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Ligands of Receptor for Advanced Glycation End-Products Produced by Activated Microglia are Critical in Neurodegenerative Diseases

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Abstract

Receptor for advanced glycation end products (RAGE) and its ligands have been reported to be involved in the progressions of neurodegenerative diseases, including Alzheimer's and Parkinson's disease. Recently microglia activated by immunological stimuli, cytokines, or oxidative stress were reported to synthesize and secrete RAGE ligands including AGEs, HMGB1, and S100 in neurodegenerative diseases. Furthermore, RAGE/ligand binding has been implicated in neuroinflammation and in the progression of neurodegenerative diseases through a RAGE-mediated pathway in neurons.

A number of RAGE inhibitors, such as, antagonists, small RAGE inhibitors, anti-RAGE antibody, and soluble RAGE, have been shown to interfere with RAGE/ligand binding and to reduce RAGE ligand accumulation, microglia activation, and neuronal cell death in neurodegenerative diseases. Accordingly, RAGE inhibitors present an attractive therapeutic target in neurodegenerative diseases, and RAGE ligands might be useful diagnostic targets. Some human studies have shown RAGE ligand distributions in brain, serum, and cerebrospinal fluid are promising biomarkers for early disease detection and that these ligands might play important roles during early disease stages. Taken together, RAGE ligands and RAGE inhibitors appear to be good therapeutic and diagnostic candidates for neurodegenerative diseases.

Relations between Microglial Activation and Neuronal Cell Death in Neurodegenerative Diseases

Neurodegenerative diseases result from the progressive loss of neuronal cell functions and structures, and Alzheimer's disease (AD) is a chronic type of neurodegenerative disease [1]. The main causes of AD have yet to be determined, although 1% to 5% of cases harbor a genetic mutation [2]. Several studies have shown chronic inflammation contributes to the pathology of AD [3,4] and which is known to be related to microglia activation [5,6]. Although the cause of AD progression is unclear, AD is characterized by inflammatory responses to amyloid-β (Aβ), microglia activation, and astrocyte recruitment by Aβ deposits [7]. Parkinson's disease (PD) is occurs by loss of dopaminergic neurons in the substantia nigra (SN) and by many other events and agents, such as, genetic events or toxic drugs or chemicals, such as, 1-methyl-4-phenyl-1,2,3-6 tetrahydropyridine or rotenone [8,9]. Pathologic changes in the PD brain are closely related to microglial activation induced inflammation, which accelerates dopamine (DA)-producing neuron death. Interestingly, positron emission tomography (PET) studies have shown noticeable microglial activation in the SN, putamen and subcortical and cortical areas of the PD brain [10,11].

Molecular genetic studies are indispensable for understanding the central role played by Aβ in the pathogenesis of AD. Amyloid precursor protein (APP) mutation mouse models, such as, the PDAPP [12], Tg2576 [13], APP23 [14], APP/presenilin (PS1) models or APP/PS1/Tau mutation models, such as, the APP/PS1 [15], 3XFAD [16] and 5XFAD [17] models. The 5XFAD model shows an amyloid plaque formation, which exhibits neuron loss in cortical layer 5 and subiculum from 9 months [18] and inn this model; microglia is activated in the cortex (Figure 1), which is a region of neuronal death [18].

Genetic mutation animal models of PD have also been well established, such as, the PINK1, PARKIN, DJ-1, PARK9, LRKK2 and α-Synuclein models [19]. Although genetic models generally show features that appear in the PD, PINK1 [20] and PARKIN [21] genetic models do not exhibit DA related behavior abnormities and the DJ-1 [22], PARK9 [23] and LRRK2 [24,25] models do not exhibit changes in the number of DA-producing neurons in SN.

However, α-Synuclein genetic model exhibits hallmark pathologic features of PD, including progressive loss of the DA-producing neurons in the SN and reduced DA levels in the striatum [26] and formation of Lewy bodies in old animals [19]. In particular, α-synuclein has been reported to be related to microglia activation in the SN and striatum [27,28]. These observations suggest microglial activation is critical for neuronal cell death.

Microglia can be activated by toxins, cytokines, injury, or inflammation [29,30] and their activation has also been reported to be a key contributor [5,6,31]. Cytokines are involved in systemic inflammation and in degenerative disease and can be produced by neurons. In AD, amyloid β (Aβ), chromogranin A (CGA), interferon gamma (IFN-γ), and matrix metalloproteinase-3 (MMP-3) are candidate participants in neuronal apoptosis and microglial activation [32-34] and the cytokines α-synuclein, CGA, IFN-γ, MMP-3,
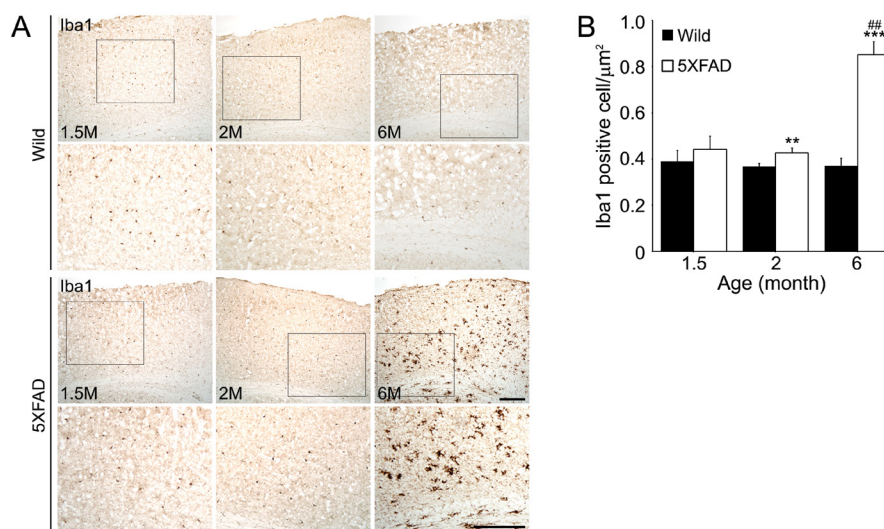
Figure 1: Microglia was activated in 5XFAD at 6 month. Activated microglia was determined by Iba1 staining and the number of Iba1 positive cells was counted. (A) Boxed area image is enlarged to the upper panel in cortex of wild type (top row) and 5XFAD mice (bottom row). (B) Quantitation of Iba1 positive cell was counted per mm2 in cortex. Scale bar; 100 μm. Statistical significance was marked with 2 symbols.
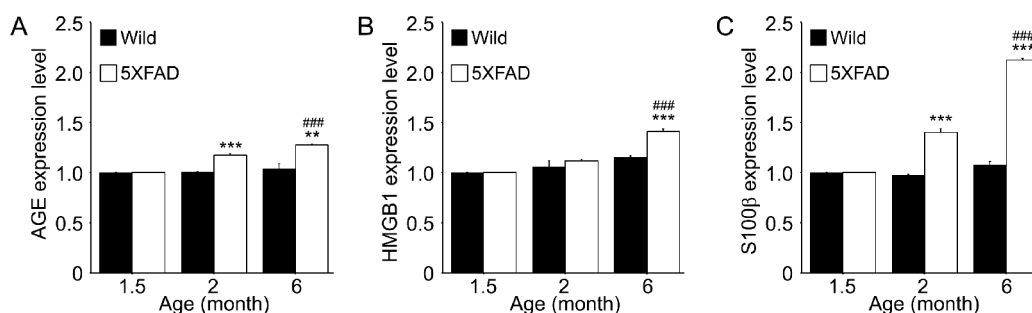 *; $p < 0.05$ versus wild type, #; $p < 0.05$ versus 1.5 month mice

Figure 2: RAGE ligands increased in 5XFAD at 6 month. The expression level of RAGE ligands including (A) AGE, (B) HMGB1, and (C) S100β was validated by In-direct ELISA in cortex of wild type and 5XFAD. Ratios represented in the graphs represented fold levels to 1.5 month mice.
Statistical significance was marked with 2 symbols
*; $p < 0.05$ versus wild type, #; $p < 0.05$ versus 1.5 month mice

neuromelanin, and tumor necrosis factor alpha (TNF-α) are candidate microglia activators in PD [35-41].

Secretion and Synthesis of RAGE Ligands by Activated Microglia in AD and PD

RAGE ligands include advanced glycation end products (AGEs), high mobility group box chromosomal protein 1 (HMGB1), lipopolysaccharide (LPS), macrophage-1 antigen (Mac-1), phosphatidylserine and S100/calgranulin and under pathologic conditions activate microglia [42-46], which then secrete and synthesize RAGE ligands, such as, AGEs, HMGB1 and S100β in AD [29] (Figure 2) and PD [47].

Advanced glycation end products (AGEs)

AGEs are considered to induce the development or support the progression of neurodegenerative diseases and their toxic properties are known to stem from oxidative stress and inflammation [48,49]. AGEs localize in senile plaques and extracellular spaces in AD [50-52] and AGE-albumin and RAGE binding stimulate the activations of diverse

signaling cascades through MAPK (mitogen-activated protein kinases) and bcl-2-like protein 4 (Bax) pathways that result in neuron apoptosis [29]. In PD, AGEs act as major structural cross-linkers, and are responsible for the formation of Lewy bodies in human dopaminergic neurons [53]. Furthermore, AGE-albumin and RAGE co-localization promote MAPK and Bax mediated DA-producing neuron apoptosis in the SN of Rotenone-exposed mice [47] in a manner similar to that observed in AD [29].

High mobility group box 1 protein (HMGB1)

Activated microglia secretes HMGB1 during inflammation in neurodegenerative diseases [54] and this secretion is increased by Aβ and promotes neuronal cell death. Furthermore, microglial infiltration and secretion of soluble HMGB1 are significantly elevated in the AD hippocampus and promote neuronal cell death, synaptic destruction and behavioral deficits [55]. The interaction between HMGB1 and RAGE activates the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway and leads to neuronal cell death via an autoregulatory loop, which exacerbates neurodegeneration and

neuroinflammation in AD [56]. HMGB1 is also released by microglia under inflammatory conditions, and in PD, binds to microglial Mac-1. Furthermore, these activities activate the NF-κB pathway and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase [57].

The S100 protein family

This low-molecular-weight protein family consists of approximately 25 proteins, which are involved in the regulation of protein phosphorylation, calcium homeostasis, transcription factors, and inflammatory response [58]. S100β is found in degenerative cells of AD and PD [59], and it has been reported S100β overexpression ameliorates AD-like pathology and enhances microgliosis and astrogliosis [60]. S100 proteins have also been reported to cause neuronal cell death via TNF-α and NF-κB in PD [61].

In the 5XFAD model, microglia activation increased at 6 months and significantly increased RAGE ligand levels at 6 months versus 1.5 months, and these ligands can promote neuron cell death at 9 or 12 months (Figure 2) [18]. Interestingly, in PD, secreted α-synuclein can activate microglia directly and LRRK2 has been related with the regulation of microglia activation in PD [62].

RAGE ligands are secreted and synthesized by activated microglia and accelerate neurodegenerative diseases via RAGE pathway (Figure 3). In particular, JNK and MAPK play important roles in neuronal cell death and seem to be induced by NF-κB in the presence of inflammation.

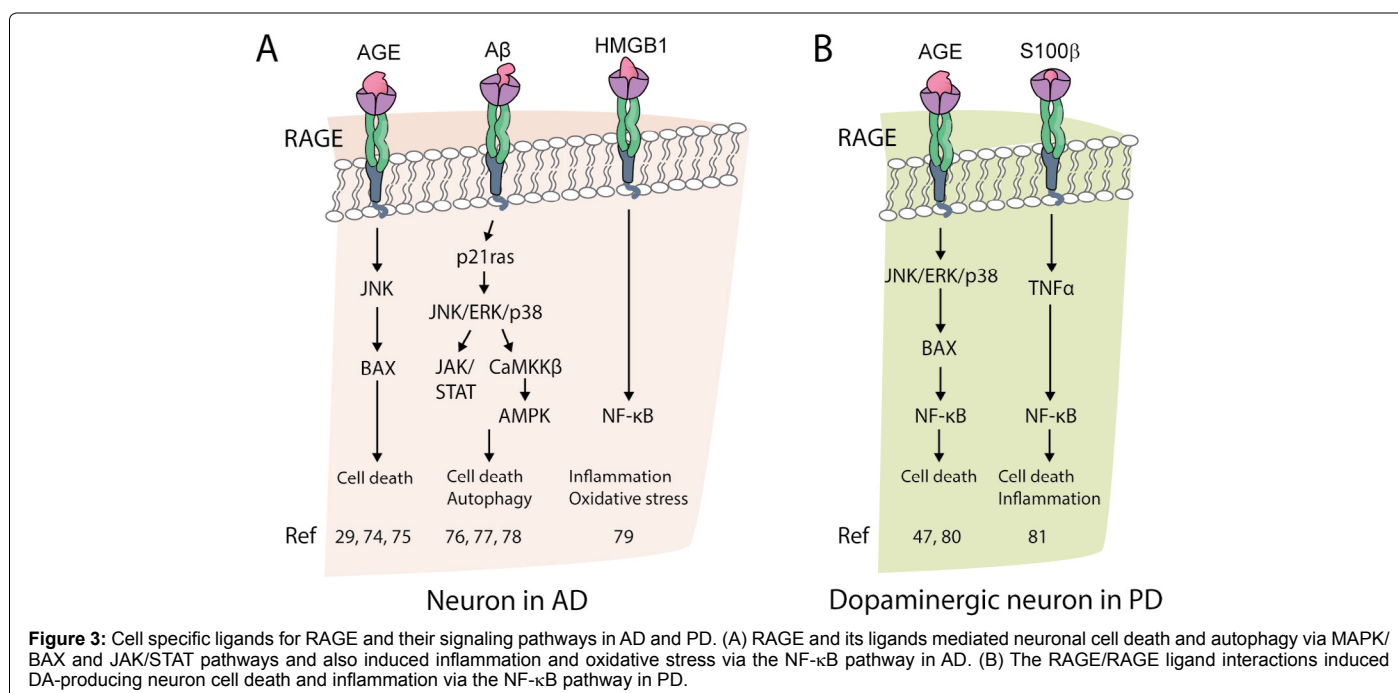## RAGE Ligands and RAGE as Potential Therapeutic and Diagnostic Targets in AD and PD

RAGE/ligand binding leads to neuronal cell death, and thus, the inhibition of this binding considered an important strategy for treating neurodegenerative diseases [29,47]. Furthermore, anti-RAGE therapy using an antagonist, small molecule RAGE inhibitors, soluble RAGE (sRAGE) or anti-RAGE antibody has been reported to protect neurons [63-66]. In AD, FPS-ZM1 (a high-affinity RAGE-specific inhibitor) was found to specifically bind to the V domain of RAGE, to cross the Blood-Brain-Barrier (BBB), and to inhibit Aβ-induced cellular stress [63], and FPS-ZM1 protected neurons from mitochondrial injury and oxidative stress by reducing RAGE/ligand binding directly or reducing Aβ levels indirectly in brain [67-69]. In addition, a number of RAGE inhibitors are undergoing clinical trials for the treatment of AD. Azeliragon (TTP488), which was developed by vTv Therapeutics (formerly TransTech Pharma), is a candidate for the treatment of mild AD and is currently the subject of a phase 3 clinical trial [70]. TransTech Pharma also developed PF-04494700, which inhibits RAGE/Aβ-42 binding. This agent, which is administered orally, crosses the BBB and helps reduce Aβ accumulation and spatial memory defects [71].

Some evidence indicates sRAGE and anti-RAGE antibody block RAGE/ligand binding in AD. sRAGE is a splice variant of RAGE that binds RAGE ligands more effectively than RAGE, and thus, down-regulates the RAGE-mediated pathway. sRAGE and anti-RAGE antibody act by inhibiting Aβ uptake and RAGE/ligand binding [29,63], but sRAGE also reduces cell death of DA-producing neuron through MAPK phosphorylation, Bax expression in PD [47]. RAGE ligands can also be used to support diagnoses of AD or PD. Generally, MRI and cerebrospinal fluid (CSF) biomarkers related to AD, do not provide evidence of neurodegenerative change or amyloid clearance [71,72]. However, it has been reported that some RAGE ligands might be useful diagnostic targets. In the human AD brain, AGEs are distributed in neuron cytoplasm in the hippocampus and para-hippocampal gyrus and in one study, serum and CSF levels of *AGEs* were suggested as biomarkers for the early detection of AD [72]. Furthermore, AGE accumulation has been observed in incidental Lewy Body diseases (a presymptomatic PD state) as well as in the Lewy bodies of PD patients [73]. These studies suggest AGEs/RAGE binding plays an important role during the early stages of neurodegenerative diseases [73].

Conclusion

The role played by activated microglia in neuronal cell death has been well established in neurodegenerative diseases. Microglia activated by immunological stimuli, oxidative stress or cytokines secrete and

Figure 3: Cell specific ligands for RAGE and their signaling pathways in AD and PD. (A) RAGE and its ligands mediated neuronal cell death and autophagy via MAPK/ BAX and JAK/STAT pathways and also induced inflammation and oxidative stress via the NF-κB pathway in AD. (B) The RAGE/RAGE ligand interactions induced DA-producing neuron cell death and inflammation via the NF-κB pathway in PD.

synthesize RAGE ligands, such as, AGEs, HMGB1 and S100β, and these ligands trigger deleterious, RAGE mediated, signaling, which results in neuron death in AD and PD. A number of RAGE inhibitors, including antagonists, small molecule RAGE inhibitors, sRAGE and anti-RAGE antibody have been demonstrated to ameliorate the pathologic processes of AD and PD. Moreover, RAGE ligands in serum or CSF can be used diagnostically to detect the presence of AD and PD. Furthermore, evidence at hand indicates RAGE inhibitors and RAGE ligands are good therapeutic and diagnostic candidates in AD and PD [74-81].

Contribution

Myeongjoo Son and Seyeon Oh have equally contributed.

Acknowledgement

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