGE on cardiovascular mortality [114]. The cohort in that study included 206 ESRD subjects, who had been treated by regular hemodialysis for more than 3 months. Even though the plasma esRAGE levels at baseline were higher in ESRD subjects than in those without kidney disease, the subjects in the lowest tertile of plasma esRAGE levels exhibited significantly higher cardiovascular mortality, but not non-cardiovascular mortality. Importantly, even in the subpopulation of non-diabetic subjects alone, low circulating esRAGE level was a predictor of cardiovascular mortality, independent of the other classical risk factors. Thus, low circulating esRAGE or sRAGE level is a potential predictor for atherosclerosis and cardiovascular diseases even in non-diabetic population.

D. Circulating sRAGE, esRAGE and metabolic syndrome

Several components of metabolic syndrome have been shown to be associated with altered plasma sRAGE or esRAGE levels. We first reported that plasma esRAGE levels are already decreased in patients with impaired glucose tolerance as compared with those with normal glucose tolerance (Figure 6A). Moreover, patients with metabolic syndrome showed significantly lower plasma esRAGE than those without it (Figure 6A). Plasma esRAGE levels are inversely correlated with many of the components of metabolic syndrome including body mass index (Figure 6B), blood pressures, fasting plasma glucose, serum triglyceride, and lower HDL-cholesterol levels [15]. The majorities of these correlations remained significant even when the non-diabetic or type 2 diabetic subpopulation was extracted for analyses. An inverse correaltion between esRAGE (or sRAGE) and body mass index was also found for control subjects [115], those with type 1 diabetes [116], and those with ESRD [114]. Patients with hypertension have been found to have lower plasma sRAGE or esRAGE levels [15, 117]. Importantly, our findings also showed that plasma esRAGE was also inversely associated with insulin resistance index, HOMA (Figure 6B), suggesting esRAGE and sRAGE as potential biomarkers for metabolic syndrome and insulin resistance, which could be associated with altered cardiovascular outcomes. Both sRAGE and esRAGE are found to be decreased in patients with liver steatosis [118, 119], which is know to be deeply associated with visceral fat accumulation and insulin resistance.

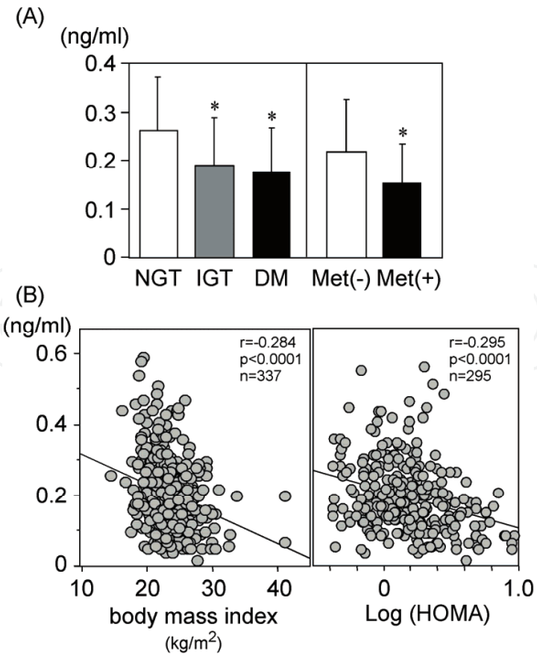

Fig. 6. Plasma esRAGE levels are decreased in glucose intolerance, metabolic syndrome, obesity and insulin resistance (A) Left panel demonstrates the levels of plasma esRAGE in subjects with normal glucose tolerance (NGT) (n=118), impaired glucose tolerance (IGT) (n=16), and type 2 diabetes (DM) (n=203). Right panel compares the plasma esRAGE levels in subjects with (n-53) or without (n=282) metabolic syndrome (Met) as characterized by modified NCEP criteria. * $p<0.05$, ANOVA with multiple comparison (Scheffe's type). (B) Plasma esRAGE levels were inversely associated with body mass index or HOMA insulin resistance index. Logarithm-transformed HOMA index was used for the analyses because of the skewed distribution. Modified from ref [15].

E. Circulating sRAGE and esRAGE in diabetes

The findings regarding plasma levels of the soluble form of RAGE in diabetes are quite confusing. We and other groups have found that plasma esRAGE level is significantly lower in type 1 and type 2 diabetic patients than in non-diabetic controls [15, 110]. Plasma sRAGE levels have also been shown to be decreased in diabetic subjects [120, 121], although conflicting findings have also been reported for type 1 [122] and type 2 diabetes [123, 124]. We examined plasma sRAGE levels by different ELISA system using esRAGE as a standard protein and different sets of antibodies against whole RAGE molecule [125]. In our hand, type 2 diabetic subjects without overt nephropathy (0.60 ± 0.28 ng/ml) exhibited significantly ($p<0.001$, Student's t-test) lower plasma sRAGE level than non-diabetic controls (0.77 ± 0.34 ng/ml) [11]. Of note, when diabetic subjects alone were extracted for analyses, a direct association was not observed between plasma soluble RAGE (both sRAGE and esRAGE) levels and the status of glycemic control (i.e. glycated hemoglobin A1c) [15, 109, 116, 120, 126]. Thus, these complex findings in diabetic subjects suggest that levels of plasma soluble forms of RAGE are not determined simply by status of glycemic control, and that even plasma esRAGE and sRAGE levels may be under the control of distinct mechanisms. Recent study suggests that sRAGE levels may be significantly influenced by ethnicity [127], which may partially explain controversial findings.

F. Circulating sRAGE and esRAGE in CKD

Another important component that can affect plasma sRAGE is the presence of chronic kidney disease. It has been shown that, in peripheral monocytes from subjects with varying severities of CKD, RAGE expression is closely associated with worsening of CKD and is strongly correlated with plasma levels of pentosidine, a marker for AGEs [128]. Circulating sRAGE levels have been shown to be increased in patients with decreased renal function, particularly those with ESRD [109, 123, 129]. Our observations revealed that plasma esRAGE levels in type 2 diabetic subjects without CKD are lower than non-diabetic controls, which is gradually elevated in accordance with progression of CKD [11]. Plasma sRAGE levels in diabetic subjects without CKD also exhibited significantly lower than those of non-diabetic controls [11]. Thus, plasma sRAGE and esRAGE are markedly affected by the presence of CKD, which might make the interpretation of the role of soluble RAGE quite complicated [130]. It remains to be determined whether the increase in plasma esRAGE in CKD is caused by decreased renal function alone or whether esRAGE levels are upregulated to protect against toxic effects of the RAGE ligands. Successful kidney transplantation resulted in significant decrease in plasma sRAGE [131], implying that the kidneys play a role in sRAGE removal.

6. RAGE and Soluble RAGE as a therapeutic target against metabolic syndrome, insulin resistance and cardiovascular disease?

6.1 Soluble RAGE as a therapeutic tool in animal disease models

Potential usefulness of soluble RAGE for prevention and treatment of inflammatory diseases has been demonstrated in many animal models. Blockade of RAGE by administration of genetically engineered sRAGE successfully prevented the development of micro- [132, 133] and macrovascular complications in diabetes [134-136]. We have also shown that adenoviral overexpression of esRAGE successfully restored the impaired angiogenic response in diabetic mice [101]. Sakaguchi et al found that administration of sRAGE markedly suppressed neointimal formation following arterial injury in non-diabetic mice [137]. Soluble RAGE has also been shown to effectively prevent the development of diabetes [138], protect against tumor growth and metastasis [58], improve the outcome of colitis [56], restore impaired wound healing [139], and suppress Alzheimer disease-like conditions [140]. These effects of soluble RAGE in animal models could be explained by its decoy function, inhibiting RAGE interaction with its proinflammatory ligands, which might be applicable to human diseases as well. Since our findings strongly suggest the role of RAGE in adiposity, metabolic syndrome and atheroslcerosis [16], RAGE/soluble RAGE axis could also be a potential therapeutic target against these pathophysiological conditions.

6.2 Potential regulatory mechanisms of circulating soluble RAGE

So far, limited findings are available regarding the mechanisms of regulation of circulating esRAGE or sRAGE in humans. A tissue microarray technique using a wide variety of adult normal human preparations obtained from surgical and autopsy specimens revealed that esRAGE was widely distributed in tissues, including vascular endothelium, monocyte/macrophage, pneumocytes, and several endocrine organs [141]. However, it is unclear at present from which organ or tissue plasma sRAGE or esRAGE originate. Circulating AGEs may be involved in regulation of the secretion or production of soluble RAGE, since AGEs are known to upregulate RAGE expression in vitro [142]. esRAGE could be simultaneously upregulated by AGEs and act as a negative feedback loop to compensate for

the damaging effects of AGEs. We and others have found positive correlations between plasma sRAGE or esRAGE and AGEs [11, 114-116, 123]. Significant positive correlation between plasma esRAGE and pentosidine was observed both in hemodialysis and non-hemodialysis subjects [11]. However, plasma CML did not significantly correlated with plasma esRAGE both in hemodialysis and non-hemodialysis subjects. AGEs-mediated regulation of soluble RAGE is also supported by the findings that the suppression of sRAGE expression in diabetic rat kidney is reversed by blockade of AGEs accumulation with alagebrium [143]. Other inflammatory mediators, such as S100, tumor necrosis factor α, and C-reactive protein, could also be potential candidates for regulation of the plasma level of soluble RAGE in humans [120, 142, 144]. Moreover, Geroldi et al [145] showed that high serum sRAGE is associated with extreme longevity, suggesting that understanding the intrinsic regulation of RAGE and soluble RAGE is important for longevity/anti-aging strategies. Without doubt, further understanding of the regulation of soluble RAGE will be most helpful in delineating potential targets for therapeutic application of soluble RAGE.

6.3 Pharmacological agents regulate circulating sRAGE and esRAGE

A. Angiotensin-converting enzyme inhibitor

It would be essential to determine whether currently available pharmacological agents can regulate plasma sRAGE or esRAGE. Potential agents that may affect circulating soluble RAGE include the angiotensin-converting enzyme (ACE) inhibitor [146], thiazolidinediones (TZD) [147] and statins [148-150], which are known to modulate the AGEs-RAGE system in culture. Forbes et al [146] showed that inhibition of angiotensin-converting enzyme (ACE) in rats increased renal expression of sRAGE, and that this was associated with decreases in expression of renal full-length RAGE protein. They also showed that plasma sRAGE levels were significantly increased by inhibition of ACE in both diabetic rats and in human subjects with type 1 diabetes. Thus, one attractive scenario is that the protective effect of ACE inhibition against progression of renal dysfunction is mediated through regulation of RAGE versus soluble RAGE production.

B. Statin

Tam et al recently reported changes in serum levels of sRAGE and esRAGE in archived serum samples from a previous randomized double-blind placebo-controlled clinical trial that explored the cardiovascular effects of atorvastatin in hypercholesterolemic Chinese type 2 diabetic patients, and found that atorvastatin can increase circulating esRAGE levels [150].

C. Thiazolidinedione

For thiazolidinedione, a randomised, open-label, parallel group study was performed with 64 participants randomised to receive add-on therapy with either rosiglitazone or sulfonylurea to examine the effect on plasma soluble RAGE [151]. At 6 months, both rosiglitazone and sulfonylurea resulted in a significant reduction in HbA1c, fasting glucose and AGE. However, significant increases in total sRAGE and esRAGE were only seen in the rosiglitazone group. In a recent study in type 2 diabetes mellitus patients, pioglitazone, but not rosiglitazone, significantly raised sRAGE levels [152], suggesting that all thiazolidinedione may not act similarly. Nevertheless, thiazolidinedione could be one promising candidate which increase circulating levels of esRAGE and sRAGE, and RAGE/soluble RAGE regulation may be involved in thiazolidinedione-mediated improvement of insulin resistance. Finally, we have started the randomized clinical trial comparing the effect of

pioglitazone with glimepiride on plasma sRAGE and esRAGE, expression of RAGE on peripheral mononuclear cells, and RAGE shedase gene expression in type 2 diabetic patients (UMIN000002055). This study will be of particular importance to understand the regulatory mechanisms of sRAGE and esRAGE in clinical setting.

7. Summary

The findings discussed here implicated pivotal role of RAGE system in initiation and progression of metabolic syndrome, insulin resistance and atherosclerosis. Provided that continuous RAGE activation represents the concept of "metabolic memory", metabolic syndrome might be conceptualized as memorized long-term subtle inflammation and oxidative stress using RAGE as an inflammatory scaffold. In this system, endogenous inflammatory RAGE ligands may be profoundly involved (Figure 7). Further, sRAGE or esRAGE could serve as a biomarker as well as a therapeutic target for these disease conditions. Obviously there are many missing parts to be veiled to further understand the role of RAGE/soluble RAGE axis in metabolic syndrome and insulin resistance. However, we believe our findings and this concept would open up a new research field which could further precede our understanding of the RAGE biology.

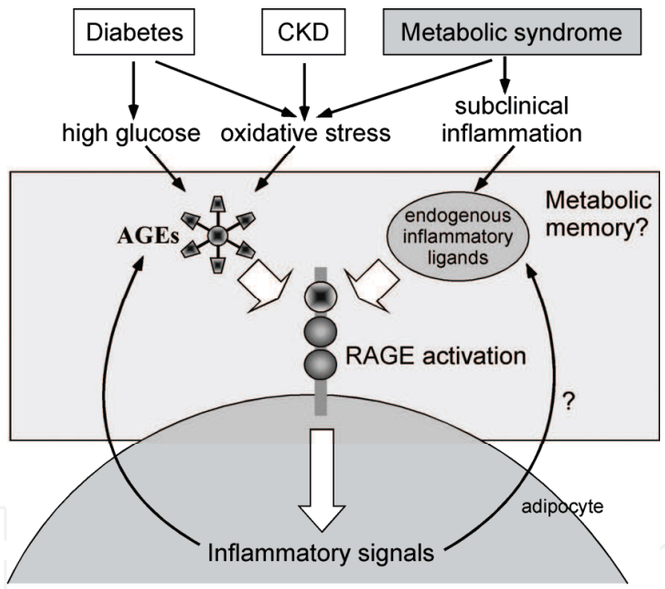

Fig. 7. Metabolic syndrome may be an aspect of "metabolic memory" conceptualized as prolonged RAGE activation through subclinical information.

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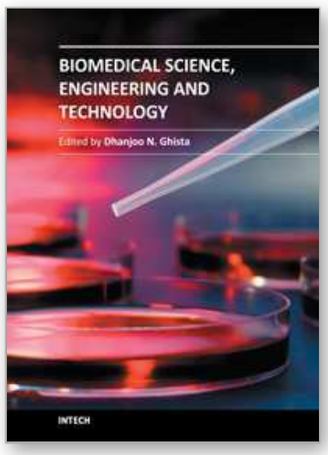

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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