

# RAGE Signaling in Cell Adhesion and Inflammation

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**Abstract:** The receptor for advanced glycation endproducts (RAGE) has been shown to play an important role in aging, neurodegeneration, diabetes, and inflammation. RAGE is a transmembrane receptor of the immunoglobulin superfamily, which recognizes a variety of ligands such as AGEs (advanced glycation endproducts), members of the S100/calgranulin family of proinflammatory mediators,  $\beta$ -sheet-fibrils, HMGB1 (amphoterin) and the  $\beta_2$ -integrin Mac-1. RAGE/ligand interactions induce oxidative stress and lead to an up-regulation of pro-inflammatory pathways involving the proinflammatory transcription factor NF- $\kappa$ B, increased expression of cytokines, chemokines, and adhesion molecules. These effects markedly propagate cellular dysfunction and cause perturbation in a diverse group of diseases, such as age-related neurodegenerative disorders, atherosclerosis, diabetic vascular complications, tumors, and chronic inflammatory disease. In addition, RAGE may also interfere with differentiation processes, which are required during organ development. In this article, we have reviewed recent advances on RAGE and RAGE/ligand function in cell adhesion and inflammation based on findings from cell cultures, animal models, and human diseases. The potential for targeting the RAGE/ligand pathway as therapeutic strategy will be discussed.

## INTRODUCTION

Advanced glycation end products (AGEs) are stable products of non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids [1,2]. Increased tissue or plasma concentrations of AGEs have been detected in a variety of common diseases including diabetes mellitus, chronic renal failure, atherosclerosis, arterial hypertension, and Alzheimer's disease [3,4]. AGEs have also been found in human tissues under physiological conditions where their concentrations increase with chronological age [5]. Glycation of macromolecules was originally thought to mark senescent proteins for subsequent degradation [6,7]. Receptors binding AGEs were regarded as scavenger receptors involved in AGE removal and cell regeneration [6,7] and defective clearance of such glycated proteins was believed to be important in aging and diseases with accelerated AGE-formation, such as diabetes or atherosclerosis. However, when the receptor for AGEs (RAGE) was cloned and first characterized in 1992 by Schmidt and colleagues [8-10], it turned out that binding of AGEs to RAGE did not accelerate their clearance and degradation. Rather, ligand-receptor interaction induced sustained post-receptor signaling, including activation of p21<sup>ras</sup>, MAP kinases, and the NF- $\kappa$ B pathway [11-13]. Thus, the concept of RAGE as a scavenger/clearance receptor had to be revised and extended.

## RAGE, A RECEPTOR WITH MULTIPLE ISOFORMS

RAGE is a protein of the immunoglobulin superfamily with an approximate size of 48-55 kDa dependent on the extent of its posttranslational N-glycosylation [8,10,14,15].

The gene is localized on chromosome 6, near the HLA locus between the genes for major histocompatibility complex II and III [16,17]. As a transmembrane receptor, full-length RAGE consists of 404 amino acids with a single hydrophobic transmembrane domain of 19 amino acids and a COOH-terminal cytoplasmic tail of 43 amino acids [8-10]. The extracellular part consists of a terminal 'V-type' and two distinct 'C-type' domains. While the 'V-type' domain confers ligand binding, the highly charged cytoplasmic tail is critical for intracellular signal transduction. Because of the short cytoplasmic tail without apparent enzymatic activity, it is speculated that RAGE may associate into a multimeric cell surface complex on activation before triggering intracellular events [18].

Recently, additional RAGE isoforms that encode several truncated forms of RAGE lacking the transmembrane region and the cytoplasmic tail were identified, but the functional significance of these secreted forms is not yet fully understood [15,19-21]. The existence of truncated isoforms from the same gene (coexpressed with the full-length RAGE transcript) indicates that the pre-mRNA of RAGE can be subjected to alternative splicing [21]. In mice, however, these truncated RAGE isoforms are likely produced by carboxyl-terminal truncation [22]. Three major types, namely full-length, N-truncated (~ 40 kD) and C-truncated (~ 35 kD) alternatively spliced isoforms have been described. N-truncated RAGE lacks the V-type domain, is incapable of binding ligands, and is expressed in the plasma membrane, whereas C-truncated RAGE lacks the transmembrane and cytoplasmic domains (soluble RAGE, sRAGE). sRAGE blocks ligand interaction with, and activation of RAGE-ligand recognizing cell surface receptors providing an effective system for blocking consequences of RAGE signaling. Recently, several new RAGE isoforms such as delta 8-RAGE, a 42 kD protein which lacks exon 8 of genomic RAGE and hRAGEsec (human RAGE secreted form) have been identified [15,19,23]. The differential abundance and distribution of RAGE isoforms in various cell

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types underlines the importance to better understand the regulation and alter-native splicing of RAGE under physiological and patho-physiological circumstances.

RAGE expression occurs in both a constitutive and inducible manner, depending on the cell type and developmental stage [24,25]. Whereas RAGE is constitutively expressed during embryonic development, its expression is downregulated in adult life [25]. However, known exceptions are skin and lung, which constitutively express RAGE throughout life [25]. Most other cells, including monocytes/macrophages, endothelial cells, smooth muscle cells, peritoneal mesothelial cells, fibroblasts, podocytes, renal tubular cells, and neuronal cells, do not express significant amounts of RAGE under physiological conditions. However, they can be induced to express RAGE in situations where either ligands accumulate and/or transcription factors regulating RAGE are activated [12,13,22,26-30]. Cellular expression of RAGE can be induced by RAGE ligands themselves. Its expression can also increase in the absence of AGEs, for instance during inflammatory tissue remodelling or after direct cytokine stimulation by TNF- $\alpha$  [31].

### RAGE, A MULTILIGAND RECEPTOR

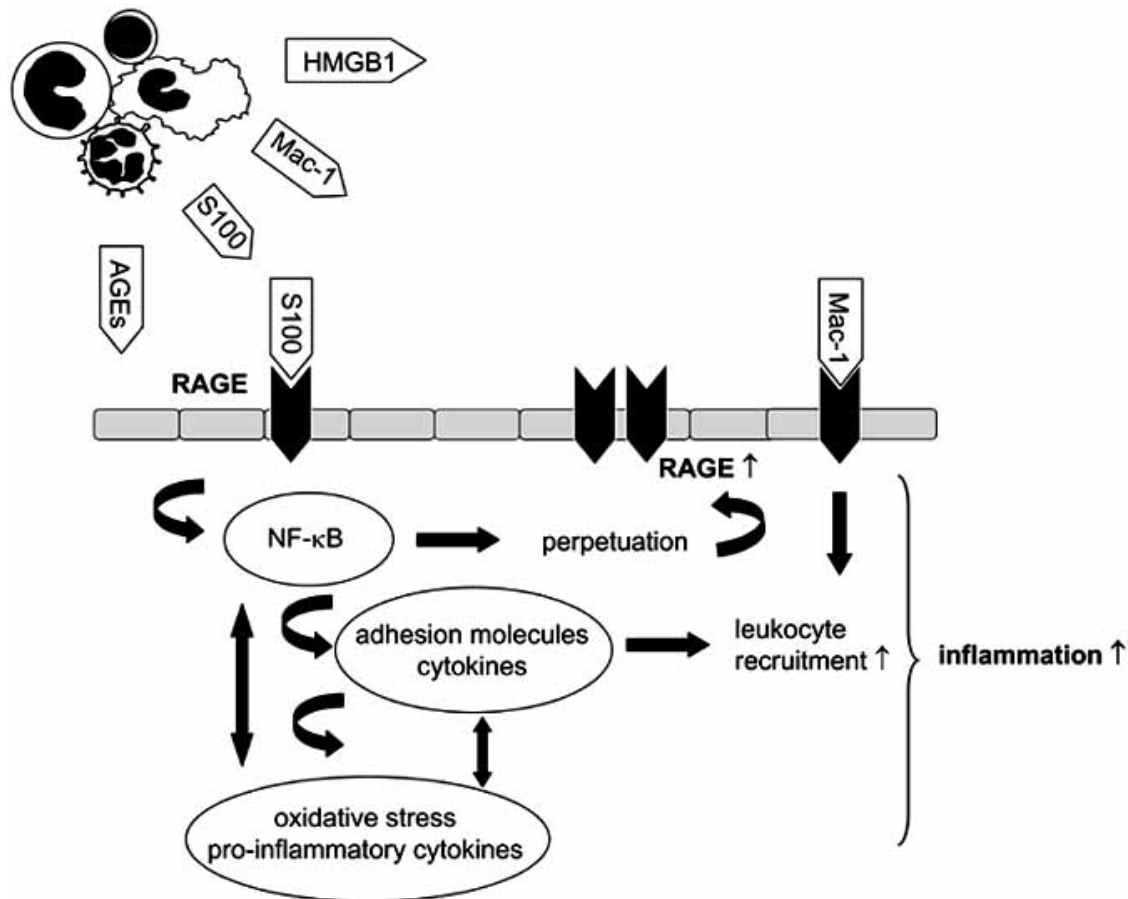
Shortly after RAGE was identified as a receptor for AGEs, it became evident that other ligands also interacted with the receptor [13,16,24,26,27,32-40]. Structural analysis of ligand-RAGE interaction revealed that RAGE recognized tertiary structures, such as  $\beta$ -sheets and fibrils, rather than specific amino acid sequences (i.e. primary structure) [13,41]. In addition to AGEs, RAGE can bind amyloid components (accumulating in Alzheimer's disease and systemic amyloidosis) [26,37,38]. Further ligands of RAGE are pro-inflammatory cytokine-like mediators of the S100/calgranulin family, which are closely related calcium-binding polypeptides with >20 yet identified members that accumulate extracellularly at sites of chronic inflammation [32,33]. Some members of the group including S100A8, S100A9, and S100A12 (calgranulin C) are released by stimulated phagocytes and may act as secretory cytokines. S100 molecules have been shown to activate endothelial cells, mononuclear phagocytes, and lymphocytes upon binding RAGE while inducing multiple proinflammatory responses, such as activation of NF- $\kappa$ B or increased cyclooxygenase (COX)-2 expression [42,43]. Another proinflammatory ligand of RAGE is the nuclear protein HMGB1 (high-mobility group B1; amphoterin) that is released upon cell necrosis (but not after apoptosis), during which HMGB1 is irreversibly bound to DNA. Extracellular HMGB1 exerts proinflammatory activities [24,34,35,44]. Besides binding ligands actively participating in chronic inflammatory and immune responses, RAGE also interacts with surface molecules on bacteria [36] and prions [40]. Recently, RAGE was identified as a new endothelial adhesion receptor for leukocyte integrins, promoting leukocyte recruitment and extravasation of infiltrating cells [27]. Thus, RAGE is much more than a receptor for AGEs, it has a broad repertoire of ligands, the latter of which share in common the propensity to accumulate in tissues during aging, chronic degenerative diseases and inflammatory disorders [35]. Therefore, RAGE is considered a pattern

recognition receptor (PRR) [16,27,28,41] engaging classes of molecules rather than individual ligands.

### RAGE-MEDIATED CELLULAR SIGNALING

Engagement of RAGE results in activation of intracellular signal transduction cascades, from which the majority has been shown to result in activation of the proinflammatory transcription factor NF- $\kappa$ B [45]. Following nuclear translocation, NF- $\kappa$ B binds to DNA-sequences and activates transcription of NF- $\kappa$ B regulated target genes, such as cytokines, adhesion molecules, prothrombotic and vasoconstrictive gene products [46]. RAGE-induced activation of NF- $\kappa$ B also amplifies RAGE expression *via* NF- $\kappa$ B-binding sites in the RAGE-promoter. One unique feature of RAGE dependent NF- $\kappa$ B activation is the perpetuation of NF- $\kappa$ B-activation through *de novo* synthesis of p65-mRNA. The latter results not only in sustained proinflammatory gene expression, but also maintains the auto-amplification of the proinflammatory signal *via* inducing RAGE expression [46-49]. Since NF- $\kappa$ B also controls a number of anti-apoptotic genes [46], NF- $\kappa$ B activation further provides a rapid and sensitive cellular response to ensure cell survival in the absence of new protein synthesis. Depending on the cell type RAGE may also stimulate necrosis, as RAGE-dependent mechanisms have been shown to contribute to remnant hepatocyte necrosis/apoptosis and failure of proliferation [50]. The failure to observe significant activation of hepatocyte NF- $\kappa$ B after 85% hepatectomy suggested that RAGE activation is prevented in the liver by yet not identified mechanisms, thereby leading to preferential activation of proapoptotic mechanisms and suppression of proliferation [50].

Furthermore, a number of studies have demonstrated that engagement of RAGE activates different cellular signaling pathways depending on the individual cell type. Activation of the mitogen-activated protein kinases (MAPK), including ERK1/2 (p44/p42) has been shown in smooth muscle cells [11], tubular epithelial cells [51], podocytes [52], chondrocytes [53], myoblasts [54], osteoblasts [55], and monocytic cells [43]. *In vitro* binding studies using human RAGE mutants with various C-terminal deletions identified the membrane-proximal cytoplasmic region of RAGE as an ERK docking site, thereby suggesting that ERK signaling occurs through direct ERK-RAGE interaction [56]. Activation of p38 and SAPK/JNK MAP kinases has been observed in monocytes/macrophages, dendritic cells, and tumor cells [54,57-59]. Furthermore, rho-GTPases, phosphoinositol-3-kinase, and the JAK/STAT pathway have been implicated in RAGE signaling [58,60-63]. In addition, RAGE-ligand interaction may directly induce generation of reactive oxygen species *via* NADPH oxidases and/or other yet not identified mechanisms [11,52,64]. Vice versa, stimulation of NADPH oxidases in endothelial cells generate reactive oxygen species (ROS), stimulate NF- $\kappa$ B and induce RAGE expression [65]. The diversity of signaling pathways identified in RAGE-mediated cellular signaling implies that different RAGE ligands might induce different pathways. A further matter of complexity in the RAGE network might be provided by cell specificity of RAGE-signaling. The consequences of such mechanisms may be critical if endogenous negative feedback pathways, responsible for returning



**Fig. (1).** RAGE-dependent mechanisms resulting in sustained inflammation. The interaction of various ligands with RAGE causes a perpetuated activation of the transcription factor NF- $\kappa$ B, up-regulation of RAGE, increased expression of adhesion molecules (ICAM, VCAM) and chemokines (MCP-1), release of pro-inflammatory cytokines (TNF- $\alpha$ ), and increased oxidative stress. In addition, RAGE acts as a counter-receptor for leukocytes by binding the  $\beta_2$ -integrin Mac-1, thereby promoting inflammatory cell recruitment.

cellular behavior to the quiescent state, are disturbed and pathways leading to cellular activation escalate.

### RAGE AND CELL ADHESION

RAGE is expressed on vascular endothelial cells and leukocytes, and plays a key role in inflammatory processes [16]. RAGE is not only involved in the regulation of NF- $\kappa$ B mediated cellular activation, but also functions as an adhesion receptor on endothelial cells during the recruitment of leukocytes into tissue [27,66]. The recruitment of leukocytes and their subsequent influx into surrounding tissues at sites of inflammation or injury is an integral part of the inflammatory process and requires multistep adhesive and signaling events [67,68]. Selectins, a family of three adhesion molecules expressed on leukocytes (L-selectin), endothelial cells (E-selectin and P-selectin) and platelets (P-selectin), mediate the capture and rolling of leukocytes along the endothelium [69]. Locally secreted chemokines (chemotactic cytokines) then trigger the activation of  $\beta_2$ -integrins which in turn mediate firm leukocyte arrest on the activated endothelium. During firm leukocyte arrest, members of the  $\beta_2$ -integrin family, (LFA-1 ( $\alpha$ L $\beta_2$ , CD11a/CD18) and Mac-1 ( $\alpha$ M $\beta_2$ , CD11b/CD18)) expressed on the leukocyte surface, interact with their endothelial counter-receptors such as ICAM-1 and VCAM-1. Whereas LFA-1 stabilizes the attachment of

leukocytes on the endothelium, Mac-1 also contributes to the emigration of leukocytes into tissue, suggesting that LFA-1 and Mac-1 serve sequential rather than parallel functions [29,70]. A recent study identified RAGE as adhesion receptor for the  $\beta_2$ -integrin Mac-1 [27,66], which at least partly explains the reduced number of emigrated leukocytes in RAGE<sup>-/-</sup> mice in the thioglycollate-induced peritonitis model [27]. This is supported by the finding, that RAGE-mediated leukocyte recruitment into the peritoneal cavity is more prominent in diabetic mice (where RAGE is up-regulated) compared to wild type mice [27]. In addition, RAGE-dependent leukocyte recruitment has also been shown in a mouse model of septic shock induced by cecal ligation and puncture (CLP). In the same model, RAGE<sup>-/-</sup> mice displayed a significant reduction of extravasated leukocytes [28]. Besides its role as Mac-1 ligand, RAGE could also exert its proinflammatory function by regulating the expression of endothelial adhesion molecules such as ICAM-1 and VCAM-1 [12]. In a mouse model of type 2 diabetes, apo E<sup>-/-</sup> db/db mice displayed RAGE-dependent enhanced expression of VCAM-1, tissue factor and matrix metalloproteinase (MMP)-9 antigen/activity in aortae compared to non-diabetic animals [71]. These results point to a role of RAGE and its ligands in different vascular diseases regulating leukocyte recruitment and adhesion molecule

expression in inflammatory processes. Antagonizing interactions between RAGE and  $\beta_2$ -integrins might provide a novel anti-inflammatory strategy in chronic inflammatory diseases associated with high RAGE expression [27].

### RAGE IN EXPERIMENTAL DISEASE MODELS

To better understand the role of RAGE in pathophysiological situations, interaction of ligands with cell surface RAGE was initially studied using soluble RAGE (sRAGE) antagonizing ligand interaction with RAGE and other RAGE-ligand recognizing cell surface receptors. Application of sRAGE *in vitro* and *in vivo* resulted in an effective blockade of RAGE in a range of animal models [12,13,32,41,58,72-82]. Mice receiving sRAGE displayed less micro- and macrovascular lesions [75,83-86], suggesting a key role for RAGE in the development of chronic vascular disorders. In models of accelerated atherosclerosis using apoE deficient mice or LDL-receptor deficient mice with streptozotocin-induced diabetes, sRAGE suppressed the accelerated atherosclerotic lesion and decreased the levels of VCAM-1 and NF- $\kappa$ B in the atherosclerotic vessel wall [75,86-89]. The blockade of RAGE failed to affect lipid or glucose plasma concentrations, thereby suggesting that RAGE acted downstream of these key risk factors [75]. Soluble RAGE prevented late complications of experimental diabetes in both autoimmune [77] and streptozotocin-induced diabetes [73,74]. Blockade of RAGE in peripheral wounds limited the inflammatory response, thereby accelerating wound closure and facilitating angiogenesis [72,78]. Rodents receiving sRAGE were protected from growth of primary tumors and metastases [58]. Blocking RAGE improved the outcome of experimental colitis in IL-10 deficient mice [32]. Soluble RAGE and anti-RAGE F(ab')<sub>2</sub>-fragments reduced Alzheimer's-like pathology in transgenic rodent models [80,81] and reduced the transport of amyloid- $\beta$ -peptide across the blood-brain barrier [90]. Since most of the data obtained with sRAGE were confirmed by application of neutralizing antibodies to the receptor and/or transfection with plasmids overexpressing dominant negative RAGE, the pattern recognition receptor RAGE has been suggested as a potentially effective therapeutic target [41,79,91]. Due to the variety of ligands recognized by RAGE, however, the observed beneficial effects might not only be a result of RAGE blockade, but rather of preventing ligand binding to RAGE and also to other cellular surface molecules.

The potential impact of RAGE blockade in diabetic complications and chronic inflammatory disease was therefore rigorously analyzed in homozygous RAGE-deficient mice (RAGE<sup>-/-</sup> mice) and mice with tissue-specific RAGE expression (tie2-RAGE and tie2-RAGExRAGE<sup>-/-</sup>) [82]. These mice are viable without any striking phenotype and display normal fertility [28,73,74,82,85]. In a murine model of arterial injury using femoral artery denudation, neointimal expansion was significantly decreased in RAGE<sup>-/-</sup> mice compared with that observed in wild type controls [85]. Induction of diabetes in RAGE<sup>-/-</sup> mice demonstrated that RAGE contributes, at least in part, to the development of diabetic complications. In experimental neuropathy, RAGE<sup>-/-</sup> mice were partially protected from diabetes-induced loss of neuronal function [74]. In diabetic nephropathy, charac-

terized by glomerular and tubular basement membrane thickening, mesangial extracellular matrix expansion, fibrotic changes, and albuminuria was increased in diabetic mice overexpressing RAGE in the vasculature [92], but significantly reduced in RAGE<sup>-/-</sup> mice [73]. RAGE<sup>-/-</sup> mice were also protected from increased inflammation, neoangiogenesis and fibrosis after long-term exposure to peritoneal dialysis fluids, promoting AGE-formation within the peritoneal cavity [93]. In a septic shock model caused by cecal ligation and puncture (CLP), which is largely dependent on the innate immunity, deletion of RAGE protected rodents from death [28]. Treatment of wild-type mice with sRAGE also improved survival, although the protective effect was not as effective as the RAGE deletion [28]. RAGE<sup>-/-</sup> mice displayed reduced NF- $\kappa$ B activity in key target organs of septic shock and increased survival.

In experimental autoimmune encephalomyelitis (EAE) blockade of RAGE either by sRAGE, anti-RAGE F(ab')<sub>2</sub> fragments, or the selective expression of dominant negative RAGE in T-cells suppressed the inflammatory response [94]. However, no significant protection was found compared with wild-type mice, when *Pasteurella-pneumotropica*-mediated EAE was induced in RAGE<sup>-/-</sup> mice [28]. In a delayed hypersensitivity (DTH) model, sRAGE significantly suppressed inflammation, while RAGE<sup>-/-</sup> mice were not protected from inflammation [26]. Moreover, treatment of RAGE<sup>-/-</sup> mice with sRAGE inhibited the inflammatory response to the same extent as in RAGE-bearing wild-type mice [28], implying that RAGE ligands rather than cell surface RAGE play a major role in the adaptive immune response [28]. Thus, ligands sequestered by sRAGE are likely to interact with additional cellular structures different from RAGE. Engaging sRAGE may therefore either target the cell surface receptor or function as a scavenger of RAGE ligands, thereby preventing their interaction with other putative cell surface receptors. These mechanisms may prove beneficial in a number of inflammatory responses. Taken together, the studies in RAGE<sup>-/-</sup> mice clearly demonstrate that RAGE participates in inflammation during innate immunity, whereas in adaptive immunity, RAGE ligands may be more important than RAGE itself.

### RAGE EXPRESSION IN HUMAN DISEASE

In patients with diabetes mellitus, RAGE is upregulated in many different tissues and contributes at least in part to the development of atherosclerosis and late diabetic complications [95]. Enhanced RAGE expression has been demonstrated in atherosclerotic plaques colocalized with cyclooxygenase-2 (Cox-2), prostaglandin E<sub>2</sub>, and matrix metalloproteinases, whereas RAGE expression was particularly pronounced in macrophages at vulnerable regions of the plaques [96].

The expression of RAGE is also increased in the human diabetic kidney [97]. The principal site of renal RAGE expression in diabetic patients is the podocyte, with virtually no expression of RAGE in the mesangium or in the tubules. Diabetes mellitus and chronic renal failure are also conditions with increased concentrations of AGEs in tissue and plasma [3,98,99]. In chronic renal failure, AGE levels increase independently of glycemia due to reduced metabolic

clearance, increased oxidative stress, and a higher rate of AGE precursor formation [100,101]. Interestingly, diabetic and non-diabetic nephropathies display different patterns of local AGE modification and distribution, thereby demonstrating an independent influence on the course of the disease [3,97,102].

In progressive chronic kidney disease (CKD), inappropriate chronic inflammation is present and reflects sustained activation of monocytes and macrophages [103]. RAGE expression is upregulated on peripheral blood monocytes from patients with CKD [103]. Enhanced RAGE expression may thereby amplify AGE-induced monocyte perturbation and contribute to monocyte-mediated systemic inflammation in CKD [103]. A variety of human RAGE gene polymorphisms have been identified and studied for their impact on disease development and progression [104-109]. Rudofsky reported a 63-bp deletion in the promoter of RAGE which correlates with a decreased risk for nephropathy in patients with type II diabetes [108]. Recently, patients from families characterized for insulin resistance were analyzed for RAGE gene polymorphism which revealed that the RAGE gene may affect the development of insulin resistance or be in linkage disequilibrium with a locus involved in this process [109].

Besides, activation of RAGE seems to contribute to the development and/or progression of human osteoarthritis and rheumatoid arthritis [110-112]. AGEs triggered the upregulation of RAGE on human chondrocytes and fibroblast-like synoviocytes, leading to increased catabolic activity and cartilage degradation [53,110]. Moreover, the proinflammatory RAGE ligand S100A11 was upregulated in human chondrocytes with osteoarthritis signaling through the RAGE/p38 MAPK pathway, thereby promoting inflammation-associated chondrocyte hypertrophy [113]. RAGE-dependent signaling has also been shown in inflammatory bowel diseases such as Crohn's disease and ulcerative colitis. Inflamed gut biopsy tissue demonstrated a significant upregulation of RAGE and increased NF- $\kappa$ B activation in adult patients with inflammatory bowel disease [114].

A role of RAGE has also been implicated in neurodegeneration. At least three major types of the RAGE isoforms (full length, C-truncated, and N-truncated) have been found in human brains as a result of alternative splicing [15]. Increases in RAGE protein expression and percentage of RAGE-expressing microglia have been demonstrated in human brains of patients with Alzheimers disease and paralleled the severity of the neurodegenerative disorder [15,80]. RAGE has also been reported in dying neurons in Huntington disease (HD). The RAGE expression paralleled the HD grade and neuronal cell death [115]. Increased RAGE expression has also been found in the frontal cortex in the early stages of Parkinsons disease [116].

So far, little is known on the physiologic function of endogenous sRAGE (sRAGE and esRAGE) found in plasma. When compared to healthy controls, levels of sRAGE were significantly reduced in the plasma of patients with Alzheimer disease [117]. Furthermore, plasma sRAGE levels were decreased in patients with coronary artery disease, hypertension and type 2 diabetes [118] while patients with type 1 diabetes demonstrated an increase in

plasmic sRAGE concentrations. In patients with rheumatoid arthritis, plasma levels of sRAGE were also reduced [111,112]. However, future prospective clinical studies will have to define the value of endogenous sRAGE as a predictive marker.

Similar to adults, increased formation and accumulation of AGEs also exist in children with type I diabetes mellitus and chronic renal failure [119-126]. Whereas RAGE itself has not been studied in pediatric diseases, recent experiments using unilateral ureteral obstruction (UO) in neonatal mice as model for congenital obstructive nephropathy, demonstrated that RAGE expression was early up-regulated following UO and may also contribute to leukocyte recruitment and interstitial inflammation in early development [29]. Furthermore, serum levels of RAGE-ligands, the glycoxidation products Nepsilon-(carboxymethyl)lysine (CML) and pentosidine are increased in children and adolescents with type 1 diabetes preceding the development of micro- and macrovascular complications. In addition, children with type 1 diabetes demonstrate increased oxidative stress, which is capable of stimulating RAGE expression and signaling [127]. Because RAGE expression is positively regulated by its ligands, accumulation of multiple RAGE ligands in pediatric diseases such as type 1 diabetes and chronic renal failure creates an environment for receptor-induced amplification of inflammation. Augmented deposition of RAGE-ligands may therefore be considered as a risk factor in these diseases. Similar to adults, continuous RAGE-ligand interactions may activate divergent signaling pathways, leading to NF- $\kappa$ B activation and sustained inflammation in a variety of chronic pediatric diseases.

## FUTURE DIRECTIONS

Several lines of evidence indicate that the RAGE/NF- $\kappa$ B axis plays a pivotal role in the development and progression of diabetic macro- and microvascular complications, aging, neurodegeneration, kidney diseases, and inflammation. The pattern recognition receptor RAGE is therefore an attractive target for future clinical interventions in a number of chronic diseases. However, its biological potential is yet to be completely tapped. Open questions remain regarding the long-term blockade of RAGE or its ligands, the identity of additional cell surface receptors, downstream signal transduction pathways, and possible differences in biological activity in humans versus animal models. Resolving these issues could provide novel mechanisms to tackle inflammation and chronic diseases.

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