Systemic inflammatory response syndrome is triggered by mitochondrial damage (Review)

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Abstract. Mitochondria are key organelles of cellular energy metabolism; both mitochondrial function and metabolism determine the physiological function of cells and serve an essential role in immune responses. Key damage-associated molecular patterns (DAMPs), such as mitochondrial DNA and N-formyl peptides, released following severe trauma-induced mitochondrial damage may affect the respiratory chain, enhance oxidative stress and activate systemic inflammatory responses via a variety of inflammation-associated signaling pathways. Severe trauma can lead to sepsis, multiple organ dysfunction syndrome and death. The present review aimed to summarize the pathophysiological mechanisms underlying the effects of human mitochondrial injury-released DAMPs on triggering systemic inflammatory responses and to determine their potential future clinical applications in preventing and treating sepsis.

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Abbreviations: DAMP, damage-associated molecular pattern; mt, mitochondrial; NFP, N-formyl peptide; FPR, formyl peptide receptor; SIRS, systemic inflammatory response syndrome; PRR, pattern recognition receptor; PAMP, pathogen-associated molecular pattern; TFAM, mitochondrial transcription factor; ROS, reactive oxygen species; CpG, 5'-cytosine-phosphoguanine; MODS, multiple organ dysfunction syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; I/R, ischemia/reperfusion; SLE, systemic lupus erythematosus; cGAS, cyclic GMP-AMP synthase; STING, stimulators of interferon genes; TLR9, toll-like receptor 9; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; MyD88, myeloid differentiation factor 88; CS, cyclic stretch; PINK1, PTEN-induced putative kinase 1; IRF3, interferon regulatory factor 3; cGAMP, cyclic GMP-AMP; ER, endoplasmic reticulum

Key words: damage-associated molecular patterns, mitochondrial DNA, systemic inflammatory response syndrome, intestinal barrier dysfunction

Contents

1. Introduction

Although systemic inflammatory response syndrome (SIRS) is commonly associated with pathogenic infection, certain patients with SIRS do not suffer from such infection, thus reflecting poor understanding of its pathophysiology (1). Therefore, other factors may also serve a key role in the occurrence and development of SIRS.

Stimulating adaptive immune response pattern recognition receptors (PRRs) is associated with development of SIRS. PRRs are derived from pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) of exogenous and endogenous invaders, respectively (2). Among known DAMPs, mitochondrial DAMPs (mtDAMPs), including mitochondrial DNA (mtDNA), N-formyl peptides (NFPs), mitochondrial transcription factor (TFAM), cardiolipin and ATP (3), have attracted increasing attention from researchers. The aforementioned molecules are considered to be danger signals released in response to tissue injury, thus triggering an immune response similar to that induced by pathogens (2). Previous studies have shown that plasma levels of mtDAMPs may be associated with clinical outcome of septic shock, major surgery or severe trauma (4-6). In addition, it has been suggested that mtDNA may be a more efficient biomarker than lactate concentration/sequential organ failure assessment score in predicting mortality rate in patients with sepsis following emergency admission (7). However, mtDNA has not been widely used in clinical practice to optimize clinical treatment. Therefore, further research is urgently required.

The present review aimed to summarize the effects and mechanisms of mtDAMPs on activation of inflammatory responses and development of SIRS. Although multiple types of mitochondrial component and metabolites, such as mtDNA, NFPs, TFAM, transcription factor A, ATP, cardiolipin, cytopigment C, succinate and mitochondrial RNA serve as DAMPs (8), the present review focused on widely studied mitochondria-derived DAMPs, such as mtDNA, NFPs and TFAM. Additionally, the present review focused on the mechanisms underlying the effects of the aforementioned DAMPs on inducing sepsis-like responses and their potential clinical value.

2. Structure and function of mitochondria

Mitochondria, the 'cellular energy factories', are organelles in eukaryotic cells, which comprise ~25% of the total cytoplasm volume. Mitochondria are complex organelles due to their unique evolutionary history and components, as well as their genome (9). Additionally, mitochondria are involved in a range of cell fate decisions, including energy metabolism, reactive oxygen species (ROS) formation, calcium homeostasis, cell proliferation and apoptosis (10). When mitochondrial homeostasis is disrupted and the apoptosis pathway is activated under severe stress conditions, including cytoskeleton alteration, extensive DNA damage, endoplasmic reticulum (ER) and replication stress, sustained ROS burst, calcium overload and mitotic defect, mitochondrial outer membrane permeabilization is targeted by the aforementioned stressors (11). The activation of the pro-apoptotic pathway regulates the structure of pro-apoptotic proteins BAX and Bcl2 homologous antagonist/killer (12). In addition, it permeabilizes the outer membrane of mitochondria to allow transport of pro-apoptotic molecules from the inner membrane into the cytosol to initiate a caspase cascade, resulting in rapid cell death (13). It has also been reported that the mitochondrial intermembrane space proteins, such as cytochrome *c*, which are released into the cytoplasm following increased membrane permeability, also mediate activation of apoptotic proteases (14). Displaced mtDAMPs have been identified following cell death or mitochondrial dyshomeostasis in patients with trauma, intestinal ischemia/reperfusion and lung injury (1,15-19). Therefore, it has been hypothesized by clinicians that mitochondria serve a vital role in catalyzing the pathophysiology of sterile inflammation following trauma (1).

3. mtDAMPs

Mitochondria produce ATP via oxidative phosphorylation; ROS are byproducts of this process (1). Therefore, mitochondria are the primary source of ROS; ATP and ROS are also considered to be DAMPs. Damage-induced mitochondrial secretion of ATP increases local levels of ATP, thereby promoting macrophage-mediated death of sepsis-causing bacteria via P2X7 and P2X4 receptors (20,21). Emerging evidence has suggested that under physiological conditions, cells produce mitochondrial components that are not actively secreted into the cytoplasm; however, these components are released via cellular disruption (18,22-24).

4. mtDNA

Human mtDNA is a 16,569-bp long superhelical closed-loop double-stranded DNA molecule that encodes essential protein subunits of the oxidative phosphorylation system, including the electron transport chain (complex I-IV) and ATP synthase (complex V), which drive oxidative phosphorylation and ATP production. Apart from the nucleus, mitochondria are the only source of DNA in cells (9,25). Unlike nuclear DNA, mtDNA is more prone to injury and lacks repair systems (26). It has been suggested that mitochondria originated from gram-negative (G^-) bacteria. Following phagocytosis of G-bacteria by eukaryotes, the bacteria may have formed a symbiotic association with the host and gradually evolved into mitochondria (25). Due to this evolutionary homology, mitochondria are similar to bacteria; both exhibit conserved hypomethylated 5'-cytosine-phosphoguanine (CpG) gene sequences and pro-inflammatory effects (9,27). Following cell injury, these endogenous mitochondrial 'enemies' are recognized by classical PRRs to induce immune responses, thereby acting as a bridge between trauma, inflammation and SIRS (9).

In critical patients with multiple organ dysfunction syndrome (MODS) and sepsis, mitochondrial dysfunction may lead to energetic and metabolic failure in white blood cells, thus altering their function and attenuating the ability of the host to fight infection (28). mtDNA is more susceptible to damage compared with nuclear DNA since it lacks introns and histones (29).

mtDNA damage affects the respiratory chain, enhances oxidative stress and inflammatory responses, and induce apoptosis, leading to cell dysfunction and tissue damage, which further aggravate mitochondrial dysfunction in cells, thus forming a feedback loop (30). Therefore, mtDNA is considered to be a trigger that stimulates the innate immune response (15). In 2013, Nakahira *et al* (31) published the first clinical trial in this area, including 200 patients from medical Intensive Care Units. The aforementioned study showed that circulating mtDNA was significantly increased in patients who died within 28 days of admission compared with those who survived. In addition, mtDNA was positively associated with mortality in patients who were hospitalized for up to 28 days. Further studies confirmed these results (32-35). Additionally, other studies have suggested that mtDNA serves a key role in the pathogenesis of severe trauma, major abdominal surgery, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), ischemia/reperfusion (I/R) injury, inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), myocarditis and myocardial infarction (1,15,19,36-38).

5. Effect of mtDNA on the occurrence and development of SIRS

During mitochondrial stress, mitochondrial membrane potential is decreased, leading to impaired membrane integrity (39,40). These changes facilitate leakage of mtDNA into the cytosol. mtDNA exhibits immunological potential and is a key DAMP. Stimulators of interferon genes (STING) is produced following activation of toll-like receptor 9 (TLR9), nucleotide-binding oligomerization domain-like

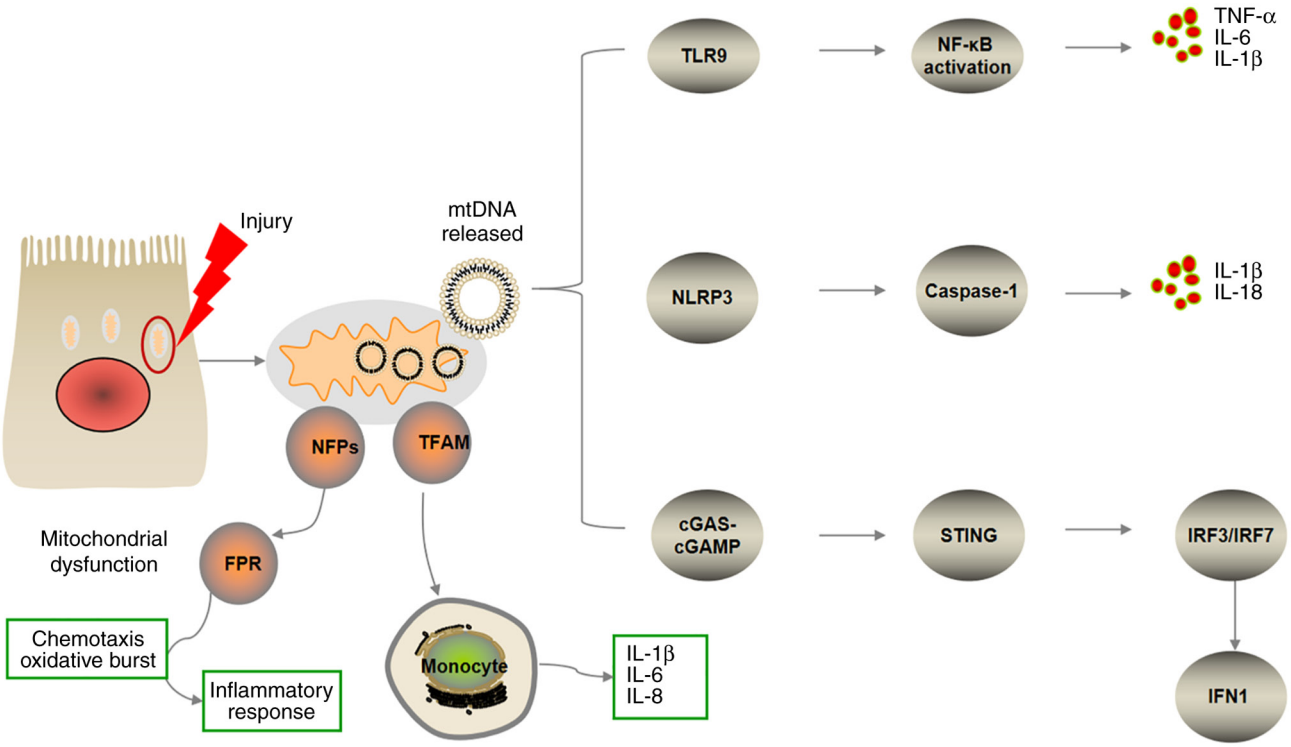

Figure 1. Overview of pro-inflammatory signaling pathways triggered by mitochondrial damage-associated molecular patterns. Mitochondrial components released via cellular disruption trigger systemic inflammatory response syndrome. mtDNA triggers pro-inflammatory signaling pathways via endosomal localized TLR9, cytosolic cGAS-STING or NLRP3 inflammasome. TLR9 binds mtDNA in the endosome, inducing NF-κB-dependent pro-inflammatory signaling. mtDNA-dependent inflammasome activity leads to caspase-1-dependent maturation or activation of IL-1 and IL-8. cGAS recognizes mtDNA in the cytosol and activates endoplasmic reticulum-localized STING to trigger an IFN response. NFPs are released into the blood circulation to activate the chemokine FPR, which recruits immune cells and promotes inflammatory responses. TFAM serves as a pro-inflammatory cell signaling molecule and is recognized by monocytes, leading to enhanced secretion of pro-inflammatory factors, such as IL-1β, -6 and -8. mtDNA, mitochondrial DNA; FPR, formyl peptide receptor; TFAM, mitochondrial transcription factor; NFP, N-formyl peptide; TLR9, toll-like receptor; NLRP3, NOD-like receptor 3; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; IRF, interferon regulatory factor; IFN, interferon.

receptor family pyrin domain-containing 3 (NLRP3), cyclic GMP-AMP synthase (cGAS) and other signaling pathways, thereby promoting the occurrence and development of SIRS by regulating the innate immune response and contribute to inflammation initiation (25,41). The potential pathophysiological mechanisms are illustrated in Fig. 1.

mtDNA-binding TLR9 activates the downstream pathway of inflammation. The discovery of membrane-bound TLR family members indicated that a number of PAMPs, including lipid, lipoprotein, protein, glycan and nucleic acid, initiate innate immune responses. TLR9 is the most common recognition receptor of mtDNA. TLR9 is primarily expressed in macrophages, dendritic cells and B lymphocytes, and recognizes the DNA CpG motif in bacteria and viruses (42). Similar to bacterial DNA, mtDNA is hypomethylated on the CpG motif (43), making it a potent activator of TLR9. In infection-mediated mitochondrial injury, the body clears damaged mitochondria and mtDNA via mitophagy, the underlying mechanisms of which have been summarized in a previous review article (44). However, when mitophagy is inhibited, released mtDNA can be recognised by nucleic acid recognition receptors in the cytoplasm (45). For example, TLR9 identifies mtDNA via the CpG motif. However, CpG-independent TLR9 activation may also occur. Activation of TLR9 leads to activation of NF-κB via the myeloid differentiation factor 88 (MyD88)-dependent (classical) pathway, which induces expression of downstream pro-inflammatory genes, especially those of early cytokines, such as TNF-α and IL-6 (45).

Lin *et al* (46) showed that cyclic stretch (CS) of lungs promotes mitochondrial injury in a mechanical ventilation rat model, resulting in release of mtDNA. mtDNA, as a DAMP, is recognized by TLR9 to activate the TLR9/MyD88/NF-κB signaling pathway, exacerbating inflammation and lung injury (46). Jing *et al* (47) studied ventilator-induced lung injury also using a CS cell culture model and suggested that PTEN-induced putative kinase 1 (PINK1)-dependent mitophagy and associated TLR9 activation is a key factor in stretch-induced cell injury. Knockdown of PINK1, which is involved in regulating mitophagy, has also been shown to promote mitochondrial dysfunction, defective mitophagy and more severe lung injury (48). By contrast, PINK1 overexpression may mitigate stretching-induced inflammation and injury. Similar effects have been observed following TLR9 overexpression to induce expression of MyD88 and NF-κB/p65. Furthermore, MyD88 silencing protects lung epithelial cells from traction injury and downregulates NF-κB/p65. These findings suggested that PINK1-dependent autophagy and TLR9 activation are key factors in stretching-induced cell damage. Release of mtDNA could activate TLR9, which induces the MyD88/NF-κB pathway, leading to lung injury (47). Inhibiting the release of mtDNA and activation of TLR9 may be a

therapeutic approach for preventing lung inflammation and injury.

Activation of mtDNA and NLRP3 inflammasome. The NLRP3 inflammasome, a member of the NLR family, is a macromolecular complex composed of NLRP3, caspase-1 and apoptosis-associated speck-like protein (40). Oxidative mtDNA binds to and activates NLRP3 inflammasomes, thereby leading to secretion of caspase-1-dependent pro-inflammatory cytokines, such as IL-1β and IL-18, resulting in enhanced inflammatory cell death (pyroptosis) (9,49). During pyroptosis, the cell bursts and releases its contents, such as DNA fragments, into the intercellular stroma (49).

Emerging evidence has suggested that mtDNA serves a key role in activating the NLRP3 inflammasome. Sok *et al* (50) revealed that inhibiting release of oxidative mtDNA decreased generation of mitochondrial ROS and inhibited activation of NLRP3 inflammasomes. Severe fever with thrombocytopenia syndrome caused by viral infection can also cause the release of oxidative mtDNA and activate the NLRP3 inflammasome, leading to intensive inflammation (51). A previous study demonstrated that inhibiting synthesis and production of oxidized mtDNA could alleviate the severity of ARDS (52). Wu *et al* (53) performed burn and delayed resuscitation experiments in rats and showed that delayed resuscitation could cause liver injury and oxidative stress. ROS can cause liver injury via destroying mitochondrial integrity and activating the mtDNA/NLRP3 axis. However, pre-intervention of mitochondria-targeted antioxidants could protect the structure and function of mitochondria and inhibit the release of mtDNA. These findings indicated that mtDNA may serve a key role in occurrence and development of systemic inflammation and organ dysfunction via activating the NLRP3 inflammasome (53). Therefore, protecting mitochondrial function and inhibiting mtDNA release to the cytosol may improve clinical symptoms of patients with SIRS/MODS).

Activation of the cGAS/STING signaling pathway by mtDNA. STING was initially identified as a key immune molecule that detects nuclear or cytoplasmic DNA fragments from pathogen-infected cells and triggers defensive immune responses (54). cGAS and STING are expressed in different types of cell, including cancer, immune and non-immune cells (55). However, increasing evidence has suggested that activation of the STING pathway can lead to both tissue inflammation and damage (55,56). mtDNA can promote the onset of inflammatory signaling responses via activating the cGAS/STING/interferon regulatory factor 3 (IRF3) pathway (57,58). The cGAS/STING complex activated by mtDNA may provide novel insights on the mechanisms of sepsis and may further emphasize the key role of mtDNA in sepsis (57). The specific signaling pathway is illustrated in Fig. 1. Cyclic GMP-AMP (cGAMP) is generated following cGAS binding to DNA. Secondary messenger cGAMP binds to STING in the endoplasmic reticulum (ER) membrane. After binding, STING changes its conformation and is activated. Activated STING is transferred from the ER to the ER/Golgi intermediate organ and Golgi apparatus. During this process, the carboxyl terminus of STING recruits and activates TANK binding kinase 1 via phosphorylating transcription factor IRF3. Phosphorylated IRF3 forms a dimer and translocates into the nucleus, where it initiates the type I interferon response (57). The type I interferon response activates innate and adaptive immunity in a pleiotropic manner (59).

In vivo experiments using a burn-induced ALI model revealed that plasma levels of mtDNA were increased, and cGAS and STING were both upregulated in lung tissue and neutrophil infiltration was enhanced following burn injury (60). These results indicated that increased plasma mtDNA-mediated activation of the cGAS-STING pathway may induce ALI and neutrophil infiltration in rats. Hu *et al* (58) showed that inhibition of mtDNA release attenuated sepsis-induced inflammatory responses and intestinal injury; therefore, it was hypothesized that inhibition of the mtDNA/cGAS/STING signaling pathway could protect against sepsis-induced organ damage and intestinal barrier dysfunction. Liu *et al* (61) revealed that levels of cyclic mtDNA and STING activation were enhanced in patients with severe ALI. In addition, STING activation may serve a key role in mtDNA-mediated lung injury, which promotes inflammatory storm and is involved in autophagy via decreasing lysosomal acidification in an IFN-dependent manner (61). STING overactivation has also been reported to be associated with the pathogenesis of SLE, neurological degeneration and sepsis (27). Consistent with a previous study (48), Sliter *et al* (62) demonstrated that PINK1, a key gene in mitophagy that remove damaged mitochondria from cells, could inhibit STING-mediated inflammatory responses, thus providing a potential novel model for studing mitophagy, and attenuating the inflammatory response.

6. NFPs

NFP is a potent chemotactic polypeptide synthesized in mitochondria (23). In the absence of cellular damage, bacteria-like NFPs are isolated within the mitochondria; however, during severe trauma and cell death, NFPs are released into the blood circulation to activate the chemokine formyl peptide receptor (FPR), which recruits immune cells and promotes inflammatory responses (63). FPR comprises conserved G-protein-coupled receptors that serve a key role in host defense and inflammatory responses (64). FPR1, FPR2/lipoxygenase A4 receptor and FPR3 have been identified in humans (1). These receptors are expressed in multiple types of cell, with the highest expression levels of FPR1 and FPR2 observed in neutrophils, and those of FPR3 in monocytes/macrophages (64). A number of structurally and chemically different ligands (such as microbial origins peptides, endogenous peptides and synthetic small molecules) activate FPRs (64), while NFP is the only common ligand for all three receptors in humans (65).

Wenceslau *et al* (66) showed that mitochondrial FPs (mtFPs) caused inflammation and vascular dysfunction via FPRs, and accelerated the development of sepsis. Another study revealed that mtFPs could cause sepsis-like syndrome, heart failure, heatstroke, vascular leakage, thrombosis and lung injury in a rat model, suggesting that NFPs may be a bridge between trauma, SIRS and cardiovascular

failure (67). Another clinical study on traumatic hemorrhagic shock-induced lung injury demonstrated that trauma-induced release of NFPs could promote infiltration of neutrophils into the lung, and aggravate SIRS and sepsis (16). This may be because mtFPs-induced FPR activation could cause sepsis-like symptoms, leading to ALI. Dorward *et al* (68) found increased bronchoalveolar lavage fluid and serum levels of mtFPs in patients with ARDS. FPR1 has been reported to be involved in neutrophil recruitment and alveolar leakage following sterile injury. Previous *in vivo* and *in vitro* studies revealed that FPR1 could also be activated in a neutrophil activation-dependent manner, suggesting that pluripotency of FPR1-induced by mtFPs may be the mechanism underlying their inflammatory effect (24,36). Therefore FPR1 may be a potential therapeutic target for treating aseptic ALI.

7. TFAM

TFAM is an abundant mitochondrial protein; each mtDNA molecule binds to ~1,000 TFAM molecules. The tight binding of TFAM with mtDNA stabilizes the structure of mtDNA and protects mt function (29,69). When mitochondria are damaged, mtDNA and TFAM are both released into the cytoplasm (17,19). TFAM serves as a pro-inflammatory cell signaling molecule and is recognized by monocytes, leading to enhanced secretion of pro-inflammatory factors such as IL-1β, IL-6 and IL-8 (70). Hepokoski *et al* (17) showed that pulmonary I/R-mediated lung injury was associated with accumulation of extracellular mtDNA and TFAM, whereas circulating TFAM promoted infiltration of neutrophils in the lung. In addition, West *et al* (71) indicated that TFAM may serve a key role in maintaining the stability of mtDNA; therefore, when TFAM levels are low, the stability of mtDNA is decreased. This was also confirmed by van der Slikke *et al* (30); this previous study demonstrated that in sepsis-induced acute kidney damage, the degree of mitochondrial damage was inversely proportional to the expression of TFAM. In conclusion, TFAM may serve a key dual role in the activation of inflammation-associated signaling pathways. Firstly, TFAM could stabilize the structure and function of mtDNA (70), and secondly, as a DAMP, TFAM could also enhance inflammatory responses, similar to other DAMPs, and cause injury to vital organs, such as the lung and kidney (17,70). However, the synergistic effect of TFAM and mtDNA on inflammatory responses requires further investigation.

8. mtDAMPs and intestinal barrier dysfunction

Intestinal mucosal epithelial cells exhibit a strong metabolism and rapidly proliferate, renewing every 4-5 days (72); therefore, the rate of mitochondrial energy metabolism and the number of mitochondria are increased in these cells compared with other cells (73). Additionally, intestinal epithelium has been reported to be prone to hypoxia; therefore, intestinal I/R can promote both intestinal mucosal epithelial cell and mitochondrial injury, resulting in increased circulating mtDNA levels (74). A previous study showed that oxidized mtDNA could trigger a powerful inflammatory response (15). The aforementioned findings suggested that mtDNA may not only serve as a marker of intestinal I/R injury, but could also be involved in inflammation and cell death.

Just as mtDNA is thought to trigger the innate immune response, the gut is also considered to promote SIRS and multiple organ dysfunction (75). Consistent with previous studies on intestinal I/R injury (15,76), Hu *et al* (15) demonstrated that mtDNA was associated with increased secretion of inflammatory cytokines and intestinal barrier injury. However, intervention with mitochondrial-targeted antioxidant MitoQ could protect the intestinal barrier during I/R (15,76). It has been reported that several inflammatory cytokines, such as TNF-α, IFN-γ and IL, are involved in regulation of intestinal tight junction integrity (77). TNF-α is a key factor in elevating gut permeability via occludin (OCLN); OCLN overexpression has been shown to mitigate cytokine-mediated increased gut permeability (78). Furthermore, anti-TNF therapy could improve epithelial barrier function (79). Based on the aforementioned studies, it was hypothesized that mtDAMPs and mtDAMP-mediated inflammatory responses could be associated with intestinal barrier function. When the intestinal barrier is damaged, bacterial translocation occurs and products of microorganisms, such as alimentary antigens, may enter the bloodstream, thus intensifying SIRS and promoting the formation of a feedback loop that facilitates development of fatal sepsis (75,80).

9. Conclusion

Injury-released mtDAMPs serve a key role in the occurrence and development of systemic inflammatory response (1). The inflammatory response exerts a protective effect on the body; however, excessive inflammatory response damages organ function, leading to the occurrence and development of sepsis, MODS and death (81). In addition, mtDAMP-mediated activation of inflammatory signaling pathways can aggravates mitochondrial damage, resulting in release of more mtDAMPs and intestinal barrier dysfunction. The aforementioned processes contribute to the development of SIRS when accompanied by displaced intestinal flora and release of harmful metabolites (15,58). Further studies on mtDAMPs are required to determine whether mtDNA serves as a biomarker for predicting disease severity or mortality, and to determine the mechanism underlying DAMP-induced SIRS pathogenesis and development during mitochondrial injury. Additionally, the effect of drugs on protecting mitochondrial function or antagonizing mtDAMP-associated receptors to interrupt this pathophysiological process should be investigated to support the potential role of mtDAMPs as a significant target for preventing and treating sepsis.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

TF designed the review and collected the literature. CK and WS drafted the manuscript. All authors reviewed the literature. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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