Short communication

RAGE and its emerging role in the pathogenesis of Parkinson’s disease

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A R T I C L E   I N F O

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A B S T R A C T

Receptor for advanced glycation end products (RAGE) is a multiligand receptor belonging to the immunoglobulin superfamily and plays crucial roles in the development of many human diseases such as neurodegenerative diseases, diabetes, cardiovascular diseases, osteoarthritis and cancer. RAGE involves in a number of cell processes such as neuroinflammation, apoptosis, proliferation and autophagy. In CNS, RAGE was primarily expressed in neurons, microglia and vascular endothelial cells. Interacting with ligands, RAGE induces a series of signal transduction cascades and leads to the activation of transcription factor NF-κB as well as increased expression of cytokines like TNF-α, IL-1. Moreover, binding to RAGE can also stimulate the generation of reactive oxygen species (ROS), which is implicated in neuron death. It was reported that RAGE were highly expressed in PD patients when compared to age-matched controls. And RAGE ablation protected nigral dopaminergic neurons against cell death in MPTP treated mice. Here we review this article to elucidate the role of RAGE in PD pathogenesis and highlight the anti-RAGE strategies in the treatment of PD.

1. Introduction

Receptor for advanced glycation end products (RAGE) is a multiligand protein belonging to the immunoglobulin superfamily, which was first identified and described in 1992 as a receptor for advanced glycation endproducts (AGEs) [36]. A broad spectrum of ligands has been identified to interact with RAGE and up-regulates the expression of RAGE, which further induces RAGE-mediated cellular dysfunction via the activation of different signaling pathways. In addition, RAGE activation has been implicated to be involved in the process of inflammation, apoptosis, autophagy, and proliferation, as well as the pathogenesis of degenerative diseases such as Alzheimer’s disease, peripheral neuropathies and amyotrophic lateral sclerosis (ALS) [46]. Recent works proposed a role of RAGE in the pathogenesis of Parkinson’s disease (PD), which is a neurodegenerative disease characterized by degeneration of dopamine-producing neurons. The exact etiology of PD is unknown, however, increasing evidence has shown that oxidative stress and neuroinflammation involved in the fundamental process contributing to the neuron death in PD [42,50]. In this review, we focus on the outcome of RAGE-ligands interaction, and highlight the potential role of RAGE activation in PD pathogenesis. Specifically, anti-RAGE strategies in the treatment of PD were summarized.

2. RAGE isoforms

The RAGE gene is composed of a 5′ flanking region that regulates its transcription, 11 exons and a short 3′ UTR. The resulting transcribed mRNA of ∼1.4 kb is translated into a protein of 404 amino acids with a molecular mass of ∼55 kDa [1]. RAGE has a complex molecular structure, which consists of an extracellular region (aa 1–342), a short hydrophobic transmembrane spanning region (aa 343–363), and a highly charged amino acid cytoplasmic tail (aa364–404). The extracellular region contains a signal peptide (aa 1–22), followed by one N-terminal V-type immunoglobulin domain (aa 23–116) and two C-type (C1 and C2; aa124–221 and 227–317) immunoglobulin domains [1,22]. And the N-terminal V-type (V-type domain) is considered as the principal binging site for potential extracellular ligands, while the cytosolic region is essential for recruiting cellular effector and triggering downstream signaling [12,28]. Traditionally, investigators demonstrated the characterization and identification of human RAGE splice variants by analysis of RAGE cDNA from tissue and cells, other 19 RAGE splice forms (RAGE_v1-19) were revealed. Some of them were not previously detected. According to the research of Barry I. Hudson et al. the RAGE_v1 (sRAGE) variant was the primary secreted soluble isoform of RAGE [22].

Recent years, RAGE isoforms were usually divided into three types (Fig. 1). The RAGE gene is located in chromosome 6 close to major histocompatibility complex III (MHC class III), indicating its involvement in immune responses [44]. The membrane-bound form of RAGE is named full-length RAGE, which consists extracellular domain, transmembrane domain and cytosolic domain. Besides, N-truncated and C-truncated forms of the receptor have been described. Two primary
mechanisms, alternative pre-mRNA splicing and proteolytic cleavage of full-length RAGE, give rise to multiple RAGE isoforms [8,57]. The N-truncated RAGE lacks V domain and is unable to engage glycated end products, therefore, it participates in the regulation of angiogenesis in a way that is independent from the classical RAGE activation pathway [22,59]. The C-terminally truncated forms majorly form a pool of soluble RAGE (sRAGE) including endogenous secretory RAGE (esRAGE) and cleaved RAGE (cRAGE). sRAGE has the ability to bind to the various RAGE ligands and therefore, it plays an antagonistic role by preventing the activation of full-length RAGE [35].

Only mature animals express RAGE. And RAGE in lung has been found to be constitutively expressed at high levels. In the lung, the basolateral membranes of alveolar type I epithelial cells and alveolar type II cells are where the expression is localized. However, the exact role or function of this high expression in the physiology of these cells remains poorly defined [43]. RAGE is also widely expressed in many cell types including neurons, cardiomyocytes, neutrophils, monocytes/macrophages, lymphocytes, dendritic cells, and vascular endothelial cells [26]. Under physiological conditions, the expression of RAGE is relatively low in most tissues [36], whereas the expression is up-regulated in the pathophysiological settings, such as neurodegenerative disorders, chronic inflammation, or diabetes [58].

3. RAGE–ligands interaction and oxidative stress and neuroinflammation

RAGE is a pattern-recognition receptor and is capable of binding to multiple types of ligands. A large number of ligands for RAGE have been identified in the brain, including advanced glycosylation end products (AGEs), S100B/calgranulins and high mobility box group 1 (HMGB-1) [24,31,48].

Advanced glycation end products (AGEs) are a heterogeneous group of proteins, lipids and nucleic acid that become glycated and oxidized after persistent contact with reducing sugars via non-enzymatic reaction [3]. AGEs has been demonstrated to accumulate in senile plaques and neurofibrillary tangles (NFTs) of AD brain and frontal cortex of PD patients [11,33]. Interestingly, RAGE is not the only receptor for AGEs. Other receptors for AGE have been known such as macrophage scavenger receptors (MSRs), AGE-R1, AGE-R2, AGE-R3, CD36 and so on. Nevertheless, these AGE-associated receptors are mainly implicated in the regulation of endocytosis and degradation of AGEs, whereas RAGE is the AGE receptor that is involved in signal transduction [47].

Similarly, S100B is a member of S100/calgranulin protein that is highly expressed in neurodegenerative diseases such as AD and PD [29,42]. The expression is localized predominantly to astrocytes and specific neuron populations [14]. In injured brain tissue, S100B over-production causes excessive neuronal RAGE stimulation that culminates in overproduction of ROS and neurotoxicity [15]. Another RAGE ligands, HMGB1, is an on histone DNA-binding protein that plays an important role in chromatin remodeling [21]. Similar to S100B, HMGB1 serves as beneficial as well as potentially deleterious effects in a RAGE-dependent manner [14].

The interaction of RAGE and its ligands triggers rapid generation of reactive oxygen species (ROS) and inflammatory cytokines up-regulation through RAGE signal transduction and activation of transcription factors [39]. In general, the major cellular pathways stimulated by RAGE–ligand interactions include Janus kinase-signal transducer and activator of transcription (JAK-STAT); Ras-Rac-Cdc42; phosphoinositol 3-kinase-3-kinase-Akt (PI3K/Akt) and mitogen-activated protein kinases (MAPKs), Ras-extracellular signal regulated kinase1/2 (ERK1/2), stress-activated protein kinase/c-jun-NH2-terminal kinase (SAPK/JNK) and p38 mitogen activated protein (MAP) kinase pathways [39,46]. RAGE activates different signal pathway in a ligand-dependent way. In microglia N-11 cells, AGEs activate signal-regulated kinases p44/p42 (ERK1/2) and phosphatidylinositol 3-kinase (PI3K/Akt) pathway [16], whereas HMGB1 mediated Rac and Cdc42, but not Ras signal pathway to induce neurite outgrowth [23]. In contrast, S100B induces brain inflammatory disorders via several inflammation-related signaling pathways, such as mDia1/Rac1/JNK/activator protein 1, Rac/Rac1/NF-κB, and Src/Ras/phosphoinositi3-kinase/Rhoα/mDia-1 [6,38]. The above signaling cascades have been shown to independently or synergistically result in activation of downstream effector nuclear factor-κB (NF-κB) and STAT3. It is known that NF-κB is a key factor in transducing a variety of inflammatory cytokines and enzymes such as interleukins (ILs), TNF-α and cyclooxygenase-2 (COX2), which plays an essential role in the neuroinflammation responses [51]. To be noticed, RAGE itself is an NF-κB regulated target gene, exhibiting a functional binding site for NF-κB in its proximal promotor. Thus, NF-κB signaling route also results in an increased cell surface expression of RAGE and forms a positive feedback loop. In turn, this feed forward process enhancing RAGE expression amplifies the initial signal and further
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