Acta Med. Okayama, 2017
Vol. 71, No. 6, pp. 459-465

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Review

Signal Diversity of Receptor for Advanced Glycation End Products

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The receptor for advanced glycation end products (RAGE) is involved in inflammatory pathogenesis. It functions as a receptor to multiple ligands such as AGEs, HMGB1 and S100 proteins, activating multiple intracellular signaling pathways with each ligand binding. The molecular events by which ligand-activated RAGE controls diverse signaling are not well understood, but some progress was made recently. Accumulating evidence revealed that RAGE has multiple binding partners within the cytoplasm and on the plasma membrane. It was first pointed out in 2008 that RAGE's cytoplasmic tail is able to recruit Diaphanous-1 (Dia-1), resulting in the acquisition of increased cellular motility through Rac1/Cdc42 activation. We also observed that within the cytosol, RAGE's cytoplasmic tail behaves similarly to a Toll-like receptor (TLR4)-TIR domain, interacting with TIRAP and MyD88 adaptor molecules that in turn activate multiple downstream signals. Subsequent studies demonstrated the presence of an alternative adaptor molecule, DAP10, on the plasma membrane. The coupling of RAGE with DAP10 is critical for enhancing the RAGE-mediated survival signal. Interestingly, RAGE interaction on the membrane was not restricted to DAP10 alone. The chemotactic G-protein-coupled receptors (GPCRs) formyl peptide receptors1 and 2 (FPR1 and FPR2) also interacted with RAGE on the plasma membrane. Binding interaction between leukotriene B4 receptor 1 (BLT1) and RAGE was also demonstrated. All of the interactions affected the RAGE signal polarity. These findings indicate that functional interactions between RAGE and various molecules within the cytoplasmic area or on the membrane area coordinately regulate multiple ligand-mediated RAGE responses, leading to typical cellular phenotypes in several pathological settings. Here we review RAGE's signaling diversity, to contribute to the understanding of the elaborate functions of RAGE in physiological and pathological contexts.

Key words: receptor for advanced glycation end products, RAGE, adaptor protein, signal transduction, inflammatory pathogenesis

The receptor for advanced glycation end products, RAGE (gene name: *AGER*), a single-pass type I transmembrane protein belonging to the immunoglobulin (Ig) superfamily [1], has critical roles in a broad range of inflammatory, degenerative and hyper-proliferative diseases [2-5]. The structure-based dimension of extracellular RAGE is composed of an N-terminal Ig-V following Ig-C1 and Ig-C2, displaying a unique binding ability to multiple substances including ligands such as advanced glycation end products (AGEs) [2],

Received May 17, 2017; accepted July 7, 2017.
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§The winner of the 2016 Incentive Award of the Okayama Medical Association in General Medical Science.

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

high-mobility group box 1 (HMGB1) [6] and S100 family proteins [7]. In several pathological settings, upon binding to ligands, RAGE activates multiple intracellular signaling pathways involving in the small GTPase Rac1/Cdc42, Ras-mediated extracellular signal-regulated kinase 1/2 (ERK1/2), Akt, stress-activated protein kinase/c-Jun-NH2-terminal kinase (SAPK/JNK), p38 MAP kinase, NF-κB transcription factor and caspases despite its very short cytoplasmic tail [8-12].

Although RAGE has long been recognized for its significant contribution to inflammatory pathogenesis, the innate mechanisms by which it regulates signal polarity in correlation to typical pathogenesis have not been systematically mapped out. Recent studies have gradually uncovered the complex mechanisms of RAGE in controlling multiple signals. A breakthrough has come from the identification and characterization of RAGE-binding proteins in the absence of extracellular ligands. In this review, we discuss newly identified RAGE-binding proteins and their roles in RAGE-mediated signals and functions.

Signal Transducers Act through Binding with the RAGE Cytoplasmic Domain

The question of how the RAGE cytoplasmic tail induces the activation of multiple signaling pathways upon the binding of ligands that correspond to diverse cellular events (such as growth, migration, invasion, apoptosis and the appearance of a secretory phenotype in correlation to inflammatory cytokines and chemokines) has long been a puzzle, since the cytoplasmic tail of RAGE is very short (41 aa). In addition, the tail has no outstanding composition in its domain and no inclusion of tyrosine as a phosphorylation target. This irregularity may be explained by the presence of various types of binding adaptors that can be expected to be critical in the process of RAGE-mediated signal transductions.

In 2008, Hudson *et al.* first tried to identify the adaptor molecules by using a yeast two-hybrid system with the human RAGE cytoplasmic domain as "bait" [13]. This approach led to the discovery of an important binding partner, Diaphanous-1 (Dia-1). Their study revealed that Dia-1 interaction induces cellular migration through the activation of certain small guanine nucleotide triphosphatases (GTPases), *i.e.*, Rac1 and Cdc42. This novel finding is in accordance with the innate function of Dia-1, since the protein plays a significant role in the regulation of cytoskeletal organization that leads to the promotion of cellular motility [14].

As there are no obvious domains or motifs associated with the guanyl-nucleotide exchange function in Dia-1, it is believed that the addition of a guanine nucleotide exchange factor (GEF) that catalyzes the change from GDP to the active form of GTP in the small GTPase is needed for the activation of Rac1 and Cdc42 through the interaction of Dia-1 with the RAGE cytoplasmic tail.

In light of this idea, we attempted to identify GEFs using an alternative method, *i.e.*, an immunoprecipitation-liquid chromatography with tandem mass spectrometry (LC-MS/MS) procedure using overexpression of the epitope tagged-human RAGE cytoplasmic domain. Fortunately, this approach enabled us to identify an atypical DOCK180-GEF, DOCK7 [15]. We found that the activation of Cdc42 by the RAGE ligand S100B in U-87MG human glioma cells that expressed an increased phenotype in cellular migration was effectively abrogated by the down-regulation of DOCK7. We thus showed that DOCK7 is also involved in the small GTPase-mediated migration axis of RAGE through interplay with the key molecule Dia-1.

It remains difficult to determine whether DOCK7 directly or indirectly binds to RAGE via Dia-1, since the preparation of the full length of a recombinant protein in an intact condition is a challenge due to the high molecular weight (2,140 aa) of DOCK7. Further advanced studies are required to settle this complex issue, but we will focus here on the interaction between Dia-1 and DOCK7 in the same RAGE signaling pathway toward the regulation of cellular motility.

Another significant role of RAGE is the effective induction of inflammatory cytokines and chemokines. It has repeatedly been shown that there is a marked similarity between RAGE and Toll-like receptor 4 (TLR4) in terms of downstream signaling [16, 17], which has turned our attention to comparisons of the amino acid sequences of the RAGE short cytoplasmic tail and the TLR4 cytoplasmic Toll/interleukin-1 receptor (TIR) homology domain, which is a signal transduction domain. To our surprise, a very similar sequence (termed the 'RT sequence' in this review) was present in both RAGE (QEEE starting at 379) and TLR4 (QDED starting at 683) (Fig. 1A). The RT sequence was also present in the same TIR domain of TLR2 as an imitated form (QELE starting at 661) but not in the TIR

domain of TLR1 or TLR3. TLR2 and TLR4 both use TIRAP and MyD88 as an adaptor complex for their signaling to induce inflammatory cytokines [18-21].

This finding gave us the opportunity to correlate the role of RAGE signaling with the roles of TLR2 and TLR4. Interestingly, further investigation demonstrated that a variant of the RT sequence in the TLR4-TIR domain lost its ability to bind with TIRAP and MyD88 (our unpubl. data), and we suspected that the sequence also plays an important role in the recruitment of adaptors beside the BB-loop sequence (an essential sequence for interactions between certain TLRs and their adaptor molecules [21]) in the TIR domain. We succeeded in identifying other important adaptor molecules, TIRAP and MyD88, in the RAGE cytoplasmic domain and found that the RAGE-TIRAP/MyD88 signaling axis led to the activation of NF-κB, resulting in the expression of genes related to the inflammatory response, such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6 [22].

The recruitment of TIRAP and MyD88 to the RAGE cytoplasmic tail is highly enhanced by stimulation with RAGE ligands. We next focused on modification events at the cytoplasmic domain of RAGE. We found that the cytoplasmic domain of RAGE was phosphorylated at Ser391 by protein kinase C-zeta (PKCζ) upon the binding of ligands (Fig. 1B). This suggests a crucial role for the residue in phosphorylation modification.

We subsequently observed that the phosphorylation greatly enhanced the affinity of RAGE to TIRAP and MyD88, indicating that a higher negative charge at the Ser391 residue is crucial for efficient binding with TIRAP and MyD88 [22]. Notably, when the residue is phosphorylated, QS(391)EE becomes equivalent to QEEE or QDEE, displaying high similarity to the RT sequence. The duplicated RT sequence (Q followed by three successive negatively charged residues) may play a role in the enhanced interaction of TIRAP and MyD88 with the RAGE intracellular domain regardless of the absence of the BB-loop (Fig. 1C).

Membrane Proteins Coupled with RAGE Act as RAGE Modulators for Downstream Signaling

The regulatory mechanism of RAGE-mediated diverse signaling may not only be dependent on cytoplasmic adaptors. For instance, after coupling, a membrane protein such as gp130 co-functions with the IL-6 receptor, triggering activation of the JAK-STAT signaling pathway [23]. In accord with this concept, we tried to identify any possible RAGE-interacting proteins on the plasma membrane. We first attempted to analyze epitope-tagged RAGE-immunoprecipitates from the membrane fraction prepared from RAGE-overexpressed cells. However, no RAGE co-precipitated proteins yielded any promising candidates (our unpubl. data). We therefore shifted our strategy to a candidate-based screening method using forced co-expression of RAGE and selected membrane proteins that were co-functioning with cytokine receptors. This led to the identification of DNAX-Activating Protein 10 (DAP10) [24] as a novel transmembrane adaptor for RAGE [25].

Our studies showed that DAP10 binding modulates RAGE-triggered signaling toward survival enhancement via the PI3K-Akt pathway after RAGE ligand stimulation. A tyrosine residue (86Y) in the YXXM motif [26] of the intracellular domain of DAP10 recruited PI3K (p85) when phosphorylated, and the event further activated the effector kinase Akt. Interestingly, the formed RAGE-DAP10 heterodimer has the ability to recruit not only PI3K (p85) but also GRB2 and GRB7 (Fig. 2, left side of the bottom panel). GRB2 and GRB7 are able to promote cellular proliferation via activation of the Ras-ERK1/2 pathway [27, 28]. These pathways (including Akt, GRB2 and GRB7) seem to be dominant in certain epithelial cancer cells and keratinocytes in inflammatory psoriatic settings, since DAP10 is upregulated in those cases.

Conversely, we also found that RAGE favors its own dimer or multimer in the absence of DAP10 after RAGE ligand stimulation (Fig. 2, upper panel). In this case, especially in the case of strong stimulation of RAGE with high concentrations of ligands, the downstream signal tends to shift toward the apoptotic pathway through TIRAP-MyD88-caspase 8. As reported previously, we observed that PKCζ, which phosphorylates RAGE at Ser391, is activated by autophosphorylation at Thr560 [29]. The homo-dimerization and homo-multimerization of RAGE resulted in the autophosphorylation of PKCζ at Thr560. Thus, the homo-dimerization and homo-multimerization of RAGE may readily induce PKCζ, activation which in turn phosphorylates the RAGE cytoplasmic tail at Ser391, eventually leading to advanced TIRAP and MyD88 recruitment. The abundant DAP10 is readily able to function to prevent RAGE homo-dimerization and homo-multimerization [25].

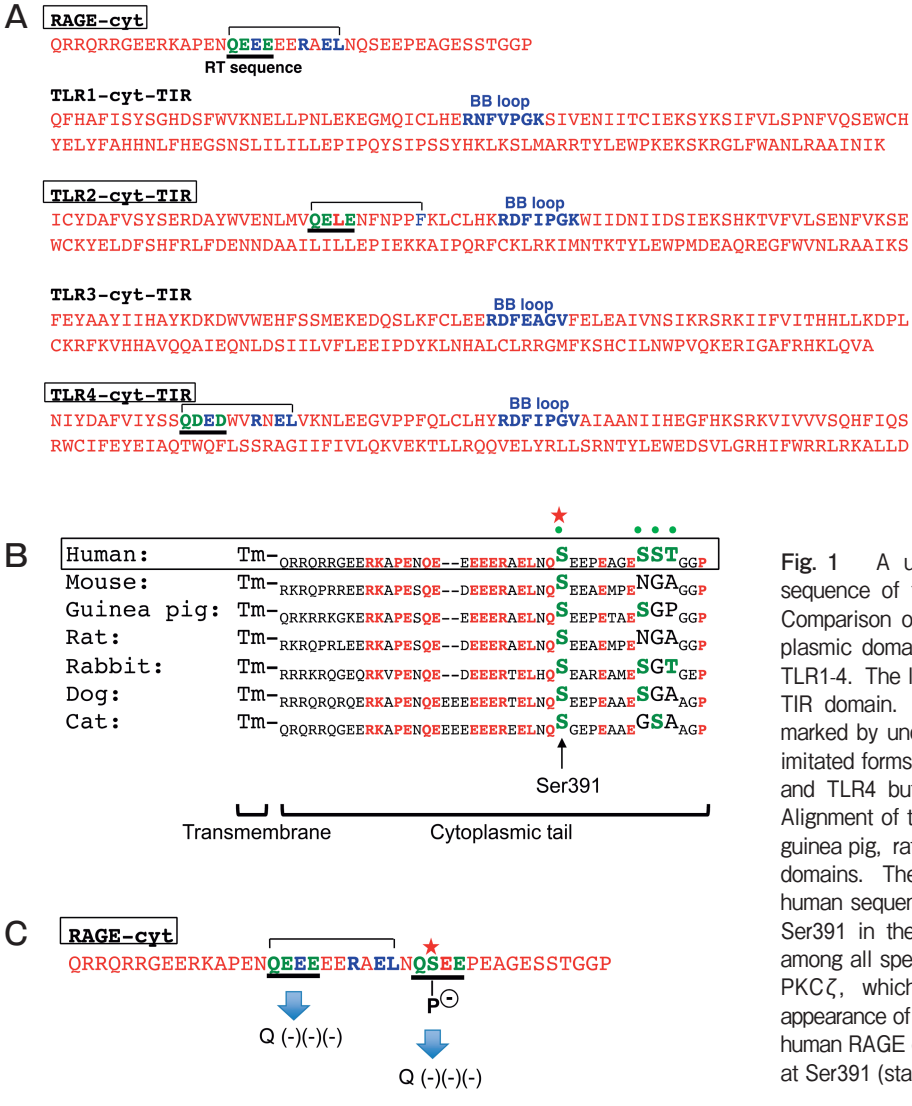

Fig. 1 A unique feature in the amino acid (aa) sequence of the human RAGE cytoplasmic tail. **A**, Comparison of sequences in the human RAGE cytoplasmic domain and the cytoplasmic TIR domains of TLR1-4. The location of the BB-loop is shown in each TIR domain. The RT sequence in human RAGE is marked by underlining. The RT sequence appears as imitated forms in the cytoplasmic TIR domains in TLR2 and TLR4 but not in those of TLR1 and TLR3: **B**, Alignment of the aa sequences of the human, mouse, guinea pig, rat, rabbit, dog and cat RAGE cytoplasmic domains. The phosphorylatable aa residues in the human sequence are marked by dots. The position at Ser391 in the human sequence is highly conserved among all species examined and is phosphorylated by PKCζ, which is marked by a star: **C**, Duplicated appearance of the RT sequence (underlined sites) in the human RAGE cytoplasmic domain after phosphorylation at Ser391 (star).

Independently or our work, Slowik *et al.* presented a very interesting result regarding the interaction of RAGE with G-protein-coupled receptors (GPCRs) [30]. Their study started from the discovery of a functional implication between RAGE and formyl peptide receptors (FPRs), *i.e.*, formyl peptide receptor 1 (FPR1) and formyl peptide receptor-like 1 (FPRL1, also known as FPR2), in the inflammatory response to neurodegenerative Alzheimer's disease. Slowik *et al.* revealed physiological interactions between RAGE and FPRs. The interactions broadened the spectrum of ligand responsiveness to FPRs; *i.e.*, RAGE ligands were also able to stimulate FPRs that were associated with increased levels of ERK1/2 phosphorylation and an accelerated consumption of cAMP in glial cells.

Interaction between GPCRs and RAGE may not be unusual. It was reported that G-protein-coupled chemokine receptors, CCR5 and CXCR4, co-function with CD4 [31] (a well-known T-cell surface glycoprotein composed of multiple Ig domains like RAGE) for human immunodeficiency virus (HIV) infection. Knowing this, Ichiki *et al.* recently succeeded in identifying another GPCR, leukotriene B4 receptor 1 (BLT1), as a RAGE partner on the cell surface [32]. Before their study, although a crucial role of BLT1 in promoting inflammation was well known, interactive proteins that modulate the pro-inflammatory function of BLT1 remained largely unidentified. The solution reported by

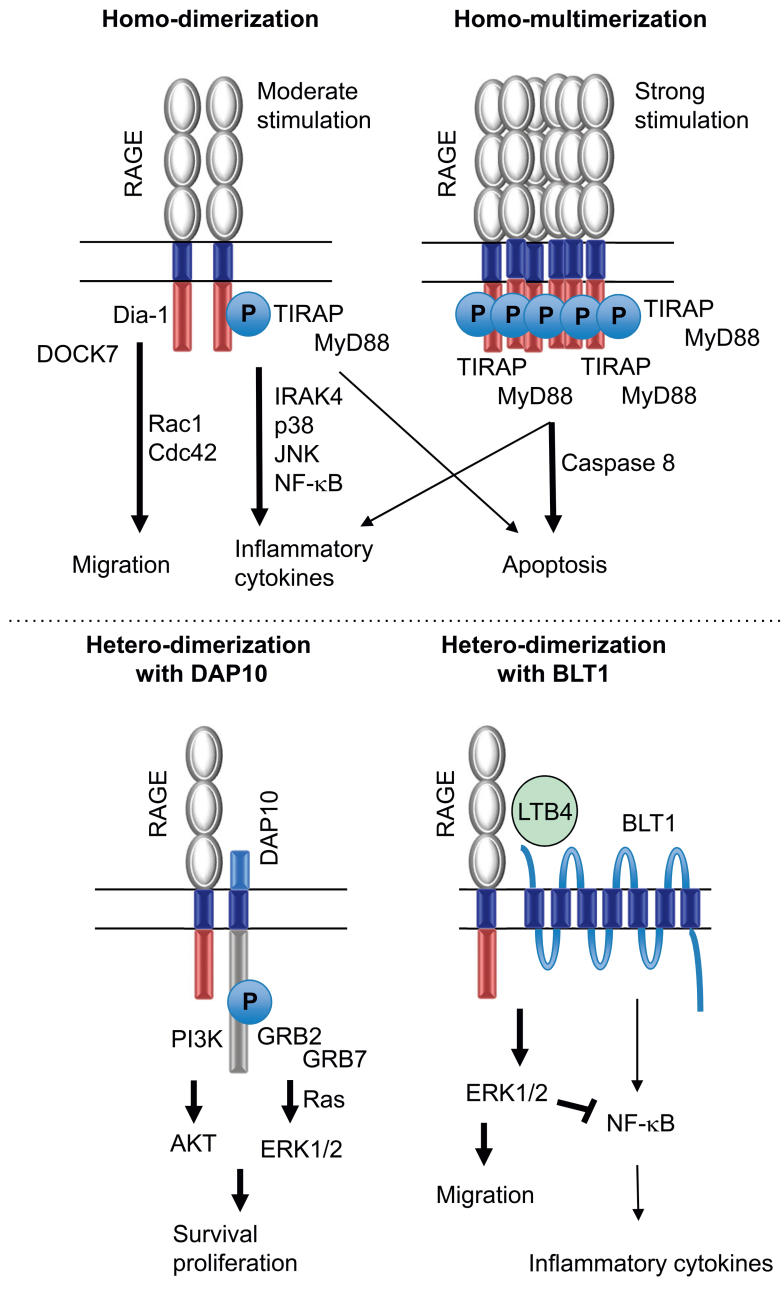

Fig. 2 Transmitting signals from RAGE-dimer, RAGE-multimer, RAGE-DAP10 complex, and RAGE-BLT1 complex. See the text for details.

Ichiki *et al.* was the novel finding of RAGE-BLT1 interaction in neutrophils. The results of their study clearly showed that RAGE binding regulates BLT1 signaling with positive and negative measures by controlling the key effector kinase, ERK1/2.

Although RAGE has an ERK1/2-mediated suppressive function for NF-κB, it remarkably enhances ERK1/2-mediated chemotaxis in neutrophils in response to LTB4 stimulation. That raises the question of how ERK1/2 suppresses NF-κB activation. The accurate mechanism still remains to be clarified. However, some clues have come from investigations [33,34] in which it was revealed that ERK1/2 negatively regulates NF-κB-mediated transcription through its regulation of the phosphorylation of the NF-κB p65 subunit or the important NF-κB cooperative protein, TATA-box binding protein (TBP). Thus, similar mechanism(s) may act in neutrophils. Taken together, these findings strongly support the idea that RAGE acts as a novel modifier for the LTB_4-BLT1 signaling pathway in inflammation-associated pathological contexts (Fig. 2, bottom panel).

Concluding remarks. In this review, we have introduced critical RAGE-binding proteins located in the cytoplasm and on the plasma membrane that modulate RAGE-mediated signaling diversity. Dia-1 and DOCK7 are recruited to the cytoplasmic tail of RAGE and activate Rac1 and Cdc42, resulting in an upregulation of cellular migration (Fig. 2, upper panel). The binding of both TIRAP and MyD88 induces multiple signals for the activation of several kinases including IRAK4, p38, JNK and IKKs. These are known to link with several cellular processes, such as the survival, apoptosis and acquisition of the secretory phenotype of inflammatory cytokines (Fig. 2, upper panel). However, under certain physiological conditions, specific signals seem to appear from ligand-stimulated RAGE in a cell type- and context-dependent manner. This makes the mechanism of RAGE signal regulation more complex. One clue to this mechanism may come from the expression levels of membrane adaptor molecules of RAGE. We identified DAP10 as a transmembrane adaptor for RAGE that is necessary to regulate the

RAGE downstream signaling for specific cellular processes such as survival and proliferation via activation of the PI3K-Akt pathway and probably GRB2/7-Ras-ERK1/2 too (Fig. 2, bottom panel).

In addition, Slowik *et al.* and Ichiki *et al.* identified FPRs and BLT1 as novel co-receptors of RAGE. RAGE's association with FPRs provides the FPRs' side with a broad ligand spectrum in glial cells, by which not only FPR ligands but also RAGE ligands lead to the active consumption of intracellular cAMP. The decreased level of cAMP may indirectly cause neuronal cell death through modulation of the neuron-interacting glial cell function in neurodegenerative settings. BLT1 interaction with RAGE is a critical determiner for neutrophil function (Fig. 2, bottom panel). The LTB4 ligand-BLT1 signals are modulated by RAGE in both negative and positive ways. While the alternately activated ERK1/2 suppresses the LTB4-BLT1-mediated activation of NF-κB, which leads to inflammatory cytokine production, it dominantly regulates the LTB4-BLT1-mediated induction of chemotaxis. We also speculate that the expression profiles for a series of proteins interacting with RAGE (including Dia-1, DOCK7, TIRAP, MyD88, DAP10, FPRs and BLT1) vary greatly depending on the cell type, in which partially overlapping or interfering signals among adaptors and receptors may be produced. This increasingly complicates the mechanism of RAGE signal regulation in cells. However, we sincerely hope that the discovery of novel binding partners for RAGE will lead to the gradual uncovering of RAGE's elaborate signal mechanisms in both physiological and pathological conditions.

Acknowledgments. This review depended in part on our studies supported by grants from the Project for Cancer Research And Therapeutic Evolution (P-CREATE) from the Japan Agency for Medical Research and Development to M.S. and JSPS KAKENHI grant #17H03577 to M.S.

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