International Journal of Cardiology xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

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

Review

Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases

Nitin Mahajan *, Veena Dhawan **

Department of Experimental Medicine & Biotechnology, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh 160012, India

ARTICLE INFO

Article history:
Received 7 March 2013
Accepted 4 May 2013
Available online xxxx

Keywords:
RAGE
Atherosclerosis
sRAGE
Inflammation

ABSTRACT

Historically, the receptor for advanced glycation end products (RAGE) was thought to exclusively play an important role under hyperglycemic conditions. However, more and more evidence suggests that RAGE in fact is an inflammation perpetuating multi-ligand receptor and participates actively in various vascular and inflammatory diseases even in normoglycaemic conditions. Various ligands include advanced glycation end products (AGEs), S100 proteins and amphoterins etc. Besides full-length RAGE, numerous truncated forms of the receptor have also been described including the well-characterized soluble RAGE (sRAGE). sRAGE has an ability to act as a decoy to avoid interaction of RAGE with its pro-inflammatory ligands. Ligand engagement of RAGE activates multiple signaling pathways and also forms a positive feedback loop for its own enhanced expression. This review will discuss the role of multi-ligand receptor i.e. RAGE in context to various vascular diseases, which have a pathophysiologically important inflammatory component in normoglycaemic conditions.

1. Introduction

Since its discovery in 1992, receptor for advanced glycation end products (RAGE) has been studied widely in different diseased conditions like diabetes, coronary artery disease, Alzheimer's disease etc [1–6]. RAGE is expressed on multiple cell types i.e. smooth muscle cells, macrophages, endothelial cells, cardiomyocytes, podocytes, epithelial cells etc [1,3]. Acting as a common receptor for a heterogeneous set of ligands, RAGE has been demonstrated to play an inevitable role in inflammation and vascular diseases [3,7–9]. RAGE has ability to recognize a diverse repertoire of endogenous ligands e.g advanced glycation end products (AGEs), amphoterins and S100 proteins/calgranulins, Mac-1 etc [3,6,10,11]. RAGE has been recognized as a key molecule in the development of severe chronic pathologies, including diabetic complications, atherosclerosis and its related manifestations, Takayasu's arteritis (TA), Kawasaki disease (KD), neurodegeneration and cancer [3,6,12–15]. Ligand engagement of RAGE activates multiple signaling pathways, depending on the availability and type of ligand, cell type and environment. In this article, we review the importance of RAGE-ligand axis in various vascular and inflammatory diseases under normoglycaemic conditions.

2. Structure and variants of RAGE

RAGE is an approximately 45 kDa protein, originally isolated from bovine lung endothelium on the basis of its ability to bind advanced glycation end products [1] and later has been characterized as a member of the immunoglobulin (Ig) superfamily of cell-surface molecules [2]. The entire mature receptor consists of 403 amino acids in man, rat, and mouse. The extracellular region of RAGE consists of one V-type (variable) immunoglobulin domain, followed by two C-type (constant) immunoglobulin domains stabilized by internal disulfide bridges between cysteine residues [16,17].

Besides full-length RAGE, numerous truncated forms of the receptor have been described [16–18] (Fig. 1). The existence of diverse RAGE isoforms from the same gene indicates that the pre-mRNA of RAGE undergoes alternative splicing. *In vitro* studies have shown that N-truncated isoform of RAGE is expressed on the cell surface in a way that is similar to full-length RAGE [19]. The V domain of RAGE has been shown to be critical for ligand binding; the N-truncated RAGE is unable to engage glycated end products. Nonetheless, it has been suggested that N-truncated RAGE could participate in the regulation of angiogenesis in a way that is independent from the classical RAGE activation pathway [20].

The C-truncated isoform, on the other hand, has received much more attention because of its potential significance in RAGE-mediated disorders. Soluble forms of RAGE are produced either by proteolytic cleavage of the full length RAGE by MMP-9 or ADAM10 metalloproteinases (sRAGE) or by alternative mRNA splicing, termed as endogenous secretory RAGE (esRAGE) [21–23]. They can act as decoy for RAGE ligands. These secreted variants, together, actually represent the total amount of

* Present address and correspondence to: N. Mahajan, Department of Molecular Pharmacology and Biological Chemistry, Robert H. Lurie Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL 60611, USA.
** Corresponding author. Tel.: +91 172 2755235; fax: +91 172 2744401.
E-mail addresses: dr.nitin20@yahoo.com (N. Mahajan), veenad2001@yahoo.com (V. Dhawan).

0167-5273/$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2013.05.013

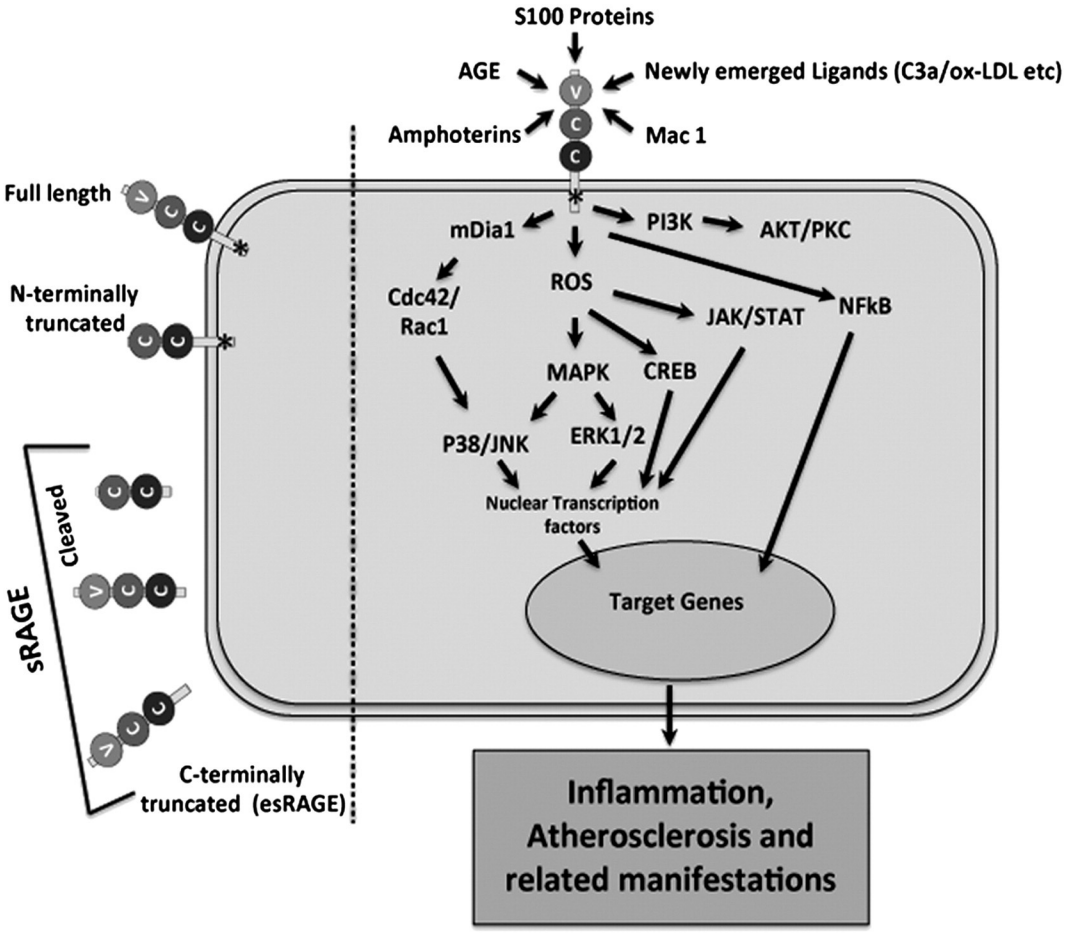

Fig. 1. Schematic representation of the different isoforms of the RAGE (left side) and key signaling events after RAGE-ligand interaction (right side). Left side: RAGE has three major isoforms i.e. full length, N-terminally truncated and C-terminally truncated. N-terminally truncated form lacks the ligand binding domain, where as C-terminally truncated forms lack the transmembrane to induce the cell signaling. C-terminally truncated forms majorly form a pool of soluble RAGE (sRAGE). sRAGE has the abilty to bind to the various RAGE ligands and therefore, it competes with full length RAGE for ligands and act as decoy molecule. Right side: Binding of RAGE to its ligands (AGEs, amphoterins, S100 proteins etc) leads to increase in reactive oxygen species (ROS), activation of various cell signaling pathways like MAPK, PI3K, JAK/STAT and NFkB. All these events finally lead to the promotion of inflammation and atherosclerosis.

soluble RAGE (sRAGE) that can be detected in the bloodstream. [6,24]. sRAGE may contribute to the removal/detoxification of a diverse repertoire of pro-inflammatory ligands that are implicated in human diseases. The potential significance of circulating sRAGE is being investigated in a variety of pathological conditions through clinical research studies. Thus, the decoy function of sRAGE suggests the presence of a regulatory negative feedback mechanism in which sRAGE can serve to prevent the activation of cell surface RAGE.

3. Vascular ligands of RAGE

Several pro-inflammatory ligands, which are implicated in vascular and inflammatory diseases i.e. advanced glycation end products (AGEs), amphoterins, S100 proteins and Mac-1 have been shown to activate RAGE [3,6,10,11] (Fig. 1).

3.1. Advanced glycation end products (AGEs)

Interaction of aldoses with proteins initiates a chain of non-enzymatic reactions leading to a covalent addition of advanced glycated end products (AGEs) to proteins. AGEs are heterogeneous in structure, exhibit characteristic yellow-brown pigmentation and fluorescence, and have a propensity to cross-link. AGEs are specifically recognized by cellular binding sites and are shown to accumulate in the course of ageing and at accelerated rates in diabetes and uremia [4,25]. Their deposition in several tissues (skin, kidney and vessel) has been linked to the activation of inflammatory cytokines and initiation of oxidative stress via generation of oxygen free radicals with subsequent development of atherosclerosis [26]. The reason for AGEs accumulation in these diseases is only partly understood and it is suggested that diminished renal clearance of AGEs may play a part in the process. AGEs have shown their effects on lipids, lipid metabolism and the development of atherosclerosis. AGEs are shown to co-localize in fatty streak, atherosclerotic lesions, lipid containing SMCs and macrophages [4,26].

The potential link between glycation and atherosclerosis and its underlying clinical manifestations has been recently investigated. AGE-modified ApoB have been found in the atherosclerotic plaques of euglycemic normolipidemic patients with atherosclerosis [27]. Moreover, AGEs have been found to be associated with coronary heart disease in both diabetic [28] and non diabetic subjects [29]. A number of potential mechanisms have been hypothesized to explain the link between glycation of lipoproteins and atherosclerosis and its clinical manifestations [30].

Activation of RAGE leads to the production of reactive oxygen (ROS) and nitrogen species (RNS) by a variety of mechanisms, which may have immediate deleterious effects in the vasculature associated with the onset of inflammation. In addition to being formed extracellularly and in the serum where they may bind RAGE, AGEs have been shown to form intracellularly in a ROS dependent manner. This may lead to accelerated deleterious effects such as amplified ROS generation and lipid oxidation causing retention of oxidized LDL (ox-LDL) in the vessel wall [5]. Sun et al. (2012) have recently shown that RAGE

Please cite this article as: Mahajan N, Dhawan V, Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.05.013

deletion attenuates atherosclerosis in LDLR −/− mice [31]. Also, RAGE was shown to mediate pro-inflammatory cell signaling in response to ox-LDL. These authors have also speculated ox-LDL to be a new ligand for RAGE in the hyperlipidaemic conditions. Binding of ox-LDL to RAGE enhances macrophage proliferation and oxidative stress [31]. Kotani et al. (2012) have recently demonstrated existence of an independent, significant and inverse association of sRAGE and ox-LDL in asymptomatic subjects, and therefore, suggests that part of the anti-atherosclerotic effects of sRAGE may be related to ox-LDL quenching [32].

3.2. High mobility box-group-1 (HMBG-1)/amphoterins

High mobility box group-1 (HMGB1) is constitutively expressed in most cell types and it resides mainly in the nucleus under physiologic conditions. Being an intracellular regulator of the transcription process it maintains the functions of DNA. Also, it acts as a potent pro-inflammatory cytokine and interacts with the RAGE and toll-like receptors (TLR) 2, 4 and 9 [33,34]. Through, its interaction with RAGE, HMGB1 stimulates cells to release TNF-α, IL-6, and IL-1β, suggesting that extracellular HMGB1 plays a critical role in inflammation [35,36].

Studies have shown markedly increased expression of HMGB1 in nuclei and cytoplasm of macrophages, SMCs in atherosclerotic lesion isolated from aorta, carotid and coronary arteries. Intense HMGB1 expression has also been observed in areas adjacent to the necrotic core of atherosclerotic lesions [37].

Increased levels of HMGB1 have shown to be associated in subjects with angiographically proven coronary artery disease (CAD) both in non-diabetic and in type 2 diabetic patients in a large patient cohort [38]. An independent association of HMGB1 with infarct size and with non-calcified plaque burden has been described in subjects with acute coronary syndrome (ACS) and with stable CAD respectively [39,40].

Studies in animals have demonstrated that the administration of recombinant HMGB1 to mice worsened myocardial injury whereas treatments with HMGB1 box A, a specific HMGB1 antagonist, reduced infarct size and other markers of tissue damage. On the contrary, the administration of recombinant HMGB1 or HMGB1 box A to RAGE-deficient mice had no effect, indicating an important role of HMGB1 RAGE interaction in ischemia–reperfusion injury of the heart [41].

3.3. S100 proteins

The S100 proteins represent the largest sub-group within the superfamily of EF-hand calcium-binding proteins. Currently, S100 proteins comprise a family of more than 25 low molecular weight (9–14kDa) acidic proteins that are characterized by the presence of two calcium-binding EF-hand motifs and display unique properties [42,43]. S100 proteins can induce different cellular responses. For example, S100B promotes concentration-dependent neuronal survival and axon growth, S100A8, S100A9 and S100A12 act as proinflammatory molecules and S100A2 and S100A4 are associated with differentiation and cell growth. Another subgroup comprising S100A5, S100A6 and S100P can promote tumor growth [44]. S100A8, S100A9, S100A12 together belong to a S100 protein subfamily termed calgranulins and are pro-inflammatory in nature [43,45].

S100A8/A9 are observed to play a significant role in cardiovascular disease in both humans and animals. The percentage of S100A8/A9 positive macrophages was found to be higher in microvessels, rupture prone and calcified lesions [46,47]. Further, increased serum levels and expression of S100A8/A9 were observed in infiltrated neutrophils in atherosclerotic plaques of patients with unstable angina [48]. Plasma levels of S100A8/A9 have also been demonstrated as a marker of CVD risk factor [45]. Anti-inflammatory effects of these S100A proteins have also been described, which might be mediated by oxidation or *S*-nitrosylation of the S100A proteins, arachidonic acid binding, or others [49]. More studies are required to enlighten these hidden facts in near future.

S100A12 has also been termed as EN-RAGE (extracellular newly identified RAGE binding protein). The knowledge on its intracellular protein targets is still limited. However, the best-known natural extracellular target protein of EN-RAGE is RAGE. Engagement of the extracellular domain of membrane RAGE by calcium-bound S100A12 activates intracellular signal cascades including MAP-kinase and NF-κB [43]. Human recombinant EN-RAGE has been reported to be chemotactic for neutrophils and monocytes *in vitro* and *in vivo* [3]. Of note, EN-RAGE also binds to sRAGE. On the other hand, EN-RAGE has been shown to activate mast cells, which do not express RAGE, thus underscoring the notion that RAGE is possibly not the sole receptor for EN-RAGE [50]. In this regard, quantification of EN-RAGE becomes relevant for diagnostic use in various inflammatory disease states and has been discussed later.

3.4. Macrophage-antigen-1 (Mac-1)

The Mac-1 integrin, (also known as αMβ2 and CD11b/CD19) is a member of the β2-integrin family and is expressed on circulating leukocytes [11]. This protein interacts with ICAM-1 on endothelial cells and is involved in firm adhesion of leukocytes to the endothelium. RAGE is recognized as a binding partner for Mac-1, mediating leukocyte recruitment that is augmented by S100B, S100A9 and HMGB1 [11,34].

3.5. Newly emerging RAGE ligands

Recent studies have increased the number of molecules which can act as ligands for RAGE. Ruan et al. (2010) have demonstrated RAGE as a receptor for complement C3a and unmethylated cytosine-guanine-rich DNA A (hCpGAs). These two molecules synergistically increase IFN-α production in a RAGE-dependent manner and stimulate an innate immune response [51]. Activation of NF-kB and secretion of TNF-α has shown to be a result of interaction between bacterial lipopolysaccharide (LPS) and RAGE. Moreover, LPS induced inflammation was inhibited by sRAGE after its binding to TLR2 and TLR4 [52]. An interaction between RAGE and pathogen-associated molecular patterns (PAMPs) has also been suggested in bacteria [53]. Binding of ox-LDL to RAGE has been shown to enhance the proliferation rate and oxidative stress in macrophages, thereby, making ox-LDL as a potential candidate in the list of newly emerged ligands for RAGE [31].

4. RAGE–ligand interaction

RAGE-ligand interaction enhances receptor expression and initiates a positive feedback loop, which triggers increased RAGE expression, which in-turn perpetuates another wave of cellular activation [3,6,54]. These activated cells may release mediators/RAGE–ligands which may amplify tissue inflammation and injury in a positive feedback loop mechanism. RAGE–ligand interaction leads to the stimulation of the major cellular pathways that include Ras-extracellular signal-regulated kinase1/2 (ERK1/2), Cdc42/Rac, stress-activated protein kinase/c-jun-NH2-terminal kinase (SAPK/JNK) and p38 mitogen activated protein (MAP) kinase pathways. This results in the activation of transcription factors like nuclear factor (NF)-kB, cAMP response element-binding (CREB) protein or a member of the signal transducers and activators of transcription family (STAT3) [9,55,56]. RAGE–ligand interaction amplifies inflammatory responses through enhanced generation of adhesion molecules, cytokines, and tissue-destructive matrix metalloproteinases (MMPs). The engagement of RAGE by various ligands may unendingly amplify inflammatory events in tissues that may be previously sensitized by lipid deposition or by immune/inflammatory triggers.

Hudson et al. (2008) have reported that cytoplasmic domain of RAGE binds to the formin family member of cellular effector molecules,

Please cite this article as: Mahajan N, Dhawan V, Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.05.013

the FH1 domain of mDia (diaphanous) [57]. Indeed, other studies have also reported that the RAGE cytoplasmic domain may bind to ERK and to TIRAP (an adaptor protein for TLRs) [58,59]. Finding an association of TIRAP (an adaptor protein for TLR2/4) with the phosphorylated RAGE suggests that these two molecules may coordinately regulate inflammation, immune response and other cellular functions [59].

5. RAGE biology in vascular and inflammatory diseases

5.1. Atherosclerosis and Coronary artery disease

Mechanisms contributing to atherogenesis are multiple and complex. Inflammation plays an important role in pathophysiology of atherosclerosis and its related manifestations [60,61]. RAGE participates in leukocyte recruitment and activation of macrophages and therefore, marks its importance in the initiation and maintenance of inflammation in atherosclerosis [3,5,11]. A study in Apo E knockout mice demonstrated a time dependent increase of RAGE expression in aortas [7]. Also, in a double knockout mice model (RAGE −/−, Apo E −/−), the expression of the adhesion molecules and matrix metalloproteinases were found to be significantly attenuated, further potentiating the importance of RAGE signaling in propagation of vascular inflammation in atherosclerosis [7]. The expression of RAGE ligands such as S100B and HMGB1 were also found attenuated in the aorta of double knock out mice (RAGE −/−, Apo E −/−). These observations further stress the fact that RAGE acts as a positive regulator of its own ligand for receptor activation [7,12,62].

Studies in human subjects have demonstrated the importance of RAGE, sRAGE and its inflammatory ligands in both diabetic and non-diabetic subjects. Burke et al. (2004) demonstrated increased expression of RAGE and EN-RAGE in atherosclerotic plaques obtained from diabetic CAD cadavers [63]. In addition, these authors related increased expression of RAGE and EN-RAGE with necrotic core expansion, thinning of the fibrous cap and plaque instability. Previously, we have demonstrated increased mRNA expression of RAGE and its inflammatory ligand EN-RAGE in peripheral blood mononuclear cells (PBMCs) isolated from angiographically proven non-diabetic young subjects with coronary artery disease (CAD) compared to healthy controls [14]. We also demonstrated presence of a positive correlation of these molecules with high sensitivity C-reactive protein (hsCRP) levels and a negative correlation with circulating levels of soluble RAGE. The ligation of EN-RAGE with cellular RAGE activates the downstream signaling pathway such as NF-kB, in addition to the increased expression of adhesion molecules and cytokine release from the lymphocytes [10,11]. Cucculrullo et al. (2006) have demonstrated modulation of RAGE expression in atherosclerotic plaques in a glucose-independent manner by inhibition of macrophage myeloperoxidase and therefore, suggested pro-atherogenic role of RAGE in various clinical settings characterized by underlying inflammation and high infiltration of activated macrophages [64].

Studies in animal models have shown that administration of sRAGE reduced inflammatory responses. Specifically, RAGE blockade by sRAGE prevented the development of micro- [65,66] and macrovascular complications in animal models of vascular disorders [54]. Soluble RAGE has been documented as an anti-atherogenic molecule and low levels of sRAGE were reported to be a significant risk factor for CAD in a non-diabetic subjects [14,67].

Plasma esRAGE levels were shown to be inversely correlated with intima media thickness (IMT) ratio in non-diabetic subjects [68]. In another study, esRGAE levels were inversely and independently correlated with several components of metabolic syndrome including BMI, insulin resistance index, blood pressure and hyperglyceridaemia. [69].

In an *in vitro* study we have demonstrated that recombinant CRP up-regulates the expression of RAGE and its ligand EN-RAGE in THP-1 cells via FcγRII and utilizes MAPK i.e. ERK, p38 and JNK pathways to transduce cell signaling [70]. Zhong et al. (2006) reported increased expression of RAGE in human endothelial cells in presence of recombinant C-reactive protein (CRP) and also, suggested that CRP enhances the binding ability of RAGE to its ligands [71]. Similarly, Levels of mRNA/protein of S100A12 were reported to be enhanced by another pro-inflammatory molecule i.e. IL-6 [72] and bacterial lipopolysaccharide (LPS) [10].

Multiple polymorphism of the gene encoding RAGE have been reported [73]. Among the known RAGE polymorphisms, some are located in the promoter region of the gene (T-429C and T-374A) and other lies within the V-type domain of the receptor (G82S) [74,75]. Poon et al. (2010) studied three distinct polymorphisms of RAGE in the promoter region (T-429C, T-374A and the 63 base pair deletion spanning -407 to -345 nucleotide) for its potential relationship to cardiovascular disease in type 2 diabetic Chinese subjects with overt nephropathy [76]. Also, A allele of the -374T/A polymorphism, is associated with a protective effect in cardiovascular disease [77]. Higher levels of sRAGE and higher expression of RAGE have also been associated with polymorphisms (Gly allele of Gly82Ser, G allele of 2184A/G and C allele of the -429T/C polymorphism) [67,78,79]. However, a recent meta-analysis demonstrates that there is no association between the RAGE 429T/C, 374T/A and G82S polymorphisms and atherosclerosis [80]. Keeping in mind the complex and polygenetic pathophysiology of atherosclerosis, role of polymorphisms as a predictor of the cardiovascular risk may probably be very small. Larger studies of different ethnic populations, especially with detailed individual information, are needed to drive firm conclusion.

5.2. Hypertension

Geroldi et al. (2005) have demonstrted that levels of sRAGE were decreased in patients with hypertension as compared to normotensive subjects [81]. We also observed that CAD subjects who were hypertensive had low levels of sRAGE as compared to the CAD subjects who were normotensive [14]. Inverse association of sRAGE levels was found to be inversely associated with pulse pressure and therefore, sRAGE may be a marker of arterial stiffness in essential hypertension (EH) [81]. Anthropometric and inflammatory variables and liver and renal function may be the determinants of sRAGE levels in non-diabetic hypertensive patients as demonstrated in a study of 271 non-diabetic patients with essential HT. Creatinine clearance and body mass index were found to be negatively associated whereas, gamma glutamyl transpeptidase and TNF-alpha were found to be positively and independently associated with sRAGE levels [82]. The exact reasons for the discrepancy between the two studies, in context to an inverse correlation between sRAGE and pulse pressure in one and a positive correlation between BMI and TNF-alpha with sRAGE in the other, are unclear. However, disease activity, ethnic origin of the subjects and difference in concentrations of analytes between the two studies could be possible reasons for the observed differences. Koyama et al. (2005) in their study reported a significant inverse correlation of esRAGE and BMI in subjects with metabolic syndrome [68]. However, we and others have demonstrated absence of any significant correlation of sRAGE with BMI [14,81]. It is possible that the interaction of RAGE-ligand(s) in macro and microvasculature may cause increased oxidative stress and inflammation which in-turn may lead to arterial stiffness Recently, Yoon et al. (2012) have demonstrated an independent correlation of serum sRAGE levels with a marker of central aortic stiffness (hfPWV) in hypertensive subjects [83].

5.3. Takayasu's arteritis (TA)

Takayasu's arteritis (TA) is an inflammatory fibrosing arteritis affecting predominately the aorta and its main branches. Till date, pathogenesis of this disease remains enigmatic [13,84–86]. Decreased plasma sRAGE levels in TA subjects compared to healthy controls

Please cite this article as: Mahajan N, Dhawan V, Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.05.013

have been reported [13,87]. Also, a negative correlation of sRAGE with matrix degrading enzymes i.e. matrix metalloproteinases (MMP-9 and MMP-3) further provides justification to the anti-atherogenic nature of sRAGE [13]. Earlier we have reported the presence of increased reactive oxygen and nitrogen species in subjects with TA as compared to healthy controls [88]. In the same set of patients decreased levels of sRAGE were also demonstrated [13]. Cumulatively these observations indicate importance of RAGE biology in TA.

Significantly increased RAGE-EN-RAGE expression in TA further confirms a prevalent oxidative stress and inflammatory milieu in such a situation. Ours is the first report in literature which demonstrates that mRNA levels of RAGE and its ligand EN-RAGE are up-regulated in subjects with TA [87]. Our observations therefore, adds on one more disease where RAGE biology may have an additional acoountibilty.

5.4. Kawasaki disease (KD)

Kawasaki disease (KD) is an acute febrile disease that usually occurs in children under 5 years of age and has become the primary cause of acquired heart disease in children. KD affects predominantly small- and medium-size arteries, particularly the coronary artery, with potential risks for coronary stenosis and thrombosis caused by coronary artery lesions (CALs), and even death caused by myocardial infarction [89,90]. Foell et al. (2003) for the first time reported involvement of S100A12 in KD inflammation [91]. Later, Wittkowski et al. (2007) have demonstrated a reverse association of acute KD with sRAGE and its proinflammatory ligand [92]. Expression levels of RAGE as well as serum levels of its another ligand i.e. HMGB1 were found to be higher in early acute phase which gradually decreases afterwards [92]. Very recently, Gong et al. have reported up-regulation of RAGE expression on the surface of circulating endothelial cells in KD and concluded regulatory role of RAGE in pathophysiology of the disease [93]. Importance of RAGE biology in acute, afebrile and sub-acute stages in KD has recently been shown by Qi et al. [94].

5.5. Systemic lupus erythematous (SLE)

Systemic lupus erythematous (SLE) is an autoimmune disease characterized by chronic inflammation. Accelerated atherosclerosis in SLE has been related to accumulation of advanced glycation end products [95,96]. Levels of HMGB-1 are increased in SLE patients with active renal disease [97]. Recently, Marten et al. (2012) have evaluated the association of RAGE polymorphisms with sRAGE, renal involvement (lupus nephritis (LN)) and its outcome [98]. The C allele of -429 T/C, the T allele of -374 T/A and the G allele of 2184 A/G were significantly more prevalent in SLE and LN compared with healthy controls, though, no association of the genotype with sRAGE was observed in SLE [98]. On the contrary, increased levels of sRAGE were found in SLE patients during active and quiescent phase compared with healthy controls [99]. These results demonstrated that increased sRAGE might reflect active inflammation or may be increased due to compensatory mechanism. Therefore, caution must be taken, in interpreting the role of sRAGE as it demonstrates anti-inflammatory properties in atherosclerotic diseases whereas; it is shown to be associated with proinflammatory conditions as observed in SLE.

6. Concluding remarks

RAGE biology may take center stage when many things may go wrong in many different ways in various inflammatory and vascular diseases. Multiple key cells in vasculature such as endothelial cells, infiltrating inflammatory cells, cardiomyocytes and fibroblasts, express RAGE. Presence of a positive feedback loop for expression of RAGE expression as well as interplay of these cells in the close proximity may set a stage for damage versus repair. The complexity of the role of RAGE in the biological setting is evident from various *in vitro* and *in vivo* studies. These results suggest that sRAGE is an endogenous protective factor against the occurrence of atherosclerosis and other vascular complications. Genetically engineered sRAGE could be helpful as treatment or prophylactic measure in RAGE mediated disorders irrespective of glycaemic conditions. Moreover, it was shown that certain polymorphisms in the RAGE gene are strongly associated with higher sRAGE levels, implicating a complex genetic regulation of sRAGE levels and suggesting that sRAGE may not merely be a marker of a disease state but also a potential target in the pathobiology of the atherosclerotic process. Certain natural compounds or plant-derived polyphenols, which may have the ability to reduce the formation of either ligands or to increase the expression of soluble receptors, can be explored in near future. We have reviewed the evidence where RAGE–ligand axis participates both as a biomarker and a mediator in various vascular and inflammatory diseases. More work is the need of the hour to elucidate the complex effects exacerbated by receptor–ligand interaction. However, new advances in understanding inflammatory signals and their link to the resolution pathways, together with new drug development, offer promise where research could be translated into clinical practice.

Acknowledgments

We apologize to those researchers whose important work we did not discuss for the sake of conciseness. We thank Dr. Markus A. Queisser and Dr. Fotini M. Kouri from Northwestern University, Chicago for their valuable suggestions and comments. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

References

[1] Schmidt AM, Vianna M, Gerlach M, et al. Isolation and characterization of two binding proteins for advanced glycosylation end products from bovine lung which are present on the endothelial cell surface. J Biol Chem 1992;267:14987–97.
[2] Neeper M, Schmidt AM, Brett J, et al. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J Biol Chem 1992;267:14998–5004.
[3] Basta G. Receptor for advanced glycation endproducts and atherosclerosis: From basic mechanisms to clinical implications. Atherosclerosis 2008;196:9–21.
[4] Del Turco S, Basta G. An update on advanced glycation endproducts and atherosclerosis. Biofactors 2012;38:266–74.
[5] Farmer DG, Kennedy S. RAGE, vascular tone and vascular disease. Pharmacol Ther 2009;124:185–94.
[6] Fritz G. RAGE: a single receptor fits multiple ligands. Trends Biochem Sci 2011;36:625–32.
[7] Harja E, Bu DX, Hudson BI, et al. Vascular and inflammatory stresses mediate atherosclerosis via RAGE and its ligands in apoE−/− mice. J Clin Invest 2008;118:183–94.
[8] Park L, Raman KG, Lee KJ, et al. Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med 1998;4:1025–31.
[9] Huttunen HJ, Fages C, Rauvala H. Receptor for advanced glycation end products (RAGE)-mediated neurite outgrowth and activation of NF-kappaB require the cytoplasmic domain of the receptor but different downstream signaling pathways. J Biol Chem 1999;274:19919–24.
[10] Hofmann MA, Drury S, Fu C, et al. RAGE mediates a novel proinflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. Cell 1999;97:889–901.
[11] Chavakis T, Bierhaus A, Al-Fakhri N, et al. The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. J Exp Med 2003;198:1507–15.
[12] Jandeleit-Dahm K, Watson A, Soro-Paavonen A. The AGE/RAGE axis in diabetes-accelerated atherosclerosis. Clin Exp Pharmacol Physiol 2008;35:329–34.
[13] Mahajan N, Dhawan V, Malik S, Jain S. Serum levels of soluble receptor for advanced glycation end products (sRAGE) in Takayasu's arteritis. Int J Cardiol 2010;145:589–91.
[14] Mahajan N, Malik N, Bahl A, Dhawan V. Receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in non-diabetic subjects with pre-mature coronary artery disease. Atherosclerosis 2009;207:597–602.
[15] Taguchi A, Blood DC, del Toro G, et al. Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases. Nature 2000;405:354–60.
[16] Koch M, Chitayat S, Dattilo BM, et al. Structural basis for ligand recognition and activation of RAGE. Structure 2010;18:1342–52.

Please cite this article as: Mahajan N, Dhawan V, Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.05.013

[17] Park H, Adsit FG, Boyington JC. The 1.5 A crystal structure of human receptor for advanced glycation endproducts (RAGE) ectodomains reveals unique features determining ligand binding. J Biol Chem 2010;285:40762–70.
[18] Ding Q, Keller JN. Evaluation of rage isoforms, ligands, and signaling in the brain. Biochim Biophys Acta 2005;1746:18–27.
[19] Hudson BI, Carter AM, Harja E, et al. Identification, classification, and expression of RAGE gene splice variants. FASEB J 2008;22:1572–80.
[20] Yonekura H, Yamamoto Y, Sakurai S, et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. Biochem J 2003;370:1097–109.
[21] Zhang L, Bukulin M, Kojro E, et al. Receptor for advanced glycation end products is subjected to protein ectodomain shedding by metalloproteinases. J Biol Chem 2008;283:35507–16.
[22] Raucci A, Cugusi S, Antonelli A, et al. A soluble form of the receptor for advanced glycation endproducts (RAGE) is produced by proteolytic cleavage of the membrane-bound form by the sheddase a disintegrin and metalloprotease 10 (ADAM10). FASEB J 2008;22:3716–27.
[23] Galichet A, Weibel M, Heizmann CW. Calcium-regulated intramembrane proteolysis of the RAGE receptor. Biochem Biophys Res Commun 2008;370:1–5.
[24] Yamagishi S, Matsui T. Soluble form of a receptor for advanced glycation end products (sRAGE) as a biomarker. Front Biosci (Elite Ed) 2010;2:1184–95.
[25] Gaens KH, Stehouwer CD, Schalkwijk CG. Advanced glycation endproducts and its receptor for advanced glycation endproducts in obesity. Curr Opin Lipidol 2013;24:4–11.
[26] Kaneko M, Bucciarelli L, Hwang YC, et al. Aldose reductase and AGE-RAGE pathways: key players in myocardial ischemic injury. Ann N Y Acad Sci 2005;1043:702–9.
[27] Stitt AW, He C, Friedman S, et al. Elevated AGE-modified ApoB in sera of euglycemic, normolipidemic patients with atherosclerosis: relationship to tissue AGEs. Mol Med 1997;3:617–27.
[28] Kiuchi K, Nejima J, Takano T, Ohta M, Hashimoto H. Increased serum concentrations of advanced glycation end products: a marker of coronary artery disease activity in type 2 diabetic patients. Heart 2001;85:87–91.
[29] Kanauchi M, Tsujimoto N, Hashimoto T. Advanced glycation end products in nondiabetic patients with coronary artery disease. Diabetes Care 2001;24:1620–3.
[30] Misciagna G, Logroscino G, De Michele G, et al. Glycated apolipoprotein B and myocardial infarction. Nutr Metab Cardiovasc Dis 2007;17:6–12.
[31] Sun L, Ishida T, Yasuda T, et al. RAGE mediates oxidized LDL-induced pro-inflammatory effects and atherosclerosis in non-diabetic LDL receptor-deficient mice. Cardiovasc Res 2009;82:371–81.
[32] Kotani K, Caccavello R, Taniguchi N, Gugliucci A. Circulating soluble receptor for advanced glycation end products is inversely correlated to oxidized low-density lipoproteins in asymptomatic subjects. J Int Med Res 2012;40:1878–83.
[33] Park JS, Svetkauskaite D, He Q, et al. Involvement of toll-like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. J Biol Chem 2004;279:7370–7.
[34] Tian J, Avalos AM, Mao SY, et al. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol 2007;8:487–96.
[35] Taniguchi N, Kawahara K, Yone K, et al. High mobility group box chromosomal protein 1 plays a role in the pathogenesis of rheumatoid arthritis as a novel cytokine. Arthritis Rheum 2003;48:971–81.
[36] de Souza AW, Westra J, Limburg PC, Bijl M, Kallenberg CG. HMGB1 in vascular diseases: its role in vascular inflammation and atherosclerosis. Autoimmun Rev 2012;11:909–17.
[37] Inoue K, Kawahara K, Biswas KK, et al. HMGB1 expression by activated vascular smooth muscle cells in advanced human atherosclerosis plaques. Cardiovasc Pathol 2007;16:136–43.
[38] Yan XX, Lu L, Peng WH, et al. Increased serum HMGB1 level is associated with coronary artery disease in nondiabetic and type 2 diabetic patients. Atherosclerosis 2009;205:544–8.
[39] Andrassy M, Volz HC, Riedle N, et al. HMGB1 as a predictor of infarct transmurality and functional recovery in patients with myocardial infarction. J Intern Med 2011;270:245–53.
[40] Andrassy M, Volz HC, Schuessler A, et al. HMGB1 is associated with atherosclerotic plaque composition and burden in patients with stable coronary artery disease. PLoS One 2012;7:e52081.
[41] Andrassy M, Volz HC, Igwe JC, et al. High-mobility group box-1 in ischemia–reperfusion injury of the heart. Circulation 2008;117:3216–26.
[42] Marenholz I, Heizmann CW, Fritz G. S100 proteins in mouse and man: from evolution to function and pathology (including an update of the nomenclature). Biochem Biophys Res Commun 2004;322:1111–22.
[43] Pietzsch J, Hoppmann S. Human S100A12: a novel key player in inflammation? Amino Acids 2009;36:381–9.
[44] Perera C, McNeil HP, Geczy CL. S100 calgranulins in inflammatory arthritis. Immunol Cell Biol 2010;88:41–9.
[45] Averill MM, Kerkhoff C, Bornfeldt KE. S100A8 and S100A9 in cardiovascular biology and disease. Arterioscler Thromb Vasc Biol 2012;32:223–9.
[46] Ionita MG, Vink A, Dijke IE, et al. High levels of myeloid-related protein 14 in human atherosclerotic plaques correlate with the characteristics of rupture-prone lesions. Arterioscler Thromb Vasc Biol 2009;29:1220–7.
[47] McCormick MM, Rahimi F, Bobryshev YV, et al. S100A8 and S100A9 in human arterial wall. Implications for atherogenesis. J Biol Chem 2005;280:41521–9.
[48] Miyamoto S, Ueda M, Ikemoto M, et al. Increased serum levels and expression of S100A8/A9 complex in infiltrated neutrophils in atherosclerotic plaque of unstable angina. Heart 2008;94:1002–7.
[49] Goyette J, Geczy CL. Inflammation-associated S100 proteins: new mechanisms that regulate function. Amino Acids 2011;41:821–42.
[50] Yang Z, Yan WX, Cai H, et al. S100A12 provokes mast cell activation: a potential amplification pathway in asthma and innate immunity. J Allergy Clin Immunol 2007;119:106–14.
[51] Ruan BH, Li X, Winkler AR, et al. Complement C3a, CpG oligos, and DNA/C3a complex stimulate IFN-alpha production in a receptor for advanced glycation end product-dependent manner. J Immunol 2010;185:4213–22.
[52] Yamamoto Y, Harashima A, Saito H, et al. Septic shock is associated with receptor for advanced glycation end products ligation of LPS. J Immunol 2011;186:3248–57.
[53] Ramsgaard L, Englert JM, Manni ML, et al. Lack of the receptor for advanced glycation end-products attenuates E. coli pneumonia in mice. PLoS One 2011;6:e20132.
[54] Sakaguchi T, Yan SF, Yan SD, et al. Central role of RAGE-dependent neointimal expansion in arterial restenosis. J Clin Invest 2003;111:959–72.
[55] Huang JS, Guh JY, Chen HC, Hung WC, Lai YH, Chuang LY. Role of receptor for advanced glycation end-product (RAGE) and the JAK/STAT-signaling pathway in AGE-induced collagen production in NRK-49F cells. J Cell Biochem 2001;81:102–13.
[56] Huttunen HJ, Kuja-Panula J, Rauvala H. Receptor for advanced glycation end products (RAGE) signaling induces CREB-dependent chromogranin expression during neuronal differentiation. J Biol Chem 2002;277:38635–46.
[57] Hudson BI, Kalea AZ, Del Mar Arriero M, et al. Interaction of the RAGE cytoplasmic domain with diaphanous-1 is required for ligand-stimulated cellular migration through activation of Rac1 and Cdc42. J Biol Chem 2008;283:34457–68.
[58] Ishihara K, Tsutsumi K, Kawane S, Nakajima M, Kasaoka T. The receptor for advanced glycation end-products (RAGE) directly binds to ERK by a D-domain-like docking site. FEBS Lett 2003;550:107–13.
[59] Sakaguchi M, Murata H, Yamamoto K, et al. TIRAP, an adaptor protein for TLR2/4, transduces a signal from RAGE phosphorylated upon ligand binding. PLoS One 2011;6:e23132.
[60] Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature 2011;473:317–25.
[61] Packard RR, Libby P. Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem 2008;54:24–38.
[62] Soro-Paavonen A, Watson AM, Li J, et al. Receptor for advanced glycation end products (RAGE) deficiency attenuates the development of atherosclerosis in diabetes. Diabetes 2008;57:2461–9.
[63] Burke AP, Kolodgie FD, Zieske A, et al. Morphologic findings of coronary atherosclerotic plaques in diabetics: a postmortem study. Arterioscler Thromb Vasc Biol 2004;24:1266–71.
[64] Cuccurullo C, Iezzi A, Fazia ML, et al. Suppression of RAGE as a basis of simvastatin-dependent plaque stabilization in type 2 diabetes. Arterioscler Thromb Vasc Biol 2006;26:2716–23.
[65] Wendt TM, Tanji N, Guo J, et al. RAGE drives the development of glomerulosclerosis and implicates podocyte activation in the pathogenesis of diabetic nephropathy. Am J Pathol 2003;162:1123–37.
[66] Bierhaus A, Haslbeck KM, Humpert PM, et al. Loss of pain perception in diabetes is dependent on a receptor of the immunoglobulin superfamily. J Clin Invest 2004;114:1741–51.
[67] Falcone C, Emanuele E, D'Angelo A, et al. Plasma levels of soluble receptor for advanced glycation end products and coronary artery disease in nondiabetic men. Arterioscler Thromb Vasc Biol 2005;25:1032–7.
[68] Koyama H, Shoji T, Yokoyama H, et al. Plasma level of endogenous secretory RAGE is associated with components of the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol 2005;25:2587–93.
[69] Norata GD, Garlaschelli K, Grigore L, et al. Circulating soluble receptor for advanced glycation end products is inversely associated with body mass index and waist/hip ratio in the general population. Nutr Metab Cardiovasc Dis 2009;19:129–34.
[70] Mahajan N, Bahl A, Dhawan V. C-reactive protein (CRP) up-regulates expression of receptor for advanced glycation end products (RAGE) and its inflammatory ligand EN-RAGE in THP-1 cells: inhibitory effects of atorvastatin. Int J Cardiol 2010;142:273–8.
[71] Zhong Y, Li SH, Liu SM, et al. C-Reactive protein upregulates receptor for advanced glycation end products expression in human endothelial cells. Hypertension 2006;48:504–11.
[72] Hasegawa T, Kosaki A, Kimura T, et al. The regulation of EN-RAGE (S100A12) gene expression in human THP-1 macrophages. Atherosclerosis 2003;171:211–8.
[73] Hudson BI, Stickland MH, Grant PJ. Identification of polymorphisms in the receptor for advanced glycation end products (RAGE) gene: prevalence in type 2 diabetes and ethnic groups. Diabetes 1998;47:1155–7.
[74] Hofmann MA, Drury S, Hudson BI, et al. RAGE and arthritis: the G82S polymorphism amplifies the inflammatory response. Genes Immun 2002;3:123–35.
[75] Leclerc E, Fritz G, Vetter SW, Heizmann CW. Binding of S100 proteins to RAGE: an update. Biochim Biophys Acta 2009;1793:993–1007.
[76] Poon PY, Szeto CC, Chow KM, Kwan BC, Li PK. Relation between polymorphisms of receptor for advanced glycation end products (RAGE) and cardiovascular diseases in Chinese patients with diabetic nephropathy. Clin Nephrol 2010;73:44–50.
[77] Pettersson-Fernholm K, Forsblom C, Hudson BI, Perola M, Grant PJ, Groop PH. The functional -374 T/A RAGE gene polymorphism is associated with proteinuria and cardiovascular disease in type 1 diabetic patients. Diabetes 2003;52:891–4.
[78] Jang Y, Kim JY, Kang SM, et al. Association of the Gly82Ser polymorphism in the receptor for advanced glycation end products (RAGE) gene with circulating levels of soluble RAGE and inflammatory markers in nondiabetic and nonobese Koreans. Metabolism 2007;56:199–205.

Please cite this article as: Mahajan N, Dhawan V, Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.05.013

[79] Hudson BI, Stickland MH, Futers TS, Grant PJ. Effects of novel polymorphisms in the RAGE gene on transcriptional regulation and their association with diabetic retinopathy. Diabetes 2001;50:1505–11.
[80] Wang J, Zou L, Song Z, et al. Meta-analysis of RAGE gene polymorphism and coronary heart disease risk. PLoS One 2012;7:e50790.
[81] Geroldi D, Falcone C, Emanuele E, et al. Decreased plasma levels of soluble receptor for advanced glycation end-products in patients with essential hypertension. J Hypertens 2005;23:1725–9.
[82] Nakamura K, Adachi H, Matsui T, Kurita Y, Takeuchi M, Yamagishi S. Independent determinants of soluble form of receptor for advanced glycation end products in elderly hypertensive patients. Metabolism 2009;58:421–5.
[83] Yoon SJ, Park S, Park C, et al. Association of soluble receptor for advanced glycation end-product with increasing central aortic stiffness in hypertensive patients. Coron Artery Dis 2012;23:85–90.
[84] Mahajan N, Dhawan V. Potential biomarkers for disease activity in Takayasu's arteritis. Int J Cardiol 2012;158:331.
[85] Mahajan N, Dhawan V, Mahmood S, Malik S, Jain S. Extracellular matrix remodeling in Takayasu's arteritis: role of matrix metalloproteinases and adventitial inflammation. Arch Med Res 2012;43:406–10.
[86] Dhawan V, Mahajan N, Jain S. Role of C-C chemokines in Takayasu's arteritis disease. Int J Cardiol 2006;112:105–11.
[87] Mahajan N, Mahmood S, Jain S, Dhawan V. Receptor for advanced glycation end products (RAGE), inflammatory ligand EN-RAGE and soluble RAGE (sRAGE) in subjects with Takayasu's arteritis. Int J Cardiol 2013, http://dx.doi.org/10.1016/j.ijcard.2013.01.002.
[88] Mahajan N, Dhawan V, Malik S, Jain S. Implication of oxidative stress and its correlation with activity of matrix metalloproteinases in patients with Takayasu's arteritis disease. Int J Cardiol 2010;145:286–8.
[89] Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974;54:271–6.
[90] Suzuki A, Kamiya T, Arakaki Y, Kinoshita Y, Kimura K. Fate of coronary arterial aneurysms in Kawasaki disease. Am J Cardiol 1994;74:822–4.
[91] Foell D, Ichida F, Vogl T, et al. S100A12 (EN-RAGE) in monitoring Kawasaki disease. Lancet 2003;361:1270–2.
[92] Wittkowski H, Hirono K, Ichida F, et al. Acute Kawasaki disease is associated with reverse regulation of soluble receptor for advance glycation end products and its proinflammatory ligand S100A12. Arthritis Rheum 2007;56:4174–81.
[93] Gong F, Zhang Y, Xie C, et al. Expression of receptor for advanced glycation end products (RAGE) on the surface of circulating endothelial cells is upregulated in Kawasaki disease. Pediatr Res 2012;71:720–4.
[94] Qi Y, Gong F, Zhang Q, Xie C, Wang W, Fu S. Reverse regulation of soluble receptor for advanced glycation end products and proinflammatory factor resistin and S100A12 in Kawasaki disease. Arthritis Res Ther 2012;14:R251.
[95] de Leeuw K, Graaff R, de Vries R, et al. Accumulation of advanced glycation endproducts in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2007;46:1551–6.
[96] de Leeuw K, Freire B, Smit AJ, Bootsma H, Kallenberg CG, Bijl M. Traditional and non-traditional risk factors contribute to the development of accelerated atherosclerosis in patients with systemic lupus erythematosus. Lupus 2006;15:675–82.
[97] Abdulahad DA, Westra J, Bijzet J, Limburg PC, Kallenberg CG, Bijl M. High mobility group box 1 (HMGB1) and anti-HMGB1 antibodies and their relation to disease characteristics in systemic lupus erythematosus. Arthritis Res Ther 2011;13:R71.
[98] Martens HA, Nienhuis HL, Gross S, et al. Receptor for advanced glycation end products (RAGE) polymorphisms are associated with systemic lupus erythematosus and disease severity in lupus nephritis. Lupus 2012;21:959–68.
[99] Nienhuis HL, de Leeuw K, Bijzet J, et al. Skin autofluorescence is increased in systemic lupus erythematosus but is not reflected by elevated plasma levels of advanced glycation endproducts. Rheumatology (Oxford) 2008;47:1554–8.

Please cite this article as: Mahajan N, Dhawan V, Receptor for advanced glycation end products (RAGE) in vascular and inflammatory diseases, Int J Cardiol (2013), http://dx.doi.org/10.1016/j.ijcard.2013.05.013