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Damage-Associated Molecular Patterns in Inflammatory Diseases

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
AD, Alzheimer's disease; ATP, adenosine triphosphate; BBB, blood-brain barrier; CHD, coronary heart disease; DAMP, damage-associated molecular pattern; DC, dendritic cell; HMGB1, high-mobility group box 1; HSP, heat-shock protein; ICD, immunogenic cell death; IFN, interferon; LT, lymphotoxin; MMP, matrix metalloproteinase; mtDNA, mitochondrial DNA; MTX, methotrexate; NET, neutrophil extracellular trap; NLR, NOD-like receptor; NLRP, NLR family, pyrin domain containing; OA, osteoarthritis; PAMP, pathogen-associated molecular pattern; PD, Parkinson's disease; PRR, pattern recognition

ABSTRACT

Damage-associated molecular patterns (DAMPs) are endogenous danger molecules that are released from damaged or dying cells and activate the innate immune system by interacting with pattern recognition receptors (PRRs). Although DAMPs contribute to the host's defense, they promote pathological inflammatory responses. Recent studies have suggested that various DAMPs, such as high-mobility group box 1 (HMGB1), S100 proteins, and heat shock proteins (HSPs), are increased and considered to have a pathogenic role in inflammatory diseases. Here, we review current research on the role of DAMPs in inflammatory diseases, including rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, atherosclerosis, Alzheimer's disease, Parkinson's disease, and cancer. We also discuss the possibility of DAMPs as biomarkers and therapeutic targets for these diseases.

Keywords: Damage-associated molecular patterns; Inflammation; Pattern recognition receptors; Inflammatory diseases

INTRODUCTION

The innate immune system is the first line of host defense that induces immediate, non-specific immune responses against pathogens (1). Inflammation is part of the innate immune system and is initiated when the innate immune system recognizes invading pathogens or molecules from tissue injury through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and inflammasomes of the innate immune system (2,3). Although inflammation is a protective response to eliminate harmful stimuli, initiate tissue repair, and restore health, it can also contribute to the development of various diseases, such as autoimmune diseases, cardiovascular diseases, and neurodegenerative diseases, if it is not properly regulated or resolved (4,5).

Damage-associated molecular patterns (DAMPs) are molecules released upon cellular stress or tissue injury and are regarded as endogenous danger signals, because they induce potent inflammatory responses by activating the innate immune system during non-infectious inflammation (6,7). Recently, emerging evidence has indicated that DAMPs play a key role in the pathogenesis of human diseases by inducing inflammation (8). This review describes the role of DAMPs in inflammatory diseases and the possibility of using DAMPs as biomarkers and therapeutic targets for these inflammatory diseases.

receptor; RA, rheumatoid arthritis; RAGE, receptor for advanced glycation end products; RLR, RIG-like receptor; SAA, serum amyloid A; SLE, systemic lupus erythematosus; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cell

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ORIGIN AND LIST OF DAMPS

Since the danger model was introduced by Polly Matzinger (9), several DAMPs have been identified, and the number of DAMPs is still increasing (7,10). DAMPs are released from the extracellular or intracellular space following tissue injury or cell death (10). These DAMPs are recognized by macrophages, and inflammatory responses are triggered by different pathways, including TLRs and inflammasomes (10,11). DAMPs can originate from different sources and include extracellular proteins, such as biglycan and tenascin C, and intracellular proteins, such as high-mobility group box 1 (HMGB1), histones, S100 proteins, heat-shock proteins (HSPs), and plasma proteins, like fibrinogen, Gc-globulin, and serum amyloid A (SAA) (10,12-15). A list of well-characterized DAMPs, along with their origin and receptors, is shown in **Table 1**.

HMGB1, a member of the HMG protein family, which is located in the cell nucleus, has a critical function in gene expression, but when released to the extracellular space, HMGB1 is known to induce inflammation by activating the NF-κB pathway by binding to TLR2, TLR4, TLR9, and the receptor for advanced glycation end products (RAGE) (16). S100 proteins are calcium-binding proteins, and their main function is the management of calcium storage

Table 1. List of DAMPs and their receptors

Origin		Major DAMPs	Receptors
Extracellular matrix		Biglycan	TLR2, TLR4, NLRP3
		Decorin	TLR2, TLR4
		Versican	TLR2, TLR6, CD14
		LMW hyaluronan	TLR2, TLR4, NLRP3
		Heparan sulfate	TLR4
		Fibronectin (EDA domain)	TLR4
		Fibrinogen	TLR4
		Tenascin C	TLR4
Intracellular compartments	Cytosol	Uric acid	NLRP3, P2X7
		S100 proteins	TLR2, TLR4, RAGE
		Heat shock proteins	TLR2, TLR4, CD91
		ATP	P2X7, P2Y2
		F-actin	DNGR-1
		Cyclophilin A	CD147
		Aβ	TLR2, NLRP1, NLRP3, CD36, RAGE
	Nuclear	Histones	TLR2, TLR4
		HMGB1	TLR2, TLR4, RAGE
		HMGN1	TLR4
		IL-1α	IL-1R
		IL-33	ST2
		SAP130	Mincle
		DNA	TLR9, AIM2
		RNA	TLR3, TLR7, TLR8, RIG-I, MDA5
	Mitochondria	mtDNA	TLR9
		TFAM	RAGE
		Formyl peptide	FPR1
		mROS	NLRP3
	ER	Calreticulin	CD91
	Granule	Defensins	TLR4
		Cathelicidin (LL37)	P2X7, FPR2
		EDN	TLR2
		Granulysin	TLR4
	Plasma membrane	Syndecans	TLR4
		Glypicans	TLR4

ER, endoplasmic reticulum; EDN, eosinophil-derived neurotoxin.

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and shuffling (10,17). Although S100 proteins have various functions, which include cell proliferation, differentiation, migration, and energy metabolism under healthy conditions (17), they also act as DAMPs by interacting with TLR2, TLR4, and RAGE after they are released from phagocytes (18). Likewise, HSPs normally function as chaperones and assist with biosynthetic pathways (10), but extracellular HSPs, which are cellular necrosis products, can induce inflammation through the activation of TLR2, TLR4, and CD91 (10,19). Adenosine triphosphate (ATP) and uric acid, which are purine metabolites, also activate NLR family, pyrin domain containing (NLRP) 3 inflammasomes to induce IL-1β and IL-18 (20,21). Finally, some plasma proteins, including SAA, fibrinogen, Gc-globulin, α1-microglobulin, and α2-macroglobulin, are extravasated to the sites of inflammation from the vasculature and function as DAMPs by stimulating macrophages to produce inflammatory cytokines through TLR2 or TLR4 (12-15).

PRRS

PRRs are important components of the innate immune system. Several families of PRRs have been identified in the diverse compartments of the cell (**Table 2**). They recognize microbes or tissue damage by specific molecular structures called pathogen-associated molecular patterns (PAMPs) or DAMPs (10,22). The main functions of PRRs are to stimulate phagocytosis and mediate inflammation by sensing various pathogens and molecules from damaged cells (2,23). As a result, PRRs activate inflammatory signaling pathways to induce innate immunity (23).

TLRs are type I transmembrane glycoproteins located at the cell surface (TLR1, 2, 4, 5, 6, and 10) or in intracellular membranes (TLR3, 7, 8, and 9) and recognize various PAMPs or DAMPs (24). TLRs induce the production of proinflammatory cytokines and type I interferons (IFNs) through the myeloid differentiation factor 88 (MyD88)-dependent signaling pathway or the toll/interferon response factor (TRIF)-dependent signaling pathway (24). NOD-like receptors (NLRs) are cytoplasmic PRRs that include NODs, NLRPs, and the IPAF subfamily (25,26). NOD1 and NOD2 initiate proinflammatory signaling by activating NF-κB (25), and NLRP3 stimulation by DAMPs, such as extracellular ATP, hyaluronan, and uric acid, can activate caspase-1 and induce the release of IL-1β and IL-18 through the formation of an inflammasome (26). RIG-like receptors (RLRs), including RIG-I, MDA5, and LGP2, detect viral RNA and self RNA in the cytoplasm (27). RLRs induce the production of IFNs by interacting with IPS-1; furthermore, RLR signaling cross-talks with the TLR or the inflammasome signaling pathway (27). C-type lectin receptors (CLRs), expressed by dendritic cells (DCs), promote NF-κB activation by modulating TLR signaling or directly through the

Table 2. PRRs and their DAMP ligands

Family	Major members	DAMP ligands
TLRs	TLR1–9	HMGB1, HSPs, S100 proteins, histones, DNA, RNA, mtDNA, syndecans, glypicans, biglycan, decorin, versican, LMW hyaluronan, heparan sulfate, fibrinogen, tenascin C
NLRs	NOD1, NOD2, NLRP family	Uric acid, Aβ, mROS, histones, biglycan, LMW hyaluronan
RLRs	RIG-I, MDA5, LGP2	RNA
CLRs	DEC-205, MMR, Dectin-1, Dectin-2, Mincle, DC-SIGN, DNGR-1	SAP130, F-actin
CDSs	AIM2-like receptor	DNA
Scavenger receptors	CD36, CD44, CD68, CD91, CXCL16, RAGE	HMGB1, HSPs, S100 proteins, calreticulin, versican
FPRs	FPR1, FPR2, FPR3	Formyl peptide, cathelicidin (LL37)

NLR, NOD-like receptor; CLR, C-type lectin receptor; CDS, cytosolic DNA sensor; FPR, formyl peptide receptor; LMW, low molecular weight.

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spleen tyrosine kinase (SYK) and RAF1 pathways (28). Scavenger receptors consist of a large family of proteins and recognize various patterns. RAGE, one of the scavenger receptors, interacts with PAMPs or DAMPs, such as advanced glycation end products (AGEs), HMGB1, and S100 proteins, thereby mediating inflammation, oxidative stress, and apoptosis (29).

DAMPS IN AUTOIMMUNE DISEASES

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease (30). Swelling, pain, and stiffness of joints are the main symptoms of RA that result from inflammation of the synovial membrane of joints (31). Although the pathology of RA is not well understood, it is clear that DAMPs are associated with RA (30). S100A8/9/11/12 proteins were upregulated in the synovial tissue, synovial fluid, or serum of RA patients (32,33). In addition, the expression of HMGB1 was increased in the serum and synovial fluid of RA patients (34,35). On the other hand, when RA patients were treated with methotrexate (MTX), a common medication for RA, HMGB1 and cartilage degradation enzymes, matrix metalloproteinase (MMP)-2 and MMP-13, were decreased compared to the levels in the RA patients without MTX treatment (36). Furthermore, neutralization of HMGB1 can protect cartilage from degradation and prevent bone destruction due to RA in experimental animal models (37,38). It is assumed that HMGB1 stimulates the production of proinflammatory cytokines, such as tumor necrosis factor (TNF) and IL-1 (39). The inflammation of joints can promote cellular stress and lead to an increase in HSPs in the synovial tissue (40). It has been reported that the levels of HSP70 were elevated in the synovial fluid of RA patients (41), and heat shock protein gp96 was increased in the synovial fluid of RA patients; this is considered to promote inflammation by activating macrophages through TLR2 signaling (42). HSP90 also contributes to the pathogenesis of RA by inducing a tumor-like synovial overgrowth by stabilizing integrin-linked kinase (ILK), extracellular signal-regulated kinase (ERK), and protein kinase B (Akt) (43).

Recently, citrullinated histones and their immune complexes have been reported to function as DAMPs in RA (44). Citrullinated H2B was increased in the synovial fluid of RA patients and activated macrophages to produce inflammatory cytokines, which were enhanced by immune complexes with RA patient-derived IgGs. Moreover, immunization with citrullinated H2B in the presence of low-grade joint inflammation induced inflammatory arthritis in an animal model of RA (44).

Systemic lupus erythematosus (SLE) is one of the chronic autoimmune diseases that invades multiple organs (45). HMGB1 expression was enhanced in SLE patients and correlated with the SLE disease activity index (46). Furthermore, the urine HMGB1 level was elevated in lupus nephritis patients (47). However, a monoclonal anti-HMGB1 antibody has no therapeutic effect on a mouse model of lupus nephritis (48). This suggests that HMGB1 could be a good biomarker, but not a potential therapeutic target for SLE. Oxidized mitochondrial DNA (mtDNA) was found in the blood neutrophils of SLE patients, and extrusion of oxidized mtDNA could stimulate IFN production by activating plasmacytoid DCs (49). Recent evidence has suggested that neutrophil extracellular traps (NETs) are implicated in SLE, and NETs derived from the low-density granulocytes of SLE patients are enriched in oxidized mtDNA, which induces the inflammatory response (50).

DAMPS IN OSTEOARTHRITIS (OA)

OA has been regarded as a degenerative joint disease that is characterized by the destruction of cartilage (51). There are several risk factors for OA pathogenesis, which include age, physical trauma, and obesity (51). However, emerging evidence suggests that DAMPs-induced inflammation plays an important role in the pathogenesis of OA (14,52,53). Although the HMGB1 level was higher in the synovial fluid of RA patients than OA patients (35), more HMGB1-positive cells were found in the knee cartilage of high-grade OA patients compared to normal cartilage (54). Another study has provided evidence that the HMGB1 and RAGE levels are upregulated in OA knees compared to those of healthy controls (55). As demonstrated in other inflammatory diseases, extracellular HMGB1 activates the NF-κB signaling pathway to induce inflammation, and HMGB1 expression is related to the grade of cartilage destruction (16,54).

S100 proteins are also involved in the pathogenesis of OA. S100A8/A9 protein expression was elevated in the synovium of a collagenase-induced OA mouse model, and when S100A8 was intra-articularly injected into the knee joint of mice, it induced the expression of inflammatory markers, including Ly6C, F4/80, CCL2, and CCR2 in the synovium (56). Although S100A12 expression was unchanged in the serum between the OA patients and the healthy controls, the S100A12 level in the synovial fluid of OA patients was greatly increased compared to the healthy controls (57). In addition, S100A12 increased the secretion of MMP-13 and vascular endothelial growth factor (VEGF) in human OA chondrocytes, suggesting that S100A12 induces the progression of OA by increasing MMP-13 and VEGF (58).

DAMPs originated from plasma may also contribute to the pathogenesis of OA. It was reported that the levels of several inflammatory mediators, such as IL-6 and MCP-1, were higher in OA sera compared to healthy sera, suggesting the inflammatory nature of OA (14). Moreover, various plasma proteins are enriched in the synovial fluid of OA patients, and some of the plasma proteins, such as Gc-globulin, α1-microglobulin, and α2-macroglobulin, induced inflammation by functioning as DAMPs by activating TLR4 (14). This result suggests that certain plasma proteins can contribute to the low-grade inflammation observed in OA patients.

DAMPS IN CARDIOVASCULAR DISEASES

Atherosclerosis is an inflammatory disease of the arterial wall, in which the vessels narrow due to accumulating plaques of inflammatory cells and lipids (59). Although innate immunity is essential to maintain a healthy arterial wall, it also has a distinct role in stimulating the development of atherosclerosis (60). Macrophages are recruited to arterial lesions, which are rich in DAMPs, and contribute to the pathogenesis of atherosclerosis not only by the formation of lipid-filled foam cells, but also by inducing inflammation through the activation of PRRs (60,61).

HMGB1 is released from macrophages and vascular smooth muscle cells (VSMCs) in the lesions; therefore, the HMGB1 levels are highly elevated in atheromatous plaques (62). Recombinant human HMGB1 induced proinflammatory responses in endothelial cells by increasing leukocyte adhesion molecules, such as ICAM-1 and VCAM-1, and by inducing

inflammatory mediators, such as IL-8, MCP-1, and TNFα (63). These results suggest that high expression of HMGB1 has the possibility to increase inflammation and accumulate atherogenesis (62,63).

S100 proteins are also involved in the pathogenesis of atherosclerosis. S100A8 and S100A9 exist in plaques, and they increase atherogenesis by activating neutrophils and monocytes in arterial lesions (64,65). S100A8, S100A9, and S100A12 have an important role in the mediation of inflammation and increase atherosclerosis in human and rodent models by interacting with RAGE, which plays an important role in endothelial dysfunction and inflammation (66,67). Consistent with the prospective population-based cohort study, S100A12 showed the strongest association with the risk of coronary heart disease (CHD), among the conventional risk factors (68). Likewise, other DAMPs are also upregulated in cardiovascular diseases. HSP70 was elevated and concentrated in the central portions of thick atheromas compared to normal arterial specimens (69). Soluble HSP60 was increased in patients with early carotid atherosclerosis (70), and HSP60 promoted atherosclerosis by inducing VSMC migration via TLR4 and ERK mitogen activated protein kinase (MAPK) activation (71). Finally, expression of α-defensin was upregulated in hyperlipidemia and CHD patients, which suggests that α-defensin can also be a potential biomarker for atherosclerosis (72).

DAMPS IN NEURODEGENERATIVE DISEASES

Alzheimer's disease (AD) is a chronic neurodegenerative disease that is characterized by several symptoms, such as amnesia, inability to manage self-care, and eventually dementia (73). Although the pathology of AD is still mostly unknown, several hypotheses have been suggested to explain it. DAMPs are also known to be involved in neuroinflammation in neurodegenerative disorders (74). The levels of HMGB1 and soluble RAGE are significantly elevated in the sera of AD patients, which was correlated with the levels of amyloid beta (75). A recent study demonstrated that HMGB1 and thrombin are triggers of inflammation and dysfunction of the blood-brain barrier (BBB) (75). In AD patients, the serum levels of S100B were intimately related to the severity of the disease (76), and the administration of pentamidine, a S100B inhibitor, reduced the levels of S100B and RAGE, thereby inhibiting neuroinflammation in the brain of an AD mouse model (77).

Parkinson's disease (PD) is a common, age-related neurodegenerative disorder, and the main symptoms of which are several cardinal motor symptoms, including bradykinesia, spasticity, and gait abnormality. The most noticeable feature of PD is chronic inflammation (78). The role of the HMGB1-TLR4 axis is very important in the pathogenesis of PD. The serum HMGB1 and TLR4 protein levels were significantly elevated in PD patients and correlated with the PD stages (79). In a rat model of PD, an anti-HMGB1 monoclonal antibody inhibited inflammation by maintaining the BBB and reducing the secretion of inflammatory cytokines, such as IL-1β and IL-6 (80). The S100B protein level was elevated in the substantia nigra and cerebrospinal fluid of PD patients, and S100B was also increased in the ventral midbrain of a mouse model treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (81). Although, the serum S100B level was similar between the PD patients and healthy individuals, it correlated with the scales for the severity of PD, such as the Hoehn and Yahr scale (82).

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DAMPS IN CANCER

The role of DAMPs in the pathogenesis of cancer is still controversial. DAMPs may mediate tumor progression by inducing chronic inflammation, which is a compound risk factor for tumor progression (83,84). To our knowledge, IL-1, IL-6, and lymphotoxin (LT)-β are well known promoters of carcinogenesis (83-85). DAMPs, such as HMGB1, S100 proteins, and HSPs, activate inflammatory pathways and release IL-1, IL-6, LT-β, IFN-γ, TNF, and transforming growth factor (TGF)-β (83). ATP, IL-1α, adenosine, and uric acid also promote carcinogenesis by inflammation, immunosuppression, angiogenesis, and tumor cell proliferation (83). In this context, it appears that DAMPs increase tumor development in the early stages of carcinogenesis (83).

In contrast, DAMPs may inhibit tumor progression via immunogenic cell death (ICD). Calreticulin functions as an important effector of ICD by inducing the DC-mediated phagocytosis of tumor cells, which reduces the tumor growth in colon carcinoma (86). In addition, extracellular ATP, released from dying tumor cells, is a significant mediator in ICD via the activation of the NLRP3 inflammasome (87). The release of HMGB1 from dying tumor cells increased the presentation of tumor antigens and regulated the TLR4-dependent immune response (88). In summary, DAMPs may increase carcinogenesis or inhibit tumor development, like a double-edged sword. Future work will be necessary to further understand the complicated roles of DAMPs in cancer.

DAMPS AS BIOMARKERS AND POTENTIAL THERAPEUTIC TARGETS

DAMPs may be valuable biomarkers for inflammatory diseases. Many researchers have worked to identify DAMPs and understand their relationships with multiple diseases. It is well established that several DAMPs are increased or decreased in various human diseases. Increased S100A8/A9 is associated with osteophyte progression in early human OA (89), suggesting that S100 proteins can be used as biomarkers for the diagnosis of the progressive grade of OA. Furthermore, many clinical studies have assessed the prognostic and predictive value of DAMPs, such as HSPs, ATP, and HMGB1, in cancer patients (90), which has raised the possibility that DAMPs may be useful prognostic factors for cancer. These results are invaluable for the management of cancer patients. Patient classification may be improved, and a suitable therapy can be given to patients by diagnosing with DAMPs (90).

The regulation of DAMPs signaling can be a potential therapeutic target to reduce inflammation and treat diseases (**Figure 1**). Administration of neutralizing HMGB1 antibodies or truncated HMGB1-derived A-box protein ameliorated arthritis in collagen-induced arthritis rodent models (38). Clinical trials with HSP inhibitors have also been reported. For non-small cell lung cancer (NSCLC), HSP27, HSP70, and HSP90 inhibitors are under investigation in clinical trials (91). In addition, treatment with dnaJP1, which is a synthetic peptide derived from DnaJ (HSP40), had a curative effect in RA patients without critical side effects (92). Taken together, DAMPs can be useful therapeutic targets for various human diseases, including cancer and autoimmune diseases.

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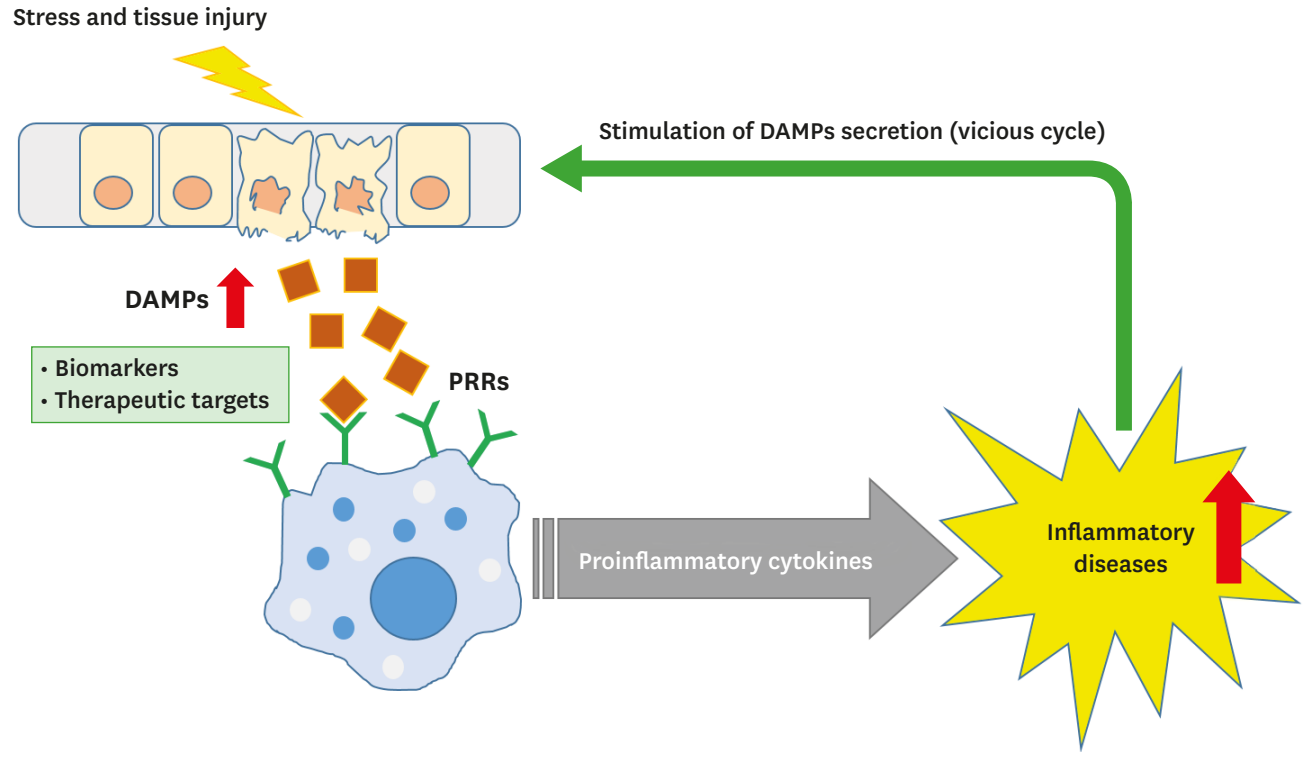

Figure 1. DAMPs as biomarkers and potential therapeutic targets.
DAMPs are released upon cellular stress or tissue injury and activate the innate immune system by interacting with PRRs to produce proinflammatory cytokines. Chronic inflammation can contribute to the development of various inflammatory diseases, which in turn stimulate the secretion of DAMPs, thus establishing a vicious cycle of DAMPs production and inflammation.

CONCLUSION

In this review, we have described the general concept of DAMPs, which play a key role in sterile inflammation, and discussed the possibility of DAMPs as biomarkers and therapeutic targets for various human inflammatory diseases. Although it is clear that DAMPs are closely related to the progress of inflammatory diseases, there are several questions that remain unclear. For example, there is little information on the interacting regions for DAMPs and their PRRs. It will be important to define the interacting regions for DAMPs and PRRs for the development of specific inhibitory molecules that can interfere with the interaction and thereby regulate inflammation. In addition, the development of medications that can inhibit the release of DAMPs will also be a promising therapeutic strategy. However, the inhibition of DAMPs should be taken into careful consideration for the treatment of human diseases, because DAMPs themselves can be effective therapeutic agents for the inhibition of tumor progression via ICD. Therefore, further research on DAMPs will be essential to significantly improve current medical problems.

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