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The Receptor for Advanced Glycation Endproducts (RAGE) and Mediation of Inflammatory Neurodegeneration

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Abstract

The Receptor for Advanced Glycation Endproducts (RAGE) is an immunoglobulin-type, transmembrane receptor that is expressed on numerous cell types in the Central Nervous System (CNS) and periphery, such as neurons, astrocytes, microglia, mononuclear phagocytes, epithelial cells and endothelial cells (ECs). RAGE binds a discrete repertoire of ligands, including non-enzymatically glycated proteins and lipids, also known as advanced glycation endproducts (AGEs), for which the receptor is named, in addition to multiple members of the S100/calgranulin family, oligomeric forms of Aβ, high mobility group box 1 (HMGB1), phosphatidylserine (PS) and lysophosphatidic acid.

Keywords: Alzheimer's disease (AD); Cerebrovascular Ischemia (CI); Parkinson's disease (PD); Amyotrophic lateral sclerosis (ALS); Dementia

Introduction

Extensive evidence has implicated RAGE as a critical player in regulating inflammation, as well as oxidative and cellular stress, in a variety of organ niches and disease settings, including the CNS during neurodegeneration [1-14].

This review will focus on the current state of knowledge regarding RAGE and neurodegeneration. Specifically, we will detail the effect of RAGE signal transduction on cellular stress, pinpoint clues into RAGE pathophysiology in the context(s) of increased RAGE ligand burden, discuss the systemic consequences of RAGE-driven inflammation in the CNS as a whole, and report on the increasing number of published genome wide association study (GWAS) findings and studies reporting on biomarkers of RAGE activity that collectively evoke strong indications for RAGE as a putative driver of cellular and systemic dysfunction during key neurodegenerative pathologies, most specifically Alzheimer's disease (AD), ischemic cerebrovascular disease, Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), frontotemporal dementia (FTD) and Multiple Sclerosis (MS).

Consequences of RAGE Signal Transduction

Our laboratory recently discovered that upon ligand engagement of the extracellular domains of RAGE, the RAGE cytoplasmic domain binds to its intracellular effector molecule, Diaphanous 1 (DIAPH1) [15,16]. DIAPH1 has subsequently been shown to be required for signal transduction induced by RAGE ligand binding, including the activation of mitogen activated protein kinases (MAPK), Rho GTPases and phosphatidylinositol 3-kinase (PI3K)/Akt signaling. RAGE-DIAPH1 signaling effects are dependent on many factors, including, but not limited to: cell-type, ligand form and ligand concentration, and the duration of signal induction (acute vs. chronic) [17-22].The implications of activation of these signaling cascades are substantial and predominantly pathological. The RAGE-DIAPH1 interaction drives the generation of reactive oxygen species (ROS), the induction of cellular migration, the upregulation of inflammatory cytokines and subsequent downregulation of ATP binding cassette (ABC) cholesterol transporters, such as ABCA1 and ABCG1, thereby mediating intracellular lipid accumulation and consequent cellular dysfunction [9,23-25].

RAGE signaling can directly impact mitochondrial health and function by modulating mitochondrial fission, ATP production, membrane potential and by promoting mitochondrial death pathways [26-30]. In pathological environments, RAGE signaling-induced cytosolic ROS production can promote production of mitochondrial ROS, thereby amplifying total ROS production [31-33].

Besides its role in RAGE-DIAPH1-mediated inflammation, DIAPH1 is a dynamic mediator of actin cytoskeleton stability and rearrangement, as well as a regulator of transcription factors [15,34-36]. It was recently reported that DIAPH1 was highly expressed in human gliomas; however, the specific details of DIAPH1 expression, including the cellular localization and the potential DIAPH1-mediated mechanisms of *in vivo* dysfunction in the rodent or human CNS, have not been elucidated [37]. Beyond this report, very little is known about DIAPH1 expression patterns and functions in the CNS of normal or degenerating models or humans; there are no known SNPs in *DIAPH1* that increase or decrease neurodegenerative disease risk. However, the impact of RAGE-DIAPH1 signal transduction in peripheral cells exhibits prominent overlap with the patterns of cellular dysfunction observed in neurodegeneration, including the increased production of ROS and pro-inflammatory cytokines and the downregulation of homeostatic molecules, such as neurotrophins and cholesterol/lipid handlers. This signaling culminates in significant alterations in critical cellular functions, such as migration, phagocytosis, replication and cell death, particularly in cells of myeloid and endothelial origin, but also in neurons [4,12,38-40].

Connecting the Dots: Potential RAGE Mechanisms in Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder that

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impacts millions of people worldwide and is not curable. While the primary risk factor for AD is advanced age, recent insights from genomic technology implicate inflammatory lipid and cytokine signaling in microglia, the myeloid cells of the CNS, as a prominent correlate of disease. Specifically, human GWAS suggest a powerful link between inflammatory pathways, including complement, chemokines and influential lipid and cholesterol molecules, such as Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), ABCA7, Apolipoprotein E variant 4 (APOE4) and others with AD susceptibility [14,20,41-49]. Additional analyses within animal models have illuminated various molecules critical to the innate immune system as major contributors to increased or decreased rate of AD progression, such as Chemokine Receptor Type 2 (CCR2), Chemokine Receptor 1 (CX3CR1 or GPR1), complement components (C1q and C3) and Chemokine Ligand 8 (CXCL8) [43,50-63].

The most prominent risk alleles and impairments were observed in humans and mice with loss-of-function mutations or deletions of the aforementioned chief lipid handling molecules. However, burgeoning data in humans and rodent models also indicate that systemic inflammation and transient infections in the periphery are sufficient to increase production of RAGE ligands, particularly AGEs and oligomeric Aβ. In contexts in which these ligands accumulate in the CNS, RAGE signaling is causally implicated in exacerbating ongoing neurodegenerative disease. In addition, RAGE has been shown to mediate mitochondrial dysfunction in neurons by transporting Aβ into the cells, which subsequently results in greater neuronal dysfunction and degeneration [64]. Atop the multiple mechanisms of augmented RAGE ligand production in AD, there is also prominent downregulation of specific detoxification mechanisms, which inhibit production of pre-AGEs such as methylglyoxal (MG) [65]. Glyoxalase 1 (GLO1), the principal enzyme that detoxifies MG, mitigates AGE production and is upregulated in the early and mid-stages of AD in human subjects. However, in the late and progressive stages of AD dysfunction, depletion of the enzyme's chief and essential cofactor, glutathione, reduces overall activity of the GLO1-AGE detoxifying system, thus facilitating increased AGE production and accumulation [65,66]. Altogether, these findings underscore a potentially profound link between peripheral and central inflammation, which prompts the question: to what extent might anti-AGE/RAGE therapies provide protective measures for neurodegeneration and AD, given the prominence of cellular stress driven by increased RAGE ligand burden [67-69].

Population-based studies have emerged suggesting links between RAGE, dementia, and AD. Genetic sequence variations in 20 genes associated with inflammatory signaling were recently probed for possible associations with dementia risk. From 1,462 Swedish dementia cases and 1,929 controls that were composed of twin and unrelated case-control samples, investigators identified a potential association of sequence variations near the gene encoding RAGE (*AGER*), to increased risk for dementia and AD, in two independent samples. Further, a recent structural analysis utilizing MRI technology revealed that atrophy of the right hippocampus substructure CA1 during AD progression was significantly correlated to the single nucleotide polymorphism (SNP) variant rs2070600 within *AGER* [70]. Notably, this variant has been previously associated with increased affinity to ligands and increased ligand-stimulated inflammation in cultured cells, in conjunction with decreased levels of circulating soluble RAGE (sRAGE) [71]. sRAGE is a short, soluble isoform of RAGE, and putative "decoy" receptor. Because it lacks the intracellular and cytoplasmic domains required for signaling, sRAGE is predicted to protect against inflammation and RAGE-dependent cellular stress by sequestering RAGE ligands and preventing their engagement of the full-length, transmembrane RAGE [72,73]. Thus, in humans bearing this SNP, lower sRAGE concentrations may directly amplify ligand burden and availability for signal transduction through full-length RAGE. This increases cellular stress, impairs lipid and cholesterol handling for the cells, in addition to promoting increased ROS production, thereby forging a feed-forward, self-perpetuating loop of inflammatory cellular stress in ECs, myeloid cells, and others within the CNS niche, including astrocytes, neurons, and oligodendrocytes.

Many of the mechanistic studies of RAGE in AD-like mouse models have been conducted in animals that are globally devoid of *Ager* and animals with dominant negative-RAGE (DN-RAGE) targeted to myeloid cells, using the macrophage scavenger receptor promoter. DN-RAGE is composed of the extracellular RAGE domains and the transmembrane domain; hence, although ligand binding to this construct is intact and it is tethered to the cell membrane, signaling is abrogated on account of deletion of the cytoplasmic domain. These DN-RAGE studies have indicated that RAGE signal abrogation confers a benefit for AD progression and suggest a role for RAGE in myeloid cells during AD [10,12,47,74]. However, there are possible caveats to these studies, particularly since it is plausible that DN-RAGE may also act as a decoy receptor and "ligand sink", much like sRAGE, and mice devoid of *Ager* or expressing DN-RAGE constitutively from birth may develop differently than a wild-type animal. Therefore, further investigation utilizing greater cell type- and temporal specificity would be key for definitively determining a role for RAGE in microglia during AD.

RAGE molecules expressed on ECs are also known to facilitate the transport of Aβ into and across the blood brain barrier (BBB) during AD, implicating RAGE in mediating the increased pools of ligand concentrations found during disease progression [9,75]. Since AGE production is increased in oxidized environments and RAGE engagement drives ROS production, there are additional entry points into the aforementioned feed-forward loop in which RAGE ligand binding drives increased RAGE ligand abundance, increased RAGE-DIAPH1 signaling and therefore increased ROS and AGEs. Together, this AGE-generating loop and the reduced expression of Low Density Lipoprotein Receptor-related Protein 1 (LRP1), the chief molecule responsible for transporting Aβ out of the brain in AD, collectively dysregulate the flux and trapping of AGEs and Aβ within the CNS as degeneration progresses [76]. Collectively, these data provide strong evidence for the RAGE-DIAPH1 signaling axis as a prominent mediator of inflammation and cellular dysfunction in a variety of cell types during AD, particularly by igniting an unconstrained iterative loop of signal propagation driving cell-intrinsic and cell-to-cell stress signals that mediate prominent impairments during AD.

Of note, the extracellular RAGE inhibitor, Azeliragon, is currently in Stage 3 clinical trials to investigate the therapeutic potential of RAGE inhibition in AD patients. Initially, in an 18 month Stage 2 clinical trial of 399 patients, the trial was preemptively halted when Azeliragon (then by the name of TPP488) was shown to be deleterious to patients at high doses (60 mg for 6 days followed by 20 mg), but protective at low doses (15 mg for 6 days followed by 5 mg) [77,78]. Currently, a Stage 3 study granted Fast Track designation by the United States Food and Drug Administration is being conducted that utilizes the low dose (5 mg for 18 months) vs. placebo. This trial, entitled the STEADFAST Study, was recently extended for an optional 2 year continuation in multiple countries across the world [79].

RAGE and Ischemic Cerebrovascular Disease: Acute and Chronic Implications

Acute and chronic ischemia of the brain leads to dramatic alterations in the health of the CNS, regardless of the mode of impact. Whether induced by stroke, cardiovascular disease, traumatic brain injury or pharmacological models of human disease, a large body of work has consistently linked cerebral ischemia to increased expression of RAGE and its ligands, particularly HMGB1, in the affected brain tissue. The same *AGER* SNP, rs2070600, associated with increased risk ratios for the development and progression of AD, has also been shown to be associated with increased risk of ischemic stroke (and Coronary Artery Disease), particularly in Chinese populations [80]. In addition, in assessments of specific sRAGE subtypes, increased levels of cell surface-cleaved soluble RAGE <48 h after the traumatic event, were significantly associated with a 2.44x increased risk ratio for poor outcomes following ischemic stroke in human populations [81]. Beyond this, very little is known about RAGE and its ligands in human manifestations of cerebral ischemia, although mechanistic studies in rodents may provide further lines of evidence for better understanding the ways in which RAGE contributes to the devastating effects of ischemic cerebrovascular disease.

Many studies in various rodent models utilize *in vivo* and *ex vivo* models of transient ischemia to study the impact of stroke and downstream adverse events of this acute event, including central post-stroke pain (CPSP) and connections to increased risk of AD. In particular, the transient middle cerebral artery occlusion (tMCAo) stroke model has been invaluable in illuminating potential roles for RAGE signaling in ischemia. Upon induction of ischemia by tMCAo, mice show an immediate and robust increase of RAGE expression in the striatum and cortex; however, inhibition of nitric oxide synthase in ECs in these regions greatly exacerbated these effects and led to an increased expression of IL-6, TNFα and RAGE [82]. Beyond receptor upregulation, subsequent mass spectroscopy studies have demonstrated that HMGB1 is upregulated in the cerebrum, spinal cord, and carotid nerve of mice and rats after ischemia [83,84]. Peripheral HMGB1 upregulation has been shown to be a specific driver of "sickness behavior" in the hyperacute injury recovery period and neutralization of HMGB1 and/or cytokines was shown to be protective for these behaviors and able to diminish peripheral immune exhaustion, which has been frequently observed after cerebral ischemia [83]. This work has paved the way for some of the most profound studies connecting RAGE regulation of the peripheral immune system and specific impacts on CNS health and disease-related behavioral abnormalities, perhaps most strikingly because cerebral ischemia, by definition, involves breakdown of the BBB and the consequent infiltration of peripheral RAGE-positive monocytes.

Subsequent work has also highlighted profound implications for hyperglycemia driving increased infarct volume and a decreased number of protective, non-inflammatory monocytes and macrophages infiltrating the injured CNS brain regions. Specifically, these studies have shown that the ablation of peripheral monocytes or RAGE/HMGB1 inhibition in peripheral monocytes, through genetic ablation of *Ager* or *Hmgb1*, provides benefits to mice with respect to hyperglycemia-induced impairments in stroke rehabilitation, including: decreased infarct area, prevention of BBB leakage, and decreased HMGB1 and RAGE expression, specifically in the cerebrum and microglia [85,86]. These findings were further supported by a subsequent study utilizing WT and AD-like mouse hippocampal slices subjected to oxygen glucose deprivation in the presence or absence of synthetic Aβ oligomers and showed that DN-RAGE targeted to the macrophage scavenger receptor promoter protected animals from ischemia and/or Aβ-induced synaptic impairments, thus implicating microglia RAGE in driving further detriments in ischemic cerebrovascular disease [87]. However, the previously mentioned caveats of DN-RAGE still pertain, and further mechanistic study of these findings utilizing more precise models would be helpful in elucidating the roles of central vs. peripheral myeloid cells and how other CNS cells, particularly ECs, are involved in RAGE-dependent cerebral ischemic impairments.

RAGE and Parkinson's Disease, Another Manifestation of Cellular Dysfunction

Parkinson's disease (PD) is another common neurodegenerative disorder that impacts millions of people worldwide and is characterized by the specific loss of nigrostriatal dopaminergic neurons and locomotor deficits [88]. While the cerebral location and neuronal subsets that degenerate in PD are distinct from AD, there are prominent cellular activation mechanisms driving inflammation and perturbation of neurons at the nexus of the two disorders. Akin to AD, the initiation of PD pathogenesis is still not clearly elucidated. However, there are many disease processes correlated to PD and AD pathogeneses, which could potentially be related to RAGE-DIAPH1 signaling, such as enhanced oxidative stress, innate immune activation, protein aggregation and neuronal death.

Multiple lines of evidence suggest a potential role for RAGE and its ligands in the pathogenesis of PD. First, the same *AGER* rs2070600 SNP that was implicated in CA1 atrophy during AD, was also correlated to the highest risk for PD development of all known *AGER* SNPs in a Turkish cohort GWAS (N=174 PD patients and N=150 healthy controls) [89]. In addition, when compared to healthy controls, PD patients have recently been shown to possess higher concentrations of RAGE ligands S100B and HMGB1 in the substantia nigra and cerebral spinal fluid (CSF) [90-92]. In rodent models, numerous studies have indicated that animals derive prominent protection from PD-like impairments when RAGE signaling was blocked through genetic ablation of S100b/Ager or by the administration of a RAGE inhibitor, FPS-ZM1, a BBB permeable, high affinity, multimodal blocker of RAGE [90]. Either strategy was sufficient to abrogate a variety of impairments observed in the PD-like rodent models, such as apoptosis of dopaminergic cells; locomotor defects; neuroinflammatory microgliosis and astrogliosis, as measured by increased ionized calcium binding adaptor molecule 1 (IBA1) and glial fibrillary acidic protein (GFAP) staining, respectively; tyrosine hydroxylase (and therefore dopamine) deficits; NF-$_{K}$B activation; and tumor necrosis factor alpha (TNFα) upregulation in the presence of PD-like syndromes induced by toxins. While many of these benefits only partially rescued cellular deficits or delayed the onset of disease, it is possible that RAGE-based interventions in AD and PD may provide meaningful avenues for therapeutic intervention in either condition of neurodegeneration.

Amyotrophic Lateral Sclerosis, Another Inflammatory Syndrome of the CNS?

Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disorder characterized by progressive loss of motor function and muscle atrophy. Much like AD and PD, many of the gene mutations linked to ALS have also been shown to drive inflammatory glial activation, oxidative stress, and neuronal loss. There is prominent overlap of disease phenotypes in ALS to other disorders with regard to the cellular consequences of RAGE-DIAPH1 signaling, although further

investigation is required to elucidate these mechanisms [93]. Several studies have reported increased concentrations of RAGE ligands in the spinal cord [94-96] and CSF of ALS patients [97]. Conversely, serum sRAGE was decreased in human ALS patients, thereby putatively increasing ligand burden available for binding to and inducing signaling through full-length RAGE [98]. While little mechanistic evidence is available linking RAGE and ALS, our laboratory recently showed that RAGE and its ligands are increased in the spinal cord of ALS patients [95].

Furthermore, this increase of RAGE and its ligands was recapitulated in one of the most commonly employed ALS rodent models, murine lines containing the familial G93A mutation in superoxide dismutase 1 (*SOD1*), as discovered in human ALS populations [3,99,100]. In these models, nerve growth factor (NGF) is post-translationally modified by oxidation and contributes to RAGE signaling-induced motor neuron death when normal motor neurons are co-cultured with SOD1 G93A astrocytes [101]. In addition, C6 rat astrocytoma cells overexpressing mutant SOD1 G93A protein displayed significantly increased RAGE ligand S100B expression and, intriguingly, inhibition of this process by siRNA targeting *S100b* ameliorated the inflammatory profile of these cells [3].

In the SOD1 G93A mice, daily administration of recombinant sRAGE extended lifespan and duration of healthy body weight, while slowing the onset of motor function loss [99]. Importantly, sRAGE treatment not only reduced motor neuron death but also decreased astrogliosis, indicating a more homeostatic profile in multiple cell types [99]. Altogether, a burgeoning body of literature suggests that RAGE activation, driven by an increased availability of ligands, is likely a contributing factor to ALS pathology. However, further work utilizing established BBB-permeable inhibitors of RAGE-DIAPH1 would be paramount in elucidating the value of targeting this signaling axis as a potential therapeutic target for slowing the progression inflammatory and neuron-perturbing signaling in ALS.

There is growing evidence that frontotemporal dementia (FTD) and ALS share certain molecular pathologies; in fact, a subset of ALS patients also exhibits behavior phenotypes of FTD [102]. Multiple genetic mutations have been linked to both ALS and FTD, including mutations within the genes: *C9orf72*, *CHCD10*, *SQSTM1* and *TBK1*, which contribute to RNA metabolism, autophagy, mitochondrial health, and microglial function [102,103]. Two reports have provided evidence of increased RAGE ligands in the CSF and cortex of FTD patients relative to control patients [104,105]. Altogether, there is probable involvement of RAGE to FTD-associated pathology when considering the increased RAGE ligands and the emerging molecular pathology overlap with ALS. It will be important to study RAGE signaling in the context of ALS/FTD mouse models such as *C9orf72* hexanucleotide repeat expansion transgenic mice to determine if approaches used to treat ALS would have any benefit to the cognitive pathologies associated with FTD.

Multiple Sclerosis and Experimental Autoimmune Encephalopathy (EAE)

Multiple Sclerosis (MS) is a debilitating neurodegenerative disease in which autoimmune tissue-destructive processes are implicated. In human subjects, the *AGER* rs2070600 SNP was associated with MS in several studies [72,106]. However, in a different study of a Hungarian community, this SNP was not identified. Although, another SNP within the *AGER* promoter suggested that altered transcription, rather than differences in ligand binding and sRAGE production, may be contributing to the risk of MS within this population [107].

With respect to sRAGE, akin to other inflammatory neurodegenerative syndromes discussed above, MS patients display lower serum levels of sRAGE relative to control patients and this decreased sRAGE inversely correlates with disease progression [108]. In addition, RAGE ligands are also increased in active MS lesions, as observed by immunohistochemistry. Further, *AGER* mRNA and RAGE ligand protein concentrations were increased in serum, CSF, and mononuclear cells in both niches during MS [108-112]. Interestingly, patients treated with disease-modifying drugs display a prominent reduction of serum HMGB1 when compared to untreated MS patients, which correlated to a better disease prognosis [111]. Fingolimod, a sphingosine-1P (S1P) analogue, has also been utilized to treat relapse-remitting MS in human patients, and induces a significant reduction in serum HMGB1 after 6 months of treatment while increasing sRAGE, albeit this study was conducted in a small patient cohort (n=17) [112].

Induction of experimental autoimmune encephalomyelitis (EAE), in which mice are immunized with myelin basic protein (MBP), has been utilized to study the molecular mechanisms underlying MS.

	RAGE SNPs	Animal Findings	Human Findings
Alzheimer's disease	rs2070600	1. Increased RAGE and ligands 2. Mitochondrial Dysfunction 3. Decreased detoxification molecules 4. Decreased sRAGE 5. Oxidative Stress 6. Microglia and ECs implicated	1. Increased RAGE and ligands 2. Hippocampal atrophy associated with SNP 3. Decreased sRAGE
Ischemic Cerebrovascular disease	rs2070600	1. Increased RAGE and ligands 2. Exacerbated by hyperglycemia in RAGE-dependent manner 3. Strong connections to peripheral monocytes, microglia and ECs	1. Increased RAGE and ligands 2. cRAGE increased acutely after stroke 3. RAGE+ Monocyte infiltration
Parkinson's disease	rs2070600	1. Increased RAGE and ligands 2. RAGE exacerbates all known symptoms of disease in models	1. Increased RAGE and ligands
Amyotrophic Lateral Sclerosis and FTD	No known SNPs associated	1. Increased RAGE and ligands 2. RAGE-induced motor neuron death 3. Stronger implication for astrocytes 4. sRAGE treatment beneficial	1. Increased RAGE and ligands 2. Decreased sRAGE
Multiple Sclerosis	rs2070600 RAGE promoter	1. Increased RAGE and ligands 2. sRAGE is protective for lifespan and peripheral infiltration 3. Most controversial due to lack of protection in global *AGER* KO	1. Lower sRAGE 2. RAGE and ligands increased in disease and MS lesions 3. Ligands go down with disease modifying drugs

Table 1: The manifestations of AD, PD, ALS and MS are distinct in nature.

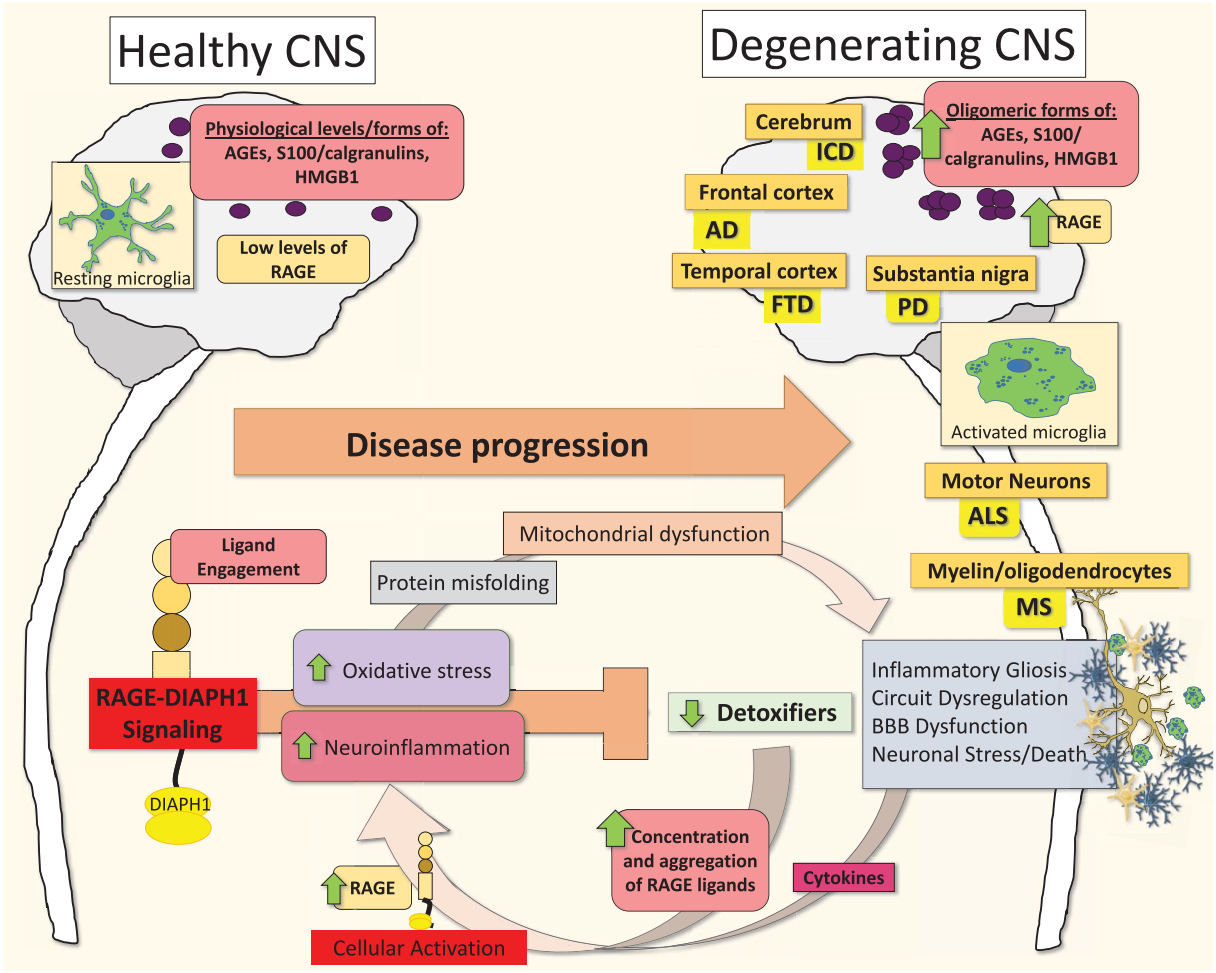

Figure 1: Working model of RAGE signaling in microglia and the pathogenesis of neurodegenerative disease.

Increases in pathological levels and oligomeric forms of RAGE ligands characterize the transition from health and homeostasis to disease-mediating activities in microglia during the progression of AD, ischemic cerebrovascular disease, PD, ALS, FTD and MS. These pathological RAGE ligands promote RAGE-DIAPH1 signaling-induced oxidative stress, cytokine production, gliosis and inflammation. Inflammatory cell activation further induces increased RAGE and RAGE ligand expression, while decreasing innate detoxifiers, thereby promoting an inflammatory feed-forward loop resulting in strikingly higher degrees of inflammatory gliosis, neuronal stress, BBB dysfunction and eventually, neuronal death. We posit that activation of the RAGE-DIAPH1 axis in microglia is an amplifying event and critical unifying pathway driving increased cellular stress and inflammation leading to neurodegeneration and the progression of AD, ischemic cerebrovascular disease, PD, ALS, FTD and MS

Abbreviations: AD: Alzheimer's Disease; AGEs: Advanced Glycation End Products; ALS: Amyotrophic Lateral Sclerosis; BBB: Blood-Brain Barrier; FTD: Frontotemporal Dementia; HMGB1: High Mobility Group Box Protein 1; ICD: Ischemic Cerebrovascular Disease; MS: Multiple Sclerosis; PD: Parkinson's Disease

Studies have reported increased RAGE expression in the spinal cords of mice with EAE [109,113], whereas blockade of RAGE signaling by recombinant sRAGE administered concomitantly with EAE induction in mice, significantly reduced immune cell infiltration into the brain and the severity of the disease [113]. However, controversy arose after a report that *Ager* deficient mice with EAE displayed no differences in disease severity [67].

Three distinct, but not exclusive possibilities may explain these seemingly conflicting results. First, recombinant sRAGE may exert some of its effects independent of RAGE signaling. It is possible that sRAGE is functioning as a pathological ligand sink in this instance that not only reduces RAGE signaling but other inflammatory signals as well through different receptors to which RAGE ligands may also bind. Second, the deletion of *Ager* from every cell may imbue detrimental effects due to unknown roles of RAGE in homeostatic functions and thus, a complete blockade of this signaling, as opposed to dampening, may reduce the benefits of RAGE inhibition. Third, it is well established that MS and EAE models in mice are characterized by periods of exacerbation vs. remittance of disease; hence, the timing of RAGE inhibition or *Ager* deletion *in vivo* may critically impact phenotypic outcomes.

Collectively, these considerations suggest that RAGE signaling is likely contributing to inflammatory perturbation in MS. Potential therapeutic interventions should investigate the possibilities of abrogating disease pathology by quenching RAGE ligands and/or preventing RAGE inflammatory signaling as well, although a much more detailed analysis of when and how to do so would still need to be conducted.

Conclusion

As summarized in the Table 1 and Figure 1, the manifestations of AD, PD, ALS and MS are distinct in nature, impacting differential

subsets of neurons and regional variability within the CNS. However, there are common underlying threads that strongly suggest similarities among these neurodegeneration syndromes, including increased accumulation of RAGE ligands and expression of RAGE, processes that trigger oxidative and cellular stress, and myeloid, neuronal, astrocytic and endothelial dysfunction. The last decade of research has generated a formidable body of evidence to suggest that RAGE signaling plays a prominent role in the pathophysiology of these inflammatory neurodegenerative syndromes, although many of the specific details remain to be fully elucidated. Although these findings are illuminative, multiple questions remain to be addressed, such as does RAGE signaling participate in disease induction and/or as a potentiation/progression mechanism in these disorders? Why do we sometimes discern differential outcomes upon the use of sRAGE, RAGE inhibitors, or, in animal models, introduction of DN-RAGE expression or genetic ablation of *Ager*? To what extent does RAGE play time-dependent roles during discrete periods of disease and in distinct cell types, in models vs. humans, and are the effects of RAGE specific to aging or prominent across the lifespan? Are there specific patient populations for which RAGE-based therapies would be most or least beneficial? To this end, the future application of recent insights from human GWAS data for the use of genetic testing in conjunction with measuring circulating sRAGE levels might be the first steps to determine the subpopulations in which the administration of RAGE inhibitors may increase healthspan. RAGE inhibition presents itself as an attractive target when aiming for therapies that assuage cognitive decline during neurodegeneration through interfering with feed-forward loops of inflammation and oxidative and cellular stress.

A new age in science is upon us where we are poised to integrate these varied questions. Excitingly, the novel discoveries that have revealed the genetics of disease susceptibility have occurred while many laboratories are concurrently flourishing in their revelations on the cellular and molecular mechanisms of RAGE signal transduction and novel fields have developed to optimize cell targeting and isolation technology, RAGE inhibitors, and more nuanced approaches for clinical trials. Does this mounting evidence suggest a prominent role for RAGE signal transduction in accelerating the pathogenesis of inflammatory neurodegeneration, irrespective of the disease subtype? Further work will undoubtedly be required to determine to what extent and in which specific contexts inhibiting RAGE signaling will protect the CNS from neurodegeneration. However, these developing studies have shown clear benefits of RAGE abrogation, and the future shows promise, particularly as we begin to take a more integrative approach to understanding the complex mechanisms of these devastating diseases and the possibilities of relief through meaningful interventions.

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