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# Pathogenic Roles of Sterile Inflammation in Etiology of Age-Related Macular Degeneration

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## 1. Introduction

Inflammation is vital for host defense against invasive pathogens via the recruitment of innate inflammatory cells, which in turn phagocytose infectious agents and produce additional cytokines that then activate adaptive immune responses. Inflammation is also crucial to protect cells and facilitate wound healing as a result of mechanic or chemical injury. Because of the absence of infection, the inflammation induced by metabolic or chemical injury has been termed as 'sterile inflammation' to distinguish from that induced by pathogens. Similar to microbially induced inflammation, the immune system has evolved mechanisms to sense necrotic cell death by responding with innate and adaptive immune response, which is marked by the recruitment of macrophages and the production of inflammatory cytokines. However, unresolved and persistent inflammation due to un-removal or un-containment of the offending agents would turn it into a destructive process that is detrimental to the host. The production of reactive oxygen species (ROS), proteases and inflammatory cytokines causes tissue destruction and fibrosis. Thus, sterile inflammation has been demonstrated to be associated with human diseases such as cardiac ischaemia-reperfusion injury, the restoration of blood flow causes tissue destruction as a result of enhanced production of ROS and inflammatory responses to necrotic cells (Camara et al., 2011).

Sterile inflammation in the etiology of age-related macular degeneration (AMD) has been highlighted by the observations that individuals with genetic mutation in complement factor H confer a significantly higher risk for AMD (Montezuma et al., 2007), an idiopathic retinal degenerative disease that leads to irreversible, profound vision loss in people over 60 year old in developed countries (Evans & Wormald, 1996). AMD occurs in two major forms: atrophic (dry) AMD and exudative (wet) AMD. The atrophic AMD is characterized by RPE atrophy and subadjacent photoreceptor degeneration and accounts for approximately 25% of cases with severe central vision loss (Klein et al., 1997). Exudative AMD, which accounts for approximately 75% of cases with severe central vision loss (Klein et al., 1997), is characterized by choroidal neovascularization (CNV) and retinal hemorrhage. These two forms of AMD are both part of the same disease process and share similar risk factors for their development. Although the vision loss results from photoreceptor damage in the central retina, the initial pathogenesis of AMD has been proposed to involve the degeneration of retinal pigment epithelial (RPE) cells (Hageman et al., 2001). The RPE cells *in vivo* has limited regenerating capability upon damage as they are in general post-mitotic and their mitochondria are very susceptible to oxidative damage (Qin & Rodrigues, 2010b). The specific genetic and biochemical mechanisms responsible for RPE degeneration in AMD

have not been determined. However, cumulative oxidative stress and chronic inflammation have been recently appreciated to play important roles in the biogenesis of drusen, the extracellular lipid-containing deposits that are the hallmark of early AMD and may therefore be central to the etiology of this disease (Hageman et al., 2001; Rodrigues, 2007). The eye with its intense exposure to light, robust metabolic activity and high oxygen tension in the macular region, is particularly susceptible to oxidative damage. Thus, there is considerable interest in elucidating the mechanisms responsible for oxidative stress- and sterile inflammation-associated RPE injury, which would provide the basis for designing new strategies to treat or prevent AMD.

Chronic sterile inflammation in the retina might cause RPE cell dysfunction and death that subsequently contribute to retinal degeneration, however, the underlining molecular mechanisms remain elusive. Recently, the damage-associated molecular pattern (DAMP) molecules, a structurally-diverse family of endogenous molecules either released from necrotic cells or breakdown products of the extracellular matrix during cellular injury, are demonstrated to alert host cells for the coming danger by inciting inflammatory responses. Persistent stimulation by the DAMP molecules leads to cell dysfunction and eventually cell death. Some of the DAMP molecules are recognized by pattern recognition receptors, which normally sense pathogen-associated molecular patterns. The role of oxidative stress in the etiology of AMD has been reviewed elsewhere (Qin & Rodrigues, 2010b). In this review, discussed are the nature of the DAMPs, DAMP-initiated inflammatory signaling and the therapeutic potentials of anti-DAMP therapy for AMD intervention.

## 2. Damage-associated molecular patterns

The danger hypothesis was first proposed by Matzinger in 1994 to explain how both infectious and non-infectious agents can stimulate adaptive immune responses (Matzinger, 1994). It is postulated that the adaptive immune system has evolved to respond not only to infection but also to non-physiological cell death due to damage or environmental stress. Necrotic cell death is considered as a sign of danger to the organism. According to this danger model, dying cells will release endogenous DAMPs, using similar nomenclature to pathogen-associated molecular patterns (PAMPs). A candidate molecule as a *bona fide* DAMP should meet at least the following three criteria as proposed by Kono and Rock (Kono & Rock, 2008). First, a DAMP should be active as a highly purified molecule rather than owing to endotoxin contamination. Second, the DAMPs should be active at concentrations that are actually present in pathophysiological conditions. Finally, selectively eliminating or inactivating DAMPs will ideally block the biological activity of necrotic cells in *in vitro* and *in vivo* assays (Kono & Rock, 2008). DAMPs are normally sequestered intracellularly and are hidden from recognition by the innate immune system by the plasma membrane under physiological conditions. However, these molecules, when cells undergo injury or necrosis, are released into the extracellular milieu and then trigger inflammation under sterile conditions. Based on their origin, DAMPs are classified into two categories: intracellular and extracellular DAMPs.

### 2.1 Intracellular DAMPs

Intracellular DAMPs are bioactive mediators of intracellular origin that directly stimulate cells of the innate system. They are pre-existed within the cells and released into extracellular environment after cell injury or death. The DAMPs associated with retinal pathogenesis are summarized in Figure 1.

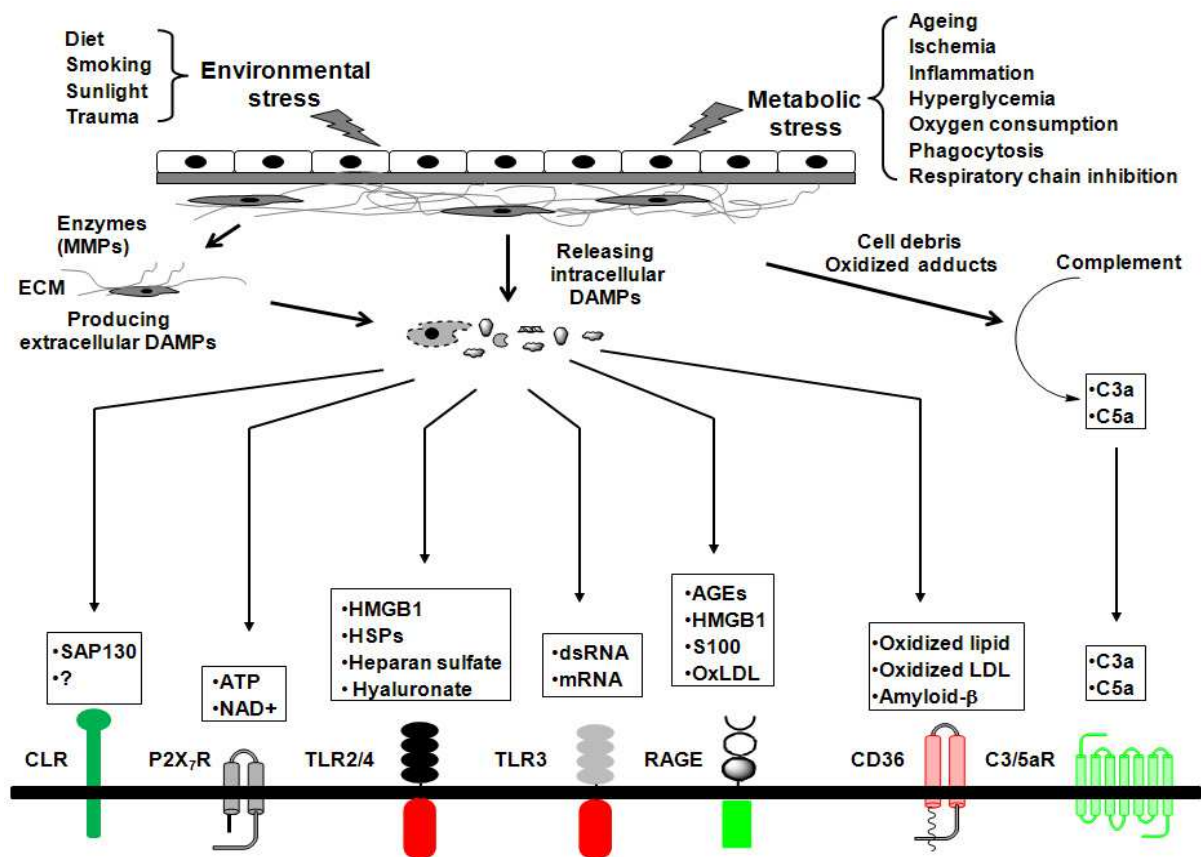


Fig. 1. Cell-surface DAMP receptors that detect a variety of DAMP molecules.

Necrotic cells due to environmental and metabolic stress release intracellular damage-associated molecular patterns (DAMPs) or hydrolytic enzymes that degrade extracellular components to generate extracellular DAMPs. Necrotic cells also activate the complement system to generate C3a and C5a. Additionally, oxidized products or oxidized adducts that are strong inflammatory stimuli are also appreciated as DAMP molecules. These DAMPs are sensed by DAMP receptors on host cells, thereby triggering host defense via sterile inflammation. AGEs, advanced glycation-end products; CLR, c-type lectin receptors; HMGB1, high mobility group box 1; HSPs, heat-shock proteins; oxLDL, oxidized low density proteins; P2X<sub>7</sub>R, purinergic receptor P2X, ligand-gated ion channel, 7; RAGE, receptor for AGEs; SAP130, spliceosome-associated protein 130; TLRs, toll-like receptors.

2.1.1 Nucleic acids

Upon releasing from dying or necrotic cells, nucleic acids such as RNA and fragments of genomic DNA can activate innate and adaptive immune systems. Necrotic synovial fluid cells from the patients with rheumatoid arthritis activated fibroblast cells with production of inflammatory cytokines in a toll-like receptor-3 (TLR-3)-dependent manner (Brentano et al., 2005), indicating that the RNA released from necrotic cells is involved in fibroblast cell activation. Heterologous RNA from necrotic cells or *in vitro* transcribed mRNA can activate dendritic cells, which is abolished by RNase pretreatment (Kariko et al., 2004). Moreover, genomic DNA released into cytosol upon cell injury has been found to activate thyroid cells in concert with histone H2B with cytokine production (Kawashima et al., 2011). Mitochondrial DNA released from injured mitochondria can activate neutrophils *in vitro*

and *in vivo*, eliciting neutrophil-mediated tissue injury (Zhang et al., 2010). Intriguingly, *Alu* RNA, a double-stranded RNA (dsRNA) isolated from drusen of the patients with geographic atrophy can cause RPE cell death *in vitro* and RPE layer degeneration *in vivo* (Kaneko et al., 2011). Knockout of TLR3, the receptor for RNA, protects necrosis-induced retinal degeneration in mouse (Shiose et al., 2011). These results implicate that released nucleic acids from necrotic cells might have a role in etiology of AMD.

### 2.1.2 Interlukin-1 $\alpha$ (IL-1 $\alpha$ )

IL-1 $\alpha$  is synthesized as a biologically active cytokine but is retained in cytosol and nucleus under physiological conditions (Cohen et al., 2010). However, IL-1 $\alpha$  is released with its cellular contents when cells undergo necrosis and released IL-1 $\alpha$  activates its cognate receptor, leading to rapid recruitment of inflammatory cells into the surrounding injured tissue (Cohen et al., 2010). IL-1 $\alpha$  in dying cells and functional IL-1R are required for neutrophilic response to dead cells and tissue injury *in vivo* while this pathway is not essential for the neutrophil response to a microbial stimulus (Chen et al., 2007). Role of IL-1 $\alpha$  in sterile inflammation appears to be dependent on its sources. IL-1 $\alpha$  released from necrotic cells primarily triggers initial neutrophil response and primes resident macrophage that produces IL-1 $\alpha$ , required for necrosis-induced sterile inflammation (Kono et al., 2010b). Interestingly, IL-1 $\alpha$  from necrotic dendritic cells primes mesothelial cells that generate chemokine (C-X-C motif) ligand 1, then recruiting neutrophils into sterile inflammation sites (Eigenbrod et al., 2008).

### 2.1.3 ATP and uric acid

The cytoplasm of each cell contains high concentrations of ATP, however, extracellular levels are quite low as ATP is quickly degraded by ecto-ATPases in normal tissues (Di Virgilio, 2007). Upon cell damage due to chemical or mechanical injury, ATP levels in extracellular environment is increased rapidly. High levels of ATP in extracellular space have been observed during airway inflammation *in vivo* (Idzko et al., 2007). The increase in extracellular ATP concentrations subsequently triggers inflammatory responses since lowering ATP levels by apyrase abolishes cardinal features of asthma such as cytokine production (Idzko et al., 2007). Addition of ATP to cell culture results in significant release/production of inflammatory mediators and causes cell death if under persistent stimulation (Surprenant et al., 1996). Stimulation of RPE cells with ATP enhances cytokine production (Relvas et al., 2009) and then RPE cell death (Yang et al., 2010). Uric acid, a ubiquitous metabolite of purine-degradation pathway, can be produced in high quantities upon cellular injury (Kono et al., 2010a). Uric acid, presented as monosodium urate (MSU) crystals in salt-rich fluids, promotes acute inflammatory responses *in vivo* which is substantially inhibited by uric acid depletion (Kono et al., 2010a).

### 2.1.4 High-mobility group box 1 protein (HMGB1)

HMGB1 is a chromatin-binding protein with key role in nuclear homeostasis. HMGB1 in extracellular milieu behaves as a cytokine, promoting inflammation and disease pathogenesis. HMGB1 was first identified to mediate endotoxin-induced lethality in mouse (Wang et al., 1999). Addition of purified recombinant HMGB1 stimulates production of inflammatory cytokines in human monocytes (Andersson et al., 2000) and knockout of HMGB1 significantly inhibits the capability of necrotic cells to promote inflammation



(Scaffidi et al., 2002). HMGB1 release has been detected from retinal cell death by oxidative stress *in vitro* and retinal detachment *in vivo* (Arimura et al., 2009). The increase in the vitreous HMGB1 level is correlated with that of monocyte chemotactic protein-1 (MCP-1) in human eyes with retinal degeneration.

### 2.1.5 Heat-shock proteins (HSPs)

HSPs are a highly conserved group of intracellular proteins classified into HSP110, HSP90, HSP70, HSP60, and small molecular HSPs based on their molecular weights, and function as molecular chaperones to promote the refolding of damaged proteins and inhibit protein aggregation under stress conditions (Georgopoulos & Welch, 1993). Purified HSP70 stimulates activation of NF- $\kappa$ B in monocytes with production of inflammatory cytokines (Asea et al., 2000) and transgenic expression of HSP70 enhances the extent of *in vivo* sterile inflammation upon  $\beta$ -cell damage (Alam et al., 2009). HSPs also can function as a chaperone to target the antigenic peptides to antigen-presenting cells, thereby initiating immune responses (Binder et al., 2007). Dying cells express higher levels of HSPs (Decanini et al., 2007), thereby providing danger signals to alert the neighboring cells for upcoming danger. However, caution should be exercised as it is still controversial whether extracellular HSPs function as cytokines.

### 2.1.6 S100 proteins

The S100 proteins are a family of about 20 related small, acidic calcium-binding proteins that modulate an array of intracellular functions, like calcium homeostasis, cell cycle and cytoskeletal organization (Heizmann et al., 2002). S100 proteins are higher in extracellular milieu at inflammation site. S100A8 and/or S100A9 stimulate migration of neutrophils and monocytes in gouty arthritis, which is inhibited by anti-S100 antibodies (Ryckman et al., 2003). Additionally, S100B induces cell death in cultured RPE cells (Howes et al., 2004). Whether S100 proteins contribute to disease pathogenesis remains to be confirmed.

## 2.2 Extracellular DAMPs

Extracellular DAMPs, such as hyaluronan, heparan sulphate and biglycan, are generated as a result of proteolysis by enzymes released from dying cells or by proteases activated to promote tissue repair and remodeling (Babelova et al., 2009). Extracellular DAMPs can also be generated from activation of complement system by the degraded or released molecules from necrotic cells (Garg et al., 2010).

### 2.2.1 Breakdown products of extracellular matrix

Extracellular matrix components, which are thought to function as structural elements, are now gaining recognition as signaling molecules triggering or enhancing sterile inflammation once cleaved by released proteolytic enzymes during tissue injury. Hyaluronan fragments generated upon cell injury activate endothelial cells *in vitro* and *in vivo* with significant production of chemokine interleukin-8 (IL-8) (Taylor et al., 2004) and induce maturation of dendritic cells (Termeer et al., 2002). In addition, biglycan has been shown to activate macrophages accompanied with NF- $\kappa$ B-dependent cytokine production (Schaefer et al., 2005). Activated macrophages also release biglycan, further amplifying inflammatory responses (Schaefer et al., 2005). Biglycan can stimulate synthesis of immature

IL-1 $\beta$  via toll-like receptor signaling and in the mean time promote the processing of immature IL-1 $\beta$  to its mature form through P2X receptor signaling (Babelova et al., 2009). Importantly, elevation of hyaluronan contributes to the development of laser-induced choroidal neovascularization with recruitment of macrophages to the lesion sites (Mochimaru et al., 2009), shedding light on understanding the roles of extracellular components in etiology of AMD.

### 2.2.2 C3a and C5a

In the retina, photooxidation causes oxidative stress and complement activation, leading to cell death *in vitro* and *in vivo* (Radu et al., 2011; Zhou et al., 2006). Thus, the chance of RPE/photoreceptor cells being attacked by activated complement systems is increased. During the process of complement cascade activation, the cleaved complement components C3a, C4a and C5a, known as anaphylotoxins, stimulate inflammation. In cultured RPE cells, treatment with C5a stimulates production of IL-8 (Fukuoka et al., 2003) and MCP-1 (Ambati et al., 2003). Furthermore, C3a and C5a have been shown to be present in drusen (Ambati et al., 2003) and are generated early in the course of laser-induced CNV where activation of C3aR or C5aR is required for CNV formation (Nozaki et al., 2006), supporting the idea that RPE cells are constantly stimulated by C3a and C5a and complement-driven sterile inflammation is involved in the etiology and progression of AMD.

## 2.3 Oxidized adducts

With its unusually abundance in poly-unsaturated fatty acids (PUFAs), glucose-enriched and oxidative environment, the retina is an ideal place to form free radicals and bioactive small molecules, then oxidizing proteins, lipids and DNA. Many oxidized adducts of proteins with lipid or glucose accumulate within and around RPE/photoreceptor cells as a function of ageing. Accumulation of these oxidized adducts triggers transcriptional alterations in genes related to cell death and inflammatory response, perturbs the lysosomal function of the RPE via delayed processing of photoreceptor outer segments (POS), thereby resulting in the disease pathogenesis. Although they are not necessarily associated with necrosis, oxidized adducts also generate pattern recognition sites such as oxidized phospholipids, oxidized lipoproteins and long-chain fatty acids that are strong sterile stimuli. These oxidized adducts play important roles in sterile inflammation and potentially in the etiology of human diseases so that they should be recognized as DAMP molecules. Discussed here are four examples of oxidized adducts, advanced glycation endproducts (AGEs), carboxyethyl pyrole (CEP)-protein adducts, oxidized low-density lipoproteins (oxLDL) and oxidized bis-retinoid pyridinium (A2E) with relevance to AMD etiology.

### 2.3.1 Advanced glycation end-products (AGEs)

AGEs are heterogeneous non-enzymatic glycation products of proteins, lipids and DNA on free amino groups by aldehyde groups on sugars. AGEs accumulate during normal ageing with their formation being accelerated in a setting of oxidative stress and inflammation (Schleicher et al., 1997). There is little or no AGE products detected in normal retina, but expression of AGE products increases concomitantly with drusen formation and development of early AMD (Howes et al., 2004). AGE products are also present in RPE lipofuscin, an enzymatically undegradable heterogeneous mixture of numerous biomolecules (Schutt et al.,

2003). With the accumulation of AGEs, receptor for AGEs (RAGE) is simultaneously induced (Yamada et al., 2006), further amplifying cellular activation. Induction of AGE formation *in vivo* leads to the increased transcription of inflammatory genes, resulting in ageing of the RPE/choroid (Tian et al., 2005). In cultured human RPE cells, activation of AGE-RAGE pathway stimulates expression of VEGF (Ma et al., 2007), and production of IL-8 and MCP-1 (Bian et al., 2001). Moreover, activation of RAGE can trigger RPE cell death *in vitro* (Howes et al., 2004), demonstrating that AGEs are toxic to retinal cells.

### 2.3.2 Carboxyethyl pyrole (CEP) adducts

Lipid peroxidation, triggered by direct photobleaching of PUFAs or indirect excitation of photosensitizers contained in RPE lipofuscin, generates a number of reactive dicarbonyl compounds (aldehydes) such as acrolein, 4-hydroxy-2-nonenal (4-HNE), malondialdehyde (MDA) and CEP (Glenn & Stitt, 2009). These aldehydes can deplete cellular thiols, resulting in cell death. Direct exposure of RPE cells to 4-HNE causes dysregulation of chemokine production, increase in cell permeability, and finally cell death (Qin & Rodrigues, 2010a). Moreover, these aldehydes can alter cell functions via formation of lipid adducts on free amino groups of proteins. Among them, CEP adducts, uniquely generated by the oxidation of the most oxidizable fatty acid docosahexaenoate in human retina (Gu et al., 2003), are the most abundant class of oxidized proteins found in drusen. CEP adducts are higher in photoreceptors from AMD patients than healthy retinas (Gu et al., 2003). Mice immunized with mouse serum albumin (MSA) adducted with CEP (CEP-MSA) develop an atrophic AMD-like phenotype including RPE loss and drusen formation with accumulation of macrophages in the interphotoreceptor matrix and C3 fragments in Bruch's membrane (Hollyfield et al., 2008). CEP-MSA also stimulates angiogenesis in ex-vivo models and subretinal injection of CEP-MSA exacerbates laser-induced CNV in mice (Ebrahim et al., 2006). These observations definitely implicate oxidized lipid adducts in the perturbation of RPE cell function, leading RPE cell death both *in vitro* and *in vivo*.

### 2.3.3 Oxidized low-density lipoproteins (oxLDL)

Low-density lipoproteins (LDL) are complex particles containing cholesterol, phospholipids, and triglycerides. The PUFAs in those molecules are susceptible to free radical-initiated oxidation, generating chemically-reactive such as MDA and 4-HNE and bioactive molecules. MDA and 4-HNE oxidize proteins, forming MDA lysine or 4-HNE cysteine protein adducts that are the major modifications observed in RPE lipofuscin (Schutt et al., 2003). OxLDL is found to be accumulated in AMD lesions (Kamei et al., 2007) and higher in patients' blood with AMD (Javadzadeh et al., 2010). Oxidation of the cholesterol within the LDL particle generates a series of cholesterol oxides, of which 7-ketocholesterol is very toxic to RPE cells (Moreira et al., 2009). Exposure of RPE cells to oxLDL inhibits POS phagocytosis, an important RPE cell function essential for outer segment renewal and survival of photoreceptors, by altering phagosome maturation (Hoppe et al., 2004b) and mis-sorting the principal lysosomal protease cathepsin D (Hoppe et al., 2004a). Moreover, oxLDL induces transcriptional alterations in genes related to lipid metabolism, oxidative stress, inflammation and apoptosis in RPE cells (Yamada et al., 2008; Yu et al., 2009). OxLDL causes RPE cell death, at least in part, through formation of 7-ketocholesterol (Rodriguez et al., 2004). Additionally, oxLDL is ligand for scavenger receptors expressed on macrophages that are recruited to the subretinal sites where oxLDL accumulates, further stressing RPE cells via amplifying inflammatory responses



(Kamei et al., 2007). Collectively, these observations suggest a causal role of oxLDL accumulation in AMD pathogenesis although the precise mechanisms are not well defined

### 2.3.4 Bis-retinoid pyridinium A2E

A2E, a byproduct of the visual cycle, is formed through the condensation of two molecules of all-trans-retinal with one molecule of phosphatidylethanolamine in the POS upon photoisomerization of 11-*cis* retinal (Mata et al., 2000). A2E accumulates as lipofuscin in RPE cells with ageing since it is resistant to enzymatic degradation. After light, in particular blue light irradiation, A2E is oxidized, initially by addition of light-excited singlet oxygen, and oxidized A2E can then generate free radicals such as superoxide anion and hydroxyl radical, or discompose to reactive dicarbonyls like methylglyoxal, triggering free radical chain reaction (Wu et al., 2010). Light exposure causes death of A2E-loaded RPE cells in other hand A2E-free RPE cells are not (Schutt et al., 2000). Moreover, photooxidation products of A2E have been shown to activate complement system in RPE cells (Zhou et al., 2006), suggesting that sterile inflammation is involved in A2E cytotoxicity. However, a causal role of A2E accumulation in AMD development remains to be confirmed.

## 3. DAMP receptors

How does the innate immune system distinguish between dead and live cells? The crucial event upon necrotic cell death is the release of intracellular DAMPs and generation of extracellular DAMPs which can be sensed by the receptors on innate immune cells. This section discusses the recent progress in the recognition of DAMPs by pattern recognition receptors and DAMP receptors that are not typically associated with microbial recognition (Figure 1).

### 3.1 Pattern recognition receptors

Pattern recognition receptors (PRRs) recognize conserved structural moieties called PAMPs found in microorganisms and in turn induce cytokine production, which is important in inflammatory and antimicrobial responses. Up to date, five classes of PRRs have been identified. They are the Toll-like receptors (TLRs), the C-type lectin receptors (CLRs), the nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), the retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) and absence in melanoma 2 (AIM2). The membrane-bound TLRs and CLRs surveillance the extracellular milieu, whereas RLRs, NLRs and AIM2-like receptors have emerged as pivotal sensors of infection and stress in intracellular compartments (Meylan et al., 2006). Among them, TLRs, CLRs, NLRs and AIM2 participate in DAMP-dependent inflammatory responses.

#### 3.1.1 Toll-like receptors (TLRs)

TLRs have been reported to be activated by intracellular DAMPs including HSPs, S100 proteins, uric acid and HMGB1, as well as extracellular DAMPs such as hyaluronan, heparan sulphate and proteoglycans (Kono & Rock, 2008). RPE cells make up the first line of defense against pathogens by expressing almost all TLR iso-forms except TLR-8 (Kumar et al., 2004). Activation of TLR3 and TLR9 leads to the production of inflammatory mediators including cytokines and adhesion molecules in cultured RPE cells (Ebihara et al., 2007). TLR3 detects mRNA (Kariko et al., 2004) and dsRNA (Dogusan et al., 2008) released from

necrotic cells while TLR9 senses endogenous DNA (Zhang et al., 2010), triggering sterile inflammatory response and subsequent toxicity. TLR3 is shown to mediate retinal degeneration caused by impaired clearance of toxic all-trans retinal in mice since TLR3 deficiency confers retina protection (Shiose et al., 2011). Choroidal neovascular membranes from AMD patients expressed higher levels of TLR3 in RPE cells (Maloney et al., 2010) and TLR3 activation by siRNA inhibits CNV as siRNA inhibition is abolished in TLR3-deficient mice (Kleinman et al., 2008). Moreover, dsRNA causes RPE cell death that is mediated by TLR3 and genetic variant in the TLR3 412Phe confers protection against geographic atrophy (Yang et al., 2008). These observations reveal a role of TLR3 in AMD development.

### 3.1.2 C-type lectin receptors (CLRs)

CLRs including DEC205, Mincle, CLEC9A and DC-SIGN are a family of surface receptors known to recognize carbohydrate moieties on viruses, bacteria and fungi (Cambi & Figdor, 2009). Stimulation of CLRs leads to activation of signaling pathways that elevate cytokine production. Although their ligands are poorly defined, Mincle (also known as CLEC4E) and CLEC9A can sense necrotic cell death (Cambi & Figdor, 2009). Mincle recognizes SAP130 from necrotic cells and triggers intracellular signaling via the associated FcR $\gamma$  adaptor, leading to the production of inflammatory cytokines (Yamasaki et al., 2008). CLEC9A, a Syk-coupled CLR, can recognize necrotic cells and present dead cell-associated antigens to CD8<sup>+</sup> T cells (Sancho et al., 2009). Similar to Mincle, the capability of CLEC9A to recognize necrotic cells makes it a potential receptor that is important for sterile inflammatory responses even though its ligands are unidentified.

### 3.1.3 NOD-like receptors (NLRs)

NLRs, consisting of the three subfamilies with 14 NALPs, 6 NODs and 2 IPAF/NAIP, are cytosolic PRRs that sense microbial invasion, eliciting an inflammatory response to alert the system to the presence of danger, mainly by assembling inflammasomes that activate caspase-1 for processing immature IL-1 $\beta$  to mature IL-1 $\beta$  (Martinon et al., 2009). NLRs contain a central nucleotide-binding oligomerization domain (NACHT), an N-terminal effector domain (pyrin domain, caspase-recruitment domain or BIR domain) and C-terminal leucine-rich repeats (LRRs). Among the NLRs identified so far, the NOD-, LRR-, and pyrin domain-containing 3 (NLRP3, also termed as NALP3) has been shown to be capable of detecting endogenous danger signals (*See discussion in NLRP3 inflammasome*).

### 3.1.4 Absence in melanoma 2 (AIM2)

AIM2 is a cytosolic protein containing a C-terminal HIN200 and an N-terminal PYD domain, which is identified to recognize dsDNA derived from virus and bacterial, triggering anti-virus responses (Burckstummer et al., 2009). AIM2 can also be activated by the transfection of synthetic dsDNA (Fernandes-Alnemri et al., 2009), highlighting that the innate response to DNA is regulated by the localization of DNA in concert with the innate receptors rather than the source of DNA. Under physiological conditions, self-DNA is localized in nuclei and mitochondria. However, injured or dying cells can release mitochondrial and genomic DNA into the cytosol where AIM2 resides. Released genomic and mitochondrial DNA have been demonstrated to cause inflammatory responses (Kawashima et al., 2011; Zhang et al., 2010). Whether there is a pathogenic role for AIM2 in sterile inflammation-related diseases remains unclear.

### 3.2 Non-PRR DAMP receptors

DAMPs can also be recognized by non-PRRs, named as DAMP receptors here. Receptor for AGEs, purinergic P2X<sub>7</sub> receptor and scavenger receptor CD36 are currently three relatively appreciated DAMP receptors.

#### 3.2.1 Receptor for AGEs (RAGE)

RAGE is a transmembrane receptor that belongs to the immunoglobulin super-family of cell surface molecules that are constitutively expressed at very low levels in numerous cells, including Muller cells, photoreceptor cells, RPE cells, and vascular endothelial cells (Barile & Schmidt, 2007; Howes et al., 2004). It recognizes AGEs, HMGB1, amyloid- $\beta$  (Bucciarelli et al., 2002) and the S100 family members (Hofmann et al., 1999). Activation of RAGE by its ligands results in the upregulation of several inflammatory signaling pathways, including NF- $\kappa$ B, phosphoinositide 3-kinase and MAPK signalling pathways, thereby producing inflammatory cytokines (Hofmann et al., 1999). Cellular expression of RAGE increases upon ligand binding, thus amplifying cellular activation. The levels of RAGE *in vivo* are correlated with drusen formation and early development of AMD (Howes et al., 2004). Transgenic expression of RAGE augmented blood-retinal barrier breakdown and leukostasis, accompanied by increased expression of VEGF and ICAM-1 in the retina in a murine diabetic model (Kaji et al., 2007), which were significantly inhibited by systemic administration of a soluble form of RAGE.

#### 3.2.2 Purinergic P2X<sub>7</sub> receptor (P2X<sub>7</sub>R)

The P2X<sub>7</sub>R belongs to the P2X receptor subfamily of P2 receptors (receptors for extracellular nucleotides) and is an ATP-gated cation channel that is widely expressed in cells of the immune system (Di Virgilio, 2007). Activation of P2X<sub>7</sub>R causes rapid efflux of K<sup>+</sup> with accompanied influx of Ca<sup>2+</sup> and Na<sup>+</sup>. ATP is the preferred agonist for P2X receptor subfamily, however, higher concentration of extracellular ATP is required for P2X<sub>7</sub>R activation than that required for the other P2X receptors (Surprenant et al., 1996). The known DAMPs that activate P2X<sub>7</sub>R are ATP and uric acid (Riteau et al., 2010). Knockout of P2X<sub>7</sub>R, or blockade of with antagonist inhibits ATP-dependent lung inflammation (Riteau et al., 2010) or hyperalgesia (Teixeira et al., 2010). Activation of P2X<sub>7</sub>R by ATP and synthetic ligand leads to RPE cell death *in vitro*, which is inhibited by P2X<sub>7</sub>R antagonist (Yang et al., 2010). Whether ATP- P2X<sub>7</sub>R is involved in RPE atrophy *in vivo* is unknown.

#### 3.2.3 Scavenger receptor CD36

CD36 is a cell surface scavenger receptor expressed on RPE cells, which recognizes oxidized POS and facilitates their uptake by RPE cells (Sun et al., 2006). RPE cells can internalize LDL and oxLDL in large quantities *in vitro* and *in vivo* (Gordiyenko et al., 2004). Treatment with oxLDL induces transcriptional alterations in genes related to lipid metabolism, oxidative stress, inflammation and apoptosis in RPE cells (Yamada et al., 2008). Failure in oxLDL clearance further recruits macrophages via cell surface scavenger receptors to the sites where oxLDL accumulates, amplifying inflammatory responses via producing inflammatory cytokines (Kamei et al., 2007). Therefore, efficient recycle of shed POS and clearance of oxLDL are essential for eye health since CD36 deficiency in mice resulted in age-associated accumulation of oxLDL and sub-retinal Bruch's membrane thickening

(Picard et al., 2010) as well as photoreceptor degeneration and choroidal involution (Houssier et al., 2008). Genetic analysis has identified that two common variants, rs3211883 and rs3173798 which do not reside in the coding sequence of *CD36* gene, are associated with neovascular AMD in a Japanese population (Kondo et al., 2009).

4. Mechanisms of sterile inflammation

In response to necrotic cell death, the innate and adaptive immune systems respond with inflammation to contain and remove the offending agents. The mechanisms by which DAMPs trigger inflammatory responses are still not fully understood, however, the outcome of sterile inflammation to structurally diverse DAMPs is quite similar. Discussed here are activation of the NF-κB/AP-1 signaling and the NLRP3/AIM2 inflammasomes for generating inflammatory mediators.

4.1 Generation of inflammatory mediators by activating cell surface DAMP receptors

Production of biologically active inflammatory mediators including cytokines and adhesion molecules during sterile injury-associated cell death is an important mechanism to alert the immune system of tissue damage and to initiate the healing response. Although the mechanistic details of these DAMP receptor signaling are not fully revealed yet, accumulating evidence shows that these DAMP receptors activate transcriptional factor NF-κB and AP-1, driving expression of inflammatory mediators required for initiating and promoting sterile inflammation (Figure 2).

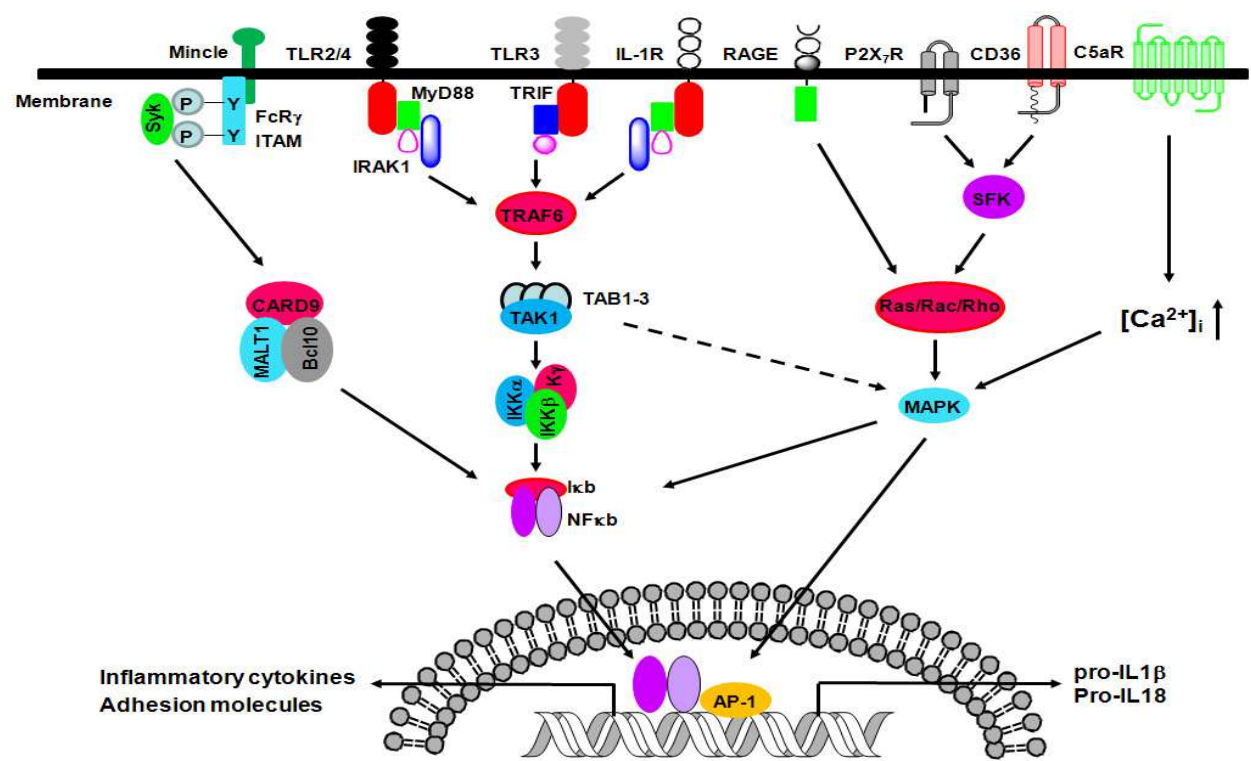


Fig. 2. Overview of cell surface DAMP receptor signaling pathways.



The presentation of DAMP molecules to host cells triggers the sequential activation of signaling cascades that activate transcriptional factors NF- $\kappa$ B and AP-1, leading to production of inflammatory mediators. AP-1, activator protein-1. Bcl10, B cell lymphoma 10. CARD9, caspase recruitment domain-containing protein-9. ITAM, immunoreceptor tyrosine-based activation motif. MyD88, myeloid differentiation primary-response gene 88. IKK, inhibitor of kappa B kinase. IRAK, IL-1 receptor-associated kinase. MAPK, mitogen-activated kinase. NF- $\kappa$ B, nuclear factor kappa B. SFK, src-family kinases. Syk, spleen tyrosine kinase. TAK1, transforming growth factor  $\beta$ -activated kinase 1. TRAF6, TNF receptor-associated factor 6. TRIF, TIR-domain-containing adapter-inducing interferon- $\beta$ .

The signals relayed from activated TLR2, TLR3, TLR4 and IL-1R convene at TNF receptor-associated factor 6 (TRAF6) that further activates NF- $\kappa$ B through TAK1-IKK or activates AP-1 through TAK1-MAPK (Sloane et al., 2010). On the other hand, CLRs Mincle and CLEC9A couple with FcR $\gamma$  adaptor and activate transcriptional factor NF- $\kappa$ B through Syk kinase-caspase recruitment domain-containing protein-9 (CARD9) pathway (Drummond et al., 2011). Activated P2X<sub>7</sub>R (Skaper et al., 2010) and CD36 (Stuart et al., 2007) first promote activation of src-family kinases that trigger NF- $\kappa$ B- and AP-1-dependent transcription via small G-protein-MAPK pathways. Although the mechanistic details of RAGE signaling and the importance of its various ligands in disease pathology continue to be areas of investigation, activated RAGE by its various ligands also leads to activation of transcription factors NF- $\kappa$ B and AP-1 by ras-MAPK signaling (Glenn & Stitt, 2009). Activated NF- $\kappa$ B and AP-1 finally drive expression of inflammatory mediators, promoting sterile inflammation. Among the inflammatory cytokines synthesized, IL-1 $\beta$  and IL-18 are produced and stored in cytosol as inactive precursors that are then converted into biological active forms by the activated NLRP3 and AIM2 inflammasomes through caspase 1-dependent proteolytic maturation, which will be discussed below.

#### 4.2 Production of active IL-1 $\beta$ by NLRP3 inflammasome

IL-1 $\beta$  is a potent pro-inflammatory cytokine that is important in sterile inflammation by induction of inflammatory mediators (Gabay et al., 2010). IL-1 $\beta$  and IL-18 are synthesized and stored in the cytosol as inactive precursors. The processing and secretion of active IL-1 $\beta$  and IL-18 by inflammatory cells depend largely on the inflammasomes, of which the hallmark is the activation of caspase 1 responsible for processing immature IL-1 $\beta$  and IL-18 into their biologically active forms (Martinon et al., 2009). Among several inflammasomes described up to date, NLRP3 (also named as NALP3) inflammasome has been demonstrated to sense DAMP molecules in sterile inflammatory responses. Understanding how NLRP3 senses diverse sterile stimuli is important for understanding the pathogenesis of possibly many sterile inflammatory disorders and for identifying potential therapeutic targets. NLRP3 inflammasome consists of NLRP3, adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) and caspase-1 (Martinon et al., 2009). NLRP3 detects the intracellular ligands by its C-terminal LRR domain, triggering oligomerization by NACHT domain interaction in an ATP-dependent manner followed by caspase-1 recruitment and activation by autocleavage. NLRP3 does not sense structurally diverse stimuli individually, but rather senses a common downstream event mainly through three pathways: ROS generation, lysosome rupture and lowering intracellular potassium (Figure 3).



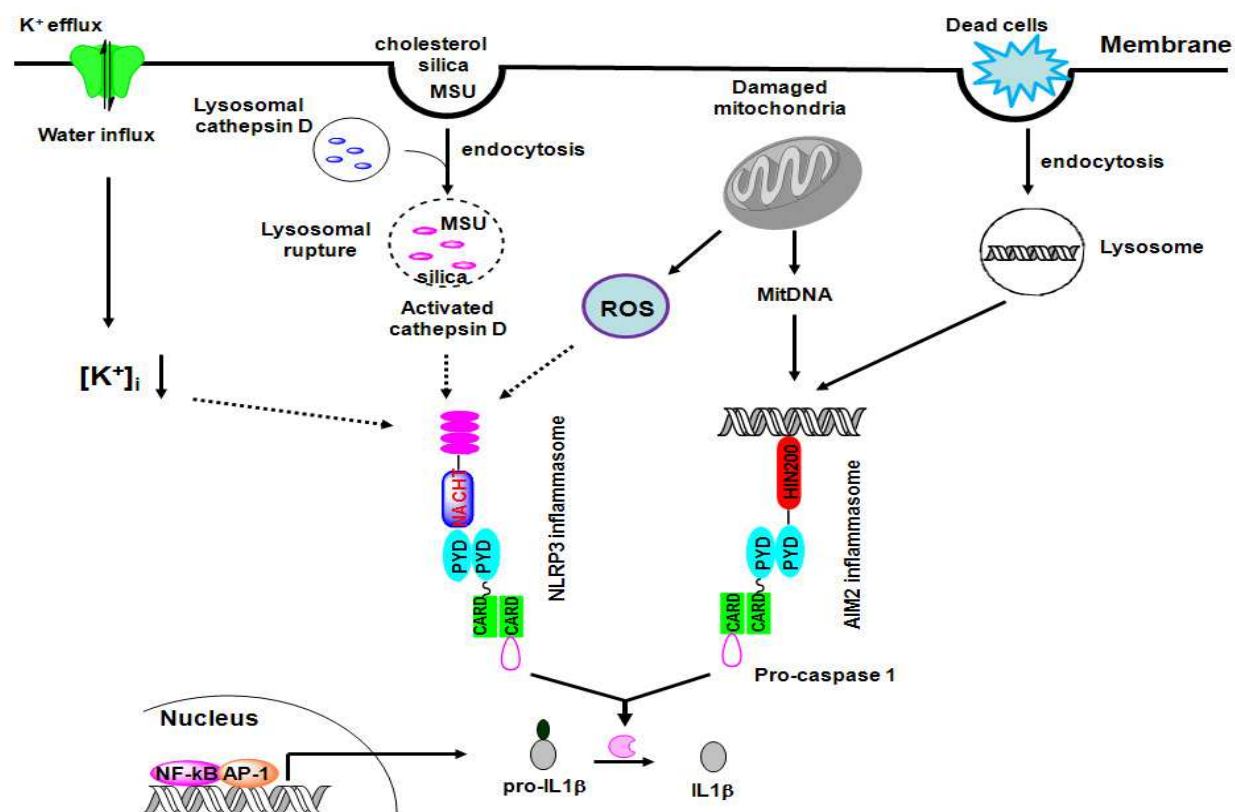


Fig. 3. Intracellular DAMP receptors that sense upcoming danger.

The nucleotide-binding oligomerization domain (NOD)-like receptor NLRP3 (NOD-, LRR- and pyrin domain-containing 3) and the PYHIN (pyrin and HIN200 domain-containing) family protein AIM2 (absent in melanoma 2) are two PRRs that surveillance intracellular DAMPs. NLRP3 can be activated by lowering intracellular potassium concentration, lysosomal damage-dependent activation of cathepsin B or generation of reactive oxygen species (ROS) during cellular stress or necrosis. On the other hand, intracellular DNA from damaged mitochondria or genomic DNA fragments activates AIM2 via binding to its HIN200 domain. Activated NLRP3 and AIM2 provide binding sites for the adaptor ASC (apoptosis-related speck-like protein) via homotypic pyrin domain (PYD) interactions. Clustered ASC then recruits pro-caspase-1 through caspase recruitment domain (CARD)-CARD interactions for assembling NLRP3 or AIM2 inflammasome. The NLRP3 and AIM2 inflammasomes activate caspase-1 which subsequently processes pro-cytokines interleukin-1 $\beta$  (IL-1 $\beta$ ) and IL-18 into their active forms. AP-1, activator protein-1. NF- $\kappa$ B, nuclear factor kappa B.

#### 4.2.1 ROS generation

The detrimental effect of ROS during sterile inflammation depends on the balance between ROS producers and ROS detoxification by antioxidants. ROS are the common integrator across silica, MSU (Dostert et al., 2008) and ATP (Cruz et al., 2007) that activate the NLRP3 inflammasome. ROS removal by *N*-acetyl-L-cysteine, DPI-inhibition of NADPH oxidase and p22<sup>phox</sup> knockdown resulted in impairment of caspase 1 activation and IL-1 $\beta$  production by these stimuli (Cruz et al., 2007; Dostert et al., 2008). The causal role of ROS in NLRP3 activation is further confirmed by Zhou *et al.* (Zhou et al., 2011) and Nakahira *et al.* (Nakahira et al., 2011),

identifying that mitochondrial ROS derived from complex I and III are responsible for NLRP3 activation. Although it is undefined how NLRP3 senses ROS, redox imbalance may be one of the unifying mechanisms by which NLRP3 senses its various activators.

#### 4.2.2 Lowering intracellular potassium

Potassium efflux has been suggested to be an essential upstream signal of NLRP3 activation. Blocking potassium efflux in cultured media abrogates NLRP3 activation by asbestos, MSU and ATP (Dostert et al., 2008). Extracellular ATP is known to open an ATP-gated cation channel that causes potassium efflux via binding to purinergic receptor P2X<sub>7</sub>R. Antibiotics such as neomycin and gramicidin stimulate NLRP3 inflammasome-dependent secretion of IL-1 $\beta$ , depending on potassium efflux but independent of P2X<sub>7</sub>R (Allam et al., 2011). Passive water influx due to sodium overload, which only dilutes cytoplasmic potassium ions, is able to activate NLRP3 inflammasome (Schorn et al., 2011). Thus, NLRP3 senses intracellular K<sup>+</sup> depletion, regardless whether it is due to the activation of specific ion channels or a non-selective increase in ion permeability as a result of cell injury.

#### 4.2.3 Lysosomal rupture

Sterile crystalline and particulate activators of the NLRP3 inflammasome such as urate and cholesterol crystals cause lysosomal destabilization and cathepsin B release, which can be detected by NLRP3. Activation of NLRP3 inflammasome by amyloid- $\beta$  (Halle et al., 2008) and silica and MSU crystals (Hornung et al., 2008) requires their internalization through endocytosis and lysosomal cathepsin B activation as inhibition of endocytosis or cathepsin B impairs NLRP3-dependent IL-1 $\beta$  production. The same is true to cholesterol crystals that activate NLRP3 inflammasome in a cathepsin B-dependent manner (Rajamaki et al., 2010). Lysosomal damage can occur during cellular injury and necrosis, therefore, lysosomal destabilization may be one of the converging points of divergent danger signals sensed by NLRP3. However, whether there is a common mechanism by which numerous heterogeneous stimuli converge on NLRP3 downstream of ROS generation, potassium efflux and lysosomal rupture, remains to be determined.

#### 4.3 Production of active IL-1 $\beta$ by AIM2 inflammasome

In addition to the NLRP3 inflammasome, the AIM2 inflammasome is the second one identified so far to be involved in sterile inflammation. In contrast to NLRP3, AIM2 has a highly restricted spectrum of activating stimuli, currently known being involved in sensing cytosolic dsDNA regardless of the DNA source. The HIN200 domain in its C terminus interacts directly with dsDNA and triggers recruitment and activation of caspase-1 in an ASC-dependent manner via its N-terminal pyrin domain, thereby processing IL-1 $\beta$  and IL-18 into their active forms (Hornung et al., 2009). Mitochondrial DNA (Zhang et al., 2010) and genomic DNA fragments (Kawashima et al., 2011) released from cellular injury can trigger inflammatory responses through activation of the AIM2 inflammasome in addition to TLR9.

### 5. Therapeutic potentials of anti-DAMP for AMD

Cell injury by chronic sterile inflammation leads to progressive loss of cell function and thus contributes to the development of AMD. Protecting retinal cells by neutralizing DAMPs and

inhibiting DAMP-initiated inflammatory signaling could potentially delay the onset or progression of this disease. A number of promising anti-DAMP agents are currently under development for AMD therapy, some of them are still in preclinical testing (Table 1).

5.1 Complement alternative pathway inhibitors

As strong association of complement alternative pathway activation with higher AMD risk has been documented, suppressing complement cascade in the retina would be expected to delay or reverse the onset of AMD. Inhibition of complement alternative pathway can be achieved via targeting factor B and factor D which participate in the amplification of the complement alternative pathway, or inhibiting targets downstream the point of conversion for all three complement pathways. TA-106 and TNX-234, anti-Factor B and anti-Factor D antibodies, are in preclinical testing and Phase I/II trial for AMD by Alexion and Genentech, respectively. JPE-1375 is a small molecule peptidomimetic antagonist targeting the C5a receptor (Ricklin & Lambris, 2007) that is in preclinical evaluation for AMD. ARC-1905, a 39-mer oligonucleotide anti-C5 aptamer is in Phase 1 for AMD by Ophthotech. POT-4 is a cyclic peptide capable of binding to human C3, resulting in broad and potent complement activation inhibition (Ricklin & Lambris, 2007). POT-4 is the first complement inhibitor that has entered into a Phase I clinical trial for AMD by Potentia and is now under development by Alcon (Table 1).

Compound	Indications	Company	State of development	Estimated completion day	Mechanism of activation
TA-106	AMD & asthma	Alexion	Pre-clinical testing	Unknown	Anti-factor B antibody
TNX-234	Geographic atrophy	Genentech	Phase I/II	Unknown ongoing	Anti-factor D antibody
JPE-1375	Geographic atrophy	Jerini	Pre-clinical testing	Under development	C5aR antagonist
ARC-1905	AMD	Ophthotech	Phase I	Mar. 2011 ongoing	Anti-C5 aptamer
POT-4	AMD	Alcon	Phase 1	Feb. 2010 completed	C3 inhibitor
Canakinumab	Wet AMD	Novartis	Phase 1	Dec. 2007 completed	Anti-IL1 $\beta$ antibody
Anakinra	Corneal neovascularization	Massachusetts Eye Infirmary	Phase I/II	Under development	IL-1 receptor antagonist
PF-04494700	Alzheimer's dementia	Pfizer	Phase II	Dec. 2010 completed	RAGE inhibitor

Table 1. Developing anti-DAMP therapies for age-related macular degeneration

5.2 IL-1 pathway inhibitor

Given the crucial role for IL-1 $\alpha$  and IL-1 $\beta$  in sterile inflammatory responses, blocking IL-1 receptor is expected to benefit patients with sterile inflammatory disorders. Some promising results have been obtained with the application of a recombinant IL-1 receptor antagonist,

anakinra. Anakinra is in clinic for the treatment of rheumatoid arthritis (Mertens & Singh, 2009). Phase I/II clinical trials are ongoing for the topical treatment of corneal neovascularization by Massachusetts Eye and Ear Infirmary. Intravitreal delivery of anakinra significantly inhibits experimental CNV in animal model (Olson et al., 2009). A benefit for patients with AMD is expecting with use of anakinra though no clinical trial is initiated. Neutralizing ligands for IL-1 receptor on the other hand would achieve similar outcomes. IL-1 $\beta$  antibody, canakinumab, has been approved for treating cryopyrin-associated periodic syndromes. Canakinumab is under Phase I evaluation for choroidal neovascularization by Novartis.

### 5.3 Anti-RAGE

The levels of RAGE, which detects AGEs, S100 proteins, HMGB1 and amyloid- $\beta$ , are very lower but dramatically increases on the Bruch's membrane around drusen and are associated with early development of AMD. Inhibiting RAGE receptor will block multi-ligand-triggered inflammatory response, thereby delaying or preventing the onset and progression of the disease. Pfizer is conducting a Phase II trial of RAGE inhibitor, PF-04494700, for treating Alzheimer's dementia, which share similar risk factors with AMD.

### 5.4 Anti-TLR-3

Activation of TLR3 by heterologous RNA from necrotic cells or *Alu* RNA causes RPE cell death and retinal degeneration. TLR3 knockout and TLR3 412Phe prevents retinal degeneration in animals and confers protection against geographic atrophy in patients, respectively. TLR3 monoclonal antibody 23C8 is currently in Phase I trial for treatment of inflammation by Innate. No trial has been reported for AMD yet.

## 6. Conclusion

Cells or tissues incite sterile inflammatory responses to clear and repair the damage by sensing DAMPs derived from necrotic cells. Persistent inflammation causes cell dysfunction and subsequent retinal degeneration. Much progress has been made in identifying sterile inflammatory triggers and understanding the molecule mechanisms, which offers opportunities to design novel targets for delaying and preventing onset of retinal diseases including AMD. However, many questions remain to be answered. As cells contain many DAMPs, which DAMPs are the most important and whether their relative importance depends on cell types or pathophysiological conditions? How do different DAMPs initiate a common sterile inflammatory response and their downstream signaling pathways? Also unknown is the significance of DAMP-receptor interactions in sterile inflammation and disease pathogenesis since some DAMPs bind to several receptors and vice versa. Once the molecular mechanisms by which necrosis triggers sterile inflammation are elucidated and the relative importance of DAMPs is determined, one can manipulate the immune response to treat and manage sterile inflammation-associated diseases.

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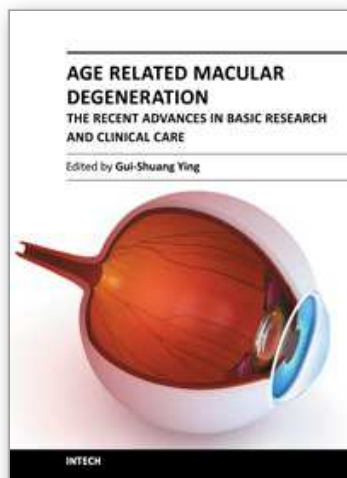


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## **Age Related Macular Degeneration - The Recent Advances in Basic Research and Clinical Care**

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Age-related Macular Degeneration (AMD) is the leading cause of vision loss and blindness in the developed countries. In the past decade, great progress has been made in understanding the pathobiology and genetics of this blinding disease, as well as in finding new therapies for its treatment. These include the discovery of several genes that are associated with the risk of AMD, new anti-VEGF treatments for wet AMD and new imaging techniques to diagnose and monitor the AMD. All chapters in this book were contributed by outstanding research scientists and clinicians in the area of AMD. I hope this timely book will provide the basic scientists and clinicians with an opportunity to learn about the recent advances in the field of AMD.

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