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Minireview

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RAGE: The Beneficial and Deleterious Effects by Diverse Mechanisms of Actions

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Receptor for advanced glycation endproducts (RAGE) is a transmembrane protein that belongs to the immunoglobulin superfamily. RAGE is expressed ubiquitously-high in lung and moderate to low in a wide range of cells-in a tightly regulated manner at various stages of development. RAGE is a pattern recognition receptor that binds to multiple ligands, including amphoterin, members of the S100/calgranulin family, the integrin Mac-1, and amyloid β-peptide (Aβ). RAGE-ligand engagement effects the activation of diverse cascades that initiate and stimulate chronic stress pathways and repair, depending on the ligand, environment, and developmental stage. Further, RAGE-ligand interaction and the consequent upregulation of RAGE through a positive feedback loop are often associated with various diseases, including vascular disease, diabetes, cancer, and neurodegenerative disease. It is unknown how RAGE mediates these events, but such phenomena appear to be linked to the inflammatory response. In this review, we summarize the findings on RAGE from published reports and ongoing studies. Also, the implication of RAGE in Alzheimer disease, the most common neurodegenerative disease in the elderly population, will be discussed, with a focus on Aβ-RAGE interactions with regard to signaling pathways and their impact on cellular activity.

INTRODUCTION

Receptor for advanced glycation endproducts (RAGE) is a transmembrane protein that belongs to the immunoglobulin superfamily and is encoded in the Class III major hiotocompatibility complex on chromosome 6. RAGE is constitutively expressed during the embryonic stage and at lower levels in adulthood (Brett et al., 1993). This multiligand receptor comprises 5 domains, 3 extracellular immunoglobulin-like domains (1 V domain, 2 C domains), a single transmembrane domain, and a 43-amino-acid C-terminal cytosolic tail (Bierhaus et al., 2005). The V type domain, which has 2 N-glycosylation sites, is the principal area to which ligands bind (Srikrishna et al., 2002). The cytosolic tail is short but appears to be essential in sending intracellular signals downstream.

Advanced glycation endproducts (AGEs) are nonenzymatically modified proteins, lipids, and nucleic acids that are formed in a time-dependent manner; they were originally believed to be the primary ligand for RAGE. However, other ligands have since been identified, such as HMGB1 (high-mobility group box 1: amphoterin), S100 proteins (proinflammatory members of the calgranulin family), the integrin Mac-1, and amyloid β-peptide. These promiscuous ligands implicate RAGE as a pattern recognition receptor, identifying 3-dimensional structures of ligands rather than specific amino acid sequences.

RAGE-AGE interactions elicit proinflammatory responses in many cell types, including endothelial cells, smooth muscle cells, and mononuclear phagocytes, mediated by nuclear factor κB (NF-κB) and consequent cytokine expression (Basta et al., 2002; Lander et al., 1997). Amphoterin, a high-mobility group I DNA-binding protein, is highly expressed in developing neurons and mediates neurite outgrowth (Hori et al., 1995; Rauvala and Pihlaskari, 1987). Amphoterin is also released from cells that undergo necrosis, and its engagement with RAGE regulates immune responses. S100/calgranulins constitute a family of nonubiquitous Ca^{2+}-binding proteins, and their interaction with RAGE has trophic and toxic effects on neurons. RAGE is also the site on the cell surface to which Aβ binds in neurons, glia, and endothelial cells and mediates Alzheimer's disease (AD) pathology (Chen et al., 2007; Hofmann et al., 1999; Lue et al., 2001; 2005; Schmidt et al., 2001; Yan et al., 1996).

Various isoforms of RAGE, including full-length RAGE (fRAGE), membrane-bound RAGE, and soluble RAGE, are generated by alternative mRNA splicing and proteolytic cleavage (Fig. 1). One splice variant of RAGE pre-mRNA produces the membrane-bound form of RAGE, which lacks the extracellular ligand binding domain (N-truncated form, ΔN RAGE) (Ding and Keller, 2005; Kalea et al., 2009). Soluble RAGE lacks a transmembrane segment, and 2 types of soluble RAGEs exist: endogenous secretary RAGE (esRAGE) and cleaved RAGE (cRAGE). Splice variant encodes the secreted form of soluble RAGE, esRAGE, and cleavage of full-length RAGE by the membrane metalloproteinase ADAM 10 yields another form of soluble RAGE (cRAGE), (Raucci et al., 2008; Yonekura et al., 2003; Zhang et al., 2008).

The proteolysis of RAGE occurs constitutively and is stimulated by protein kinase C (PKC) activation (Zhang et al., 2008). In the sequential cleavage of RAGE, the ectodomain is shed by the α-secretase ADAM10 (a disintegrin and metalloproteinase

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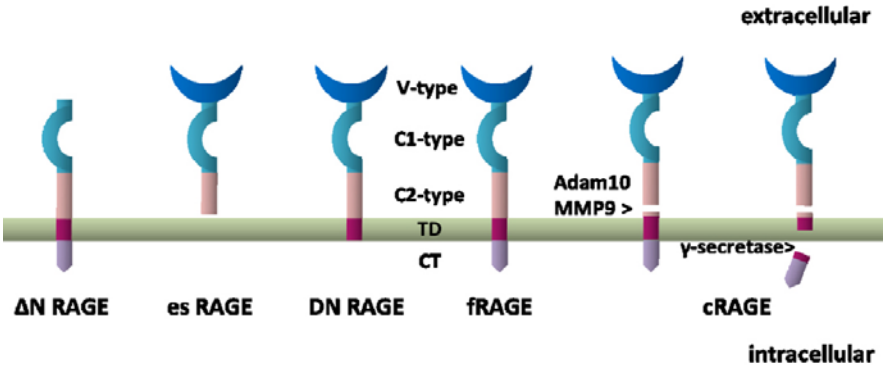

Fig. 1. Isoforms of RAGE, with the variable domains in different colors. RAGE isoforms are generated from splice variants (Ding and Keller, 2005; Kalea et al., 2009; Yonekura et al., 2003) or proteolysis by metalloproteinase 9 and γ-secretase cleavage (Galichet et al., 2008; Raucci et al., 2008; Zhang et al., 2008). fRAGE, full-length RAGE; ΔN RAGE, N-truncated forms of RAGE; esRAGE, endogenous secretory RAGE; DN RAGE, dominant-negative RAGE; cRAGE, cleaved RAGE; TD, transmembrane domain; CT, cytosolic tail.

10) and metalloproteinase 9 (MMP9) to generate sRAGE, and the remaining membrane domain is proteolyzed by γ-secretage (Galichet et al., 2008; Kojro and Postina, 2009; Raucci et al., 2008; Zhang et al., 2008). Calcium is an essential regulator of RAGE proteolysis. sRAGE and the RAGE intracellular domain (RICD), generated by ADAM10 and γ-secretage, are released into extracellular space and cytoplasm/nucleus, respectively; consequently, the change in subcellular localization of RICD induces apoptosis (Galichet et al., 2008). Notably, ADAM10 mediates both APP processing and RAGE shedding. Soluble RAGE is a decoy receptor that sequesters circulating ligands. RAGE splicing is fairly tissue-dependent-whereas fRAGE is the prevalent form in lung, esRAGE is the major isoform in endothelial cells. In serum, cRAGE is the predominant form of sRAGE, not spliced esRAGE (Raucci et al., 2008).

RAGE constitutes the epicenter of AD pathophysiology for several reasons. Neuronal RAGE binds to Aβ and upregulates RAGE expression followed by more Aβ generation, causing neuronal toxicity and synaptic dysfunction (Arancio et al., 2004; Cho et al., 2009; Origlia et al., 2008; Yan et al., 1996). RAGE also mediates Aβ-induced microglial proliferation and migration and stimulates and amplifies inflammatory responses - distinct hallmarks of AD (Bianchi et al., 2010; Fang et al., 2010; Origlia et al., 2010). RAGE in the blood brain barrier (BBB) is the primary means by which Aβ enters the brain compartment (Deane and Zlokovic, 2007; Mackic et al., 1998; Yan et al., 1996). Thus, RAGE appears to be pivotal in AD pathology, and we will discuss the details of this relationship.

RAGE and Aβ

The abnormal aggregation of Aβ and its resulting increases in intra- and extracellular accumulation constitute the disease-causing cascade of AD (Hardy and Selkoe, 2002; Meyer-Luehmann et al., 2008). Aβ peptide is generated by the sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases; the predominant adducts of cleaved APP are the Aβ40 and -42 fragments. Aβ tends to aggregate and produce Aβ oligomers, amorphorous aggregates, and fibrils. Aβ42 is the chief component of amyloid plaque, and Aβ40 is the most prevalent form in circulation (Zhang et al., 2009). Aggregation of Aβ peptide in neuronal inclusions and plaques has long been postulated to be the hallmark of AD pathology (Hardy and Selkoe, 2002; Mucke, 2009).

Since RAGE was reported to be the binding site of Aβ on cells and the mediator of Aβ-induced cellular alterations and toxicity, the function of RAGE in AD pathology has attracted much attention. There is much experimental support for the interaction between RAGE and Aβ, as evidenced by immunochemical colocalization in the neurons and microglia of AD brain tissue. Further, the expression of RAGE is elevated in murine AD models and human AD patients, implicating the importance of RAGE-Aβ interactions in the pathogenesis of AD (Deane et al., 2003; Yan et al., 1996; 1998). Notably, the amounts of Aβ deposits and plaques increase by overexpression of full-length RAGE, not by sRAGE (Cho et al., 2009). RAGE binds to diverse forms of Aβ: Aβ oligomer and aggregate and nonfibrillar and fibrillar forms of Aβ (Sturchler et al., 2008; Verdier et al., 2004). Kinetic studies suggest that purified RAGE binds specifically to Aβ ($K_d = 57 \pm 14$ nM), similar to K_d values in endothelial and cortical neurons (40 ± 10 nM and 55 ± 15 nM, respectively) (Yan et al., 1998). sRAGE interacts with oligomeric Aβ with high affinity ($K_d = 17$ nM), in addition to the soluble and fibrillar forms (Chen et al., 2007). Based on evidence that oligomerized ligands activate RAGE more robustly than the monomeric form and stimulate inflammatory programs and tissue injury-initiating genes (Herold et al., 2007), the binding of aggregation-prone Aβ to RAGE appears to effect neuronal damage and dysfunction in AD pathology.

It is unknown what causes this effect of the binding of oligomerized ligands, but several mechanisms are possible. The receptor can dimerize or oligomerize, as has been reported for cytokine receptor activation (Grotzinger, 2002). In addition, different binding sites can exist for aggregated ligands. RAGE is implicated in Aβ oligomer- and Aβ aggregate-induced apoptosis in SH-SY5Y cells (not Aβ fibrils), and distinct regions of RAGE mediate the binding of various conformations of Aβ; the V_d domain is important for Aβ oligomer binding to RAGE, and the C_{1d} domain controls the ligation of Aβ aggregates (Sturchler et al., 2008).

RAGE-Aβ interactions trigger diverse signaling cascades in endothelial cells, microglia, and neurons (Fig. 2), enhancing the expression and release of macrophage-colony stimulating factor (M-CSF) from neurons and microglia (Du Yan et al., 1997; Lue et al., 2001). In neurons, RAGE-Aβ engagement induces M-CSF expression through an oxidant-mediated NF-κB-dependent pathway. Increased amounts of M-CSF interact with microglial cognate receptor (c-fms) and trigger chemotaxis, microglial proliferation, and expression of macrophage scavenger receptor, which effect the inflammatory responses in AD (Du Yan et al., 1997). Also, newly activated NF-κB increases the expression of RAGE; the *RAGE* promoter contains 2 NF-κB-binding sites (Li and Schmidt, 1997). Thus, RAGE-Aβ-M-CSF axis stimulates the expression of RAGE and M-CSF in microglia and neurons and accelerates downstream signaling pathway. This positive feedback loop has often been attributed to the accumulation of RAGE ligands and subsequent RAGE

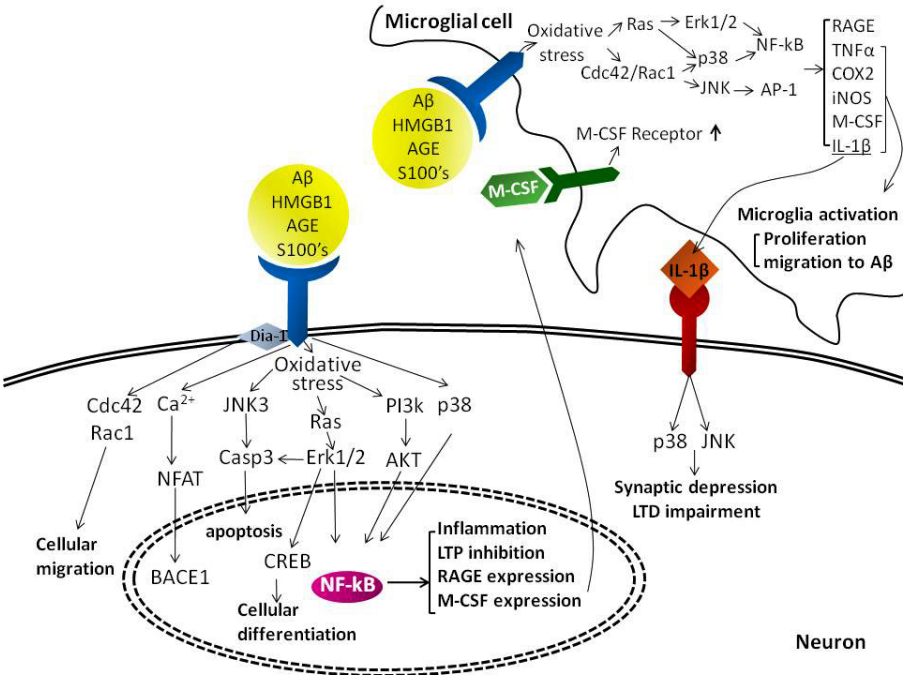

Fig. 2. Complexity of signal transduction pathways induced by RAGE-ligand engagement. See main text for details and references. RAGE binds to many ligands and activates diverse signal transduction pathways in different cell types.

engagement (Clynes et al., 2007).

RAGE-Aβ interaction induces oxidative stress in endothelial and neuronal cells and then activation of the transcription factor NF-κB, which is blocked by the inactivation of RAGE by anti-RAGE IgG or soluble RAGE (Yan et al., 1996). NF-κB exists as inactive form that is bound to nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha (IκBα) in the cytoplasmic compartment in the resting state; IκBα is degraded by phosphorylation on activation. The released NF-κB translocates into the nucleus and activates the transcription of NF-κB-regulated genes, including cytokines, adhesion molecules, antiapoptotic proteins, and RAGE. RAGE-induced NF-κB activation is prolonged, allowing cells to maintain and amplify chronic inflammatory responses (Barnes and Karin, 1997; Bierhaus et al., 2001).

A recent study observed the activation of p38 mitogen-activated protein kinase and ERK1/2 by RAGE-Aβ interaction (Origlia et al., 2008). It is unknown how RAGE cytoplasmic tail without kinase activity or phosphorylation site generates the diverse repertoires of RAGE signaling. To date, 2 direct binding partners for RAGE C-terminus have been identified–diaphanous-1 and ERK (Hudson et al., 2008; Ishihara et al., 2003). RAGE-mediated Rac-1 and Cdc42 activation requires the direct binding of diaphanous-1 to the C-terminus of RAGE to stimulate cell migration in certain cell type (Hudson et al., 2008). ERK also binds directly to the intracellular compartment of RAGE in the juxtamembrane region (18 amino acids) in a ligand binding dependent manner (Ishihara et al., 2003), which implicates a conformational change or clustering of receptors, leading to a direct interaction with the intracellular binding partner on ligand engagement.

RAGE expression increases 2.5-fold in AD patients compared with age-matched controls in neurons and endothelial cells that have experienced oxidative stress near Aβ deposits (Yan et al., 1996). Also, AD patients show higher microglial RAGE immunoreactivity in the dentate gyrus, CA, and subiculum regions of the hippocampus, which correlate significantly with Braak staging and plaque scores (Lue et al., 2001). Notably, RAGE expression is enhanced not only in cortical neurons but also in regions near Aβ deposits or cells that contain neurofibrillary tangles in AD, while RAGE expression in adults is restricted to cortical neurons.

Thus, Aβ appears to transduce signals in multiple pathways through interaction to RAGE in many cell types. Further, the upregulation of RAGE in AD and its proximity to Aβ deposits define the function of RAGE in AD pathophysiology.

RAGE binds to multiple ligands and initiates diverse signaling cascades

RAGE engages with multiple, structurally dissimilar ligands and activates diverse signaling pathways, depending on ligand, cell type, and developmental stage (Fig. 2). RAGE-AGE interaction activates oxidative stress-mediated p21 ras/MAPK and NF-κB activation in rat pulmonary artery smooth muscle (Lander et al., 1997). The JAK/STAT cascade is initiated by RAGE-AGE in rat kidney fibroblasts to regulate collagen production (Huang et al., 2001). The nuclear factor of activated T-cells 1 (NFAT1) pathway is also stimulated by RAGE-AGE interactions in cultured cells and AD animal models, mediated by calcineurin-induced dephosphorylation of NFAT1 and subsequent increases in intracellular calcium (Cho et al., 2009). NFAT1 binds to the promoter region of β-site APP-cleaving enzyme I (BACE1), a protease that is essential for Aβ production, and enhances its expression, thereby increasing Aβ deposits. Amphoterin binds to RAGE specifically with high affinity (K_d = 6.4 ± 1.0 nM) (Hori et al., 1995). RAGE-amphoterin engagement triggers several pathways, including the p44/42, p38, and SAP/JNK (c-Jun N-terminal kinase) MAPK pathways, which are linked to tumor proliferation and matrix metalloproteinase expression (Taguchi et al., 2000). Amphoterin induces Rac-Cdc42 activation and the ERK1/2-cyclic AMP response element-binding protein (CREB) pathway through interactions with RAGE; these pathways regulate neurite outgrowth and differentiation, respectively (Huttunen et al., 1999). Further, increased expression of chromogranin by

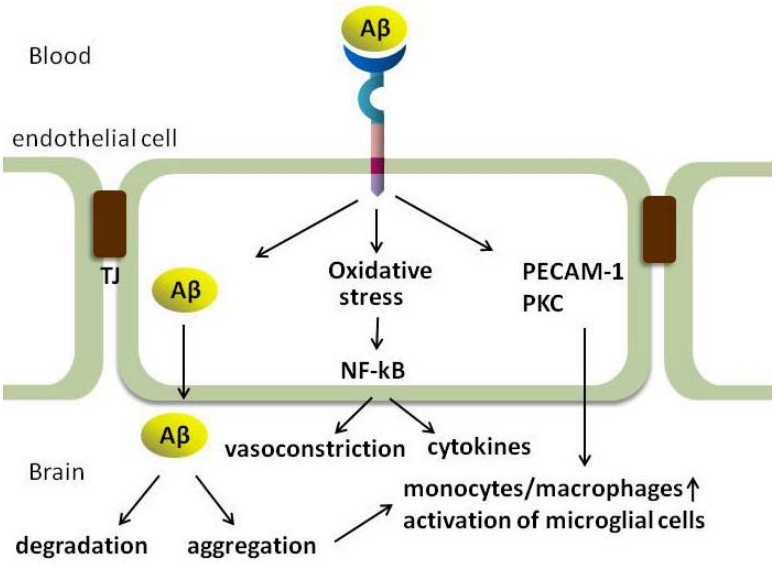

Fig. 3. Schematic of RAGE functions in the BBB. RAGE mediates Aβ transcytosis, Aβ-induced NF-κB activation, and monocyte/macrophage migration across the BBB (Deane et al., 2003; Giri et al., 2000; Mackic et al., 1998). TJ, tight junction.

ERK1/2-Rsk2-dependent CREB phosphorylation has been shown to mediate the neuronal differentiation that is stimulated by RAGE-amphoterin engagement (Huttunen et al., 2002). S100 is released into the extracellular compartment to regulate cellular survival and growth in a paracrine manner. Of the many subtypes in the S100 family, S100A12 and S100B are ligands for RAGE (Hofmann et al., 1999). S100B-RAGE engagement activates many pathways and affects many outcomes, such as Ras-MEK (mitogen-activated protein kinase)-ERK 1/2-NF-κB pathway for neural protection by upregulation of the antiapoptotic factor Bcl-2 and the GTPases Rac1/Cdc42 for neurite outgrowth (Huttunen et al., 2000). Specifically, upregulation of the antiapoptotic factor Bcl-2 by low concentrations of S100B through RAGE appears to be how S100B protects against Aβ toxicity, in addition to its function as a competitive inhibitor against Aβ for the same receptor, RAGE. Src kinase has been proposed to be an upstream regulator of RAGE-S100B-induced responses, because a Src kinase inhibitor, PP2, blocks RAGE-S100B-induced activation of MAPK, NF-κB, and STAT3; superoxide production; phosphorylation of caveolin-1; and expression of pro-inflammatory genes (Reddy et al., 2006). Oxidative stress by interaction of high concentration of S100B to RAGE is mediated by phosphoinositide 3- (PI3) kinase and NAPDH oxidase, and the caspase-3 cascade leads to apoptosis in dorsal root ganglia neurons, which is a likely mechanism by which diabetes neuropathy develops (Vincent et al., 2007).

RAGE expression in neurons, microglia, and the blood brain barrier

RAGE is expressed in neurons, microglia, and endothelial cells and is essential for neuronal development and neurite outgrowth during retinoic acid-induced differentiation (Wang et al., 2008). The activation of NF-κB mediates neuronal differentiation, and cdc42 activation, followed by GTPase and Rac1 activation, controls neurite outgrowth. In addition, neuronal RAGE is implicated in synaptic functions. The function of RAGE in Aβ-mediated alterations in synaptic function is complex, based on Aβ concentration and coordination between neurons and microglia.

The literature suggests that synthetic and naturally secreted Aβ impairs long-term potentiation (LTP) in the hippocampus and cortex through JNK, cyclin-dependent kinase 5 (CDC5), and p38 MAPK (Origlia et al., 2009; Wang et al., 2004). Inactivation of protein kinase A (PKA) and reduced CREB phosphorylation have also been suggested to form the underlying mechanism of Aβ-induced inhibition of LTP in hippocampal neurons (Vitolo et al., 2002). Neuronal RAGE inhibits LTP by nanomolar concentrations of Aβ treatment in the entorhinal cortex, mediated by p38 MAPK (Origlia et al., 2008; Wang et al., 2004).

Meanwhile, Aβ-mediated alteration of long-term depression (LTD) is controversial. Micromolar concentrations of Aβ impair hippocampal LTD through the endocytosis of surface and synaptic AMPA receptor via p38 MAPK and calcineurin activation (Hsieh et al., 2006); but other evidence suggests that Aβ facilitates LTD in the hippocampus and entorhinal cortex or does not affect it (Li et al., 2009; Origlia et al., 2008; Wang et al., 2002). Moreover, RAGE-null mice show normal LTD in the entorhinal cortex, suggesting that RAGE has no bearing on the expression of LTD (Origlia et al., 2008). Nevertheless, oligomeric Aβ, extracted directly from the cerebral cortex of AD patients, inhibits LTP, enhances LTD, reduces dendritic spine density, and impairs the memory of learned behavior in normal rodents (Shankar et al., 2008). Recent study by Origlia et al. proposes that the pivotal role of microglial RAGE to regulates Aβ-induced synaptic depression and LTD impairment (Origlia et al., 2010).

RAGE-Aβ interactions induce neuronal toxicity that is mediated by oxidant stress and NF-κB activation (Yan et al., 1996). RAGE causes reduction in MTT assay through exogenous treatment of the PC12 cell line with Aβ and this MTT reduction is manifested by RAGE overexpression. In addition, RAGE also mediates the neurotoxic effects of endogenous Aβ (Onyango et al., 2005). Based on studies in double-transgenic (Tg) mice that express mutant APP/RAGE (mAPP/RAGE), RAGE is implicated in Aβ-induced neurotoxic effects (Arancio et al., 2004). At the 3-4 months of age, significantly decreased number of cholinergic fibers is detected in the subiculum of mAPP/RAGE Tg mice compared with mAPP Tg, RAGE Tg, and nontransgenic mice. LTP, spatial learning, and memory are impaired in RAGE/mAPP Tg mice but not in mAPP Tg mice, and DN-RAGE/mAPP Tg mice (dominant-negative RAGE/mAPP, C-terminal-

truncated RAGE/mAPP) have intact spatial learning and memory and experience alleviation of neuropathology. Oxygen and glucose deprivation (OGD) in PC12 cells increases RAGE expression and induces cell death, which are mitigated by blockade of RAGE with a selective anti-RAGE antibody (Zhai et al., 2008).

Microglia is the resident macrophage in the CNS. Because microglia initiates Aβ-induced inflammatory responses and RAGE has the binding site for Aβ, the function of microglial RAGE in AD pathology is assured. Similar to neuronal RAGE, microglial RAGE expression rises in the hippocampus, parahippocampal gyrus, and superior frontal gyrus of the AD brain (Lue et al., 2001). Microglial RAGE regulates M-CSF expression through Aβ, chemotactic responses, and positive feedback of M-CSF and RAGE. Also, monocyte chemoattractant protein-1 (MCP-1) and TNF-α secretion is linked to microglial RAGE (Lue et al., 2005). Evidence suggests that microglial RAGE activation with ligand upregulates the expression of proinflammatory cyclo-oxygenase 2 (Cox-2) by two parallel axis of Ras-Cdc42-Rac1-dependent activation of JNK and Ras-Rac1-dependent NF-κB activation (Bianchi et al., 2010). Also, IL-1β and TNF-α expression is upregulated via simultaneous stimulation of NF-κB and AP-1 transcriptional activity through microglial RAGE engagement and different MAPKs are involved in IL-1 production (Bianchi et al., 2010; Kim et al., 2004). These upregulation of proinflammatory mediators implicates the role of microglial RAGE in neuroinflammation-related neurotoxicity.

Indeed, in recent study by Origlia et al. (2010), microglial RAGE is suggested as a main receptor to regulate Aβ-induced synaptic depression and LTP impairments in the entorhinal cortex. The Aβ-induced synaptic depression and LTD impairment was restored by the suppression of microglial RAGE using microglia-targeting dominant negative RAGE, however, not by the suppression of neuronal RAGE (Origlia et al., 2010). Also, interleukin-1β, p38MAPK and JNK appear to mediate Aβ-induced synaptic depression and LTP impairments in the entorhinal cortex. In subsequent study, microglial RAGE signaling by Aβ was investigated, effecting neuroinflammation through the secretion of proinflammatory mediators (TNF-α, IL-1β), Aβ accumulation, and neurotoxicity, leading to impaired learning and memory (Fang et al., 2010).

RAGE controls the entry of Aβ into the brain across the blood brain barrier (BBB, Fig. 3) (Deane et al., 2003). RAGE expression is enhanced in blood vessel walls near Aβ deposits in the AD brain (Yan et al., 1996). RAGE binds soluble Aβ dose-dependently at nanomolar concentrations and mediates Aβ transcytosis across the BBB in a time- and temperature-dependent manner (Mackic et al., 1998; Yan et al., 1996). RAGE mediates the transport and accumulation of pathophysiological concentrations of Aβ across the BBB in Aβ-enriched environments and in a transgenic mouse model, resulting in Aβ-induced stress in the vasculature and vasoconstriction through proinflammatory cytokine expression (Deane et al., 2003). RAGE-mediated Aβ transport across the BBB is blocked by RAGE-specific antibody or treatment with sRAGE and is absent in RAGE-deficient mice (Deane et al., 2003).

Moreover, RAGE in human brain endothelial cells mediates Aβ-induced migration of monocytes, which is a key event in the pathophysiology of Aβ-related vascular disorders, including AD (Giri et al., 2000). Like Aβ deposits, increased numbers of activated monocytes and microglial cells are observed in the AD brain. RAGE-Aβ interaction in endothelial cells initiates transendothelial migration of monocytes via platelet endothelial cell adhesion molecule (PECAM-1) and PKC. Thus, increased RAGE expression is also regarded as a mechanism that underlies enhanced Aβ transport and monocyte disposition into the brain in sporadic AD and its progression (Deane and Zlokovic, 2007; Giri et al., 2000).

CONCLUSION

RAGE has beneficial and deleterious effects, most of which are tied to the inflammatory response. Because RAGE is expressed in a wide range of cells, including neurons, microglia, astrocytes, and BBB endothelial cells, and interacts with multiple ligands, their coordinated responses in different places by various ligands have varied effects. Moreover, the existence of different isoforms of RAGE makes it more complicated to predict the outcome event. Yet, it is noteworthy that RAGE binds to Aβ and regulates Aβ-induced neuronal dysfunction and toxicity; thus, RAGE is an essential cofactor in Aβ-induced processes in AD neuropathology, rendering it a potential therapeutic target and biomarker.

It is unlikely that RAGE is the sole pathway by which Aβ induces neuronal alterations and toxicity, raising of the possibility that RAGE is unnecessary for the effects of Aβ (Liu et al., 1997). Aβ might exert its effects through mitochondrial dysfunction, defects in the endoplasmic reticulum, changes in intracellular calcium concentration, and disruption of cellular homeostasis. However, because RAGE is a specific receptor for Aβ and because RAGE expression increases in AD mouse models and human AD patients, RAGE should act as a eminent cofactor for Aβ in AD pathology.

sRAGE is a decoy receptor for Aβ. Intraperitoneal injection of sRAGE significantly decreases total Aβ and Aβ42 levels in the hippocampus in mAPP Tg mice (Deane et al., 2003). Formation of sRAGE-Aβ complexes and the sequestration of Aβ in circulation on treatment with sRAGE block the entry of Aβ into the brain, thereby reducing Aβ deposits in brain. Aβ-induced synaptic dysfunction and impaired behavior in mAPP/mPS1 Tg mice are restored by chronic treatment of sRAGE (Chen et al., 2007), implicating the therapeutic efficacy of sRAGE in AD.

In addition to its function as a decoy receptor, sRAGE inhibits Aβ polymerization *in vitro*, which strengthens the beneficial effects of sRAGE in AD (Chaney et al., 2005). This model has been challenged by several clinical trials and preclinical studies that have used RAGE antagonists or fusion proteins with the extracellular region of RAGE as potential treatments for AD. Using RAGE as a therapeutic target for AD might ultimately be accomplished with a better understanding of how RAGE balances beneficial and deleterious pathways of cellular activity.

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