Review

Soluble receptor for advanced glycation end products: a new biomarker in diagnosis and prognosis of chronic inflammatory diseases

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The formation of advanced glycation end products (AGEs) is a result of the non-enzymatic reaction between sugars and free amino groups of proteins. AGEs, through interacting with their specific receptor for AGEs (RAGE), result in activation of pro-inflammatory states and are involved in numerous pathologic situations. The soluble form of RAGE (sRAGE) is able to act as a decoy to avoid interaction of RAGE with its pro-inflammatory ligands (AGEs, HMGB1, S100 proteins). sRAGE levels have been found to be decreased in chronic inflammatory diseases including atherosclerosis, diabetes, renal failure and the aging process. The use of measuring circulating sRAGES may prove to be a valuable vascular biomarker and in this review, we describe the implications of sRAGE in inflammation and propose that this molecule may represent a future therapeutic target in chronic inflammatory diseases.

Key words: Advanced glycation end products, Receptor for advanced glycation end products, Soluble form of receptor for advanced glycation end products, Biomarker, Atherosclerosis, Inflammation, Chronic inflammatory diseases.

Introduction

Advanced glycation end products (AGEs) result from a non-enzymatic reaction between sugars and free amino groups of proteins. AGEs and their specific receptor, receptor for AGEs (RAGEs), were initially reported to be involved in microvascular and macrovascular complications of diabetes mellitus, renal failure and peritoneal injury of long-term peritoneal dialysis patients [1–6]. AGEs are also implicated in various other pathologic situations such as aging, neurological disorders and inflammatory states [7, 8].

In animals, intraperitoneal injection of the recombinantly produced extracellular domain of RAGE [soluble RAGE (sRAGE)] can block AGE/RAGE interaction, and leads to early intense inflammatory response to the excision wound, which promotes better granulation tissue and thus causes early blunting of inflammatory response, which overall results in better wound healing [9]. More recently, in human studies, circulating endogenous sRAGE has been identified as a potential biomarker where decreased levels have been seen in vascular disease states including coronary artery disease (CAD), hypertension, vascular dementia, atherothrombotic stroke and the diabetic state (type 1 and type 2 diabetes) [10–15]. The purpose of the present review is to assess the implications of sRAGE in human inflammatory diseases.

AGEs, RAGEs and sRAGEs

AGEs

AGEs result from non-enzymatic glycation and glycoxidation of proteins and lipids. The increased formation and accumulation of AGEs have been reported in several pathophysiologic situations such as diabetes, renal failure, aging and inflammation, as well as Alzheimer’s disease [7, 8]. The pool of AGEs in vitro reflects not only their endogenous formation, but also their accumulation from exogenous sources including the consumption of foods rich in AGEs and from smoking [16]. Glucose reacts with free amino group of lysine or arginine, producing Schiff bases, which are rapidly transformed into Amadori products. After a series of complex reactions, these form into AGEs, which include Nε-carboxymethyl-lysine (CML), pentosidine, furosine, gold and mold. AGEs are divided into two classes according to their spontaneous fluorescence or their non-fluorescent characteristics. AGEs can be identified by high-performance chromatography and mass spectrometry [17]. Some compounds like CML and pentosidine are antigenic and can be detected by immunological techniques [18]. Two major mechanisms are described to explain AGEs’ toxicity: the cross-linking of protein leading to alterations in the tissue/vessel structure, and the interaction with cell surface receptors including RAGE, the AGE-receptor complex (AGE-R1, AGE-R2 and AGE-R3), MSRII, CD36 and LOX-1 [19].

RAGE and annexin receptors

During the past two decades, numerous receptors for AGEs have been identified on multiple cell types: endothelial cells, leucocytes, macrophages, mesothelial cells and neuronal cells [20]. AGE-R1 is a macrophage scavenger receptor also named as OST48 and functions as an oligosaccharide transporter (OST). The AGE-R2 p90 protein kinase (80KH) binds AGEs; it is associated with the fibroblast growth factor receptor (FGF-R) and plays a role in signal transduction. AGE-R3 is similar to galactin3 [19]. Mice deficient in AGE-R3 gene develop an accelerated glomerulosclerosis indicating that this receptor may act as a scavenger for AGEs [21, 22]. AGE-R1-3 was initially identified to act as an ‘AGE-receptor complex’; however, this concept has not been fully explored.

The most characterized AGE receptor up to-date is RAGE, which is a member of the immunoglobulin super family. RAGE, in addition to its role as a receptor for AGEs, has been latterly identified to be a multi-ligand receptor. Ligands other than AGEs include...
numerous members of the S100/calgranulin family of pro-inflammatory cytokine-like mediators, the high mobility group B1 (HMGB1/amphoterin, a pro-inflammatory protein, which is also involved in the CNS maturation) and the amyloid-fibrils. The common feature of these ligands is their association and co-accumulation with RAGE in inflammatory states [23]. The human RAGE gene is located on chromosome 6 in the MHC class III region [24]. The resulting transcribed mRNA of ~1.4 kb is translated into a protein of 404 amino acids with a molecular mass of ~55 kDa [1]. Moreover, numerous splice variants of RAGE have been identified and some of them can be secreted as soluble form [25, 26].

RAGE contains an intra-cellular domain, a short transmembrane domain and an extracellular domain consisting of three immunoglobulin-like regions, one ‘V’ type followed by two ‘C’ types. The ‘V’ type is essential for ligand binding [27]. RAGE is expressed at low levels in normal tissues and vasculature, but is up-regulated in sites where its pro-inflammatory ligands accumulate [27]. RAGE interaction with its ligands is followed by a range of signalling pathways activation including nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the transcription factor NF-kB, triggering generation of reactive oxygen species [28]. The cell response promotes inflammation through overexpression of various cell adhesion molecules (vascular cell adhesion molecule-1 and inter-cellular adhesion molecule-1 and cytokine production such as IL-6) playing a major role in the inflammatory response [5, 29].

sRAGE
It has been identified that sRAGE exists in the circulation of humans. sRAGE corresponds to the extracellular domain of RAGE lacking cytosolic and transmembrane domains. As the N-terminal ‘V’ type domain is included, sRAGE has the same ligand-binding specificity as RAGE and may act as a ‘decoy’ by binding pro-inflammatory ligands and preventing them from reaching membrane RAGE. There are a number of mechanisms that have been identified to produce sRAGE, including the alternative splicing to remove the transmembrane region and the proteolytical cleavage from the cell surface. It has been identified that the primary splicing mechanism of producing sRAGE is from the alternative splicing of intron 9/exon 10 of the RAGE gene. This variant termed ‘RAGE_v1’ was identified as the primary secreted splice variant of RAGE and previously named esRAGE (endogenous secretory RAGE) [25, 26]. The other mechanism responsible for producing the circulating pool of sRAGE derives from membrane-bound full-length RAGE (fRAGE) by proteolytical processing. This extracellular form of RAGE is named cRAGE (cleaved RAGE). Both esRAGE and cRAGE are functionally equivalent and interact with same RAGE ligands (Fig. 1). Cleavage of RAGE can be inhibited with metalloprotease inhibitors and cells deficient in Adam10 produce a small amount of sRAGES, suggesting that Adam10 is responsible for RAGE cleavage. Moreover, it has been also demonstrated that RAGE shedding is promoted by HMGB1, one of the RAGE ligands [24].

The measurement of sRAGE levels in human plasma is possible by two distinct ELISAs. The first measures the total sRAGE pool resulting from both cleavage and alternative splicing of RAGE (Quantikine sRAGE ELISA) and the specific measurement of RAGE_v1/esRAGE (esRAGE ELISA). Direct comparisons between the levels measured with these ELISAs indicate that esRAGE represent only of the sRAGE pool (~20%) [30]. However, no studies have definitely examined the relationship between these two distinct methodologies and therefore a conclusion of the exact ration of sRAGEs cannot be made. Numerous studies reported that a correlation exists between sRAGE levels and some pathologic inflammatory states. Here, we review sRAGE implications in inflammatory diseases.

sRAGE and chronic inflammatory diseases

Chronic inflammatory diseases

RA. RA is a chronic inflammatory synovitis. RAGE is expressed by many of the cells that participate in the development of synovial inflammation (RA and OA) [31]. HMGB1, one of the inflammatory RAGE ligand, is a potent pro-inflammatory cytokine increased in synovial tissues of RA patients [32]. HMGB1 induces arthritis in healthy mice when IA administered [33]. Compared with healthy controls and patients with non-inflammatory joint disease (NID), RA patients display significantly decreased blood levels of sRAGE. Low sRAGE level could, at least in part, explain arthritis by the lack of HMGB1–RAGE interaction blockade by sRAGE [34]. In addition, SF sRAGE levels in RA patients are two times lower than in corresponding control blood samples. The SF levels of sRAGE were comparable with NID. There is a moderate correlation (r = 0.48) between blood and synovial levels of RAGE. Compared with non-treated RA patients, synovial sRAGE levels are higher in MTX-treated RA patients. Blood and synovial sRAGE levels in RA patients are not associated with age, duration disease, erosive disease or level of CRP. Taken together, such data suggest that RA patients have lower sRAGE blood and synovial levels than controls and that MTX could counteract this feature. It is not determined if low sRAGE levels are a consequence or a contributing factor of RA.

Kawasaki disease. Kawasaki disease (KD) is a systemic vasculitis affecting small- and medium-sized arteries in childhood. Aetiology and pathogenesis of KD remain unclear, but it has been reported that S100A12 is involved in KD inflammation [35]. S100A12 and sRAGE levels in children with KD (as a model of acute inflammation) were compared with children with juvenile idiopathic arthritis (JIA) (some with systemic-onset JIA as acute inflammation and others with articular-onset JIA as chronic inflammation) and to healthy controls to investigate the relationship between S100A12 and sRAGE [36]. Compared with controls, it was observed that sRAGE levels are lower in KD and systemic-onset JIA and higher in articular-onset JIA. Levels of S100A12 are higher in KD and JIA than in controls and the S100A12/sRAGE ratio is significantly increased in children with KD or JIA. After treatment in KD patients, S100A12/sRAGE ratio is in the same range than controls. These results emphasize that sRAGE level is decreased in acute inflammation but could be increased in chronic inflammation, maybe as a result of an anti-inflammatory feedback mechanism. The increase in the S100A12/sRAGE ratio in inflammation may then be normalized after resolution of inflammation, suggesting that this ratio is of greater interest than individual parameters. It remains unclear if lower sRAGE levels are associated with higher susceptibility to the pro-inflammatory effects of S100A12 or if higher S100A12 levels are associated with greater reduction of sRAGE by elimination of sRAGE–S100A12 complexes.

SS. SS is a chronic inflammatory autoimmune disease characterized by lymphocytic infiltration of the lacrimal and salivary glands [37]. RAGE is expressed in the labial salivary glands of both normal and SS patients but appears to be overexpressed in SS tissues [38]. Based on these previous results, sRAGE levels were measured in blood samples from primary and secondary SS and patients with a positive ANA titre [39]. Mean sRAGE levels were found to be lower in the primary SS group compared with the two other groups without any difference between these later groups. The authors conclude that RAGE system might be involved in the pathogenesis of primary SS.

Inflammatory bowel diseases. Inflammatory bowel diseases (IBDs) such as Crohn’s disease (CD) and ulcerative colitis (UC)
display chronic intestinal inflammation with pro-inflammatory S100 family implication. Since S100A12 is reported to be a RAGE ligand, serum and mucosal levels of S100A12 and sRAGE were measured in children with newly diagnosed IBD compared with children with coeliac disease and non-IBD controls [40]. Compared with coeliac disease and non-IBD children, serum S100A12 levels are increased in IBD children. Mucosal S100A12 levels in IBD and coeliac disease children were higher than in non-IBD children, with serum and mucosal S100A12 levels in the same range in IBD children. These studies identified that there was no difference in serum sRAGE levels between these groups. As serum sRAGE is detectable, the presence of sRAGE is not detected in intestinal mucosal biopsies. Thus, there is an imbalance with high S100A12 and low sRAGE mucosal levels in IBD children with a lack of antagonist regulation by sRAGE that could allow increased RAGE activation via ligation by the S100s. This study suggests that serum sRAGE levels were not indicators/markers of inflammation in IBD. However, the results are still interesting and suggest that the lack of antagonist regulation by sRAGE could allow increased RAGE activation via ligation by the S100s inflammation in mucosa seen in IBD patients.

SLE. SLE is an autoimmune inflammatory disease with an accelerated atherosclerosis leading to an increased prevalence of cardiovascular disease [41, 42]. To determine whether AGEs and sRAGEs are implicated in SLE, skin autofluorescence (as an estimate of tissue AGEs accumulation), blood levels of AGEs and sRAGE were studied in 10 SLE patients during quiescent and active disease [43], and compared with 10 healthy age- and sex-matched controls. It was reported that the deposition of AGEs is higher in SLE patients, whereas blood levels of AGEs are comparable with controls. Blood sRAGE levels are higher in SLE patients compared with controls. Compared with quiescent SLE, blood sRAGE levels are significantly increased during active disease. It is therefore hypothesized that increased levels of sRAGE in SLE patients are protective against AGEs-elicited cellular activation by complexing AGEs and promoting cellular activation by complexing AGEs and promoting cellular activation by complexing AGEs and promoting cellular activation by complexing AGEs and promoting.

FIG. 1. Mechanism of sRAGE production. RAGE is composed of an intracellular domain, a short transmembrane domain and an extracellular domain consisting of three immunoglobulin-like regions, one ‘V’ type followed by two ‘C’ types. The ‘V’ type is essential for ligand binding. sRAGE corresponds to the extracellular domain of RAGE lacking cytosolic and transmembrane domains. It may be produced by alternative splicing of RAGE mRNA (esRAGE/RAGEv1) or by proteolytical cleavage of RAGE from the cell surface (cRAGE). C: constant; V: variable.
their clearance. This mechanism may be insufficient to prevent increased tissue AGE accumulation.

The results of this work are in contradiction to previous studies demonstrating that low sRAGE levels are associated with active inflammatory diseases such as RA, SS or KD. We suggest that sRAGE, RAGE and its ligands could positively or negatively interact during SLE flares, but further studies are needed to carry out with larger subject numbers on that concern.

**Atherosclerosis**

Atherosclerosis is now commonly described as an inflammatory disease [44]. Premature accelerated atherosclerosis is reported in chronic inflammatory diseases such as SLE or Wegener’s granulomatosis [41, 42, 45]. The first study to report sRAGE levels in human subjects focused on the involvement of sRAGE levels in human non-diabetic atherosclerosis such as CAD or peripheral arterial disease (PAD) [46].

Plasma sRAGE levels in non-diabetic males with angiographically documented CAD were compared with age-matched control males [47] and found to be lower in CAD patients than in controls. In a multiple logistic regression analysis, plasma sRAGE concentration was found to be a risk factor for CAD, independent of hypertension, smoking and high density lipoprotein (HDL) cholesterol levels. In addition, plasma sRAGE levels are significantly lower in non-diabetic patients with PAD than age-matched control patients [46].

A study of atherosclerosis by intima-media thickness (IMT) ratio demonstrated that plasma esRAGE levels are inversely correlated with IMT in non-diabetic subjects [48]. Furthermore, in multiple logistic regression analysis, plasma esRAGE level was demonstrated to be inversely and independently correlated with several components of metabolic syndrome including BMI, insulin resistance index, blood pressure and hypertriglyceridaemia. Additionally, sRAGE level has been inversely correlated with BMI and waist/hip ratio in metabolic syndrome [49].

These results highlight that low levels of sRAG in plasma is not only associated with atherosclerosis, but is also inversely correlated with metabolic syndrome, suggesting that low plasma sRAGE level should be associated with higher cardiovascular risk.

Although a series of studies has been published assessing the role of sRAGE in different animal models of atherosclerosis [50], the biological importance of sRAGE within the ligand–RAGE axis is not clearly understood in humans.

Since RAGE is expressed to a great extent by monocyte/macrophages and by endothelial cells, we can put forward how RAGE–ligand axis is involved in premature atherosclerosis or severe atherosclerotic disease seen in classic inflammatory states like SLE or RA.

**From bench to bedside**

**Feedback**

The balance between the levels of RAGE ligands, RAGE and sRAGE may represent a dynamic system. It has been demonstrated that numerous pathophysiological situations enhance the expression of RAGE and its ligands, including diabetes mellitus, renal failure, aging and smoking. Inflammation increases the production and accumulation of AGEs, HMGB1, S100 proteins and amyloid fibrils deposits [1, 6–8, 51] and subsequently leads to the increased activation of RAGE and further enhances the inflammatory state [52]. The relationship between the up-regulation of RAGE/RAGE ligands and the level of ‘protective’ sRAGE levels is of obvious clinical interest. On the other hand, in vitro studies recently revealed that treatment of cells with HMGB1 increased the formation of soluble cRAGE released in the supernatant [30]. Similarly, a positive correlation between serum AGEs and sRAGE levels in non-diabetic subjects has been highlighted, suggesting that interaction of RAGE with its ligands enhances sRAGE synthesis [53]. However, sRAGE has been shown to have a negative feedback on RAGE interaction with its ligands (Fig. 2). Therefore it seems that sRAGE, RAGE and its ligands are three elements of a balance with positive and negative feedbacks which could be modified by pathophysiological situations. The precise mechanisms responsible for the fine balance between membrane-bound RAGE and its secreted/cleaved soluble variant are currently unknown, and the elucidation of the mechanism(s) responsible for their regulation is an important biological question.

**sRAGE as a treatment**

Prior to the recent studies of sRAGE levels as a potential biomarker in humans, the administration of recombinant sRAGE was used as therapeutic treatment in inflammatory murine models. An experimentally induced delayed-type hypersensitivity (DTH), a model of acute inflammation, was performed with mice sensitized with methylated BSA (mBSA) displaying a strong inflammatory response when injected in footpad [54]. Administration of murine sRAGE by intraperitoneal injection prior to and after local injection of mBSA results in dose-dependent suppression of inflammation, either with clinical and histological scores of inflammation.

In a murine model of IBD, most of the mice treated with sRAGE for 6 weeks do not display inflammation when rectosigmoid colon is explored [54]. Expression of NF-κB in nuclear extracts prepared from colonic tissue of sRAGE-treated mice is significantly reduced associated to an ~8.7-fold decrease in plasma levels of TNF-α supporting the anti-inflammatory properties of sRAGE. Compared with control vehicle-treated mice, histological scoring of synovial hyperplasia/hyperthropy and cartilage and bone destruction are significantly lower in sRAGE-treated collagen-induced arthritis mice [55].

More recently, it has been confirmed that intraperitoneal injection of sRAGE protect mice from HMGB1-induced arthritis [56]. In order to understand the mechanism of sRAGE action, both sRAGE and HMGB1 were injected IA but no anti-inflammatory effects have been observed, suggesting that direct binding of HMGB1 by sRAGE does not block the pro-inflammatory activities of HMGB1 in vivo. Paradoxically, IA injection of sRAGE alone displays synovitis. sRAGE may have pro-inflammatory effects by turning inflammatory response from the peripheral organs to the site of injection (i.e. peritoneum); accordingly, peritoneal lavage fluid cells in mice treated with intraperitoneal injection of sRAGE were assessed and increased leucocytes extravasation was observed.

Experimental autoimmune encephalitis (EAE) corresponds to a murine model of multiple sclerosis, a devastating neuroinflammatory and autoimmune disorder of the CNS [57]. Daily intraperitoneal injection of sRAGE has a strong protective effect against induced EAE. Treated mice show lower clinical scores of severity and there is no prominent inflammatory infiltration in histological analysis of spinal cord tissue [58].

In addition, administration of sRAGE attenuates early acceleration of atherosclerosis and stabilized established atherosclerotic plaques in diabetic mice deficient in apolipoprotein E [50, 59]. All these results suggest that the use of sRAGE as a therapeutic agent may prevent some inflammatory/autoimmune diseases in animal models, and therefore highlights the administration of sRAGE or the V-domain ligand binding as potential therapeutic targets for inflammatory disease.

**The modulation of sRAGE levels as a human therapeutic target**

No clinical trial has explored the consequences of sRAGE injection in human, but modulation of sRAGE levels by different
treatments has been reported in few studies. Plasma AGEs and sRAGE levels were studied in type 1 diabetes patients at baseline and after 24 months; patients have been randomized to receive placebo, perindopril [angiotensin-converting enzyme inhibitors (ACEi)] or nifedipine (a calcium antagonist). Compared with untreated and nifedipine-treated groups, patients treated with perindopril have significantly decreased AGEs and increased sRAGE blood levels [60]. The authors speculate that the increase in sRAGE could act as a mechanism to divert AGEs from binding the fRAGE, acting as a ‘decoy’ because this truncated form of the receptor has no downstream signalling capacity. Through this newly described protective mechanism of agents that interrupt the renin–angiotensin system, it could be at least in part explained how treatment with ACEi attenuates retinal overexpression of VEGF (induced by AGEs) in patients with proliferative diabetic retinopathy [61]. In addition, such sRAGE modulation could explain that angiotensin II receptor blocker inhibits abnormal accumulation of AGEs and retinal damage in a rat model of type 2 diabetes [62].

sRAGE modulation by diabetes therapeutic drugs and statins have also been evaluated [13, 63]. Plasma sRAGE levels were measured in hypercholesterolemic patients without treatment, hypercholesterolemic patients with CVD treated with statins for ≥3 months and healthy control subjects. Patients with untreated hypercholesterolaemia have lower sRAGE levels than patients of the two other groups. In order to ascertain whether statins could influence sRAGE, sRAGE levels were measured in the group of patients with hypercholesterolaemia after 8 weeks of treatment with atorvastatine or pravastatine. Atorvastatine-treated patients have signifi- cantly increased sRAGE levels [13]. Serum sRAGE and esRAGE were determined in type 2 diabetes patients before and after treatment [add-on therapy with either rosiglitazone (thiazolidinedione class) or sulphonylurea (oral hypoglycemic agent) for 6 months]. Rosiglitazone-treated patients have significantly increased sRAGE and esRAGE levels. Furthermore, rosiglitazone-treated patients with 8 mg/day have higher sRAGE and esRAGE levels than those with 4 mg daily [63].

These results suggest that various drugs, especially implicated in cardiovascular field, could influence sRAGE levels, but long-term prospective studies are needed to evaluate if modulating sRAGE levels can prevent or delay complication of inflammation.

Perspectives

sRAGE is produced either by alternative splicing (esRAGE) or by proteolytic cleavage from membrane-bound fRAGE by metalloproteases (cRAGE) [30]. RAGE and sRAGE have the same ligand-binding specificity that is why sRAGE is reported to act as a decoy, blocking the interaction of membrane-bound fRAGE and its pro-inflammatory ligands.

Serum sRAGE levels are decreased in patients with chronic inflammatory diseases including atherosclerosis compared with healthy subjects. In a recent SLE study, higher sRAGE levels were found in 10 SLE patients compared with healthy controls [43]. It must be noted that some of the SLE patients (3/10) used ACEi that increases sRAGE levels.
Many questions about sRAGE remain unclear: is there an individual variability of sRAGE level during nychtemeron or during longer periods? Are sRAGE levels influenced by nutrition, infection, stress or fatigue? Finally, if RAGE-ligands, RAGE and sRAGE represent a dynamic system with positive and negative feedbacks, it may be necessary to consider ratios of sRAGE to RAGE or to RAGE ligands rather than sRAGE level only.

It has been suggested that there may be a pre-existing low sRAGE level in some individuals. Indeed, sRAGE levels were measured in healthy centenarians, non-diabetic patients <40 years of age who experienced an acute myocardial infarction (AMI) and healthy subjects of <40 years of age [64]. Healthy centenarians had a significantly higher sRAGE levels than healthy subjects <40 years and AMI patients had lower sRAGE levels than healthy subjects of age <40 years. As sRAGE level rather seems to decrease with age [48], these results suggest that healthy centenarians have an ‘innate’ high sRAGE level. That should be a contributing factor to longevity and low plasma sRAGE level should be a risk factor for inflammatory diseases and AMI. It is important to note that current evidence of RAGE-ligand axis seems more substantial in atherosclerosis or vascular complications than in classic inflammatory diseases like RA or SLE. It would be necessary to carry out long-term prospective and large studies to confirm whether low sRAGE level is a contributing factor to the development of inflammatory diseases.

If it is confirmed that low sRAGE level is a risk factor for inflammation, it would be interesting to define a high-risk population to study whether a long-term increase of sRAGE level with treatments may have beneficial consequences. More specific treatments may be developed to modulate RAGE-ligand/sRAGE system, such as anti-RAGE antibodies that could block the interaction between RAGE and its ligands and then, inflammatory development.

Rheumatology key messages

- sRAGE is able to act as a decoy to avoid interaction of RAGE with its pro-inflammatory ligands.
- The specific role of sRAGE levels in true inflammatory diseases is yet to be confirmed.
- Some diabetes and atherosclerosis therapeutic drugs are able to modulate the RAGE ligand/sRAGE system.

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