

RAGE Signaling in Cell Adhesion and Inflammation

Bärbel Lange-Sperandio¹, Markus Sperandio¹, Peter Nawroth² and Angelika Bierhaus^{2,*}

Department of¹Pediatrics and²Internal Medicine I, University Heidelberg, 69120 Heidelberg, Germany

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, β -sheet-fibrils, HMGB1 (amphoterin) and the β_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- κ 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^{ras}, MAP kinases, and the NF- κ 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

*Address correspondence to this author at the Department of Medicine I, University of Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany; Tel: +49-6221 564752; Fax: +49-6221 564754; E-mail: angelika_bierhaus@med.uni-heidelberg.de

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- α [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 β -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- κ 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- κ B [45]. Following nuclear translocation, NF- κ B binds to DNA-sequences and activates transcription of NF- κ B regulated target genes, such as cytokines, adhesion molecules, prothrombotic and vasoconstrictive gene products [46]. RAGE-induced activation of NF- κ B also amplifies RAGE expression *via* NF- κ B-binding sites in the RAGE-promoter. One unique feature of RAGE dependent NF- κ B activation is the perpetuation of NF- κ 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- κ B also controls a number of anti-apoptotic genes [46], NF- κ 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- κ 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- κ 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

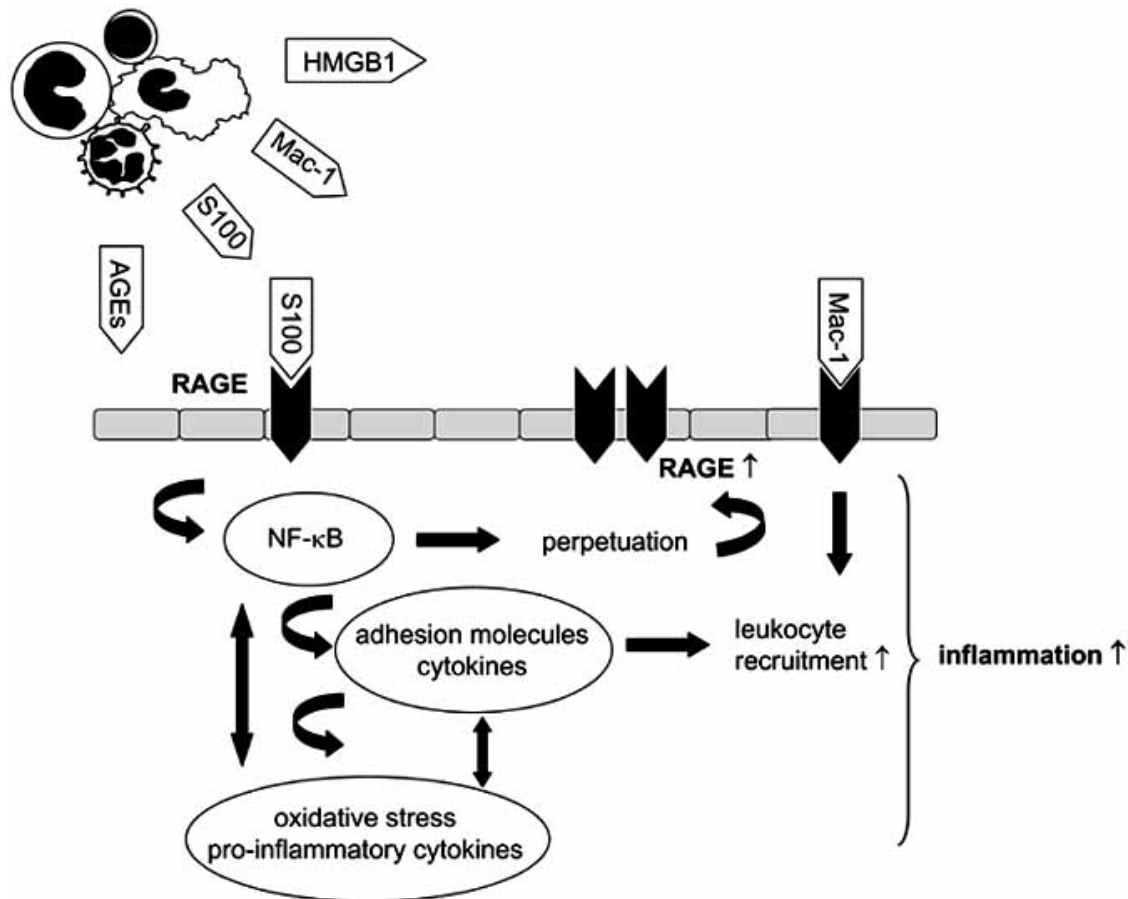


Fig. (1). RAGE-dependent mechanisms resulting in sustained inflammation. The interaction of various ligands with RAGE causes a perpetuated activation of the transcription factor NF- κ B, up-regulation of RAGE, increased expression of adhesion molecules (ICAM, VCAM) and chemokines (MCP-1), release of pro-inflammatory cytokines (TNF- α), and increased oxidative stress. In addition, RAGE acts as a counter-receptor for leukocytes by binding the β_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- κ 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 β_2 -integrins which in turn mediate firm leukocyte arrest on the activated endothelium. During firm leukocyte arrest, members of the β_2 -integrin family, (LFA-1 (α L β_2 , CD11a/CD18) and Mac-1 (α M β_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 β_2 -integrin Mac-1 [27,66], which at least partly explains the reduced number of emigrated leukocytes in RAGE^{-/-} 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^{-/-} 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^{-/-} 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 β_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- κ 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')₂-fragments reduced Alzheimer's-like pathology in transgenic rodent models [80,81] and reduced the transport of amyloid- β -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^{-/-} mice) and mice with tissue-specific RAGE expression (tie2-RAGE and tie2-RAGExRAGE^{-/-}) [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^{-/-} mice compared with that observed in wild type controls [85]. Induction of diabetes in RAGE^{-/-} mice demonstrated that RAGE contributes, at least in part, to the development of diabetic complications. In experimental neuropathy, RAGE^{-/-} 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^{-/-} mice [73]. RAGE^{-/-} 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^{-/-} mice displayed reduced NF- κ 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')₂ 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^{-/-} mice [28]. In a delayed hypersensitivity (DTH) model, sRAGE significantly suppressed inflammation, while RAGE^{-/-} mice were not protected from inflammation [26]. Moreover, treatment of RAGE^{-/-} 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^{-/-} 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 E₂, 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- κ 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- κ B activation and sustained inflammation in a variety of chronic pediatric diseases.

FUTURE DIRECTIONS

Several lines of evidence indicate that the RAGE/NF- κ 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.

ACKNOWLEDGEMENTS

This work was in part supported by grants from the Deutsche Forschungsgemeinschaft (La 1257/2-2 and SFB 405 to PPN), the European Foundation for the Study of Diabetes (AB), and the Juvenile Diabetes Research Foundation (AB, PPN).

REFERENCES

- [1] Bierhaus A, Humpert PM, Morcos M, *et al.* Understanding RAGE, the receptor for advanced glycation end products. *J Mol Med* 2005; 83(11): 876-886.
- [2] Ramasamy R, Vannucci SJ, Yan SS, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common

- thread in aging, diabetes, neurodegeneration, and inflammation. *Glycobiology* 2005; 15(7): 16R-28R.
- [3] Bohlender JM, Franke S, Stein G, Wolf G. Advanced glycation end products and the kidney. *Am J Physiol Renal Physiol* 2005; 289(4): F645-F659.
- [4] Ramasamy R, Yan SF, Schmidt AM. The RAGE axis and endothelial dysfunction: maladaptive roles in the diabetic vasculature and beyond. *Trends Cardiovasc Med* 2005; 15(7): 237-243.
- [5] Dyer DG, Dunn JA, Thorpe SR, *et al.* Accumulation of Maillard reaction products in skin collagen in diabetes and aging. *J Clin Invest* 1993; 91(6): 2463-2469.
- [6] Vlassara H, Bucala R, Striker L. Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. *Lab Invest* 1994; 70(2): 138-151.
- [7] Vlassara H, Brownlee M, Cerami A. Accumulation of diabetic rat peripheral nerve myelin by macrophages increases with the presence of advanced glycosylation endproducts. *J Exp Med* 1984; 160(1): 197-207.
- [8] 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(21): 14998-15004.
- [9] 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(21): 14987-14997.
- [10] Schmidt AM, Mora R, Cao R, *et al.* The endothelial cell binding site for advanced glycation end products consists of a complex: an integral membrane protein and a lactoferrin-like polypeptide. *J Biol Chem* 1994; 269(13): 9882-9888.
- [11] Lander HM, Tauras JM, Ogiste JS, Hori O, Moss RA, Schmidt AM. Activation of the receptor for advanced glycation end products triggers a p21(ras)-dependent mitogen-activated protein kinase pathway regulated by oxidant stress. *J Biol Chem* 1997; 272(28): 17810-17814.
- [12] Basta G, Lazzarini G, Massaro M, *et al.* Advanced glycation end products activate endothelium through signal-transduction receptor RAGE: a mechanism for amplification of inflammatory responses. *Circulation* 2002; 105(7): 816-822.
- [13] Bucciarelli LG, Wendt T, Rong L, *et al.* RAGE is a multiligand receptor of the immunoglobulin superfamily: implications for homeostasis and chronic disease. *Cell Mol Life Sci* 2002; 59(7): 1117-1128.
- [14] Schmidt AM, Yan SD, Brett J, Mora R, Nowygrad R, Stern D. Regulation of human mononuclear phagocyte migration by cell surface-binding proteins for advanced glycation end products. *J Clin Invest* 1993; 91(5): 2155-2168.
- [15] Lue LF, Yan SD, Stern DM, Walker DG. Preventing activation of receptor for advanced glycation endproducts in Alzheimer's disease. *Curr Drug Targets CNS Neurol Disord* 2005; 4(3): 249-266.
- [16] Schmidt AM, Yan SD, Yan SF, Stern DM. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. *J Clin Invest* 2001; 108(7): 949-955.
- [17] Sugaya K, Fukagawa T, Matsumoto K, *et al.* Three genes in the human MHC class III region near the junction with the class II: gene for receptor of advanced glycosylation end products, PBX2 homeobox gene and a notch homolog, human counterpart of mouse mammary tumor gene int-3. *Genomics* 1994; 23(2): 408-419.
- [18] Xu D, Kyriakis JM. Phosphatidylinositol 3'-kinase-dependent activation of renal mesangial cell Ki-Ras and ERK by advanced glycation end products. *J Biol Chem* 2003; 278(41): 39349-39355.
- [19] Malherbe P, Richards JG, Gaillard H, *et al.* cDNA cloning of a novel secreted isoform of the human receptor for advanced glycation end products and characterization of cells co-expressing cell-surface scavenger receptors and Swedish mutant amyloid precursor protein. *Brain Res Mol Brain Res* 1999; 71(2): 159-170.
- [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(Pt3): 1097-1109.
- [21] Schlueter C, Hauke S, Flohr AM, Rogalla P, Bullerdiek J. Tissue-specific expression patterns of the RAGE receptor and its soluble forms--a result of regulated alternative splicing? *Biochim Biophys Acta* 2003; 1630(1): 1-6.
- [22] Hanford LE, Enghild JJ, Valnickova Z, *et al.* Purification and characterization of mouse soluble receptor for advanced glycation end products (sRAGE). *J Biol Chem* 2004; 279(48): 50019-50024.
- [23] Park IH, Yeon SI, Youn JH, *et al.* Expression of a novel secreted splice variant of the receptor for advanced glycation end products (RAGE) in human brain astrocytes and peripheral blood mononuclear cells. *Mol Immunol* 2004; 40(16): 1203-1211.
- [24] Hori O, Brett J, Slattery T, *et al.* The receptor for advanced glycation end products (RAGE) is a cellular binding site for amphoterin. Mediation of neurite outgrowth and co-expression of rage and amphoterin in the developing nervous system. *J Biol Chem* 1995; 270(43): 25752-25761.
- [25] Brett J, Schmidt AM, Yan SD, *et al.* Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. *Am J Pathol* 1993; 143(6): 1699-1712.
- [26] Du YS, Zhu H, Fu J, *et al.* Amyloid-beta peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: a pro-inflammatory pathway in Alzheimer disease. *Proc Natl Acad Sci U S A* 1997; 94(10): 5296-5301.
- [27] 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(10): 1507-1515.
- [28] Liliensiek B, Weigand MA, Bierhaus A, *et al.* Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response. *J Clin Invest* 2004; 113(11): 1641-1650.
- [29] Lange-Sperandio B, Schimpfen K, Rodenbeck B, *et al.* Distinct roles of Mac-1 and its counter-receptors in neonatal obstructive nephropathy. *Kidney Int* 2006; 69(1): 81-88.
- [30] Lai KN, Leung JC, Chan LY, *et al.* Differential expression of receptors for advanced glycation end-products in peritoneal mesothelial cells exposed to glucose degradation products. *Clin Exp Immunol* 2004; 138(3): 466-475.
- [31] Tanaka N, Yonekura H, Yamagishi S, Fujimori H, Yamamoto Y, Yamamoto H. The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-alpha through nuclear factor-kappa B, and by 17beta-estradiol through Sp-1 in human vascular endothelial cells. *J Biol Chem* 2000; 275(33): 25781-25790.
- [32] Hofmann MA, Drury S, Fu C, *et al.* RAGE mediates a novel pro-inflammatory axis: a central cell surface receptor for S100/calgranulin polypeptides. *Cell* 1999; 97(7): 889-901.
- [33] 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(4): 1111-1122.
- [34] Andersson U, Tracey KJ. HMGB1 in sepsis. *Scand J Infect Dis* 2003; 35(9): 577-584.
- [35] Treutiger CJ, Mullins GE, Johansson AS, *et al.* High mobility group 1 B-box mediates activation of human endothelium. *J Intern Med* 2003; 254(4): 375-385.
- [36] Chapman MR, Robinson LS, Pinkner JS, *et al.* Role of *Escherichia coli* curli operons in directing amyloid fiber formation. *Science* 2002; 295(5556): 851-855.
- [37] Yan SD, Chen X, Fu J, *et al.* RAGE and amyloid-beta peptide neurotoxicity in Alzheimer's disease. *Nature* 1996; 382(6593): 685-691.
- [38] Yan SD, Zhu H, Zhu A, *et al.* Receptor-dependent cell stress and amyloid accumulation in systemic amyloidosis. *Nat Med* 2000; 6(6): 643-651.
- [39] Wang H, Bloom O, Zhang M, *et al.* HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 1999; 285(5425): 248-251.
- [40] Sasaki N, Takeuchi M, Chowei H, *et al.* Advanced glycation end products (AGE) and their receptor (RAGE) in the brain of patients with Creutzfeldt-Jakob disease with prion plaques. *Neurosci Lett* 2002; 326(2): 117-120.
- [41] Schmidt AM, Yan SD, Yan SF, Stern DM. The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. *J Clin Invest* 2001; 108(7): 949-955.

- [42] Roth J, Vogl T, Sunderkotter C, Sorg C. Chemotactic activity of S100A8 and S100A9. *J Immunol* 2003; 171(11): 5651.
- [43] Shanmugam N, Kim YS, Lanting L, Natarajan R. Regulation of cyclooxygenase-2 expression in monocytes by ligation of the receptor for advanced glycation end products. *J Biol Chem* 2003; 278(37): 34834-34844.
- [44] Begany DP, Carcillo JA, Herzer WA, Mi Z, Jackson EK. Inhibition of type IV phosphodiesterase by Ro 20-1724 attenuates endotoxin-induced acute renal failure. *J Pharmacol Exp Ther* 1996; 278(1): 37-41.
- [45] Bierhaus A, Schiekofer S, Schwaninger M, *et al.* Diabetes-associated sustained activation of the transcription factor nuclear factor-kappaB. *Diabetes* 2001; 50(12): 2792-2808.
- [46] Barnes PJ, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; 336(15): 1066-1071.
- [47] Li J, Schmidt AM. Characterization and functional analysis of the promoter of RAGE, the receptor for advanced glycation end products. *J Biol Chem* 1997; 272(26): 16498-16506.
- [48] Bierhaus A, Chen J, Liliensiek B, Nawroth PP. LPS and cytokine-activated endothelium. *Semin Thromb Hemost* 2000; 26(5): 571-587.
- [49] Schiekofer S, Balletshofer B, Andrassy M, Bierhaus A, Nawroth PP. Endothelial dysfunction in diabetes mellitus. *Semin Thromb Hemost* 2000; 26(5): 503-511.
- [50] Cataldegirmen G, Zeng S, Feirt N, *et al.* RAGE limits regeneration after massive liver injury by coordinated suppression of TNF-alpha and NF-kappaB. *J Exp Med* 2005; 201(3): 473-484.
- [51] Li JH, Wang W, Huang XR, *et al.* Advanced glycation end products induce tubular epithelial-myofibroblast transition through the RAGE-ERK1/2 MAP kinase signaling pathway. *Am J Pathol* 2004; 164(4): 1389-1397.
- [52] Gu L, Hagiwara S, Fan Q, *et al.* Role of receptor for advanced glycation end-products and signalling events in advanced glycation end-product-induced monocyte chemoattractant protein-1 expression in differentiated mouse podocytes. *Nephrol Dial Transplant* 2006. Feb; 21(2): 299-313. Epub 2005 Nov 1.
- [53] Loeser RF, Yammani RR, Carlson CS, *et al.* Articular chondrocytes express the receptor for advanced glycation end products: Potential role in osteoarthritis. *Arthritis Rheum* 2005; 52(8): 2376-2385.
- [54] Sorci G, Riuzzi F, Agneletti AL, Marchetti C, Donato R. S100B causes apoptosis in a myoblast cell line in a RAGE-independent manner. *J Cell Physiol* 2004; 199(2): 274-283.
- [55] Cortizo AM, Lettieri MG, Barrio DA, Mercer N, Etcheverry SB, McCarthy AD. Advanced glycation end-products (AGEs) induce concerted changes in the osteoblastic expression of their receptor RAGE and in the activation of extracellular signal-regulated kinases (ERK). *Mol Cell Biochem* 2003; 250(1-2): 1-10.
- [56] 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(1-3): 107-113.
- [57] Yeh CH, Sturgis L, Haidacher J, *et al.* Requirement for p38 and p44/p42 mitogen-activated protein kinases in RAGE-mediated nuclear factor-kappaB transcriptional activation and cytokine secretion. *Diabetes* 2001; 50(6): 1495-1504.
- [58] Taguchi A, Blood DC, del Toro G, *et al.* Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases. *Nature* 2000; 405(6784): 354-360.
- [59] Ge J, Jia Q, Liang C, *et al.* Advanced glycosylation end products might promote atherosclerosis through inducing the immune maturation of dendritic cells. *Arterioscler Thromb Vasc Biol* 2005; 25(10): 2157-2163.
- [60] 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(28): 19919-19924.
- [61] 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(1): 102-113.
- [62] Hasegawa T, Kosaki A, Kimura T, *et al.* The regulation of EN-RAGE (S100A12) gene expression in human THP-1 macrophages. *Atherosclerosis* 2003; 171(2): 211-218.
- [63] Brizzi MF, Dentelli P, Rosso A, *et al.* *FASEB J* 2004; 18(11): 1249-1251.
- [64] Wautier MP, Chappey O, Corda S, Stern DM, Schmidt AM, Wautier JL. Activation of NADPH oxidase by AGE links oxidant stress to altered gene expression via RAGE. *Am J Physiol Endocrinol Metab* 2001; 280(5): E685-E694.
- [65] Mukherjee TK, Mukhopadhyay S, Hoidal JR. The role of reactive oxygen species in TNFalpha-dependent expression of the receptor for advanced glycation end products in human umbilical vein endothelial cells. *Biochim Biophys Acta* 2005; 1744(2): 213-223.
- [66] Chavakis T, Bierhaus A, Nawroth PP. RAGE (receptor for advanced glycation end products): a central player in the inflammatory response. *Microbes Infect* 2004; 6(13): 1219-1225.
- [67] Butcher EC. Leukocyte-endothelial cell recognition - Three (or more) steps to specificity and diversity. *Cell* 1991; 67: 1033-1036.
- [68] Springer TA. Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. *Annu Rev Physiol* 1995; 57: 827-872.
- [69] Vestweber D, Blanks JE. Mechanisms that regulate the function of the selectins and their ligands. *Physiol Rev* 1999; 79(1): 181-213.
- [70] Dunne JL, Collins RG, Beaudet AL, Ballantyne CM, Ley K. Mac-1, but not LFA-1, uses intercellular adhesion molecule-1 to mediate slow leukocyte rolling in TNF-alpha-induced inflammation. *J Immunol* 2003; 171(11): 6105-6111.
- [71] Wendt T, Harja E, Bucciarelli L, *et al.* RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. *Atherosclerosis* 2005 Mar; 185(1):70-7. Epub 2005 Aug 1.
- [72] Lalla E, Lamster IB, Stern DM, Schmidt AM. Receptor for advanced glycation end products, inflammation, and accelerated periodontal disease in diabetes: mechanisms and insights into therapeutic modalities. *Ann Periodontol* 2001; 6(1): 113-118.
- [73] 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(4): 1123-1137.
- [74] 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(12): 1741-1751.
- [75] 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(9): 1025-1031.
- [76] Drinda S, Franke S, Ruster M, *et al.* Identification of the receptor for advanced glycation end products in synovial tissue of patients with rheumatoid arthritis. *Rheumatol Int* 2005; 25(6): 411-413.
- [77] Chen Y, Yan SS, Colgan J, *et al.* Blockade of late stages of autoimmune diabetes by inhibition of the receptor for advanced glycation end products. *J Immunol* 2004; 173(2): 1399-1405.
- [78] Goova MT, Li J, Kislinger T, *et al.* Blockade of receptor for advanced glycation end-products restores effective wound healing in diabetic mice. *Am J Pathol* 2001; 159(2): 513-525.
- [79] Hudson BI, Schmidt AM. RAGE: a novel target for drug intervention in diabetic vascular disease. *Pharm Res* 2004; 21(7): 1079-1086.
- [80] Lue LF, Walker DG, Brachova L, *et al.* Involvement of microglial receptor for advanced glycation endproducts (RAGE) in Alzheimer's disease: identification of a cellular activation mechanism. *Exp Neurol* 2001; 171(1): 29-45.
- [81] Arancio O, Zhang HP, Chen X, *et al.* RAGE potentiates Abeta-induced perturbation of neuronal function in transgenic mice. *EMBO J* 2004; 23(20): 4096-4105.
- [82] Constien R, Forde A, Liliensiek B, *et al.* Characterization of a novel EGFP reporter mouse to monitor Cre recombination as demonstrated by a Tie2 Cre mouse line. *Genesis* 2001; 30(1): 36-44.
- [83] 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(4): 1123-1137.

- [84] 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(12): 1741-1751.
- [85] Sakaguchi T, Yan SF, Yan SD, *et al.* Central role of RAGE-dependent neointimal expansion in arterial restenosis. *J Clin Invest* 2003; 111(7): 959-972.
- [86] Kislinger T, Tanji N, Wendt T, *et al.* Receptor for advanced glycation end products mediates inflammation and enhanced expression of tissue factor in vasculature of diabetic apolipoprotein E-null mice. *Arterioscler Thromb Vasc Biol* 2001; 21(6): 905-910.
- [87] Yan SF, Ramasamy R, Naka Y, Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. *Circ Res* 2003; 93(12): 1159-1169.
- [88] Jandeleit-Dahm K, Lassila M, Davis BJ, *et al.* Anti-atherosclerotic and renoprotective effects of combined angiotensin-converting enzyme and neutral endopeptidase inhibition in diabetic apolipoprotein E-knockout mice. *J Hypertens* 2005; 23(11): 2071-2082.
- [89] Jandeleit-Dahm KA, Lassila M, Allen TJ. Advanced glycation end products in diabetes-associated atherosclerosis and renal disease: interventional studies. *Ann N Y Acad Sci* 2005; 1043: 759-766.
- [90] Mackic JB, Stins M, McComb JG, *et al.* Human blood-brain barrier receptors for Alzheimer's amyloid-beta 1-40. Asymmetrical binding, endocytosis, and transcytosis at the apical side of brain microvascular endothelial cell monolayer. *J Clin Invest* 1998; 102(4):734-743.
- [91] Hudson BI, Bucciarelli LG, Wendt T, *et al.* Blockade of receptor for advanced glycation endproducts: a new target for therapeutic intervention in diabetic complications and inflammatory disorders. *Arch Biochem Biophys* 2003; 419(1): 80-88.
- [92] Yamamoto Y, Kato I, Doi T, *et al.* Development and prevention of advanced diabetic nephropathy in RAGE-overexpressing mice. *J Clin Invest* 2001; 108(2): 261-268.
- [93] Schwenger V, Morath C, Salava A, *et al.* Damage to the peritoneal membrane by glucose degradation products is mediated by the receptor for advanced glycation end-products. *J Am Soc Nephrol* 2006; 17(1): 199-207.
- [94] Yan SS, Wu ZY, Zhang HP, *et al.* Suppression of experimental autoimmune encephalomyelitis by selective blockade of encephalitogenic T-cell infiltration of the central nervous system. *Nat Med* 2003; 9(3): 287-293.
- [95] Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; 54(6): 1615-1625.
- [96] Cipollone F, Iezzi A, Fazio M, *et al.* The receptor RAGE as a progression factor amplifying arachidonate-dependent inflammatory and proteolytic response in human atherosclerotic plaques: role of glyceemic control. *Circulation* 2003; 108(9): 1070-1077.
- [97] Tanji N, Markowitz GS, Fu C, *et al.* Expression of advanced glycation end products and their cellular receptor RAGE in diabetic nephropathy and nondiabetic renal disease. *J Am Soc Nephrol* 2000; 11(9): 1656-1666.
- [98] Makita Z, Radoff S, Rayfield EJ, *et al.* Advanced glycosylation end products in patients with diabetic nephropathy. *N Engl J Med* 1991; 325(12): 836-842.
- [99] Vlassara H. Advanced glycation in health and disease: role of the modern environment. *Ann N Y Acad Sci* 2005; 1043: 452-460.
- [100] Miyata T, Horie K, Ueda Y, *et al.* Advanced glycation and lipidoxidation of the peritoneal membrane: respective roles of serum and peritoneal fluid reactive carbonyl compounds. *Kidney Int* 2000; 58(1): 425-435.
- [101] Miyata T, Sugiyama S, Suzuki D, Inagi R, Kurokawa K. Increased carbonyl modification by lipids and carbohydrates in diabetic nephropathy. *Kidney Int Suppl* 1999; 71: S54-S56.
- [102] Suzuki D, Miyata T, Saotome N, *et al.* Immunohistochemical evidence for an increased oxidative stress and carbonyl modification of proteins in diabetic glomerular lesions. *J Am Soc Nephrol* 1999; 10(4): 822-832.
- [103] Hou FF, Ren H, Owen WF, *et al.* Enhanced expression of receptor for advanced glycation end products in chronic kidney disease. *J Am Soc Nephrol* 2004; 15(7): 1889-1896.
- [104] Hudson BI, Stickland MH, Grant PJ, Futers TS. Characterization of allelic and nucleotide variation between the RAGE gene on chromosome 6 and a homologous pseudogene sequence to its 5' regulatory region on chromosome 3: implications for polymorphic studies in diabetes. *Diabetes* 2001; 50(12): 2646-2651.
- [105] Hudson BI, Stickland MH, Futers TS, Grant PJ. Study of the -429 T/C and -374 T/A receptor for advanced glycation end products promoter polymorphisms in diabetic and nondiabetic subjects with macrovascular disease. *Diabetes Care* 2001; 24(11): 2004.
- [106] 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(6): 1505-1511.
- [107] 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(7): 1155-1157.
- [108] Rudofsky G Jr, Isermann B, Schilling T, *et al.* A 63bp deletion in the promoter of rage correlates with a decreased risk for nephropathy in patients with type 2 diabetes. *Exp Clin Endocrinol Diabetes* 2004; 112(3): 135-141.
- [109] Sullivan CM, Futers TS, Barrett JH, Hudson BI, Freeman MS, Grant PJ. RAGE polymorphisms and the heritability of insulin resistance: the Leeds family study. *Diab Vasc Dis Res* 2005; 2(1): 42-44.
- [110] Steenvoorden MM, Huizinga TW, Verzijl N, *et al.* Activation of receptor for advanced glycation end products in osteoarthritis leads to increased stimulation of chondrocytes and synoviocytes. *Arthritis Rheum* 2006; 54(1): 253-263.
- [111] Pullerits R, Bokarewa M, Dahlberg L, Tarkowski A. Decreased levels of soluble receptor for advanced glycation end products in patients with rheumatoid arthritis indicating deficient inflammatory control. *Arthritis Res Ther* 2005; 7(4): R817-R824.
- [112] Moser B, Hudson BI, Schmidt AM. Soluble RAGE: a hot new biomarker for the hot joint? *Arthritis Res Ther* 2005; 7(4): 142-144.
- [113] Cecil DL, Johnson K, Rediske J, Lotz M, Schmidt AM, Terkeltaub R. Inflammation-induced chondrocyte hypertrophy is driven by receptor for advanced glycation end products. *J Immunol* 2005; 175(12): 8296-8302.
- [114] Andrassy M, Igwe J, Autschbach F, *et al.* Posttranslationally modified proteins as mediators of sustained intestinal inflammation. *Am J Pathol* 2006; 169(4): 1223-1237.
- [115] Ma L, Nicholson LF. Expression of the receptor for advanced glycation end products in Huntington's disease caudate nucleus. *Brain Res* 2004; 1018(1): 10-17.
- [116] Dalfo E, Portero-Otin M, Ayala V, Martinez A, Pamplona R, Ferrer I. Evidence of oxidative stress in the neocortex in incidental Lewy body disease. *J Neuropathol Exp Neurol* 2005; 64(9): 816-830.
- [117] Emanuele E, D'Angelo A, Tomaino C, *et al.* Circulating levels of soluble receptor for advanced glycation end products in Alzheimer disease and vascular dementia. *Arch Neurol* 2005; 62(11):1734-1736.
- [118] 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(9):1725-1729.
- [119] Hwang JS, Shin CH, Yang SW. Clinical implications of N epsilon-(carboxymethyl)lysine, advanced glycation end product, in children and adolescents with type 1 diabetes. *Diabetes Obes Metab* 2005; 7(3): 263-267.
- [120] Galler A, Muller G, Schinzel R, Kratzsch J, Kiess W, Munch G. Impact of metabolic control and serum lipids on the concentration of advanced glycation end products in the serum of children and adolescents with type 1 diabetes, as determined by fluorescence spectroscopy and nepsilon-(carboxymethyl)lysine ELISA. *Diabetes Care* 2003; 26(9): 2609-2615.
- [121] Berg TJ, Clausen JT, Torjesen PA, Dahl-Jorgensen K, Bangstad HJ, Hanssen KF. The advanced glycation end product Nepsilon-(carboxymethyl)lysine is increased in serum from children and adolescents with type 1 diabetes. *Diabetes Care* 1998; 21(11): 1997-2002.
- [122] Nicoloff G, Baydanoff S, Petrova C, Christova P. Antibodies to advanced glycation end products in children with diabetes mellitus. *Vascul Pharmacol* 2002; 39(1-2): 39-45.

- [123] Misselwitz J, Franke S, Kauf E, John U, Stein G. Advanced glycation end products in children with chronic renal failure and type 1 diabetes. *Pediatr Nephrol* 2002; 17(5): 316-321.
- [124] Sebekova K, Podracka L, Blazicek P, Syrova D, Heidland A, Schinzel R. Plasma levels of advanced glycation end products in children with renal disease. *Pediatr Nephrol* 2001; 16(12): 1105-1112.
- [125] Sebekova K, Podracka L, Heidland A, Schinzel R. Enhanced plasma levels of advanced glycation end products (AGE) and pro-inflammatory cytokines in children/adolescents with chronic renal insufficiency and after renal replacement therapy by dialysis and transplantation--are they inter-related? *Clin Nephrol* 2001; 56(6): S21-S26.
- [126] Bayazit AK, Vogt BA, Dell KM, *et al.* Effect of the peritoneal dialysis prescription on pentosidine in children. *Pediatr Nephrol* 2003; 18(10): 1049-1054.
- [127] Varvarovska J, Racek J, Stetina R, *et al.* Aspects of oxidative stress in children with type 1 diabetes mellitus. *Biomed Pharmacother* 2004; 58(10): 539-545.

Received: 16 June, 2006

Revised: 12 September, 2006

Accepted: 14 October, 2006