Short Communication

Danger-Associated Molecular Patterns (DAMPs) - the endogenous alarm signals

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Abstract

Danger-Associated Molecular Patterns (DAMPs), or alarmins, are increasingly gaining importance as mechanisms that mediate inflammation in the absence of infectious agents. These are endogenous molecules, produced either intracellularly or extracellularly. These are mainly constitutive substances which are necessary for the normal functioning of the cell, but during conditions of cellular insult or stress, they act as danger signals. It was recently shown that DAMPs can also directly sense and report damage occurring in live cells undergoing physiological stress, even without loss of subcellular compartmentalization. DAMPs have been found to play a role in the pathogenesis of various disorders like arthritis, atherosclerosis, lupus, Crohn's disease and many neoplastic diseases. Further research into this relatively new class of molecules can lead to the potential development of targeted and specific anti-inflammatory treatments.

Keywords: alarmins, Danger-Associated Molecular Patterns, danger signals, inflammation

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Introduction

The human body is posed with danger every moment. So-called 'danger signals' are recognized by the host, followed by induction of an innate and then adaptive immune response.[1,2] Certain endogenous biomolecules that aid in this process are Damage-Associated Molecular Patterns (DAMPs), also known as Danger-Associated Molecular Patterns or alarmins. These molecules trigger and perpetuate an inflammatory response that is non-infective.

Although different "danger signals "have been described by researches over many decades, "DAMP" was first described by Seong and Matzinger in 2004.[3] More recently, in the year 2016, the Nobel Prize in Physiology or Medicine was awarded to Yoshinori Ohsumi for his breakthrough work on Autophagy, in which DAMPs are implied to play a significant role.[4]

In this short communication, some of the best studied DAMPs, their production and release, mechanisms of action, physiological significance and clinical implications are discussed.

Some Examples of DAMPs

DAMPs encompass a group of heterogenous molecules. The best known DAMPs are high mobility group box-1 (HMGB1), S100A8 (MRP8, calgranulin A) and S100A9 (MRP14, calgranulin B), and Serum amyloid A (SAA).[5]

Other molecules that function as DAMPs include mRNA, and single stranded RNA, uric acid, LDH, ATP, hyaluronan, Heat Shock Proteins, heparin sulfate, and syndecan to name a few.[6-8]

The production and release of DAMPs

DAMPs are released from the extracellular or intracellular space following tissue stress and injury or cell death.

Extracellular Matrix (ECM) as a source of DAMPs: The extensively studied ECM-derived DAMPs are Proteoglycans.[9] Because of their complex structure with a protein core and various glycosaminoglycan side chains, these molecules are capable of interacting with numerous specific receptors and orchestrating their signalling cross-talk. Versican, a chondroitin sulfate, acts as a ligand to the Toll Like Receptor TLR2/TLR6 heterodimer and to its adaptor CD14, thereby promoting metastatic spread of cancer.[10] Hyaluronan, a non-sulfated glycosaminoglycan, when partially cleaved by hyaluronidasesevokes a danger signal in response to an injury.[10] Several glycoproteins, such as fibronectin, extravascularly deposited fibrinogen, and tenascin C, can act as DAMPs via TLR4 receptors. [10]

Intracellular sources of DAMPs: Intracellular danger molecules are a vast and heterogenous group containing many different classes of substances. Cells undergoing any form of necrosis or apoptosis release biomolecules from various organelles or intracellular compartments which can act as extracellular soluble DAMPs. Mitochondria are the major source for various types of DAMPs. Moreover, mitochondria have the ability to act as DAMPs by themselves following release during cell death. Mitochondria derived DAMPs include intra-mitochondrial components such as mtDNA, formylated peptides, and ATP.In the human brain, mitochondrial transcription factor A (Tfam) can be released into the extracellular space and can be recognized by microglia, thereby inducing a pro-inflammatory response.[8] ATP is released from dying autophagic cells and Interleukin-1β can be actively secreted from the cells in response to other DAMPs or can also be passively released by necrotic cells. Both these molecules have the capacity to act as DAMPs.

High mobility group box-1 (HMGB1) is a non-histone nuclear protein. In normal conditions, it helps in gene transcription by binding to DNA. When there is an injury or stress, HMGB1 is released from the cell and promotes inflammation.HMGB1 is passively released by necrotic but not apoptotic death of normal cells. As such, HMGB1 is not a pro-inflammatory cytokine by itself. But it binds to mediators of inflammation and induces signalling pathways leading to NF-κB activation. This potentiates the inflammatory responses.[11]

Another important endogenous immunological danger signal is uric acid. It is a normally present in all cells, but its levels increase following cell injury. It is the end product of purine nucleotide breakdown. Dying cells release uric acid extracellularly, which then evokes immune responses.

The Calcium binding proteins S100A8 and S100A9 have been extensively implicated in the induction of inflammation. They are released from phagocytes in response to cell stress and act as DAMPs. According to a recent study, S100A9 is released from undamaged macrophages and act by augmenting pro-inflammatory responses and cell death.[12]

Heat shock proteins (HSPs) are chaperones which are found in normal cells where they assist in the correct folding of protein. Under certain circumstances, however, HSPs can also act as DAMPs by interacting with Toll Like Receptors when they are released from the intracellular space.[13] HSPs are generally released from dying cells following apoptosis, necrosis, and cellular stress.

Thus, both intracellular and released products can act as DAMPs under the appropriate pro-inflammatory stimuli.

Mechanism of Action of DAMPs

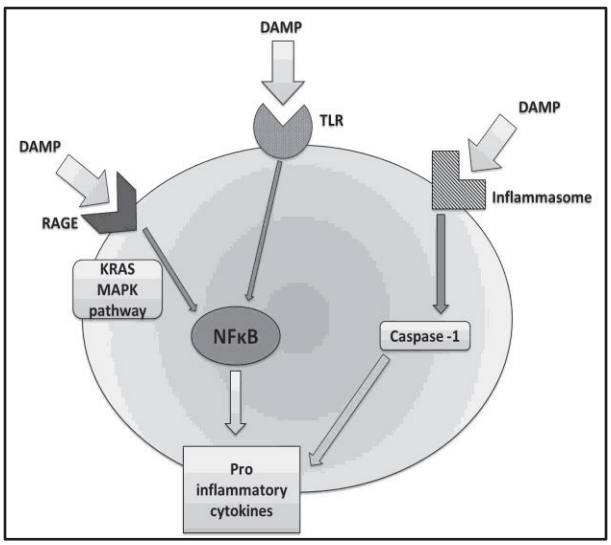
Toll Like Receptors (TLRs): These are integral proteins of the plasma membrane which have the capacity to recognize a variety of stimuli, one of which is DAMP. Ten TLRs have so far been described in humans.[14] Almost all classes of DAMPs can bind to TLRs. With the aid of different accessory and adaptor molecules of TLRs, some DAMPscan target diverse non-immune receptors, thereby refining the final outcome of combined signalling cascades.[9]

The Receptor for Advanced Glycation End Products (RAGE): RAGE is able to bind several ligands and therefore is referred to as a pattern-recognition receptor. An interesting aspect of RAGE is that the ligands for RAGE can up-regulate its expression. Because of this property, the initial response is amplified manifold. Despite the structural diversity of RAGE ligands, activation of RAGE leads to a common pathway: the activation of NF-κB, cell proliferation, and TGF-β production.[15]

The Inflammasome: The inflammasome is a multi-protein oligomer responsible for the activation of inflammatory responses.[16] A particular NLRP3 inflammasome plays a role in DAMP action. It contains the NLRP3 protein, an adaptor protein and the cysteine protease caspase-1.[16] Assembly of the inflammasome leads to the cleavage of caspase-1 to its active form, which, in turn, cleaves the pro-IL-1β precursor into mature IL-1β, which mediates inflammation.[16]

Hence, all DAMPs act via specific receptors and trigger cell signalling processes that are pro inflammatory in nature (Figure 1).

Figure 1: A schematic representation of the mechanism of action of DAMPs.[14-16]



Through TLR, RAGE and inflammosomes, DAMPs increase the production of pro-inflammatory mediators[14-16]

Physiological Significance and Clinical implications of DAMPs

Increased serum levels of DAMPs have been associated with many inflammatory diseases, including arthritis, atherosclerosis, lupus, Crohn's disease and cancer. Therapeutic strategies are being developed to modulate the expression of these DAMPs for the treatment of these diseases. For instance, in a study by Boyapati *et al.*, the mitochondrial DNA – TLR9 has been identified as a therapeutic target in the treatment of inflammatory bowel diseases.[17] Similarly, according to Pasqua *et al.*, inflammasome antagonists can be a plausible potential treatment option for hypertension.[18] DAMP pathways have been identified in the pathogenesis of a number of metabolic diseases like type 2 diabetes mellitus, obesity, steato-hepatitis, and atherosclerosis and as Garcia-Martinez *et al.* have rightly pointed out, targeting these pathways can be effective intervention strategies in these diseases.[19]

Conclusion

The concept of DAMPs is relatively new and in this short communication, some of their salient features have been discussed, including the different molecules that can act as DAMPs, how they are formed, the pathways through which they act and their potential role as therapeutic targets.

It has to be emphasized that most molecules that play a role as DAMPs, under normal conditions, are present constitutionally and are essential for the functioning of the cells. It will therefore be a challenge to target these molecules specifically when they act as DAMPs, but without hindering their normal role in the body. Targeted inhibition of DAMPs or their modifiers can serve as potential new anti-inflammatory treatments for a variety of diseases.

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Conflicts of Interest: Nil

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