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REVIEW

Mitochondrial quality control mechanisms as potential therapeutic targets in sepsis-induced multiple organ failure

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Abstract

Sepsis is a dysregulated response to severe infection characterized by life-threatening organ failure and is the leading cause of mortality worldwide. Multiple organ failure is the central characteristic of sepsis and is associated with poor outcome of septic patients. Ultrastructural damage to the mitochondria and mitochondrial dysfunction are reported in sepsis. Mitochondrial dysfunction with subsequent ATP deficiency, excessive reactive oxygen species (ROS) release, and cytochrome *c* release are all considered to contribute to organ failure. Consistent mitochondrial dysfunction leads to reduced mitochondrial quality control capacity, which eliminates dysfunctional and superfluous mitochondria to maintain mitochondrial homeostasis. Mitochondrial quality is controlled through a series of processes including mitochondrial biogenesis, mitochondrial dynamics, mitophagy, and transport processes. Several studies have indicated that multiple organ failure is ameliorated by restoring mitochondrial quality control mechanisms and is further amplified by defective quality control mechanisms. This review will focus on advances concerning potential mechanisms in regulating mitochondrial quality control and impacts of mitochondrial quality control on the progression of sepsis.

Keywords Sepsis · Mitochondrial dysfunction · Mitochondrial biogenesis · Mitophagy · Mitochondrial dynamics

Introduction

The definition of sepsis has been updated to include infection-induced multiple organ dysfunction. Sepsis is the leading cause of intensive care units (ICU) mortality worldwide, and the mortality varies between 20 and 50% [1, 2]. The incidence of sepsis has increased recently, and an increasing elderly population, cancer, immunosuppression, and antimicrobial resistance contribute to the increased incidence [2–5]. Although there have been advances in sepsis management, both mortality and morbidity remain high [6]. Most patients displaying an initial overwhelming hyper-inflammatory response die rapidly days or weeks later [7, 8]. Additional investigations demonstrated that immunosuppression plays a central role in the late phase of sepsis and contributes to multiple organ dysfunction [9–11]. Immunosuppression is caused by dysfunction and apoptosis of immune cells including $CD4^+$ and $CD8^+$ T cells, B cells, and dendritic cells (DCs). Although there are strategies targeting immunosuppression, the outcome of sepsis is still poor [12, 13]. Therefore, it is critical to understand the specific mechanisms of immunosuppression and subsequent multiple organ failure in sepsis.

Ultrastructural damage to the mitochondria and mitochondrial dysfunction has been reported in immune cells, cardiomyocytes, skeletal muscle, and hepatocytes under septic exposure [14–18]. Furthermore, ATP depletion, depletion of intracellular antioxidant systems, and respiratory chain (electron transport chain) inhibition are all observed in septic patients and experimental models of sepsis [16, 17]. Persistent mitochondrial dysfunction contributes to sepsis-related organ failure and poor outcome of septic patients. Thus, removal of

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dysfunctional mitochondria and generation of healthy mitochondria improve recovery of organ function in sepsis. However, consistent mitochondrial dysfunction shows defective mitochondrial quality control mechanisms. Recent studies have demonstrated that organ dysfunction is amplified by defective mitochondrial quality control mechanisms and is ameliorated by recovery of mitochondrial quality control mechanisms [19–21].

In this review, we illustrate how mitochondrial quality control allows the mitochondrial network to segregate or recognize and eliminate damaged mitochondria, and generate new mitochondria (Fig. 1). Furthermore, we provide an overview of the role of the mitochondrial quality control mechanisms on organ dysfunction under septic exposure (Table 1).

Mitochondrial dysfunction

Mitochondria are subcellular organelles that provide energy termed ATP via oxidative phosphorylation (OXPHOS) that are responsible for most oxygen consumption. Mitochondria are also associated with calcium homeostasis, intracellular ROS generation, and cell signaling functions [22, 23]. In response to sepsis, the inflammatory cytokines of the innate immune response including TNF-α, IL-1β, and IL-6 promote mitochondrial permeability transition, inhibit oxidative phosphorylation, and improve ROS production [24, 25]. In addition, oxidative stress caused by the imbalance of ROS generation and antioxidant protective mechanisms leads to peroxidation of the mitochondrial lipids cardiolipin, mtDNA damage, and more ROS formation under septic conditions [26, 27]. Nitric oxide (NO) and ROS also inhibit electron transport chain (complex IV and complex I). High Ca^{2+}, low ATP, mtDNA mutations, mitochondrial permeability pore opening, and oxidative stress are all observed in sepsis. These changes lead to mitochondrial swelling that damages the mitochondrial ultrastructure and results in release of cytochrome *c* and apoptosis-related markers into the cytoplasm [28]. Mitochondrial dysfunction has been demonstrated to activate cell apoptosis and ultimately results in organ failure. Interestingly, targets for mitochondrial therapy augment multiple organ function during sepsis [29]. For example, L-carnitine, succinate, ATP-$MgCl_2$, cytochrome *c*, and ubiquinol (coenzyme Q) administration can target the electron transport system (ETS) and all have been reported to increase the survival rate in septic models by restoring ETS function and increasing oxygen consumption and phosphorylation [30–34]. In addition, mitochondrial antioxidants, including MitoQ/PBN/SkQ, SS peptides, glutathione, and melatonin all can ameliorate multiple organ failure during sepsis by decreasing oxidative stress markers [35–37].

Mitochondrial biogenesis

Mitochondrial biogenesis is regulated by multiple molecular signals in response to energy demand and contributes to an increase in mitochondrial mass and recovery of the mitochondrial

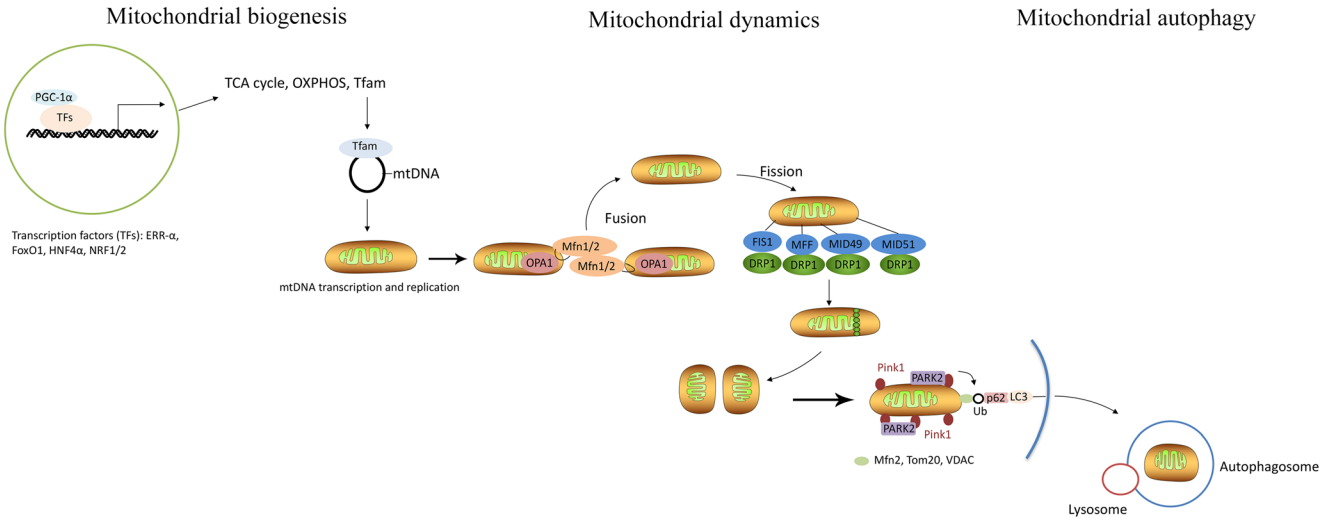


Fig. 1 Mitochondrial quality control mechanisms. Mitochondrial biogenesis generates new mitochondria to recover the mitochondrial network. PGC-1α is a central regulator of mitochondrial biogenesis. PGC-1α interacts with various transcription factors including estrogen-related receptor α (ERR-α), forkhead box class-O (FoxO1), hepatocyte nuclear factor 4a (HNF4a), nuclear respiratory factor (NRF1), and NRF2 to activate the transcription of nuclear genes encoding mitochondrial proteins. Tfam is imported into mitochondria and activates mtDNA transcription and replication. Mitochondria undergo fusion and fission to modulate mitochondrial morphology, number, and size. Mitochondrial fission and fusion are regulated by evolutionarily conserved dynamin-related GTPases that include fission protein dynamin-related protein 1 (Drp1) and its receptors mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (Mff), mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51), and the fusion proteins mitofusin (Mfn)1, Mfn2, and optic atrophy 1 (OPA1). Mitophagy is regulated by Pink1/PARK2 pathway and eliminates damage mitochondria via fusing with lysosome

Table 1 Effects of mitochondrial quality control mechanisms modulation on major organs in sepsis

Organs	Interventions	Effects	Outcomes	Reference
Heart	α-Myosin heavy chain promoter (*Becn1*-Tg)	Enhanced autophagy/mitophagy	Decreased cytokine levels Decreased cardiac content	99
	PARK2 knockout	Suppressed mitophagy	Impaired cardiac contractility	98
	administration of Rapamycin	Enhanced autophagy	Improved cardiac function Decreased cytokine levels	109
Liver	PGC-1a knockout	Inhibited mitochondrial biogenesis	Increased pro-inflammatory cytokines Increased hepatic apoptosis	43
	Administration of carbon monoxide	Activated mitochondrial biogenesis	Improved survival and decreased inflammation	49
	Administration of Mdivi-1	Suppressed mitochondrial fission	Reduced hepatic apoptosis	21
	Deletion of *Atg7* or Silencing ATG7 by siRNA	Suppressed autophagosome formation	Increased serum ALT levels and increased hepatic apoptosis	103,106,108
	Administration of carbamazepine	Enhanced autophagy	Reduced cytokines and AST/SGOT	105
Lung	MKK3 knockout	Enhanced mitochondrial biogenesis and mitophagy	Improved survival and reduced inflammatory cell infiltration	100
	LC3 overexpression	Enhanced autophagy	Improved survival and attenuated lung infiltration	111
	Administration of APC and rapamycin	Enhanced autophagy	Reduced lung inflammatory cell infiltration and lung apoptosis	110
	Deletion of *Atg4b*	Suppressed autophagy	Increased lung inflammatory cell infiltration	
Kidney	PGC-1a knockout	Inhibited mitochondrial biogenesis	Increased BUN and Cr levels	51
	Administration of rapamycin	Enhanced autophagy	Lower renal damage	112
	Deletion of *Atg7*	Suppressed autophagosome formation	Increased BUN and Cr levels and apoptosis	113
Brain	Administration of Mdivi-1	Suppressed mitochondrial fission	Attenuated hippocampus damage and apoptosis	77

network. These molecular signals include several DNA-binding transcriptional factors, such as peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), nuclear respiratory factor 1 (NRF1) and NRF2, and mitochondrial transcription factor A (TFAM) [20, 38]. PGC-1α is a central regulator of mitochondrial biogenesis. PGC-1α interacts with various transcription factors including estrogen-related receptor α (ERR-α), forkhead box class-O (FoxO1), hepatocyte nuclear factor 4a (HNF4a), nuclear respiratory factor (NRF1), and NRF2 to regulate nuclear gene expression [39]. In addition, PGC-1α and NRF1 coactive the expression of TFAM, TFB1M, and TFB2M that mediate mtDNA transcription and replication [40]. NRF1 and NRF2 are two key regulators of mitochondrial biogenesis and are activated by PGC-1α. Activated NRF1 and NRF2 reportedly regulate the expression of proteins related with mitochondrial respiratory function and mitochondrial translation encoded by nuclear genes [41]. Following activation by PGC-1α and NRF1, TFAM and TFB2M are translocated from the cytosol into mitochondria. In mitochondria, TFAM binds to mitochondrial DNA and regulates mtDNA transcription and replication [42].

It has been shown that the activation of mitochondrial biogenesis transcription factors is earlier in survivors than non-survivors, which indicates the earliest recovery of mitochondrial function is crucial in sepsis. A deep investigation found that mRNA expression of PGC-1α is only elevated in survivors and the decrease in transcription of respiratory chain subunits is less in survivors than non-survivors [20]. In the liver, key regulators of mitochondrial biogenesis such as PGC-1α, NRF1, NRF2, and TFAM are markedly increased in experimental models following septic exposure [43, 44]. In an age-dependent model, the results show that young mice exhibit a time-dependent increase in nuclear levels of PGC-1α, whereas mature mice exhibit a decrease in nuclear levels of PGC-1α after sepsis [45]. In the lung, PGC-1α expression is increased more than sixfold and TFAM expression is increased fourfold during murine sepsis [46]. Furthermore, previous studies have shown that expression levels of PGC-1α, NRF1, NRF2, and TFAM are all increased in the heart and in astrocytes under septic conditions [47, 48]. Several pharmacological therapies can prevent organ failure partly through activation of mitochondrial biogenesis in sepsis. Septic models with inhaled CO show rescue of liver failure from sepsis through activation of mitochondrial biogenesis [49]. Additionally, the lipophilic antioxidant CoQ_{10} can prevent LPS-induced mitochondrial dysfunction in multiple organs by improving mitochondrial biogenesis [50]. Conversely, mice with lipopolysaccharide (LPS)-induced acute kidney injury (AKI) show a decrease in PGC-1α mRNA in the renal cortex [51, 52]. The overexpression of PGC-1α promotes recovery from LPS-induced acute kidney injury, and both global and

tubule-specific PGC-1α-knockout mice suffer persistent impaired kidney function [51]. These results indicate that key factors of mitochondrial biogenesis are mostly increased in sepsis, and therapies targeting mitochondrial biogenesis could partly reverse organ failure under septic conditions.

In the initial stage of sepsis, inflammatory cytokines including TNF-α, IL-1β, and IL-6 are increased and the increased cytokine production ultimately leads to an inflammatory cytokine storm, which is a main cause of death in the initial stage of sepsis. Global ablation of the PGC-1α gene in mice increases the expression levels of IL-6 and TNF-α, and the subsequent chronic elevation of circulating IL-6 [53]. Activation of PGC-1α protects endothelial cells from LPS-induced loss of mitochondrial function and decreases LPS-induced high IL-6 concentration [54]. The mechanisms linking PGC-1α activation to the downregulation of inflammation genes may be related to recovery of mitochondrial function and reduction of ROS generation by PGC-1α activation. Recent studies have shown that overexpression of PGC-1α inhibits intracellular and mitochondrial ROS production [55]. Mice with muscle-specific PGC-1α-knockout show decreased expression of anti-ROS genes, which makes a substantial contribution to the observed increase of cytokine expression [56].

Activation of mitochondrial biogenesis by pharmacological agents emerges as therapeutic strategies in sepsis. Clinical data showed that patients with dyslipidemias treatment presented a better clinical outcome during sepsis [57, 58]. Bezafibrate, an agonist of peroxisome proliferator-activated receptor (PPAR), is a commonly used drug in dyslipidemias, which has been reported to increase PGC-1α expression [59]. A recent study demonstrated that bezafibrate treatment presented anti-inflammatory effects in experimental sepsis [60]. However, whether the protective effects of bezafibrate on sepsis is probably through activating mitochondrial biogenesis has not been evaluated so far. Another pharmacological agent which has been reported to activate mitochondrial biogenesis is metformin, a commonly used drug in diabetes [61]. Several studies have demonstrated that metformin treatment ameliorated induced brain and cardiac injury in experimental sepsis [62, 63]. However, clinical data showed that pretreatment with metformin in both diabetes and sepsis patients presented no difference in the outcome of sepsis [64].

Mitochondrial dynamics

Mitochondria are highly dynamic organelles and frequently undergo fission and fusion to modulate mitochondrial morphology, number, and size. In physiological conditions, mitochondrial fusion and fission is balanced to maintain mitochondrial and cellular homeostasis. During sepsis, mitochondrial dysfunction results in activation of mitochondrial fission and inactivation of mitochondrial fusion, which promotes dysfunctional mitochondrial fragmentation and ultimately results in organ failure [65]. Mitochondrial fragmentation contributes to BAX activation, outer membrane permeabilization (MOMP), remodeling of mitochondrial cristae, and increased ROS production and ATP depletion that results in cell death immediately and ultimately organ failure [66, 67]. Mitochondrial fission and fusion are regulated by evolutionarily conserved dynamin-related GTPases that include fission protein dynamin-related protein 1 (Drp1) and its receptors mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (Mff), mitochondrial dynamics proteins of 49 and 51 kDa (MiD49 and MiD51), and the fusion proteins mitofusin (Mfn)1, Mfn2, and optic atrophy 1 (OPA1) [68]. Mfn1 and Mfn2 are located on the mitochondrial outer membrane, whereas OPA1 is located on the mitochondrial inner membrane. During the process of mitochondrial outer membrane fusion, Mfn1 and Mfn2 form homo-oligomeric and hetero-oligomeric structures to tether two adjacent mitochondria for fusion [69]. Unlike Mfns, OPA1 does not require the oligomerization of OPA1 to mediate inner membrane fusion. The coordinated actions of Mfns and OPA1 starts with outer membrane fusion and ends with mitochondrial inner membrane fusion [68]. During mitochondrial fission, Drp1 is transported from the cytosol to the mitochondrial outer membrane and forms oligomeric Drp1 complexes. The Drp1 protein oligomeric structure wraps around and constricts the mitochondrial tubule, which dissects the parent organelle into two daughters [70, 71]. The signaling mechanism of Drp1-recruitment to the mitochondria has been proposed to depend on several mitochondrial outer membrane proteins such as Fis1, Mff, MiD49, and MiD51. However, the exact functions of these proteins in mitochondrial fission remain unclear.

There are studies that monitored mitochondrial morphology and conserved dynamin-related GTPases in sepsis, but the number of studies is very limited. It has been suggested that fragmented mitochondria and Drp1 expression levels are increased in skeletal muscle under septic conditions [72]. Treatment with the de novo sphingolipid biosynthesis inhibitor myriocin ameliorates dysfunction of skeletal muscle by reverting mitochondrial morphology and decreasing Drp1 expression levels induced by sepsis [72]. Gonzalez et al. demonstrate that Mfn2 is decreased at 4–6 h, and mitochondrial fragmentation is increased at 6 h in liver after LPS treatment [21]. In contrast, Mfn2 is decreased at 12–18 h and Drp1 is increased at 4 h in liver after cecal ligation and puncture (CLP) surgery [21]. Additionally, TNF-α induces the expression levels of mitochondrial Drp1, increases phosphorylated Drp1, and enhances mitochondrial fragmentation in H9C2 cardiomyocytes [73]. Notably, Mfn2 is decreased in CD4 + T cells after HMGB1 treatment [74, 75]. The upregulation of Mfn2 protects CD4 + T cells from immune dysfunction and apoptosis induced by HMGB1. It still

unclear whether the upregulation of Mfn2 to prevent the dysfunction lymphocyte apoptosis is associated with improved mitochondrial dynamics. However, mitochondrial fusion and fission rates of human PBMC obtained from a control group and sepsis group showed an insignificant difference [76].

Mdivi-1 is a pharmacological inhibitor of Drp1 and has been reported to revert sepsis-induced fragmented mitochondria to tubular mitochondria. Recent studies have shown that Mdivi-1 reduces the inhibition of mitochondrial ETC complex and hepatocyte apoptosis induced by CLP [21]. Mdivi-1 administration also ameliorates LPS-induced brain injury. Mechanically, Mdivi-1 inhibits the Drp1 increase and attenuates the OPA1 decrease in hippocampus under septic exposure [77]. There are other non-specific pharmacological therapies that attenuate organ damage through regulating mitochondrial dynamics in sepsis. For example, heme oxygenase (HO)-1/carbon monoxide attenuates acute lung injury in sepsis partly through balancing mitochondrial fusion and fission [78].

Mitochondrial autophagy

Autophagy is a central process in cell survival under stress and non-selectively or selectively eliminates damaged proteins and organelles by formation of a double-membrane autophagosome, which then fuses with lysosomes [79]. Mitophagy is the selective autophagy of mitochondria and requires receptors to recognize damaged mitochondria for degradation. Mitophagy is regulated by several pathways including the PTEN-induced putative protein kinase 1 (Pink1) and the E3 ubiquitin ligase (Park2/Parkin), FUN14 domain-containing protein 1 (FUNDC1), NIX/BNIP3, and BCL2L1.

The Pink1/Park2 pathway is the main regulator of mitophagy and has become a topic of scientific research due to its involvement in the pathogenesis of Parkinson's disease (PD) [80, 81]. In healthy mitochondria, Pink1 translocates on the outer mitochondrial membrane (OMM) via the TOM components, and then inserts into the inner mitochondrial membrane (IMM) through the TIM23 complex. When the N-terminal mitochondrial targeting sequence (MTS) of Pink1 that drives the translocation reaches the matrix, a matrix processing peptidase (MPP) recognizes and cleaves Pink1 [82]. Subsequently, the IMM protease PARL cleaves Pink1 p64 and generates the Pink1 p53, which then is released to the cytosol and is degraded by the proteasome [83]. In sepsis, the dysfunctional mitochondria prevent the import of Pink1 through TIM23 and this results in accumulation of Pink1 on the outer mitochondrial membrane. PINK1 recruits Park2 to translocate to the outer mitochondrial membrane from the cytosol and activates Parkin by phosphorylation of Ser65 on Park2 [84]. In the cytosol, Park2 remains "closed," which means the repressor element of Park2 (REP) blocks E2-binding site in RING1 and RING0 shields catalytic C431 [85, 86]. Under stress conditions, Pink1 undergoes autophosphorylation at Ser228 and Ser402 and then phosphorylates basal OMM ubiquitin, which can attract Park2 to accumulate on the OMM [87]. When Park2 binds to Ps65-Ub, the constructs of Park2 are changed and this includes replacement of the inhibitory N-terminal ubiquitin-like (UBL) domain and segmentation of REP, which means that Park2 is "open" [85, 88]. The activated Park2 is further phosphorylated by Pink1 and induces more Park2 recruitment.

Activated Park2 ubiquitinates several mitochondrial proteins on the outer membrane without stringent selection, including mitochondrial fusion proteins Mfn1/2, Miro, and voltage-dependent anion channel (VDAC) 1/2/3 [89, 90]. Mfn1/2 and Miro belong to K48-linked chains, and K48 modification by Park2 induces degradation of proteins by the proteasome. The degradation of Mfn1/2 prevents mitochondrial fusion that thereby promotes mitochondrial fragmentation and mitophagy [91, 92]. When the mitochondrial transport protein Miro is degraded, all mitochondrial mobility is arrested, and this arrest may segregate damaged mitochondria before mitophagy [93, 94]. The VDAC1/2/3 are K63 ubiquitin chains and K63 is associated with the recruitment of mitophagy receptors [95]. In addition, Park2 builds ubiquitin chains on the outer mitochondrial membrane that could be sufficient to recruit autophagic receptors such as optineurin, nuclear dot protein 52 (NDP52), p62 (SQSTM1), and Tax1-binding protein 1 (TAX1BP1) [96, 97]. Optineurin and NDP52 are the primary receptors in this process, and following recruitment of optineurin and NDP52, ULK1, DFCP1, and WIPI1 are independently recruited to focal spots proximal to initiate autophagosome formation [96]. At late stages of mitophagy, LC3 bind to the autophagosome membrane to form a complete autophagosome that fuses with lysosomes for degradation.

In sepsis, mitochondrial dysfunction induces a loss of mitochondrial membrane potential that triggers mitophagy. In the heart, mitophagy is induced during sepsis and this is evidenced by the presence of several double-membrane autophagosomes, increased LC3B-II and p62 expression, and mitochondrial recruitment of Park2, BNIP3L, and BNIP3 [98, 99]. *Park2*-deficient mice exhibit impaired recovery of cardiac function and constant cardiac mitochondrial dysfunction in the heart during sepsis [98]. Cardiac-specific overexpression of Beclin-1 promotes PINK1/Park2-dependent mitophagy, improves cardiac function, and reduces cardiac inflammation in response to LPS [99]. LC3B-II expression in the lung is increased and LC3 colocalizes with citrate synthase in the mitochondria, which indicates mitophagy occurs during sepsis [46]. *MKK3*-deficient mice increase PINK1/Park2-dependent mitophagy, and this reduces lethality of mice and lowers the levels of lung and mitochondrial injury in sepsis [100]. The data also show that heterozygous *PINK1* null mice are more susceptible to death and heterozygous *PINK1*, *MKK3* null mice have higher survival than

heterozygous *PINK1* null mice in sepsis. The findings demonstrate the inhibition of mitophagy increases mortality of mice in sepsis. Compared with non-septic patients, both higher MMK3 and PINK1 activation are detected in PBMCs from septic patients [100]. Hepatocyte exposure to LPS induces translocation of PINK1 and Park2 to the mitochondria and colocalization of LC3 to mitochondria [101]. In the kidney, increased autophagosomes co-localize with damage and citrate in mitochondria during sepsis [102]. Collectively, these studies support that mitophagy is induced in several organs during sepsis.

Autophagy

Although several studies have demonstrated that mitophagy is induced in major organs in sepsis, the effect of mitophagy in sepsis remains unclear. Studies examining the role of mitophagy in sepsis are very limited, and therefore, we discuss the role of autophagy in sepsis. Several studies have shown that impaired autophagy contributes to amplifying organ failure in sepsis.

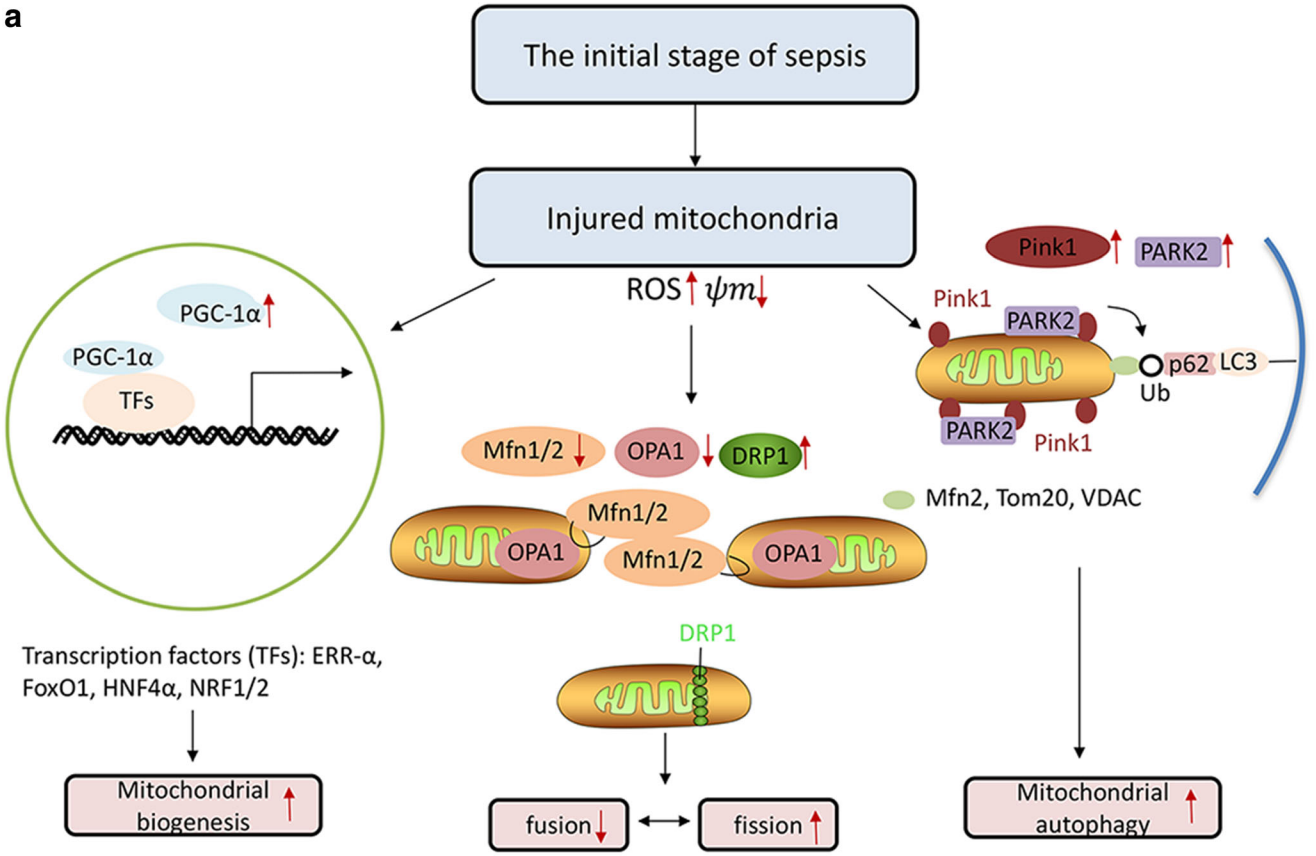
In the CLP model, the whole autophagic process (autophagic flux) is characterized by increased levels of LC3B-II, ATG5, ATG7, Beclin1, and p62; the presence of autophagosomes; and further increased levels of LC3B-II and p62 after chloroquine treatment early in liver. These changes are followed by incomplete autophagic flux and even suppression of autophagy at the late stage of sepsis [103–105]. Liver failure and apoptosis occur as soon as autophagic flux is suppressed, which indicates that suppression of autophagy is associated with liver failure after CLP. A previous study reported autophagy deficiency by downregulation of ATG7, an essential gene for autophagosome formation, aggravates hepatic mitochondrial dysfunction and liver damage and apoptosis after CLP [106]. Additionally, liver injury and apoptosis are accelerated in liver-specific *ATG5*-deficient mice under sepsis [19]. Chloroquine is a pharmacologic inhibitor of autophagic flux and contributes to amplifying liver failure and increases mortality during sepsis [104]. One pharmacologic therapy is the autophagic flux enhancer carbamazepine, which improves survival rates of septic mice and attenuates liver injury, inflammation, and apoptosis in the CLP septic model [105]. In the LPS-treated model, complete autophagic response is induced in hepatocytes [107, 108]. The suppression of autophagy by chloroquine and knockout out of ATG7 sensitizes mice to LPS-induced liver injury [107, 108]. In the heart, studies have shown that autophagic flux is induced in two prototype sepsis models: endotoxemia and cecal ligation and puncture (CLP) [99, 109]. Increasing Beclin-1-dependent autophagy improves cardiac function and decreases cytokine levels and protects myocardium from fibrosis following LPS challenge [99]. Moreover, rapamycin is the best-known pharmacologic agent to induce autophagy and CLP mice treated with rapamycin increase ATP generation and decrease cytokine levels [109]. Similarly, the protective effect of autophagy in sepsis can also be found in lung, kidney, skeletal muscle, and immune cells [110–115]. Collectively, these studies demonstrated that the induction of autophagy ameliorates organ failure and suppression of autophagy amplifies organ failure in sepsis.

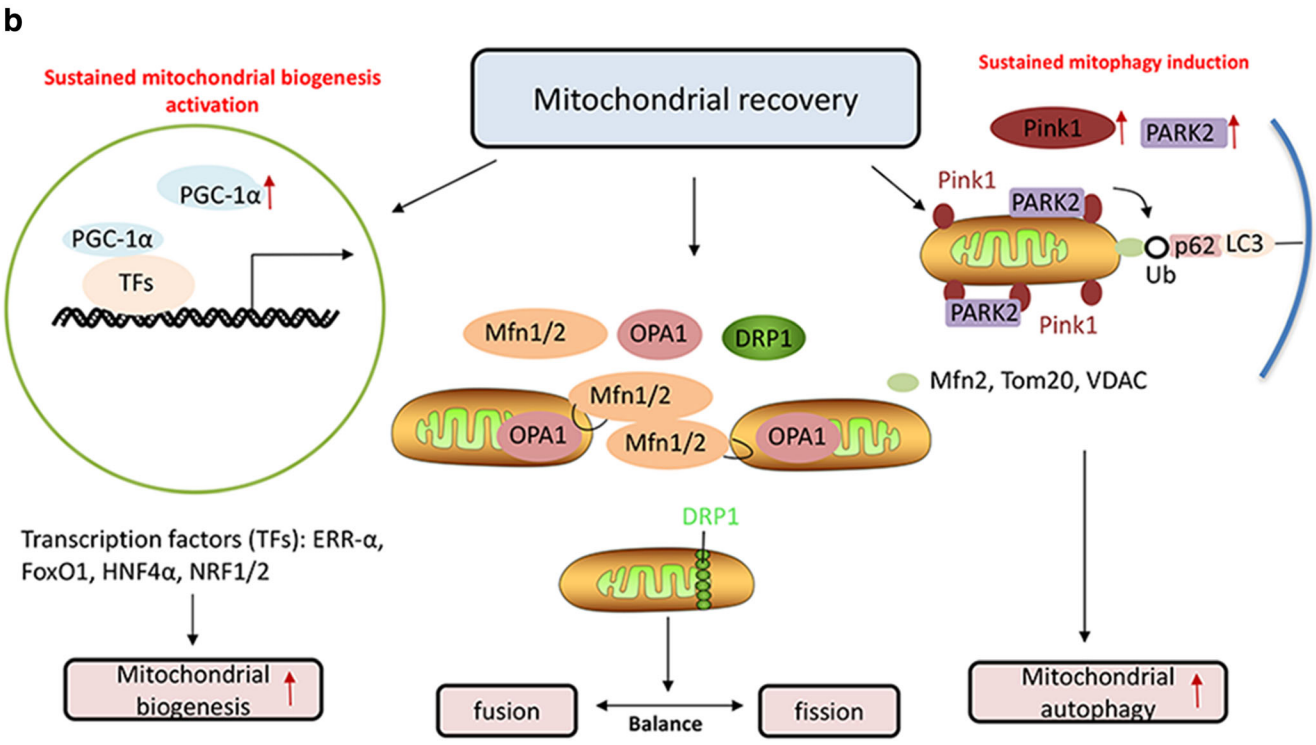
An interesting finding showed that critically ill patients receiving over or standard feeding presented worse outcome than those subjecting to underfeeding [116]. Starvation is a main inducer of autophagy, and reduction of sepsis mortality in critically ill patients with underfeeding may be probably related to sustained induction of autophagy. Therefore, pharmacological induction of autophagy is a potential therapeutic strategy in sepsis. Rapamycin, a commonly used pharmacological agent for autophagy induction, has been reported to protect against sepsis-induced organ injury and improve the survival rate of septic mice [110, 117]. However, rapamycin treatment also affects many other metabolic pathways, and therefore clinical use of it for sepsis has little progress. There are other pharmacological agents for autophagy induction without affecting many signaling pathways, including carbamazepine, sodium valproate, and lithium, but fewer studies have demonstrated the effect of these agents on sepsis.

Conclusion

Both septic patients and animal septic models suggest that mitochondrial quality control mechanisms including mitochondrial biogenesis, dynamics, and mitophagy are induced in the early stage of sepsis (Fig. 2). In sepsis,

Fig. 2 Changes in mitochondrial quality control mechanisms under sepsis. **a** In the initial stage of sepsis, the upregulation of PGC-1α and transcription factors promotes mitochondrial biogenesis. And a decrease in Mfn1/2 and OPA1 expression and an increase in DRP1 expression induce that the balance of mitochondrial fusion and fission shifts to mitochondrial fission. Furthermore, the accumulation of PINK1 on mitochondria induces PARK translocation from cytoplasm into mitochondrial outer membrane, which triggers mitophagy. **b** The mitochondrial functions are recovered in the survival of sepsis. Changes in mitochondrial quality control mechanisms are presented as following. Sustained high levels of PGC-1α and transcription factors continuously activate mitochondrial biogenesis to provide new and healthy mitochondria. The balance of mitochondrial fusion and fission is recovered. Additionally, sustained induction of mitophagy can also be found in the survival of sepsis. **c** In the progression of sepsis, injured mitochondria cannot be restored and turn into mitochondrial dysfunction. Changes in mitochondrial quality control mechanisms are presented as follows. The decreased levels of PGC-1α and transcription factors prevent mitochondrial biogenesis. And persistent decreased Mfn1/2 and OPA1 expression levels and increased DRP1 expression levels results in more mitochondrial fragmentation generation. Additionally, expression levels of PINK1, PARK2, p62, and LC3 are all decreased, which indicates mitophagy deficiency


a
The initial stage of sepsis
Injured mitochondria
ROS↑ ψm↓
PGC-1α↑
PGC-1α
TFs
Pink1↑ PARK2↑
Pink1
PARK2
p62 LC3
Ub
PARK2
Pink1
Mfn1/2↓ OPA1↓ DRP1↑
Mfn1/2
OPA1
Mfn1/2
OPA1
Mfn2, Tom20, VDAC
DRP1
Transcription factors (TFs): ERR-α, FoxO1, HNF4α, NRF1/2
Mitochondrial biogenesis↑
fusion↓
fission↑
Mitochondrial autophagy↑


b
Sustained mitochondrial biogenesis activation
Mitochondrial recovery
Sustained mitophagy induction
PGC-1α↑
PGC-1α
TFs
Pink1↑ PARK2↑
Pink1
PARK2
p62 LC3
Ub
PARK2
Pink1
Mfn1/2 OPA1 DRP1
Mfn1/2
OPA1
Mfn1/2
OPA1
Mfn2, Tom20, VDAC
DRP1
Transcription factors (TFs): ERR-α, FoxO1, HNF4α, NRF1/2
Mitochondrial biogenesis↑
fusion
Balance
fission
Mitochondrial autophagy↑

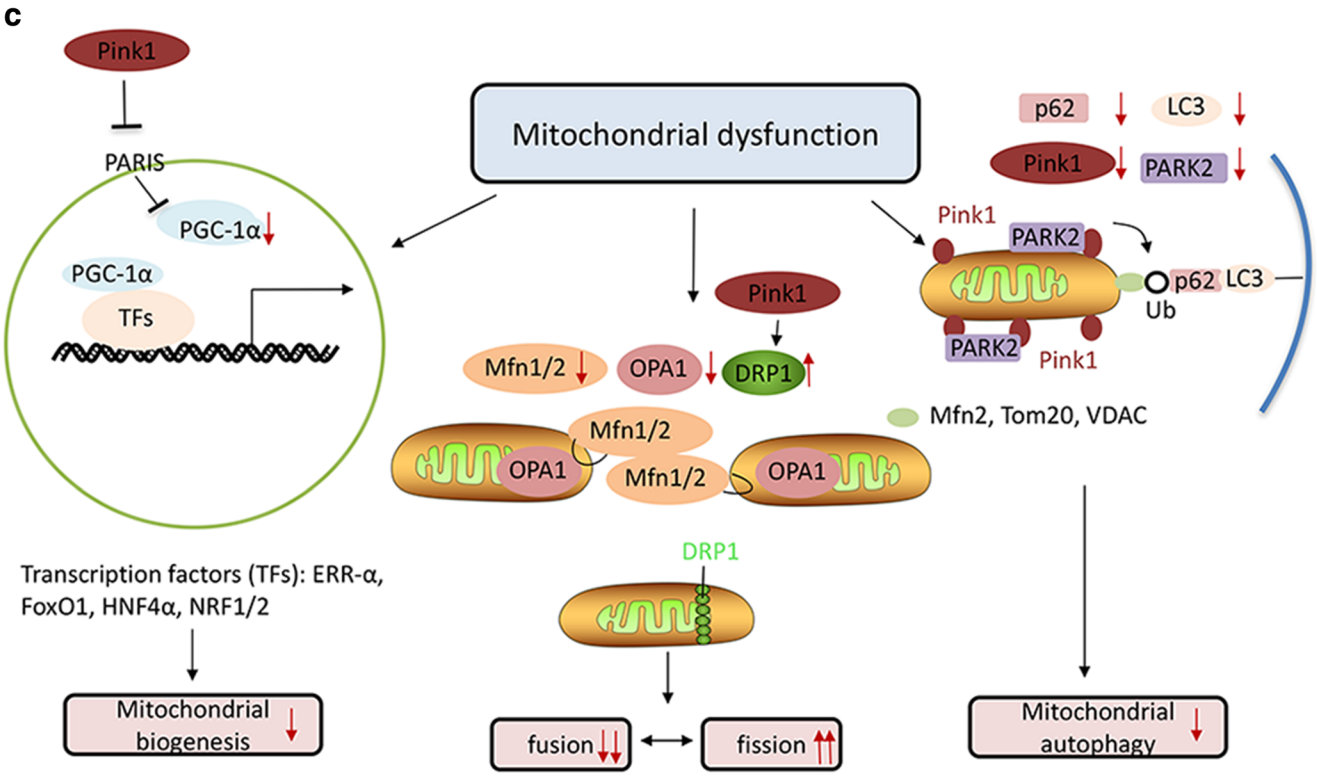


Fig. 2 (continued)

mitochondrial dysfunction is amplified as soon as LPS/CLP-induced mitochondrial biogenesis and autophagy return to baseline level. Deficient mitochondrial biogenesis and autophagy result in healthy mitochondria depletion and increased mitochondrial fragmentation caused by mitochondrial fission. Moreover, persistent mitochondrial dysfunction leads to multiple organ failure during sepsis.

Several studies have shown that impaired mitochondrial quality control mechanisms contribute to and amplify organ failure in sepsis. Using pharmacologic therapeutic agents to activate mitochondrial biogenesis or mitochondrial autophagy or decrease mitochondrial fission in septic model can ameliorate organ mitochondrial dysfunction and organ failure. However, further investigations are required to monitor the changes of mitochondrial quality control mechanisms in septic patients and translate these animal therapies into clinical therapies. Furthermore, the role of other potential mitochondrial quality control mechanisms in sepsis requires investigation.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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