Advanced glycation end-products produced systemically and by macrophages: A common contributor to inflammation and degenerative diseases

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A B S T R A C T

Advanced glycation end products (AGEs) and their receptor have been implicated in the progressions of many intractable diseases, such as diabetes and atherosclerosis, and are also critical for pathologic changes in chronic degenerative diseases, such as Alzheimer’s disease, Parkinson’s disease, and alcoholic brain damage. Recently activated macrophages were found to be a source of AGEs, and the most abundant form of AGEs, AG-Albumin excreted by macrophages has been implicated in these diseases and to act through common pathways. AGEs inhibition has been shown to prevent the pathogenesis of AGEs-related diseases in human, and therapeutic advances have resulted in several agents that prevent their adverse effects. Recently, anti-inflammatory molecules that inhibit AGEs have been shown to be good candidates for ameliorating diabetic complications as well as degenerative diseases. This review was undertaken to present, discuss, and clarify current understanding regarding AGEs formation in association with macrophages, different diseases, therapeutic and diagnostic strategy and links with RAGE inhibition.

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Abbreviations: AD, Alzheimer’s disease; ADMA, asymmetric dimethylarginine; AGEs, advanced glycation end products; AFDL, alcoholic fatty liver disease; ALI, acute lung injury; ALS, amyotrophic lateral sclerosis; APP, amyloid beta precursor protein; Aβ, amyloid beta; Bax, BCL2 associated X, apoptosis regulator; CaMKII, calcium/calmodulin-dependent protein kinase; CCL3, chemokine (C–C motif) ligand 3; CCL4, chemokine (C–C motif) ligand 4; CD36, cluster of differentiation 36; CKD, chronic kidney disease; CMA, N(ω)-carboxymethylarginine; CML, N(6)-carboxymethyllysine; COPD, chronic obstructive pulmonary disease; CTGF, connective tissue growth factor; CVD, cardiovascular diseases; DAMPS, damage-associated molecular pattern molecules; DN, diabetic nephropathy; EGC, epigallocatechin gallate; Egr-1, early growth response-1; ERK1/2, extracellular signal-regulated kinase 1/2; FEEL-1, fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-1; FEEL-2, fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-2; HDL, high-density lipoprotein; HMGB1, high mobility group protein B1; HUVEC, human umbilical vein endothelial cell; IL-6, interleukin-6; IL-10, interleukin-10; IL-1β, interleukin-1 beta; INF-γ, interferon gamma; IPF, idiopathic pulmonary fibrosis; JAK, janus kinase; JNK, c-Jun N-terminal kinase; Lox-1, lectin-like oxidized low-density lipoprotein receptor-1; LPS, lipopolysaccharide; Mac-1, macrophage-1 antigen; MAPK, mitogen activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; MMP-13, matrix metalloproteinase 13; NAPDH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NO, nitric oxide; NOS, nitric oxide synthase; OA, osteoarthritis; PAR, protease-activated receptor; PAR1, protease-activated receptor 1; PAR2, protease-activated receptor 2; PAR3, protease-activated receptor 3; PAR4, protease-activated receptor; PD, Parkinson’s disease; PGDF, platelet-derived growth factor; PGE2, prostaglandin E2; PPAR-α, peroxisome proliferator activated receptor-alpha; PPAR-γ, peroxisome proliferator-activated receptor gamma; RA, rheumatoid arthritis; Rac2, ras-related C3 botulinum toxin substrate 2; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; S100A8, S100 calcium binding protein A8; S100A9, S100 calcium binding protein A9; S100A12, S100 calcium binding protein A12; SAPK, stress-activated protein kinase; SC, spinal cord injury; sRAGE, soluble RAGE; SR-BI, scavenger receptor class B type I; TGF-β, transforming growth factor beta; TNF, tumor necrosis factor; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

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1. Introduction

Advanced glycation end products (AGEs) have long been considered potent toxic molecules that promote host cell death and contributing to organ damage in man. AGEs can induce the development or progression of not only diabetic complications but the pathophysiology of many diseases, including cardiovascular diseases (CVDs) and neurodegenerative diseases like Alzheimer’s disease (AD), Parkinson’s disease (PD), and alcoholic brain damage (Bayarsaikhan et al., 2016; Byun et al., 2012a, 2014; Simm et al., 2007; Srikanth et al., 2011; Yan et al., 2007). AGEs bind with their receptor RAGE (receptor for advanced glycation oxidative stress, neovascularization, in

2. Advanced glycation end-products (AGEs)

AGEs are a heterogeneous group of irreversible products resulting from nonenzymatic glycation and oxidation of proteins, nucleic acids, and lipids (Goldin et al., 2006; Singh et al., 2001). Glycation produces AGEs compounds with toxic properties associated with inflammation and oxidative stress (Takeuchi & Yamagishi, 2004). AGEs accumulate in the extra cellular matrix of various tissues and critically contribute to chronic diseases (Bierhaus et al., 1998; Tessier et al., 1999). Furthermore, AGEs have been shown to become antigenic, and thus, to induce immune responses (Ge et al., 2005; Kurien & Scofield, 2008). AGEs also have adverse effects on cellular functions by cross-linking intracellular and extracellular proteins, which trigger diverse diseases, such as arthritis, neurological disorders, cancers, diabetes and cardiovascular disorders, (Abe et al., 2004; Jono et al., 2002; Russo & Frangogiannis, 2016; Ryan et al., 2014) (Fig. 1).

2.1. Formation of AGEs

2.1.1. Formation of AGEs

AGEs are formed by glycation, which is a nonenzymatic reaction between ketones or aldehydes and the amino groups of various proteins and contributes to protein aging (Gkogkolou & Böhm, 2012; Ramasamy et al., 2012). Protein glycation occurs in both normal and hyperglycemic condition, and forms irreversible AGEs. This process begins with the conversion of reversible Schiff base adducts to more stable, covalently-bound Amadori rearrangement products and finally the Maillard reaction (Ansari & Baldelli, 2016), aging (Karumanchi et al., 2015), kidney disease (Arsov et al., 2014), or autoimmune diseases (Nienhuis et al., 2009). In addition, AGEs are derived from foods (e.g. milk, meat, coffee, cheese), especially those prepared under high temperature conditions, stored for long periods, or with food additives (Luevano-Contreras & Chapman-Novakofski, 2010).

2.1.2. Toxic properties of AGEs

Elevated levels of AGEs support the formations of reactive oxygen and nitrogen species which in turn induce further AGEs formation. AGEs induce oxidative stress by activating RAGE, which results in mitochondrial dysfunction (Lane et al., 2015; Ward et al., 2013). Under oxidative stress, mitochondrial Ca2+ accumulation leads to a cell death signal (Mahali et al., 2011), and AGEs exerted by activated macrophages also induce mitochondrial dysfunction and cell death. Extensive studies have demonstrated that mitochondrial dysfunction is an important factor in the pathogenesis of AD (Aliev et al., 2010), alcoholic fatty liver disease (AFLD) (Song et al., 2014), diabetes (Rolo & Palmeira, 2016), and chondrocyte degeneration (Blanco et al., 2004) (Fig. 2).

3. Receptors for AGEs

AGEs can interact with two types of cell surface receptors. Scavenger receptors are predominantly involved in AGEs capture, removal and degradation. This group of receptors includes type I and type II macrophage scavenger receptors, cluster of differentiation 36 (CD36), fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-1 (FEEL-1) and fasciclin EGF-like, laminin-type EGF-like, and link domain-containing scavenger receptor-2 (FEEL-2), scavenger receptor class B type I (SR-BI) and scavenger receptor class B type II.
(SR-BII), and lectin-like oxidized low-density lipoprotein receptor 1 (Lox-1) (Miyazaki et al., 2002; Ott et al., 2014). The other type of AGEs receptor, RAGE initiates specific cellular signaling events in response to AGEs exposure. RAGE is a member of immunoglobulin (Ig) superfamily, and binds multi-ligands like AGEs (Huttunen et al., 1999), high mobility group protein B1 (HMGB1) (Dhumale et al., 2015), S100 (Donato, 2007), Aβ (Stern et al., 2002), amphoterin, and calgranulins, and then activates several condition-dependent cellular pathways (Li et al., 2004). RAGE is expressed in various tissues including brain, heart, liver, lung, kidney, and cartilage and it plays an important role in disease progression. Expression level of RAGE is minimal under normal conditions but increases in disease states, such as AD, PD, alcoholic brain damage, AMI; Acute myocardial infarction, LC; Liver cirrhosis, IPF; Idiopathic pulmonary fibrosis, DN; diabetic nephropathy, OA; osteoarthritis, F; fibrosis, I; inflammation, O; oxidative stress, A; autophagy, D; degeneration, Cd; cell death.
damage, vascular disease, diabetes, acute myocardial infarction (AMI), chronic kidney disease (CKD), hepatic fibrosis, chronic obstructive pulmonary disease (COPD), and inflammatory disease, which may be the result of cell damage caused by the overproductions of ROS, cytokines, and pro-inflammatory molecules (Fig. 3, Supplementary Table 1).

3.1. Intracellular signaling pathway of RAGE in disease

RAGE is highly expressed on neurons during neurodegenerative processes, such as AD, PD, stroke, alcoholic brain damage, and amyotrophic lateral sclerosis (ALS). In the presence of inflammation, binding of AGEs to RAGE strongly induces the activations of the NF-κB pathways (Teismann et al., 2012; Wang et al., 2013, 2014). Furthermore, the interaction between AGE-albumin and RAGE induces neuronal cell death through stress-activated protein kinase (SAPK)/c-Jun N-terminal kinase (JNK)/BCL2 associated X, apoptosis regulator (Bax) in AD (Byun et al., 2014) and the SAPK/JNK/p38 pathway in the alcoholic brain damage (Byun et al., 2014). Furthermore, increased HMGB1 binding with RAGE can cause neuronal cell death through NF-κB activation in stroke and AD (Bortolotto & Grilli, 2016; Wang et al., 2010). S100 protein induces neuronal cell death through the NF-κB/tumor necrosis factor alpha (TNF-α) pathway in PD (Abdelsalam & Safar, 2015; Sathe et al., 2012), and in AD, binding of Aβ to RAGE also leads to neurodegeneration and neuronal cell death through p21ras, ERK1/2, p38, SAPK/JNK, phosphoinositol-3 kinase, and the janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway (Origlia et al., 2010; Son et al., 2012).

3.1.1. Relations between RAGE and neuronal death

RAGE is dependent RAGE expression is well documented in many diseases. The signaling pathways downstream of RAGE are similar and eventually lead to mitochondrial dysfunction and cell death. The detailed summary is provided below and in Fig. 3 and Supplementary Table 1.

3.1.2. Cardiomyocytes and RAGE

RAGE expression of cardiomyocytes is increased in acute myocardial infarction by AGEs, HMGB1 and S100, and these proteins induce cell death via activation of the MAPK pathway (Aleshin et al., 2008; Andrassy et al., 2008; Tsoporis et al., 2010).

3.1.3. Hepatocytes and RAGE

Binding of AGEs to RAGE strongly induces the phosphorylation of uncoupling protein-2 (UCP-2) and ATP synthesis (Kuhla et al., 2011). HMGB1 released from damaged hepatocyte after injury interacts with RAGE and leads to hepatic fibrosis by activating SMAD2 and phosphorylating ERK1/2 (Kao et al., 2014) or JNK/ERK1/2 during early growth response-1 (Egr-1) (Zeng et al., 2009).

3.1.4. Alveolar epithelial cells and RAGE

The RAGE binding with AGES and HMGB1 has been well described in idiopathic pulmonary fibrosis (IPF). Binding of AGEs and RAGE induces TGF-β1 induced ERK1/2 and SMAD phosphorylation (Song et al., 2011) and up-regulates Egr-1, which also activates RAGE transcription in COPD (Reynolds et al., 2008b). In addition, the interaction between HMGB1 and RAGE leads to alveolar disruption and fibrosis due to the activation of TGF-β1 via the productions of platelet-derived growth factor (PDGF) in IPF (He et al., 2007).

3.1.5. Renal tubular epithelial cells and RAGE

Interaction between AGES and RAGE stimulates oxidative stress and promotes diabetic nephropathy (DN) progression. Importantly, AGES-RAGE acts to the mitogen activated protein kinase (MAPK)/NF-κB and protein kinase C signaling pathway (Yamagishi & Matsui, 2010) or promote to connective tissue growth factor (CTGF) and TGF-β during inflammation and fibrotic process (Cheng et al., 2015a). Up-regulation of HMGB1 binding to RAGE provokes inflammatory reactions via ERK1/2/NF-κB signaling, which turn on transcription of TNF-α, interleukin-6 (IL-6), chemokine (C–C motif) ligand 3 (CCL3), chemokine (C–C motif) ligand 4 (CCL4) and C–C motif chemokines 12 (CXC12), and enhances asymmetric dimethylarginine (ADMA) in CKD (Nakamura et al., 2009).

3.1.6. Chondrocytes and RAGE

The binding AGES to RAGE activate the JNK/p38, peroxisome proliferator-activated receptors alpha (PPAR-α), and NF-κB signaling pathway and these signaling pathways associated with inflammatory and oxidative responses in osteoarthritis (OA). Furthermore, high levels of HMGB1 have been reported in the synovial fluid of arthritis patients (Kokkola et al., 2002), and the interaction between HMGB1 and RAGE induces the expressions of TNF-α and interleukin 1 beta (IL-1β) on chondrocytes (Terada et al., 2011). Furthermore, when the expression of S100 calcium binding protein A12 (S100A12) and A4 (S100A4) is increased and it stimulates inflammation and degeneration via the RAGE mediated MAPK, NF-κB and MMP-13/vascular endothelial growth factor (VEGF)/p38 and NF-κB signaling pathway in OA (Nakashima et al., 2012; Yammani et al., 2009).

4. Mediators of macrophage activation and AGE formation

The macrophages originate from bone marrow and then migrate and circulate in different tissues, such as the brain, liver, heart, kidney, and cartilage (Kraft & Harry, 2011; Valerol et al., 2015). Activated macrophages often induce inflammatory degeneration of host cells or dysfunction in AD, PD, stroke, vascular disease, and inflammatory diseases. Macrophages are activated by exposure to various stimuli, such as cytokines, proteases, prostanoids (PGs), nitric oxide (NO), free radicals or RAGE ligands, including Aβ, AGEs, HMGB1 and lipopoly-saccharide (LPS), under pro- and inflammatory conditions (Fig. 4).

4.1. Cytokines

Cytokines are involved in systemic inflammation and degenerative diseases. They can be released by neurons, cardiomyocytes, hepatocytes, alveolar epithelial cells, neutrophils, eosinophils, or mast cells at various levels when cells are stimulated or in the presence of disease conditions. These cytokines such as α-synuclein (Kim & Joh, 2006), Chromogranin A (Heneka et al., 2010, and Interferon gamma (INF-γ) (Gensel & Zhang, 2015) were well reported as activating macrophages under disease conditions.

4.2. Proteases

Serine proteases cleave their receptors to modulate important biological processes including host defense, chemotaxis, cytokine and growth factor release, vascular function, tissue repair, apoptosis, inflammation and immune response (Steinhoff et al., 2005). Protease-activated receptors (PARs) compose a subfamily of G protein-coupled receptors with seven transmembrane receptors that couple to guanine nucleotide-binding proteins (Brass & Molino, 1997). The PAR family has four members, namely, protease-activated receptor 1 (PAR1), protease-activated receptor 2 (PAR2), protease-activated receptor 3 (PAR3), and protease-activated receptor 4 (PAR4), and of these, PAR2 can modulate the activities of various cells, including epithelial cells, smooth muscle cells, endothelial cells, and macrophages in a variety of tissues (Nystedt et al., 1996; Steinhoff et al., 2005).

4.3. Prostaglandins (PGs)

PGs act as critical regulators during the initiation of inflammatory processes. PG expressions are significantly increased in infected tissues, and contribute to the development of the principal signs of the acute
inflammatory phase (Ricciotti & FitzGerald, 2011). Prostaglandin E₂ (PGE₂) is one of the most abundant PGs and exhibits variable biological activities, which include the regulations of blood pressure, gastrointestinal integrity, and immune response (Legler et al., 2010).

4.4. Acute phase proteins (APPs)

APPs response to inflammation may be an increase (positive acute-phase proteins, APPs) or decrease (negative APPs) in plasma concentration (Gruys, Toussaint, Niewold, & Koopmans, 2005). Positive APPs are involved in different physiological functions in the immune system. For example, haptoglobin acts to inhibit or prevent microbe growth and alpha 2 macroglobulin and serpins provide negative feedback on the inflammatory processes (Jain, Gautam, & Naseem, 2011).

Some of these proteins act to inhibit or prevent microbe growth, while others modulate negative feedback from inflammatory processes which include albumin, transferrin, transthyretin, transcortin, retinol-binding protein and anti-thrombin (Gruys et al., 2005; Ritchie et al., 1999).

4.5. Nitric oxide and free radicals

4.5.1. Nitric oxide (NO)

NO is a free radical and an important cellular signaling mediator related to various pathological and physiological processes, including the modulation of blood pressure, neurotransmission, and of macrophage cytotoxicity. NO is synthesized by nitric oxide synthase (NOS) from oxygen and NADPH as cofactor of NOS (Mayer et al., 1990). Positive APPs are known as endogenous mediator during vasodilator inflammatory processes (Wallace, 2005).

4.5.2. Oxidative stress

In oxidative stress, greater amounts of oxygen free radicals are found under disease states or after exposure to toxic agents and are increased by environmental stresses such as UV or heat. Oxidative stress elevates the expressions of inflammatory mediators, which induce macrophage activation in the presence of inflammation (Macdonald, Galley, & Webster, 2003), AMI (Di Filippo, Cuzzocrea, Rossi, Marfella, & D’Amico, 2006), COPD (Rahman, 2005), OA (Ziskoven et al., 2010) and neurodegenerative disease, such as AD (Zhu et al., 2004), and PD (Dias, Junn, & Mouradian, 2013).

4.6. RAGE ligands

RAGE ligands including Aβ, AGEs, HMGB1, LPS, macrophage-1 antigen (Mac-1), phosphatidylserine and S100 also modulate important biological processes required for macrophage activation (Chavakis et al., 2004; He et al., 2011; Hofmann et al., 1999; Schmidt et al., 2001). The various types of RAGE ligands that induce macrophage activation in degenerative diseases are summarized in Table 1. Aβ is cleaved from amyloid precursor protein and is the main cause of AD, a major component of amyloid plaque (Fang et al., 2010). Nuclear HMGB1 regulates pro-inflammatory factors, and HMGB1 can be released by neurons in the damaged brain (Fang et al., 2010). HMGB1 up-regulation leads to microglial activation in many diseases including alcoholic brain damage (Crews & Vetreno, 2014, 2016), stroke (Liesz et al., 2015; Xiong et al., 2016), spinal cord injury (SCI) (Kikuchi et al., 2011), AMI (Herzog et al., 2014) and acute lung injury (ALI) (Deng et al., 2013). LPS can stimulate macrophages and monocytes to secrete various inflammatory mediators, including IL-6 (Hirohashi & Morrison, 1996). LPS also induces macrophage activation in SCI (Xie et al., 2004), hypertension (Hernanz et al., 2004), ALI (Zhu et al., 2013), liver cirrhosis (Jirillo et al., 2002), IPF (Freeburn et al., 2005), and COPD (Miles et al., 1999). S100 members also activate macrophages, and are also secreted by activated macrophages (Donato, 1999).

![Fig. 4. Activators of macrophages and secreted proteins from activated macrophages. RAGE ligands also induce activation of macrophages and they are secreted from activated macrophages.](image-url)

### Table 1

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<th>Cytokine</th>
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<td>HMGB1</td>
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<td>Spinal cord injury</td>
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<td>Aβ</td>
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<td>Chronic obstructive pulmonary disease</td>
<td>Miles, Bowman, Rao, Baatz, and Huffman (1999)</td>
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<td>Idiopathic pulmonary fibrosis</td>
<td>Freeburn, Armstrong, and Millar (2005)</td>
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<td>Acute lung injury</td>
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4.7. Proteomic analysis of activated macrophages

To further understand the molecular mechanism responsible for macrophage activation, proteomic studies have been recently conducted in a variety of disease models, including neurodegenerative disease (Ma et al., 2013; Reynolds et al., 2008a; Yoo et al., 2015; Zhou et al., 2005), acute lung injury/acute respiratory distress syndrome (Dong et al., 2013), kidney stone disease (Singh et al., 2013), metabolic diseases (Freiwald et al., 2013; Kratz et al., 2014), cancer (Kobayashi et al., 2009; Zhu et al., 2015), atherosclerosis (Burillo et al., 2009; Kang et al., 2006), and virus infections (Lietzén et al., 2011; Miettinen et al., 2012). The proteins secreted by activated macrophages are being actively investigated in terms of their abilities to damage or protect tissues.

4.7.1. Secretome analysis of activated macrophages

The most dramatically inducible proteins secreted by activated macrophages are inflammatory molecules, such as cytokines and chemokines. Among cytokines, surprisingly, various types of RAGE ligands, such as AGEs (most abundantly in albumin), HMGB1 and S100 proteins, are secreted by activated macrophages. HMGB1 and S100 protein are damage-associated molecular pattern molecules (DAMPs) that are released by damaged and stressed cells. DAMPs, which are also called alarmins or danger signals, are host-derived endogenous molecules that can trigger immune response, and are recognized by DAMP receptors, which include RAGE (Said-Sadier & Ojcius, 2012).

HMGB1 can be released from necrotic or damaged cells or by activated immune cells, and regulates endothelial cell activation, cell migration, inflammation, proliferation, and differentiation (Bertheloot & Latz, 2016; Said-Sadier & Ojcius, 2012). In post-ischemic brains, HMGB1 was found to be induced in and secreted by activated microglia (Kim et al., 2008; Kim et al., 2012; Shin et al., 2014). Interestingly, the release and translocation of HMGB1 in macrophages were observed to be inhibited by various molecules that can reduce inflammation and mortality in sepsis models (Cheng et al., 2015b; Elfrey et al., 2016; Hagiwara et al., 2009; Kim et al., 2015; Ye et al., 2012; Zhang et al., 2014; Zhou et al., 2014). HMGB1 secretion was also significantly increased by macrophages in the presence of chronic inflammation diseases and in models of atherosclerosis (Kalinina et al., 2004), COPD (Mortaz et al., 2015), rheumatoid arthritis (RA) (Zetterström et al., 2008), and renal tubule-interstitial fibrosis (Tian et al., 2015). The S100 protein family is composed of approximately 25 proteins (Gross et al., 2014), and among them, S100A8 and S100 calcium binding protein A9 (S100A9) are often found abundantly in macrophages (Farris et al., 2011; McCormick et al., 2005; Rammes et al., 1997; Xu & Geczy, 2000; Xu, Yen, & Geczy, 2001). These two proteins are also released by activated macrophages in patients with inflammatory muscle diseases, and induced myoblast apoptosis via caspase 3 activation (Seeliger et al., 2003).

4.7.2. Albumin and AGE-albumin synthesis in macrophages

The liver is known as responsible for production of albumin in body, however there are also reports of non-hepatic origins. These include pancreas, kidney (Nahon et al., 1988), skeletal muscle (Kobayashi & Tashima, 1990; Müller & Heizmann, 1982), thyroid gland (De Vijlder et al., 1992). Activated macrophages are also known as alternate source of MAPK, NF-κB, and IFN-γ (Kim & Joh, 2006). Furthermore in AD, Aβ interacts with AGEs and induces microglial activation and neuroinflammation via ERK1/2 and NF-κB activation (Lv et al., 2014). Several authors have demonstrated AGEs accumulation in the brains of patients with AD (Ahn et al., 2008) or alcoholic brain damage (Byun et al., 2014). In addition, Aβ stimulated human microglial cells significantly synthesize and release more albumin (Ahn et al., 2008), and abundant quantities of AGE-albumin, a new RAGE ligand (Byun et al., 2012). Aβ plaques are co-localized with AGE-albumin in Aβ1-42 injected rat and human AD brain (Byun et al., 2012b) and the AGE-albumin induces calcium influx via up-regulation of RAGE, and this leads to neuronal death in AD (Byun et al., 2012a). Furthermore, alcohol-stimulated microglial cells also exhibit much increased synthesis and release of AGE-albumin and induce neuronal cell death (Byun et al., 2014).

5. Development of therapeutics against AGES

Developmental efforts have resulted in many agents that reduce the damage induced by AGES. These agents can be summarized as AGES inhibitors and breakers, angiotensin II receptor antagonists and angiotensin converting enzyme inhibitors, antioxidants, natural substances, and anti-inflammatory molecules (Table 2).

5.1. AGES inhibitors & breakers

AGES inhibitors that prevent AGES formation and AGES cross-link breakers were identified as initial efforts. Aminoguanidine was the first AGES inhibitor found to inhibit the formation of AGES, and was also reported to effectively reduce the pathologic effects of the nephropathy and vascular complications associated with AGES in diabetes (Bolton et al., 2004; Brownlee et al., 1986; Freedman et al., 1999). Several AGES cross-link breakers have also been reported to effectively reduce AGES products and proposed as possible therapeutics for the treatment of diabetic vascular complications. Alagrumet and related compounds including ALT-711, ALT-462, ALT-486, and ALT-946 apparently break some existing AGES cross-links (Krautwald et al., 2011). ALT 711 was initially reported to effectively reduce the severity of AGE-induced pathological lesions (Vasan et al., 2001). Another AGES-breaker, TRC4186, was reported to inhibit AGES formation or break AGES cross-links and to ameliorate diabetes-related cardiomyopathy and nephropathy (Joshi et al., 2009).

5.2. Angiotensin II receptor antagonist and angiotensin converting enzyme inhibitor

Telmisartan, an anti-hypertension drug and angiotensin II receptor blocker, was found to decrease AGES formation. For example, a clinical study demonstrated that telmisartan decreased RAGE expression by activating PPAR-γ in liver (Yoshida et al., 2006). In addition, pyridoxamine has been reported as preventing the Amadori reaction leading to AGES formation (Adrover et al., 2008; Thomas et al., 2005).

5.3. Antioxidants

Antioxidants have been developed to inhibit AGES. Statins, which have antioxidant activity, are commonly used to lower blood cholesterol levels. The antioxidant effect of statins was found to inhibit reactive protein C release effectively from toxic AGES, and thus, to prevent diabetes-associated vascular complications (Ajit et al., 2006, 2008; Takeuchi et al., 2010). Atorvastatin was introduced as means of decreasing serum AGES levels in patients with type 2 diabetes in a soluble RAGE (sRAGE) and a splice variant of sRAGE dependent manner (Jinnouchi et al., 2006; Tam et al., 2010). Other study supported the notion that atorvastatin restored reduced glutathione levels, inhibited RAGE up-regulation, and down-regulated the expression of RAGE and MCP-1 (Feng et al., 2011). Recently, a RAGE antagonist from the part of human serum albumin was found to reduce the increased NF-κB signaling by anti-
inflammatory mechanism (Maltais et al., 2016). Ascorbic acid, alpha-lipoic acid, carnosine, and quercetin have been shown to inhibit AGEs effectively (Abdul & Butterfield, 2007; Ashraf et al., 2015; Bierhaus et al., 1997; Giotto et al., 2005; Zafar, 2012). Recently the glucagon-like peptide-1 receptor agonist exendin, and NF-κB inhibitor-pyrollidine dithiocarbamate were also showed to provide strong in vitro protection against AGEs-induced neuronal apoptosis by reducing the overexpression of RAGE (Chen et al., 2016).

5.4. Natural substances

Studies have shown that some natural substances, such as resveratrol and curcumin, can prevent AGEs-induced pathology (Mizutani et al., 2000). Resveratrol inhibited the AGE-induced proliferation of collagen in smooth muscle cells of blood vessels (Mizutani et al., 2000), and curcumin blocked the effect of AGEs on the RAGE expression (Tang, 2014). Recently, new pirenflavonoids were reported to inhibit the formations of N(6)-carboxymethyllysine (CML) and N(omega)-carboxymethylarginine (CMA) in the methanol extract of the aerial portions of Epimedium Herb (Nakashima et al., 2016). Similarly, p-cymene, a monoterpene was demonstrated to act as AGEs breakers for AGEs cross-linking (Joglekar et al., 2014; Lee et al., 2014). Recently, sulphoraphene was demonstrated to inhibit inflammation in AGEs-exposed human umbilical vein endothelial cells (HUVECs) and AGEs-infused rat aorta partly by suppressing RAGE expression (Matsui et al., 2016). Vitamin D also reported as reducing the risk of CVDs. AGEs, such as CML, have been implicated in diabetic vascular complications via oxidative stress-mediated pathways (Salum et al., 2013). Gymnema also reported to contribute to the anti-hyperglycemic effects (Sugihara et al., 2000), and metformin has been reported to restore glycated high-density lipoprotein (HDL)-mediated cholesterol efflux (Matsui et al., 2009). Epigallocatechin gallate (EGCG), a major component of green tea polyphenols, showed protective effects against AGEs-induced damage in neuron cells (Lee & Lee, 2007), and S-allyl cysteine from aged garlic has been reported to act as a potent antioxidant and inhibit AGEs protein formation (Ahmad & Ahmed, 2006). Ramipril has also been reported to be an efficient AGEs inhibitor as well (Gosse & Schumacher, 2014).

5.5. Anti-inflammatory molecules and AGEs inhibitors that act on activated macrophages

Anti-inflammatory molecules have also been found to reduce the toxic effects of AGEs. In particular, LR-90 had been shown to inhibit the NF-κB activation, which stimulates the gene expressions of proinflammatory molecules in human monocytes (Figarola et al., 2007).

Bisphosphonates were found to inhibit toxic AGEs-mediated inflammation and finally stopped ROS formation during the pathogenesis of the vascular complications of diabetes (Takeuchi et al., 2010). Similarly, another nitrogen-containing bisphosphonate, minodronate, inhibited signaling pathways initiated by the interaction between AGEs and RAGE in diabetic retinopathy (Yamagishi et al., 2006). It appears that inhibitors of AGEs with anti-inflammatory effects can deactivate macrophages and reduce tissue damage as well.

Because most known therapeutic reagents used to treat diabetes target AGEs in blood, AGEs inhibition in activated macrophages located in tissues has been investigated as a novel targeting strategy. The SRAGE-based masking of secreted AGEs has shown strong potent therapeutic effects in several diseases, such as AD, PD, alcoholic brain damage, and AMI (Bayarsaikhan et al., 2016; Byun et al., 2012a; Byun et al., 2012b; Byun et al., 2014) (Fig. 5). Since sRAGE is the extracellular part of RAGE, it can bind to AGEs, and thus, prevent their adverse effects. Targeting AGEs in activated macrophage probably could be one of the most ideal strategies for AGEs related diseases.

6. Conclusion and future perspectives

The role played by the AGEs-RAGE interaction in the aggravation of the chronic complications of diabetes, CVDs, and degenerative
diseases has been well established. The interaction between AGEs and RAGE on the plasma membrane triggers the downstream signaling of inflammation, oxidative stress, and apoptosis in many cells, including neurons, endothelial cells, lung cells and muscle cells. Therapeutic agent development has focused mainly on suppressing AGEs or RAGE formation or preventing the AGEs-RAGE interaction. Although agents have been devised to prevent AGEs formation and activity, most are under in the early phase of clinical studies. Similarly, studies on natural substances like resveratrol and curcumin have been described to inhibit RAGE-associated vascular damage and the long-term complications of diabetes. Furthermore, sRAGE and its variants can inhibit the interaction between AGEs and RAGE effectively and have also been suggested to be promising therapeutic agents.

Recently, it was found that activated macrophages are one of primary contributors to AGE-albumin accumulation in tissues, and suggested that AGE-albumin is a potentially useful therapeutic and diagnostic biomarker with high sensitivity and resolution. In addition, labeling and visualizing accumulated AGE-albumin with proper antibodies may provide a near ideal theragnostic means to combat AGEs/RAGE associated diseases.

In conclusion, more studies are required to determine how to prevent, remove, and estimate the AGEs/RAGE interaction in relation to macrophage activation and to elucidate its pathophysiologic mechanism in many intractable diseases.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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References


Fig. 5. A proposed model of AGE albumin from activated macrophage and its relevancy to cell death in various tissues.


