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REVIEW

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Mitochondrial dysfunction in sepsis: mechanisms and therapeutic perspectives

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Abstract

Sepsis is a severe medical condition characterized by a systemic inflammatory response, often culminating in multiple organ dysfunction and high mortality rates. In recent years, there has been a growing recognition of the pivotal role played by mitochondrial damage in driving the progression of sepsis. Various factors contribute to mitochondrial impairment during sepsis, encompassing mechanisms such as reactive nitrogen/oxygen species generation, mitophagy inhibition, mitochondrial dynamics change, and mitochondrial membrane permeabilization. Damaged mitochondria actively participate in shaping the inflammatory milieu by triggering key signaling pathways, including those mediated by Toll-like receptors, NOD-like receptors, and cyclic GMP-AMP synthase. Consequently, there has been a surge of interest in developing therapeutic strategies targeting mitochondria to mitigate septic pathogenesis. This review aims to delve into the intricate mechanisms underpinning mitochondrial dysfunction during sepsis and its significant impact on immune dysregulation. Moreover, we spotlight promising mitochondria-targeted interventions that have demonstrated therapeutic efficacy in preclinical sepsis models.

Keywords Sepsis, Mitochondrial dysfunction, Immune response, Mitochondria-targeted therapy

Introduction

To advance understanding of sepsis and septic shock, the task force convened by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine introduced the "Sepsis-3" definition between 2014 and 2015 [1]. This update redefined sepsis as life-threatening organ dysfunction caused by a dysregulated inflammatory response to infection [1]. Sepsis contributes to 11 million deaths out of the 48.9 million reported cases, accounting for 19.7% of all global deaths in 2017 [2, 3]. The request for novel therapeutic targets in sepsis management assumes paramount importance.

Mitochondria are primary energy generators and participate in cellular processes, such as maintaining redox balance, buffering Ca^{2+}, and initiating apoptosis [4]. A mitochondrion contains two membranes, the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), forming the matrix and intermembrane space (IMS) [5]. The mitochondrial

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respiratory chain comprises five complexes localized within the IMM: complex I, II, III, IV, and V. Complexes I–IV receive electrons, creating an electrochemical gradient of proton across the IMM referred to as mitochondrial membrane potential (ΔΨm). This ΔΨm is utilized by the complex V (F_1F_0 ATP synthase) to drive the production of ATP [6].

Accumulative evidence suggests that mitochondria play crucial roles in the pathogenesis of sepsis [7, 8]. Both laboratory studies and clinical investigations have documented the increase in mitochondrial damage during sepsis [9, 10]. Mitochondrial dysfunction occurs when mitochondria, fail to function properly upon damage. Mitochondria are not only involved in energy production, but also play critical roles in regulating cell metabolism and several cellular processes. The effects of mitochondrial dysfunction are enormous, including energy deficiency and activation of multiple pathways that alter cell function and fate. In the context of sepsis, the damaged mitochondria actively partake in shaping the inflammatory response via various signaling pathways [11]. Advances in mitochondria-targeted therapeutics have demonstrated that improving mitochondrial quality can reduce sepsis-induced inflammation, organ failure, and consequent mortality [12–14]. Thus, regulating mitochondrial quality is emerging as a promising strategy for sepsis treatment.

This review seeks to explore the complex mechanisms underlying mitochondrial dysfunction in sepsis and its profound influence on immune dysregulation. Additionally, we highlight promising interventions targeted at mitochondria that have shown therapeutic effectiveness in preclinical sepsis models. By comprehensively understanding the interplay between mitochondrial integrity and immune responses, we strive to pave the way for the development of novel and effective therapeutic approaches in combating sepsis-associated morbidity and mortality.

Mitochondrial stress and damage during *sepsis*

Sepsis triggers significant stress to mitochondria within immune cells and various tissues, leading to structural distortions, potential loss, and a marked decrease in respiratory activity. This section explores the specifics of the mitochondrial damage and the underlying mechanisms.

Mitochondrial damage

Despite the limited amount, clinical data clearly indicate mitochondrial dysfunction during sepsis. For instance, Japiassu and colleagues demonstrated that peripheral blood mononuclear cells (PBMCs) from septic shock patients have impaired mitochondrial ATP synthase activity [15]. Garrabou et al. observed inhibition of respiratory complexes in the PBMCs from septic patients without shock or multi-organ failure (MOF), suggesting that mitochondrial impairment precede these symptoms [16]. The platelets from septic patients showed lower activity of mitochondrial nicotinamide adenine dinucleotide dehydrogenase (NADH), complex I, I/III, and IV [17]. In addition to blood cells, muscle tissue of septic patients has also been reported with mitochondrial dysfunction and ATP depletion [18, 19]. Severe cardiac impairment has been observed in the non-surviving septic patients, with histologic analysis of heart sections showing mitochondrial cristae derangement (Table 1) [20].

In animal models, cecal ligation and puncture (CLP), endotoxins/bacteria administration, and colon ascendens stent peritonitis (CASP) are commonly utilized to trigger sepsis [21]. Studies using these models support the clinical findings, highlighting the substantial impact of sepsis on mitochondrial homeostasis (Table 1). However, it is essential to acknowledge the presence of conflicting data showing unchanged or even increased mitochondrial activity in some cases, as previously discussed [22, 23]. Variables such as the nature of the septic insult, the severity of sepsis, timing of assessments, and methods of measurement may contribute to the discrepancies [24–26].

In addition, the common practice of using isolated cells or mitochondria from septic tissues for complex activity assays may not accurately reflect the in vivo mitochondrial status. This issue arises from the absence of circulating substances, such as cytokines, in vitro, which play pivotal roles in regulating mitochondrial respiration [16]. For instance, Boulos et al. demonstrated that serum from septic patients significantly reduced endothelial cell mitochondrial respiration compared to serum from healthy individuals, revealing the impact of circulating substances on mitochondrial function during sepsis [27].

Furthermore, normalization methods profoundly influence the evaluation of mitochondrial function. In a previous study, Fredriksson et al. measured the complex I activities in intercostal muscle mitochondria from septic patients and observed a 60% decrease when normalized to the dry weight of the muscle. However, no difference was found when normalization was conducted against citrate synthase activity. This was because the citrate synthase activity also declined during sepsis [28], emphasizing the importance of meticulous methodological consideration in such analyses.

Mechanisms of mitochondrial damage

Mitochondrial injury during sepsis is regulated by several factors, including reactive nitrogen species (RNS)/reactive oxygen species (ROS), mitophagy, mitochondrial

Table 1 Mitochondrial damage during sepsis

Species	Inducer	Tissue/cell	Time/stage	Mitochondrial assessments	Refs.
Human	N.A	PBMCs	With shock	Oxygen consumption reduced; ATP synthase activity declined	[15]
Human	N.A	PBMCs	Early stages without shock or MOF	CI, CIII, and CIV activity decreased; ΔΨm reduced; Oxygen consumption reduced; Circulating free mtDNA in plasma increased	[16]
Human	N.A	Platelet	Severe sepsis or septic shock	Mitochondrial NADH, CI, CI & III, and CIV, succinate dehydrogenase (SDH) activity decreased	[17]
Human	N.A	Leg and serratus anterior muscle	With MOF and requiring mechanical ventilation	Leg muscle: CI activity unchanged; CIV activity and ATP reduced; morphology unchanged Serratus anterior muscle: CI activity decreased; CIV activity, ATP, and morphology unchanged The observed changes probably because of reduced mitochondrial mass	[28]
Human	N.A	Vastus lateralis muscle	With MOF	Structure swollen or damaged; Respiratory protein subunits and transcripts reduced	[19]
Human	N.A	Heart	Post-mortem	Mitochondrial cristae impaired	[20]
Mouse	LPS	Heart	24 h	Mitochondrial number and volume reduced; Mitochondrial displayed internal vesicles, disrupted structure, and loss of cristae; expression of OXPHOS genes decreased	[29]
Mouse	LPS	Kidney	18 h	Mitochondrial swollen and cristae reduced; Cytochrome c oxidase protein level and activity decreased; Mitochondrial gene expression was suppressed	[30]
Mouse	LPS	Liver	0–48 h	mtDNA levels/integrity, complex I activity, and ATP level reduced; mtROS increased	[31]
Mouse	LPS	Leg muscle	28 days	Mitochondrial respiration reduced; CV activity was reduced; Mitochondrial fission increased;	[32]
Mouse	CLP	Brain	24 h	Oxidative phosphorylation uncoupled; ΔΨm dissipated; CIV activity reduced; CI-III activity unchanged	[33]
Mouse	CLP	Heart	12 h	mtDNA copy number reduced; mitochondrial respiration reduced; ATP level declined; mitochondrial biogenesis marker PGC1β reduced; mitochondrial Ca^{2+} uptake capacity declined	[34]
Mouse	CLP	Kidney	6–36 h	ROS increased; CI, CII & CIII activity and ATP decreased; CIV activity unchanged	[35]
Rat	LPS	Heart	0–24 h	Mitochondria displayed structural abnormalities; CI, II, and IV activities reduced; ATP synthesis decreased	[36]
Rat	LPS	Liver	2 h	Mitochondrial oxygen consumption reduced despite the total oxygen consumption unchanged; mitochondria became swollen and pale, with indistinct cristae and disrupted membranes; ATP/ADP ratio unchanged	[37]
Rat	*S. pneumoniae*	Heart	24 h	ROS increased; mtDNA damaged; mitochondrial membrane disrupted; CI, II-III, IV and V activity reduced	[38]
Cat	LPS	Liver	4 h	Respiratory activity was impaired; mitochondrial ultrastructural injured (swollen and membrane disruption)	[39]
Baboon	*E. coli*	Heart	72 h or after death	CI, and II activities reduced; CIII was less affected	[25]

Table 1 (continued)

MOF multi-organ failure. CI, II, III, IV, V: mitochondrial respiratory complex I, II, III, IV, V. ΔΨm: mitochondrial membrane potential

dynamics, and mitochondrial membrane permeabilization, etc. In this section, we will examine the regulatory roles of these factors in mitochondrial health amidst septic conditions.

RNS/ROS burst

One of the well-exploited triggers of mitochondrial damage is nitric oxide (·NO), an RNS that is produced by inducible nitric oxide synthase (iNOS) [40]. ·NO could be converted to other reactive nitrogen species such as nitrite (NO_2^-) and nitrogen dioxide ($\cdot NO_2$) (Fig. 1) [41]. Escames et al. have investigated the role of iNOS in skeletal muscle mitochondria using a CLP mouse model. They observed a reduction in mitochondrial respiratory complex activity accompanied by elevated expression of iNOS during sepsis. In contrast, the iNOS-deficient mice did not exhibit such mitochondrial impairment [40]. A similar observation has been observed in the liver mitochondria of LPS-treated mice [42]. In line with these, inhibition of mitochondrial respiration induced by septic serum could be mitigated by the nitric oxide synthase inhibitor [27]. These data collectively suggest that iNOS play a crucial role in mitochondrial damage during sepsis.

Sepsis also stimulates the formation of ROS. Superoxide radical ($O_2^{\cdot-}$) originates from nicotinamide adenine dinucleotide phosphate oxidases (NOXs) and mitochondria ETC [43]. $O_2^{\cdot-}$ is considered unstable and can be converted to other types of ROS (Fig. 1) [44]. On the other hand, declines in the antioxidative system happen during sepsis. For example, sirtuin proteins, which can protect cells from oxidative stress, have been found to decrease after septic insults [45, 46]. Oxidative stress occurs when ROS level overwhelms the antioxidant defense system in cells, causing damage to lipids, proteins, and nucleic acids [47].

Mechanistically, ·NO selectively binds to complex IV, where it competes with O_2 for the binuclear Cu_B/cytochrome a_3 center, resulting in a reversible inhibition of the complex IV [48]. While ·NO is relatively unreactive, its reaction with ROS gives rise to a series of more reactive derivatives [49]. Peroxynitrite (ONOO–) is one of the highly toxic derivatives (Fig. 1). Peroxynitrite can cause impairments to mitochondria via oxidation, irreversibly inhibiting mitochondrial complex I, CII, CIV, ATP synthase, and several critical enzymes. Consequently, the RNS/ROS exert a profound inhibitory effect

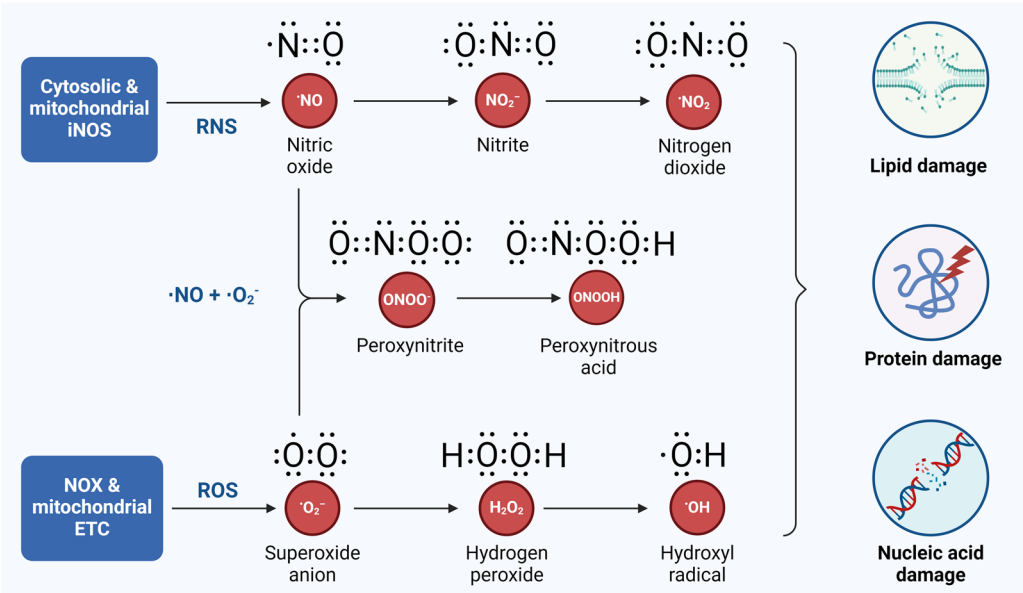

Fig. 1 Pathways of RNS and ROS production in sepsis. Excessive nitric oxide is generated by both cytosolic and mitochondrial iNOS during sepsis. The nitric oxide can be converted to other reactive nitrogen species (RNS), such as nitrite and nitrogen dioxide. On the other hand, excessive reactive oxygen species (ROS) are produced by NOXs and mitochondrial electron transport chain (ETC). Nitric oxide and superoxide react to form additional derivatives, notably the highly toxic peroxynitrite. The accumulation of these reactive species inflicts damage to cellular components, including lipids, proteins, and nucleic acids, thereby compromising mitochondrial respiration and integrity

on mitochondrial respiration and contribute to mitochondrial damage during sepsis [50].

Mitophagy

Mitophagy is a specialized form of autophagy that selectively degrades damaged mitochondria (Fig. 2a) [51]. Impaired mitophagy prevents mitochondrial turnover, leading to the accumulation of dysfunctional mitochondria [52]. Growing evidence shows that inhibition of mitophagy occurs in immune cells during the inflammatory response. Yu et al. found that Caspase-1 in macrophages cleaves Parkin to inhibit mitophagy upon inflammasome activation [53]. Similarly, Patoli et al. demonstrated mitophagy inhibition in the LPS/IFN-γ-treated macrophage cells, CLP mouse model, and septic patients, revealing caspases 1/11 dependent PINK1 degradation in the early stage of inflammation [54]. Additionally, inflammation-induced pro-IL-1α can interact with cardiolipin, preventing it from serving as a mitophagy receptor [55]. AMP-activated protein kinase (AMPK) is a regulator of autophagy, which positively regulates mitochondrial clearance by activating unc-51 like autophagy activating kinase 1 (ULK1) [56]. TLR4 signaling has been reported to prevent the activation of AMPK in neutrophil and macrophage [57]. Thus, lack of AMPK activation could be another reason for the accumulation of damaged mitochondria in sepsis.

Interestingly, activation of mitophagy also occurs during immune response. Ip and colleagues showed that interleukin 10 (IL-10) promotes mitophagy by inhibiting the mammalian target of rapamycin (mTOR) in macrophages [58]. Moreover, nuclear factor κB (NF-κB) facilitates mitophagy by inducing the expression of autophagic receptor p62. This NF-κB-p62-mitophagy pathway exists as a self-limiting mechanism to prevent excessive inflammation and maintain homeostasis [59]. Sestrin 2 (SESN2) also play a role in the p62-dependent mitophagy [60]. Extended LPS stimulation upregulates

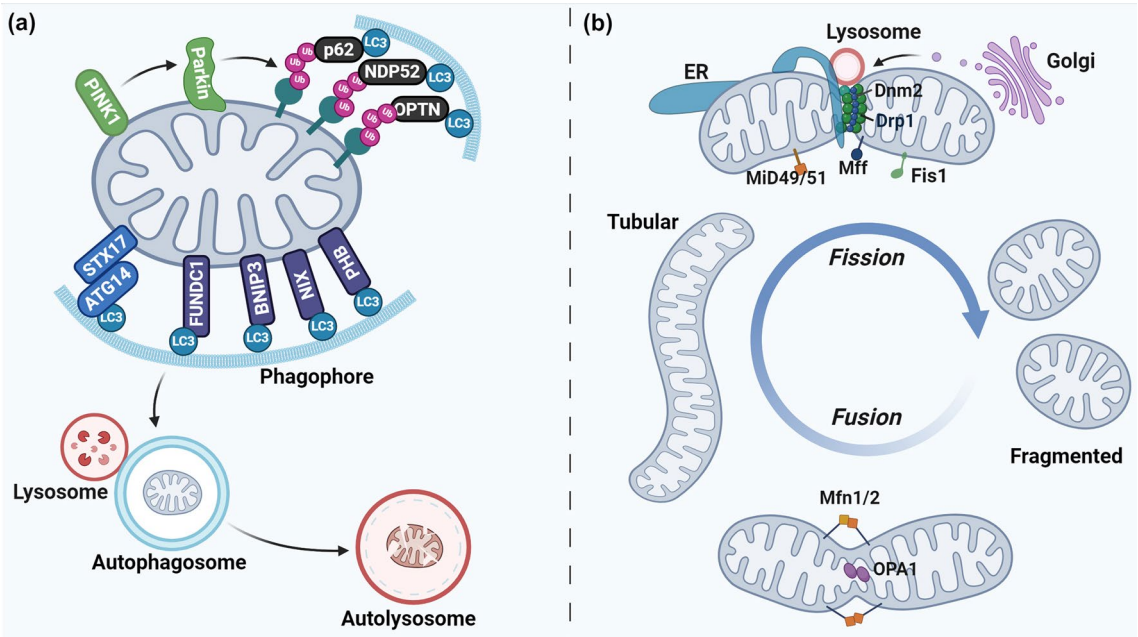

Fig. 2 Pathways of mitophagy and mitochondrial dynamics. **a** The most extensively studied mitophagy pathway involves PTEN-induced kinase 1 (PINK1) and E3 ubiquitin ligase Parkin. Upon ΔΨm loss, PINK1 is stabilized on the OMM, where it recruits and activates Parkin. Parkin subsequently ubiquitinates mitochondrial surface proteins, signaling the autophagosome to encapsulate the dysfunctional mitochondrion. Adaptor proteins including p62, Optineurin (OPTN), calcium binding and coiled-coil domain-containing protein 2 (NDP52), tax1-binding protein 1 (TAX1BP1), and next to BRCA1 gene 1 protein (NBR1) play a role in linking the ubiquitin chains to microtubule-associated protein 1 light chain 3 (LC3) on phagophores. On the other hand, some mitochondrial receptor proteins (or lipids) such as FUN14 domain containing 1 (FUNDC1), prohibitin (PHB), BCL2 interacting protein3 (BNIP3), Nip3-like protein X (NIX), cardiolipin, and syntaxin 17 (STX17) can recruit phagophore membranes independent of ubiquitin. The autophagosome finally fuses with a lysosome for the degradation and recycling of mitochondria. **b** Mitochondrial dynamics is regulated by several dynamin-related GTPases, including Mfn1/2, OPA1, Drp1, Fis1, MiD49/51, and Mff. Mfn1/2 facilitate the fusion of the OMM, while OPA1 is responsible for the fusion of the IMM. The fission process is initiated by the endoplasmic reticulum (ER)-mediated pre-constriction of mitochondria. Drp1 is recruited to the pre-constricted sites by receptors (Mff, Fis1, and MiD49/51). After binding to OMM, Drp1 oligomerizes into ring-shaped filaments. Hydrolysis of GTP by Drp1 results in constriction and closure of the ring. Dnm2 is finally recruited to the constricting site to complete the fission. In addition to the ER, lysosome and Golgi-derived vesicles have also been reported to regulate mitochondrial fission

the protein level of SESN2, which interacts with p62 to facilitate its aggregation on mitochondria. Besides, SESN2 activates the autophagic machinery by raising the ULK1 protein level [60]. Overall, the accumulation of damaged mitochondria is likely to result from both forward and reverse regulation of mitophagy. How these different mitophagic pathways are spatiotemporally coordinated in sepsis is still elusive. Given the critical role of damaged mitochondria in promoting immune response (which will be discussed in the later section), it is plausible that early-stage inhibition of mitophagy promotes the accumulation of dysfunctional mitochondria and benefit bacterial defense [54], while late-stage activation of mitophagy represents a cellular attempt to mitigate inflammation and restore host homeostasis [59].

Unlike in immune cells, the overall mitophagy in various organs is enhanced during sepsis. The heart samples from LPS-challenged mice have shown decreased mitochondrial number and volume, suggesting autophagic removal of mitochondria [29, 61]. Immunoblot analysis of kidney tissue from LPS or CLP-treated mice has shown a decrease in mitochondrial protein levels (TOM20 and TIM23) compared with control mice, providing substantial evidence that mitophagy is induced during the sepsis-caused acute kidney injury [62]. It was also demonstrated that the mitophagy is mainly mediated by the PINK1/Parkin/OPTN pathway [62]. Reductions of mitochondrial mass were also reported in the liver of CLP or LPS-treated septic mice [63]. These studies collectively suggest that mitophagy is enhanced in various organs during sepsis.

Mitochondrial dynamics

Mitochondria constantly undergo fusion and fission processes (Fig. 2b). Fusion forms interconnected mitochondrial networks, promoting content exchange, which is essential for the integrity of the mitochondrial genome and proteome. Conversely, fission fragments mitochondria, aiding in the elimination of dysfunctional parts [64, 65]. Dysregulation of mitochondrial dynamics is a crucial mechanism that induces mitochondrial stress [66].

During sepsis, excessive mitochondrial fragmentation happens in various tissues, revealing the change in mitochondrial dynamics [62, 67, 68]. To exploit the influence of mitochondrial fission in sepsis, Gonzalez et al. treated rats with the Drp1 inhibitor mdivi-1 before CLP administration. This treatment restored mitochondrial shape and prevented the reduction of complex activities and apoptosis in hepatocytes [68]. Similar beneficial effects of mdivi-1 have been confirmed in other studies [13, 69, 70]. Pharmacological administration of alternative fission inhibitors, such as P110 (inhibit Drp1/Fis1 interaction), also showed protection to mitochondria under septic stress [71, 72]. These findings demonstrate that excessive fission significantly contributes to the impairment of mitochondria during sepsis. Inhibition of this process, therefore, is an effective method to restore mitochondrial function.

Mitochondrial membrane permeabilization

Mitochondrial membrane pores cause mitochondrial swelling, content loss, and $\Delta\Psi m$ dissipation [73]. Three principal mechanisms involved in pore formation during sepsis are mitochondrial outer membrane permeabilization (MOMP), mitochondrial permeability transition (MPT), and more recently characterized gasdermins (GSDMs)-mediated mitochondrial membrane opening (Fig. 3).

MOMP is mediated by Bcl-2 family proteins Bax and Bak, which open the OMM in response to apoptotic signals. MOMP leads to mitochondrial damage and release of intermembrane space molecules like cytochrome C [74]. Large Bax/Bak pores also allow the IMM to protrude out of mitochondria, releasing matrix contents [75, 76]. Cytokines such as INF-γ and TNF-α could be recognized by the cell membrane death receptors, thereby activating caspase-8 during sepsis [77]. The activated caspase-8 cleaves Bid, generating a truncated form of Bid (tBid), which translocates to mitochondria and activates Bax/Bak to induce MOMP and cell death [78–80]. Chuang et al. have observed increased tBid in mitochondrial fractions of various tissues from the CLP-treated mouse, while Bid deficiency significantly reduced the downstream cell death [81]. In addition to caspase-8, caspase-1 has also been reported to cleave Bid and induce MOMP during the inflammatory response of macrophage [82].

The occurrence of MPT has been described in several septic models [83–86]. Pharmacological inhibition of MPT by cyclosporin A (CsA) can significantly attenuate mtDNA release and mitochondrial dysfunction in these models, suggesting MPT's crucial role in sepsis-induced mitochondrial damage [83–85]. Although the exact molecular composition and mechanism of MPT remains a topic of ongoing research, key components are believed to include the F_1F_O (F)-ATP synthase, adenine nucleotide translocator (ANT), cyclophilin D (Cyp-D), and voltage-dependent anion channel (VDAC) [87]. These components assemble into a supramolecular pore (MPTP) at the interface of the IMM and OMM [88]. Elevated ROS levels can induce MPTP opening through oxidative modifications of MPT constituents or other mitochondrial proteins [89, 90].

GSDMs are key players in immune response, particularly in mediating pyroptosis. During inflammation, GSDMs are cleaved by caspases to release their active

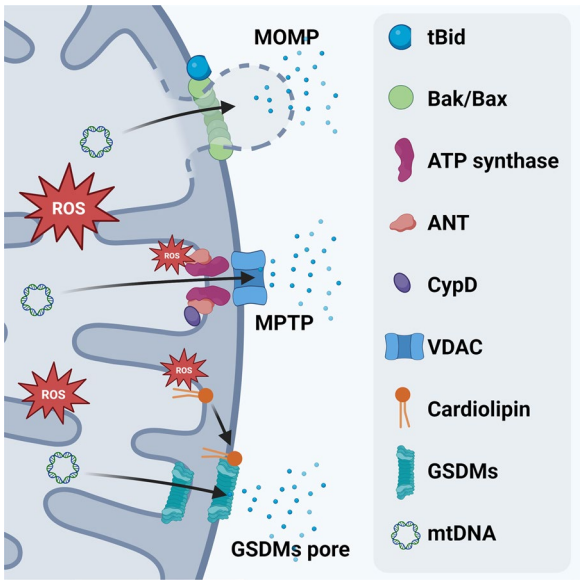

Fig. 3 Mechanisms of mitochondrial membrane permeabilization in sepsis. Three principal mechanisms are implicated in sepsis-related mitochondrial membrane pore formation. Mitochondrial outer membrane permeabilization (MOMP) is mediated by Bcl-2 family proteins Bax/Bak and regulated tBid. Large BAK/BAX pores allow the protrusion of IMM into the cytosol, therefore, enabling the escape of mitochondrial matrix contents. Mitochondrial permeability transition pore (MPTP) represents another type of mitochondrial pore in sepsis. Despite the opening mechanism of MPTP is still elusive, mitochondrial components such as F_1F_O (F)-ATP synthase, ANT, and Cyp-D have been confirmed to play pivotal roles in this process. Gasdermins (GSDMs) are well-known to form pores on plasma membrane during immune response. Recent advances have demonstrated that GSDMs target both the inner and outer mitochondrial membranes via their strong binding preference to cardiolipin. ROS promote the externalization of cardiolipin from IMM to OMM, thus, positively regulate GSDMs-mediate pore formation. Overall, mitochondrial membrane permeabilization leads to mitochondrial swelling, content loss, and dissipation of membrane potential during sepsis

N-terminal fragments (GSDMs-N). GSDMs-N translocate to the plasma membrane, forming pores and disrupting the membrane [91]. Recent findings indicate that GSDMs also target mitochondrial membranes, representing a new pathway of mitochondrial permeabilization [92–97]. Time-lapse imaging analysis revealed that mitochondrial damage occurs much earlier than the opening of cell membrane, suggesting that GSDMs-N permeabilizes the mitochondria before cell membrane [92, 93]. This phenomenon has been attributed to the strong binding preference of GSDMs-N to mitochondrial cardiolipin [92]. Of note, ROS promote the externalization of cardiolipin from IMM to OMM, explaining the accumulation of GSDMD-N on OMM, as cardiolipin predominantly localizes in the IMM under normal conditions [95]. Overall, GSDM-mediated pore formation represents a novel pathway of mitochondrial permeabilization during immune response.

Damaged mitochondria are potent triggers of immune response and metabolic reprogramming

The innate immune response plays a key role in the pathophysiology of sepsis. Upon activation, pattern recognition receptors (PRRs) initiate signaling cascades, leading to the nuclear translocation of NF-κB, interferon regulatory factor (IRF), and other transcription factors. These transcription factors initiate the production of pro-inflammatory cytokines, chemokines, type I interferons (IFNs), etc. [98]. In the past few decades, damaged mitochondria have been widely demonstrated as a crucial regulator of innate immunity, particularly through the NLRP3, TLR9, and cGAS pathways. Thus, mitochondria damage is not simply a passive outcome under stress conditions, but actively contributes to the inflammatory response that is essential for the defense of pathogens. However, in the context of sepsis, excessive or persistent inflammation can cause a fatal inflammatory imbalance in the body, which ultimately leads to tissue and organ damage [99]. In this section, we will highlight the roles of mitochondria in regulating inflammatory pathways.

NLRP3 inflammasome pathway

NLRP3 inflammasome activation

The NLRP3 inflammasome activates pro-caspase-1, which cleaves pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18) to promote their maturation [100]. Current studies, mainly in monocytes/macrophages, have revealed several regulatory roles of mitochondria in NLRP3 inflammasome activation. Mitochondrial ROS (mtROS) have been demonstrated as essential molecules for NLRP3 inflammasome activation. In sepsis models, inhibition of mtROS reduces the NLRP3 inflammasome-mediated cytokine production [101–103]. Several studies have provided insights into the mechanisms by which ROS modulate NLRP3 activation. In 2010, Zhou et al. identified thioredoxin (TRX)-interacting protein (TXNIP) as a binding partner of NLRP3. Under basal conditions, TXNIP binds to TRX, being unavailable to NLRP3. ROS promote NLRP3 activation by triggering the dissociation of TXNIP from TRX [104]. In another study, mtROS were confirmed to facilitate NLRP3 inflammasome activation through promoting its deubiquitination [105]. Interestingly, Bauernfeind and colleagues reported that ROS increase the NLRP3 expression instead of activating it,

suggesting a translational regulation of NLRP3 by ROS [106].

mtDNA also regulates NLRP3 inflammasome activation. Nakahira et al. demonstrated that preventing MPT-mediated mtDNA release significantly reduces IL-1β secretion in macrophages after LPS + ATP challenge [83]. Interestingly, NLRP3 inflammasome is preferentially activated by oxidized mtDNA (ox-mtDNA), rather than normal mtDNA [107]. Zhong et al. found that TLR4 signalling promotes de novo mtDNA synthesis to sustain the generation of ox-mtDNA, since the newly synthesized mtDNA is not packaged and is highly susceptible to oxidation [108]. Before being released into cytosol, the ox-mtDNA undergoes a cleavage process to become 500–650 bp fragments. Xian et al. recently identified the flap structure-specific endonuclease 1 (FEN1) as the key mediator of this process [109]. AIM2 inflammasome can also be activated by the mtDNA. Unlike NLPR3 inflammasome, AIM2 inflammasome is activated by normal DNA to ox-mtDNA [107, 108].

Spatial association between mitochondria and NLRP3

The spatial association of NLRP3 inflammasome with organelles is critical for its activation. Early studies posited mitochondria or mitochondria-associated membrane (MAM) as the docking sites of NLRP3, while more recent publications have implicated trans-Golgi network (TGN) and microtubule-organizing center (MTOC) [110–114].

Zhou et al. reported that inflammatory stimuli trigger NLRP3 to co-localize with mitochondria and MAM in 2010 [112]. This spatial vicinity may facilitate the sensing of mitochondria-derived inflammatory signals [112, 115]. Microtubules also play a role in the mitochondria-NLRP3 association. Mechanistically, mitochondrial dysfunction during inflammation reduces NAD^+ (oxidized form of nicotinamide adenine dinucleotide) generation, which in turn inhibits NAD^+-dependent α-tubulin deacetylase sirtuin 2, leading to an increase in α-tubulin acetylation. The acetylated α-tubulin subsequently promoted dynein-dependent transport of mitochondria to NLRP3 [116]. Inflammatory stimuli also trigger the transport of NLRP3 towards mitochondria, which is orchestrated by microtubule-affinity regulating kinase 4 (MARK4). Depletion of MARK4 impairs NLRP3 spatial arrangement and inflammasome activation [111].

Mitochondrial antiviral-signaling protein (MAVS) and cardiolipin mediate the anchorage of NLRP3 on mitochondria [117–121]. MAVS lacking mitochondrial targeting domain cannot recruit NLRP3 or induce NLRP3 oligomerization, suggesting its mitochondrial localization is essential for NLRP3 inflammasome activation [120]. Given the well-established role of MAVS in recognizing virus RNA, it is plausible that microbial RNA plays a role in promoting the MAVS-dependent recruitment of NLRP3 during bacterial infection [121, 122]. In line with this, virus or *Escherichia coli*-induced activation of NLRP3 inflammasome was confirmed to greatly depend on MAVS [121], whereas LPS + ATP or LPS + nigericin (without microbial RNA) induced NLRP3 inflammasome activation is only partially affected by MAVS [117, 120, 121]. Cardiolipin also interacts with NLRP3 and contributes to the inflammasome activation [118]. A recent study suggested that cardiolipin recruits both NLRP3 and caspase-1, serving as a platform for inflammasome assembly [119].

Several recent publications have highlighted the involvement of Golgi apparatus and MTOC in NLRP3 inflammasome activation [113, 114, 123]. It is likely that NLRP3 protein is first transported to meet mitochondria along the microtubules, after which NLRP3 redistributes to the adjacent Golgi apparatus [115, 124]. Then, the NLRP3 is transported to the MTOC and reorganized into a single speck structure. At the MTOC, NLRP3 engages with NEK7, a centrosome-localized kinase that is essential for NLRP3 inflammasome activation (Fig. 4) [111, 114, 123, 125, 126].

cGAS-STING pathway activation

The cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway is another mitochondria-regulated inflammatory pathway. cGAS detects cytosolic double-stranded DNA and initiates an innate immune response [127] (Fig. 4). Both normal and oxidized mtDNA can be recognized by cGAS [128], but ox-mtDNA is more resistant to degradation by the cytosolic nuclease 3' repair exonuclease 1, increasing its likelihood of interaction with cGAS [129].

In the CLP mouse model, Huang et al. have demonstrated that mtDNA can be released via the GSDMD pore to activate cGAS-STING pathway [94]. This pathway not only enhances the inflammatory response but also suppresses lung endothelial cell proliferation, which compromises the recovery capacity of host. Notably, the deletion of *cGas* gene provided mice with substantial protection from lung injury 72 h post-CLP, suggesting that cGAS-STING pathway is crucial in septic lung inflammation [94].

Studies have shown that circulating cell-free mtDNA levels are elevated in septic patients and animal models, correlating with poor prognosis [130–133]. Like cytosolic mtDNA, circulating mtDNA activates the cGAS-STING pathway and promotes inflammation during sepsis [133]. In CLP mice, the mtDNA-cGAS-STING signal promotes intestinal inflammation and gut barrier dysfunction, which could be significantly attenuated by removing

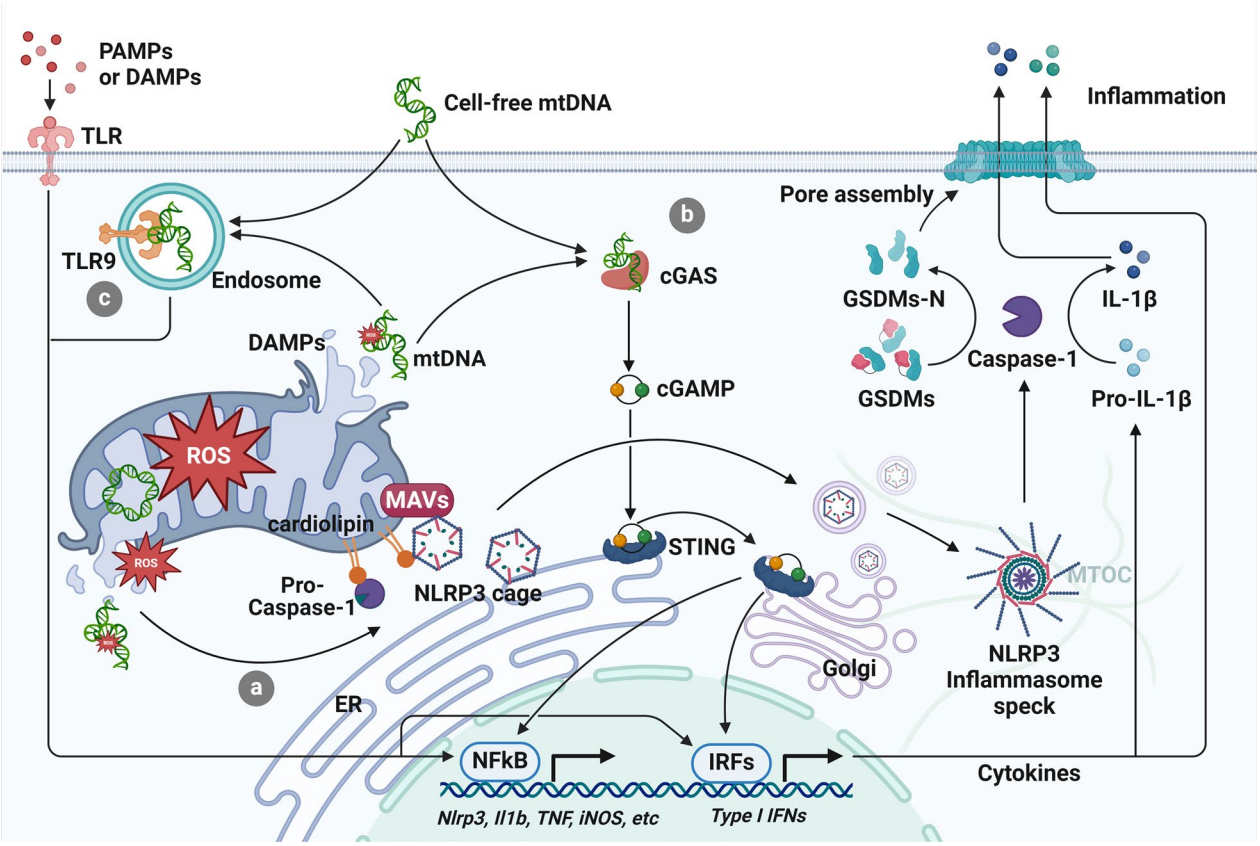

Fig. 4 Mitochondria-regulated inflammatory pathways in sepsis. Pattern recognition receptors (PRRs) of immune cells recognize pathogen-associated molecular patterns (PAMPs) from microbes or damage-associated molecular patterns (DAMPs) released by damaged host cells. **a** Mitochondria orchestrate the activation of the NLRP3 inflammasome. mtROS and ox-mtDNA promote the NLRP3 inflammasome activation after their release from the damaged mitochondria. Additionally, mitochondrial antiviral-signaling protein (MAVS) and cardiolipin mediate the spatial association between mitochondria and NLRP3, which may facilitate a rapid and efficient sensing of the inflammatory signals from the damaged mitochondria by NLRP3. Early studies posited mitochondria or mitochondria-associated membrane (MAM) as the docking sites of NLRP3, while more recent publications have indicated the involvement of Golgi and microtubule-organizing center (MTOC). It could be plausible that NLRP3 proteins are first transported to meet mitochondria, after which NLRP3 redistributes to the adjacent Golgi apparatus as oligomeric cages. Then, the NLRP3 cages are transported to MTOC and reorganized into a single inflammasome speck. Activated NLRP3 inflammasome mediates the activation of pro-caspase-1, which proteolytically processes GSDMs and pro-inflammatory cytokines. The matured cytokines are released from the GSDMs pores to transmit inflammatory signals. **b** Mitochondria regulate the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway. cGAS is activated upon mtDNA binding, leading to the synthesis of cyclic GMP-AMP (cGAMP). cGAMP then induces a conformational change in STING, leading to its activation at ER. Activated STING translocates to Golgi, where it activates transcription factors interferon regulatory factor 3 (IRF3) and nuclear factor κB (NF-κB) to initiate the production of type I interferons and other pro-inflammatory cytokines that are required for effective immune response against pathogens. **c** Mitochondria regulate the TLR9 pathway. mtDNA shares similarities with bacterial DNA, thus can be recognized by TLR9. As with other TLRs and cGAS-STING axis, TLR9 pathway activates IRF3 and NF-κB to regulate the inflammatory response

circulating mtDNA with DNase I [134]. Mechanistically, host nuclear DNA, mtDNA and bacterial DNA can be recognized by cGAS, while to what extent mtDNA contributes to the cGAS-STING pathway activation awaits investigation [135, 136].

TLR9 pathway activation

TLR9 is initially known for sensing unmethylated CpG DNA motifs (consisting of a central cytosine-guanine dinucleotide plus flanking regions) from bacterial and viral DNA during innate immune response [137, 138]. However, a subsequent study suggests that TLR9 also recognizes endogenous mtDNA, which shares similarities with bacterial DNA [139]. This interaction stands for another inflammatory pathway regulated by mitochondria in sepsis (Fig. 4).

Experimental models have shown that intravenous administration of mitochondrial debris can elicit an immune response comparable to that of CLP treatment. However, *Tlr9* knockout (KO) or DNase pretreatment of

the mitochondrial debris greatly attenuates the inflammatory response, suggesting the crucial role of the mtDNA-TLR9 axis in sepsis [140]. In line with this, TLR9 inhibitor OND-I suppresses caspase 1 activation and IL−1β production in LPS-challenged cardiomyocytes [38]. Moreover, *Tlr9* KO reduced renal dysfunction and splenic apoptosis after CLP treatment, and increased survival at 96 h [141]. Interestingly, Plitas and colleagues found that *Tlr9* KO mice exhibited better bacterial clearance and greater survival than wide type (WT) mice after CLP treatment. The protective effects were associated with increased recruitment of granulocytes to the peritoneum by dendritic cells (DCs) [142]. These findings suggest that TLR9 might have a major role in the immunopathogenesis of polymicrobial sepsis compared to other TLRs [142].

Metabolic reprogramming

During sepsis, a widespread alteration in the metabolic pattern occurs in virtually all cell types, leading to a shift from oxidative phosphorylation (OXPHOS) to glycolysis—a phenomenon known as "metabolic reprogramming" [143]. The metabolic reprogramming is driven by the downregulation of OXPHOS due to mitochondrial dysfunction and the upregulation of glycolysis through the enhancement of glycolytic pathways [144]. This shift in metabolism profoundly affects immune response and organ function in sepsis.

In the immune context, glycolysis, albeit less efficient than OXPHOS, allows rapid generation of ATP and synthesis of metabolic intermediates necessary for immune cell activation and proliferation [145]. Glycolytic inhibitors, such as 2-deoxyglucose (2-DG), have been shown to reduce systemic inflammation in sepsis, indicating their potential in therapeutic interventions [146, 147]. The metabolic reprogramming is also implicated in the development MOF. An early histopathologic study of patients dying of sepsis has revealed that the actual cell death in most organs is minimal, despite severe clinical signs of MOF [148]. This observation indicates that the organ failure is functional rather than structural [149]. Given that mitochondrial dysfunction results in less efficient ATP production, cells in affected organs face an energy crisis during sepsis. Consequently, metabolic reprogramming and the resultant bioenergetic failure are recognized as critical contributors to MOF in sepsis [150]. A key question regarding MOF in sepsis is whether it represents an adaptive or maladaptive event. Singer et al. have suggested that sepsis-induced MOF might be an adaptation by the host to increase the chances of cell survival against the infection. This response mirrors a state of "hibernation" in which non-essential functions are downregulated [9, 149].

Mitochondria-based therapeutic interventions

Effective treatments are crucial for aiding critically ill patients with sepsis. Previous research has shown that sepsis survivors responded early to the illness with induction of mitochondrial biogenesis and antioxidant defense, indicating the potential of maintaining mitochondrial homeostasis for sepsis therapy [19].

Antioxidants

Given the roles of ROS in triggering mitochondrial damage and inflammation, antioxidants have been extensively studied as therapeutic agents against sepsis. Mitochondria-targeted antioxidants have shown better effects on reducing inflammation compared to the untargeted equivalents [101, 151, 152]. The most frequently used mitochondria-specific antioxidants include MitoQ, MitoVitE, and MitoTempol (Fig. 5) [153].

MitoQ

MitoQ is synthesized by conjugating ubiquinone with the lipophilic cation decyl-triphenylphosphonium (TPP^+). Although it has not received approval from the U.S. Food and Drug Administration (FDA), MitoQ has been the subject of several clinical trials aiming to explore its potential benefits for treating oxidative pathologies [154]. Lowes et al. demonstrated that MitoQ protects mitochondria during sepsis, and suppresses pro-inflammatory cytokine release, leading to reduced acute liver and renal dysfunction [102]. The beneficial effects have also been confirmed in other organs, including the lung, intestinal barrier, skeletal muscle, and heart, leading to the increased survival rate of septic animals [12, 155–157]. Notably, MitoQ treatment 6 h after sepsis induction yielded comparable outcomes in comparison with immediate treatment in the diaphragm muscle. This property makes MitoQ a good candidate for clinical application, considering the typical delay between sepsis onset and treatment initiation [157].

MitoVitE

MitoVitE is a modified form of vitamin E, attached to the TPP^+ [158]. Zang et al. examined its effects on cardiac dysfunction in a rat pneumonia-related sepsis model, and confirmed that a single dose of MitoVitE protected cardiac mitochondria, suppressed cytokine burst, and neutrophil infiltration in the myocardium, ultimately improving the cardiac function [101]. Another study using LPS/peptidoglycan (PepG)-induced sepsis rat model revealed that MitoVitE offers similar protection

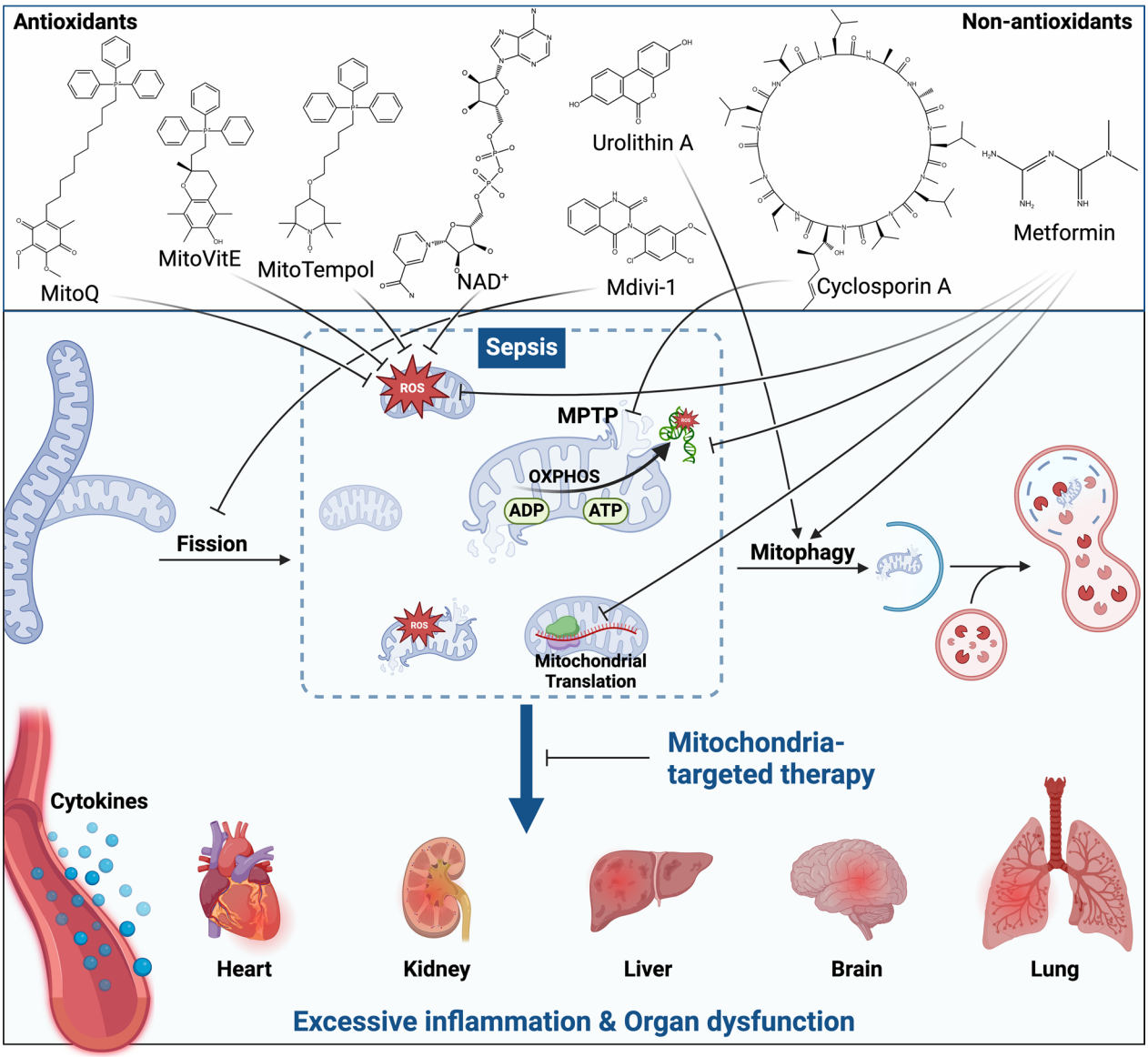

Fig. 5 Mitochondria-based therapeutic interventions. Mitochondria-targeted antioxidants such as MitoQ, MitoVitE, and MitoTempol are selectively targeted to mitochondria by conjugating to a lipophilic cation decyl-triphenylphosphonium (TPP^+). The positive charge of cation enables the molecules to accumulate in mitochondrial matrix, therefore, specifically quench the mitochondrial ROS. Non-antioxidants Urolithin A, Mdivi-1, and Cyclosporin A improve mitochondrial quality by promoting mitophagy, inhibiting mitochondrial fission, and blocking MPTP, respectively. Metformin plays multiple roles on mitochondria, including enhancing mitophagy, reducing mtROS, preventing ox-mtDNA production, and inhibiting mitochondrial protein translation. These compounds target different aspects of mitochondria and exhibit great potential in reducing sepsis-induced mitochondrial damage, excessive inflammation, and organ dysfunction

as MitoQ in improving mitochondrial health, mitigating inflammation, and reducing organ dysfunction [159].

MitoTempol

MitoTempol, constructed by combining the piperidine nitroxide (Tempol) with TPP^+, is another mitochondria-targeted antioxidant [160]. In a rat model of fecal peritonitis, MitoTempol administration reduced IL-1β level, renal oxidative stress, and improved renal function [161]. Interestingly, while this study showed no beneficial effect on the core body temperature and survival rate [161], another investigation revealed that even a 6 h delayed MitoTempol therapy significantly improved core body temperature and increased the survival rate from 40 to 83% in CLP mice [35]. These contradictory results may be related to MitoTempol dosage. Insufficient dosing may

fail to provide benefits, whereas excessive dosing may lead to over-accumulation of this cationic agent, resulting in mitochondrial damage [35]. Thus, fine-tuning the dosage is essential to minimize side effects and maximize therapeutic benefits.

NAD^+

NAD^+ is known for its functions in redox metabolism, immune response, aging, and DNA repair [162]. NAD^+ shortage occurs during sepsis, prompting the exploration of NAD^+ supplementation as a potential therapeutic strategy [163, 164]. NAD^+ precursors, such as nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR), are emerging as novel candidates for sepsis treatment. These precursors, naturally present in food and widely used as health supplements, have shown potential in preclinical studies by mitigating mitochondrial dysfunction, oxidative stress, inflammatory response, and multiorgan injury associated with sepsis [164–166]. The precise regulatory mechanisms of NAD^+ in sepsis remain incompletely understood. As a critical co-enzyme, NAD^+ plays a role in alleviating oxidative stress, in part through the activation of sirtuins, like Sirt3, a mitochondria-localized sirtuin [164, 165].

Non-antioxidants

Several non-antioxidant agents targeting mitophagy, mitochondrial dynamics, mitochondrial permeabilization, and other pathways have been reported to mitigate sepsis (Fig. 5).

Urolithin A Urolithin A (UA) is a natural anti-aging compound known for inducing mitophagy [167]. It has attracted significant attention for the role in regulating inflammation [168, 169]. Two clinical trials in elderly individuals have shown that UA is safe, bioavailable, and well-tolerated [170, 171].

UA has been reported to sustain mitochondrial health in cardiomyocytes challenged with LPS in vitro [172]. In mice, UA administration alleviated the LPS-induced cardiac depression [173]. Interestingly, this protection was diminished upon FUNDC1 knockout, indicating UA activates mitophagy in a FUNDC1-dependent manner [173]. UA pre-administration was also found to alleviate pulmonary injury upon LPS challenge, and improve the survival rate [174]. Overall, while research on UA for sepsis treatment is still nascent, the existing evidence suggests significant therapeutic potential. Future research using more appropriate sepsis models would be recommended, as LPS treatment does not recapitulate the complex pathophysiological consequence of human sepsis [175, 176].

Mdivi-1

Mdivi-1 was first identified as an inhibitor of mitochondrial fission via chemical screening in 2008, [177]. Thereafter, numerous articles have been published on Mdivi-1, confirming its potency in inhibiting mitochondrial fission, improving mitochondrial health, and protecting cells from stress under various circumstances [178]. The wide application of Mdivi-1 promotes the development of novel therapeutic strategies for mitochondria-related diseases, including sepsis.

Mdivi-1 was shown to protect liver and brain function in the CLP mice model [179, 180]. Moreover, Zhu et al. showed that Mdivi-1 significantly restored the function of multiple organs in CLP-treated rats, and extended the average survival time from 8.83 h to 60.3 h. In this study, Mdivi-1 was administered 12 h after sepsis, which mirrors a clinically relevant scenario [13]. Other fission inhibitors, like P100 and irisin, have also been reported to mitigate organ injury and reduce mortality after sepsis [71, 72, 181].

Cyclosporin A

CsA is an FDA approved compound that has been utilized as an anti-inflammatory drug to treat ocular surface diseases [182]. Cyclosporin A has been widely used as an immunosuppressant to prevent immune responses against transplanted organs in clinic [183]. CsA potentially inhibits immune response via two pathways. First, CsA inhibits MPTP by interacting with Cyp-D, thus, reducing DAMPs release from mitochondria [184]. Second, CsA forms a complex with cyclophilin A to inhibit calcineurin. This inhibition thereafter impairs the nuclear translocation of nuclear factor of activated T cells (NFAT) and NFκB in immune cells, leading to reduced production of iNOS, inflammatory cytokines and prostaglandins [185].

Over the past two decades, CsA has been reported to attenuate mtDNA release and mitochondrial damage in various septic models [83–85, 186]. These studies confirmed the protective effects of CsA on sepsis-induced organ dysfunction and mortality [83–85, 186]. CsA and NIM811 (a cyclophilin non-binding derivate of CsA that inhibits MPTP) rather than tacrolimus (a potent immunosuppressive compound which does not inhibit MPTP) provided protection against septic insult, suggesting that the beneficial effects of CsA were predominantly related to the inhibition of MPTP [84, 187]. However, Joshi et al. reported that tacrolimus provided similar cardiac protection as CsA upon LPS treatment [188]. This discrepancy maybe due to the severity of mitochondrial injury; CsA's MPTP inhibitory function becomes critical only when mitochondrial damage is severe.

Metformin

Metformin has been widely used to treat type 2 diabetes, whose clinical experience and trial data have raised almost no safety concerns [189, 190]. Several studies have highlighted the capacity of metformin in combating sepsis. For instance, Liu et al. demonstrated that metformin prevents excessive inflammation and the development of immunosuppression, increasing bacterial clearance in the lungs of septic mice [191]. Metformin also preserves brain, lung, liver, and colon barrier function by suppressing sepsis-induced inflammatory responses in animal models [192–194]. In human patients, several retrospective studies have been performed to evaluate the effect of metformin on sepsis. However, some of these studies revealed that metformin users (mainly diabetic patients) had lower in-hospital mortality than nonusers [195–197], while others showed that pre-admission of metformin did not change the mortality in septic patients [198, 199]. Two meta-analyses on these published cohort data were, therefore, performed to confirm the contribution of metformin in the mortality in septic adult patients. The results supported the positive effect of metformin in lowering the mortality of sepsis [200, 201]. Recently, three clinical trials (NCT05979038, NCT06181422, NCT05900284) evaluating the efficiency and safety of metformin in sepsis patients are ongoing, which will improve our understanding about the clinical feasibility of metformin in sepsis therapy.

The pharmacological mechanisms of metformin are multifaceted. Metformin regulates inflammation through both AMPK-dependent and independent pathways [202]. Mechanistically, metformin activates AMPK and suppresses the nutrient sensor mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), which promotes autophagy. Autophagic elimination of damaged mitochondria subsequently limits NLRP3 inflammasome activation [203, 204]. AMPK also phosphorylate the PGC-1α to promote mitochondrial biogenesis [205]; or regulate transcription factors to reduce ROS and cytokine production [206, 207]. The activation of AMPK by metformin appears to be dose-dependent: Low-dose metformin drives AMPK activation through the lysosomal pathway, while high-dose metformin takes effect by inhibiting the complex I of respiratory chain, resulting in ATP shortage [208]. Xian et al. have revealed that the metformin-triggered ATP shortage can prevent the production of ox-mtDNA, thus, reducing NLRP3 inflammasome activation [204]. Metformin also diminishes IL-6 secretion, likely via the suppression of JNK and p38 MAPK [204]. Very recently, Marlies Cortés and colleagues uncovered that metformin's anti-inflammatory effects rely on the expression of ZEB1, which restricts amino acid uptake, thereby downregulating the mTORC1 signaling and mitochondrial protein translation, leading to the inhibition of both acute and chronic inflammation [209].

Conclusion

Sepsis is a significant medical challenge characterized by a systemic inflammatory response. During sepsis, factors such as RNS/ROS, impaired mitophagy, altered mitochondrial dynamics, and membrane permeabilization result in the accumulation of defective mitochondria in immune cells and tissues. These damaged mitochondria promote the immune response via key pathways governed by NLRP3, TLR9, and cGAS. Preclinical studies have identified several agents that target mitochondrial quality control to reduce mitochondrial damage. These agents effectively attenuate inflammation and mortality, offering a novel approach for sepsis treatment.

Abbreviations

AKI	Acute kidney injury
ALI	Acute lung injury
AMPK	AMP-activated protein kinase
ANT	Adenine nucleotide translocator
BNIP3	BCL2 interacting protein3
CALCOCO2/NDP52	Calcium binding and coiled-coil domain-containing protein 2
CASP	Colon ascendens stent peritonitis
cGAS	Cyclic GMP-AMP synthase
CLP	Cecal ligation and puncture
CsA	Cyclosporin A
Cyp-D	Cyclophilin D
DAMPs	Damage-associated molecular patterns
DCs	Dendritic cells
Drp1	Dynamin-related protein 1
ER	Endoplasmic reticulum
ETC	Electron transport chain
FDA	U.S. food and drug administration
FEN1	Flap structure-specific endonuclease 1
Fis1	Fission 1
FUNDC1	FUN14 domain containing 1
GSDMs	Gasdermins
ICUs	Intensive care units
IFNs	Interferons
IL	Interleukin
IMS	Intermembrane space
IRF	Interferon regulatory factor
KO	Knockout
LC3	Microtubule-associated protein 1 light chain 3
L-OPA1	Long OPA1 isoforms
LPS	Lipopolysaccharides
MAM	Mitochondria-associated membrane
MARK4	Microtubule-affinity regulating kinase 4
MAVS	Mitochondrial antiviral-signaling protein
Mff	Mitochondrial fusion factor
Mfn1/2	Mitofusin 1/2
MOF	Multi-organ failure
MOMP	Mitochondrial outer membrane permeabilization
MPT	Mitochondrial permeability transition
mtDNA	Mitochondrial DNA
MTOC	Microtubule-organizing center
mTOR	Mammalian target of rapamycin
mtROS	Mitochondrial ROS
NADH	Nicotinamide adenine dinucleotide dehydrogenase
NBR1	Next to BRCA1 gene 1 protein
NFAT	Nuclear factor of activated T cells

NF-κB	Nuclear factor κB
NIX	Nip3-like protein X
NLRs	NOD-like receptors
NOXs	Nicotinamide adenine dinucleotide phosphate oxidases
OMM	Outer mitochondrial membrane
OPA1	Optic atrophy 1
OPTN	Optineurin
ox-mtDNA	Oxidized mitochondrial DNA
PAMPs	Pathogen-associated molecular patterns
PBMCs	Peripheral blood mononuclear cells
PepG	Peptidoglycan
PGC-1 β	Peroxisome-proliferator-activated receptor γ coactivator 1 β
PHB	Prohibitin
PINK1	PTEN-induced kinase 1
PRRs	Pattern recognition receptors
RNS	Reactive nitrogen species
SESN2	Sestrin 2
S-OPA1	Short OPA1 isoforms
STING	Stimulator of interferon genes
STX17	Syntaxin 17
TAX1BP1	Tax1-binding protein 1
tBid	Truncated form of Bid
TCA	Tricarboxylic acid
Tempol	Piperidine nitroxide
TFAM	Mitochondrial transcription factor A
TGN	Trans-Golgi network
TLRs	Toll-like receptors
TPP^+	Decyl-triphenylphosphonium
TRX	Thioredoxin
TXNIP	Thioredoxin-interacting protein
UA	Urolithin A
UCPs	Uncoupling proteins
ULK1	Unc-51 like autophagy activating kinase 1
VDAC	Voltage-dependent anion channel
WT	Wide type
ΔΨm	Mitochondrial membrane potential

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