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Review

DAMPs as mediators of sterile inflammation in aging-related pathologies

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ABSTRACT

Accumulating evidence indicates that aging is associated with a chronic low-level inflammation, termed sterile-inflammation. Sterile-inflammation is a form of pathogen-free inflammation caused by mechanical trauma, ischemia, stress or environmental conditions such as ultra-violet radiation. These damage-related stimuli induce the secretion of molecular agents collectively termed danger-associated molecular patterns (DAMPs). DAMPs are recognized by virtue of specialized innate immune receptors, such as toll-like receptors (TLRs) and NOD-like receptor family, pyrin domain containing 3 (NLRP3). These receptors initiate signal transduction pathways, which typically drive inflammation in response to microbe-associated molecular patterns (MAMPs) and/or DAMPs. This review summarizes the current knowledge on DAMPs-mediated sterile-inflammation, its associated downstream signaling, and discusses the possibility that DAMPs activating TLRs or NLRP3 complex mediate sterile inflammation during aging and in aging-related pathologies.

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1. Introduction

Microbial-derived pro-inflammatory agents are some of the most potent triggers of inflammation. However, numerous types of sterile stimuli including mechanical trauma, ischemia, stress and environmental cues such as ultra-violet radiation trigger pathogen-free inflammation state termed 'sterile inflammation' (Rock et al., 2010). These damage-related stimuli induce the secretion of molecular agents collectively termed damage-associated molecular patterns (DAMPs). These DAMPs in turn activate a milieu of innate immune effectors, which drive a sterile inflammatory reaction. Central amongst these innate immune effectors are the family of toll-like receptors (TLRs) and the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome complex, widely studied for their role as inducers of inflammation.

TLRs exhibit the most diverse repertoire of DAMP ligands amongst all innate immune receptors. These receptors control potent downstream inflammatory mediators, such as interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor (TNF)-α and IL-12 (Liu et al., 2009), by way of myeloid-differentiation factor-88 (MyD88)-dependent and independent signaling pathways. In addition, DAMPs-mediated TLR signaling is tightly regulated by membrane bound sialic acid-binding immunoglobulin-type lectins (Siglec)-G and cluster of differentiation (CD)-24. Similarly to TLRs, the NLRP3

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inflammasome is also activated in response to a diverse repertoire of endogenous DAMPs that induce sterile inflammation in the absence of overt infection (Youm et al., 2013). The NLRP3 inflammasome controls caspase-1 activation, which is required for the secretion of potent cytokines such as IL-1β and IL-18 to regulate inflammation (Youm et al., 2013). Thus, both TLRs and NLRP3 induce inflammation when activated by microbes, and promote 'sterile-inflammation' in response to environmental harmful cues.

During aging, sterile-inflammation is more prevalent due to reduced regulation of the immune system. Thus, chronic inflammation is associated with many aging-related pathologies, such as atherosclerosis, Alzheimer's disease (AD), Parkinson's disease (PD), age-related macular degeneration (AMD) and gout. These age-related pathologies are typically associated with specific DAMPs (see 'DAMPs in aging' section). These DAMPs, in turn, almost exclusively activate macrophages and microglia via TLRs or NLRP3, resulting in cytokine secretion, which drives inflammation. However, as will be discussed below, the underlying mechanisms of TLRs and NLRP3 activation by aging-related pathology-specific DAMPs are not fully understood. It is also unclear whether aging-related DAMP-mediated sterile inflammation is related to these pathologies or the result of the aging process.

2. Toll-like receptors (TLRs)

In mammals the TLR family comprises of 10–12 transmembrane pattern-recognition receptors that initiate intracellular signals in response to diverse microbial-associated molecular patterns (MAMPs) (Kawai and Akira, 2007). The fact that TLRs respond to 'patterns' rather than specific ligands enables specific members of the TLR family to detect a large variety of microbes. In addition to MAMPs, this trait might also be related to the large repertoire of DAMPs detected by members of the TLR family of receptors, most evidently, TLRs 2 and 4 (Yu et al., 2010). Despite of this, the mechanism of interaction between TLRs and DAMPs has not been elucidated to date. TLRs are thus essential components in the initiation of the innate immune response to microbes and tissue damage. TLRs are expressed by a variety of immune-related cells (Eriksson et al., 2006; Gerondakis et al., 2007; Iwamura and Nakayama, 2008; Kaisho and Akira, 2006; Sabroe and Whyte, 2007; Sutmuller et al., 2007; Yoshimoto and Nakanishi, 2006) as well as brain residing cells (Gibson et al., 2008; Yoshimoto and Nakanishi, 2006) such as microglia (Olson and Miller, 2004), astrocytes (Bowman et al., 2003), oligodendrocytes (Tang et al., 2007b) and neurons (Bsibsi et al., 2002).

TLR activation relies on receptor dimerization (Kawai and Akira, 2007) and multimerization (Bell et al., 2005; de Bouteiller et al., 2005) to achieve specificity in ligand recognition. Although most TLRs form homodimers, certain TLRs such as TLR2 form heterodimers with either TLR1 or 6. TLRs may be segregated into three distinct groups based on the nature of MAMP they recognize. The first group recognizes ligands with various lipid groups and includes TLR 1, 2, 4 and 6; TLR4 recognizes lipopolysaccharides, while TLR2/1 and TLR2/6 recognize lipopeptides. The second group of TLRs includes TLR5 and TLR11, which are activated in response to bacterial protein ligands (Uematsu et al., 2008; Akira et al., 2006). TLRs 3, 7, 8 and 9 comprise the third group in the TLR family, and are generally localized in intracellular membranes, where they are ideally positioned for activation by nucleic acids of bacterial and viral origin. TLR3 is activated in response to viral double stranded RNA (dsRNA). Human TLR8 and its murine orthologue TLR7 recognize imidazoquinoline and viral single stranded RNA. TLR9 recognizes unmethylated CpG dinucleotides found in bacteria as well as viral genomes.

Three crystal structures resolved so far highlight three diverse modes of TLRs-MAMPs interaction. The first involves direct TLR–ligand interaction such as TLR3–dsRNA interaction (Liu et al., 2008). The second involves TLR homo- or heterodimerization, for example TLR1–TLR2 interact through a hydrophobic lipopeptide that fits in an internal hydrophobic pocket of the other (Jin et al., 2007). The third involves the use of co-receptors and accessory molecules, for instance the structure of the TLR4–MD2–LPS complex (Park et al., 2009; Piccinini and Midwood, 2010). Following MAMP-induced TLR receptor dimerization, TLRs activate signaling components that initiate transcription of defensive host immune responses. The cytoplasmic region of TLRs shares a stretch of Toll/IL-1 receptor (TIR) domain, which mediates interactions between TLRs and TIR-domain containing adaptor proteins. TLRs recruit four possible activating TIR adaptor proteins and one inhibitory TIR adaptor protein via homophilic interaction of their TIR domains. TLR signaling can be broadly classified into MyD88-dependent and MyD88-independent pathways as MyD88 is the universal adapter protein recruited by all TLRs except TLR3 (Kawai and Akira, 2007). In response to damage signals, the MyD88-dependent pathway recruits members of IL-1 receptor-associated kinase (IRAK) family. This family activates a signal transduction pathway, allowing nuclear factor-kappa B (NF-κB) to translocate into the nuclei and activating activator protein 1 (AP-1). The transcription factors NF-κB and AP-1 control inflammatory response by inducing transcription of pro-inflammatory cytokines, such as TNFα, IL-6, IL-1β and IL-12. In addition to this pathway, which is common to all TLRs, TLR7 (in mice)/8 (in humans) and TLR9 can also activate a signal transduction pathway that results in interferon regulatory factor 7 (IRF7) translocation into the nuclei. Together, all these transcription factors can stimulate type 1 interferon (IFN), which is involved in antiviral immune response. The Myd88-independent pathway recruits the TIR domain-containing adapter inducing IFN-β (TRIF) mediators and TRIF-related adapter molecule (TRAM), which translocate IRF3 into the nuclei, as well as activate NF-κB and AP-1, required for a type 1 IFN induction. Taken together, both MyD88-dependent and independent pathways induce inflammatory response by virtue of pro-inflammatory cytokines and type 1 IFN gene transcription (Kawai and Akira, 2006).

In contrast to MAMPs, no crystal structures of DAMPs bound to any TLRs have been reported so far. In addition, evidence indicates that DAMPs require co-receptors and accessory molecules that differ from those recruited by MAMPs. For example, CD44 is a co-receptor for TLR4, when activated by low-molecular weight (LMW)-hyaluronic acid (HA), whereas CD44 does not participate in LPS-induced TLR4 activation. Moreover, downstream signaling events propagated by DAMPs-mediated TLR activation can differ from downstream signaling events that are generated by MAMPs (Piccinini and Midwood, 2010). These differences are extensively discussed below in the 'Damps identified by TLRs' section.

3. The NLRP3 inflammasome

Inflammasomes are a group of cytosolic protein complexes that function as a molecular platform for caspase-1-dependent proteolytic maturation and secretion of IL-1β and IL-18 (Miao et al., 2010). Of the members of the NLR inflammasomes, the NLRP3 inflammasome, is the most extensively studied (Kim and Jo, 2013). The NLRP3 inflammasome is activated by two steps: an initial step that induces expression of both NLRP3 and pro-IL-1β; and a second step that triggers the assembly of the NLRP3 inflammasome protein components after exposure to MAMPs or DAMPs (Kim and Jo, 2013). The NLRP3 inflammasome is made up of three components: the cytoplasmic innate immune receptor NLRP3, the adaptor apoptosis-associated speck-like protein containing a CARD (ASC),

and the cysteine protease caspase-1. Once the NLRP3 inflammasome is assembled, pro-caspase-1 initiates self-cleavage and forms the active heterotetrameric caspase-1. Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 allowing it to be secreted from the cell via a non-classical pathway (Gu et al., 1997; Latz et al., 2013; Thornberry et al., 1992). In addition to releasing IL-1β and IL-18, active caspase-1 has been associated with the release of IL-1α (Fettelschoss et al., 2011; Gross et al., 2012) as well as the high mobility group box 1 (HMGB1) protein (Keller et al., 2008; Willingham et al., 2009).

The NLRP3 inflammasome's two-step activation system ensures the regulation of the activation of the inflammasome, in order to avoid triggering unnecessary inflammation. NLRP3 and pro-IL-18, unlike the rest of the inflammasome components, are not found naturally at adequate levels for assembly, therefore the priming stage is required for inflammasome activation (Bauernfeind et al., 2009). NLRP3 priming for oligomerization can be accomplished by transcriptional up-regulation via the transcription factor NF-κB or TLR4-MyD88-dependent deubiquitination of the polyubiquinated cytosolic NLRP3 by way of the deubiquitinase (DUB), BRCA1-BRCA2-containing-complex (BRCC3) (Py et al., 2013). NF-κB up-regulation is achieved by different pathways including the stimulation of IL-1 receptor-1 (IL-1R1), TLRs, NOD-like receptors (NLRs), TNF receptors 1 and 2 (Bauernfeind et al., 2009; Fettelschoss et al., 2011; Franchi et al., 2009; Gross et al., 2012; Gu et al., 1997; Keller et al., 2008; Latz et al., 2013; Thornberry et al., 1992; Willingham et al., 2009) as well as the production of reactive oxygen species (ROS) (Bauernfeind et al., 2011) (Fig. 1). TLR4 signaling through MyD88 can non-transcriptionally prime NLRP3 by stimulating DUB in a ROS dependent manner. The DUB enzyme targets a specific polyubiquitin chain or a specific domain in NLRP3 (Juliana et al., 2012). Py et al. demonstrated that BRCA1-BRCA2-containing-complex (BRCC3) is a critical regulator of NLRP3 deubiquitination and inflammasome activity and it plays a critical role in DNA damage response. BRCC3 is responsible for the stable accumulation of the Breast Cancer 1 (BRCA1-A) complex, which is associated with ABRAXAS (Shao et al., 2009) and the cytosolic BRISC complex (Cooper et al., 2009). ABRAXAS is required for DNA repair and checkpoint signaling (Wang and Elledge, 2007), whereas BRISC complex facilitate injury through the deubiquitination and activation of NLRP3 (Py et al., 2013).

NLRP3 inflammasome oligomerization is mediated through mitochondria assisted shuttling of ASC to closer proximity with NLRP3 (Martinon, 2010). Inducers of the NLRP3 inflammasome cause aberrant mitochondrial homeostasis that diminish the concentration of the coenzyme NAD(+), which in turn inactivates the NAD(+)-dependent deacetylase sirtuin 2; this results in the accumulation of acetylated α-tubulin, which is no longer deacetylated by sirtuin 2. Acetylated α-tubulin mediates a dynein-dependent transport of mitochondria resulting in apposition of ASC on mitochondria to NLRP3 on the endoplasmic reticulum (Misawa et al., 2013).

Specific activation of the NLRP3 inflammasome is achieved by exogenous and endogenous agonists, which promote the oligomerization of the NLRP3 inflammasome and activation of caspase-1. The NLRP3 inflammasome activation induction has been proposed in multiple manners (Fig. 2). Exogenous crystalline molecules, such as alum, silica, asbestos, and monosodium urate (MSU) induce 'frustrated phagocytosis', leading to cellular stress and possible lysosomal rupture inducing NLRP3 activation. Other exogenous molecules such as nigericin activate membranal channels allowing entrance of different molecules into the cell, some of which are toxic for the cell. Ion fluxes also play a role in NLRP3 inflammasome activation, such as K^+ efflux via ATP activation of its receptor P2X7 and calcium influx via multiple receptors. Mitochondrial-generated ROS also has been suggested to influence NLRP3 activation (Ratsimandresey et al., 2013). The mitochondria have been associated with the creation of ROS as a byproduct of stressors such as hypoxia, acidosis and membrane damage (Rajamäki et al., 2013). ROS production causes the knockdown of thioredoxin (TRX) of the TRX-thioredoxin-interacting protein (TXNIP) complex, allowing TXNIP to be free to help the assembly of the NLRP3 inflammasome complex (Zhou et al., 2010). ROS can also be created as a result of phagolysosomal destabilization (Halle et al., 2008).

The activation of the NLRP3 inflammasome has been thoroughly investigated as its wide range of activators are structurally dissimilar making the possibility for direct interaction with all the agonists unlikely, therefore it is thought that a single ligand mediates the binding of DAMPs to NLRP3 to activate (Cassel et al., 2009). The interaction between these different pathways is still not fully understood and requires further investigation.

4. DAMPs

Infected cells as well as cells under different types of stressors release molecules known as DAMPs. The most widely studied DAMPs are HMGB1, heat shock proteins (HSPs), and purine metabolites such as ATP and uric acid. HMGB1 is a nuclear protein that binds to nucleosomes and promotes DNA bending. It is present at variable levels in most cells, and is released to the extracellular matrix from necrotic cells. Physiologically, HSPs act as chaperones and reside in the cytosol or the nucleus (HSP22 and HSP70), mitochondria (HSP60 and HSP70), or the endoplasmic reticulum (gp96). In contrast to intracellular DAMPs, extracellular DAMPs are the product of extracellular matrix degradation during tissue injury. Extracellular matrix fragments, such as LMW-HA, heparan sulphate and biglycan, are polysaccharides and proteoglycans that are cleaved during pathological conditions. These fragments are generated as a result of proteolysis by enzymes released from dying cells or by proteases activated to promote tissue repair and remodeling (Chen and Nuñez, 2010).

The above intracellular and extracellular DAMPs are recognized by pattern recognition receptors (PRRs) and non-PRRs on both immune and non-immune cells. The recognition of DAMPs by PRRs can lead to varied transcriptional outcomes (Said-Sadier and Ojcius, 2012). Below, we discuss the activation of the PRRs TLRs and NLRP3 by intracellular and extracellular DAMPs.

5. Damps identified by TLRs

Under normal, non-inflammatory conditions, TLRs and their cognate DAMPs exhibit mutually exclusive cellular compartmentalization preventing a physiological interaction. Under pathological conditions, however, DAMPs are either passively released from injured/inflamed tissues, dying cells or actively secreted unconventionally through the lysosome (Pöllänen et al., 2009). This secretion allows for the activation of TLR by DAMPs. TLR-activating DAMPs include LMW-HA (Scheibner et al., 2006), fibrinogen (Smiley et al., 2001), fibronectin (Okamura et al., 2001), beta-defensins (Biragyn et al., 2002), heparin sulphate (Johnson et al., 2002), proteoglycans (Frey et al., 2013), heat shock proteins (Asea, 2008; Vabulas et al., 2002b), S100 proteins (Foell et al., 2007), uric acid (Ghaemi-Oskouie and Shi, 2011), HMGB1 (Yu et al., 2006) and endogenous nucleic acids (Barrat et al., 2005; Pandey and Agrawal, 2006). Endogenous ligands can initiate innate immune inflammatory responses in the absence of microbes, via TLRs activation (Shimada et al., 2008) (for a comprehensive review see reference (Miyake, 2007)). Most DAMPs studied to date are TLR4 and TLR2 dependent, whereas only a few DAMPs bind and stimulate other TLRs. This could stem from the fact that TLR2 and 4 are the most intensively studied TLRs, and that additional TLRs will emerge

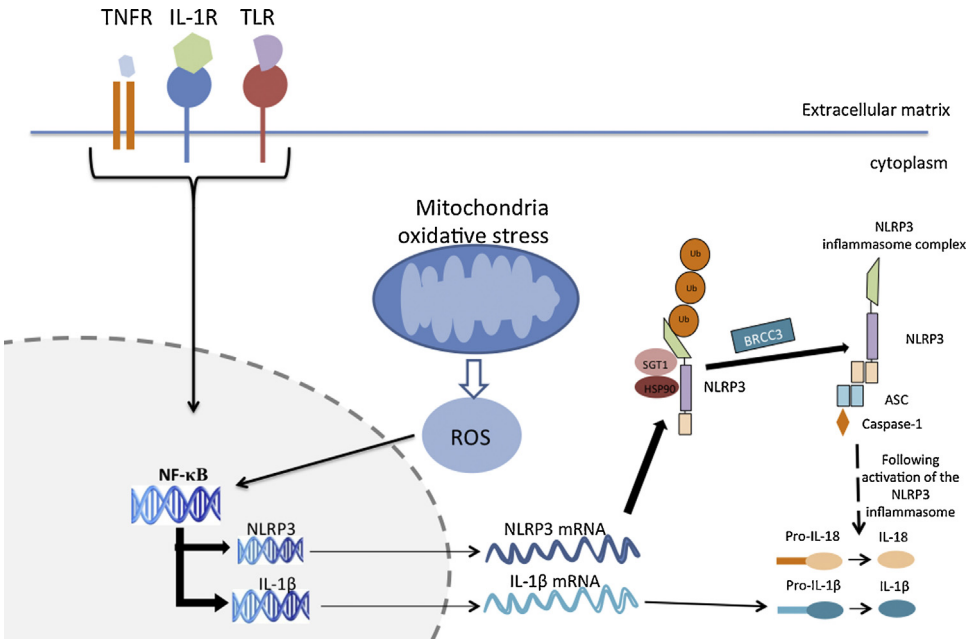

Fig. 1. NLRP3 inflammasome priming. Upon recognition by PRRs such as TLRs or cytokine receptors like IL-1R and TNF-R or mitochondrial release of ROS, intracellular signaling initiate NF-κB-mediated transcription of NLRP3 and IL-β. The cytoplasmic NLRP3 is polyubiquinated as well as stabilized by the SGT1-HSP90 dimer. The enzyme BRCC3 de-ubiquitinates NLRP3 and the SGT1-HSP90 complex is removed as to allow NLRP3 to undergo oligomerization with ASC and Caspase-1. Once the complex is activated, caspase-1 cleaves both pro-IL-1β and pro-IL-18 presenting them in their mature secreted form.

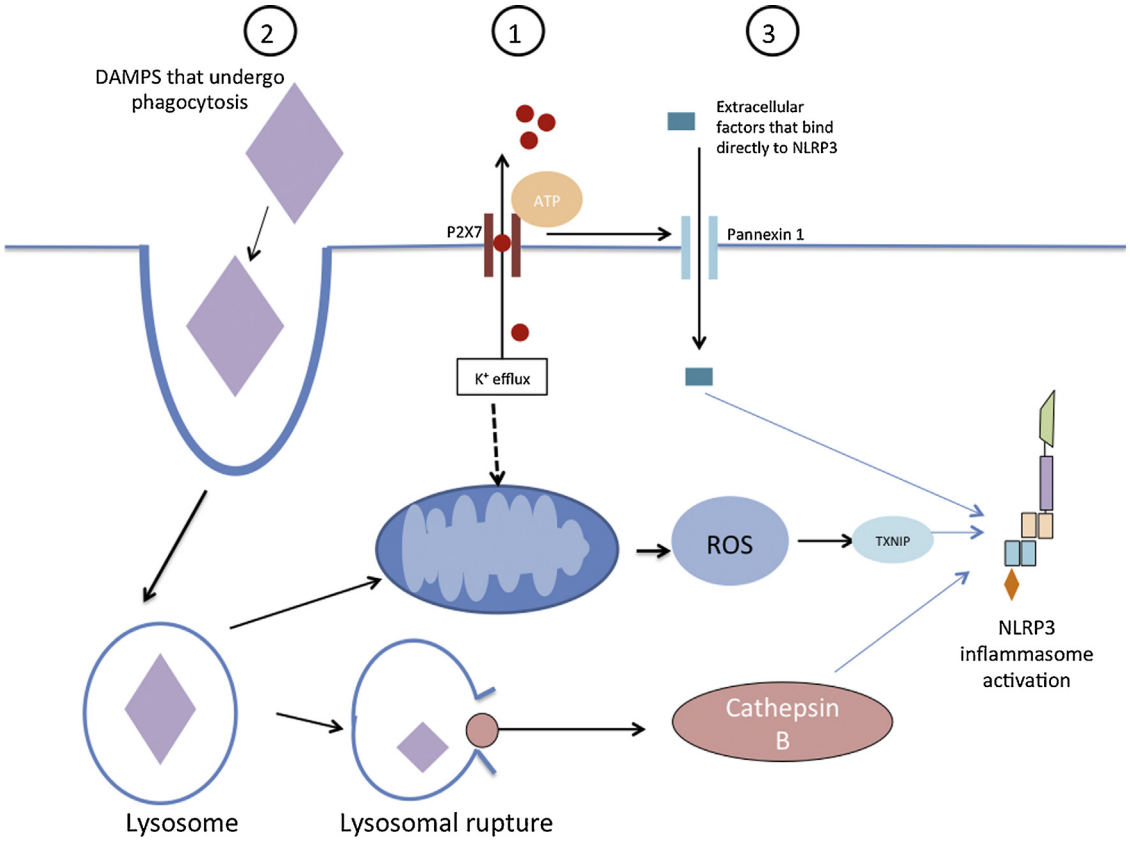

Fig. 2. Three proposed models of DAMP induced NLRP3 inflammasome activation: (1) *Channel Model of NLRP3 inflammasome activation*: extracellular ATP attaches to ionophore P2X7 and induces K^+ efflux, which causes the formation of the pannexin1 pore. This pore allows the cytoplasmic entry of extracellular factors that directly bind and activate the NLRP3 inflammasome. (2) *Lysosomal rupture model:* DAMPS such as amyloid-β, alum and silicia undergo phagocytosis, which leads to the lysosomal rupture and cathepsin B releasing, followed by either direct or indirect activation of the NLRP3 inflamsasome. (3) *The ROS model:* ROS can be induced by way of cellular stress induced by DAMPs, such as cholesterol, amyloid-β, high glucose etc. ROS can also be produced by "frustrated phagocytosis", in which DAMPs such as Alum, Silica, asbestos undergo phagocytosis causing cellular stress. ATP induced K^+ efflux is an additional hypothesized ROS production pathway, and it is thought to be involved in releasing TXNIP from it complex with TRX, promoting inflammasome oligomerization.

Table 1
TLR categorization by their MAMP and DAMP ligands. High-mobility group box 1 (HMGB1), heat-shock protein (HSP), Low molecular weight hylauronic acid (LMW-HA), monosodium urate crystalas (MSU), Human beta-defensin-3 (HβD-3), surfactant protein A (SPA), surfactant protein D (SPD), Eosinophil-derived neurotoxin (EDN), *Antiphospholipid antibodies* (APLAs), Serum amyloid A (SAA), Beta-defensin 2 (BD-2), Heparan sulfate (HS), double strand RNA (dsRNA), single strand RNA (ssRNA) and small interfering RNA (siRNA) and Immunoglobulin G (IgG).

TLR	Membrane localization	MAMPs	DAMPs
2	Extracellular	Lipopeptide (Takeda et al., 2002)	Biglycan (Schaefer et al., 2005), HMGB1 (Yu et al., 2006), HSP60 (Zanin-Zhorov et al., 2003), HSP70 (Vabulas et al., 2002a), human cadiac myosin (Zhang et al., 2009), LMW-HA (Scheibner et al., 2006), MSU crystals (Liu-Bryan et al., 2005), Gp96 (Warger et al., 2006), HβD-3 (Guo et al., 2013), SPA (Montalbano et al., 2013; Murakami et al., 2002), SPD (Montalbano et al., 2013), EDN (Yang et al., 2008), APLAs (Satta et al., 2011), SAA (Cheng et al., 2008) and Versican (Wang et al., 2009)
4		Lipopolysaccharide (Lu et al., 2008)	Biglycan (Schaefer et al., 2005), BD-2 (Biragyn et al., 2002; Vora et al., 2004), fibrinogen (Hodgkinson et al., 2008), fibronectin (Okamura et al., 2001), *HS* (Frey et al., 2013), HMGB1 (Yu et al., 2006), HSP22 (Roelofs et al., 2006), HSP60 (Cohen-Sfady et al., 2005), HSP70 (Vabulas et al., 2002a), HSP72 (Chase et al., 2007), LMW-HA (Dang et al., 2013), MSU crystals (Liu-Bryan et al., 2005), OxPAPC (Erridge et al., 2008), resistin (Tarkowski et al., 2010), S100 proteins (Foell et al., 2007), SPA (Yamada et al., 2006), tenascin-C (Midwood et al., 2009), Gp96 (Warger et al., 2006), Neutrophil elastase (Devaney et al., 2003), APLAs (Mulla et al., 2009), Lactoferrin (Curran et al., 2006), SAA (Sandri et al., 2008), Oxidised LDL (Howell et al., 2011) and Saturated fatty acids (Huang et al., 2012)
5 and 11		Proteins (Yarovinsky et al., 2005; Yoon et al., 2012)	?
3	Intracellular	Viral dsRNA (Alexopoulou et al., 2001)	mRNA (Karikó et al., 2004)
7 (in mice) and 8 (in humans)		Imidazoquinoline (Colak et al., 2014) and viral ssRNA (Colak et al., 2014; Diebold et al., 2004)	ssRNA (Diebold et al., 2004), siRNA (Robbins et al., 2009) and APLAs (Hurst et al., 2009), TLR8 can recognize human cardiac myosin (Zhang et al., 2009)
9		Unmethylated CpG dinucleotides (Takeshita et al., 2001)	IgG chromatin complexes (Boulé et al., 2004), DNA (Rutz et al., 2004) and HMGB1 (Ivanov et al., 2007)

as receptors for yet-to-be discovered DAMPs. In addition, DAMPs such as HMGB1 exhibit the potential to interact with multiple TLRs in different cells (Apetoh et al., 2007; Tang et al., 2007a; Tian et al., 2007). A summary of the endogenous DAMPs and their cognate TLR receptors is presented in Table 1.

Unlike MAMPs-mediated TLR activation, DAMPs do not activate the canonical TLR pathway. Rather, DAMP-induced signaling depends on the presence of MAMPs; in the absence of infection (no MAMPs are present), cytokine-related transcription is suppressed. In this case, DAMPs bind to TLRs, activating cytokine transcription pathway, while simultaneously binding the CD-24–Siglec-G complex inhibiting cytokines transcription. This cytokine transcription inhibition contributes to the protection from autoimmune diseases as CD-24–Siglec-G complex discriminate between self and non-self. Although DAMP-TLR binding with the CD24–Siglec-G complex inhibits cytokines transcription, this connection is involved in NF-κB activation, which regulates apoptotic, tumorigenic, inflammatory, and various autoimmune genes (Liu et al., 2009). However, in the context of infection (MAMPs are present), cytokine transcription is not repressed (Chen et al., 2014). In this case, bacterial sialidase, interrupts the interaction between CD-24 and Siglec-G, disrupting its inhibitory effect, leading to enhanced cytokine production (Paulson and Kawasaki, 2011) (Fig. 3). This demonstrates that the context of TLRs activation dictates the outcome of the cellular transcriptional plan.

Recognition of DAMPs by TLRs enables the immune system to not only sense an ongoing inflammatory process and to recruit more immune cells, but also to initiate the repair of damaged tissue (Medzhitov, 2008) by ways of signal transduction processes. For example, oxidative stress that cause cell necrosis or apoptosis and thus results in DAMPs release, activates two different signal transduction pathways through TLR2 and TLR4. One pathway has been attributed to the activation of c-Jun N-terminal kinase (JNK)/p38 which play a key role in cytokine- and stress-induced apoptosis. A second pathway activates extracellular signal-regulated kinase (ERK) which is thought to be involved in cell survival (Mkaddem et al., 2010). This example indicates that although DAMPs induce inflammation, they can also induce tissue repair through the activation of TLRs.

6. Damps identified by the NLRP3 inflammasome

The NLRP3 inflammasome can be activated by numerous MAMPs, such as LPS of gram-negative bacteria, as well as endogenous and exogenous DAMPs. Environmental cues that trigger DAMPs secretion include particulates such as alum, asbestos, silica, skin irritants and UVB radiation. Endogenous crystalline DAMPs includes monosodium urate crystals (MSU), pyrophosphate dehydrate (CPPD), cholesterol, amyloid deposits (Halle et al., 2008; Masters et al., 2010), hydroxyapatite crystals (Jin et al., 2011), LMW-HA (Yamasaki et al., 2009). Endogenous non-crystalline DAMPs include ATP (Mariathasan et al., 2006), high glucose levels (Zhou et al., 2010) and saturated fatty acids (Wen et al., 2011).

Although the exact mechanism for NLRP3 inflammasome priming and activation is not fully understood, it is agreed that cytoplasmic K^+ concentration crucially affects inflammasome activation (Pétrilli et al., 2007). Indeed, K^+ efflux inhibition, through increasing high extracellular K^+ concentration, blocks inflammasome activation in response to DAMPs such as MSU, ATP, or asbestos (Martinon et al., 2009). ROS generation is frequently accompanied by K^+ efflux (Kowaltowski et al., 2009), although the mechanism for this remains unclear. The involvement of mitochondria in NLRP3 activation remains controversial (Ratsimandresey et al., 2013) despite several examples for DAMP-induced NLRP3 inflammasome activation (Tschopp and Schroder, 2010). Activation of the NLRP3 inflammasome by asbestos and silica has been associated with the production of ROS. This excessive ROS production is the result of "frustrated phagocytosis" in which the particles are too large to engulf inducing cellular stress (Dostert et al., 2008). This is demonstrated by the inactivation of caspase-1 when N-acetyl cysteine (NAC), a ROS scavenger, is added to asbestos treated cells (Dostert et al., 2008). ROS can also be generated in a phagocytosis-independent manner via extracellular ATP attaching to the purinoreceptor P2X7 and induces K^+ efflux (Cruz et al.,

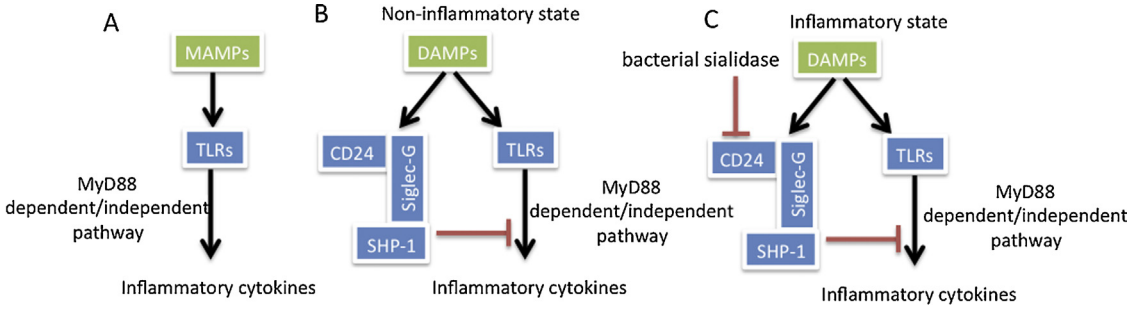

Fig. 3. MAMPs and DAMPs signal transduction through TLRs. (A) MAMPs-mediated signaling (B) Infection-free DAMPs-mediated signaling (C) Infection-related DAMPs-mediated signaling.

2007) (Fig. 2). Environmental triggers such as skin sensitizer 2,4 dinitrochlorobenzene (DNCB) and UV have been proven to produce cellular redox imbalance ROS (Bossi et al., 2008).

Lysosomal rupture is also involved in DAMP induced NLRP3 activation (Ratsimandresey et al., 2013). For example, silica, asbestos and amyloid-β (Aβ) are phagocytized normally but once they are in the lysosomal compartment, the large crystals can damage or disintegrate the lysosomal membrane (Hornung et al., 2008; Sharp et al., 2009). This process requires acidification of the phagosome and depends in part on the lysosomal protease cathepsin-B (Halle et al., 2008; Hornung et al., 2008; Sharp et al., 2009). Table 2 summarizes the known DAMPs that activate NLRP3, and their proposed signaling pathways as described above.

7. DAMPs as mediators of sterile inflammation

During infection, collateral damage in the form of tissue damage is inevitable in order to contain potentially life-threatening situations. Moreover, because infections are often rapidly cleared by immune mechanisms, the duration of the inflammatory response (and hence its collateral damage) is often limited. However, the cost-benefit ratio may be very different in situations of sterile inflammation. Here the inciting stimulus may not be life threatening to the host, and in any case, the innate immune mechanisms that are mobilized may exert little or no benefit. As a result, the dominant inflammatory effect in these situations may be collateral damage in an otherwise healthy tissue. This process, if sufficiently robust, can cause acute disease and/or exacerbate damage from other etiologies (Rock et al., 2010). A number of these acute and chronic conditions are described below.

8. DAMPs in aging and aging-related pathologies

Lifelong exposure to different antigens and stressors results in chronic oxidative stress situation (Baylis et al., 2013). Free ROS produced by cells under oxidative stress causes oxidative damage in biomolecules, a process thought to be a strong contributor to the process of aging (Barja, 2014). This oxidative process leads to the releases of DAMPs that initiate a sterile inflammation process through PRRs such as TLRs and NLRP3. Furthermore, during aging, the innate immune system becomes dysregulated and is characterized by persistent inflammatory responses that involve multiple immune and non-immune cell types, and that vary depending on the cell activation state and tissue context (Shaw et al., 2013). For example, older adults have elevated levels of pro-inflammatory cytokines (Michaud et al., 2013), clotting factors (Luxembourg et al., 2009) and acute phase reactants in the steady state (Milman et al., 1988). This immune dysregulation together with the oxidative stress may affect conditions associated with chronic inflammation, such as atherosclerosis, AD, PD, AMD and gout (Shaw et al., 2013).

Clinical and epidemiological studies have shown that aging contributes to the development of atherosclerosis, a chronic inflammatory arterial disease characterized by the deposition of lipids within the arterial wall. Cholesterol crystals, oxidation-specific epitopes, and IL-1α secreted from damaged cells or tissue, all act as DAMPs, triggering pro-inflammatory responses in this disease. Cholesterol crystals activate NLRP3 via a mechanism of releasing lysosomal cathepsins, ROS and K^+ efflux. NLRP3 activation by cholesterol crystals results in robust IL-1β release leading to inflammatory response (Duewell et al., 2010; Rajamäki et al., 2010). Oxidation-specific DAMPs also activate TLRs, and thus generates inflammation. For example, activation of TLR4 on endothelial cells by oxidized 2-Arachidonoyl-1-palmitoyl-*sn*-glycero-3-phosphocholine initiates secretion of pro-inflammatory cytokines and chemokines, and adhesion molecule expression, leading to monocyte recruitment (Zheng et al., 2011). Release of such DAMPs from necrotic cells can induce inflammation in aged people who suffer from atherosclerosis.

AD is a neurodegenerative disorder characterized by widespread neuronal cell death in the central nervous system and progressive dementia. Non-heritable AD mostly appears in adults above the age of 65. It is hypothesized that the extracellular accumulation of Aβ in senile plaques is a contributing factor to the pathogenesis of AD. Halle et al. demonstrated that the endogenous peptide $A\beta_{1-42}$, which forms insoluble fibrils in the brains of patients with AD, activates the NLRP3 inflammasome and that NLRP3 is involved in the process of Aβ phagocytosis by microglia and macrophages. In addition, they suggest that the NLRP3–caspase-1 pathway induces secretion of critical pro-inflammatory, chemotactic and potentially neurotoxic cytokines, including TNF and nitric oxide (Halle et al., 2008). Thus, Aβ acts as a NLRP3-activating DAMP in AD, promoting sterile-inflammation in this disease.

PD is a neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, the accumulation of α-synuclein in Lewy bodies and neurites, and neuroinflammation (Alvarez-Erviti et al., 2011; Béraud et al., 2011; Codolo et al., 2013; Gao et al., 2008; Marques and Outeiro, 2012; Parihar et al., 2008). A growing body of evidence suggests that misfolded α-synuclein promotes inflammation and oxidative stress resulting in neurodegeneration (Codolo et al., 2013; Dias et al., 2013; Gao et al., 2008; Hsu et al., 2000; Marques and Outeiro, 2012; Parihar et al., 2008). α-Synuclein has been directly linked to microglial activation, which is governed in part, by PRRs that detect foreign material and additionally recognize changes in homeostatic cellular conditions. Importantly, α-synuclein activates microglia through a mechanism that involves CD36; however other PRRs also seem to respond to α-synuclein, as microglia derived from CD36 knockout mice are still activated following exposure to α-synuclein, albeit to a lesser extent (Su et al., 2008, 2009). Upon pro-inflammatory pathway initiation, activated microglia contribute to oxidative stress

Table 2
Proposed signaling pathways of NLRP3 inflammasome activation via DAMPs and environmental irritants. Danger-associated microbial patterns (DAMPs), Microbe-associated molecular Pattern (MAMPs), Aβ (Amyloid β), Ultra Violet (UV), modosodium urate (MSU), pyrophosphate dehydrate (CPPD), reactive oxidative diseases (ROS).

	Activators	Proposed signaling pathway		Refs
Endogenous danger signals (DAMPs)	Extracellular ATP		ROS and channel formation	Cruz et al. (2007)
	Hyluronan		Not yet determined	
	Glucose		ROS	Zhou et al. (2010)
	MSU		ROS	Pétrilli et al. (2007)
	CPPD		Not yet determined	
	Aβ		ROS and lysosome rupture	Parajuli et al. (2013), Halle et al. (2008)
Environmental irritants	Skin irritants and UV		ROS	Bossi et al. (2008)
	Silica		ROS and lysosome rupture	Dostert et al. (2008), Hornung et al. (2008)
	Asbestos		ROS	Dostert et al. (2008)
	Alum		ROS and lysosome rupture	Hornung et al. (2008)
Endogenous Microbial Signals (MAMPs)	Bacteria	Listeria monocytogenes, *Staphylococcus aureus*, *Vibrio cholera*, *Neisseria gonorrhoeae*	ROS or not yet determined	Duncan et al. (2009), Khare et al. (2012), Kim et al. (2010), Mariathasan et al. (2006), Warren et al. (2008), Wu et al. (2010)
	Fungi	*Candida albicans*, *Saccharomyces cerevisiae* (72)	Not yet determined	Gross et al. (2009)
	Virus	Sendai virus, Influenza Adenovirus, MCMV	ROS or not yet determined	Allen et al. (2009), Ito et al. (2012), Kanneganti et al. (2006)
	Protozoa	*Plasmodium malariae*	Not yet determined	Dostert et al. (2009), Shio et al. (2009)

through release of cytokines, nitric oxide, and other ROS, which may adversely impact adjacent neurons. These data suggest that α-synuclein can act as a DAMP activating microglial PRRs and inciting oxidative stress (Béraud et al., 2011).

AMD is the most prevalent cause of blindness in older individuals in the developed world. AMD is a progressive disease characterized by the accumulation of focal extracellular deposits on the Bruch's membrane below the retinal pigment epithelium in the macula, recognizable as drusen deposits, extracellular particulate protein aggregates. These characteristics typify known activators of the sterile inflammatory response that is mediated by NLRP3. Thus, NLRP3 exhibits a protective role against the major pathology of AMD as a DAMP receptor (Doyle et al., 2012).

Gout is characterized by recurrent attacks of acute inflammatory arthritis. The probability to have this disease increases with rich diet consumption, alcohol consumption, genetic background and aging. Formation of MSU, a DAMP specific for this disease is believed to occur when levels of uric acid (UA) in serum reach a saturation point and combine with Na^+ ions to form crystals. Alternatively, these crystals form following a robust release of UA during cell death. Cellular recognition of MSU occurs through variety of not mutually exclusive mechanisms that likely depend on how and where the crystals form. One mechanism is TLR2 and TLR4 signaling pathway resulting in NLRP3 inflammasome activation (Robbins et al., 2014).

9. Concluding remarks

While TLR and NLRP3 inflammasome activation stimulate a pro-inflammatory transcriptional response, the underlying mechanism is not fully understood. For example, it is highly unlikely that either TLRs or NLRP3 physically attaches to all the reported agonists. Thus it has been suggested that there is a single ligand activating NLRP3, who has yet to be determined and will require further investigation (Cassel et al., 2009). As indicated above, aging-related pathologies cause chronic-sterile-inflammation via TLRs and NLRP3 activation (Table 3). However, in contrast to classical DAMP ligands, inflammation in aging-related diseases is pathology-specific (cholesterol crystals, oxidation-specific epitopes, and IL-1α for atherosclerosis; Aβ for AD; α-synuclein for PD; drusen for AMD; and MSU for gout). These DAMPs activate TLRs and NLRP3 inflammasome causing a 'sterile-inflammation'. Thus, inhibition of these two central pathways is hypothesized to reduce the severity of innate immune response in these aging-related diseases.

Table 3
DAMPs and their receptors in aging-related pathologies. Alzheimer's disease (AD), Parkinson's disease (PD), Age-related macular degeneration (AMD), nitric oxide (NO).

Aging disease	DAMP	Receptor	Cell secretion	Result	Reference
Atherosclerosis	Cholesterol crystals	NLR	IL-1β	Inflammation	Shaw et al. (2013)
	Oxidation-specific epitopes	TLR	Proinflammatory cytokines and chemokines		
	IL-1α	IL-1-R1	IL-17 and interferon-γ		
AD	Aβ	NALP3	Proinflammatory, chemotactic and potentially neurotoxic cytokines, including TNF and NO	Inflammation	Halle et al. (2008)
PD	α-Synuclein	PRR	Cytokines, NO, and other ROS	Oxidative stress	Béraud et al. (2011)
AMD	Drusen	NLRP3	Proinflammatory cytokines	Inflammation	Doyle et al. (2012)
Gout	MSU	TLR4 and TLR2 directly and NLRP3 indirectly	Cytokines and chemokines	Inflammation	Robbins et al. (2014)
Healthy aging	?	?	?	?	

A generalized therapeutic intervention could possibly be achieved by targeting the assembly of the NLRP3 complex. BRCC3 was recently described to deubiquitinate NLRP3, thus promoting its maturation. It is currently unknown whether the DUB BRCC3 has substrates other than NLRP3 (Py et al., 2013), however, given the relatively high specificity of DUBs to their substrates (Wilkinson, 2009), it is plausible that targeting BRCC3 could exhibit therapeutic efficacy in reducing neuro-inflammation. While no specific inhibitor was developed yet for BRCC3, G5 is DUB inhibitor, that inhibits deubiquitination and subsequently the activation of NLRP3, resulting in reduced inflammation (Py et al., 2013).

Blocking IL-1 receptor-mediated signaling (Chen and Nuñez, 2010) is another highly promising pathway to reduce NLRP3-induced inflammatory response. In addition to inhibiting NLRP3, blocking TLR signaling pathways by pharmacological antagonists is expected to prevent the release of inflammatory mediators (He et al., 2015) placing it as another potential therapeutic pathway for cases of chronic inflammation.

One of the main hypothesized causes of aging is the constant production of free radicals and ROS under oxidative stress leading to the release of DAMPs. As shown in Table 3, different age related chronic diseases, such as atherosclerosis, AD, PD, AMD and gout, are directly related to DAMP induced TLR or NLRP3-mediated sterile inflammation response. However, as each disease has a unique DAMP signature, there are possibly more DAMPs yet to be discovered. Since DAMPs associated with age-related diseases stimulate the same receptors, a therapeutic method should be considered through targeting of these pathways. Despite the numerous studies on DAMPs in aging-associated pathologies, however, studies on DAMPs in healthy aging are scarce. It is known, however, that oxidative-stress, one of the main aging-related events, promotes inflammation in a TLRs and NLRP3 dependent manner (Cannizzo et al., 2011). Both TLR2 and TLR4 are stimulated by oxidized lipoproteins resulting in inflammation (Chávez-Sánchez et al., 2010), and NLRP3 is directly activated by the presence of sustained amounts of ROS (Chen and Nuñez, 2010). These insights suggest that DAMPs are one of the causative agents of aging associated pathologies, and that TLR and NLRP3-induced ROS drives sterile-inflammation. Excessive amounts of ROS can lead to an overwhelming oxidative stress to cells, and many studies have shown that the effects of ROS can be attenuated by enzymes with antioxidant activity (Chen and Nuñez, 2010). Thus, antioxidant treatment should be beneficial in order to prevent and attenuates the progression of aging-related pathologies.

In contrast to aging-associated pathologies, the involvement of DAMPs in healthy aging is largely unknown. Chronic-inflammation, however, is known to be caused by TLRs and NLRP3 activation via ROS. Thus it should be determined whether these receptors can be stimulated only by ROS itself, or whether DAMP is a connective factor in this chronic-inflammatory pathway. Whatever the answer will be, antioxidant treatment is hypothesized to be beneficial in order to prevent and attenuates aging-related pathology progression.

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