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Emerging Role of Mitochondrial Damage-Associated Molecular Patterns in Immune Responses

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ABSTRACT

Cell infection, injury and stress often lead to release or exposure of intracellular molecules called damage-associated molecular patterns (DAMPs). These molecules are recognized by the innate immune system by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), RIG-I-like receptors (RLRs). DAMPs could be derived from any intracellular contents of the cells including plasma membrane, nucleus, endoplasmic reticulum and cytosol. Recently, mitochondria have emerged as an important source of DAMPs and play crucial roles in the initiation of innate immune response or contribute in several pathological processes. Here, we highlight the significance of mitochondrial DAMPs and discuss their contribution in stimulating immune responses.

Keywords: Mitochondria; DAMPs; Immune responses.

THE ORIGIN OF MITOCHONDRIA: ENDOSYMBIOTIC THEORY

Of all intracellular components, mitochondria, which have evolved from aerobic prokaryotes more than a billion years ago on the basis of 'endosymbiont hypothesis' [1,2]. Mitochondria still reserve many morphological and biochemical features of their bacterial ancestors, such as

a double-membrane structure, unique cell membrane lipids [e.g. cardiolipin (CL)], a circular genome containing CpG DNA, deficiency of histones, the ability to replicate independently of the cell nucleus, the use of separate sets of rRNAs and tRNAs encoded by the mitochondrial genome and the ability to form N-formyl peptides (NFPs), which are distinct byproducts of mitochondrial translation and also reflect their prokaryotic origin [3].

DAMPS DERIVED FROM MITOCHONDRIA

In 1994 Polly Matzinger proposed the 'danger theory', which states that the immune system is capable of distinguishing between dangerous and innocuous endogenous signals [4]. Such dangerous signals are provided by intracellular molecules secreted, released and/or exposed by dying, injured or stressed cells, which are named as DAMPs and act as the danger signals to alert the immune system while abnormal cell injury or death [5]. DAMPs can modulate the function of antigen-presenting cells (APCs; e.g. dendritic cells and macrophages) [6], as well as other cell types, such as eosinophils [7-9], mast cells [7] and neutrophils [10]. Following infection, microorganisms are initially sensed by PRRs of the innate immune system, which recognize pathogen-associated molecular patterns (PAMPs) by microbial structural components, nucleic acids and proteins. DAMPs can also be recognized by membrane-bound or cytoplasmic PRRs that include TLRs, RLRs, NOD-like receptors (NLRs) and purinergic receptors [11], which indicate that similarities exist between pathogen-induced immune responses and non-infectious inflammatory responses induced by DAMPs [12]. DAMPs could be derived from any intracellular contents of the cells including plasma membrane, nucleus, endoplasmic reticulum and cytosol [13]. Recent data have revealed the extracellular function of mitochondria as a source of endogenous DAMPs. According to endosymbiotic origin of mitochondria, mitochondria could be recognized as a source of PAMPs- like DAMPs [3]. In this chapter, we discuss the DAMPs derived from mitochondria, here we call mito-DAMPs to avoid confusion. We highlight the prokaryotic features of some of these mito-DAMPs, as well as how they might contribute to the stimulation of immune responses.

MITOCHONDRIAL DNA AND IMMUNE RESPONSES

Mitochondrial DNA (mtDNA), similar to bacterial genomes, consists of circular loops and contains significant number of unmethylated DNA as CpG islands [14]. Recently, the role of mtDNA as a DAMP in inflammation initiation has gained much attention. Mounting evidence revealed the role of mtDNA in provoking the immune response directly via the activation of TLR9 with its CpG motifs [10,15]. The study in our laboratory have shown that cell necrosis induced by cationic nanocarriers and the resulting leakage of mtDNA could trigger severe inflammation *in vivo*, which is mediated by a pathway involving TLR9 and MyD88 signaling [16]. Interaction of TLR9 with mtDNA activates the nuclear factor kappa B (NFκB) signaling and increases the expression of pro-inflammatory cytokines. It is reported that mtDNA can be detected in the synovial fluids of rheumatoid arthritis patients but not in healthy individuals [17], which is also increased in the plasma of patients with femur fracture [10]. These data indicate that mtDNA plays a vital role in

DAMP-associated inflammation in different pathological disorders, such as systemic inflammatory response syndrome (SIRS), heart diseases and rheumatoid arthritis (RA) [10,15,17].

mtDNA also plays a key role in the activation of the NLR-family pyrin domain containing 3 (NLRP3) inflammasome, which might be associated with the induction of inflammatory disease. The NLRP3 inflammasome could be activated by Reactive oxygen species (ROS), mtDNA, CL, and altering of NAD/NADH (NAD, Nicotinamide adenine dinucleotide) [18-23](Figure 1). It has been demonstrated that mtDNA damage leads to mitochondrial dysfunction and increases the secretion of IL-1β, which directly promotes atherosclerosis [14]. However, mtDNA also participate in immune responses against foreign pathogen. It has been shown that eosinophils can eject mtDNA specifically, which functions as an extracellular trap to assist in immobilization of the microbial pathogens, and thus, the eosinophils can recognize and kill the microorganism [24]. Recently another study has observed that escaped mtDNA after mtDNA stress can boost innate antiviral defenses to dampen viral replication by activation of the cGAS-cGAMP-STING-IFN I pathway [cGAMP, cyclic GMP-AMP; cGAS, cGAMP synthase; STING, stimulator of interferon genes; IFN I, type I interferon] [25]. In summary, mtDNA has a very important role in the stimulation of immune responses, including inflammatory responses and innate immune response against bacterium and virus.

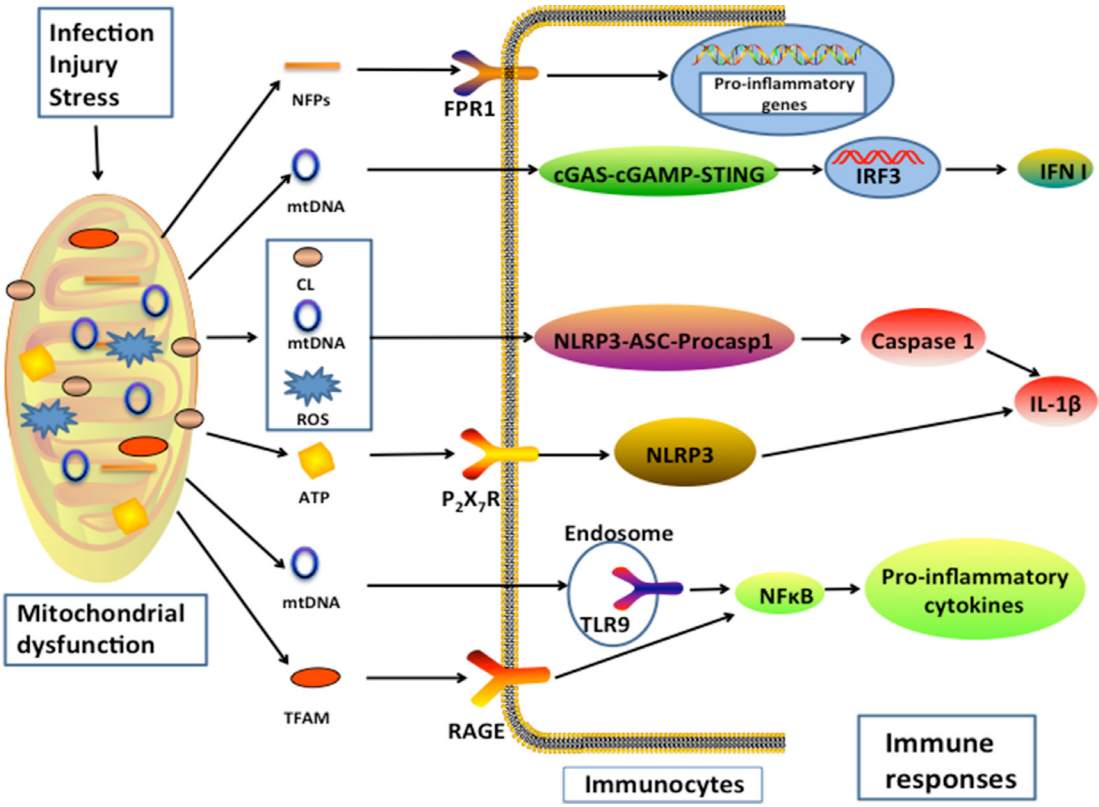

Figure 1: Mito-DAMPs and immune responses. Mitochondrion is a cellular organelle that might function as a source of DAMPs that are released during cell infection, injury and stress. Once these mito-DAMPs (such as mtDNA, NFPs, TFAM, ATP, ROS and CL) are released into the extracellular space, they can stimulate the immune responses. Immunocytes detect mtDNA through TLR9, NFPs via FPR1, and TFAM through RAGE, leading to activation and transcription of pro-inflammatory cytokine genes. ATP engages P_2X_7R and promotes the activation of the NLRP3 inflammasome, which can also be stimulated by CL, mtDNA and ROS, resulting in increased secretion of the IL-1β. On the other hand, escaped mtDNA after mtDNA stress can stimulate the the cGAS-cGAMP-STING-IRF3-IFN I pathway to dampen viral replication.

N-FORMYL PEPTIDES AND MITOCHONDRIAL TRANSCRIPTION FACTOR A AS PROINFLAMMATORY MEDIATORS

Unlike eukaryotes, where protein synthesis is initiated from a nonformylated methionine residue, mitochondria starts protein synthesis with N-formylated methionine, resulting in N-formyl peptides, which resembles that of prokaryotes [26]. It has been shown that NFPs derived from bacteria are very potent chemoattractants for neutrophils since 1975 [27], and in 1982, researchers discovered that mitochondrial NFPs also had such activity [28]. Indeed, necrotic cells after local thermal injury *in vivo* released NFPs, which recruit neutrophils into the injury site

[29].NFPs are generally recognized by high-affinity formyl peptides receptors (FPRs), which are G-protein-coupled receptors expressed in a range of somatic cells such as neutrophils, monocytes, dendritic cells, hepatocytes, and endothelial cells [30].By binding FPR-1, mitochondrial NFPs can provoke intracellular calcium mobilization, MAPKs (Mitogen-activated protein kinases) activation and cell migration, which results in the stimulation of proinflammatory signals including matrix metalloproteinase-8 and Interleukin-8 (IL-8) [10,15,31]. It has been reported that mitochondrial NFPs derived from necrotic cells can also induce chemotaxis of thrombin-activated platelets [32]. Thus, the release of NFPs from damaged tissues and cells in trauma has important implications for the initiation and perpetuation of inflammation in subsequent SIRS [3]. So NFPs derived from mitochondria in tissue damage might play a role in the aggregation and accumulation of inflammatory cells at injury sites.

It has been observed that release of IL-8 in monocytes can't be provoked by the stimulation of synthetic bacterial N-formyl-Met-Leu-Phe (fMLF) and the NFP sequence of ND6 (fMMYALF) alone *in vitro*, but can be induced by ND6 with the help of Mitochondrial transcription factor A (TFAM) [33].TFAM is highly abundant mitochondrial protein that is functionally and structurally homologous to high- mobility group box protein 1 (HMGB1) [34] and is normally bound to and remains associated with mtDNA when released from damaged cells [35]. Some study have demonstrated that TFAM bound to mtDNA can activate plasmacytoid dendritic cells (pDC) via endosomal processing and PI3K, ERK and NF-κB signaling, whereas exposure of TFAM alone was inadequate to induce pDC activation. Moreover, TFAM, which was dependent upon receptor for advanced glycation endproducts (RAGE), can amplify TLR9-mediated immune responses [36,37]. Additionally, Chaung et al. showed that TFAM was increased in the circulation in rats after haemorrhagic shock and the intravenous administration of TFAM elicited inflammatory responses, which resulted in organ injury in healthy animals [38]. It is concluded that TFAM is a novel and potent endogenous danger signal in eliciting inflammatory responses [39].

RELEASE OF ATP FROM APOPTOTIC AND NECROTIC CELLS

80–90% of the oxygen in cells are consumed by mitochondria to support oxidative phosphorylation and mitochondria acts as the energy factories, which is the major system for Adenosine 5'-triphosphate (ATP) production [40]. It is now clear that the extracellular ATP is a ubiquitous way for the modulation of different cellular functions, including cell adhesion, proliferation, differentiation, mobility, survival and death [41,42]. Several studies have shown that cells that underwent different types of cell deaths appeared to release or secrete ATP [43]. Extracellular ATP could activate purinergic receptors, which are made up of two classes: the G-coupled protein P_2Y receptors and the cation-permeable ligand-gated ion channel P_2X receptors [44]. Activation of P_2Y_2 receptors induced the recruitment of monocytes and macrophages to the side of apoptosis [45]. Another study has reported that the successful chemotherapy-elicited anticancer immune response require ATP derived from secondary necrotic cancer cells

[46]. On the other hand, the binding of ATP to purinergic P_2X_7 receptor activated the NLRP3 inflammasome, which increased subsequent secretion of proinflammatory cytokine IL-1β from innate immune cells including macrophages and dendritic cells [47]. IL-1β together with antigen presentation, contribute to the increase of interferon-γ (IFN γ)-producing $CD8^+$ T cells and adaptive immune response to cancer cells [48]. ATP can also be released in accidental necrosis. A study has demonstrated that after local thermal injury, hepatocytes died via accidental necrosis and released ATP activated the NLRP3 inflammasome, which alerts neutrophils to the injury sites [32]. These studies suggest that ATP is a danger signal derived from apoptotic, secondary necrotic and accidental necrotic cells.

MITOCHONDRIA-DERIVED ROS AND IMMUNE RESPONSES

ROS are the side products of electron transport in mitochondrial respiratory chain where superoxide radicals ($O2^-$) and hydrogen peroxide (H_2O_2) are produced [49]. Mitochondria, as the major source of ROS, are highly involved in oxidative stress [50]. Mitochondrial ROS (mROS), Ca^{2+} and mitochondrial permeability transition (MPT), form integral components of amplification loop that trigger irreversible mitochondrial damage [49]. Many studies indicate that mROS may have a central role in the regulation of RLR–MAVS (MAVS, mitochondrial antiviral signaling protein) signaling during viral infection and mounting evidence have showed that mROS also play an important role in macrophage-associated antibacterial immune responses. Thus, mROS are the major host defense mechanism against infection and harmful agents [51]. mROS can also interact with and directly modify the function of all kinds of macromolecules, including DAMPs [3]. During apoptosis, the generation of ROS by mitochondrial oxidized HMGB1 in turn enabled its immunostimulatory capacity [52]. Moreover, a study has reported that blockade of mitophagy/autophagy results in the accumulation of damaged, ROS-generating mitochondria, and this, in turn, stimulates the NLRP3 inflammasome [18]. Thus, ROS-generating mitochondria act as integrators across different stimuli activating the NLRP3 inflammasome, which regulate immune responses and contribute to the development of inflammatory diseases [53].

CARDIOLIPIN IN IMMUNE RESPONSES

Cardiolipin (CL), an anionic phospholipid that acts to anchor cytochrome c to the inner membrane and provides support to proteins necessary to carry out oxidative phosphorylation [39]. What is interested in CL is its presence in the bacterial plasma membrane and the membranes of hydrogenosomes, which are mitochondrion-like organelles in protists [54,55]. The presence of oxidized CL in apoptotic cells of atherosclerotic lesions has implied its role in the pathological immune response in atherosclerosis [56]. Moreover, in dysfunctional mitochondria, CL localizes to the outer mitochondrial membrane, where it recruits, binds to, and activates the NLRP3 inflammasome [57,58]. Therefore, we can also think of CL as a DAMP derived from mitochondria.

CONCLUSION

Mitochondria are recently discovered and investigated as DAMP-containing organelles (Table 1) (Figure1). DAMPs derived from, or modified by mitochondria function as key modulators in immune responses in different pathologies. DAMPs are generally released after cell death and/or tissue damage and play key roles in the development of SIRS, atherosclerosis, heart disease, rheumatoid arthritis, liver injury, as well as in antibacterial immunity and antiviral signaling [10,14,15,17,32,50]. Due to the hypothesis that mitochondria probably originated from α-Proto-bacteria more than a billion years ago, mitochondria are often considered as 'dangerous organelles', which still possess many features of their bacterial ancestors. The circular genome containing CpG DNA and the ability to form N-formyl peptides are mainly responsible for its immunostimulatory effect [16]. In addition, the ATP and ROS derived from mitochondria might also be involved in the regulation and activation of immune responses as DAMPs. Mito-DAMPs modulate innate immunity via different inflammatory pathways or by the direct activation of the NLRP3 inflammasome, and in some cases, these pathways may work together, leading to an overstimulation of inflammatory response (Figure1). The understanding of pro-inflammatory mito-DAMPs in different pathologies is of great importance in discovering novel and potent target for disease treatment.

Table 1: DAMPs derived from mitochondria and released into the extracellular space.

Mito-DAMPs	Characteristics	Receptors	Function(s)
mtDNA	Prokaryotic feature	TLR-9	Activation of neutrophils, monocytes/macrophages, activation of NLRP3
NFPs	Prokaryotic feature	FPR-1	A chemoattractant for neutrophils, thrombin-activated platelets, monocytes
TFAM	Prokaryotic feature	RAGE	Activation of pDCs, macrophages
ATP	Most efficiently produced by mitochondria in oxidizing conditions	P_2X_7, P_2Y_2	A chemoattractant for neutrophils, monocytes/macrophages, activation of NLRP3
ROS	Efficiently produced by mitochondria in oxidizing conditions	?	Modification of DAMPs, defense against infection, activation of NLRP3
CL	Prokaryotic feature	?	Exposed on the surface of dead cells, activation of NLRP3

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