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Receptor for Advanced Glycation End Products:

Fundamental Roles in the Inflammatory Response: Winding the Way to the Pathogenesis of Endothelial Dysfunction and Atherosclerosis

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Abstract

The multiligand receptor for advanced glycation end products (RAGE) of the immunoglobulin superfamily is expressed onmultiple cell types implicated in the immune–inflammatory response and in atherosclerosis. Multiple studies have elucidated that ligand–RAGE interaction on cells, such as monocytes, macrophages, and endothelial cells, mediates cellular migration and upregulation of proinflammatory and prothrombotic molecules. In addition, recent studies reveal definitive rules for RAGE in effective T lymphocyte priming *in vivo*. RAGE ligand AGEs may be formed in diverse settings; although AGEs are especially generated in hyperglycemia, their production in settings characterized by oxidative stress and inflammation suggests that these species, in part via RAGE, may contribute to the pathogenesis of atherosclerosis. In murine models of atherosclerosis, vascular inflammation is a key factor and one which is augmented, in parallel with even further increases in RAGE ligands, in diabetic macrovessels. The findings that antagonism and genetic disruption of RAGE in atherosclerosis-susceptible mice strikingly reduces vascular inflammation and atherosclerotic lesion area and complexity link RAGE intimately to these processes and suggest that RAGE is a logical target for therapeutic intervention in aberrant inflammatory mechanisms and in atherosclerosis.

Keywords

receptor for advanced glycation end products; inflammation; atherosclerosis; adaptive immunity; T cell priming

RAGE: A Multiligand Receptor

Our evolving understanding of the biology of the receptor for advanced glycation end products (RAGE) has been facilitated by the demonstration that RAGE is a multiligand member of the immunoglobulin superfamily. [1] RAGE was first described as a receptor for the products of nonenzymatic glycation and oxidation of proteins, the advanced glycation

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Conflict of Interest
The authors declare no conflicts of interest.

end products or AGEs.2 Although initially considered as modified species that are formed to accelerated degrees in hyperglycemia, it has been shown that AGE formation may be stimulated even in normoglycemia. For example, stresses, such as renal failure, oxidative stress, inflammation, and aging, may provoke AGE generation.1

In addition to AGEs, natural ligands of the receptor, including certain members of the S100/calgranulin family3,4 and amphoterin (or high mobility group box-1 [HMGB1]),5,6 also interact with RAGE. Interestingly, HMGB1 was originally described as an intracellular (nuclear) protein. Its release by stimulated cells, however, suggested new roles for this molecule in inflammation and cell stress.7 Interaction of HMGB1 with RAGE increases expression of proinflammatory molecules. *In vivo* studies supported the critical role of HMGB1 and RAGE in inflammation. For example, blockade of either ligand–RAGE interaction or HMGB1 (in the latter case, using antibodies to HMGB1) suppressed inflammation in a rodent model of inflammatory arthritis.[8,9] Indeed, intra-articular injection of HMGB1 was sufficient to induce arthritis in rodents.10

Furthermore, RAGE has been shown to be a receptor for Mac-1, thus establishing additional mechanisms by which ligation of RAGE may mediate inflammatory cell migration and activation in susceptible foci.[11] Taken together, these lessons, learned from the multiligand nature of RAGE, suggest it plays key roles in the inflammatory response.

RAGE Is a Signal Transduction Receptor

A central mechanism by which ligand–RAGE interaction mediates cell stress and upregulates inflammatory pathways is via activation of signal transduction pathways. Multiple signaling pathways have been shown to be activated by RAGE. For example, ligand–RAGE interaction stimulates activation of mitogen-activated protein kinases (MAP kinases) such as p44/42, p38, and JNK MAPK.[12,13] Further, activation of Jak/STAT pathways, rho and rac GTPases, and $p21^{ras}$ have been linked to RAGE.[14–16] Definitive studies both *in vitro* and *in vivo* indicate that the impact of RAGE ligands is due to activation of signal transduction. When the cytoplasmic domain of RAGE is deleted, resulting in a construct in which ligands may bind at the extracellular domain, the loss of the intracellular domain evokes a dominant negative (DN) effect such that when ligands bind RAGE, they are unable to modulate gene expression in the absence of interaction with intracellular signaling partners.

The variety of signaling pathways triggered by RAGE ligands likely reflects both the specific cell type and the time course and duration of activation. RAGE is expressed by multiple cell types at low levels in homeostasis across a varied array of cell types.[17] In most cases, expression of RAGE is upregulated in disease states, such as in diabetic aorta, kidney, and retina.[18–20] Interestingly, in lung tissue even at base line, high levels of RAGE expression have been observed. The precise roles for RAGE in lung homeostasis and disease have yet to be elucidated.

RAGE and Inflammation: First Insights in Animal Models

The discovery of S100/calgranulins and HMGB1 as RAGE ligands shed first light on potential roles for RAGE in diabetes-independent inflammatory responses. We and others used soluble RAGE (sRAGE), the extracellular ligand-binding decoy of RAGE, and $F(ab')_2$ fragments prepared from anti-RAGE IgG or anti-S100A12 IgG to test if blockade of the ligand–RAGE interaction suppressed delayed type hypersensitivity reactions in mice sensitized and challenged with methylated bovine serum albumin. Compared to appropriate vehicles and controls, blockade of ligand–RAGE suppressed the challenge phase of footpad edema. Infiltration of inflammatory cells, granuloma formation, and edema responses were

significantly suppressed in the presence of such blockade.3 Consistent with marked suppression of proinflammatory mechanisms, nuclear extracts retrieved from the treated mouse food pads revealed strikingly diminished activation of nuclear factor kappa B (NF-κB).[3] In other experiments, Interleukin (IL)-10-deficient mice displayed significantly reduced gut inflammation and activation of NF-κB when treated with sRAGE compared to treatment with a vehicle.3

These studies suggested for the first time that RAGE played important roles in the immune response. In this review, representative experiments underscoring such roles for RAGE in immunity are discussed.

Roles for RAGE in the Pathogenesis of Type 1 Diabetes

T lymphocytes play essential roles in the pathogenesis of autoimmune diabetes. In addition to macrophages, RAGE is expressed in $CD4^+$ and $CD8^+$ T lymphocytes and B lymphocytes.[21] Roles for RAGE in inflammation linked to the pathogenesis of type 1 diabetes were established by administration of sRAGE to nonobese diabetic (NOD)/scid mice subjected to adoptive transfer of diabetogenic spleen cells (from NOD mice). Upon transfer of these splenocytes, increased expression of both RAGE and proinflammatory S100A12 in the islets was observed.

When the mice receiving diabetogenic splenocytes were treated with sRAGE, a significantly increased time to hyperglycemia was noted. In addition to delays in development of diabetes, downregulation of IL-1β and tumor necrosis factor (TNF)-α in the islet tissue was observed compared to vehicle treatment. Further, IL-10 and TGF-β transcripts were increased in the islets in the presence of sRAGE compared to vehicle treatment.[21]

These experiments established for the first time that RAGE might play roles in the pathogenesis of type 1 diabetes and linked this receptor to tissue-damaging inflammation.

Roles for RAGE in the Alloimmune Response

Based on these findings in NOD mice, we sought to extend these concepts and probe if RAGE contributed to alloimmune responses in organ transplantation. We employed an established model of heterotopic allogeneic heart transplantation in which fully mismatched grafts (donor,$H2^q$) were transplanted into C57BL/6 recipients ($H2^b$). sRAGE was administered to the animals and graft survival was assessed. The mean graft survival time in vehicle phosphate-buffered saline solution-treated mice was 7.3±0.7 days. However, mice treated with 100μg/day sRAGE displayed significantly increased graft survival at 11.7±1.7 days. At a higher dose of sRAGE (200μg/day), even greater graft survival time was observed (19.5±2.8 days).[22]

Extensive analysis of the allograft tissue samples revealed that inflammatory cell infiltration (especially that of T lymphocytes), expression of RAGE and its ligands, edema, and necrosis in the sRAGE-treated hearts were greatly reduced. To directly probe roles for RAGE in alloimmune responses relevant to this setting, purified T cells and MHC class II^+ antigen-presenting cells (APCs) were retrieved from MHC-mismatched mice. Incubation with sRAGE resulted in a dose-dependent decrease in lymphocyte proliferation versus IgG control-treated cultures. In addition, cells in the mouse allogeneic mixed lymphocyte culture were incubated with blocking antibodies to RAGE. Compared to non-immune IgG, incubation with monoclonal anti-RAGE IgG resulted in a significant dose-dependent decrease in lymphocyte proliferation.[22] Similar results using sRAGE and antibodies to RAGE were observed in human mixed-lymphocyte reaction responses *in vitro*.[22]

Roles for RAGE in Experimental Autoimmune Encephalomyelitis: Implications for Roles for RAGE in T Lymphocyte Migration

One key feature of RAGE-dependent roles in the inflammatory response implicates this receptor in T lymphocyte migration and infiltration into vulnerable foci. These concepts were tested in a murine model of experimental autoimmune encephalomyelitis (EAE). Administration of sRAGE suppressed EAE induced by myelin basic protein (MBP) or when EAE occurred spontaneously in T cell receptor (TCR)-transgenic mice devoid of endogenous TCR-alpha and TCR-beta chains. These studies revealed that in sRAGE-treated animals, significantly decreased infiltration of the spinal cord by immune and inflammatory cells was evident. As inflammation and spinal cord injury are intimately linked to T lymphocyte responses, we directly addressed the role of CD4 T lymphocyte RAGE signal transduction in EAE and inflammatory damage to the spinal cord.

Transgenic mice were generated with targeted over-expression of DN RAGE in $CD4^+$ T cells. As indicated above, signal transduction initiated by ligand–RAGE interaction is required for changes in gene expression to occur in a RAGE-dependent manner. Thus, wild-type littermate mice were compared to hemizygous CD4-DN RAGE-transgenic mice. Compared to littermates, transgenic CD4 DN RAGE mice were resistant to MBP-induced EAE.[23] Migration of T lymphocyte effector cells into spinal cord was strikingly suppressed when CD4 T lymphocyte RAGE signaling was suppressed.

RAGE Is Required for Effective T Lymphocyte Priming *In Vivo*: Definitive Studies *In Vitro* and *In Vivo*

Taken together, these representative studies in animal models of inflammation and autoimmunity strongly suggested that Tlymphocyte RAGE responses were integral to the host response and led us to test if RAGE played direct roles in Tlymphocyte priming. To accomplish this, we employed I-A^b- restricted ovalbumin (OVA)-specific OT-II CD4 TCR-transgenic cells. RAGE was expressed in primary OT-II CD4 cells.[24]

As RAGE is also expressed in dendritic cells (DC) and macrophages,[25] it was necessary to dissect the distinct contributions of RAGE on T lymphocytes and host non-T lymphocytes in adoptive transfer systems. Labeled RAGE-expressing and null OT-II $CD4^+$ $CD45.1^+$ cells were transferred into syngeneic C57 BL.6 $CD45.2^+$ RAGE-expressing or null hosts and the mice were subsequently immunized intraperitoneally with complete Freund's adjuvant (CFA)/OVA. Although homing of naive Tlymphocytes to secondary lymphoid organs was comparable in all unimmunized mice, significant roles for RAGE in priming were evident. Deletion of RAGE on T lymphocytes dramatically reduced T lymphocyte proliferative responses upon OVA exposure in wild-type recipients. RAGE expression on host cells also contributed to T lymphocyte priming as transferred RAGE-expressing OT-II cells divided to a greater degree in RAGE-expressing mice than in RAGE-null recipients.[24] The effects were additive as deletion of RAGE on both host cells and transferred OT-II cells resulted in the lowest proliferative response. *In vitro* experiments extended these findings, as RAGE deficient T lymphocytes showed strikingly impaired proliferative responses to nominal and alloantigen. Cytokine production of interferon (IFN)-γ and IL-2 was significantly reduced in the absence of RAGE.[24]

Taken together, these data provided supportive evidence that RAGE contributes to early T lymphocyte expansion during priming *in vivo*. Further, these studies also suggest important roles for additional cellular contributions (beyond Tlymphocytes) in adaptive immune responses.

In this context and in contrast to other reports,25 our studies did not reveal significant roles for RAGE in APC/DC responses, as RAGE-deficient DC did not reveal functional impairment in antigen presentation, maturation, or migratory capacities.[24] In addition to T lymphocytes, macrophages, and DC, RAGE is expressed on B lymphocytes. Studies are in progress to discern if expression of RAGE in B lymphocytes contributes to adaptive immunity. Lastly, it is essential to consider that endothelial cells (EC) RAGE responses are critically linked to the integrated cellular responses evoked in priming of T lymphocytes.

Endothelial Dysfunction: Integral to the Inflammatory Response and the Pathogenesis of Endothelial Dysfunction and Atherosclerosis

Testing the Role of RAGE in Atherosclerosis: Effects of sRAGE

Studies in endothelial dysfunction and atherosclerosis were originally approached from the context of diabetes and acceleration of macrovascular disease that typifies this disorder. In our first studies, mice deficient in apolipoprotein E were used, as these animals displayed spontaneous hypercholesterolemia and increases in atherosclerotic lesion area and complexity versus wild-type mice. Importantly, these animals develop atherosclerosis on normal rodent chow. To address the impact of diabetes on atherosclerosis, relative insulin-deficient (type 1) diabetes in these mice was induced with streptozotocin (stz). In hyperglycemic animals, significantly increased atherosclerosis and vascular inflammation were observed compared to nondiabetic apo E-null mice of the same age.[18,26] To block ligand–RAGE interaction in these animals, sRAGE was administered once daily by intraperitoneal administration to apoE-null mice rendered diabetic with stz. Soluble RAGE was begun in the diabetic mice immediately at the time of documentation of hyperglycemia and was continued for 6 weeks. Compared to vehicle-treated mice, sRAGE-treated animals displayed a dose-dependent decrease in atherosclerosis area at the aortic root in parallel with decreased features of lesion complexity.18 RAGE actions were directed at amplification mechanisms linked to the acceleration of vascular inflammation as RAGE blockade did not affect levels of lipids or glucose, thereby suggesting that RAGE acted downstream of these key risk factors.18

As these studies illustrated the effects of sRAGE in prevention of early progression, the role of RAGE in diabetic apo E-null mice with established atherosclerosis was then addressed. sRAGE was administered to diabetic mice commencing only after 6 weeks of sustained hyperglycemia; sRAGE or vehicles were continued for an additional 6 weeks. Control diabetic animals received murine serum albumin. These studies revealed that sRAGE-treated mice displayed significant stabilization of lesion area at the aortic root compared to vehicle-treated diabetic mice.[27] Of particular importance, vascular inflammation and oxidant stress were markedly attenuated in the aortas of sRAGE-treated animals as reflected by decreased cox-2 and nitrotyrosine epitopes, JE-MCP-1, tissue factor antigens; matrix metalloproteinase (MMP)9 antigen activity; and phosphorylated p38 MAP kinase.[27] As in the case of animals treated with sRAGE commencing immediately at the onset of hyperglycemia, in these animals, there were no differences in glucose, insulin, or lipid number or profile.27

Administration of stz induces a relative insulin-deficient diabetes. Thus, an essential step was to test the premise that RAGE modulated atherosclerosis in murine models of type 2 diabetes. To accomplish this, apoE-null mice were bred into the db/db background. In apo E-null db/db mice, atherosclerosis was accelerated compared to littermate apo E-null mice without diabetes.[28] Administration of sRAGE from age 8 to 11weeks resulted in a highly significant decrease in atherosclerotic lesion area in parallel with decreased vascular expression of proinflammatory RAGE ligand S100/calgranulins and vascular cell adhesion molecule-1 (VCAM-1) and MMPs.[28]

Of note, in animal models and in human cardiovascular disease, there is increased accumulation of RAGE ligands in atherosclerotic plaques even in the absence of diabetes. These considerations are not surprising as vascular inflammation and oxidative stress drive generation of AGEs as well as increased expression of proinflammatory S100/calgranulins and HMGB1. Thus, when sRAGE was administered to nondiabetic apoE-null mice (C57BL/6 background) and to apoE-null mice in the db background, sRAGE-treated nondiabeticmice displayed significantly decreased atherosclerosis and vascular inflammation compared to vehicle-treated control mice.[27,28]

Therefore, although diabetes represents a state of highly exaggerated RAGE ligand generation, even in nondiabetic atherosclerotic disease, oxidative stress evoked by hyperlipidemia and inflammation evoke AGE formation and, thus, clearly contribute integrally to the pathogenesis of atherosclerosis.

Testing the Role of RAGE in Atherosclerosis: Effects of Genetic Modulation of RAGE

Studies in RAGE-modified Mice

Two distinct genetic strategies were employed to dissect the role of the ligand–RAGE interaction in apoE-null mice. First, homozygous RAGE-null mice were bred into the apoE-null background. Second, to probe the role of endothelial RAGE in atherosclerosis, a transgenic mouse was prepared to express human DN RAGE specifically in EC by the pre-proendothelin-1 (PPET) promoter.[29]

At age 14weeks, compared to apoE-null mice, apoE-null mice in the RAGE-null background and in the transgenic PPET DN RAGE background displayed significantly less atherosclerotic lesion area and complexity; there was no differences in plasma cholesterol or triglyceride among the three groups of mice.[29]

Fundamental protection from endothelial dysfunction in apoE-null mice was observed by modulation of RAGE. Exposure of aortic rings to increasing doses of acetylcholine revealed that endothelium-dependent relaxation was significantly improved in rings retrieved from apoE-null/RAGE-null and apoE null/Tg PPET DN RAGE mice compared to apoE-null mice aortic rings.[29]

Deletion of RAGE or introduction of DN RAGE in EC in apoE-null mice resulted in significantly lower levels of mediators of vascular inflammation in aorta tissue as observed by decreased levels of VCAM-1, MCP-1, MMP-2 protein and activity, IL-10, and CD40 compared to apoE-null aorta. In plasma, levels of sVCAM-1 were significantly lower in apoE-null/ RAGE-null and Tg PPET DN|RAGE/apoE-null mice versus apoE-null mice.

Studies in RAGE-modified EC

To specifically dissect the signal transduction mechanisms linking RAGE to endothelial dysfunction, EC were isolated and purified from the aortas of wild-type C57BL/6 and RAGE- null and Tg PPET DN RAGE mice.[29]

Wild-type, RAGE-null, and DN RAGE EC were stimulated with the prototypic RAGE ligand S100b. Increased VCAM-1 antigen was observed in a manner dependent on RAGE and RAGE signaling. Key roles for RAGE in activation of JNK MAP kinase were illustrated by significant reduction in S100b-induced phosphorylation of this MAP kinase in RAGE-null or Tg PPET DN RAGE EC versus stimulated wild-type cells. Pretreatment of the EC with the JNK MAP kinase inhibitor, SP600125, resulted in highly significant reduction of S100b-mediated VCAM-1 upregulation. Introduction of small interfering (si)RNA to knock-

down JNK expression blunted the effect of S100b on upregulation of VCAM-1 as well. In contrast, introduction of scrambled siRNA or the ERK MAP kinase inhibitor, PD98059, had no effect on S100b stimulation of mouse primary EC.

These concepts were extended to human aortic EC. Lentiviral gene transduction was employed to introduce full-length RAGE (to further increase human RAGE expression) or DNRAGE into primary cultures of human aortic EC. S100b induced a significant increase in monolayer permeability of full-length RAGE-expressing EC compared to unstimulated, full-length, RAGE-expressing cells.[29] In DN RAGE-expressing human EC, S100b failed to increase monolayer permeability. 29 In addition, siRNA was employed to suppress RAGE expression in human aortic EC. RAGE siRNA suppressed S100b-stimulated upregulation of VCAM-1 compared to cells treated with scramble siRNA and S100b. The impact of S100b on upregulation of VCAM-1 was dependent on JNK MAP kinase signaling, as pretreatment with SP600125 significantly reduced VCAM-1 antigen, as did introduction of siRNA to knockdown JNK expression.29

Conclusions and Future Directions

Studies from atherosclerosis to the complications of diabetes to experiments in purified inflammatory and EC strongly implicate RAGE in amplification of inflammatory mechanisms linked to cellular injury in each of these settings. Most importantly, experiments in atherosclerosis demonstrate that RAGE regulates expression of VCAM-1 and MCP-1 in the atherosclerosis-vulnerable aorta. Thus, the link between activated inflammatory cells and primed endothelium suggest that RAGE is a key interface mediating vascular permeability, infiltration, and activation of inflammatory cells into the vessel wall, and then subsequently injury phenotypes. In aorta-derived vascular rings, deletion of RAGE or blockade of RAGE signaling in EC significantly improved the response to acetylcholine in apoE-null vascular tissue. In atherosclerosis, experiments using pharmacological antagonism of ligand–RAGE, and genetic modulation of RAGE support the premise that RAGE critically impacts vascular inflammation.

The next steps in dissecting the role of RAGE in vascular inflammation and atherosclerosis include intense focus on the role of RAGE and RAGE signaling in T and B lymphocytes, macrophages, and DC in vascular injury, both in the absence and presence of hyperglycemia. To dissect the underlying mechanisms, we must take the next step forward by dissecting, in intricate detail, the role of RAGE and RAGE signaling in each of these cell types alone and via their interaction with EC in the pathogenesis of vascular inflammation and atherosclerosis.

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