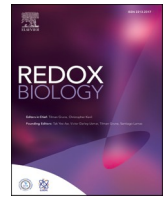




Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

The use of the soluble receptor for advanced glycation-end products (sRAGE) as a potential biomarker of disease risk and adverse outcomes

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ARTICLE INFO

Keywords:

Biomarker
Cardiovascular disease
Disease risk
Inflammation
Frailty
Mortality
Prognostic
Soluble receptor for advanced glycation end products

ABSTRACT

The soluble receptor for advanced glycation end-products (sRAGE) has been classically considered a sink for pro-inflammatory RAGE ligands and as such has been associated with protection from inflammatory stress and disease. An alternative, though not mutually exclusive view is that high levels of sRAGE in circulation reflect the overstimulation of cell surface RAGE which if persistent, lead to the amplification of pro-inflammatory processes and the exacerbation of pathological states. With these two scenarios in mind this review focuses on the potential role of sRAGE as a prospective biomarker of disease risk and adverse outcomes.

1. Introduction

The receptor for advanced glycation end-products (RAGE) and its soluble forms - collectively known as sRAGE - are increasingly implicated in host defence from infections, inflammation, cardiometabolic disorders and age-related diseases [1–3]. Over the last twenty years hundreds of papers have described correlations between sRAGE levels and pathophysiological states or disease prognosis, but findings have been inconsistent [4,5].

In this paper I review briefly the biology underlying the generation of sRAGE isoforms and the factors that modulate their levels in the circulation. Then, I discuss the potential functions of sRAGE molecules as well as their relationship with oxidative stress, to finally focus on the evidence supporting their potential use as a biomarker of disease risk and adverse outcomes.

2. RAGE signalling

RAGE is a multiligand pattern recognition cell surface receptor belonging to the immunoglobulin superfamily [1]. Advanced glycation end-products (AGEs), which arise from the non-enzymatic glycation and oxidation of proteins, lipids and nucleic acids, were the first RAGE ligands to be described [6], giving this receptor its name. Over the years following its discovery, it became increasingly recognized that RAGE

binds also a variety of other ligands, including molecules derived from stressed or damaged cells — e.g., amyloid β peptide, high-mobility group box 1 (HMGB1) and S100 proteins — collectively known as damage associated molecular patterns (DAMPs), cell adhesion molecules — e.g. the β 2 integrin MAC-1 —, and molecules originating from bacteria, viruses and parasites (reviewed in Refs. [1,7]). As such RAGE plays an important role in the innate immune response and as a mediator of pro-inflammatory processes. Upon ligand binding RAGE-mediated intracellular signalling (reviewed in Ref. [2]) can lead to an increase in the production of reactive oxygen species (ROS) [8–10] and to the sustained activation of the transcription factor NF κ B [11]. The latter stimulates the expression of pro-inflammatory modulators (e.g., IL1- β , VCAM-1 and TNF- α) [12,13], and of RAGE itself [12], thus providing a positive feedback mechanism to amplify the inflammatory response (see Fig. 1).

RAGE is constitutively expressed at high levels in the lungs and skin of healthy adults [14,15], whereas expression in other tissues is either virtually absent — e.g. in skeletal muscle [16] — or low — e.g. in cells of the cardiovascular, immune and central nervous systems (reviewed in Refs. [2,16]). However, in cardiometabolic, inflammatory or age-related diseases RAGE expression increases in different cell types [2,16], this upregulation being a direct consequence of an increase in ligand levels associated with these conditions [1]. Similarly, expression also increases in acute muscle injury [16] and during the host response to infection [3].

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<https://doi.org/10.1016/j.redox.2021.101958>

Received 15 February 2021; Received in revised form 21 March 2021; Accepted 24 March 2021

Available online 29 March 2021

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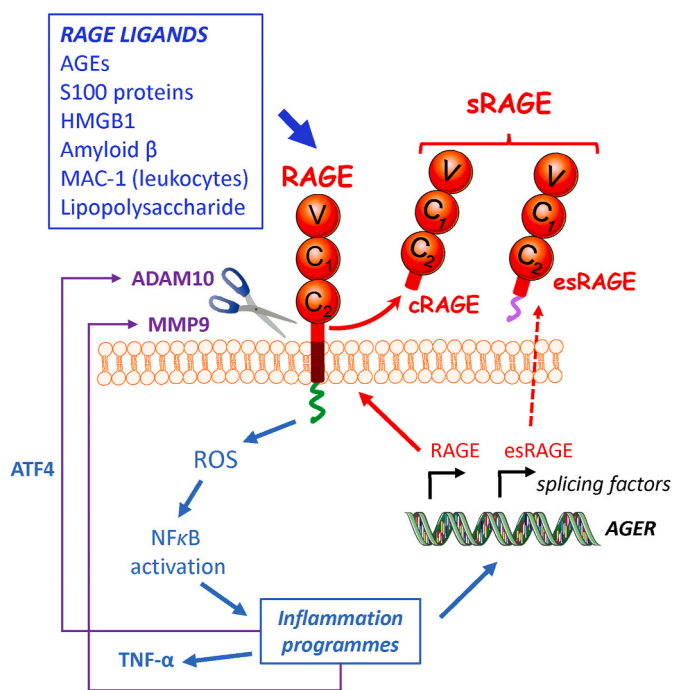


Fig. 1. Mechanisms of sRAGE generation. Plasma membrane-bound RAGE consist of three main regions: an intracellular tail (green), a transmembrane helix (brown) and an extracellular domain (red) formed by the immunoglobulin-like subdomains V, C₁ and C₂. Ligand binding to the extracellular domain initiates intracellular signalling, leading to the generation of ROS and to the activation of the transcription factor NFκB. The latter induces gene expression of pro-inflammatory cytokines such as TNF-α and of RAGE itself. RAGE downstream signalling events in turn promote the upregulation of MMP9 and ADAM10, which cleave membrane-bound RAGE, causing the release of its extracellular portion (cRAGE). ATF4 is linked to ADAM10 upregulation. cRAGE constitutes the majority of sRAGE. Alternative splicing of the RAGE gene (*AGER*) results in the generation of esRAGE, which also contributes to the sRAGE pool. A unique amino acid sequence in esRAGE (purple) distinguishes it from cRAGE.

3. The sources of soluble RAGEs and their regulation

In addition to cell membrane-anchored RAGE, there are two major soluble forms of this receptor detected in blood and other body fluids, both of which lack its transmembrane and cytoplasmic domains [4]. These two RAGE isoforms are jointly known as soluble RAGE (sRAGE). One form of sRAGE, sometimes called cRAGE, is generated at the cell surface by the proteolytic cleavage of RAGE at the boundary between its extracellular and transmembrane portions [17,18]. This RAGE ectodomain shedding is stimulated by inflammatory signals, including HMGB1 [18], lipopolysaccharide [19] and TNF-α [19]. In addition, activation of G protein-coupled receptors [20], intracellular calcium mobilization [21] and elevation of cAMP levels [22] have also been reported to promote this process. Two metalloproteases have been implicated in the generation of the cleaved form of sRAGE, MMP9 [17,19] and ADAM10 [17–19]. MMP9 expression is known to be up-regulated by ROS and the activation of the RAS-ERK-NFκB pathway (reviewed in Ref. [23]). Furthermore, TNF-α and RAGE overexpression can also increase MMP9 expression [19]. Similarly, TNF-α and RAGE overexpression can stimulate ADAM10 activation via an ATF4-dependent mechanism [19]. Taken together, these events are consistent with RAGE downstream signals promoting sRAGE shedding through an amplification mechanism involving auto-induction and/or induction of other inflammatory cytokines (Fig. 1).

The second form of sRAGE, called esRAGE (for endogenous secretory RAGE) or RAGEv1, results from alternative splicing of RAGE pre-mRNA

[24,25] and accounts for less than 25% of total circulating sRAGE [26] (Fig. 1). The precise mechanism which regulates the formation of esRAGE is not entirely understood. The alternative splicing of RAGE pre-mRNA generates more than 20 splice variants, of which full length membrane-bound RAGE and esRAGE are the two most abundant [24]. The RAGE gene (*AGER*) has 11 exons. esRAGE is produced by inclusion of part of intron 9 with exon 9 and exclusion of exon 10. This results in a variant which has a reading frame shift at amino acid residue 332 and lacks the intracellular and transmembrane domains [24]. In neuroblastoma, human umbilical vein endothelial cells and HepG2 cells two splicing factors, namely heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) and Transformer 2β-1 (Tra2β-1), have been shown to regulate the ratio between full length RAGE and esRAGE by exerting antagonistic effects on the selection of alternative exons [27]. Furthermore, in neuroblastoma cells glucose deprivation induced an up-regulation of hnRNP A1 and down-regulation of Tra2β-1, resulting in a decrease in esRAGE expression and an increase in the RAGE/esRAGE ratio [27]. These findings suggest that impaired glucose metabolism may be one factor affecting the regulation of esRAGE levels.

sRAGE isoforms are highly stable [28] and can be measured from stored frozen serum or plasma samples using antibody-based ELISA assays. There are two types of assays. One assay detects total sRAGE, whereas the other measures specifically esRAGE. The latter uses an antibody directed against the unique COOH-terminal sequence of RAGE-v1 and does not cross-react with the cleaved form of sRAGE. esRAGE and sRAGE levels are strongly correlated [26,29–31] and values in plasma and serum are quite comparable [28].

Average sRAGE concentrations in different studies generally fall within a similar range, although there is substantial variability between individuals [26,30–41]. For example, in sera of 1228 European community dwelling older adults enrolled in the FRAILOMIC study, the median value of sRAGE was 1228 pg/ml with an interquartile range of 943–1638 pg/ml [41]. Importantly, sRAGE levels are invariably higher in people with diminished kidney function [26,30,42] and in some studies they also tend to be higher in diabetics [33,43].

Part of the variability in blood levels of sRAGE is probably determined by genetic differences between individuals. *AGER* is a highly polymorphic gene [44], with some variants affecting levels of both the cleaved form of sRAGE and esRAGE [30]. Furthermore, sRAGE levels may be influenced by polymorphisms in other genes, for example in ADAM10 [45]. Finally, levels of both sRAGE isoforms are strongly affected by ethnicity, being lower in people from Afro-Caribbean and Hispanic origin than in Caucasians [26,30,35].

Other studies in patients with cardiometabolic conditions have shown that the concentration of sRAGE isoforms in blood can be influenced by therapeutic agents, including angiotensin receptor blockers (ARBs), angiotensin converting enzyme inhibitors, calcium channel antagonists, statins and thiazolidinediones (reviewed in Ref. [4]). ARBs were found to decrease sRAGE levels in angiotensin II-treated endothelial cells and in patients with essential hypertension [46]. Similarly, the calcium channel blocker azelnidipine was shown to reduce sRAGE in non-diabetic chronic nephropathy [47]. In contrast, statins and thiazolidinediones cause an increase in blood levels of both total sRAGE and esRAGE in type 2 diabetes [48–50]. Likewise, physical exercise has been reported to increase esRAGE levels in people at low/intermediate risk of cardiovascular disease (CVD) [51]. The detailed mechanisms underlying the different effects of these interventions are not known, though in the case of statins, these were reported to stimulate RAGE shedding by an ADAM10-mediated mechanism [52]. In addition, some of the drugs may affect sRAGE levels by inhibiting inflammation pathways [53] or by improving renal function [26,42].

4. The function of sRAGE

The function that sRAGE plays in human biology has been the subject of substantial debate. A widely held view is that sRAGE fulfills a

protective anti-inflammatory role by acting as a decoy receptor, binding RAGE ligands and thus blocking their interaction with membrane-bound RAGE. In support of this possibility experiments in animals models of diabetes and/or CVD have shown that administration of recombinant sRAGE improves vascular and renal function, reduces myocardial ischaemic injury, as well as atherosclerosis, vascular inflammation and other diabetic complications (Reviewed in Ref. [1]). In addition, sRAGE administration has been shown to decrease inflammation in an animal model of multiple sclerosis [54]. In considering the function of sRAGE as a decoy receptor, it is relevant to note that in RAGE-deficient mice (*Ager*^{-/-}) sRAGE can still block certain inflammation responses, probably by preventing putative RAGE ligands from interacting with other receptors [55].

Aside from behaving as a decoy receptor sRAGE may also act as a ligand of the leukocyte integrin MAC-1 and transduce pro-inflammatory signals, thereby inducing leukocyte recruitment to sites of injury or inflammation [56,57]. Consistent with this role, bacterial burden and neutrophil infiltration was shown to worsen following sRAGE administration in a mouse model of bacterial lung infection, suggesting that in acute settings sRAGE may actually sustain inflammation [58]. In contrast, sRAGE has been shown to prevent leukocyte recruitment in a diabetic mouse model of acute peritonitis [59].

sRAGE forms have been measured in humans in search for associations with disease states or their risk factors (reviewed in Refs. [60,61]). Many of these studies reported sRAGE levels to be lower in people with cardiometabolic and other chronic conditions than in healthy subjects, providing further support to the notion that sRAGE fulfills a protective role [60]. Nevertheless, positive associations between sRAGE levels and prevalent ill health have also been described, most notably in the contexts of diabetes and renal disease [60,61], and more recently also in frailty [62]. These contrasting lines of evidence suggest that the status of sRAGE in human pathophysiology deserves further examination. In this regard, an alternative view argues that the amount of sRAGE generated in vivo may not be sufficient to compete effectively with membrane-bound RAGE for ligand binding, particularly in situations where RAGE itself is also upregulated [2]. Furthermore, an increase in total circulating levels of sRAGE may reflect increased RAGE activation and autoinduction [18,63], and in this way attest to a condition of low-grade chronic inflammation, rather than to a healthy state.

5. The relationship between sRAGE and oxidative stress

Several lines of evidence indicate that RAGE activation by AGEs and other ligands cause oxidative stress [8,9,64,65]. Consistent with this notion and in keeping with the decoy receptor concept described above, sRAGE has been shown to reduce markers of oxidative stress when administered to animal models of vascular dysfunction [66,67]. Hence, sRAGE is sometimes attributed an 'anti-oxidant role'. This view has been also supported by reports from small clinical studies of atherosclerotic vascular disease or cardiometabolic disorders describing inverse correlations between sRAGE levels and makers of oxidative stress [68–73], and by a study describing a positive correlation with plasma anti-oxidant defenses in Alzheimer's disease patients [74]. However, it should be noted that these types of associations are not universal. Thus for example in acute liver failure, both a protein oxidation marker and sRAGE levels were shown to be elevated [75], whereas in patients with sickle cell disease an increase in sRAGE was positively correlated with an increase in the levels of ferritin, which in this condition is indicative of iron overload [76]. In addition, in a recent study of patients with type 2 diabetes, compared to non-diabetic controls both sRAGE levels and malondialdehyde were shown to be elevated, whereas antioxidant thiol levels were shown to be reduced [77]; furthermore, this study reported that these differences were even more pronounced in individuals who had developed diabetic retinopathy [77]. Mechanistically, a ROS-induced up-regulation of MMP9 [23], which in turn would result in an increase in RAGE ectodomain shedding, provides a reasonable

explanation for these findings.

Human interventional studies that examined sRAGE levels and markers of oxidative status, provide further insights into the relationship between these parameters in vivo. In master athletes a Mediterranean diet was shown to reduce both sRAGE and malondialdehyde [78]. Furthermore, in type 2 diabetes it was recently demonstrated that treatment with metformin for three months resulted in a reduction in sRAGE levels and oxidative stress markers, and also in an increase in antioxidant defenses [79]. Thus, taken together the above examples caution against considering a comparatively high level of sRAGE, a sign of low oxidative burden and/or good health.

6. sRAGE as a marker of incident disease and adverse outcomes

A variety of prospective studies have examined the relationship between sRAGE and the incidence of chronic diseases and/or the occurrence of adverse clinical outcomes. Table 1 summarizes examples of such studies in population samples of different health characteristics. For adults who in the main had no documented pre-existing chronic conditions at baseline, findings were mixed. In non-prescreened adults from the general population, positive [80] or no significant associations [40,81] were generally reported, whereas for individuals with no prior history of CVD, the associations with incident disease or adverse events were found to be negative [38,82,83]. In contrast, studies carried out in diabetics (type 1 or type 2) consistently reported that high levels of sRAGE were predictive of cardiovascular events and/or mortality [26, 36,84–86]. Similarly, other studies have shown that in individuals with pre-existing heart failure [31,34,37,87], coronary artery disease [39, 88], frailty [41,89] or physical disability [32], high sRAGE levels were associated with a higher incidence of adverse cardiovascular events and/or mortality. On the other hand, absence of associations with adverse events, have also been described, including in patients with advanced chronic kidney disease [90,91], in another cohort of individuals with pre-existing heart failure [92], and in a large cohort of people with chronic obstructive pulmonary disease and high cardiovascular risk [93]. Finally, a negative association between total sRAGE or esRAGE and mortality has been reported in cancer [29]. Taken together, these observational studies indicate that the relationship between total sRAGE (or esRAGE) and disease risk or the occurrence of adverse events, including mortality, is complex. Explanations for conflicting findings between different studies could be related to the demographic, genetic and health characteristics of the populations under investigation. In particular, the presence of frailty, diabetes and impaired kidney function may have a strong influence on these relationships [41,61]. In addition, some studies could have been statistically underpowered to detect significant prospective associations or might have not accounted for potentially relevant confounders (e.g., renal function).

In addition to its evaluation as a prognostic biomarker in chronic conditions, sRAGE has also been studied in acute settings. Consistent with the notion that RAGE is highly overexpressed in lung epithelium and that RAGE signalling may play a central role in the pathological manifestations of lung injury, elevated sRAGE levels, were found to predict 90-day mortality in patients suffering from acute respiratory distress syndrome [94]. Similarly, elevated sRAGE levels are associated with looming mortality in sepsis [95] and acute liver failure [75], reflecting the prominent role that DAMPs play in RAGE activation in these conditions [3].

7. Concluding remarks

Although sRAGE has been studied as a marker of disease risk and adverse outcomes for many years, its potential prognostic value continues to be questioned due to the inconsistency in the directionality of the associations observed in different clinical settings. As a telltale footprint left from the sustained RAGE stimulation and the concomitant

Table 1

Human observational studies exploring the association between sRAGE levels and incidence of chronic diseases or adverse outcomes.

Population/pre-existing health status	Age	Sample size	Follow-up (years)	Clinical outcome associated with sRAGE	Reference
USA communities (ARIC Study), no history of CVD	47–68	1201	18	Coronary adverse events, diabetes, all-cause mortality ↓	[38]
USA communities (ARIC Study), no history of CVD	63	1086	20	Heart failure ↓	[82]
Malmo Diet and Cancer Cohort, no history of CVD	58	4612	21	CIMT progression, coronary adverse events, all-cause mortality ↓	[83]
USA community (Framingham Heart Study)	>50	3523	14.3	All-cause mortality ↑	[80]
German community (CARLA study)	64.5	1756	12	All-cause mortality, CVD mortality or cancer mortality ↔	[40]
Older adults from Rotterdam Study	72.9	945	18.7	Dementia ↔	[81]
Dutch T1D patients, no history of CVD	~43	339	12.3	Cardiovascular events (incl. stroke and PVD), all-cause mortality ↑	[84]
Finnish T1D patients from FinnDiane Study	38	3100	9.1	Cardiovascular and all-cause mortality ↑	[36]
T2D patients from CARDS Trial, UK & Ireland	~62	718	3.9	Coronary adverse events ↑ *	[26]
Japanese T2D patients, no history of CVD	~61	276	5.6	Adverse cardiovascular events ↑	[85]
T2D patients with CVD from ADVANCE Trial, Worldwide	66.9	3763	5	All-cause-mortality, new or worsening kidney disease↑	[86]
Japanese heart failure patients without renal dysfunction	68	162	2.4	Cardiac death or rehospitalization ↑	[34]
Spanish heart failure patients	72	106	1.3	Cardiac death or rehospitalization ↑	[37]
Dutch heart failure patients (COACH Study)	71	580	1.5	All-cause mortality and hospitalization ↔	[92]
Spanish heart failure patients without severe renal dysfunction	69.5	102	5	Adverse cardiac events ↑ *	[31]
Stable CAD patients on statin from TNT Study, Worldwide	61.5	1506	4.9	Cardiovascular adverse events (including stroke) ↑	[39]
German CAD patients	68.9	886	3	Cardiovascular adverse events (including stroke) ↑	[88]
Spanish patients with ACS without severe renal dysfunction	69.3	102	5	Adverse cardiac events ↔	[31]
USA community physically disable women	>65	559	4.5	CVD mortality ↑	[32]
European frail older adults	75	691	6	All-cause mortality ↑	[89]
European frail older adults with CVD	75	1016	8	All-cause mortality ↑	[41]
COPD patients with cardiovascular risk (SUMMIT trial), Worldwide	66	1649	2.2	All-cause mortality, cardiovascular death, COPD exacerbations ↔	[93]
Swedish patients with CKD	67	184	3.4	All-cause mortality, CVD mortality ↔	[90]
Korean patients with CKD	57.1	199	3.7	All-cause mortality ↔	[91]
German cancer patients (melanoma)	59.6	229	2.9	Mortality ↓ *	[29]

Abbreviations: ACS, acute coronary syndromes; CAD, coronary artery disease; CIMT, carotid intima-media thickness; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; PVD, peripheral vascular disease; T1D, type 1 diabetes; T2D, type 2 diabetes.

Age is indicated as median, mean or range.

*also reported association with esRAGE.

↔, no significant association; ↑, positive significant association; ↓, negative significant association.

relentless cellular stress caused by an enduring inflammatory milieu, sRAGE may be a useful prognostic biomarker of irreversible loss of homeostasis and eventual mortality. As such sRAGE may not be useful for prognosis in the general “healthy” population. Instead, its clinical application may be more suited to multimorbid individuals or to those who have been afflicted by a chronic illness for a considerable length of time. Thus, for example, in the cardiovascular setting, elevated sRAGE levels have been recently shown to be highly predictive of mortality in patients who were also frail [41]. Similarly, in acute conditions a dramatic and sustained increase in sRAGE levels may be also a sign of impending irreversible organ damage and mortality, for example in acute lung injury/acute respiratory distress syndrome [96]. Theoretically, this could be relevant in respiratory viral illnesses such as Covid-19, where increased levels of DAMPs are associated with disease severity (reviewed in Ref. [97]) and serum sRAGE appears to be raised [98]. In such contexts, determination of sRAGE levels could be useful for risk stratification and potentially, to inform clinical management, e.g., to select a course of treatment. In this respect, a clinically relevant threshold of sRAGE has so far not been established. Based on our own studies in frail older adults, we suggested that values of sRAGE in the range of 1600–1800 pg/ml might be relevant to set up a threshold which could be used for risk stratification [41,89]. Nevertheless, further studies will be required to narrow down and validate this value, for this and other clinical conditions. In this respect, future studies should also aim to establish if following changes in sRAGE levels over time, could be used to ascertain if an individual is responding to a selected course of treatment.

Funding

Part of the work described in this manuscript was supported by the European Union Seventh Framework Programme under grant agreement number 305483.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

ADAM10	disintegrin and metalloproteinase domain-containing protein 10
AGER	advanced glycation end-products receptor gene
AGEs	advanced glycation end-products
ATF4	activating transcription factor 4
HMGB1	high mobility group box 1
MAC-1	macrophage 1 antigen
MMP9	matrix metalloprotease 9
NFκB	nuclear factor kappa B
ROS	reactive oxygen species

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