Review Article

The S100B/RAGE Axis in Alzheimer's Disease

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Increasing evidence suggests that the small EF-hand calcium-binding protein S100B plays an important role in Alzheimer's disease. Among other evidences are the increased levels of both S100B and its receptor, the Receptor for Advanced Glycation Endproducts (RAGEs) in the AD diseased brain. The regulation of RAGE signaling by S100B is complex and probably involves other ligands including the amyloid beta peptide (Aβ), the Advanced Glycation Endproducts (AGEs), or transtheyretin. In this paper we discuss the current literature regarding the role of S100B/RAGE activation in Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly [1]. AD patients suffer from a progressive decline of cognitive functions that include language, personality, and memory impairments.

The pathological hallmarks of the disease are characterized by the presence of senile plaques (SPs), neurofibrillary tangles (NFTs), and severe gliosis in the cerebral cortex and the hippocampus [2]. Senile plaques result from the accumulation of extracellular amyloid-β (Aβ) fibrils [3] and contain elevated levels of zinc and copper ions [4]. Neurofibrillar tangles are mainly constituted of intracellular, abnormally phosphorylated tau protein [5–7]. AD brain is also characterized by increases in inflammatory responses, oxidative stress, dysregulation of calcium homeostasis [8], and by elevated levels of several S100 calcium-binding proteins namely S100B, S100A6, S100A9, and S100A12 [9–12].

Neurons, microglia, and endothelial cells, surrounding the senile plaques express higher levels of the receptor for advanced glycation endproducts (RAGEs) as the pathology progresses [13, 14]. Although its exact role in AD remains to be clearly established, RAGE appears to initiate several signal transduction cascades in response to ligands, related to AD including Aβ, AGEs, transthyretin, and S100 proteins. The present paper will focus and discuss the current knowledge on the role of S100B/RAGE axis in AD.

2. The Receptor for Advanced Glycation Endproducts

RAGE is an immunoglobulin-like cell surface receptor that is often described as a pattern recognition receptor due to the structural heterogeneity of its ligands. RAGE was initially identified as receptor for the advanced glycation endproducts (AGEs) [15, 16]. AGEs are formed by nonenzymatic modification of proteins or lipids by reducing carbohydrates, are highly heterogeneous (reviewed in [17]), and are often found elevated at sites of inflammation where they can trigger RAGE-dependent oxidative stress and NF-κB activation. NF-κB activation leads to increased RAGE expression because of the presence of NF-κB response elements within the promotor region of RAGE [18]. Activation of RAGE in turn results in sustained NF-κB activation [19]. Positive feedback loops between RAGE, oxidative stress, and inflammation can thus develop [20]. In this view high levels of AGEs have been found at site of inflammation and colocalize with neurofibrillar tangles and senile plaques in AD brain [21–23].

A second group of RAGE ligand is formed by amyloid-forming proteins or peptides such as Aβ peptide [13], and transthyretin (TTR) [24]. The amyloid β-peptide results from amyloid precursor protein (APP) processing by the beta and gamma secretases. Aβ accumulation in the brain plays a key role in the development of the disease [13, 25]. RAGE has been shown to mediate the transport of Aβ through the neuronal cell membrane and blood brain barrier [13, 26, 27].

In contrast, TTR has been suggested to have a protective effect in AD by binding to Aβ in a chaperone-like manner [28].

RAGE can also be activated by amphoterin (High Mobility Group Box 1, HMGB1) that plays a role in neuronal development and cancer [29]. Although it also plays a role in inflammation, we will not discuss the putative role of amphoterin in AD in this paper [30].

Another group of RAGE ligand is constituted by the S100 proteins. S100 proteins are small EF-hand calcium-binding proteins that regulate calcium homeostasis and modulate various enzymes involved in cellular functions such as cell growth, differentiation, and metabolism (reviewed in [31–33]). Twenty one members of S100 proteins have been described [34]. They all share high amino acid and structural homologies. Among them S100B, S100A6, S100A9 and S100A12 have been linked to Alzheimer's Disease [9–12].

Various alternatively spliced isoforms of RAGE exist [16, 35]. The two prevalent isoforms appear to be the full-length RAGE (RAGE) and the secreted isoform RAGE_v1 [36]. Full-length RAGE is composed of an extracellular part (314 aa), a single transmembrane spanning helix (27 aa), and a short cytosolic domain (41 aa) (Figure 1) [16]. The extracellular part of RAGE contains an Ig-like V-domain (residues 24–127) and two constant Ig-like C type domains frequently referred to as C1 (residues 132–230) and C2 domains (residues 239–320). RAGE possesses two N-glycosylation sites, one adjacent to the V-domain (residue 26) and the second one within the V domain (residue 81) (Figure 1) [16, 37]. Recent studies suggest that glycosylation may modulate the interaction of certain AGEs with RAGE [38, 39]. The RAGE_v1 splice isoform lacks the transmembrane and cytoplasmic portion and is released in the extracellular space (Figure 1) [36, 40–42]. The distribution and relative expression of the different RAGE isoforms are tissue specific. The full-length RAGE isoform is present at low levels in most adult tissues but at relatively high levels in lungs [43]. The truncated variant RAGE_v1 appears to be the prevalent isoform in endothelial cells and in human brain (Figure 1) [41, 44]. Interestingly, the soluble form of RAGE (sRAGE) can also be produced by proteolytic cleavage [45–47]. sRAGE produced either by splicing or shedding has been suggested to play the role of a decoy that interacts with free circulating RAGE ligand. RAGE_v1 expression is reduced in hippocampal neurons of AD patients. This could potentially lead to a sustained RAGE activation [48, 49]. In this view, sRAGE formed as a result of proteolysis could prevent Aβ peptide transport across the blood brain barrier and protect against Alzheimer's disease [50]. In the last five years, soluble RAGE has emerged as a new biomarker with potential clinical and therapeutic applications (reviewed in [51, 52]) and polypeptides based on RAGE_v1 are currently tested in clinical trials for their therapeutic effects against deleterious effects triggered by RAGE activation by its ligands.

However, the role of sRAGE and its regulation appears to be very complex. Indeed recent studies aiming at comparing the concentration of sRAGE in the serum of patients versus controls in various pathophysiological conditions have shown both negative and positive correlation between
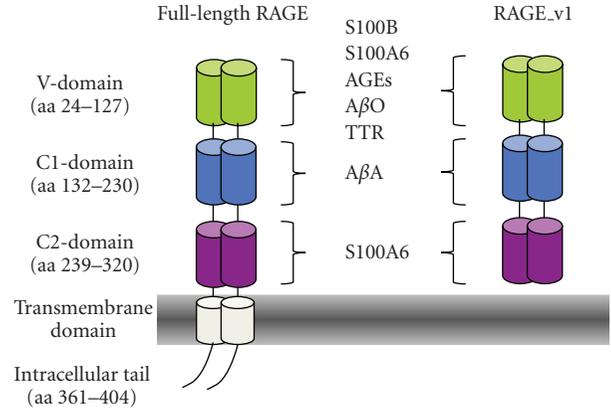
FIGURE 1: Schematic representation of the two main RAGE isoforms, full-length RAGE and RAGE_v1. Full-length RAGE is an immunoglobulin like receptor with one variable-like domain (V) and two constant-like domains (C) comprising residues. A short transmembrane domain anchors RAGE to the cell surface. A 41 residues intracellular tail is critical for signal transduction. RAGE_v1 does not possess the transmembrane domain and the intracellular tail. It is soluble in the circulation and plays the role of decoy to antagonize the activation of full-length RAGE by its ligands. A soluble form of RAGE can also be generated by proteolysis. S100B, AGEs Aβ oligomers, and TTR bind to RAGE V domain. Aβ aggregates binds to RAGE C1 domain. S100A6 binds both to the V and C2 domain but exerts its cellular effects preferentially through the C2 domain. The exact oligomerization states of full-length RAGE and RAGE_v1 are currently unknown. RAGE is arbitrarily represented as a dimer.

the concentration of sRAGE and the severity of the disease ([53, 54] and reviewed in [55]). Moreover, blocking RAGE function might not be beneficial in all pathologies. Indeed RAGE has been shown to modulate the regeneration of peripheral nerves in a mouse model of axotomy and blockade of RAGE signaling using sRAGE resulted in impaired regeneration in these animals [56–58]. Although a large number of studies with rodent models of human diseases have demonstrated the short-term benefit of treatment with sRAGE (reviewed in [52]), the long-term effects of such treatments remain also to be studied. The role of sRAGE as a decoy that would neutralize the excess of RAGE ligands also needs to be reconsidered at the view at recent studies showing very low concentrations (10–50 pM) of sRAGE in the serum of both patients and healthy individuals [53–55].

In order to understand the role of RAGE in the various RAGE-related pathologies including AD, it is important to understand how the different RAGE ligands interact with the receptor. Binding and activation of RAGE by S100B was first demonstrated in HUVEC cells [59]. In recent years, our laboratory and others have studied in detail the interaction of S100B with RAGE. S100B interacts preferentially with the V domain of RAGE and might involve multimerization of the receptor [60–62]. The V domain of RAGE is also the binding site of AGEs and TTR [63–66].

Aβ-RAGE interactions are more complex since Aβ exhibits several conformational states. Aβ is generated

by proteolytic cleavage of the transmembrane β-amyloid precursor protein (APP) (reviewed in [67]). The resulting 1-40 or 1-42 amino acid $A\beta$ peptides can form soluble oligomers ($A\beta$O), beta-sheet containing fibrils, and insoluble aggregates ($A\beta$A) [25, 68–74]. It is now believed that the synaptic dysfunction and neuronal death observed in AD patients are caused mainly by $A\beta$ oligomers and $A\beta$ fibrils [25, 71–73, 75–78]. We recently showed that the interaction of $A\beta$ with RAGE is driven by conformational states of $A\beta$. Indeed $A\beta$O and $A\beta$A were found to bind to distinct domains of RAGE, the V-, and C1-domain, respectively. Furthermore, $A\beta$O RAGE interaction was found to modulate ERK activity and to induce neuronal death [25].

Although S100B, AGEs, and $A\beta$O interact with the V domain of the receptor, it is currently not known if they interact within the same region of the V domain. Future studies will answer this question.

3. RAGE in Alzheimer's Disease

RAGE is up-regulated in the brain of Azheimer's disease and triggers the generation of proinflammatory cytokines at the blood brain barrier [13, 27]. The role of RAGE in AD has been demonstrated in cell culture and in animal models. In various cell types that include neurons, endothelial cells, and microglia, engagement of RAGE by $A\beta$ can lead to the formation of reactive oxygen species (ROS), the activation of NF-κB, or the expression of cell adhesion molecules mediating the recruitment of inflammatory cells [79, 80]. Neurons overexpressing RAGE showed higher susceptibility to $A\beta$-induced cell death than control cells [81]. Several models of transgenic mice have been used to demonstrate the role of RAGE in AD. The double transgenic RAGE/APP mouse model combines the overexpression of RAGE with the expression of mutants of APP [82, 83]. RAGE/APP mice show impaired spatial learning and memory capabilities, reduced basal synaptic transmission and long-term potentiation (LTP) compared to their single transgenic littermates. At the cellular level, these mice show reduced density of cholinergic fibers and synapses, characteristics often associated with AD-like pathology [83]. At the molecular level, RAGE/APP mice show enhanced activation of inflammation and stress-related MAP kinases and of the transcription factors NF-κB [83]. Despite these evidences the role of RAGE in Alzheimer's disease is still to be understood in detail. Indeed, recent experiments performed on RAGE (-/-) arcA-beta double transgenic animals showed that RAGE deletion could not prevent the decline in cognitive performance of the mice nor the age-related cerebral accumulation of $A\beta$ peptides [84]. These discrepancies may be due to differences in the mouse models used in the distinct studies. The Arc mutation is characterized by a change in amino acid within the $A\beta$ peptide sequence and thus may generate distinct peptide conformations that have less or no affinity for RAGE. Interestingly, the arcBeta transgenic mice showed reduced clearance of $A\beta$ across blood vessels [85]. This could reflect a decrease in the binding capacity of the arcAbeta for another of its receptor, LRP that has been shown to mediate brain efflux of $A\beta$ [86].

4. S100B

S100B is a member of the S100 protein family mainly expressed in the CNS [87]. Animal studies using S100B transgenic mice revealed that S100B plays important roles in spatial and fear memory, learning capabilities, and epileptogenesis [88–90].

Unlike other members of the S100 protein family, the gene of S100B is located on human chromosome 21 [91, 92]. S100B possesses two Ca^{2+}-binding sites of the EF-hand type, defined as a helix-loop-helix motif connected by a central hinge region. The C-terminal domain contains the classical EF-hand with a canonical 12 amino acid Ca^{2+}-binding loop whereas the N-terminal domain contains the S100B specific 14 amino acid Ca^{2+}-binding loop [93, 94]. S100B binds two calcium ions per subunit with moderate affinity (2–20 μM) [95]. Binding of calcium to the EF-hands triggers structural changes that allow the interaction with target proteins [32, 96]. Besides calcium, S100B also binds zinc (K_D = 0.1–1 μM) and copper (K_D = 2.2 μM), two metal ions highly abundant in senile plaques [32, 96–98]. Interestingly, binding of zinc to S100B results in higher affinity for both calcium and S100B's target proteins. The extracellular function of S100B may thus be altered in the brain of AD patients due to the high levels of zinc and copper [99].

S100B interacts with various intracellular targets. These targets have been extensively described in previous reviews [98, 100, 101]. S100B interacts with elements of the cytoskeleton (microtubules, type III intermediate filaments), with enzymes of the glycolytic pathway (fructose 1,6-bisphosphate aldolase, phosphoglucomutase), and with the tumor suppressor p53. S100B also regulates calcium homeostasis, protein phosphorylation and degradation [100]. S100B is mainly found as homodimer but can also form active tetramers, or hexamers exhibiting distinct functions [61, 102–104]. Furthermore, S100B is also able to interact with S100A1. This protein complex exhibits distinct physiological functions compared to S100B or S100A1 homodimers [32, 61, 102–105].

Besides its known intracellular function, S100B can also be secreted in the extracellular space where it acts as a cytokine. The secretion of S100B occurs via both the classical endoplasmic reticulum-Golgi pathway and an alternative pathway involving cytoskeletal tubulin [106, 107].

High levels of extracellular S100B have been detected in various clinical conditions that include brain trauma, ischemia and neurodegenerative, and inflammatory and psychiatric diseases [108, 109]. S100B is also a well-established prognostic marker for melanoma and high serum concentration of S100B correlate with poor prognosis [110, 111].

In the brain, S100B is actively secreted from astrocytes in the extracellular medium (Figure 2) [112]. S100B release is driven by the developmental stage of the astrocytes [112], and metabolic stress (oxygen, serum, or glucose deprivation) [113]. S100B can also be released in response to external stimuli such as glutamate [114], serotonin [115], the pro-inflammatory cytokines TNF-alpha [116] and IL-1beta [117], beta-amyloid peptides [118], 1-methyl-4-phenyl 1,2,3, and 6 tetrahydropyridine (MPTP) [119],
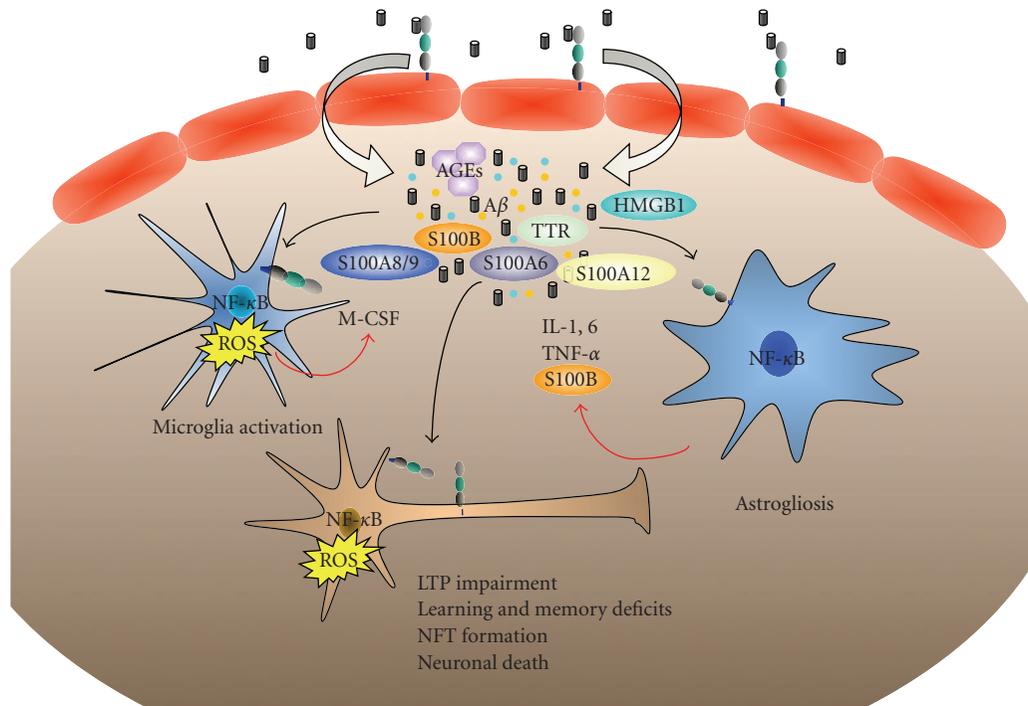
FIGURE 2: Crosstalk between RAGE and its ligands in Alzheimer's disease. RAGE mediates Aβ brain influx and accumulation. Aβ directly or indirectly triggers dysregulation of calcium homeostasis thereby activating the S100 proteins. RAGE-mediated activation of glia cells results in the activation of NF-κB driven gene transcription, and the release of inflammatory cytokines such as IL-1, IL-6, TNF-α, IL-1β, M-CSF and S100B. The brain of AD patients becomes the site of intense inflammation and oxidative stress that facilitates formation of AGEs. S100B, Aβ and AGEs as well as other RAGE ligands including TTR, HMGB1, S100A6, S100A8/A9, and S100A12 accumulate in the brain during the course of the disease. Secreted S100B and chronic RAGE activation trigger several AD-associated neuropathological features including microglia activation, the production of reactive oxygen species (ROS), neurite degeneration, NFT formation, and neuronal apoptosis ultimately leading to memory impairment.

forskolin, lysophosphatidic acid [120], and the plant natural antioxydants resveratrol and epicatechin [121, 122] and by the increase of calcium concentration [107].

Extracellular S100B has been shown to modulate the activity of neurons, microglia, astrocytes, monocytes, and endothelial cells (Figure 2). On neurons, S100B triggers trophic or toxic effects, depending on its concentration. Nanomolar concentration of S100B is neuroprotective, induces neurite outgrowth, and triggers glial cell proliferation in a RAGE dependent manner, whereas micromolar concentration of S100B is neurotoxic [120, 123–126]. At the molecular level, nanomolar concentration of S100B induces the upregulation of the antiapoptotic factor Bcl-2 resulting in neuroprotection. In contrast, when present in micromolar concentration S100B induces the up-regulation of caspase 3 through the activation of the oxidant stress-dependent MEK/ERK pathways, leading to apoptosis [126]. In addition, S100B can also modulate the toxicity of other extracellular molecules. In rat hippocampal neurons low concentration of S100B protects the cells against the toxic effect of N-methyl-D-aspartate, through the activation of NF-κB and possibly through the engagment of RAGE [127]. S100B also protects astrocytes and microglia against toxicity of trimethyltin [128]. Similar protection is observed in LAN-5 neuroblastomas, in the presence of Aβ peptide

[129]. Importantly, in these cells, higher concentration of S100B (micromolar) potentiates the toxicity of Aβ peptide.

S100B activates astrocytes in an autocrine manner and triggers the release of TNF-α and IL-6, probably through the activation of RAGE [130] leading to cellular inflammation (Figure 2).

Extracellular S100B can also stimulate endothelial cells, resulting in perpetuated activation of NF-κB and the up-regulation of vascular cell-adhesion molecule (VCAM-1) and the monocyte chemoattractant protein 1 (MCP-1) through the engagement of RAGE [59, 131]. Stimulation of endothelial cells by S100B results in adhesion and transendothelial migration of monocytes, leading to further inflammation in adjacent tissue [132]. Engagement of RAGE by S100B could thus contribute to the chronicity of inflammation observed to Alzheimer's disease [19].

5. S100B in Alzheimer's Disease

A role of S100B in AD is suggested by a large number of clinical studies showing elevated levels of S100B in the brain or cerebrospinal fluid of AD patients [9, 108, 133–137]. Furthermore, studies showed enhanced susceptibility to neuroinflammation and neuronal dysfunction after infusion

of Aβ in transgenic mice overexpressing S100B supporting a role for S100B in AD [138]. Additional supporting evidence comes from recent studies using double transgenic mice over-expressing S100B and carrying mutation in APP (Tg2576/S100B) [139]. Over-expression of human S100B in these mice promotes brain inflammation as shown by astrogliosis and microgliosis and enhances Aβ generation from APP.

Evidence also suggests a role of S100B in the formation of neurofibrillar tangles. Hyperphosphorylated tau protein is the main component of neurofibrilar tangles. S100B binds directly to tau protein in the presence of calcium resulting in the inhibition of its phosphorylation by Ca^{2+}/Calmodulin-dependent kinase II [140]. Intriguingly, extracellular S100B has also been found to promote RAGE-dependent hyper-phosphorylation of tau protein through the modulation of the JNK and Wnt pathways [141]. Thus, S100B exhibits opposite effects depending on its localization. In AD patients S100B is actively released and may promote the hyper-phosphorylation of tau protein and the development of neurofibrillary tangles in a RAGE dependent manner [129, 142, 143]. The secretion of S100B itself might be triggered by RAGE endocytosis [144, 145].

Thus, it is tempting to speculate that the role of S100B in Alzheimer's disease is mediated by RAGE and numerous studies mentioned in this paper support this hypothesis. Targeting specifically RAGE/S100B interaction in the brain might be beneficial to AD patients. Another interesting therapeutic approach may be to inhibit the binding of both S100B and Aβ to the V domain of RAGE using specific antibodies or small molecules.

6. Other RAGE Ligands in Alzheimer's Disease

Besides S100B, RAGE can also be engaged by other ligands that are all relevant in Alzheimer's disease.

S100A6 is another member of the S100 protein family. S100A6 is upregulated in astrocytes of animal models and in patients with AD [10]. High levels of this protein were also found in the senile plaques of AD patients [10]. The exact role of S100A6 in AD is currently unknown but our recent studies suggest that S100A6 might play a role through RAGE. Indeed we recently showed that S100A6 interacts with both the V- and C2-domains of RAGE *in vitro*. However, in contrast to S100B, the cellular effects triggered by S100A6 appeared to occur via the C2-domain only [62]. Two other S100 family members, S100A8/A9 and S100A12 may play a role in AD as well by participating in inflammatory-mediated events contributing to neurodegeneration. High levels of S100A9 and S100A12 have been found in microglia of patients suffering from sporadic AD [11, 12]. As with S100B, the effects triggered by S100A8/A9 and S100A12 could involve RAGE. Indeed, these two cytokine-like S100 proteins have been shown to interact with RAGE and to trigger RAGE-dependent cellular signaling [59, 146, 147] leading to sustained inflammation [24, 28, 148–153]. Thus, RAGE can be engaged by distinct ligands associated with AD.

Beside S100 proteins the senile plaques also contain elevated levels of AGEs, and TTR. The role of TTR in AD is suggested from both in vitro experiments and animal models studies [151–153]. RAGE interacts with both soluble and fibrillar TTR [149, 150]. TTR might have a protective effect in AD by binding to Aβ in a chaperone-like manner [28]. In AD settings, production of cytokines as a result of local inflammation would suppress TTR expression and reduce its protective role. However in other conditions TTR could also trigger NF-κB activation through RAGE resulting in sustained inflammation and cellular stress [24, 150].

7. Synergistic Effects between RAGE Ligands

Recent cell-based experiments have shown synergistic effects between the different RAGE ligands. In cultured neurons, AGEs and Aβ act synergistically resulting in increased APP and RAGE expression [142]. In microglia, Aβ acts as an amplifier of the inflammatory response when cells are preactivated with AGEs [143]. In endothelial cells, only AGEs pretreated cells could respond to stimulation by S100A8/A9 [154]. As mentioned earlier, S100B can also potentiate the toxic effect of Aβ in LAN-5 neuroblastomas [129].

8. Conclusion

Alzheimer's disease is a complex disease involving many molecular partners including RAGE and S100B. Following the large number of promising studies where blockade of RAGE could reverse a large number of symptoms in animal models, RAGE became a well-pursued therapeutic target. We mentioned earlier in the paper that polypeptides based on the sequence of sRAGE were currently evaluated in clinical trials [155]. Small molecule compounds are also currently in phase 2 clinical trials (Pfizer: PF-04494700 [156]). Targeting RAGE would be beneficial to treat chronic RAGE-dependent pathologies. However, the recent studies on the role of RAGE in peripheral nerve regeneration also suggest that care must be taken when blocking RAGE signaling.

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