Reasons to Investigate the Soluble Receptor for Advanced Glycation End-Product (sRAGE) Pathway in Aortic Disease

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Abstract

Aortic disease has a high rate of morbidity and mortality, and there are no documented screening methods to date. Yet biochemical research does show a significant link between soluble receptor for advanced glycation end-products (sRAGE) protein and cardiovascular disease. Therefore, it can be hypothesized that sRAGE plasma levels may help differentiate patients with aortic disease from the general population, which this paper will review and present.

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Introduction

According to the latest data from the Centers for Disease Control and Prevention, approximately 13,000 people die annually in the United States of aortic aneurysms in various anatomic localizations, with almost 80% of these deaths among people 65 years and older. This makes aortic aneurysms the 19th leading cause of death in all individuals and the 15th most common in individuals older than age 65 years [1]. Referred to as a silent disease by physicians, aneurysms are most commonly asymptomatic [2]. Often, the first symptom is either death or major complications that threaten to produce death, such as aortic rupture or dissection [3]. Therefore, identification of biomarkers that would enable early detection of individuals at risk of aneurysm development is critically important.

Recently, several studies suggested a potential role for soluble receptor for advanced glycation end-products (sRAGE) as a biomarker for cardiovascular disease [3–10]. Receptor for advanced glycated end-products (RAGE) is a multiligand cell surface receptor notably present on cardiac myocytes and blood vessels [11]. Several ligands have been identified that activate this receptor, including advanced glycated end-products (AGEs), amphoterin, amyloid B peptide, S100 proteins, and other inflammatory mediators that have all been reported to increase under pathological states [10,12–15]. Recently, in human studies, the circulating soluble isoform of RAGE, sRAGE, has been shown to be present in low concentration in the serum of patients with vascular diseases, namely atherosclerosis and coronary artery disease (CAD) [10,14–16]. Other studies have suggested a potential role for prospective clinical application of sRAGE for early detection of such cardiac diseases [11,17–19].

However, no studies have evaluated the levels of sRAGE in patients with aortic disease, specifically an-

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Table 1. Summary of sRAGE in cardiovascular disease

Reference	Disease	Principal finding
Bucciarelli et al., 2002 [14] McNair et al., 2009 [15] Norata et al., 2009 [32] Qi et al., 2012 [33]	Atherosclerosis	sRAGE administration in Apo-E-null mice suppressed early acceleration of atherosclerosis Plasma esRAGE levels were inversely correlated with IMT in nondiabetic patients with atherosclerosis
Falcone et al., 2005 [16]	Coronary artery disease	Inverse association between plasma sRAGE levels and CAD
Wittkowski et al., 2007 [34] Qi et al., 2012 [33]	Kawasaki disease	Lower sRAGE levels in KD children versus control under acute inflammatory state
Geroldi et al., 2005 [4]	Hypertension	Plasma sRAGE levels are decreased in patients with primary HTN and are inversely related to pulse pressure
Basta et al., 2010 [35]	Aortic valve stenosis	Patients with severe AVS have lower levels of sRAGE than control group Inverse relationship between sRAGE levels and calcium score + deposits
Park et al., 2009 [36] Montaner et al., 2008 [9] Yokota et al., 2009 [37]	Stroke	sRAGEs were significantly higher in control patients than in the acute ischemic stroke patients
McNair et al., 2009 [15]	Myocardial infarction	Serum levels of sRAGE were low in non-ST elevation myocardial infarction patients Negatively correlated with extent of lesion, inflammatory mediators
McNair et al., 2010 [38]	Restenoses	Low serum sRAGE levels and high AGE/sRAGE ratio have predictive value for post-PCI restenosis
	Aortic aneurysm	

s-RAGE, indicates Soluble receptor for advanced glycation end-product; Apo-E, apolipoprotein E; esRAGE, endogenous secretory RAGE; CAD, coronary artery disease; IMT, intima-media thickness; KD, Kawasaki disease; HTN, hypertension; AVS, aortic valve stenosis; PCI, percutaneous coronary intervention.

eurysm and dissection. The objective of this review is to analyze published reports regarding plasma levels of sRAGE in patients with cardiovascular diseases, to evaluate the role of the RAGE-ligand system in the pathophysiology of aortic aneurysms, and to establish the potential role of sRAGE in aortic disease.

The Biology of RAGE-Ligand Axis

Advanced glycation end-products are irreversible aggregates that endogenously result from a multistep reaction beginning with nonenzymatic glycoxidation of proteins or lipid peroxidation [3,20]. This process occurs physiologically at a low rate based on diet and plasma glucose levels in individuals over long periods of time, with a slight increase of levels as age in-

creases. At the same time, AGEs have been observed in an accelerated form in several pathological conditions, including diabetes, inflammation, renal failure, and Alzheimer's disease, as well as micro- and macrovascular disease [11,12]. The major mechanism for toxicity of AGEs arises from structural protein cross-linking in tissue/arterial wall (type 1 collagen and elastin). This leads to alteration in function, generation of oxidative stress via reactive oxygen species (ROS), and interactions with cell-surface receptors including RAGE, the multiligand AGE receptor [13,14].

RAGE was first isolated and characterized in 1992 from the endothelial surface [21]. This multiligand cell-surface receptor has been shown to be expressed on several other cell lines, including smooth muscle cells, mononuclear phagocytes, T-lymphocytes, cardiac myocytes, and
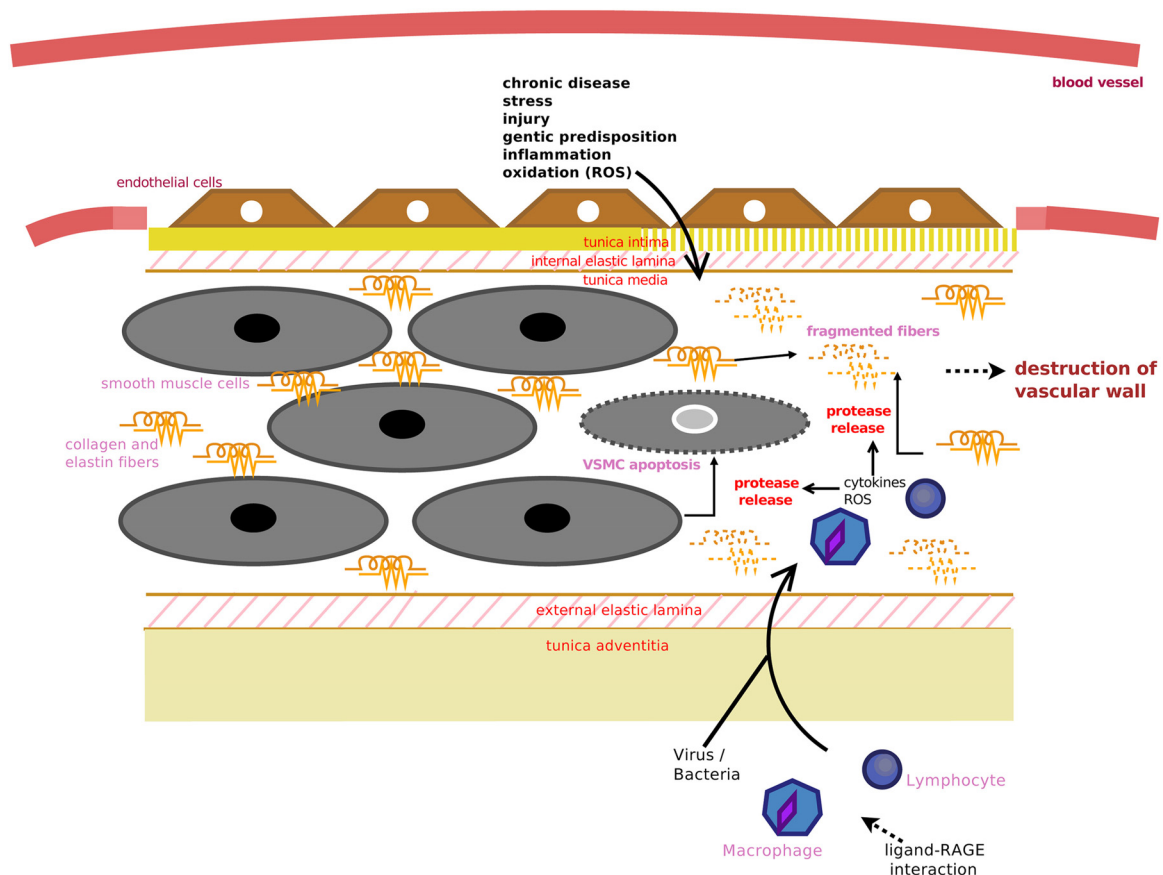
Figure 1. Inflammatory process in aortic aneurysm and possible triggers. Increased presence of macrophage-generated and lymphocyte-generated cytokines (TNF, interleukin-1) recruits T-cells and leukocytes (as well as induces expression and activation of matrix metalloproteinases), leading to extracellular matrix degradation. The trigger to the increase in inflammatory chemokines that activates the proteolytic enzymes has not yet been established, but potential candidates include infections, reactive oxygen species, biochemical/mechanical stress, genetic contributions, and/or other chronic diseases which cause vessel weakening (such as atherosclerosis). Signals from the RAGE-ligand complex cotriggers the inflammatory cascade resulting in the acceleration of the virulent process.

neurons [22,23]. The full-length RAGE (flRAGE) is made up of three separate domains: an extracellular multiple receptor-containing domain, a transmembrane domain, and an intracellular cytoplasmic tail [24]. Increased production and subsequent binding of AGEs and other ligands to RAGE cellular receptors induce signal transduction and alter gene transcription [18,19]. The most predominant circulating AGE, carboxy-methyl-lysine (CML), interacts with RAGE to prime proinflammatory mediators, via activation of nuclear factor κ B (NF-KB) [25]. Similar proinflammatory cytokine induction leading to macrophage and lymphocyte infiltration and oxidative stress in the vasculature is reported with different RAGE ligands, such as S100 proteins and HMGB1 (amphoterin). During times of stress these ligands accumu-

late, as well as trigger an increase in RAGE expression, in the vasculature [14,26,27]. RAGE-ligand interaction is an established participant in the pathological processes of several diseases, in which the RAGE complex seems to propagate and amplify cellular dysfunction [10,11].

The Soluble Receptor for Advanced Glycated End-Products

sRAGE is the secreted soluble isoform of RAGE that lacks the transmembrane and cytosolic domains, and exists in the circulation. Two mechanisms have been identified to produce sRAGE: 1) processing of full-length RAGE by proteosomes, such as matrix metalloproteinase
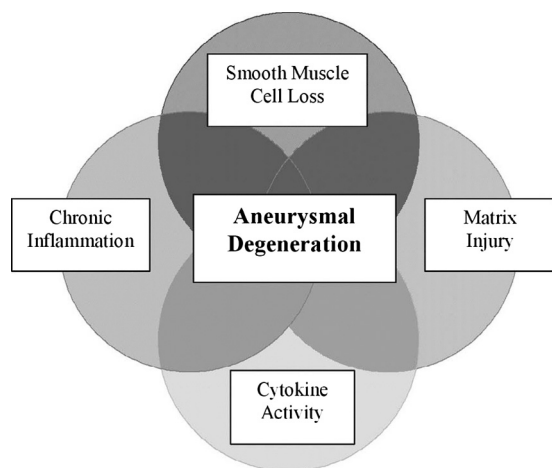
Figure 2. Diagram demonstrating the confluence of inflammatory, proteolytic, and smooth muscle cell abnormalities in producing aortic aneurysms. (Reprinted from Hackmann AE, Thompson RW, LeMaire SA. Long term suppressive therapy: Clinical reality and future prospects. In: Elefteriades JA, Ed. Acute Aortic Disease. Vol 61. New York: Informa Healthcare; 2007;309-330).

(MMP)—cleaved RAGE (cRAGE); and 2) the mechanism via alternative splicing at the RAGE gene expression level, resulting in alternative mRNA—endogenous secretory RAGE (esRAGE) [12,17,28,29]. As the extracellular domain in sRAGE is still maintained, the same ligand-binding specificity for RAGE exists. Thus sRAGE is able to act as a "decoy"/scavenger receptor, by binding proinflammatory ligands and restraining them from binding with membrane-bound RAGE [19]. Similarly, sRAGE can act as a competitive inhibitor of ligand-RAGE interaction and was demonstrated by measuring the parameters of inflammation and the expression of prothrombotic mediators after the infusion of sRAGE in atherosclerotic mice. The RAGE-induced cellular changes diminished significantly; specifically the activity of cyclooxygenase-2 (COX-2), vascular cell adhesion molecule-1 (VCAM-1), matrix metalloproteinase-9 (MMP-9), and monocyte chemotactic protein-1 (MCP-1) within aortic tissue were all ameliorated [13]. Research work on abdominal aortic aneurysms (AAAs) reported similar effects on AGE/RAGE-induced MMP-9 levels when macrophages were treated with sRAGE to inhibit the RAGE signaling [30].

The quantification of human sRAGE in plasma can be done using two enzyme-linked immunosorbent assays (ELISAs). Quantikine sRAGE ELISA measures the total pool of sRAGE resulting both from cleavage (cRAGE) and from the less prevalent method of alternative splicing

(esRAGE) (suggested by comparison studies to make up ~20% of the sRAGE pool) MBL International, Woburn, MA, USA [31]. The second ELISA is specific for measurement of only esRAGE protein. Measurement of plasma sRAGE levels has been documented in multiple studies for research purposes. The first study to report total serum sRAGE level in relation to disease presence demonstrated that patients with the lowest levels of sRAGE presented with a higher risk for CAD—a dose-dependent inverse relationship [14]. Additionally, other vascular disorders have been examined for sRAGE levels and are summarized in Table 1 [32–38]. Such research has led to possible establishment of a biomarker for non-ST segment myocardial infarction (NSTEMI) [15]. Other studies have suggested a low sRAGE level as a positive predictor of restenosis following percutaneous coronary intervention (PCI) [38].

Literature Search

We conducted a literature search for sRAGE in aortic disease, looking to see if we could identify studies that describe similar relationships between sRAGE plasma levels and aortic disease. The search criteria and conduct were as follows.

Electronic search was performed using MEDLINE (1966-June 2013) and EMBASE (1974-June 2013) using MeSH terms: "aneurysm," "dissection," "aortic," "disease," "sRAGE," and "protein." Articles were also searched by using the function "map term to subject heading" in EMBASE for "sRAGE in aortic aneurysms." The search query yielded no related results. The sRAGE level in aortic disease has not, to our knowledge, been investigated or published.

Pathogenesis of Aortic Aneurysm

The pathogenesis of aneurysms has been studied extensively. Historically, aortic aneurysm pathogenesis has been attributed to medial degenerative necrosis—mechanical failure of structural components, including collagen and elastin, in the blood vessel wall [39,40]. The poor intrinsic quality of the vessel matrix results from an imbalance of matrix synthesis and matrix degradation. Degradation is enhanced by the proteolytic enzymes MMP-2 and MMP-9; degradation is inhibited by the tissue inhibitors of metalloproteinases (TIMPs) [39,41–43]. We found an increase in proteolytic activity in ascending aortic aneurysms and dissections (MMP-1, -2, -9), and a

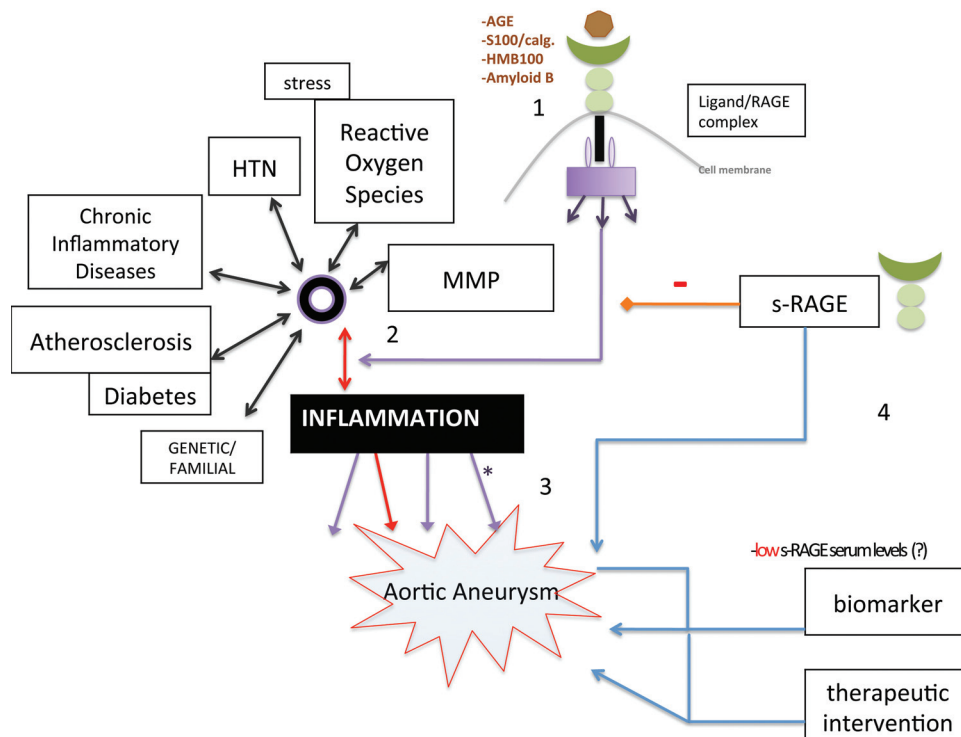Proposed relationship among RAGE, sRAGE, and aortic aneurysm

Figure 3. The potential role of the receptor for advanced glycation end-products (RAGE)-ligand system in the pathophysiology of aortic aneurysms. (1) Ligands that bind to the RAGE receptor, such as AGEs, S100, HMGB1, amyloid B, etc., primarily induce inflammation. An activated transmembrane RAGE receptor induces cytokine activation and genetic transcription within the cell. (2) Other factors, such as hypertension, matrix metalloproteinases, atherosclerosis, etc., play a role in the pathogenesis of aortic aneurysms. (3) All these factors activate the inflammatory cascade and produce an inflammatory response of the aorta. *RAGE-ligand interaction seems to accelerate the pathogenesis through amplifying signal transduction. (4) Soluble receptor for advanced glycation end-products (sRAGE) is produced by cleavage of a full-length RAGE receptor or alternative splicing of the RAGE mRNA. In the circulation, sRAGE may exert inverse influences to RAGE-induced damage.

marked decrease in TIMPs, correlating with the drastic aortic thinning seen clinically [44]. In further homeostatic disruption, vascular smooth muscle cell (VSMC) apoptosis in ascending aortas with bicuspid aortic valve (BAV) disease was seen, namely in the aortic convexity—an area of high stress, and in parallel with high MMP content and composition [45]; this observation has been also seen in endarterectomic samples, which reveal expression of RAGE colocalized with S100A12 ligand [46]. A recent study of S100A12 ligand binding in transgenic mice showed an associated disruption of aortic wall architecture, with notably increased levels of MMP-2 and ROS, with subsequent development of aneurysm [47]. The mechanistic recognition of the role of MMPs in the pathobiology of aortic aneurysm (AA) suggests the potential for innovative drug therapy via MMP inhibitors or sRAGE manipulation.

In addition to the role of MMP in the pathogenesis and VSMC apoptosis, an increasing histological finding in aneurysm disease is inflammatory cell infiltration in the adventitia and media of the aortic wall, implicating inflammatory pathways in AA genesis [41]. Increased presence of macrophage-generated and lymphocyte-generated cytokines recruits T-cells and leukocytes (as well as induces expression and activation of MMPs), leading to extracellular matrix (ECM) degradation [35,42] (Fig. 1). The trigger to the increase in inflammatory chemokines that activates the proteolytic enzymes has not yet been established, but potential candidates include infections, ROS, biochemical/mechanical stress, genetic contributions, other chronic diseases (such as atherosclerosis—mainly in AAA), and the novel role of RAGE binding ligands [30,47–49].

Potential Role of sRAGE Monitoring in Aortic Disease

Experimentally, mice that were treated with sRAGE infusions for atherosclerosis had significantly lower levels of inflammatory signaling molecules of VCAM-1 and tissue factor in aortic tissue; they also had significantly lower antigen/activity of MMP-9, as occurred in AAA experiments [13,30]. These observations signify RAGE-ligand interaction as a coplayer in triggering the pathogenesis of aneurysms. The biological function of sRAGE is to act as a decoy for RAGE ligands, a fundamental inverse relationship between the ligand and sRAGE [11]. The current confluence of inflammatory, proteolytic, and smooth muscle cell abnormalities in producing aortic aneurysms has been schematized in Figure 2.

Exploration of sRAGE levels in the context of aortic aneurysms could lead to a potential biomarker to predict the presence, progression, and prognosis of AA—especially important for this predominantly silent disease. No established circulating biomarker with screening, monitoring, or predicting capabilities or prediction of complications currently exists in widespread clinical use [39].

The standard pathological components of proteolysis, VSMC apoptosis, and inflammation have been widely investigated in the causation of aneurysm disease. In contrast, the RAGE-ligand interaction, a recent and rapidly advancing field of research, has few investigations in aneurysm disease. We believe that the attributes of sRAGE may have a cardinal potential for detection and monitoring of aneurysmal disease. Due to the lack of research in the field of sRAGE and aortic disease, a potential approach to understanding and mapping of these concepts has been illustrated in Figure 3. In addition to the previously mentioned mediators of aortic disease, the RAGE-ligand system interacts in the pathogenesis via interconnecting relationships. These interactive relationships involve several RAGE binding ligands and other mediators, including MMPs and inflammatory cascades. Concurrently the soluble RAGE, sRAGE, is able to inhibit the cellular action of AGEs and other RAGE ligands, and thus can be presumed to exert inverse influences to RAGE-induced damage. Distinguishing and clarifying the function of the RAGE-ligand system in the context of aneurysm pathogenesis and the following sRAGE capabilities holds great potential: for identification of aortic disease, for monitoring of aortic disease, and for prediction of aortic behavior (Fig. 3).

Conclusion

The silent nature of aortic aneurysms makes their timely detection a challenge for physicians, therefore requiring scientists to search for potential biomarkers and risk factors for aneurysm development. Given the apparent interconnection of the complex sRAGE functions with the pathophysiologic pathways of aortic aneurysm development, we believe that there is a reasonable likelihood that the levels of plasma sRAGE may differentiate patients with aortic disease from the general population. We feel this promising concept warrants investigation.

Comment on this Article or Ask a Question

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