



Danger-Associated Molecular Patterns (DAMPs): the Derivatives and Triggers of Inflammation

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Abstract

Purpose of Review Allergen is an umbrella term for irritants of diverse origin. Along with other offenders such as pathogens, mutagens, xenobiotics, and pollutants, allergens can be grouped as inflammatory agents. Danger-associated molecular patterns (DAMPs) are altered metabolism products of necrotic or stressed cells, which are deemed as alarm signals by the innate immune system. Like inflammation, DAMPs play a role in correcting the altered physiological state, but in excess, they can be lethal due to their signal transduction roles. In a vicious loop, inflammatory agents are DAMP generators and DAMPs create a pro-inflammatory state. Only a handful of DAMPs such as uric acid, mtDNA, extracellular ATP, HSPs, amyloid β , S100, HMGB1, and ECM proteins have been studied till now. A large number of DAMPs are still obscure, in need to be unveiled. The identification and functional characterization of those DAMPs in inflammation pathways can be insightful.

Recent Findings As inflammation and immune activation have been implicated in almost all pathologies, studies on them have been intensified in recent times. Consequently, the pathologic mechanisms of various DAMPs have emerged. Following PRR ligation, the activation of inflammasome, MAPK, and NF- κ B is some of the common pathways.

Summary The limited number of recognized DAMPs are only a fraction of the vast array of other DAMPs. In fact, any misplaced or abnormal level of metabolite can be a DAMP. Sophisticated analysis studies can reveal the full profile of the DAMPs. Lowering the level of DAMPs is useful therapeutic intervention but certainly not as effective as avoiding the DAMP generators, i.e., the inflammatory agents. So, rather than mitigating DAMPs, efforts should be focused on the elimination of inflammatory agents.

Keywords Immune system · Innate immunity · DAMPs · Inflammation

Introduction

Allergen is an often-confused, enigmatic term which encompasses elements from diverse origin, living and non-living; microbial-, plant-, or animal-derived; and natural or synthetic. Allergens are pervasive and they have the ability to deteriorate quality of life. In layman parlance, allergen is nothing but an irritant. Allergens generate inflammation through specific immune response mechanisms while irritants may also produce inflammatory responses through a variety of mechanisms. Different mechanisms may require different therapeutic

approaches. On encountering the irritant, the immune surveillance is activated. The whole evolution-designed process has been fine-tuned to keep the organism safe in the face of a barrage of “offense and defense” components from other organisms in the environment. To discourage the entry of allergens, the human body is equipped with numerous sensors. The skin is the first line of defense which has antimicrobial compounds like cathelicidins [1]. Different body openings, depending on the organ type, can secrete saliva, mucus, oil, wax, or tears to entangle the allergen. Olfactory sensors on perceiving offensive odor molecules can order the respiratory pipe to tighten and epithelial cells to secrete excess mucus [2]. Blood can coagulate to prevent the entry of invaders into the circulation system [3]. The stressed body constantly generates neutrophils and eosinophils, and elaborates pro-inflammatory cytokines; C-reactive protein (CRP) level is high; blood becomes thicker; lymph glands are swollen; olfactory receptors are developed in higher number; antimicrobial peptides (AMPs) are generated in excess [4]; mucus secretion

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overwhelms the respiratory, gut, and urinogenital tracts; enzymes behave aberrantly [5, 6]. There is a myriad of other ways by which the body handles intruders. Common allergies include atopic dermatitis, urticaria, asthma, rhinitis, sinusitis, and conjunctivitis [7]. Some allergens are responded to so violently that life-threatening conditions such as anaphylaxis can occur [8].

But, when the allergens are persistent and exposure occurs in higher dosage, the defense arsenals cannot vanquish or trap them [7]. In such encounters, in anticipation of the threat, the body transitions into stress mode and a suite of adaptive changes occur as a defense strategy. These maintenances of a defensive body occur at the cost of normal health. Just like infection, an allergy-riddled body is incapable of successful pregnancy due to the alternative metabolic profiles. If the allergens are not eliminated chronic exposure sets the stage for brain pathologies, polycystic ovary syndrome (PCOS) [9], multiple sclerosis (MS), cancers [10], diabetes, cardiovascular diseases, arthritis, among other ailments. So, allergen can be a cause of mortality, dependent on the ingestion, inhalation, dermal contact degree, and the hypersensitivity it provokes. Host factors are responsible for the scale of the immune retaliation. For example, an allergen which can be dismissed by oral entry can be severe on landing on the skin or when inhaled.

In fact, with the advent in computational biology, the conventional division between pathogen and allergen is getting blurry [11]. Pathogen-origin non-living parts such as lipopolysaccharide (LPS), peptidoglycan, spores [12], and toxins are considered allergens. Allergen can be a carrier of pathogens too, e.g., bat guano-virus, chicken dropping virus. Also, allergen-provoked inflammation can cause lesions, which facilitate infections, bacterial translocations [13, 14], and sepsis. Some microbes are not pathogenic to human but produce allergens. For example, cyanobacteria in water and plants cannot replicate in human body but its metabolite is hepatotoxin [15] and neurotoxin [16], respectively. *Curvularia lunata*, *Alternaria alternata*, etc. are fungal plant pathogens, but their serine protease can cause allergy in human by inducing rapid release of IL-33 and consequent mucosal hypersensitivity [17, 18]. Some microorganisms like *Aspergillus fumigatus* are deemed both a pathogen and an allergen [19]. Red yeast rice, the fermentation product of mold *Monascus purpureus*, is a dietary supplement, but it is laced with multiple mycotoxins [20]. The human immune system recognizes PAMPs (pathogen-associated molecular patterns) on the pathogens.

Similarly, milk protein [21], egg albumin [21], nematode secretome, insect chitin [22], bee sting [23], fish tropomyosin, snake venom [24], mouse droppings, pet dander, saliva, etc. are animal-origin allergens. Lectin (peanut lectins, R-type lectins) [25, 26], pollen (lipid transfer protein (LTPs), hydroxyproline-rich glycoprotein) [27], latex (hevein) [28], pathogenesis-related proteins (PRs), profilin, phenol (e.g.,

urushiol [29]), oxalic acid, and essential oil (pinene [30], citral [31], geranial [32] limonene, and linalool, etc.) are plant-origin allergens. Drugs [33], cosmetics, metals (nickel etc.) [34], and construction materials (asbestos, crystalline silica, particulate matter) [35] are also allergens. Fragrance compounds [36], synthetic dye, emulsifiers in food, pesticides, fire retardants, smog, and vehicle exhaust are allergens as well [37]. So, a large number of entities are potential allergens. Arthropod-origin allergens such as cockroach [38], house dust mite [39], and tick [40] parts are major immunogens and responsible for multiple health nuisances. Above allergens have been recognized based on their conserved protein domains, metals, biochemical structure, etc. Though not technically pathogens, biological allergens also possess PAMPs. Be that pathogens or allergens, they are regarded as inflammatory agents by the immune system. As the allergens are a subset of inflammatory agents, and the latter is a more appropriate word for irritants, in the following sections, it is used in the text along with and in place of allergens.

DAMPs and Their Dual Roles

Cell surfaces have a multitude of receptors to sense adversaries by their patterns. These pattern recognition receptors (PRRs) can be of several types such as Toll-like receptors (TLRs), retinoic acid-inducible gene 1-like receptors (RLRs), RIG-I-like RNA helicases (RLHs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), and AIM2-like receptors (ALRs), among others [41–43]. The PRRs can recognize PAMPs on pathogens [44, 45] [43] and biological allergens. As a result of the recognition, inflammasomes are activated [46]. Acidosis, hypoxia, extracellular matrix (ECM) reorganization, and tissue remodeling follow in order to combat the stressors. Resultantly, the intracellular signaling induces the elaboration of inflammatory mediators from the stressed cells. This repertoire of alarm signals is known as danger-associated molecular patterns (DAMPs) or alarmins. Produced in large quantities during cellular stress, tissue damage, inflammation, and necrotic cell death, DAMPs are meant to eliminate the pathogens [47] and to activate repair mechanism as well [48]. Therapeutic interventions as solid organ transplantation and cancer immunotherapy enhance DAMP generation [49•]. It is well-validated that the excess of even protective components is detrimental to the human body. For example, glucose, estrogen, aromatase, dopamine, cortisol, prolactin, calcium, among others are vital but excess can upset homeostasis and cause disease. Similarly, in milder form, DAMPs are life-saving but in extreme form, they can cause multi-system organ failure by autoimmune function. DAMPs associated with Alzheimer disease, myocardial infarction, ischemia reperfusion injury, and pre-eclampsia have been recognized. In critical care illnesses, DAMPs are major threats

[50]. As the ailing body generates excess DAMP, the collective signal leads to a robust proinflammatory response, beyond the tolerance limit of the patient. Self-tissues are injured and pathologies like colitis, cirrhosis, cystic fibrosis, systemic lupus erythematosus (SLE), vitiligo, and lung injury occur [51]. Necroptosis in the skin and gut, systemic inflammatory response syndrome, and ischemia reperfusion injury generate DAMP and elicit strong inflammatory response [52]. The DAMP profile might be different for different diseases.

Inflammatory agents are DAMP generators, as they pose stress on human tissues and systems, leading to the DAMP production. The DAMP generation ability of various inflammatory agents is variable. Some allergens like pollens, eggs, and peanuts have got ample public recognition. But they are only a fraction of the vast spectrum of allergens. Mold spore in the bathroom, dust mite in the bedspread, dog's saliva, plastic fumes in the workplace, metal ornaments, fungicide in the yoghurt, perfume in the closet, laundry smell from neighborhood, and silica dust from the mining operation might be the cause of airway hypersensitivity, skin rashes, neural issues, blood cancer, multiple sclerosis, or infertility. Food additive, cosmetics, pesticides, occupational exposures, and antibiotics are DAMP generators.

Conventionally, DAMPs are supposed to be produced from the stressed or dead cells. The cellular DAMPs are classified to be of cytosol, nuclear, mitochondria, or endoplasmic reticulum origin. Common DAMPs include uric acid, creatinine, ferritin, mitochondrial DNA (mtDNA), extracellular ATP, heat shock proteins (HSPs), amyloid β ($A\beta$), S100 family proteins, chromogranin A, oxidized phospholipids and oxidized cholesteryl esters, and high mobility box 1 (HMGB1). However, ECM proteins (elastin, fibronectin, laminin, collagen, platelet-derived growth factors (PDGFs), transforming growth factor β -induced protein (TGF β 1p)) [53], proteoglycans (biglycan, perlecan, versican, etc.) [54, 55], glycoproteins [56, 57], peptides (angiotensin), hormones, and extracellular RNA (eRNA) can be DAMPs. A publication classifies the heterogeneous group of DAMP into five classes such as class I (chromatin, HMGB1, HSPs), class II (ROS, monosodium urate, extracellular ATP, genomic DNA), class III (stress-induced soluble major histocompatibility complex class I-related chains A/B (MIC-A, MIC-B), and UL-binding proteins), class IV (neoantigens such as non-muscle myosin II (NMHC-II), actin cytoskeleton and oxidized phospholipids), and class V (altered pattern of molecules) [58]. These DAMPs mediate inflammation by MAPK, NLRP3, NKG2D, the complement cascade via the classical lectin receptors and alternative pathways, and dyshomeostasis (hypoxia, acidity, osmolarity change, accumulation of unfolded or misfolded proteins, respectively [58]).

High uric acid indicates the iron overloading in the blood and the need to chelate them. Excess free iron can cause hyperuricemia, proteinuria, gout, and kidney stones. In PCOS

patients, high uric acid level can cause suboptimal glomerular filtration rate (GFR) [59]. Ferritin, an iron storage protein, is vital for iron homeostasis and the protection of DNA from excess iron-induced damage [60]. High serum ferritin level is a feature of coronary artery disease, malignancy, insulin resistance and hyperglyceridemia, and PCOS [61]. Ferritin is localized in cytosol, nucleus, and other organelles. So, once the cell is ruptured, ferritins ooze out into the extracellular space. High levels of uric acid and ferritin are related, indicating iron overload [62]. High blood urea and creatinine can cause renal injuries. CRP is the hallmark of PCOS [59]. Genomic DNA also can ignite danger signal once leached outside the cell. Drugs can cause hepatocyte death and subsequent release of its DNA, which acts as DAMP, activates TLR9, and stimulates cytokine production in adjacent sinusoidal endothelial cells [63]. Mitochondrial membrane permeabilization can lead to the escape of mtDNA into the cytosol [64]. The mtDNA in extracellular milieu is a DAMP which acts via TLR9 and causes endothelial cell activation [65]. Histone functions as DAMPs after ischemic injury via TLR9 and sets off inflammation [66]. Neutrophil extracellular traps (NETs), the complex of DNA, histones, and proteases, are released from granulocytes such as neutrophils, following immune activation [67, 68]. NETs are weapons to decimate virulence factors and pathogens. But, the NETs create a prothrombotic state, which is hazardous to the host [69]. ATP is the energy source, but in extracellular form, it can be a signaling molecule and mitogen, inducing cell proliferation by cell-cycle progression and tyrosine phosphorylation [70]. ATP mediates the pathologies by binding to P2 receptors, which can be cation-selective receptor channels or G protein-coupled metabotropic receptors [71]. Heat shock proteins (HSPs), the chaperones for proper protein folding, also offer the cells tolerance against stressors. In extracellular form, HSP can activate signaling pathways [72]. Excess amyloid beta ($A\beta$) peptide production, along with the hyperphosphorylation of tau protein, is a hallmark of the dementia Alzheimer's disease [73–76]. Chromogranin A, a granin family acidic secretory glycoprotein, is a circulating biomarker for neuroendocrine tumors [77, 78]. HMGB 1 or amphoterin, a nuclear protein, is elaborated by activated leucocytes, at the site of injury. It interacts with the nucleosomes, transcription factors, and histones [79–81], and is capable of violating endothelial tight junctions (ZO-1/ZO-2) and causing sepsis [82]. IL-1 α is secreted by epidermal epithelial cells, in fact all non-hematopoietic cells, and is upregulated during hypoxia [83]. It causes tumor invasiveness and angiogenesis [84]. IL-33, TNF- α , IL-6, and IL-17 cause inflammation [85], leading to adiposity, cancer, neural damage, etc. F-actin is the filamentous polymerized form of monomeric (G-actin) [86, 87]. If F-actin cannot revert back to the G-actin form, and is recognized by DNGR-1, a receptor for dead cells, it causes multiple problems such as hearing loss, aortic aneurysms, and myopathies

[88, 89]. Cyclophilin A, an immunophilin, secreted from human monocytes, can cause vascular tissue damage [90]. Extracellular S100 proteins have wide-ranging regulatory role on monocytes, macrophages, microglia, neutrophils, lymphocytes, mast cells, and vascular smooth muscle cells, which influences innate and adaptive immune responses, cell migration and chemotaxis, tissue development and repair, and leukocyte and tumor cell invasion [91]. S100 protein member psoriasin is secreted by keratinocytes and tongue epithelia, etc., and possesses antibacterial role [92]. Calreticulin is a calcium-binding lectin and chaperone for glycoproteins including major histocompatibility complex (MHC) class I molecules [93, 94]. Oxidized phospholipids and oxidized cholesteryl esters indicate inflammation and are the markers of atherosclerosis, thrombosis, and angiogenesis [95]. These markers are recognized by receptors of innate immunity, including scavenger receptors, natural antibodies, and CRP, following which the apoptotic cells are removed [96].

Necrotic or apoptotic cells release a complex array of elements apart from the above-mentioned few. After all, the cytosol is a reducing milieu surrounding organelles with high oxidative functions [97]. ECM includes proteins (elastin, fibronectin, laminin, collagen, platelet-derived growth factors (PDGFs), transforming growth factor β -induced protein (TGF β Ip) [53], proteoglycans (biglycan, perlecan, versican, etc.) [54, 55], glycoproteins [56, 57], peptides (angiotensin), hormones, and extracellular RNA (eRNA). On enzymatic degradation, the ECM derivatives can ligate to TLRs, inflammasomes, and purinergic receptors, behaving as DAMPs [98].

Similarly, several metabolites are immunologically quiescent in one location, but when translocated or leaked into another part of the body, can behave as DAMP. For example, uromodulin is inert inside the tubular lumen, but once oozed into the interstitial compartment, it can turn into a DAMP [99].

So, the full range of DAMPs ought to be studied. Some likely DAMPs have been discussed below. The DAMP profile is in fact exhaustive, though only a few have got recognition as DAMPs. It is naïve to consider only them as the villains, as virtually all abnormal level metabolites are sort of DAMP. No entity, irrespective of their biochemical class and size are redundant in the human system, so their abnormal level signals danger. If S100 protein is DAMP, other defense peptides such as β -defensin, cystatin, granulysin, hepcidin, and cathelicidin can be DAMP too [4]. The DAMP S100 and chromogranin A are already known as cancer biomarkers, so other cancer markers such as α -fetoprotein (AFP), BCR-ABL, BRCA1/BRCA2, β -2-microglobulin (B2M), human chorionic gonadotropin (HCG), bladder tumor antigen (BTA), CA, calcitonin, carcinoembryonic antigen (CEA), soluble mesothelin-related peptides (SMRPs), immunoglobulins, free light chains, inhibin, lactate dehydrogenase (LDH), neuron-specific enolase (NSE), NMP22, prostate-specific antigen (PSA), thyroglobulin, and

prostatic acid phosphatase (PAP) might be DAMP as well [100]. Bradykinin, substance P, oxytocin, angiotensin, and endothelin can be DAMP. High blood glucose level can cause DNA damage in the form of single-strand breaks (SSBs) and double-strand breaks (DSBs) [101]. Pompe disease occurs when lysosomal acid α -glucosidase is deficient and progressive glycogen accumulation in the lysosomes of muscle cells occurs [102]. In the face of excess free radicals, malondialdehyde (MDA), an end product of lipid peroxidation, is produced in high level. High MDA indicates oxidative stress [103] and has been often associated with preeclampsia [103]. Chronic hyperglycemia is a major cellular stress [104]. Hemoglobin in its glycated form (HbA1c) is a marker of diabetes [105]. The DAMP cyclophilin A is secreted from high glucose-activated monocytes [90]. In fact, most vasoactive, peptides neurotransmitters, and growth factors are DAMPs. Some common as well as likelsy, and DAMPs have been listed in Table 1.

Mechanisms of Inflammation and the Role of DAMP

Hypersensitivity and immune activation mechanisms of different inflammatory agents have been discussed below. All the factors and their effects are interrelated. PAMPs are of microbial origin, dead or alive; and DAMPs are endogenous. Yet, they interact with each other, and the same PRR can ligate to PAMPs as well as a DAMPs [106]. Some common protein domains often associated with allergenicity include leucine-rich repeat (LRR) [107], ChtBD [108], CBM [109], and PreSET (Dillon et al. [110]; Binda et al. [111]). These domains are PAMPs, and on recognition, they induce the generation of DAMPs.

Own body components in unregulated level are DAMP generators as well as DAMPs, forming a vicious loop. In response to stress, extracellular pH turns acidic [112]. The accumulation of free radicals creates an acidic and hypoxic condition [113]. Acidic milieu acts as a DAMP generator [113, 114]. The link between, acidosis, hypoxia, tumorigenesis, and drug resistance is well-studied [115–119]. Acidosis affects ECM proteins, which must be in functional state for tissue integrity, gene expression, and immune response [57]. Proteases, and metalloproteinases (MMPs), are responsible for ECM remodeling [57, 120, 121]. Metabolic acidosis activates acid-sensing ion channels (proton-gated sodium channels), which begets pathologies [122–124]. Also, the acidosis affects membrane polarization state and resultantly mitochondrial function is affected [125]. Acidic environment imposes ER stress, promoting autophagy [126]. In inflammation, transporters/pumps, transcription factors, and gene expressions are modified and all enzymes are activated, influenced by the acidic milieu. So, serine protease [6], cathepsin [5], chitinase [22], chondroitin sulfate lyase [127], etc. are active and they

Table 1 DAMPs, their origins, receptors, and references

Intracellular location	DAMPs	Receptors	References
Nucleus	Histones	TLR 2, 4, 9	[66]
	Genomic DNA	TLR 9	[63•]
	HMGB 1	TLR 2, 4, RAGE, TIM3	[79–81]
	IL-1 α	IL-1R	[84]
	IL-33	ST2	[85]
Cytosol	ATP	P2Y2, P2X7	[70]
	F-actin	DNGR 1	[88]
	Cyclophilin A	CD147	[90]
	HSPs	CD91, TLR2, 4, SREC 1, FEEL 1	[72]
	Uric acid crystals	NLRP3	[59]
	Ferritin	TLR 2, 4, RAGE	[60]
	S100 s		[92]
Mitochondria	Mitochondrial DNA	TLR9, RAGE, TLR9	[65•]
Endoplasmic reticulum	Calreticulin	CD91	[93].

disrupt multiple pathways. Aromatase, a cytochrome P450 (CYP) enzyme, is activated [128]. It generates excess estrogen, leading to estrogen dominance [129]. A multi-protein complex inflammasome (NLRP), made of (LRR), caspase recruitment domain (CARD), and pyrin domain (PYD) [130], perceives the cytokines IL-1 β and IL-18 and the cysteine proteases (caspase 1 and 11) [131]. They can lead to membrane polarization, cytoskeletal changes, and breached epithelial integrity [132]. All of the cellular and extracellular-derived DAMPs activate NLRP3 inflammasomes [133]. Paradoxical it may sound, but all these changes are survival adaptations.

DAMPs are chemotactic and they interact with dendritic cells (DCs) [134]. DAMPs like uric acid and HMGB1 stimulate DC maturation, so that the immune cells can present foreign antigens and stimulate T lymphocytes [135]. PRRs such as CD36, and TLR-4, natural antibodies, and CRP recognize common oxidation-specific DAMPs such as oxidized phospholipids and oxidized cholesteryl esters [136]. Nuclear factor kappa B (NF- κ B) activation and pro-inflammatory cytokine (TNF- α , IL1 and IL6, and IL10) secretion follow DAMP recognition by innate immunity [137].

Example of some inflammatory agents and their role in DAMP generation pathway has been presented below. Chitin, a polymer, is a high-grade inflammatory agent and DAMP trigger, capable of nerve damage, vasculitis, blood coagulation, lymph gland swelling, bacterial translocation, etc. [22, 138]. Epidermal or epithelial cells can recognize chitin via PRRs, which leads to cytokine/chemokine secretion, leukocyte recruitment, and alternative macrophage activation [139]. *Streptococcus pneumoniae* pore-forming toxin pneumolysin affects alveolar epithelial cells and leads to the release of DAMP which include mtDNA [140]. Fungus serine protease exposure induces the rapid release of IL-33, causing mucosal hypersensitivity [18]. Mite allergen levies ER stress,

leading to higher level of apoptotic marker expression, which is deleterious to the host cells [141]. For anticancer drugs such as cisplatin, ER is a cytosolic target [142]. Plant allergen such as proteases can disrupt membrane permeability by manipulating transmembrane adhesion proteins such as occludin, claudin-1, ZO-1, and E-cadherin, eliciting IgE antibodies [143, 144]. If the allergen is a chitinase, it can cleave the glyco moieties from these glycoproteins, which can affect protein functions, and eventually cell integrity, leading to DAMP secretion. Nickel irritates the immune system by activating urease enzyme [34] via NLRP3-ASC-caspase-1-IL-1 β immune signaling pathway [145]. Excess urease can cause gastric cancers. Even if the DAMPs do not cause harm, the autoantibodies against them can cause tissue damage. So, either way, their persistence is hazardous for health.

Several previously published reports have explained the pathologic mechanisms of DAMPs in in-depth manner, which should be referred to for detailed understanding on the DAMP immunogenic machinery [98, 146].

DAMP Mitigation Strategies

Drugs taken to alleviate some DAMPs can end up generating some other DAMPs. So, alternative therapies are sought to normalize DAMP levels. Some plant extracts and phytochemicals such as quercetin, kaempferol, rutin, and apigenin can inhibit xanthine oxidase activity and lower uric acid level [147]. Due to high anthocyanin content, blueberries have shown the ability to prevent the aggregation of A β plaques [148]. Ginseng saponin Rg decreased the levels of A β [149]. *Hibiscus sabdariffa* consumption has shown to reduce the urinary concentration of uric acid, citrate, tartrate, calcium, sodium, potassium, and phosphate [150]. However, DAMP

reduction is not a sustainable solution, as they are mere results of inflammatory agent-induced cellular and extracellular stress. The inflammatory agents leading to their generation ought to be recognized and avoided.

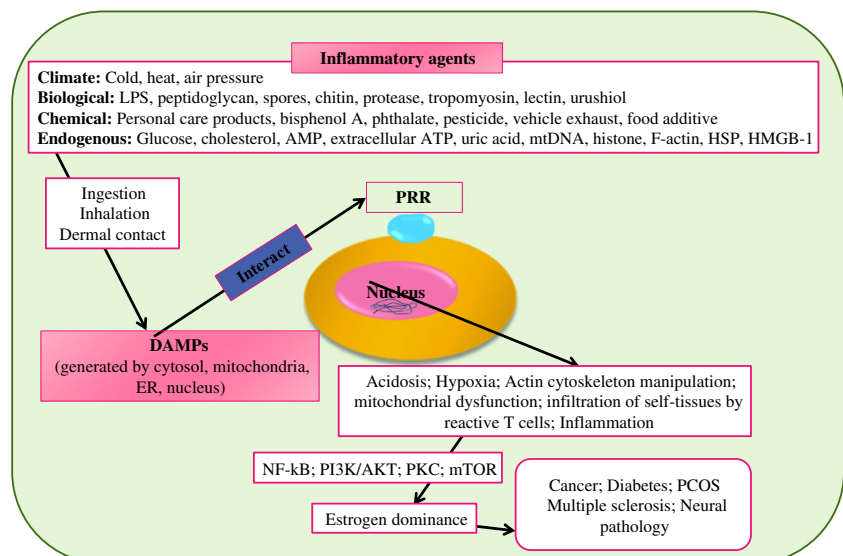
Discussion

Host factors are different and the immunogenic strength of inflammatory agents is variable for people of different age, gender, co-morbidity, etc. Inflammatory agent for one person can be harmless for another person, but human health is dynamic and this response can vary and evolve depending on changing environment and lifestyle. Today's immunity or non-sensitivity may not last tomorrow. Though the vice-versa is not as common. Chitin is likely to evoke stronger immune response in reproductive age females than males. Among other ailments, asthma, fibromyalgia, migraine, chronic fatigue syndrome, etc. show strong female predominance, due to hormonal difference [151–153]. Drug dosage cannot be same for a non-pregnant and pregnant female. An antihypertensive drug might be more toxic to a patient with diabetes. It is increasingly coming forth that if the host physiological milieu is disturbed, and inflammatory, all biomolecules will behave abnormally. In this stressed state, even benign exogenous agents will be suspected as a threat. The immune system of an individual with severe inflammatory state may find the touch or semen [154] of another human as DAMP generator. Their exposure can cause urticaria, angioedema, or even anaphylaxis [154]. Human macrophage-expressed chitinase has ChtBDs which can sense chitin-related proteoglycan in another human skin and react [155]. It is understandable as SCP (sperm coating protein), a domain with α - β - α sandwich conformation, is found in allergen such

as nematode secretome, and insect allergen too. Apart from ChtBD and SCP, other conserved and virulence-related domains include IENR1, HNHc, HELICc, Pro-kuma_activ, Tryp_SPc, Lactamase_B, PbH1, CBM49, acidPPc, G3P_acyltransf, RPOL8c, KbaA, HAMP, HisKA, Hr1, Dak2, APC2, Citrate_ly_lig, DALR, VKc, YARHG, WR1, PWI, ZnF_BED, TUDOR, MHC_II_beta, Integrin_B_tail, Excalibur, DISIN, cadherin, actin, PROF, Robl_LC7, MIT, Kelch, GAS2, B41, Cyclin_C, Connexin_CCC, OmpH, Bac_rhodopsin, AAA, Knot1, NH, Galanin, IB, Elicitin, ACTH, Cache_2, CHASE, AgrB, PRP, IGR, and Antimicrobial21 [156]. So, the term DAMPs should not be used only for the endogenous molecules but also for any immune elicitors. As numerous microbes reside in and on human body, and their metabolites are major signaling molecules [157], their abnormal levels are also perceived as DAMPs. So, in fact, PAMPs should be considered a subset of DAMPs.

For all the pathologies that DAMP cause, they are meant to alarm the immune system. So, they are protective in evolutionary intention. But, why does the host need recurrent protection? It is because of the inflammatory condition-caused systemic injuries. So, resolving inflammation is the key to avoid excess DAMP. Health is the first priority, so if needed to escape the hazards of inflammatory agents, dietary habits, grooming practice, occupations, and dwelling places ought to be changed. Several agonies might be resolved by adherence to inflammatory agent-free lifestyle. Boycotting sunscreen and deodorant might suppress the “estrogen dominance” and bring back fertility to a woman. Skipping cigarette might heal lung health of an emphysema patient. A myriad of such correlations can be established. In this era, where people seek a quick fix for every simple health issue, a range of anti-allergic, anti-pruritic, anti-inflammatory, even immune suppressants have piled up. However, there are no fixes without risks.

Fig. 1 Inflammatory agents induce DAMP generation, which ligate to PRRs, and cause multiple pathologies



Often, these small pills or interventions can lead to bigger health problems. Corticosteroids can suppress immune system and lead to the activation of opportunistic pathogens, causing fatal infectious diseases [158, 159]. Steroids can lead to carcinogenesis. Immunotherapy is successful in antigen suppression to some degree [160], but it is not a sustainable solution. Any therapeutic intervention might reduce the DAMP level transiently, but cannot block the tissue damage which causes the DAMP generation. Only recognizing the cause of inflammation and avoiding it can prevent tissue damage and DAMP elaboration.

It is deplorable that in the current times, inflammatory agents of all kinds have become a fixture. In the old times, the prevalence of inflammatory agents was there, but never as broad, dense, or ubiquitous. Industrialization has generated toxic gases, soots, metal particles, and acid effluents. It is not surprising that people inhabiting industrial area are affected with multiple health issues. Similarly, agricultural revolutions ushered in the abuse of fertilizers and pesticides, which are causing health catastrophes. Then, the wave of processed foods, cosmetics, and drugs arrived. Air pollution is leading to inflammations and paving the path for several diseases. To lead an inflammatory agent-free disciplined life, awareness is the first requirement. Figure 1 presents a schematic diagram of the inflammatory agents inducing DAMP generation, which ligate to PRRs, and result in multiple pathologies.

Conclusion

So, any threats to the body, despite multiple and confounding names such as stressors, inflammatory agents, toxins, mutagens, allergens, pathogens, venoms, immunogens, immune elicitors, irritants, xenobiotics, genotoxins, endocrine disruptors, and so on are irritants, and are DAMP generators. The irritants provoke the immune system, and to mitigate the irritant, acidosis-hypoxia-inflammation-aromatase-estrogen-hyperplasia axis is activated. DAMPs are the markers of irritant-afflicted body. So, only awareness and disciplined lifestyle adherence can prevent allergies and autoimmune, inflammatory, or metabolic ailments. This article has discussed on this aspect of DAMP-inflammation nexus in comprehensive manner.

Compliance with Ethical Standards

Conflict of Interest The author declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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