Receptor for Advanced-Glycation End Products
Key Modulator of Myocardial Ischemic Injury

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Background—The beneficial effects of reperfusion therapies have been limited by the amount of ischemic damage that occurs before reperfusion. To enable development of interventions to reduce cell injury, our research has focused on understanding mechanisms involved in cardiac cell death after ischemia/reperfusion (I/R) injury. In this context, our laboratory has been investigating the role of the receptor for advanced-glycation end products (RAGE) in myocardial I/R injury.

Methods and Results—In this study we tested the hypothesis that RAGE is a key modulator of I/R injury in the myocardium. In ischemic rat hearts, expression of RAGE and its ligands was significantly enhanced. Pretreatment of rats with sRAGE, a decoy soluble part of RAGE receptor, reduced ischemic injury and improved functional recovery of myocardium. To specifically dissect the impact of RAGE, hearts from homozygous RAGE-null mice were isolated, perfused, and subjected to I/R. RAGE-null mice were strikingly protected from the adverse impact of I/R injury in the heart, as indicated by decreased release of LDH, improved functional recovery, and increased adenosine triphosphate (ATP). In rats and mice, activation of the RAGE axis was associated with increases in inducible nitric oxide synthase expression and levels of nitric oxide, cyclic guanosine monophosphate (cGMP), and nitrotyrosine.

Conclusions—These findings demonstrate novel and key roles for RAGE in I/R injury in the heart. The findings also demonstrate that the interaction of RAGE with advanced-glycation end products affects myocardial energy metabolism and function during I/R. (Circulation. 2006;113:1226-1234.)

Key Words: advanced-glycation end products ■ ischemic injury ■ metabolism ■ nitric oxide synthase ■ receptors

R eperfusion strategies, specifically thrombolytic and antiplatelet therapies, have remarkably improved the clinical outcome in patients with acute myocardial infarction. However, the beneficial effects of reperfusion therapies are limited by the amount of ischemic damage that occurs before reperfusion. Several investigators have focused on developing adjunctive pharmacological interventions to enhance myocardial tolerance to ischemia/reperfusion (I/R) injury. To enable development of interventions to reduce cell injury, our research has focused on understanding mechanisms involved in cardiac cell death after I/R injury. In this context, our laboratory has been investigating the role of the receptor for advanced-glycation end products (RAGE) in myocardial I/R injury.

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RAGE, a multiligand receptor of the immunoglobulin superfamily, interacts with distinct families of ligands that mediate diverse functions in a broad array of cell types, including cellular migration and activation of proinflammatory mechanisms. Initially, RAGE was described as a receptor for advanced-glycation end products (AGEs) that accumulate in hyperglycemic conditions. Subsequent studies have shown that S100/calgranulins, amphoterin (or high-mobility group box 1), and amyloid-β-peptide also can bind to RAGE, resulting in activation of signal transduction and modulation of gene expression. In chronic disease states such as diabetes, immune/inflammatory foci, and neurodegenerative disorders, upregulation of RAGE was associated with tissue injury. Recently, RAGE was shown to modulate the response to acute nerve injury and cell death–promoting mechanisms in severe hepatectomy. Furthermore, one of the ligands for RAGE, S100B, was shown to modulate cardiac hypertrophy, apoptosis, and remodeling after infarction. These studies led us to investigate whether RAGE mediates injurious stress responses in myocardium after I/R.

In this study we used 2 strategies to address the role of RAGE in cardiac I/R injury. The first strategy used rat hearts
treated with soluble decoys that modulate ligand-RAGE signaling subjected to I/R injury, and the second approach used homozygous RAGE-null mice subjected to I/R injury. Our findings reveal a key modulatory role for RAGE in myocardial I/R injury.

Methods

Animal Studies
All studies on male mice and rats were performed with the approval of the Institutional Animal Care and Use Committee of Columbia University, New York, NY. This investigation conforms with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. Male Wistar rats from Harlan Sprague-Dawley Farms (Indianapolis, Ind) weighing 250 to 300 g were used for the heart perfusion studies. Soluble RAGE (sRAGE), 500 μg/d, or equal volumes of its diluent, PBS (vehicle), was administered by intraperitoneal route for 3 days before the study. sRAGE was prepared in a baculovirus expression system, and the material was purified to homogeneity with the use of fast pressure liquid chromatography. After purification, the material was devoid of any contaminating lipopolysaccharide with the use of Detox-igel columns (Pierce) and was sterile filtered (0.2 μm). The total volume of injected material was 0.5 mL/d. sRAGE acts as a decoy to bind the ligands of the receptor and block its activation.

Homzygous RAGE-Null Mice
Homzygous RAGE-null mice5,6 were backcrossed >10 generations into C57BL/6 before study. Male RAGE-null and littermate control mice were used.

Western Blotting
In all cases, in rats and mice, only the left ventricles were retrieved for biochemical or molecular analysis. Hearts were retrieved from the indicated mice or rats, and lysates were prepared. Lysates were subjected to SDS-PAGE and Western blotting with the use of anti-RAGE IgG (1 μg/mL),4 anti–inducible nitric oxide synthase (iNOS) IgG (0.25 μg/mL, Santa Cruz Biotechnology), or anti–nitrotyrosine IgG (Upstate Biotechnology). In all cases, after probing with the primary antibodies, membranes were stripped of bound material and reprobed with anti–voltage-dependent anion channel (VDAC) IgG (Calbiochem). Analysis of band density was performed with the use of Image Quant/Molecular Dynamics software. Results are reported as arbitrary units based on the ratio of test antibody densitometry units per β-actin or per VDAC densitometry units, as indicated.

To determine the level of RAGE expression at baseline, 500 μg of cleared lysate proteins from control and sRAGE-treated hearts were coimmunoprecipitated with 10 μg of rabbit polyclonal antibody specific for AGEs overnight with gentle shaking for 4°C. Protein complexes were further incubated at 4°C for 2 hours after addition of 20 μL of protein A/G agarose beads (Pierce). Nonspecific IgG was used as a negative control. Pelleted complexes were spun down and were washed 3 times with ice-cold lysis buffer (Cell Signaling).

Real-time Quantitative Polymerase Chain Reaction
Total RNA was extracted from rat heart with the use of TRIzol reagent (Invitrogen Corp). Total RNA (0.5 μg) was processed directly to cDNA synthesis with the use of the TaqMan Reverse Transcription Reagents kit (Applied Biosystems) according to the manufacturer’s protocol. The polymerase chain reaction (PCR) primers and TaqMan probes for rat RAGE and 18s rRNA were commercial from Applied Biosystems. All reactions were performed in triplicate in the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems). 18s rRNA was used as an active and endogenous reference to correct for differences in the amount of total RNA added to the reaction mixture and to compensate for different levels of inhibition during reverse transcription of RNA and during PCR.

Immunohistochemistry
Hearts were retrieved from the indicated animals, and sections were prepared for immunohistochemistry according to previously published methods. The following antibodies were used in these studies: anti–RAGE IgG4 and anti–carboxymethyl lysine (CML)-AGE IgG.2 In all cases, immunostaining with nonimmune IgGs of the relevant species was negative and did not reveal any staining in the heart compared with staining with primary antibodies.

Levels of Total Nitrite and Nitrate and Cyclic Guanosine Monophosphate
Hearts were retrieved and rapidly snap-frozen in liquid nitrogen after the period of I/R. Lysates were then prepared, and levels of total nitrite and nitrate and cyclic guanosine monophosphate (cGMP) were measured with a kit from Oxis Research Products according to the manufacturer’s instructions.

Isolated Perfused Heart and Measurement of Cardiac Function
Experiments were performed with the use of an isovolumic isolated heart preparation as previously published and modified, as indicated, for use in mice hearts.10–12 Mice and rats were anesthetized with a mixture of ketamine/xylazine (80 and 10 mg/kg, respectively, diluted in PBS) by an intraperitoneal route. After deep anesthesia was achieved, hearts were rapidly excised, placed in iced saline, and retrogradely perfused at 37°C in a nonrecirculating mode through the aorta. In mice, the perfusion rate was 2.5 mL/min, and in rats, the perfusion rate was 12.5 mL/min. Rat and mice hearts were perfused with modified Krebs-Henseleit buffer containing the following (in mM/L): NaCl 118, KCl 4.7, CaCl2 2.5, MgCl2 1.2, NaHCO3 25, glucose 5, palmitate 0.4, bovine serum albumin 0.4, and insulin (70 μL/mL). The perfusate was equilibrated with a mixture of 95% O2 to 5% CO2, which maintained perfuse PO2 >600 mm Hg. Left ventricular developed pressure (LVDP) and left ventricular end-diastolic pressure (LVEDP) were measured with the use of a latex balloon in the left ventricle. LVDP, heart rate, and coronary perfusion pressure were monitored continuously on a 4-channel Powerlab (AD Instruments).

The I/R protocol was as follows. Hemodynamic function was monitored throughout the protocol. Mice hearts were paced at 420 bpm with the use of pacing electrodes placed on the right atrium. Rat hearts were paced at 300 bpm. Hearts were subjected to 30 minutes of global (zero-flow) ischemia (flow stopped) and 60 minutes of reperfusion. Perfusate temperature was maintained at 37°C at all times during the protocol (ie, during baseline, ischemia, and reperfusion). After an equilibration period of 30 minutes, both groups of hearts were perfused with modified Krebs-Henseleit buffer through-out I/R.

LDH release was measured in the effluents for the entire 60 minutes of reperfusion in each heart. The levels of LDH were assayed with the use of commercially available kits from Sigma Aldrich according to the manufacturer’s instructions. LDH release is expressed as IU/g dry weight of tissue.

Measurement of 3-Methylglyoxal and Adenosine Triphosphate
3-Methylglyoxal (3MG) and adenosine triphosphate (ATP) were measured in the neutralized perchloric acid extracts of hearts by
high-performance liquid chromatography (HPLC) methods according to previously published procedures.11–13

Statistical Analysis
Significant differences between experimental groups were detected by ANOVA for unpaired variables. Post hoc comparisons were performed with Tukey or Dunnett procedures as indicated. SAS package software was used in the statistical analyses, and statistical significance was ascribed to the data when \( P<0.05 \).

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to manuscript as written.

Results
Ligand/RAGE Axis in Ischemic Rat Heart
To examine the potential impact of the RAGE axis in myocardial I/R injury, we first explored the expression/distribution of RAGE and its ligands (AGEs) in perfused rat hearts. These studies were performed at baseline and at the end of I/R. First, we examined epitopes for CML-AGEs. CML-AGEs have been demonstrated by numerous investigators as principal AGEs that accumulate in vivo.14,15 Furthermore, we have demonstrated that CML-AGEs are specific AGEs that activate the signal transduction receptor RAGE.2 In hearts subjected to normoxic perfusion, CML epitopes were not detected (Figure 1a). In contrast, heart tissue retrieved from ischemic hearts displayed immunoreactive epitopes for CML-AGE (Figure 1b). In parallel with expression of AGEs, ischemic hearts displayed increased RAGE antigen compared with normoxic hearts by immunohistochemistry (Figure 1d and 1c, respectively) and Western blotting (\( P<0.03 \)) (Figure 1e). RAGE was principally expressed in vascular cells after I/R and at low levels in cardiomyocytes (Figure 1d). In addition to CML epitopes, the key AGE precursor 3MG, measured by HPLC, was increased in ischemic versus normoxic-perfused hearts (Figure 1f; \( P<0.03 \), I/R control versus baseline control).

To test the impact of RAGE blockade, we administered sRAGE, the extracellular ligand-binding domain of RAGE. sRAGE is a decoy that acts to bind up RAGE ligands and prevents their interaction with, and activation of, cell surface RAGE.4 sRAGE was administered to rats commencing 3 days before the study. Hearts from sRAGE-treated rats were isolated and subjected to I/R. In rats treated with sRAGE, significantly lower levels of 3MG were observed in heart tissue compared with vehicle-treated rats after I/R (Figure 1f; \( P<0.02 \), I/R control versus I/R-sRAGE).

To determine whether the changes in RAGE expression (Figure 1e) in I/R hearts were due to changes in RAGE transcripts, we performed quantitative real-time PCR studies on these hearts. Transcripts for RAGE were increased by 1.8-fold in I/R hearts compared with sham-treated (baseline-perfused) controls (Figure 1g). These data indicate that I/R induces RAGE transcript changes in rat hearts.

sRAGE Attenuates I/R Injury in the Rat Heart
On the basis of the observation that RAGE and AGEs were increased in the ischemic rat heart, we next sought to assess the potential impact of sRAGE pretreatment on cardiac dysfunction consequent to I/R. Two indices of cardiac recovery were assessed: LVDP and release of LDH on reperfusion, the latter an index of myocardial injury and infarction. LDH release was significantly higher in control hearts than in sRAGE-treated hearts (\( P<0.05 \)) (Figure 2a). Furthermore, vehicle control rat hearts displayed a marked decrease in LVDP recovery on reperfusion compared with sRAGE-treated rat hearts subjected to the same degree of I/R (\( P<0.05 \)) (Figure 2b). In addition, the levels of ATP in the hearts were significantly higher in sRAGE-treated rat hearts than in untreated controls after I/R (Figure 2c; \( P<0.05 \)).

Because sRAGE reduced the enhanced generation of ligands for RAGE (Figure 1f), we sought to assess whether sRAGE influences RAGE expression. Immunoprecipitation of heart extracts with antibody to AGE followed by detection with antibody for RAGE demonstrated that RAGE expression was indeed reduced in sRAGE-treated hearts (Figure 3).

Ischemia Increases Expression of iNOS and Protein Nitration in the Rat Heart: Impact of RAGE
To explore the potential impact of RAGE in modulating key pathways linked to perturbation and generation of oxidant stress in the heart, we first assessed levels of iNOS in the rat heart. Compared with nonischemic hearts, ischemic rat hearts displayed increased iNOS antigens by Western blotting; in the presence of treatment with sRAGE, levels of iNOS antigen were significantly lower (\( P<0.05 \)) (Figure 4a). In parallel with increased levels of iNOS antigen in ischemic rat hearts, levels of total nitrite and nitrate and cGMP were increased after I/R (\( P<0.05 \)); in the presence of sRAGE, levels of total nitrite and nitrate and cGMP after I/R were significantly lower (\( P<0.05 \) and similar to those observed in normoxic hearts (Figure 4b and 4c, respectively). Because previous studies associated changes in iNOS expression with protein tyrosine nitration,16,17 we examined the hearts from these animals to detect nitrotyrosine epitopes, markers of oxidative injury. Mitochondrial and postmitochondrial (cytosolic) fractions from hearts at baseline, without I/R, exhibited decreased nitrotyrosine epitopes in the presence of sRAGE versus control normoxic hearts (Figure 4d). Furthermore, treatment with sRAGE reduced mitochondrial protein tyrosine nitration after I/R (Figure 4e).

Homologous RAGE-Null Mice Are Protected From the Adverse Impact of I/R
Because sRAGE acts as a ligand decoy, the next set of studies were performed in mice in which RAGE was deleted. We assessed the impact of injury secondary to I/R on functional recovery in homozygous RAGE-null mice. Levels of 3MG, AGE precursors, were significantly reduced in RAGE-null mice compared with littermates at baseline and after I/R (Figure 5a). These data are suggestive of the interdependence between AGE levels and RAGE expression. LVDP recovery was significantly higher in RAGE-null mice versus littermate hearts after I/R (\( P<0.02 \)) (Figure 5b). In parallel, levels of LDH measured in the effluent in I/R-subjected animals were significantly lower in RAGE-null mouse hearts than in littermate hearts (\( P<0.01 \)) (Figure 5c). In addition, levels of cardiac ATP were significantly higher in RAGE-null hearts.
Figure 1. RAGE and its ligands are expressed in the ischemic rat heart. Perfused rat hearts were subjected to immunohistochemistry for detection of RAGE and its ligands. Immunostaining of CML/AGEs and RAGE in baseline (a, c) and after I/R (b, d) hearts is shown. Bar=50 μm. In a to d, representative sections from at least n=3 rats per group are illustrated. In e, Western blotting with the use of anti-RAGE IgG was performed for detection of RAGE antigen in the indicated rat hearts. In each case, after probing with anti-RAGE IgG, bound antibodies were removed, and membranes were reprobed with anti-β-actin IgG. Results are reported as the ratio of RAGE/β-actin densitometry units. In f, the concentration of the key AGE precursor 3MG is shown for control (CON) and sRAGE-treated hearts under baseline (B) and after I/R. In e and f, n=6 rats per group. In g, real-time PCR data compare RAGE transcripts in B (baseline perfusion for 90 minutes sham group) and I/R rat hearts.
than in littermate controls in I/R ($P < 0.03$) (Figure 5d). The levels of ATP were comparable in both the mice hearts during the normoxic perfusion period before induction of ischemia. At the end of the ischemic period, ATP levels in RAGE-null mice hearts were $4.6 \pm 0.3 \, \text{mol/g dry wt}$, whereas in littermate hearts ATP levels were significantly lower at $1.9 \pm 0.2 \, \text{mol/g dry wt}$ ($P < 0.05$).

We observed that iNOS antigen (Figure 6a) and levels of total nitrite and nitrate (Figure 6b) in the heart after I/R were significantly lower in RAGE-null mice hearts after I/R than in wild-type mice. In parallel, levels of cGMP were lower in RAGE-null versus wild-type hearts after I/R (Figure 6c).

**Discussion**

Mechanisms underlying myocardial I/R injury span a broad range of fundamental biological changes, including metabolic, ionic, and oxidant stress. Here we demonstrate that RAGE is a key factor in myocardial I/R injury. Cells within the vascular milieu may be induced to produce NO and superoxide, at least in part via the direct action of high glucose itself and by its downstream effector species, such as AGEs. The interaction of NO and superoxide may yield generation of peroxynitrite, a potent longer-lived oxidant whose biological impact is both diverse and deleterious. For example, cytotoxicity ascribed to peroxynitrite anion ensues secondary to its ability to inhibit mitochondrial electron transport, oxidize sulfhydryl groups in proteins, initiate lipid peroxidation in a transition metal ion-free environment, and nitrate amino acids, such as tyrosine. Uncoupling of endothelial NOS by peroxynitrite triggers further generation of superoxide and magnifies oxidant stress. Recent studies have identified that peroxynitrite induces formation of CML-modified adducts by cleavage of Amadori products and the generation of glucosone and glyoxal from glucose, thus providing a “refueling mechanism,” at least in diabetes, whereby generation of CML leads to oxidant stress, followed by further generation of CML adducts. In the present study we show that even in the absence of diabetes, CML-AGEs may be formed by I/R. Our findings extend previous observations on the role of iNOS in cellular injury in the ischemic heart and link RAGE to generation of NO and pathogenic species. Indeed, the observation that CML-AGEs activate RAGE via signal transduc-
tion and augment vascular and inflammatory cell activation underscores critical roles for the ligand/RAGE pathway in cellular perturbation and in amplifying pathogenic ligand generation, at least in part by accelerated oxidant stress and generation of peroxynitrite.

**RAGE, NOS, and Nitrotyrosine**

During the period of reperfusion, the release of LDH from the heart, a marker of ischemic injury to cardiac muscle cells, was significantly lower in sRAGE-treated rats and in homozygous RAGE-null mice in comparison to control hearts. Although many contributory mechanisms may underlie these differences in myocardial pathology, it is likely that inhibition of the synthesis of NO by iNOS plays an important role. Our results are consistent with previous studies of acute ischemia and reperfusion in which administration of semiselective inhibitors of iNOS or iNOS-null mice were associated with enhanced cardiac performance and/or reduction of myocardial infarct size. Other studies by several groups have indicated that increased myocardial expression of iNOS and increased NO synthesis by this isoform occur during acute cardiac allograft rejection and are associated with contractile dysfunction, electric instability, increased nitration of cardiac proteins, and death of cardiomyocytes by necrosis and by...
apoptosis. These changes are reduced if heart transplantation is performed with the use of iNOS-null animals or by the administration of inhibitors of iNOS enzymatic activity.

Recent studies have also associated increases in iNOS activity with increased protein tyrosine nitration in hearts. Mungrue et al demonstrated that cardiomyocyte overexpression of iNOS led to increases in peroxynitrite generation and sudden cardiac death. Furthermore, studies have demonstrated that cytosolic and mitochondrial proteins are nitrosylated in hearts because of high levels of NOS activity. In the present study we show increased protein tyrosine nitration in both cytosolic and mitochondrial fractions after I/R and that blockade of RAGE attenuates these changes in protein nitration. The data presented here suggest that RAGE mediates cardiac ischemic injury, at least in part via increased iNOS expression and activity and associated changes in protein nitration.

RAGE and Myocardial Energy Metabolism

RAGE influenced myocardial energy metabolism, as seen in experiments with sRAGE-treated rats and RAGE-null mice. At the end of the period of global ischemia, levels of myocardial ATP were reduced significantly in wild-type hearts; however, higher levels of ATP were observed in RAGE-null mice than in littermates. In RAGE-null mice and sRAGE-treated rats, levels of ATP were higher in hearts versus littermates after I/R. Synthesis of ATP by oxidative phosphorylation ceases during global ischemia because of reduced coronary flow and reduced oxygen delivery. In this ischemic setting, ATP production then results primarily from anaerobic glycolysis. A potential mechanism underlying NO-
mediated inhibition of anaerobic glycolysis is nitrosylation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Several groups have reported that GAPDH, a critical enzyme in the glycolytic pathway, can undergo S-nitrosylation and auto-ADP-ribosylation by NO, leading to inhibition of its enzymatic activity.33,34 Recent findings demonstrated reduced myocardial GAPDH activity and levels of glyceraldehyde-3-phosphate at the end of the ischemic period and normalization of these changes by inhibition of iNOS.35 Higher iNOS expression and NO production have been shown in part to impair glycolysis and reduce ATP levels in ischemic hearts. Our data demonstrating reduced iNOS expression (and total nitrite and nitrate levels) and improved ATP levels in RAGE-inhibited ischemic hearts are consistent in part with RAGE blockade improving anaerobic glycolysis.

RAGE and Cardiac Ischemic Injury

Our findings stress the impact of RAGE in generation of iNOS, nitrite and nitrate, and cGMP in the heart, especially consequent to I/R. Of note, our findings do not suggest that RAGE is expressed to appreciable degrees in cardiomyocytes. These findings have parallels in the expression of iNOS in the heart; when expressed in myocytes, iNOS activity is essential in regulating the response to β-adrenergic stimulation during sepsis. However, iNOS expression in inflammatory cells such as neutrophils was shown to mediate direct damage to myocytes.36 Our findings link RAGE in the rat and mouse heart to iNOS expression and enhanced injury in the setting of I/R, as measured by LDH release. Furthermore, the finding that levels of ATP are restored in RAGE-null mice in I/R provides a direct link between oxidant stress, NOS, and energy metabolism.

In our studies in rats definitively showed that pharmacological blockade of RAGE protected the isolated perfused heart from damage and dysfunction, the latter measured by LVDP. In the mouse heart, release of LDH was attenuated in RAGE-null hearts. Furthermore, the protection in RAGE-null mice hearts was also associated with improved functional and metabolic recovery.

In conclusion, these studies have definitively linked RAGE to myocardial ischemic injury–associated cardiac dysfunction. We propose that blockade of RAGE will provide a novel means to exert cardioprotection in the heart, particularly consequent to injury exacerbated by I/R.

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Disclosures

Dr Schmidt receives research support and is a member of the scientific advisory board of Trans Tech Pharma, Inc. The other authors report no conflicts of interest.

References


CLINICAL PERSPECTIVE

Numerous mechanisms with diverse etiologies have been postulated to contribute to myocardial damage in ischemic hearts. Although reperfusion therapy has revolutionized the treatment of acute myocardial ischemia in humans, beneficial effects are limited by the amount of ischemic damage that occurs before and after reperfusion. In this article the authors show that the receptor for advanced-glycation end products (RAGE) and its binding molecules, the advanced-glycation end products (AGEs), are upregulated after ischemia/reperfusion injury in the heart. These studies show that ischemia/reperfusion rapidly generates AGEs and demonstrate that blockade of the AGE-RAGE signaling with a soluble receptor decoy (sRAGE) leads to protection of the ischemic/reperfused heart. Specifically, sRAGE enhanced functional recovery, diminished myocyte necrosis, and maintained levels of adenosine triphosphate (ATP) in the stressed heart. Taken together, these studies provide evidence linking the AGE-RAGE pathway to mechanisms that cause damage in myocardial infarction and stroke.
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