DAMPs : The trigger molecules of persistent inflammation

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Abstract

Damage-associated molecular Patterns (DAMPs) are endogenous molecules released on the onset of tissue injury, which activate various innate signalling cascades through pattern recognition receptors (PRRs). DAMPs are released due to stress, external stimuli, and cell death. They have been reported to play a crucial role in various disease conditions such as autoimmune disorders, cancer, chronic kidney disease, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD). Crucial DAMPs, such as HMGB1, HSP90, S100 proteins, and ATP, tend to exert their inflammatory activity primarily through cell surface receptors, including TLR4, RAGE, CD36, P2X7, and P2Y2. The DAMPs often activate NF-κB, MAPK, and NLRP3 inflammasome formation, further increasing the inflammation via positive feedback. In the past decades, various inhibitors of DAMPs and interacting receptors have been developed, which have to be evaluated for their safety and efficacy. Further, the various signalling mechanism of the DAMPs contributing to its inflammatory function needs to be elucidated. However, DAMPs inevitably remain as a potent mediator of persistent inflammation that needs to be addressed for developing therapeutics to overcome the catastrophic effects of DAMP molecules.

Keywords: DAMPs, PRRs, inflammation, NLRP3

1. Introduction

Inflammation is a key process that initially serves as the first line of defence against external stimuli such as pathogens and damaged cells. While acute inflammation is essential for normal recovery and healing, chronic inflammation often leads to a plethora of diseases, including autoimmune disorders, cancer, chronic kidney disease, diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD) (1,2). In the absence of infection, the inflammatory response is called sterile inflammation, indicating that endogenous molecules play a role in triggering the inflammatory response. Inflammation is a fundamental component of the innate immune response, initiated when pattern recognition receptors (PRRs) detect invading pathogens or endogenous molecules released during tissue injury (3).

Upon tissue injury, endogenous molecules known as damage-associated molecular patterns (DAMPs), released from the cells, serve as the triggering molecules of inflammation by activating the innate immune system. This mechanism promotes the chemotactic recruitment of immune effector cells, such as neutrophils, phagocytes, and macrophages, to the site of cellular damage for the clearance of necrotic debris. Furthermore, DAMPs can disseminate to distal tissues or organs, where they propagate systemic inflammatory responses and mediate inter-organ communication through an inflammatory signalling network (4). DAMPS originates from various sources and includes components of the extracellular matrix, such as biglycan and tenascin-C; intracellular constituents like high-mobility group box 1 (HMGB1), S100 family

proteins, and heat shock proteins (HSPs); and plasma proteins, including fibrinogen, Gc-globulin, and serum amyloid A (SAA). PRRs such as Toll-like receptors (TLRs), RAGE, and scavenger receptors recognize various DAMPs and activate various signalling pathways, leading to the progression of persistent inflammation and related diseases (3). Thus, DAMPs are important triggers and mediators of inflammation.

2. Release of DAMPs

Various types of DAMPs tend to follow similar release patterns from injured or dying cells. They are primarily released during different forms of regulated cell death, including apoptosis, ferroptosis, cuproptosis, pyroptosis, necroptosis, and NETosis, as shown in Figure 1.

2.1. Apoptosis

Apoptosis is a form of programmed cell death that occurs without compromising the integrity of the plasma membrane, which includes distinct morphological changes like cell shrinkage, membrane blebbing, chromatin condensation, and fragmentation of DNA. During apoptosis, several molecules such as HMGB1, histones, extracellular RNAs (exRNAs), cell-free DNA (cfDNA), and ATP have been reported to be released into the extracellular environment (5).

2.2. Necroptosis

Necrosis, triggered by severe physical or chemical stress, leads to cell swelling and membrane rupture, often due to ATP depletion and oxidative damage. This passive cell death results in the release of DAMPs such as HMGB1, ATP, histones, HSPs, exRNAs, cfDNA, and possibly eCIRP. Reperfusion can further exacerbate damage through oxidative stress (5).

2.3. Pyroptosis

Pyroptosis is a caspase-dependent inflammatory cell death triggered by inflammasomes like NLRP3, activating caspase-1, or by caspase-4/5/11. Activated caspases cleave gasdermin D (GSDMD), forming membrane pores that release intracellular contents. Pyroptosis mainly releases IL-1β through GSDMD pores, while other DAMPs like HMGB1, ATP, and cfDNA are also released, often through cell lysis. Notably, HMGB1 release requires specific post-translational modifications before pyroptosis occurs (5).

2.4. Ferroptosis

A programmed cell death with characteristics such as mitochondrial membrane loss, chromatin condensation, cell swelling, and rupture of the plasma membrane, dependent on iron and lipid peroxidation. Ferroptosis has been shown to release HMGB1, ATP, HSPs, and cell-free DNA and calreticulin (5,6).

2.5. Cuproptosis

Similar to ferroptosis, Cuproptosis is a form of cell death regulated by the copper ion, characterized by its accumulation and proteotoxic stress and has been implicated in inflammatory diseases, such as atherosclerosis, inflammatory bowel disease, tumors, and neurodegenerative diseases (5).

2.6 NETosis

NETosis is a unique process by which neutrophils, a type of white blood cell, defend the body by casting out web-like structures known as neutrophil extracellular traps (NETs). These sticky nets, made of loosened DNA and antimicrobial proteins, help capture and destroy invading microbes. While this response is vital for fighting infections, it can sometimes go too far, triggering excessive inflammation and damaging healthy tissues, especially in autoimmune and inflammatory diseases. Histones, extracellular DNA, HMGB1, S100A8/A9, LL-37, and Myeloperoxidase (MPO) are released by NETosis, which aggravates various inflammatory diseases (7).

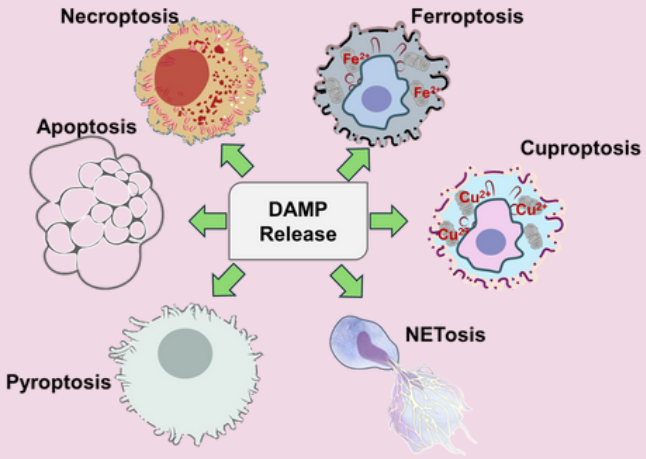

Figure 1. Various forms of regulated cell death contribute to the release of DAMPs.

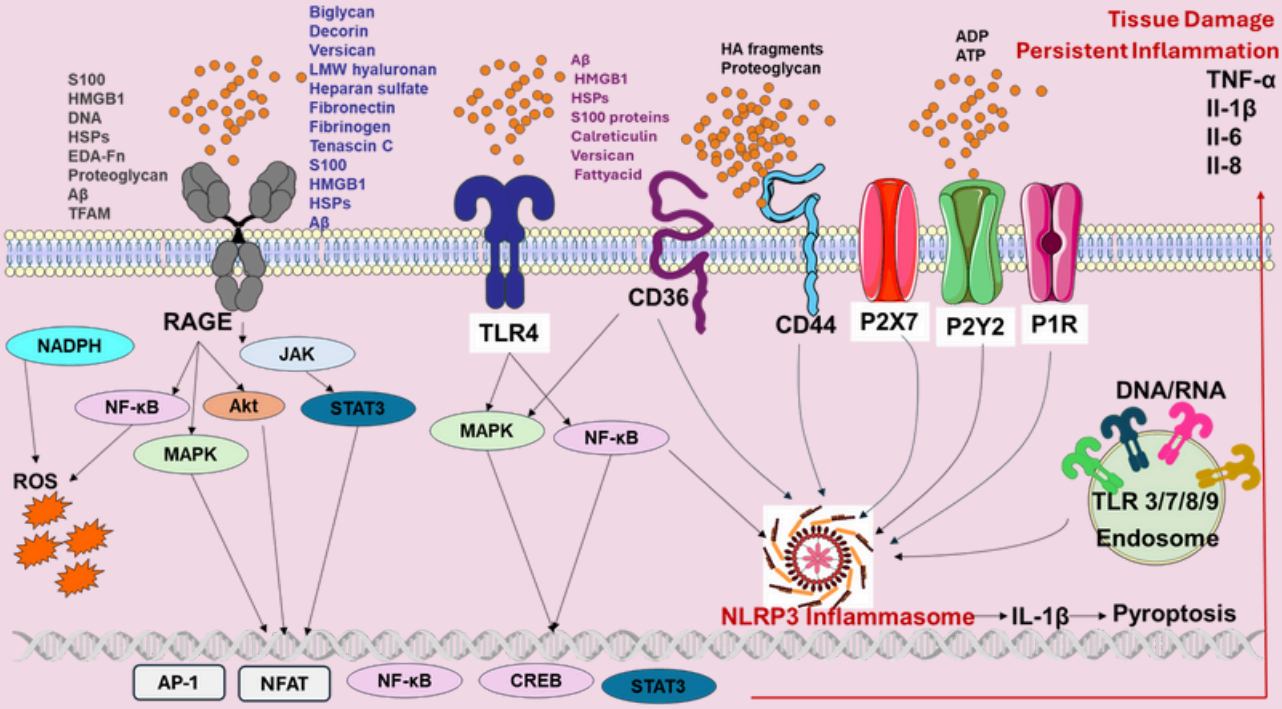

Figure 2. DAMPs and their interacting receptors with downstream effectors responsible for persistent inflammation. Aβ – Amyloid beta; Akt – Protein Kinase B; AP-1 – Activator Protein 1; ATP – Adenosine Triphosphate; CREB – cAMP Response Element-Binding protein; DNA – Deoxyribonucleic acid; EPA-Ffa – Eicosapentaenoic Acid–Free Fatty Acids; Fibronectin – Extracellular matrix glycoprotein; HMGB1 – High-Mobility Group Box 1; HSPs – Heat Shock Proteins; JAK – Janus Kinase; LMW hyaluronan – Low Molecular Weight Hyaluronan; MAPK – Mitogen-Activated Protein Kinase; NADPH – Nicotinamide Adenine Dinucleotide Phosphate (reduced form); NF-κB – Nuclear Factor kappa-light-chain-enhancer of activated B cells; NFAT – Nuclear Factor of Activated T-cells; NLRP3 – NOD-, LRR- and Pyrin domain-containing protein 3; P1R – Purinergic P1 Receptor; P2X7 – Purinergic Receptor P2X, Ligand-Gated Ion Channel 7; P2Y7 – Purinergic P2Y Receptor (possibly P2Y2/P2Y6); S100 – S100 calcium-binding proteins (e.g., S100A8/A9); STAT3 – Signal Transducer and Activator of Transcription 3; TFAM – Transcription Factor A, Mitochondrial; TLR 3/4/7/8/9 – Toll-Like Receptors 3, 4, 7, 8, and 9.

3. Role of DAMPs in inflammation and associated diseases

DAMPs like HMGB1, S100 proteins, and HSPs signal through PRRs such as TLRs, FPRs, C-type lectins, and RAGE receptors, which PAMPs also use. These activate key inflammatory pathways (e.g., NF-κB, MAPKs, inflammasomes), leading to cytokine release (IL-1β, IL-6, TNF, IFNγ) and immune cell recruitment. Chronic inflammation, especially via IL-1, IL-6, and LT-β, along with ectopic lymphoid structures near damaged tissue, may drive cancer development. DAMPS tend to initiate immunosenescence by inducing chronic inflammation or facilitating immune dysfunction, leading to tumor formation (8). The serum levels of HSP90, HMGB1, and S100A9 have been identified as potential biomarkers of cancer metastasis in cancer patients (9). HMGB1 expression is regarded as associated with hallmarks of cancer and interacting with RAGE activates oval cells and inflammation-associated liver cancer. However, it also activates NF-κB and MAPK-dependent pathways, along with cytokine release (10).

In the case of autoimmune disease, such as rheumatoid arthritis, the critical role of DAMPs has been well documented. Various studies have shown the upregulated levels of DAMPs such as HMGB1, HSP90, and S100A8, S100A9, S100A8/A9, and S100A12 in the serum, synovial fluid, and synovial tissues of RA patients. Furthermore, the proteins tend to interact predominantly with RAGE and TLR4 receptors and trigger various immunological cascades, aggravating the pathogenesis of the diseases, as shown in Figure 2. Neutralization of HMGB1 expression in the arthritic animal models has protected them from cartilage destruction (3).

In osteoarthritis, the hyaluronan, which acts as DAMP, is an ECM glycoprotein that confers its protective effect. However, when cleaved into its lower molecular weight, it exhibits proinflammatory effects via triggering cartilage destruction, production of proinflammatory cytokines, and matrix-degrading enzymes upon interaction with TLRs. Various studies have shown that the low molecular weight hyaluronan has aggravated the pathogenesis of OA (11,12). The DAMPs and their interacting receptors, along with their associated diseases, are provided in Table 1. Thus, the DAMPs play a critical role in the sustenance of inflammation in diseased conditions.

Table 1. List of DAMPs with their putative receptors and associated inflammatory diseases (3,16)

Location	DAMP	Receptor(s)	Associated Diseases
Nucleus	Histones	TLR2, TLR4, NLRP3	Kidney injury, sepsis, APAC
	Genomic DNA	TLR9	SLE, AGS, liver injury, etc.
	HMGB1	TLR2, TLR4, RAGE, TREM1, TLR9, cGAS, Casp11, AIM2	Sepsis, stroke, spinal cord injury, and viral infection
	IL-1α	IL-1R	Inflammatory diseases
	IL-33	ST2	Inflammatory and autoimmune diseases
	ATP	P2X7, P2Y2, NLRP3	RA, pain, infection, CAPS
	Uric acid/ sUA	NLRP3, P2X7	Renal fibrosis, gout
	F-actin	DNGR-1	Infection, sepsis
	Cyclophilin A	CD147	RA, lung inflammation, liver injury

Cytosol	Heat Shock Proteins (HSPs)	TLR2, TLR4, CD91	RA, tumors, vascular diseases
	Ferritin	TLR2, TLR4, RAGE	Inflammatory conditions
	S100 proteins	TLR2, TLR4, RAGE, EGFR, CD36, GPCR	Psoriasis, arthritis, tumors
	Aβ	*TLR2, CD36, RAGE, NLRP1, NLRP3*	Alzheimer's disease
Mitochondria	mtDNA	TLR9, RAGE	SLE, liver injury, infection
	TFAM	RAGE	Inflammation
	Formyl peptides	FPR1	Intracerebral hemorrhage, injury
	mROS	NLRP3	Oxidative stress-related diseases
ER	Calreticulin	CD91	Tumors
Granules	Cathelicidin (LL-37)	P2X7, FPR2	Infection
	Defensins	TLR4	Infection, inflammation
	EDN	TLR2	Inflammation
	Granulysin	TLR4	Infection, immune modulation
Plasma Membrane	Syndecans	TLR4	Inflammation
	Glypicans		Inflammation
ECM	Biglycan	TLR2, TLR4, NLRP3	Sepsis, fibrosis, RA
	Hyaluronan (LMW)		RA, obesity, IBD, OA
	Heparan sulfate	TLR2, RAGE, TLR5 TLR4	Inflammation, OA
	Fibronectin (EDA)		RA, fibrosis, tumors
	Tenascin C		RA, colitis, OA

Nucleic Acids	Various DNA types	TLR9, AIM2, cGAS, RAGE, IFI16, CLEC2D, NLRP3, ZBP1	SLE, cancer, AGS, ALS, etc.
	RNA types	TLR7, TLR8, TLR3, RIG-I, MDA5, ZBP1	SLE, infection, tumor, AGS
Others	Misfolded proteins	IRE1, PERK, PKR, ATF6	T2D, cancer, inflammation
	Lipid metabolites	NLRP3, TLR4, TRPA1, CD14	AS, inflammation, tumor
	Fatty acids	TLRs, NLRP3, CD36, GPR43	Obesity, T2D, NAFLD
	Citrate, succinate	HIF-1α, NLRP3	Infection, inflammation
	cGAMP	STING	Viral infection, cancer

AGS – Aicardi-Goutières Syndrome, AIM2 – Absent in Melanoma 2, ALS – Amyotrophic Lateral Sclerosis, APAC – Acute Pancreatitis and Acute Cholangitis, AS – Ankylosing Spondylitis, ATF6 – Activating Transcription Factor 6, CAPS – Cryopyrin-Associated Periodic Syndromes, CD14 – Cluster of Differentiation 14, CD36 – Cluster of Differentiation 36, CD91 – Cluster of Differentiation 91, CD147 – Cluster of Differentiation 147, cGAS – Cyclic GMP-AMP Synthase, CLEC2D – C-Type Lectin Domain Containing 2D, DNGR-1 – Dendritic Cell Natural Killer Lectin Group Receptor-1, EGFR – Epidermal Growth Factor Receptor, FPR1 – Formyl Peptide Receptor 1, FPR2 – Formyl Peptide Receptor 2, GPCR – G-Protein-Coupled Receptor, GPR43 – G-Protein-Coupled Receptor 43, HIF-1α – Hypoxia-Inducible Factor 1-alpha, IBD – Inflammatory Bowel Disease, IFI16 – Interferon Gamma Inducible Protein 16, IL-1R – Interleukin-1 Receptor, IRE1 – Inositol-Requiring Enzyme 1, MDA5 – Melanoma Differentiation-Associated Protein 5, NAFLD – Non-Alcoholic Fatty Liver Disease, NLRP1 – NOD-, LRR- and Pyrin Domain-Containing Protein 1, NLRP3 – NOD-, LRR- and Pyrin Domain-Containing Protein 3, OA – Osteoarthritis, P2X7 – Purinergic Receptor P2X, Ligand-Gated Ion Channel, 7, P2Y2 – Purinergic Receptor P2Y, G-Protein Coupled, 2, PERK – Protein Kinase RNA-Like Endoplasmic Reticulum Kinase, PKR – Protein Kinase R, RA – Rheumatoid Arthritis, RAGE – Receptor for Advanced Glycation End Products, RIG-I – Retinoic Acid-Inducible Gene I, SLE – Systemic Lupus Erythematosus, ST2 – Suppression of Tumorigenicity 2, STING – Stimulator of Interferon Genes, T2D – Type 2 Diabetes, TLR – Toll-Like Receptor, TREM1 – Triggering Receptor Expressed on Myeloid Cells 1, TRPA1 – Transient Receptor Potential Ankyrin 1, ZBP1 – Z-DNA Binding Protein 1

4. Currently available DAMP, Receptors, and downstream effectors inhibitors.

Various molecules and biologics have been identified that target DAMPs, their receptors, and downstream signaling pathways. Several of these agents have been approved for clinical use, while others are currently under preclinical or clinical evaluation. A comprehensive summary is presented in Table 2 (DAMP inhibitors) and Table 3 (receptor antagonists).

Table 2. DAMPs Inhibitors

DAMP	Inhibitor(s)	Mechanism	Ref
HMGB1	Glycyrrhizin, Ethypyruvate, FPS-ZM1	Binds to HMGB1 or blocks its interaction with receptors	(17–19)
S100A9	Paquinimod, Tasquinimod	Binds to S100A9, preventing receptor interaction	(20)
Mitochondrial DNA (mtDNA)	MitoTEMPO	Reduces mtROS	(21)
ATP	Apyrase, P2X7 receptor blockers (e.g., A438079, KN-62)	Degrades extracellular ATP or blocks P2X7	(22)
HSPs (e.g., HSP70, HSP90)	Geldanamycin, 17-AAG (Tanespimycin)	Inhibits HSP function	(23)

Table 3. DAMPs Receptors Antagonists

Receptor	Inhibitor(s)	Mechanism	Ref
TLR4	TAK-242 (Resatorvid), Eritoran	Blocks TLR4–MD2 interaction	(24)
RAGE	FPS-ZM1, Azeliragon (TTP488), sRAGE (soluble decoy)	Blocks ligand binding or acts as a decoy	(25–27)
TLR2	OPN-301, CU-CPT22	TLR2 antagonists	(28,29)
CD36	Sulfosuccinimidyl oleate (SSO), AP5055	Blocks fatty acid/DAMP binding	(30,31)
P2X7	A438079, AZD9056	Inhibits ATP-mediated inflammasome activation	(32)
NLRP3 inflammasome	MCC950, OLT1177, CY-09, Dapansutrile	Blocks inflammasome assembly	(33,34)

5. Future perspectives

In recent times, the critical role of DAMPs has been explored in various diseases. Multiple studies have shown and established DAMPs as a potent biomarker of inflammation and therapeutic targets in various diseases. Thus, there is a wide arena for further exploration to identify the therapeutic DAMPs and develop therapeutics for the treatment of inflammatory diseases.

6. Conclusion

Conclusively, it can be said that the DAMPs are persistent mediators of inflammation, aggravating the pathogenesis of various diseases, but not limited to cancer, SLE, Rheumatoid arthritis, and osteoarthritis. Thus, the development of potent and safe DAMP inhibitors is crucial now to mitigate the catastrophic effects of DAMPs in inflammatory diseases.

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