Review

RAGE on the Toll Road?

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Mammalian Toll-like receptors (TLRs) are cellular pattern-recognizing receptors (PRRs) that recognize the molecular patterns of pathogens. After engaging the pathogenic patterned ligands, the cytosolic portion of the TLRs in monocytes and macrophages, recruits adaptor proteins, *via* a receptor-driven signaling cascade, activates the transcription factor NF-κB, leading to the expression of proinflammatory cytokines, which trigger inflammation. Such rapid, innate cellular responses serve as the first line of host defense against infection by pathogens, and also stimulate the adaptive immune system to clear the invading microbes. Increasing evidence suggests that TLRs also recognize host-derived ligands, linking this group of PRRs to diseases that may not have an etiology that is associated directly with infections. Advanced glycation end products (AGEs) are nonenzymatically glycated or oxidated proteins, lipids and nucleic acids that are formed in the environment of oxidant stress and hyperglycemia. Binding of AGEs to their receptor RAGE initiates cellular signals that activate NF-κB, which results in transcription of proinflammatory factors. RAGE can also interact with other endogenous ligands generated by cell death and tissue injuries. RAGE has been implicated in chronic diseases such as diabetes, atherosclerosis, neurodisorders, cancers, as well as aging. This review discusses the possible role of RAGE as a PRR that may use signaling mechanisms parallel to TLRs', to solicit inflammatory reactions. Thus, in this scenario, RAGE may play a prominent role in the regulation of cellular homeostasis in the context of complex disease progression. *Cellular & Molecular Immunology*. 2006;3(5):351-358.

Key Words: TLR, RAGE, NF-κB, innate immunity, inflammation, noncanonical Toll

Introduction

Innate immunity is an evolutionarily conserved defense mechanism, shared by all multicellular organisms (1). In insects, the hallmark of innate immune response is the rapid production of antimicrobial peptides that combat the pathogen (1, 2), whereas in mammals, innate response from macrophages and other phagocytes culminates at production and secretion of proinflammatory cytokines. Cytokine-mediated inflammation contains infectious organisms, and by activating adaptive immune mechanisms, clears the pathogens from the body (2). Despite the different effector events, across phyla, parallel signaling mechanisms to recognize invading pathogens and to initiate innate immune responses are employed by organisms ranging from insects to mammals (Figure 1).

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Thus far, 11 different TLRs have been identified in humans, and 13 in mice (3). These TLRs recognize various pathogens through their signature patterns, such as the cell wall components of bacteria and fungi, and single and double-strand RNA from viruses. In addition, intracellular non-Toll pathogen sensors have also been identified (4). Engagement of TLRs with their ligands results in recruitment of adaptor proteins by the cytosolic portion of the receptor, which shares a high homology with the interleukin 1 (IL-1) receptor cytosolic tail (the Toll-IL-1-receptor domain, TIR). Through a cascade of intracellular proteins, the signal from TLRs is relayed to the nucleus, leading to translation of effectors of the innate immune system (3, 5). Such an evolutionarily conserved surveillance mechanism enables the cell to detect a wide range of pathogens and to mount a rapid immune response. However, TLR-mediated innate immunity is also a double-edged sword that has been implicated in complex diseases such as atherosclerosis and rheumatic heart disease (6, 7). Although inflammation resolves infection, it also contributes to and exacerbates diseases. Persistent inflammation can tilt the protective innate immunity towards harmful effects, resulting in tissue injury and fibrosis. Despite the epidemiologic association of pathogen infections and chronic diseases (8), a direct, mechanistic link between pathogen infections and the development of a chronic disease is still lacking (9, 10).

The identification of endogenous TLR ligands hints at a

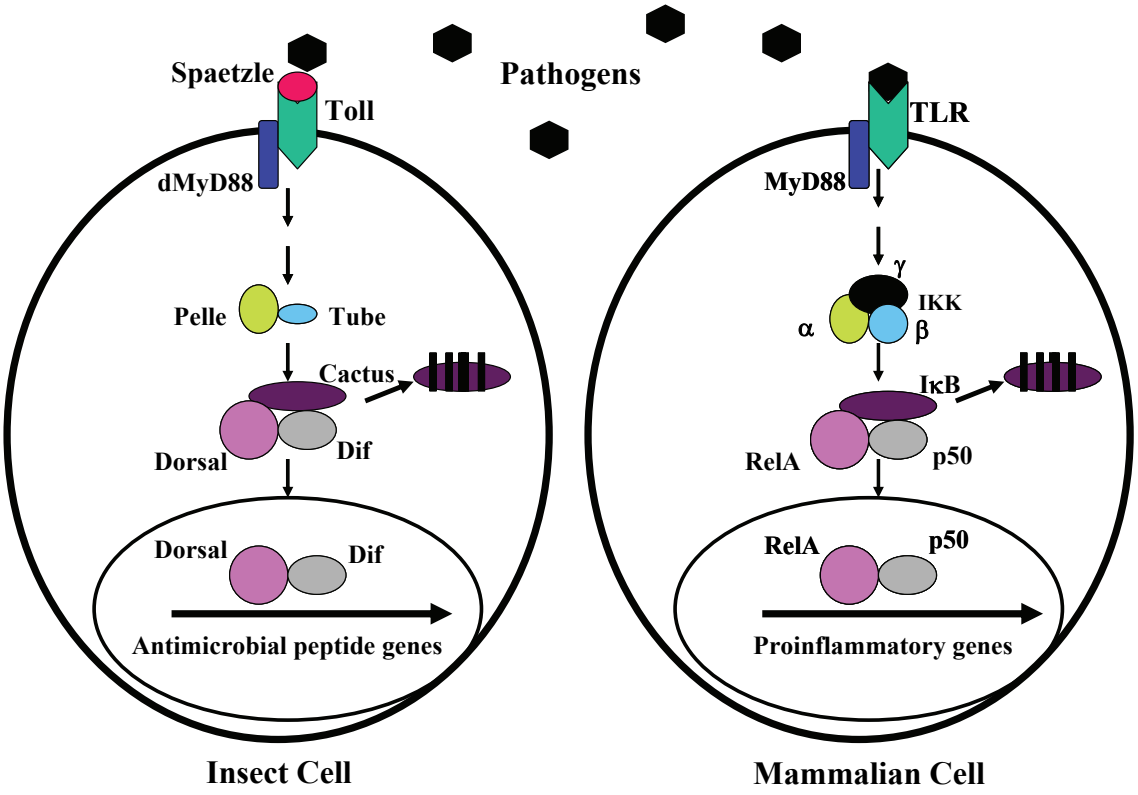

Figure 1. Parallel innate immune signaling mechanisms used by insects and mammals. In insects (*Drosophila* as the example), the invading microbes are sensed by Toll receptors in the fat-body cells (equivalent to liver in mammals) together with the circulating cytokine-like protein Spaetzle. The activated Toll then recruits MyD88 and passes the signal to downstream kinases Pelle and Tube, which phosphorylate Cactus, the ortholog of mammalian IκB, leading to its ubquitination and the subsequent degradation by the proteasome. The Rel proteins Dorsal and Dif (orthologs of NF-κB RelA and p50 subunits) are released into the nucleus upon degradation of Cactus, and their engagement with the κB-elements triggers transcription of antimicrobial peptides. Mammalian TLRs expressed on the cell surface of macrophages and monocytes recognize the molecular pattern of the pathogen and initiate the signaling relay similar to *Drosophila*. The signal converges at the IKK signalsome, which consists of two kinases IKKα and β, and a scaffold protein IKKγ. The IKK signalsome directly phosphorylates NF-κB inhibitor IκB and preconditions the inhibitor for ubiquitination and proteasomal degradation. The released RelA and p50 subunits then translocate into the nucleus and promote κB-elements-dependent transcription, which produces proinflammatory cytokines.

role for TLRs in complex diseases. For example, the role of TLRs in non-infectious lung injury has been reported (11). It is possible that generation and accumulation of endogenous TLR ligands, and their interactions with TLRs during a long-term maladaptive or aging process, may affect the physiological homeostasis *in vivo*, and trigger chronic inflammation that forms the basis for the development of the disease. The sources for endogenous TLRs include necrotic and apoptotic cells originated from tissue injury or patho-physiological conditions (12, 13), oxidized lipids and proteins (14, 15), stress-induced cellular factors such as heat shock proteins (16, 17), and extracellular matrix (18, 19). However, so far, endogenous ligands have been found to interact only with a limited number of TLRs (TLR2 and 4). Whether TLRs' interactions with endogenous and exogenous TLR ligands produce different consequences still remains unclear (6).

AGEs are nonenzymatically glycated or oxidated proteins, lipids, nucleic acids that are formed in the environment of oxidant stress and hyperglycemia (20). Pathological conditions such as diabetes mellitus, life styles such as smoking and unhealthy diets, environmental pollutions, and the aging process all contribute to AGE production and accumulation (21). This group of patterned ligands interacts with their receptor, RAGE, and initiates cellular signaling programs, including activation of transcription factor NF-κB, leading to chronic inflammation (22). RAGE and its ligands have been implicated in multiple complex diseases that do not have a clear etiology of pathogen infection. The expression of RAGE on macrophages and monocytes, and the wide-range of AGE sources make the RAGE-ligand axis a suspect for mediating chronic inflammation (22, 23). The role of RAGE in chronic diseases has been widely reported and extensively reviewed (20, 24-27). The current review discusses the possibility of RAGE functioning as a "noncanonical Toll" that binds AGEs and other endogenous patterned ligands, and triggers inflammations. Such functions may render RAGE to play a key role in the development and

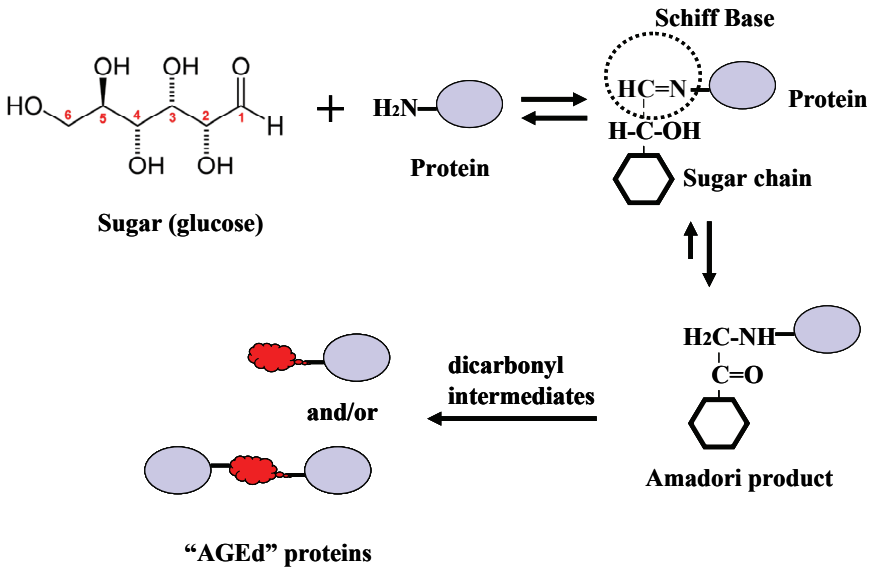

Figure 2. Formation of AGE. The carbonyl group of a reducing sugar (glucose as the example) interacts with the free amino group of a protein *via* nucleophilic addition to form the Schiff base (dotted circle). The labile Schiff base then rearranges to generate a more stable Amadori product that can further undergo dicarbonylate-mediated reaction to form complex AGEs. This spontaneous reaction depends on the degree and duration of hyperglycemia and oxidation. The red numbers in the glucose structure represent the location of carbon atoms.

progression of the disease.

Pattern-recognition by RAGE

AGEs are complex, heterogenous molecules generated by glycation and oxidation *in vivo*. Protein glycation (also known as the Maillard reaction) occurs between reducing sugars and free amino groups of a protein *via* nucleophilic addition that forms a Schiff base. The labile Schiff base rearranges to form a stable, and essentially irreversible Amadori product, that can further undergo reaction with dicarbonyl intermediates to form various AGEs (Figure 2). The identified AGEs can be classified into three major groups: fluorescent cross-linking species (e.g., pentosidine and crossline), non-fluorescent cross-linking species (e.g., arginine-lysine imidazole), and non-cross-linking species (e.g., pyrraline and N-carboxymethyllysine). All three AGE classes have been identified and isolated from tissue, serum, and urine samples (20, 21).

The intracellular concentration of monosaccharides including glucose, fructose and fructose-3-phosphate is increased under pathophysiological conditions, such as hyperglycemia. Reducing sugars and their derivatives provide the main source for *in vivo* glycation reactions. The AGE adducts can be formed on cell matrix, and these adducts can also circulate in body fluids (21). Thus, the effect of AGEs can be either local or systemic. RAGE was initially identified as a receptor for N-carboxymethyllysine (CML) modified proteins (28, 29), a major AGE *in vivo* (30). Later, it was found that RAGE also interacts with other non-glycated endogenous peptide ligands such as amphoterin (also termed as high mobility group box 1 protein, HMGB1) (31, 32), S100/calgranulin (22), and amyloid fibrils (33). The common characteristics of these ligands are the presence of multiple β-sheets (34-36), and it is likely that RAGE recognizes these ligands through their shared three-dimensional structure. The RAGE-ligand interactions lead to prolonged inflammation, a result of RAGE-dependent expression of proinflammatory cytokines and chemokines. As a pattern-recognizing receptor, RAGE is expressed in phagocytes such as macrophages and monocytes, smooth muscle cells, endothelial cells, and astrocytes (20). Vascular smooth muscle cells (VSMCs) form the media of vasculature, and their proliferation and migration into the intima serves as an index for the progression of atherosclerosis and vascular aging (37). It is noteworthy that none of the TLRs are expressed in VSMCs (38). The expression and activation of RAGE in VSMCs, thus, may enhance the expression of various tissue factors, adhesion molecules, and chemokines that aid proliferation and migration of VSMCs, and further attract leucocytes to ignite inflammation in an "AGEd" environment. Because of such ability to interact with a wide-range of endogenous ligands, RAGE may function as an excellent sensor for the environmental cues, and hence play a crucial role in the regulation of homeostasis and pathogenesis.

How does RAGE signal to NF-κB?

The signature downstream event for TLR-ligand interaction is the activation of the heterodimeric transcription factor NF-κB (Figure 1). Upon ligation, the cytosolic TIR domain

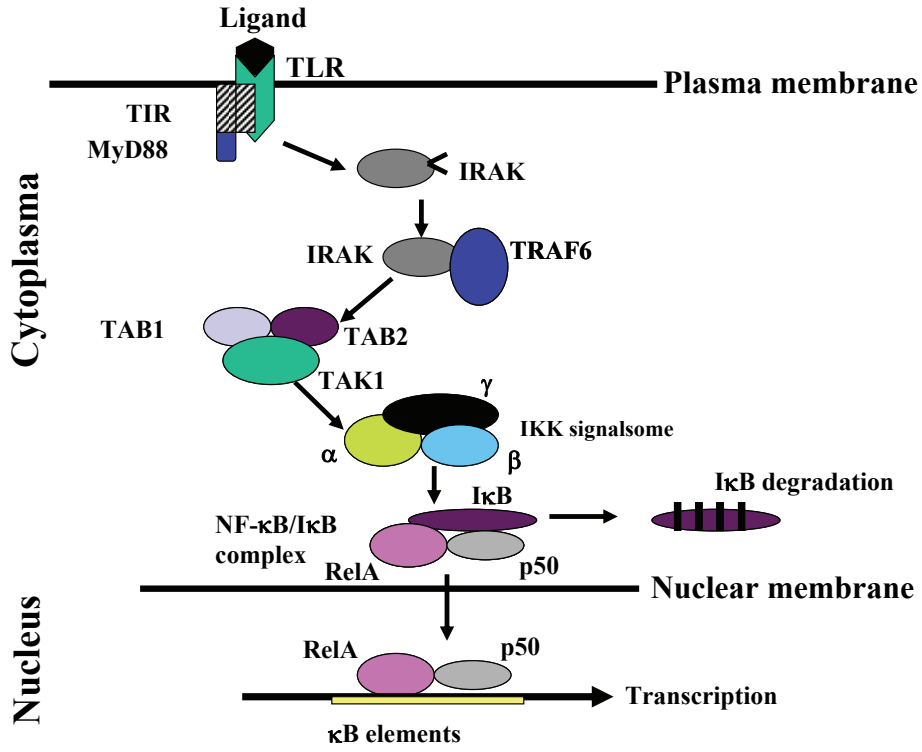

Figure 3. The prototypical TLR-mediated NF-κB activation. See text for the details.

of TLRs recruits a series of adaptor molecules to initiate the signal relay that transduces signals from the cell surface to the nucleus (39). The mechanism of the recruitment is based on the oligomerization of the TIR from the TLR cytosolic tail with intracellular TIR-containing adaptor proteins. Five TIR-containing adaptor proteins have since been identified: myeloid differentiation factor 88 (MyD88); MyD88 adaptor-like protein (Mal, also termed TIRAP); TIR domain containing adaptor inducing interferon β (TRIF); TRIF-related adaptor molecule (TRAM); sterile alpha (SAM) and armadillo (ARM) motif-containing proteins (SARM). These adaptor proteins interact with, and activate the downstream IL-1 receptor-associated kinase (IRAK). In the prototypic scenario (Figure 3), the tumor necrosis factor receptor-associated factor 6 (TRAF6) links this adaptor-IRAK module to a trimolecular complex consisting of transforming growth factor β-activated kinase-1 (TAK1), TAK-1-binding proteins 1 and 2 (TAB1 and 2). TAK1 complex phosphorylates and activates IκB kinase complex termed IKK signalsome, which directly phosphorylates NF-κB inhibitors IκBs (40). The site-specifically phosphorylated IκBs are destined to ubiquitination and the subsequent degradation by the proteasome. The released NF-κB then translocates into the nucleus and promotes the κB element-dependent transcriptional programs that are responsible for the expression of various proinflammatory cytokines, chemokines, adhesion molecules, and tissue factors. Since many of the proinflammatory cytokines are also potent NF-κB inducers, their production positively feeds the transcription program. With such persistent stimulation, the signaling events often produce "domino effects", driving further the recruitment and activation of inflammatory cells, and leading to chronic inflammation.

Although it has been demonstrated that the binding of various AGEs and endogenous ligands to RAGE activates NF-κB, the signaling pathway of RAGE leading to NF-κB activation is largely unknown. RAGE has a short cytosolic portion that contains 43 amino acids only (29), whereas the cytosolic portion of TLRs and IL-1 receptor is much longer. The core TIR domain that is responsible for the subsequent recruitment of downstream adaptors contains 150-200 residues that form a string of loop-linked short α-helixes (41). So far, no adaptors and/or scaffold proteins that interact with the cytosolic tail of RAGE have been identified. The short RAGE tail is highly charged and remarkable for an arginine-rich region followed by a glutamic acid-rich region (29). The RAGE mutant lacking the 43-residue tail fails to activate NF-κB, and expression of this tailless mutant receptor produces dominant negative effects that quench the production of proinflammatory cytokines from macrophages (22, 32). These observations suggest a critical role of the RAGE cytosolic portion in transducing the signal from the cell surface to the downstream network.

How does the signal relay from RAGE to NF-κB? Since there is no obvious homology between the cytosolic portion of RAGE and TIR or other known receptors that also

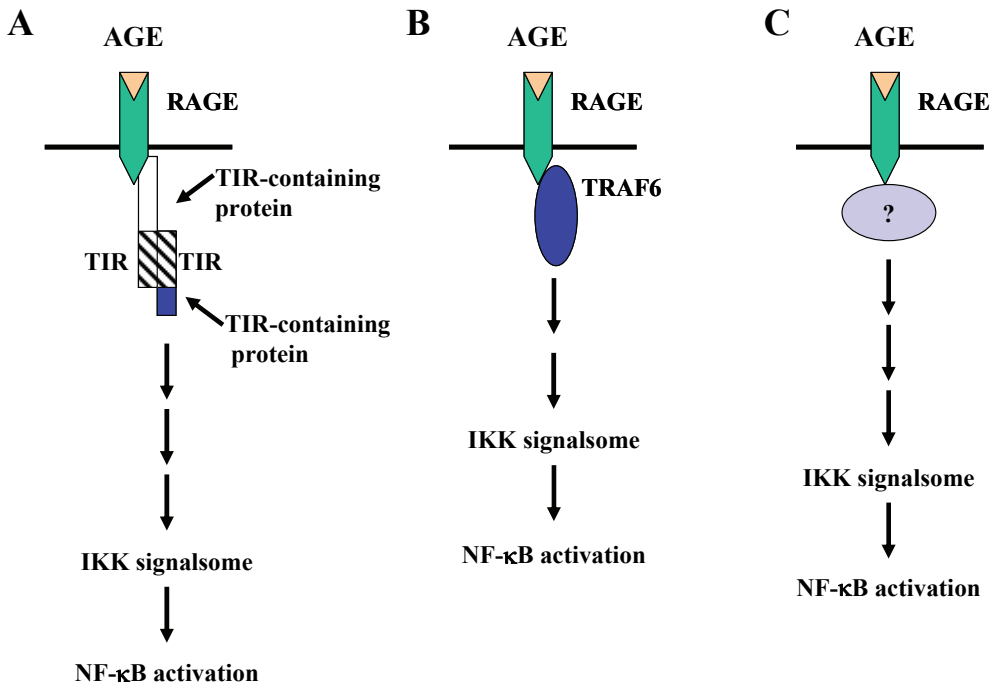

Figure 4. Transmitting signals from RAGE to NF-κB. (A) "Adaptor's adaptor" strategy: RAGE cytosolic tail interacts with a TIR-containing protein and through this adaptor, recruits another TIR-containing protein that interacts with the known NF-κB signaling pathway component(s). (B) "Cut-into-line" strategy: RAGE bypasses the TIR-related recruitment steps, and directly interact with NF-κB signaling pathway component(s) such as TRAF6. TRAF6 is known to interact with highly charged protein domains. (C) RAGE employs a novel signaling pathway that merges with the IKK signalsome downstream of the network.

transmit signals to NF-κB such as tumor necrosis factor receptor (TNFR), or T cell receptor (TCR), in the absence of experimental data, three possible scenarios can be drawn (Figure 4). First, after binding of AGEs and/or other ligands, the RAGE tail interacts with a yet-to-be-identified TIR-containing protein. This "adaptor's adaptor" then recruits the downstream TIR-containing proteins, in a way similar to TLR-mediated signaling relay. Such an "adaptor's adaptor" recruitment strategy has been widely employed in the cell for linking multi-protein complexes to their target substrates or as a regulatory step. Testing interactions between TIR domain-containing proteins and the RAGE tail should provide an answer. The second scenario is that the cytosolic portion of RAGE, following the ligation at cell surface, bypasses the TIR-containing adaptor and directly interacts with member(s) of the signaling cascade. Such "cut-into-line" or "cross-talk" cellular signaling strategy is also common. For example, herpesvirus oncoprotein Tio induces NF-κB by directly interacting with TRAF6 *via* its highly charged N-terminal portion (42). Thirdly, since the well studied TNFR and TCR employ different upstream adaptors to transmit signals to the IKK signalsome to activate NF-κB, it is possible that RAGE may conduct a completely novel signaling route to NF-κB, by recruiting its own yet-to-be-identified adaptors. Certainly, extensive experimental work is needed in order to test the proposed scenarios and to dissect the detailed signaling route leading from RAGE to NF-κB.

Does RAGE participate in innate immune response?

Besides the common intracellular TIR tail, all TLRs share common extracellular leucine-rich repeats (39). RAGE, on the other hand, is a member of the immunoglobulin (Ig) superfamily and does not exhibit leucine-rich repeats in the extracellular portion. The extracellular, N-terminal portion of RAGE contains three Ig domains, among which two are C-type domains and one V-type domain that functions as the ligand-binding module. RAGE also contains two N-linked glycosylation sites and a single transmembrane domain that anchors the receptor to the cellular plasma membrane (29). Ig superfamily members including IL-1 and IL-18 receptors signal to NF-κB with a mechanism similar to TLRs. However, IL-1 and IL-18 receptors recognize specific peptide ligands and do not belong to PRRs (39).

Although the signaling mechanism is unclear, the existing experimental evidence supports the role of RAGE in innate immune responses. In addition to the ability of pattern-recognition and the triggering NF-κB activation, RAGE-ligand interaction also activates mitogen-activated protein kinase (MAPK) family members such as Jun-N-terminal kinase (JNK), p38, and extracellular signal-regulated kinase

(ERK) (25, 31). Parallel multiple signaling events also occur upon TLR ligation *via* the TRAF linage (43). Such a consortium of signaling events contributes to the expression of inflammatory mediators and regulators of apoptosis. Like TLRs, RAGE is also richly expressed in macrophages and monocytes. These traveling lymphocytes possess all the cellular armamentarium to mount an innate immune response. It has been demonstrated that interaction of RAGE with the peptide family of S100/calgranulin triggers macrophage activation *via* NF-κB, leading to production of proinflammatory cytokines IL-1β and TNF-α in these macrophages. Administration of soluble RAGE, a truncated extracellular portion of the receptor, blocks activation of NF-κB by AGEs or endogenous ligands, and hampers production of the proinflammatory cytokines from macrophages (22). These observations suggest that RAGE ligation can effectively activate macrophages. Most intriguingly, RAGE is encoded within the major histocompatibility (MHC) class III locus (44). MHC class III region is known for encoding members of the innate immune system (45), and the $RAGE^{-/-}$ mice are protected from the lethal effects of septic shock (46), suggesting a strong link of RAGE to innate immunity.

To date, RAGE has been found to interact mainly with endogenous ligands, and these ligands have been detected at sites of chronic inflammation. It is not clear whether RAGE also interacts with ligands from pathogens. Although there are other multi-ligand pattern recognition receptors, such as macrophage scavenger receptors, which also interact with AGEs, these receptors exhibit more effective endocytosis upon binding to AGEs (47-49). RAGE, in contrast, is less effective in mediating endocytosis and disposal of bound AGEs *via* degradation, but much more effective in soliciting downstream signaling and causing cellular perturbation and inflammation (22, 25, 31).

Prospective remark

Chronic inflammation serves as the basis for many complex diseases including atherosclerosis (38). It has been reported that TLR-4 or MyD88-deficient mice are resistant to development of diet-induced atherosclerosis, suggesting a role of TLR signaling pathway in this inflammation-based disease (50). This observation also implies that TLR-pathogen interaction may not be a precursor for the development of chronic inflammation. Consistent with this notion, studies have shown that microbial-free hypercholesterolemic *apoE* knockout mice have similar incidences of atherosclerosis as their non-sterile counterparts (51). Endogenous ligand-mediated innate immunity has just emerged as an important concept for the generation of chronic inflammation that exacerbates rather than impedes diseases (6, 52, 53). However, to date, only TLR2 and 4 have been found to interact with endogenous ligands (6, 38), although it is possible with time, more TLR-endogenous ligand liaisons will be revealed. Because the Ig superfamily member RAGE functions as a PRR that recognizes AGEs as well as other non-glycated endogenous ligands, and activates expression programs that encode innate immune responsive genes, it represents an attractive and, perhaps, more meaningful alternative to TLRs, with respect to a central role in chronic inflammation-based diseases. Importantly, ligation of RAGE leads to persistent inflammation that is not protective, as seen in TLR-mediated pathogen clearance. Compared to TLR signaling, the 'dots" between RAGE to NF-κB are yet sufficiently connected to establish this receptor as a "noncanonical Toll". Mapping out the signaling route from RAGE to NF-κB should not only establish the RAGE axis as a possible common etiological factor that contributes to multiple inflammation-based chronic diseases, but also provide significant insights underlying the relationship between *in vivo* environmental cues-induced inflammation and aging process. Such efforts should also reveal a wealth of potential and novel targets for interventions and drug development that prevent or cure these diseases.

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