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Rethinking post-sepsis syndrome: linking cellular dysfunction to the clinical picture

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Abstract

Post-sepsis syndrome (PSS) encompasses a range of long-term complications, including immune dysregulation, chronic inflammation, and neuromuscular impairment, that persist beyond the resolution of the acute septic episode. While these clinical phenotypes are increasingly recognized, the underlying molecular mechanisms remain incompletely defined. Mitochondrial dysfunction, particularly in the form of persistent mitochondrial senescence, is emerging as a potential unifying factor driving multiple PSS trajectories. Accumulating evidence suggests that damaged mitochondria not only lose their bioenergetic capacity but also actively contribute to chronic immune and inflammatory signalling. Based on this, we propose a dual-intervention strategy ("mitochondrial flush") which involves the coordinated elimination of senescent mitochondria and stimulation of mitochondrial biogenesis. The regenerative component, supported by established preclinical research on Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (PGC-1α) activation, represents a partially developed therapeutic arm, while the selective clearance of dysfunctional mitochondria remains an area of active investigation. This concept raises important questions regarding regenerative capacity, therapeutic timing, and cellular resilience following critical illness. We further propose a working definition of PSS as a state of persistent mitochondrial dysfunction, possibly driven by ongoing oxidative stress, which may underlie a broader range of clinical phenotypes than currently recognized. A deeper understanding of mitochondrial quality control may offer a new therapeutic framework for reversing the chronic physiological decline observed in sepsis survivors.

Keywords Post-sepsis syndrome, Sepsis, Mitochondrial dysfunction, Mitochondrial senescence, Mitophagy, Mitochondrial-targeted dual therapy, Post-sepsis clinical phenotypes, Mitochondrial flush, Mitochondrial biogenesis, Oxidative stress

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Introduction-why understanding the molecular mechanisms of post-sepsis syndrome matters

Advancements in medical science have significantly improved the management of sepsis, making survival increasingly achievable. However, the long-term consequences remain insufficiently understood, particularly due to the emergence of a symptom constellation now recognized as Post-Sepsis Syndrome (PSS) [1]. This group of symptoms, which includes chronic fatigue, immunosuppression, neuromuscular impairment, cognitive decline, and other manifestations not yet fully described, is beginning to form identifiable clinical patterns. Still, the molecular mechanisms behind them are not fully clarified. Although PSS and Persistent Inflammation, Immunosuppression, and Catabolism syndrome (PICS) have traditionally been viewed as separate entities, recent observations suggest that their boundaries may overlap more than previously appreciated [1, 2]. In the following sections, we aim to highlight several molecular mechanisms that are increasingly associated with the pathogenesis of post-sepsis syndrome.

Neutrophil extracellular traps (NETs) that normally contain infection can instead cause tissue damage and sustain inflammation [3]. Retter et al. report that uncleared mitochondrial NET fragments, rich in extracellular DNA, may preserve tissue-factor activity and promote immunothrombosis. This persistence may be associated with coagulopathy during acute sepsis and could influence outcomes [4]. Tissue-factor-positive extracellular vesicles and circulating microparticles correlate with systemic inflammatory markers and reinforce this environment [5, 6]. Collectively, NET-derived mitochondrial DNA and tissue-factor-bearing vesicles may help to maintain a prothrombotic and pro-inflammatory state described after sepsis, although robust longitudinal evidence is still limited. These observations support a model in which persistent NETs not only release pro-inflammatory and pro-coagulant signals but also act as structural hubs linking chronic inflammation with immunothrombosis (see Fig. 1 and the TLR9 discussion in Sect."Persistent inflammatory phenotype".

Taken together, findings from [7] and [8] support the working hypothesis that mitochondrial dysfunction could be involved in the long-term pathogenesis of PSS. Mitochondria are essential for energy metabolism and immune regulation, yet are particularly susceptible to oxidative damage during sepsis. The accumulation of reactive nitrogen and oxygen species interferes with mitochondrial respiration and reduces adenosine triphosphate (ATP) production, which contributes to cellular energy failure [9]. Notably, a positive feedback loop between mitochondrial damage and the accumulation of reactive oxygen species perpetuates mitochondrial injury and cellular dysfunction, while reactive nitrogen species, including nitric oxide, further impair mitochondrial respiration [9, 10] (see Figs. 2, 3). Sepsis often leaves survivors with diverse long-term health consequences [8]. These chronic conditions may be partly explained by mitochondrial and oxidative disturbances reported in other studies [7] and may align with features described in proposed post-sepsis phenotypes, suggesting that PSS and PICS could share overlapping pathophysiological pathways. This remains hypothetical and warrants further investigation.

The process of significant mitochondrial dysfunction can induce the release of damage-associated molecular patterns (DAMPs). These DAMPs have been shown to play a crucial role in the perpetuation of inflammation [11, 12]. They act through pattern recognition receptors such as Toll-like receptor 4 (TLR4) and the NLR family pyrin domain containing 3 (NLRP3) inflammasome, which are implicated in immune activation and may contribute to persistent dysregulation after sepsis [13].

Even after the resolution of infection, key pathways such as Nuclear Factor κ-Light-Chain-Enhancer of Activated B Cells (NF-κB) can continue to shape immune dynamics through persistent epigenetic reprogramming and context-dependent inflammatory signalling [14, 15]. Mitogen-Activated Protein Kinases (MAPKs) and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) pathways are activated during sepsis and, through extensive crosstalk with NF-κB, may contribute to long-term immune dysregulation [14, 15]. These alterations are implicated in post-sepsis immunosuppression, characterised by prolonged immune impairment and heightened vulnerability to subsequent infections and viral reactivations, sometimes referred to PSS [15]. Given the alarming global scale of sepsis [16], we should not lose sight that, as diagnostics and care improve and more patients survive, we will increasingly have to address the post-sepsis phase (including PSS). Furthermore, long-term metabolic and energy-related disturbances, especially in organs with high energy requirements, are increasingly recognized as contributing factors in the sustained organ dysfunction observed in sepsis survivors [17, 18].

Clarifying these mechanisms is essential not only for understanding PSS, but also for identifying biomarkers and therapeutic targets that can guide early intervention strategies. Given the substantial clinical and epidemiological burden of sepsis, especially in prehospital settings [19], we propose that the long-term consequences of sepsis should be acknowledged as a critical frontier in research and clinical care.

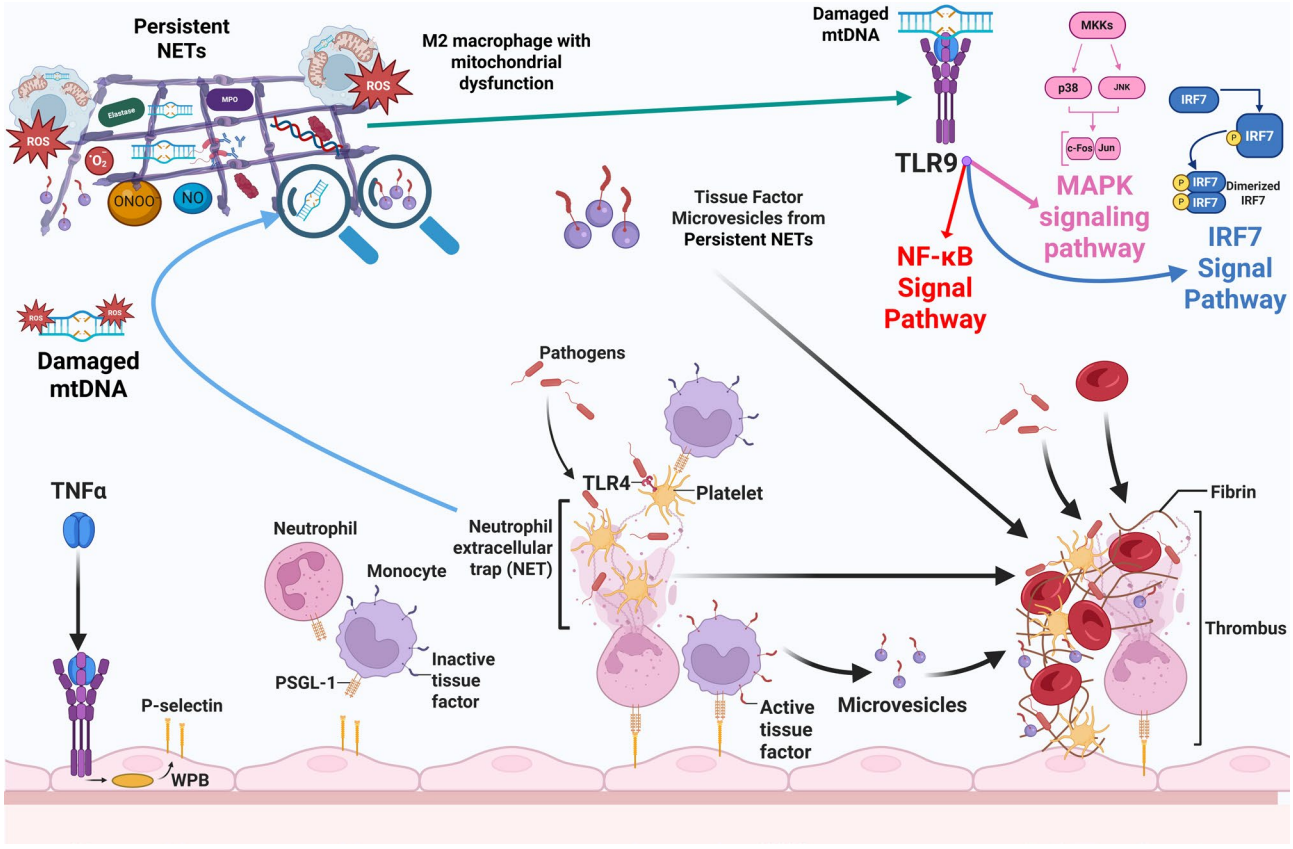

Fig. 1 Mechanisms of persistent NETosis, chronic inflammation, and immunothrombosis potentially implicated in post-sepsis syndrome (PSS) **Acute phase**. During acute sepsis, engagement of Toll-like receptor 4 (TLR4) by pathogen- and damage-associated ligands triggers a strong inflammatory response that injures endothelium and mitochondria and primes platelet-leukocyte-NET interactions. P-selectin binds P-selectin glycoprotein ligand-1 (PSGL-1) on neutrophils and monocytes and enhances leukocyte recruitment and platelet-leukocyte-NET aggregates. These contacts promote tissue factor (TF) expression in monocytes and the generation and capture of TF-bearing microvesicles. Within these acute networks, oxidative and nitrosative reactions generate reactive oxygen species (ROS) such as superoxide ($O_2^{-}\bullet$) and reactive nitrogen species (RNS) such as nitric oxide (NO) and peroxynitrite ($ONOO^-$), amplifying mitochondrial injury and endothelial damage. **Transition**. The combined injury and inefficient clearance of NETs by metabolically altered macrophages (M2-like) permit accumulation of persistent neutrophil extracellular traps (NETs) composed of DNA, histones, antimicrobial proteins and myeloperoxidase (MPO). Oxidative damage promotes extracellular release of mitochondrial DNA (mtDNA). **Chronic self-sustaining loop**. mtDNA released from persistent NETs acts as a DAMP, is internalized by phagocytes, and activates endosomal TLR9. Through MyD88 it coordinates the NF-κB, MAPK, and IRF7 pathways, which together drive secretion of pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and type I interferons (IFN-α/β). On the background of mitochondrial dysfunction, this response remains metabolically dysregulated and low grade yet persistent. NETs serve as thrombo-inflammatory scaffolds that retain platelets and monocytes and capture TF-positive microvesicles released by activated monocytes and other cells, initiating extrinsic coagulation (TF-FVIIa → FX → thrombin → fibrin). **Summary**. This sequence links an acute TLR4-dominated injury to a chronic, TLR9-driven self-amplifying state that underlies the persistent inflammatory, immunosuppressive and pro-thrombotic manifestations of post-sepsis syndrome. **Abbreviations**: NET – neutrophil extracellular trap; mtDNA – mitochondrial DNA; DAMP – damage-associated molecular pattern; TLR – Toll-like receptor; TLR4 – Toll-like receptor 4; TLR9 – Toll-like receptor 9; MyD88 – myeloid differentiation primary response 88; IRAK – interleukin-1 receptor-associated kinase; TRAF6 – TNF receptor-associated factor 6; NF-κB – nuclear factor-kappa B; MAPK – mitogen-activated protein kinase; MKK (MAP2K) – MAPK kinase; p38 – p38 mitogen-activated protein kinase; JNK – c-Jun N-terminal kinase; AP-1 – activator protein 1; IRF7 – interferon regulatory factor 7; IL – interleukin; TNF-α – tumor necrosis factor-alpha; IFN-α – interferon-alpha; IFN-β – interferon-beta; MPO – myeloperoxidase; ROS – reactive oxygen species; RNS – reactive nitrogen species; NO – nitric oxide; $O_2^{-}\bullet$ – superoxide; $ONOO^-$ – peroxynitrite; PSGL-1 – P-selectin glycoprotein ligand-1; WPB – Weibel–Palade body; TF – tissue factor; TF–FVIIa – tissue factor–factor VIIa complex; FVIIa – activated factor VII; FX – factor X; FXI – factor XI; FXII – factor XII; M2 – alternatively activated macrophage

Identification and analysis of post-sepsis syndrome phenotypes: the role of mitochondrial dysfunction

Although this section analyzes immunosuppressive, neuromuscular, and inflammatory phenotypes (proposed phenotypic frameworks) as distinct entities for conceptual clarity, in practice these phenotypes may coexist or overlap. The unifying framework proposed here emphasizes the central role of mitochondrial dysfunction as a shared contributor to their pathophysiology, while allowing for variation in clinical presentation across individuals and time.

The arguments and insights presented in this Perspective article are informed by an extensive review of the scientific literature, conducted by the authors to

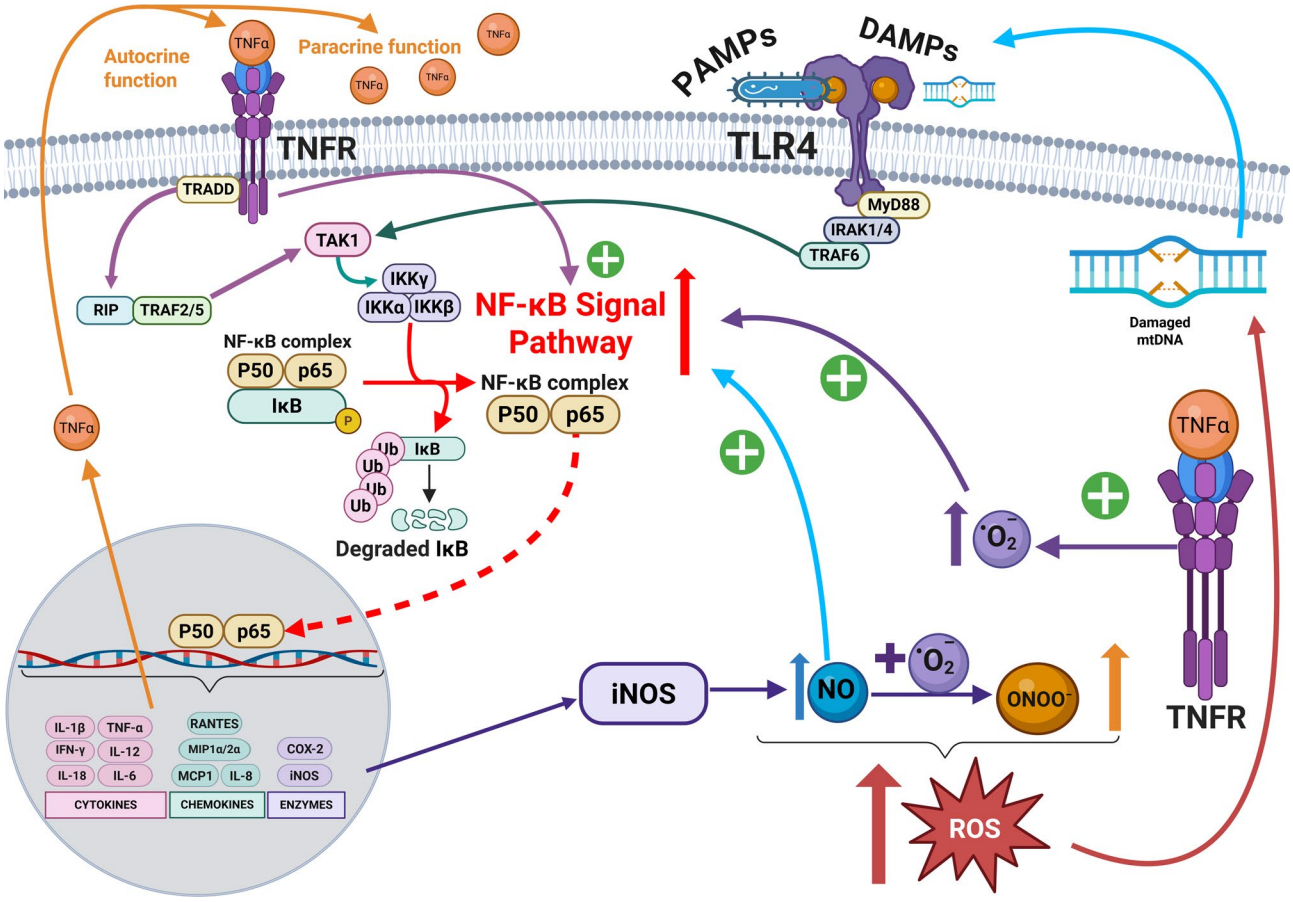

Fig. 2 Amplification loop linking TLR4 and TNFR signalling to mitochondrial oxidative stress and mtDNA damage in sepsis. This figure depicts the signalling cascade initiated by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) through Toll-like receptor 4 (TLR4) and tumor necrosis factor receptor (TNFR). Upon activation, adaptor molecules such as MyD88 and TRADD recruit downstream kinases (IRAK1/4, TRAFs, RIP, TAK1), which converge on the IκB kinase (IKK) complex to activate the canonical NF-κB pathway. Phosphorylation and ubiquitination of IκB lead to its degradation, allowing nuclear translocation of the RelA (p65)/p50 NF-κB complex. This triggers transcription of pro-inflammatory cytokines (e.g., TNFα, IL-1β), chemokines (e.g., MCP-1, IL-8), and enzymes such as inducible nitric oxide synthase (iNOS). TNFα has both autocrine and paracrine functions: it reinforces NF-κB activation within the same cell and promotes inflammatory signaling in neighboring cells. TNFα signaling through TNFR, together with TLR4 activation, stimulates the production of superoxide anion ($O_2^{\bullet-}$) via mitochondrial pathways and NADPH oxidases, thereby amplifying cellular oxidative stress. The iNOS pathway increases nitric oxide (NO) production, which reacts with $O_2^{\bullet-}$ to form peroxynitrite ($ONOO^-$), a potent oxidant and nitrating agent. These ROS and RNS lead to profound oxidative damage of mitochondrial membranes and respiratory complexes, culminating in disruption of the electron transport chain, collapse of mitochondrial membrane potential, and impaired ATP synthesis. Damaged mitochondria release oxidized mitochondrial DNA (mtDNA), which functions as a secondary DAMP. Extracellular or cytosolic mtDNA can be sensed via TLR4 (via HMGB1), TLR9 and other innate sensors, reactivating NF-κB and perpetuating a vicious cycle of inflammation and oxidative stress. Ultimately, this feed-forward loop leads to sustained NF-κB hyperactivation, ROS and RNS accumulation, and irreversible mitochondrial injury. **Abbreviations**: ATP – adenosine triphosphate; ADP – adenosine diphosphate; COX-2 – cyclooxygenase-2; DAMPs – damage-associated molecular patterns; HMGB1 – high-mobility group box 1; IFN-γ – interferon gamma; iNOS – inducible nitric oxide synthase; IRAK1/4 – interleukin-1 receptor-associated kinase 1/4; IκB – inhibitor of NF-κB; IKK – IκB kinase complex; IL-1β – interleukin-1 beta; IL-6 – interleukin-6; IL-8 (CXCL8) – interleukin-8; IL-12 – interleukin-12; IL-18 – interleukin-18; MCP-1 (CCL2) – monocyte chemoattractant protein-1; MIP-1α (CCL3) – macrophage inflammatory protein-1 alpha; MIP-2 (CXCL2) – macrophage inflammatory protein-2 [murine usage; human homolog CXCL2]; mtDNA – mitochondrial DNA; MyD88 – myeloid differentiation primary response 88; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NO – nitric oxide; $O_2^{\bullet-}$ – superoxide anion; $ONOO^-$ – peroxynitrite; P – phosphorylated residue (phosphate modification); PAMPs – pathogen-associated molecular patterns; p65/p50 – NF-κB subunits (RelA/p50); RANTES (CCL5) – Regulated on Activation, Normal T Cell Expressed and Secreted; RIPK1 (RIP) – receptor-interacting serine/threonine-protein kinase 1; RNS – reactive nitrogen species; ROS – reactive oxygen species; TAK1 – TGF-β-activated kinase 1; TLR4 – Toll-like receptor 4; TLR9 – Toll-like receptor 9; TNFα – tumor necrosis factor alpha; TNFR1 – tumor necrosis factor receptor 1; TRADD – TNF receptor-associated death domain; TRAF2/5 – TNF receptor-associated factor 2/5; TRAF6 – TNF receptor-associated factor 6; Ub – ubiquitin

identify and synthesize key and impactful studies. Our approach focused on peer-reviewed, English-language publications primarily from 2010 to 2025, sourced from major databases including PubMed, Scopus, and Google Scholar. This timeframe allowed for the inclusion of recent advancements, which were supplemented by seminal older articles recognized for providing critical mechanistic insights into mitochondrial regulation,

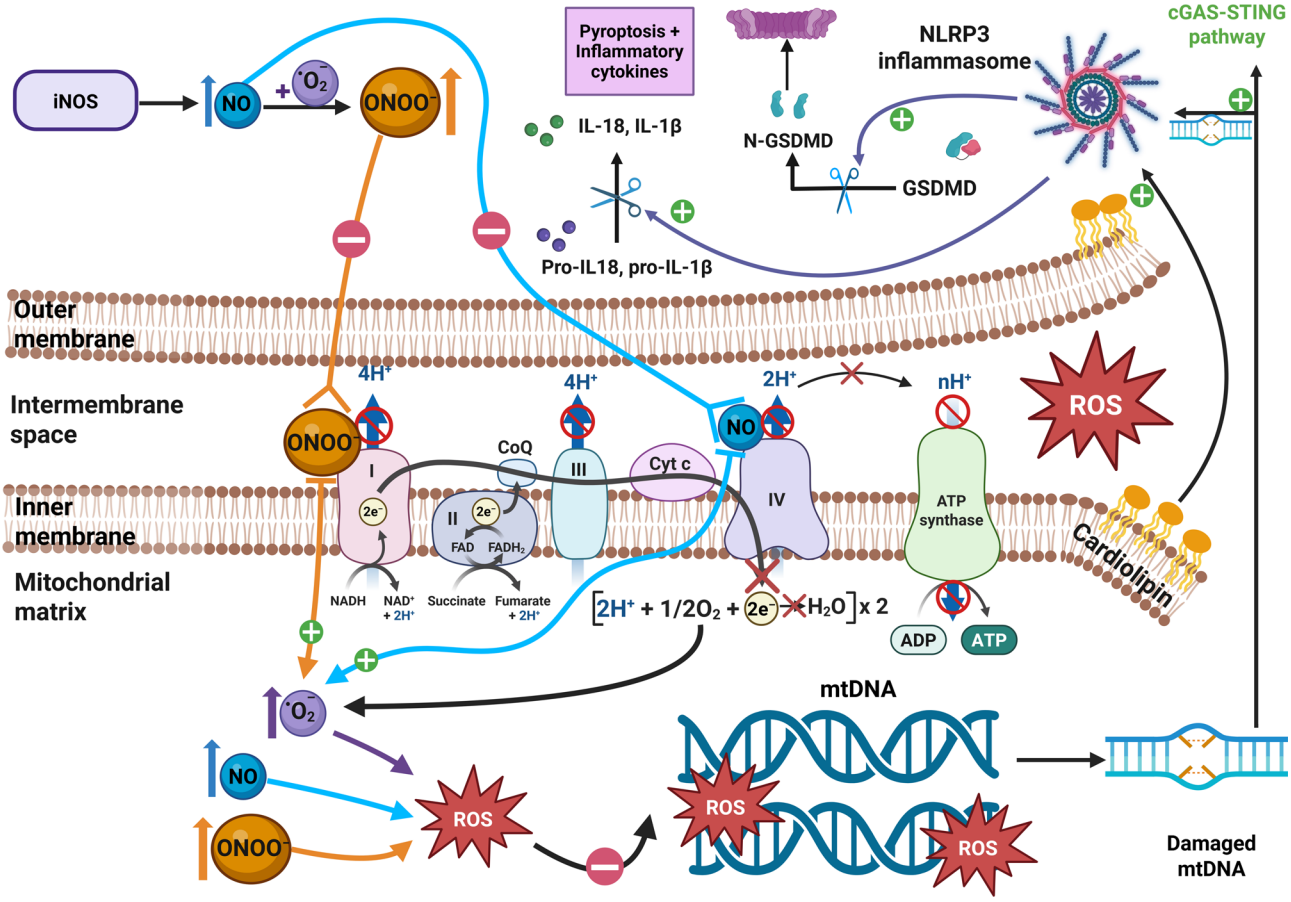

Fig. 3 Comprehensive molecular mechanisms involved in mitochondrial dysfunction and chronic inflammation activation in post-sepsis syndrome. Nitric oxide (NO), generated by inducible nitric oxide synthase (iNOS), initially inhibits mitochondrial respiratory chain complex IV, leading to impaired electron transport and accumulation of superoxide radicals (O_2^-). These superoxide radicals react with NO to form peroxynitrite ($ONOO^-$), a highly reactive nitrogen species (RNS). Peroxynitrite exacerbates mitochondrial dysfunction by inhibiting mitochondrial respiratory complex I, further amplifying oxidative and nitrosative stress within the mitochondria. Concurrently, cumulative mitochondrial dysfunction impairs ATP synthesis due to inhibition of electron transport through complexes I-IV, involving key electron carriers such as NADH, NAD^+, $FADH_2$, succinate, fumarate, and coenzyme Q (CoQ). This energy deficit and enhanced ROS production culminate in significant oxidative damage and cellular dysfunction. Excessive reactive oxygen and nitrogen species (ROS and RNS) subsequently induce oxidative damage to mitochondrial membranes, particularly affecting cardiolipin, a mitochondrial-specific phospholipid. Oxidized cardiolipin contributes to mitochondrial membrane instability and directly activates the NLRP3 inflammasome. Additionally, this oxidative damage disrupts mitochondrial membranes, especially the outer membrane, facilitating the release of mitochondrial DNA (mtDNA) into the cytosol and extracellular environment. Once released, cytosolic mtDNA, particularly oxidized mtDNA, acts as a damage-associated molecular pattern (DAMP), further activating the NLRP3 inflammasome and initiating the cGAS-STING signalling pathway. Activation of the NLRP3 inflammasome leads to the conversion of pro-caspase-1 into active caspase-1, which subsequently cleaves Gasdermin D (GSDMD) into its active N-terminal fragment (N-GSDMD). This fragment forms pores in the plasma membrane, triggering pyroptosis, a form of inflammatory cell death. These pores facilitate the release of the mature pro-inflammatory cytokines IL-1β and IL-18, which are cleaved from their inactive pro-forms by active caspase-1. Extracellular mtDNA further activates Toll-like receptor 9 (TLR9) signalling pathways in immune cells, potentially amplifying systemic inflammation, thus perpetuating chronic inflammatory and metabolic disturbances characteristic of post-sepsis syndrome. **Abbreviations**: ROS – reactive oxygen species; RNS – reactive nitrogen species; O_2^- – superoxide; $ONOO^-$ – peroxynitrite; NO – nitric oxide; iNOS – inducible nitric oxide synthase; mtDNA – mitochondrial DNA; DAMP – damage-associated molecular pattern; NLRP3 – NOD-like receptor protein 3 inflammasome; GSDMD – Gasdermin D; N-GSDMD – N-terminal fragment of Gasdermin D; cGAS–STING – cyclic GMP–AMP synthase–stimulator of interferon genes; IL – interleukin; Pro-IL-1β – pro-interleukin-1 beta; Pro-IL-18 – pro-interleukin-18; IL-1β – interleukin-1 beta; IL-18 – interleukin-18; TLR9 – Toll-like receptor 9; Complex I – NADH-ubiquinone oxidoreductase; Complex II – succinate dehydrogenase; Complex III – cytochrome c-ubiquinone oxidoreductase; Complex IV – cytochrome c oxidase; ATP – adenosine triphosphate; ADP – adenosine diphosphate; NADH – nicotinamide adenine dinucleotide (reduced); NAD^+ – nicotinamide adenine dinucleotide (oxidized); FAD – flavin adenine dinucleotide (oxidized); $FADH_2$ – flavin adenine dinucleotide (reduced); CoQ – coenzyme Q; Cyt c – cytochrome c; O_2 – molecular oxygen; H_2O – water; H^+ – proton; e^- – electron

immunometabolism, or systemic recovery following sepsis.

To specifically explore the role of mitochondrial dysfunction within each PSS phenotype, our literature analysis concentrated on identifying studies addressing core concepts relevant to each area, guided by illustrative search terms. This expert-driven selection prioritized studies for their direct relevance in

supporting the mechanisms and perspectives discussed. For instance, in examining the immunosuppressive phenotype, we focused our review on literature connecting post-sepsis syndrome and mitochondrial dysfunction with key immunological elements such as (but not limited to) 'Tregs', 'PD-1', and 'HLA-DR', often in combination with terms like 'post-sepsis syndrome' and 'mitochondrial dysfunction'. Similarly, for the neuromuscular phenotype, our analysis targeted studies on sepsis survivors and mitochondrial impairment by exploring concepts including 'PGC-1α', 'SS-31', 'muscle stem cells', and 'critical illness myopathy', in conjunction with terms like 'sepsis survivor' and 'mitochondrial dysfunction'. In addressing the persistent inflammatory phenotype, we examined research on mitochondrial dysfunction in the context of chronic inflammation, focusing on mechanisms involving 'NLRP3', 'oxidative stress', 'trained immunity', and 'mitophagy', alongside terms such as 'mitochondrial dysfunction'. Sources identified through this exploration were manually reviewed, with terms and references added as patterns emerged. Tables present selected examples to illustrate key mechanisms and are not intended as a systematic or exhaustive review.

While several animal and in vitro studies centered on acute-phase sepsis were considered, they were included for citation when their mechanistic findings were clearly applicable to understanding long-term mitochondrial dysfunction or post-sepsis trajectories. Articles deemed not directly pertinent to mitochondrial quality control, post-septic recovery, or the core arguments of this Perspective were not prioritized for inclusion. The final reference list, therefore, reflects a curated synthesis of high-impact and relevant studies aligned with the distinct PSS phenotypes chosen to best support the insights and framework proposed herein.

Limitations of the review. A substantial portion of the literature cited derives from preclinical models, particularly in rodents, which may not fully replicate the complexity of human post-sepsis trajectories. While these studies offer valuable mechanistic insights into mitochondrial dysfunction, caution is warranted when extrapolating findings to clinical settings.

Immunosuppressive phenotype

In the aftermath of sepsis, the immune system often shifts into a prolonged immunosuppressive phase. This shift likely reflects a compensatory response to the overwhelming inflammation present in early sepsis. Unlike transient inflammatory responses, this immunoregulatory shift persists well beyond the resolution of critical illness, contributing significantly to the immunosuppressive profile described within the PSS framework (conceptually overlapping with PICS) [15].

Interleukin 4 (IL-4), Interleukin 10 (IL-10), and Interleukin 37 (IL-37) are commonly elevated during prolonged immune suppression following sepsis, and represent key cytokines involved in dampening inflammatory responses [38–40]. These cytokines, particularly IL-10 and with preclinical support for IL-37, are associated with the expansion of immunosuppressive cell types, including regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [39, 40]. IL-37, in particular, has been recognized for its capacity to limit antigen presentation and reduce expression of HLA-DR on monocytes. High IL-37 concentrations observed in sepsis patients may contribute to more profound immune impairment [40, 41]. These cytokine-cell relationships are summarized in Figs. 4, 5.

Expansion of Treg and MDSC populations occurring alongside anti-inflammatory cues and heightened checkpoint pathway activity, further sustains the immunosuppressive environment. Tregs normally represent ~5–10% of the CD4 + T cell pool and are crucial in maintaining immune tolerance. While their numbers increase in sepsis and may persist in some patients, the regulatory pathways involved in this prolonged expansion remain incompletely understood. Potential mechanisms include altered cytokine signaling and elevated expression of immune checkpoints such as T cell immunoglobulin and mucin-domain containing-3 (TIM-3), programmed death-1 (PD-1), and Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) [23, 40, 42–45]. Forkhead-box P3 (Foxp3) gene expression, regulated via epigenetic modifications necessary for Treg stability, increases during sepsis-induced lymphocyte depletion, reinforcing this immunoregulatory state [40].

MDSCs, a diverse group of immature myeloid cells, persist in elevated numbers long after sepsis resolution and contribute to both innate and adaptive immune suppression [40, 46]. This is often accompanied by a marked decrease in Human Leukocyte Antigen-DR Isotype (HLA-DR) expression on monocytes, with levels being up to 70% lower in septic patients compared to nonseptic individuals. Reduced expression of HLA-DR on monocytes, particularly below 30% as used in clinical immunophenotyping studies such as the PROVIDE trial, but with limited sensitivity there, is associated with persistent immune suppression in patients recovering from sepsis [40, 47, 48].

The immune landscape continues to shift as macrophages transition from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, producing IL-10, transforming growth factor β (TGF-β), and IL-1 receptor antagonist (IL-1Ra), thus perpetuating an anti-inflammatory state [39, 40]. In murine macrophage cultures IL-4 or IL-13 activates Signal Transducer and Activator of Transcription 6 (STAT6), restores fatty-acid

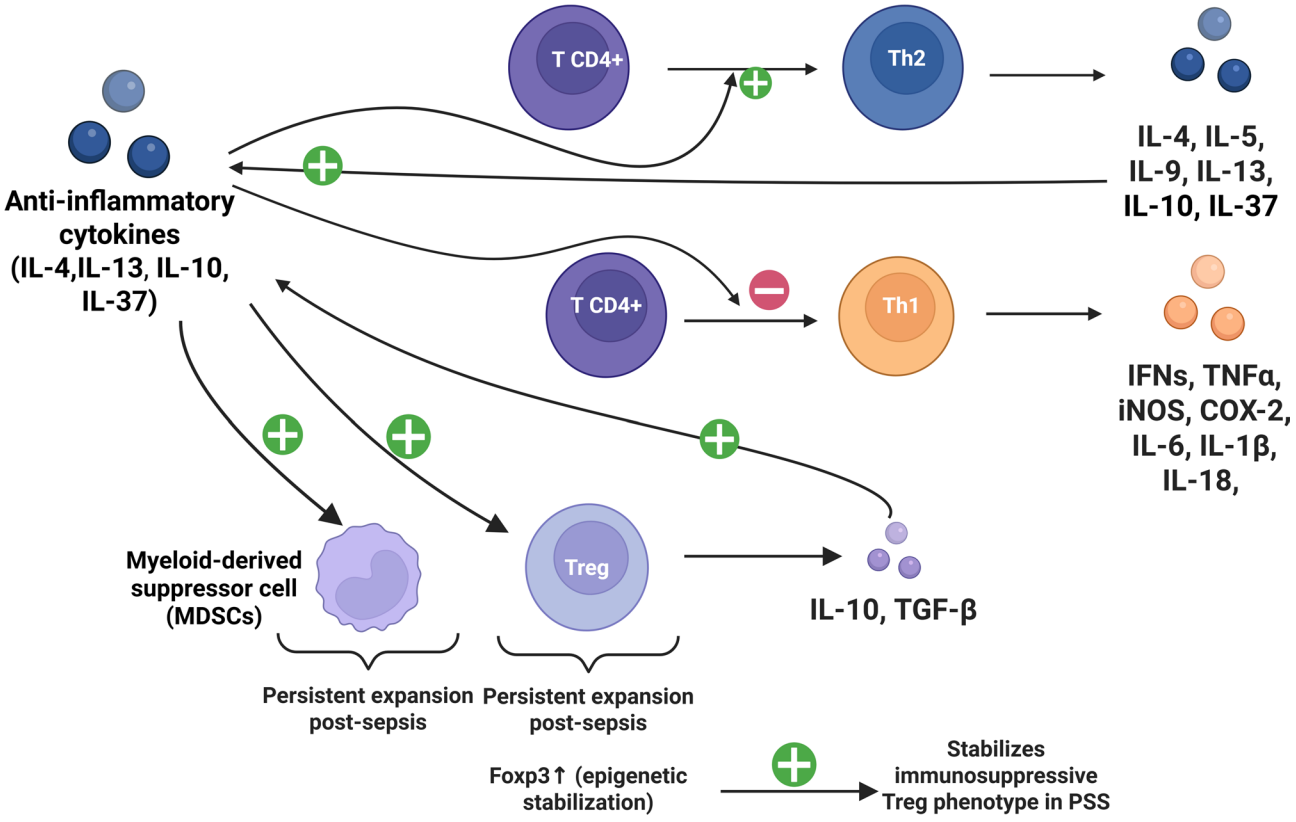

Fig. 4 Cytokine-driven regulation of T cell subsets and immunosuppressive cell populations in post-sepsis syndrome (PSS). Anti-inflammatory cytokines (IL-4, IL-10, IL-13, and IL-37) promote polarization of $CD4^+$ T cells toward a Th2 phenotype and suppress Th1 responses. This cytokine environment also induces the expansion of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), both of which persist beyond the acute phase of sepsis. IL-10 and TGF-β secreted by Tregs reinforce immunoregulation. Epigenetic stabilization of Foxp3 in Tregs contributes to the maintenance of their immunosuppressive phenotype in PSS. These interactions support a long-term shift toward immune tolerance and impaired pro-inflammatory responses in sepsis survivors. **Abbreviations**: IL – interleukin; TGF-β – transforming growth factor beta; T $CD4^+$ – CD4-positive T cell; Th1 – T-helper 1 cell; Th2 – T-helper 2 cell; Treg – regulatory T cell; MDSC – myeloid-derived suppressor cell; Foxp3 – Forkhead box P3 transcription factor; PSS – post-sepsis syndrome; COX-2 – cyclooxygenase-2; iNOS – inducible nitric oxide synthase; TNF-α – tumor necrosis factor alpha; IFNs – interferons

oxidation and mitochondrial respiration, and yields a reparative M2-like phenotype [20, 49]. Conversely, Lipopolysaccharide (LPS), IFN-γ, succinate and iNOS-derived nitric oxide keep NF-κB active, boost Reactive Oxygen Species (ROS) generation and lock cells in a glycolytic pro-inflammatory M1 state [17, 20, 50]. Studies in NADPH Oxidase family (NOX1/NOX2) double-knockout mice and in macrophages treated with selective NOX2 inhibitors reveal an expanded CD206-positive pool, indicating that superoxide from these oxidases restrains the shift toward the reparative programme [20]. NOX4 is constitutively active and its H_2O_2 output can support STAT6 phosphorylation and M2 gene expression in primary macrophages, while complete loss of NOX4 diverts cells toward a sustained M1 profile characterized by elevated NF-κB activity and increased NOX2 expression [49]. Taken together, these findings support a model in which balanced ROS signalling enables acquisition of the M2 metabolic state, whereas persistent superoxide generation maintains the inflammatory M1 phenotype. Recent work shows that in septic patients and Cecal Ligation and Puncture (CLP) mice, Sphingosine-1-phosphate receptor 2 (S1PR2)-driven dynamin-related protein 1 (Drp1)-dependent mitochondrial fragmentation is negatively associated with HLA-DR expression and sustains macrophage immunoparalysis, while genetic or pharmacologic inhibition of this axis restores mitochondrial function and host defence [51]. When monocytes are isolated from sepsis survivors and examined outside the body, both glycolytic flux and oxidative phosphorylation are markedly reduced, indicating that the mitochondria in these circulating precursor cells remain functionally impaired [17]. Because blood monocytes give rise to tissue macrophages, the bioenergetic defect is expected to be transmitted to newly formed M2 cells, whether they arise through direct differentiation of monocytes or by repolarisation of M1 macrophages that already carry mitochondrial injury. Although these macrophages display the canonical M2 surface markers and secrete high levels of IL-10 and TGF-β, the inherited mitochondrial

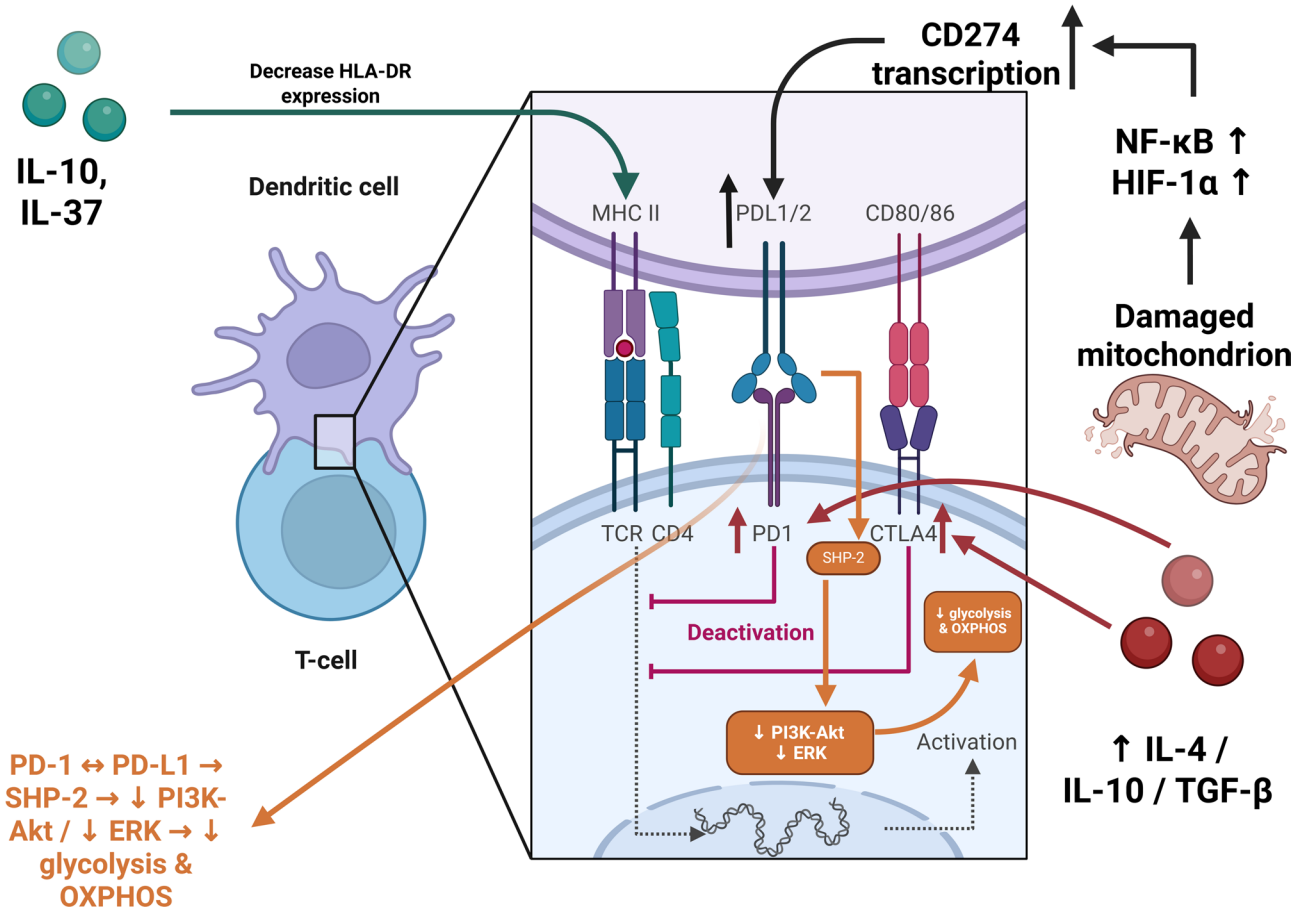

Fig. 5 Checkpoint-mediated inhibition of antigen presentation and T-cell activation in post-sepsis syndrome (PSS). After the acute septic episode, converging signals progressively disable adaptive immunity. Persistent IL-10 and IL-37 reduce HLA-DR on dendritic cells and restrict peptide–MHC II display. Damaged, depolarized mitochondria sustain ROS that maintain NF-κB and HIF-1α activity and drive CD274 transcription, loading monocytes and macrophages with PD-L1. PD-L1 engagement of PD-1 on $CD4^+$ T cells recruits SHP-2 and suppresses PI3K–Akt and ERK signaling, collapsing glycolysis and OXPHOS. The resulting checkpoint-rich environment up-regulates PD-1 and CTLA-4 on T cells, while the high-affinity interaction of CTLA-4 with CD80/86 withdraws co-stimulation. Tolerogenic cytokines (IL-4, IL-10, TGF-β) expand Tregs and MDSCs. Together, these processes lock adaptive immunity into the energy-depleted paralysis that defines PSS. **Abbreviations**: Akt – protein kinase B, CD4 – cluster of differentiation 4, CD80/86 – co-stimulatory molecules CD80 and CD86, CD274 – gene encoding PD-L1, CTLA-4 – cytotoxic T-lymphocyte-associated protein-4, ERK – extracellular-signal-regulated kinase, HIF-1α – hypoxia-inducible factor-1α, IL – interleukin, MDSC – myeloid-derived suppressor cell, MHC II (HLA-DR) – major histocompatibility complex class II, NF-κB – nuclear factor-κB, OXPHOS – oxidative phosphorylation, PD-1 – programmed death-1, PD-L1 – programmed death-ligand-1, PI3K – phosphoinositide-3-kinase, ROS – reactive oxygen species, SHP-2 – Src-homology-2-domain-containing phosphatase-2, TGF-β – transforming growth factor-β, Treg – regulatory T cell

deficit leaves them ATP-poor, blunting their programmes. The outcome is a metabolically impaired M2-like macrophage population that fails to sustain antimicrobial defense and exhibits limited capacity for tissue repair, due to sepsis-induced mitochondrial dysfunction [17, 20, 52]. The macrophage component of this shift including the NOX-controlled redox switch is illustrated in Fig. 6. Additionally, epigenetic alterations in macrophages following inflammation are associated with their long-term functional impairment and sustained immunosuppressive phenotype [53]. This phenotypic shift is accompanied by changes in gene expression and signalling pathways, that may contribute to the maintenance of immunosuppression over time.

Disruption of mitochondrial metabolism is increasingly implicated in sustaining immunosuppression following sepsis [7, 9, 11, 54]. After sepsis, impaired mitochondrial activity reduces ATP availability, elevates ROS production, and perturbs immune cell metabolism. These mitochondrial abnormalities compromise cellular energetic balance and are linked to reduced cytokine production as well as limited cell expansion and responsiveness [9, 11, 54]. These energetic defects align with immune-tolerance programs and are accompanied by increased expression of checkpoint molecules that suppress immune activation [11, 23, 45, 54].

Damage to mitochondria can trigger stress signals that reprogram immune cells long-term: pro-inflammatory

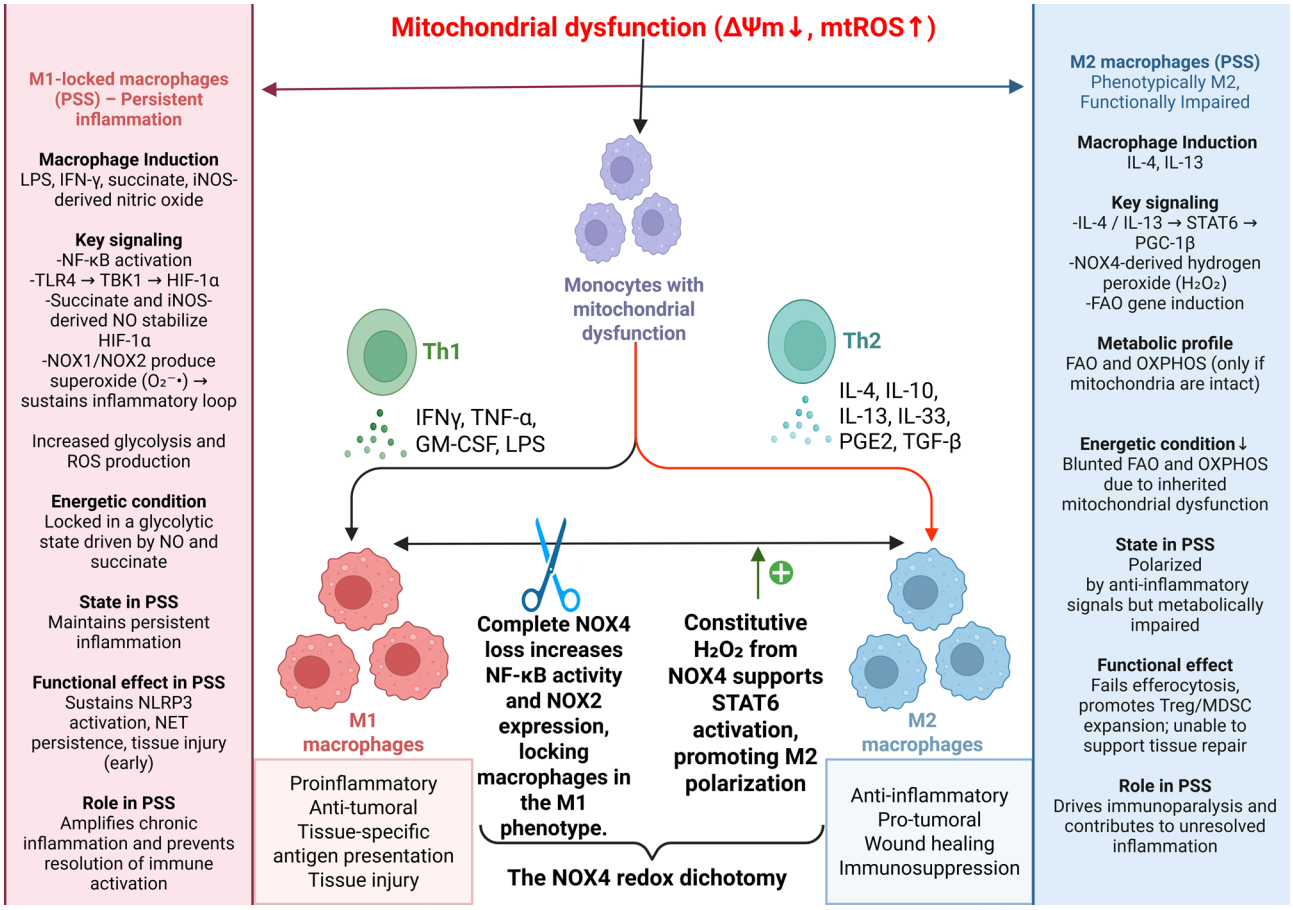

Fig. 6 Mitochondrial dysfunction redirects macrophage fate and sustains dual immune imbalance in post-sepsis syndrome. Monocytes from sepsis survivors carry persistent mitochondrial defects, including reduced membrane potential and elevated mitochondrial ROS, which alter their differentiation capacity. However, metabolic dysfunction also develops within macrophages themselves. Those initially polarized to the pro-inflammatory M1 state progressively accumulate mitochondrial damage during the immune response. Consequently, macrophages that later adopt an M2 phenotype, whether derived directly from circulating monocytes or by transitioning from M1, inherit an impaired mitochondrial network that limits their energy production and reparative function. **Left panel**: M1-locked macrophages (non-resolving inflammation, Sect."Persistent inflammatory phenotype"). Exposure to IFN-γ, LPS, succinate and nitric oxide derived from iNOS activates the TLR4 to TBK1 to HIF-1α signalling axis and enhances NF-κB activity. Superoxide ($O_2^{-\bullet}$) produced by NOX1 and NOX2 reinforces this inflammatory loop by promoting glycolysis, activating the NLRP3 inflammasome and sustaining early tissue injury. **Central axis:** The NOX4 redox dichotomy. Under normal conditions, constitutive hydrogen peroxide (H_2O_2) produced by NOX4 supports STAT6 signalling and enables M2 gene expression. In the absence of NOX4, this redox signal is lost, NF-κB and NOX2 activity increases, and macrophages remain fixed in the M1 phenotype. **Right panel:** Phenotypically M2 but functionally impaired macrophages (immunosuppressive phenotype, Sect."Immunosuppressive phenotype"). Although IL-4 and IL-13 still activate STAT6 and PGC-1β, mitochondrial dysfunction passed on from monocytes or M1 macrophages impairs fatty acid oxidation and oxidative phosphorylation. These ATP-deficient M2 cells express canonical anti-inflammatory markers and secrete IL-10 and TGF-β. While they retain the ability to promote regulatory cell expansion such as Tregs and MDSCs, they fail to clear apoptotic material or support tissue regeneration, thereby contributing to persistent immunoparalysis. This figure illustrates how mitochondrial dysfunction, whether inherited from precursor monocytes or acquired during early inflammatory activation, reshapes macrophage fate and traps the immune system between ongoing inflammation and ineffective resolution, two defining features of post-sepsis syndrome. **Abbreviations**: ATP – adenosine triphosphate, ΔΨm – mitochondrial membrane potential, FAO – fatty acid oxidation, H_2O_2 – hydrogen peroxide, HIF-1α – hypoxia-inducible factor 1-alpha, IL – interleukin, IL-33 – interleukin-33, iNOS – inducible nitric oxide synthase, LPS – lipopolysaccharide, MDSC – myeloid-derived suppressor cell, mtROS – mitochondrial reactive oxygen species, NET – neutrophil extracellular trap, NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells, NO – nitric oxide, NOX – NADPH oxidase, NOX1 – NADPH oxidase 1, NOX4 – NADPH oxidase 4, NLRP3 – NOD-like receptor family pyrin domain containing 3, OXPHOS – oxidative phosphorylation, PGC-1β – peroxisome proliferator-activated receptor-γ coactivator-1β, PSS – post-sepsis syndrome, ROS – reactive oxygen species, STAT6 – signal transducer and activator of transcription 6, TBK1 – TANK-binding kinase 1, TGF-β – transforming growth factor beta, Th1/Th2 – T helper cell type 1/type 2, TLR4 – toll-like receptor 4, Treg – regulatory T cell, GM-CSF – Granulocyte-Macrophage Colony-Stimulating Factor, IFN-γ – Interferon gamma, TNF-α – Tumor Necrosis Factor alpha, PGE_2 – Prostaglandin E_2. Note: Some pathways shown derive from preclinical macrophage studies and rodent disease models, including myocardial infarction (MI) and post-sepsis, and are presented for mechanistic context and hypothesis generation. These elements are not established causal relationships in human sepsis, may be context-dependent, and require direct validation in sepsis/post-sepsis

genes become epigenetically repressed and metabolism shifts toward glycolysis, leading to weaker responses to later challenges [39, 40, 54, 55].

Among the most clinically relevant downstream effects, the sustained upregulation of immune checkpoint regulators like PD-1 and programmed death-ligand-1 (PD-L1) has been reported in sepsis survivors. Their upregulation is correlated with significant immunosuppressive effects, including reduced T cell proliferation, impaired phagocytic responses, increased susceptibility to nosocomial infections, and elevated mortality rates [23, 42, 43, 56]. These mechanisms collectively obstruct immune recovery and present major challenges in managing patients with long-term consequences of sepsis [23, 39, 40]. Damaged and partly depolarised mitochondria in sepsis survivors may generate excess reactive oxygen species, release oxidised mitochondrial DNA, activate TLR9 and cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING), and prime the NLRP3 inflammasome. This state of mitochondrial dysregulation, which includes suppressed PGC-1α - Mitochondrial Transcription Factor A (TFAM) - dependent biogenesis, is associated with persistently active NF-κB and Hypoxia-Inducible Factor-1 Alpha (HIF-1α) and may persist beyond the acute phase in some survivors, although longitudinal human evidence is limited [7, 11, 32, 54, 57]. Figure 5 presents a conceptual model that synthesizes these relationships. These transcription factors drive CD274 transcription, raise PD-L1 on monocytes and macrophages [23, 45]. Ligation of PD-L1 to PD-1 on T lymphocytes recruits SHP-2, leading to the inactivation of Phosphoinositide 3-Kinase - Protein Kinase B (PI3K-Akt) and Extracellular-Signal-Regulated Kinase (ERK) signalling pathways and contributing to T cell dysfunction, which can involve metabolic alterations such as impaired glycolysis, a state of immune impairment shown to be partially reversible with PD-1 or PD-L1 blockade in the CLP sepsis model [23, 45]. Chronic exposure to this checkpoint-rich environment may be associated with increased expression of PD-1 and CTLA-4 on circulating $CD4^+$ T cells, a change consistently documented in both clinical cohorts and animal models of sepsis [45, 58].

Understanding the immunological and metabolic basis for this sustained immunosuppression is essential for advancing new treatments. Possible approaches include mitochondrial-targeted therapies, immunomodulation to counter excessive Treg and MDSC expansion, and interventions aimed at recalibrating cytokine responses. However, comprehensive mechanistic studies are still required to guide precision strategies and restore effective immunity in post-sepsis survivors. The evidence summarized in Table 1 supports a link between mitochondrial function and this phenotype.

Neuromuscular phenotype

This section highlights the central role of persistent mitochondrial dysfunction in the pathogenesis of PSS, with a specific focus on the neuromuscular phenotype. While a multitude of molecular mechanisms may contribute to this phenotype, mitochondrial impairment is widely regarded as the primary source.

Recent data suggest that mitochondrial dysfunction is associated with prolonged neuromuscular impairment in PSS, with effects that persist beyond the acute phase in experimental models [7, 26, 54]. Several investigations indicate that individuals recovering from sepsis exhibit a marked decline in skeletal muscle mitochondrial efficiency and altered activity across complexes I to IV. These alterations often include decreased Complex I contribution, while varied changes in the activity of Complexes II and III have been reported, with some studies noting a potential compensatory upregulation of their function in remaining mitochondria within muscle affected by prolonged critical illness [25, 29, 54]. In sepsis, inflammatory signaling, particularly IL-6, suppresses the PGC-1α program in mature myofibers and drives mitochondrial ROS and atrophy. The same stress may imprint muscle stem cells with a perturbation of the PGC-1α axis that could extend into the post-sepsis period and impede regeneration [25, 29, 30, 54]. As a master regulator of mitochondrial biogenesis, PGC-1α orchestrates the expression of numerous genes essential for mitochondrial structure, function, and oxidative metabolism. Its reduction or loss, therefore, critically compromises these vital cellular processes. In a mouse caecal ligation and puncture model, sustained down-regulation of PGC-1α increases mitochondrial ROS and precipitates muscle atrophy, whereas genetic restoration of PGC-1α normalises mitochondrial function and preserves muscle mass and contractile force, establishing a direct causal link [30]. Pharmacological activation of the PGC-1α axis, most clearly through metformin-mediated AMPK activation and through NAD^+ precursors such as Nicotinamide Mononucleotide (NMN) or nicotinamide riboside, likewise improves mitochondrial performance and muscle energetics in inflammatory and catabolic settings [54, 57, 59].

Ye et al. demonstrated that TLR4/Myeloid Differentiation Primary Response 88 (MyD88) activation in Schwann cells promotes macrophage infiltration, directly contributing to neuromuscular dysfunction in a murine model of sepsis (CLP) [60]. Similarly, Schmitt et al. reported lasting transcriptional changes in muscle stem cells, including disrupted mitochondrial metabolism, sirtuin and estrogen signalling, with oxidative phosphorylation genes remaining transcriptionally upregulated four weeks post-sepsis. Importantly, the muscle stem cells (MuSC) findings summarised above were obtained in the standard murine cecal-ligation-and-puncture (CLP)

Table 1 Linking mitochondrial dysfunction to persistent immunosuppression in post-sepsis syndrome (PSS)

Author (Ref ID)	Mitochondrial mechanism identified	Cell type/tissue	How this drives post-sepsis immunosuppression	Study type/ model
Park DW et al., 2017 [17] (★)	↓ Glycolysis + ↓ Oxidative Phosphorylation (OXPHOS) → ↓ ATP = bioenergetic failure	Peripheral monocytes from post-septic patients; review also covers neutrophils, macrophages & T-cells	Energy deficit → blunted cytokine release & poor restimulation → persistent immunoparalysis	Narrative review (clinical & experimental literature synthesis)
Kong Y et al., 2024 [20] (o)	Fatty Acid Oxidation (FAO) + intact Electron Transport Chain (ETC) → ↑OXPHOS → IL-10/TGF-β M2-like macrophage; Ndufs4 knockout (complex I) → ↑ROS, pro-inflammatory macrophage features, impaired transition to repair; ROS scavenging mitigates defects	Cardiac resident & monocyte-derived macrophages (mouse MI) ± Bone-Marrow-Derived Macrophages (BMDM) in vitro	Mechanism identified in myocardial infarction: an intact ETC supports resolution via FAO/OXPHOS and M2-like polarization; ETC dysfunction → ↑ROS, sustained pro-inflammatory state, and delayed tissue repair. Sepsis is not examined here, but many inflammatory pathways overlap; extrapolation to sepsis is plausible, requires validation, and may help explain failed resolution/ secondary immunosuppression	Narrative review (summarises in-vivo mouse MI studies)
Zhu CL et al., 2021 [21] (★)	Sepsis → damaged mitochondria → mitophagy (PINK1/Parkin or BNIP3/ FUNDC1) → removal of defective mitochondria → ↓ mtROS and ↓ mitochondrial DNA (mtDNA) DAMPs	Heart, kidney, lung, liver parenchyma & macrophages (mouse CLP/LPS models, patient data – literature synthesis)	Efficient mitophagy → ↓ mtROS/DAMPs → ↓ NLRP3 activation → ↓ cytokine production; Mitophagy failure → damaged mitochondria persist → prolonged inflammation → tendency toward immunosuppression via sustained inflammation (hypothesis)	Narrative review (mechanistic synthesis of in-vivo & in-vitro studies)
Hwang JW et al., 2021 [22] (★)	Exogenous mitochondria → ↑ respiration & ATP → early TNF-α ↓; late (tolerant) TNF-α ↑ + E. coli phagocytosis ↑ → immunoparalysis ↓ → bacterial load ↓ → survival ↑	Splenic leukocytes (rat cecal-slurry sepsis) + LPS-tolerised human Peripheral Blood Mononuclear Cell (PBMC) monocytes	Restored bioenergetics reverses the immunosuppressive phase. A mechanism also plausible for PSS	Experimental in vivo
Zhang T. et al., 2023 [23] (o)	Inflammation/hypoxia → STAT1/HIF-1α/NF-κB activation → PD-L1 up-regulation on monocytes & macrophages	T-cells, monocytes, macrophages (literature on CLP mice + patients)	PD-L1 binds PD-1 on T cells → SHP-2 recruitment (±SHP-1) → PI3K dephosphorylation → Akt & ERK/MAPK inhibition → T-cell exhaustion → persistent immunoparalysis	Review (evidence synthesis)

ATP – adenosine 5′-triphosphate; OXPHOS – oxidative phosphorylation; ETC – electron transport chain; ROS – reactive oxygen species; mtROS – mitochondria-derived ROS; mtDNA – mitochondrial DNA; PINK1 – PTEN-induced kinase 1; Parkin – ubiquitin E3 ligase mediating mitophagy; FAO – fatty acid oxidation; PD-1 – programmed cell death protein 1; PD-L1 – programmed death-ligand 1; HIF-1α – hypoxia-inducible factor-1α; CLP – cecal ligation and puncture sepsis model; IL-10 – Interleukin 10; TGF-β – Transforming growth factor beta; M2-like – M2 macrophage phenotype (pro-repair/anti-inflammatory); Ndufs4 – NADH dehydrogenase [ubiquinone] iron-sulfur protein 4; BMDM – Bone Marrow-Derived Macrophages; BNIP3 – BCL2 Interacting Protein 3; FUNDC1 – FUN14 Domain Containing 1; DAMPs – Damage-Associated Molecular Patterns; NLRP3 – NOD-, LRR- and pyrin domain-containing protein 3; TNF-α – Tumor necrosis factor alpha; PBMC – Peripheral Blood Mononuclear Cells; STAT1 – Signal transducer and activator of transcription 1; NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells; SHP1/2 – Src homology 2 domain-containing phosphatase 1 and 2; PI3K – phosphoinositide 3-kinase; Akt – Protein Kinase B (PKB); ERK – Extracellular signal-regulated kinases; MAPK – Mitogen-Activated Protein Kinase; PSS – Post-sepsis syndrome; LPS – Lipopolysaccharide; MI – Myocardial Infarction; E. coli – Escherichia coli. Study-type codes: in vivo – animal model; in vitro – cultured cell lines; clinical – data obtained directly from patients; experimental in vivo – original animal work reported in the cited paper; evidence synthesis – narrative, integrative or systematic review compiling primary studies. ★ - Strong evidence for post-sepsis syndrome & mitochondrial dysfunction. o - Partial evidence for post-sepsis syndrome & mitochondrial dysfunction (Partial evidence = biologically valid, but not correlated with persistent clinical manifestations of post-sepsis syndrome (which define PSS))

model without surgical source-control of the necrotic cecum [25]. Retaining the infected cecum sustains a chronic intra-abdominal inflammatory focus, which can prolong systemic cytokine secretion and potentially amplify the transcriptional and functional impairment of MuSCs beyond what is seen in sepsis models that include early source-control. The translational implications of this model choice, together with alternative rodent approaches and large-animal data, are discussed in Sect. 3. Although increased expression of mitochondrial complex genes may reflect attempted compensation, multiple studies indicate that mitochondrial function often remains impaired despite such transcriptional changes, suggesting unresolved dysfunction rather than successful adaptation in sepsis [54].

Although apoptosis was not directly observed, other studies suggest that persistent muscle weakness in PSS is mainly driven by persistent mitochondrial impairment rather than widespread apoptotic loss [24, 27]. Ultrastructural studies frequently reveal swollen mitochondria with disorganized cristae in muscle biopsies of sepsis survivors, findings linked (in experimental models) to impaired ATP production and increased ROS accumulation [26, 27, 54]. Accumulating ROS worsens mitochondrial stress and is associated with activation of muscle proteolytic pathways such as the ubiquitin–proteasome system, contributing to persistent weakness [24, 27, 54]. Oxidative stress contributes not only to direct mitochondrial damage but also promotes excessive mitochondrial fission, probably via Drp1 activation, leading to mitochondrial fragmentation and impaired bioenergetics. In

skeletal muscle, this imbalance in mitochondrial dynamics exacerbates post-sepsis skeletal muscle weakness by impairing mitochondrial function and quality-control processes [27, 54]. Consistent with these findings, recent studies suggest that preserving or restoring mitochondrial function through approaches like mitochondria-targeted antioxidants or Drp1 inhibition may reduce muscle wasting and improve long-term outcomes in preclinical sepsis models [26, 27, 54].

Furthermore, impaired mitophagy (the selective removal of dysfunctional mitochondria) is suggested to be an important contributor to PSS-related neuromuscular dysfunction. Deficient expression or activity of key regulators like Phosphatase and tensin homolog (PTEN) - induced kinase 1 (PINK1) and 3 ubiquitin ligase involved in mitophagy (Parkin) reduces the clearance of damaged mitochondria, increasing cellular stress [11, 28, 54]. Satellite cell dysfunction [25], compounded by post-sepsis energy depletion and oxidative stress [24, 28], likely further compromises muscle repair and regeneration and may perpetuate neuromuscular deficits in PSS patients.

Evidence from animal and in vitro studies shows that skeletal muscle stem cells are required for long-term recovery after sepsis and display persistent alterations in oxidative phosphorylation and other mitochondrial pathways [25], while genetically enhancing mitophagy via Parkin overexpression attenuates sepsis-induced muscle wasting and preserves mitochondrial morphology and protein content in mice [28].

Clinically, these cellular and mitochondrial abnormalities may translate into significant and persistent neuromuscular impairments in individuals affected by PSS. For instance, elderly individuals recovering from sepsis frequently experience persistent swallowing difficulties, which may continue after discharge and impair recovery [61, 62]. Moreover, persistent muscle weakness and poor physical recovery have been documented for months after sepsis in preclinical and translational studies, with mitochondrial integrity emerging as a key determinant of neuromuscular outcomes [26, 27].

In conclusion, mitochondrial dysfunction stands as a defining feature of the neuromuscular phenotype in PSS. Therapeutic strategies targeting mitochondrial restoration, including interventions that enhance oxidative phosphorylation, promote mitophagy, or bolster antioxidant defenses, may significantly improve rehabilitation outcomes, reduce long-term morbidity, and enhance quality of life for individuals recovering from post-sepsis syndrome. The evidence summarized in Table 2 supports a link between mitochondrial function and this phenotype.

Persistent inflammatory phenotype

Persistent low-grade inflammation after sepsis can hinder tissue repair and predispose survivors to a range of long-term complications. An important contributor to this process is mitochondrial dysfunction, whereby compromised ATP production and heightened oxidative stress perpetuate immune activation and chronic cellular stress [2, 63].

The consequence of sepsis is a series of changes to the structure and function of the mitochondria that are accompanied by a significant upregulation of ROS production. These changes may result in the amplification of inflammatory cascades [11, 24]. Consecutive, mitochondrial injury promotes the release of damage-associated molecular patterns (DAMPs) such as ATP, cardiolipin, and mitochondrial DNA (mtDNA), which can activate innate immune responses through the NLRP3 inflammasome, with mtDNA additionally binding to and activating Toll-like receptor 9 (TLR9) [21, 32, 64]. Figures 1 and 2, and 3 provide an integrated, multi-scale perspective on the molecular mechanisms sustaining inflammation in PSS. Figure 2 illustrates the early activation of innate immune signalling through surface receptors such as TLR4 and Tumor Necrosis Factor Receptor (TNFR), leading to NF-κB activation, iNOS expression, and the production of reactive oxygen and nitrogen species (ROS and RNS), which initiate mitochondrial stress. Figure 3 builds upon this by depicting how oxidative damage to mitochondria leads to the release of damage-associated molecular patterns (DAMPs), including mtDNA and cardiolipin. These intracellular signals further amplify inflammation through activation of the NLRP3 inflammasome and cGAS–STING pathways. Figure 1 extends the model into the extracellular context, where persistent NETosis and impaired resolution allow oxidized mtDNA to engage endosomal TLR9 in metabolically dysfunctional immune cells. This process contributes to a low-grade, chronic inflammatory response. Together, these figures describe a coordinated sequence of events that links receptor-level signalling, mitochondrial dysfunction, and extracellular immune dysregulation in the pathogenesis of PSS.

Among sepsis survivors, chronic persistent inflammation has been reported and may be maintained by enduring stimuli such as systemic mitochondrial dysfunction and disruptions in mitochondrial quality control. These alterations can sustain mitochondrial reactive oxygen species and pro-inflammatory signaling. During the acute phase, a regulated inhibition of mitophagy acts as a host defense by increasing mitochondrial ROS, engaging NLRP3-dependent pathways, promoting IL-1β release, and reinforcing immune activation. If these processes persist or become dysregulated, they can fuel long-term inflammation [31, 64].

Table 2 Linking mitochondrial dysfunction to neuromuscular phenotype in post-sepsis syndrome (PSS)

Author (Ref ID)	Mitochondrial mechanism identified	Cell type/tissue	Impact on chronic muscle weakness/wasting	Study type/model
Owen AM et al., 2019 [24] (★)	Cristae disruption & ETC I/II/IV dysfunction → ↓ Oxygen-Consumption Rate (OCR) + ↑ ROS/RNS (inferred from markers: protein carbonyls, 3-nitrotyrosine) → oxidative protein damage	Skeletal muscle (tibialis anterior, extensor digitorum longus, gastrocnemius)	Maximal specific force in EDL drops by ~25% in males and ~20% in females at 2 weeks, and in males remains ~17% lower at 1 month; the effect is independent of muscle size (force normalized to physiological cross-sectional area)	Experimental in vivo – non-surgical cecalslurry sepsis; no surgical source control; antibiotic and fluid therapy; 1 month followup
Schmitt RE et al., 2023 [25] (★)	ETC I–V transcript dysregulation & mitochondrial dysfunction in satellite cells → ↓MuSC proliferation & morphology defects → impaired muscle regeneration → persistent lean-mass deficit (Pax7-DTA)	Skeletal muscle satellite cells (MuSCs) from hindlimb muscles	~5–8% lean-mass loss maintained throughout the experiment (~Day 30) with MuSC ablation (Pax7-DTA); regeneration capacity ↓ after secondary injury	In vivo, cecal ligation and puncture + daily chronic stress; antibiotics and fluids; up to 7 weeks followup (Day 50 postsepsis)
Kingren MS et al., 2024 [26] (★)	Sepsis → loss of ETC complexes I/II/V (IV partially ↓) + Complex I/II activity ↓ + mitochondrial ultrastructure damage → chronic skeletal muscle weakness; cascade is blocked by MnSOD overexpression or Elamipretide (SS-31, a cardiolipin-targeted peptide)	Skeletal muscle (plantarflexor muscles; gastrocnemius & soleus)	Plantarflexor force shows ~69% deficit at 2 weeks, partially recovers to ~57% at 10 weeks despite full muscle mass recovery; MnSOD-TG (MnSOD Transgenic) or SS-31 completely prevents chronic weakness	Experimental in vivo – non-surgical cecalslurry sepsis; no surgical source control; antibiotics and fluids; 10week followup
Huang D et al., 2025 [27] (★)	S100A8/A9 ↑ → RAGE → Drp1-Ser616-P ↑ → mitochondrial fragmentation → ATP ↓ → skeletal muscle atrophy (rescued by paquinimod, RAGE−/−, or Mdivi-1)	Skeletal muscle (murine TA, GA, EDL + CT-derived L3 SMI in septic patients)	Mouse: CSA & muscle weight ↓; ~25% body weight loss; Human: 56% sarcopenic at discharge, ΔSMI independently predicts 60-day mortality (OR ≈ 5.9)	Combined study – CLP sepsis mice (no surgical source control; 2week followup) + retrospective clinical cohort ($n = 86$ septic patients; 60 day followup)
Leduc-Gaudet JP et al., 2020 [28] (o)	Parkin overexpression ↑ → ETC I/IV & VDAC content preserved → improved mitochondrial morphology → skeletal muscle atrophy prevented (48 h)	Skeletal muscle (gastrocnemius)	CLP-induced myofiber diameter loss fully prevented at 48 h	Experimental in vivo – CLP sepsis mice with AAVParkin; no surgical source control; 48 h followup
Jiroutková K et al., 2016 [29] (o)	Mitochondrial density ↓ (~31%, P=0.051) → FAO capacity ↑ (~157% vs controls, P=0.015) → after 6 days of FFA exposure: spare respiratory chain capacity ↑ only in ICUAW myotubes	Human vastus-lateralis myotubes ((Intensive Care Unit-Acquired Weakness (ICUAW) patients))	Fatty acid oxidation capacity increased by 157% despite decreased mitochondria; metabolic adaptation supports residual energy demand during weakness	Ex vivo primary human culture; biopsies from 6 ICU-acquired weakness vs. 7 controls
Yang B et al., 2022 [30] (o)	IL-6 knock-out → ↑ PGC-1α expression → ↓ mitochondrial reactive oxygen species (ROS) → Suppression of atrophy genes Atrogin-1 and MuRF-1	Skeletal muscle (EDL)	Cecal ligation and puncture-induced cross-sectional area loss and force deficit attenuated at 48 h	In vivo, interleukin-6 knock-out + cecal ligation and puncture; focus left in situ (no surgical source control); antibiotic therapy not specified; 48 h follow-up

ΔSMI (delta SMI) – 30-day standardized change in skeletal muscle index; AAV – adeno-associated virus; ATP – adenosine 5′-triphosphate; Atrogin-1 – muscle atrophy F-box gene 1; CLP – cecal ligation and puncture; Complex I–V – individual oxidative phosphorylation complexes 1 to 5; CSA – cross-sectional area; CT – computed tomography; Drp1 – dynamin-related protein 1; EDL – extensor digitorum longus; ETC – electron transport chain; FAO – fatty acid oxidation; FFA – free fatty acids; GA – gastrocnemius; ICUAW – intensive care unit–acquired weakness; IL-6 – interleukin 6; Mdivi-1 – mitochondrial division inhibitor 1; MnSOD – manganese superoxide dismutase; MuRF-1 – muscle RING-finger protein 1; MuSC – muscle satellite cell; OCR – oxygen consumption rate; Parkin – ubiquitin E3 ligase triggering mitophagy; PGC-1α – Peroxisome proliferator-activated receptor-gamma coactivator 1-alpha; PSS – post-sepsis syndrome; RAGE – receptor for advanced glycation end products; RNS – reactive nitrogen species; ROS – reactive oxygen species; S100A8/A9 – S100 calcium-binding proteins A8/A9; SMI – skeletal muscle index; SS-31 – Elamipretide (cardiolipin-targeted peptide); TA – tibialis anterior; TG – transgenic; VDAC – voltage-dependent anion channel. Study type codes: Experimental in vivo – original animal model of sepsis with mechanistic readouts; Combined study – single paper integrating an animal model with a human patient cohort; Clinical ex vivo – primary cells or tissues obtained from patients and analysed outside the organism. ★ – Strong evidence for post-sepsis syndrome & mitochondrial dysfunction. o – Partial evidence for post-sepsis syndrome & mitochondrial dysfunction (Partial evidence = biologically valid, but not correlated with persistent clinical manifestations of post-sepsis syndrome (which define PSS))

Furthermore, metabolic reprogramming of $CD4^+$ T cells, characterized by enhanced glycolysis and sustained IL-17 production, has been implicated in chronic inflammation, suggesting a potential mechanistic link to ongoing immune dysregulation [33]. TLR4-dependent signalling engages multiple kinase intermediates and intersects with metabolic pathways that can modulate the activity of transcription factors such as HIF-1α. This pathway reinforces the metabolic reprogramming and sustained inflammation characteristic of acute sepsis and possibly of post-sepsis syndrome, thereby suggesting potential therapeutic targets. The metabolic shift is

driven principally by HIF-1α, which enhance glycolytic flux, rely less on oxidative phosphorylation and favour the differentiation of $CD4^+$ T cells toward the Th17 subset. Following antigenic stimulation, $CD4^+$ T cells increase the expression of glucose transporters and glycolytic enzymes under the integrated control of Myc and HIF-1α. Although this adaptation supports effector function, failure to achieve timely resolution perpetuates a pro-inflammatory environment. A parallel circuit operates in macrophages. NOX-dependent superoxide, including that generated by NOX1 and NOX2, together with the tricarboxylic-acid-cycle intermediate succinate, can sustain a glycolytic M1 programme. By contrast, NOX4 is context dependent. A tonic output of H_2O_2 from NOX4 sustains STAT6 signalling and promotes M2 polarisation, whereas complete loss of NOX4 removes this H_2O_2-mediated restraint on NF-κB and redirects macrophages toward an M1 phenotype. By contrast, in murine models of post-sepsis, knock-down of NOX4 restores mitochondrial ATP synthesis in the kidney and attenuates inflammatory signalling in both the lung and kidney. Even so, the altered post-septic redox state, characterised by excess superoxide and the absence of the NOX4-derived H_2O_2 signal that normally drives STAT6, can trap these M1-skewed macrophages in their inflammatory state and prevent transition to the reparative M2 programme. Together with continuous mitochondrial reactive oxygen species that activate the NLRP3 inflammasome, these intersecting metabolic circuits in T cells and macrophages may provide a mechanistic explanation for the persistent, non-resolving inflammation observed in post-sepsis syndrome [17, 20, 37, 49, 52, 65, 66]. An integrated view of how mitochondrial dysfunction locks macrophages between an inflammatory M1 loop and an ATP-deficient, ineffective M2 subset is provided in Fig. 6.

After sepsis, many survivors exhibit a pro-inflammatory state linked to sustained metabolic changes and heightened cytokine output in certain compartments [34]. Although acute models demonstrate that ROS generated by NOX4 drive early inflammatory injury [67], subsequent evidence shows that immune cells can remain hyper-responsive for extended periods, a phenomenon consistent with trained immunity and persistent dysregulation [34]. In particular, excess ROS can favour glycolysis over oxidative phosphorylation, promoting ongoing pro-inflammatory signalling [11, 34]. This glycolytic bias, as suggested by acute ROS-driven models [67], consolidate into persistent metabolic reprogramming that is accompanied by epigenetic remodeling of innate immune cells and may underpin enduring immunological dysfunction after sepsis [55]. This altered metabolic state enhances proinflammatory cytokine production and may help sustain inflammatory activation beyond the acute phase of sepsis [34]. While the primary findings derive from in vitro-trained human monocytes, the HIF-1α-dependent glycolytic pathway was validated in vivo using myeloid-specific HIF-1α knockout mice, strengthening the translational value of this pathway [65].

Emerging data suggest that microRNA-223 (miR-223) helps limit NLRP3 inflammasome activation, a mechanism potentially relevant to the excessive inflammatory response observed in post-sepsis syndrome [68]. In line with the previous statement, in cellular and murine models of acute sepsis, miR-223-3p reduces NLRP3 expression or activation and limits pyroptosis [69]. Clinically, higher miR-223 expression in blood leukocytes is linked to better outcomes. Over-expression of miR-223 in vitro decreases lymphocyte apoptosis and increases their proliferation, whereas blocking miR-223 does the opposite [70]. Whether inadequate restoration of miR-223 after the acute episode maintains inflammasome activity and chronic inflammation in PSS remains speculative.

In parallel with the mechanisms outlined at the beginning of this section, TLR4 signalling during sepsis activates downstream MAP-kinases such as ERK [60], while activation of the Akt–mTOR axis stabilises HIF-1α and shifts cellular metabolism toward glycolysis. This metabolic programme sustains pro-inflammatory M1-like macrophages and favours Th17 differentiation [20, 33, 65]. As previously established, glycolytic reprogramming is a recognised feature of trained immunity, persisting months after sepsis in murine CLP models and in β-glucan-trained human monocytes [34, 65]. Removing HIF-1α from myeloid cells abrogates this programme and the associated trained immunity and protection [65].

Taken together, documented dysregulations such as inadequate miR-223 regulation (which can contribute to increased NLRP3 activation) [69], persistent mitochondrial distress (a source of DAMPs that can activate inflammasomes) [11], and distinct metabolic reprogramming, including an HIF-1α-driven bias characteristic of trained immunity [65], are interconnected and likely relevant. We hypothesize that their long-term interplay could reinforce low-grade inflammasome activity, which may help sustain the chronic inflammation observed in sepsis survivors with persistent syndromes such as PICS [71] conceptually related to PSS. This highlights potential therapeutic angles, including restoration of miR-223 regulation and support of mitochondrial quality control.

The persistent inflammatory phenotype, often sharing mechanistic overlaps with PICS, has been linked to lasting epigenetic shifts in DNA methylation and histone marks, which may contribute to a long-lasting, poorly regulated immune response [55, 72]. Such epigenetic modifications may prime an exaggerated inflammatory response after a second hit, consistent with observations in post-sepsis models rather than proving a uniformly extended hyperinflammatory state [34]. Additionally,

faulty mitophagy caused by weak PINK1-Parkin signalling can drive the accumulation of damaged mitochondria, which further fuels the process [21]. As a result, these combined factors may help maintain a durably dysregulated immune environment characteristic of PSS/PICS, with some studies specifically highlighting concurrent immunosuppressive shifts and impaired inflammatory responses [55].

Moreover, conceptual and observational evidence suggests that a plausible vicious cycle involving mitochondrial dysfunction (particularly in skeletal muscle), alterations in the gut microbiota, and a compromised intestinal epithelial barrier potentiates systemic inflammation and contributes to multiorgan dysfunction [64, 73, 74]. Furthermore, lower levels of Short-Chain Fatty Acids (SCFAs) are observed in sepsis [64] and may correlate with stronger inflammatory activity and impaired recovery in septic patients, although the available evidence is observational and confounded (e.g., antibiotics, nutrition) [73, 74]. Causality remains uncertain. The evidence summarized in Table 3 supports a link between mitochondrial function and this phenotype.

Discussion–mitochondrial senescence as a therapeutic target in post-sepsis syndrome: from hypothesis to intervention

The clinical profile of post-sepsis syndrome (PSS) suggests that mitochondrial dysfunction is not merely a downstream effect but an active contributor to its chronic pathology. We hypothesize that persistent mitochondrial failure may underlie key PSS features such as immune dysregulation, chronic inflammation, and neuromuscular impairment, largely through mechanisms involving long-term mitochondrial senescence, a concept introduced here and consistent with observations in [63]. These senescent mitochondria are not simply inactive but continue to generate oxidative stress and pro-inflammatory signals, which may drive the sustained dysfunction observed in PSS. In this context, we refer to "mitochondrial senescence" as the persistence of dysfunctional mitochondria that escape quality control mechanisms and retain the potential to propagate damage through fusion-fission cycles. These mitochondria not only fail to recover but also contribute to pathological signalling at the cellular level, amplifying oxidative stress and inflammatory responses. Post-mortem analyses, such as those by Takasu et al. [75], demonstrate preserved structural integrity of renal and cardiac cells in septic patients despite profound organ dysfunction. This has led to the concept of 'metabolic shutdown' or cellular hibernation. However, such interpretations may underestimate the clinical impact of persistent subcellular dysfunction, particularly mitochondrial damage, which may not cause overt necrosis but profoundly alters cellular resilience and recovery potential. Persistent mitochondrial senescence may therefore represent a molecular bottleneck that impedes tissue recovery in individuals recovering from sepsis. Addressing this bottleneck could represent a critical inflection point in the therapeutic management of PSS. While previous studies have emphasized restoring mitochondrial health in the acute phase, the long-term consequences of unresolved mitochondrial dysfunction remain insufficiently explored [63, 64].

Two recent rodent studies demonstrate that supplementing the endogenous mitochondrial pool can improve outcomes in sepsis models. In a rat cecal-slurry model, intravenous infusion of mitochondria isolated from the L6 rat myoblast cell line improved 14-day survival, enhanced bacterial clearance and increased splenic respiratory-control ratios while simultaneously blunting early hyper-inflammation and late immune paralysis [22]. Complementary work in a mouse CLP model subjected to cecal ligation and puncture showed that muscle-derived mitochondria distributed rapidly to lung, liver, kidney and brain, reduced systemic cytokine release, limited multi-organ injury and increased 7-day survival to 75% [36]. A recent study by Kingren et al. [26] provides important support for the role of mitochondrial dysfunction in post-sepsis muscle impairment. Using a cecal slurry-induced sepsis model in aged mice, the authors showed that early mitochondrial protection with Manganese Superoxide Dismutase (MnSOD) or Elamipretide (SS-31) prevented long-term muscle weakness. This reinforces the idea that mitochondria are central to post-sepsis outcomes and supports the rationale of our model. Recent findings indicate that impaired mitophagy leads to the accumulation of dysfunctional mitochondria during sepsis, and that mitochondrial fusion allows content exchange within interconnected networks. As described by Hu et al. [54], dysregulation of mitochondrial dynamics is associated with mitochondrial stress. In this context, strategies targeting only biogenesis or antioxidant defense may be insufficient. Instead, therapeutic approaches that integrate both the removal of damaged mitochondria and support for mitochondrial regeneration are highlighted as promising directions for restoring mitochondrial homeostasis. Nevertheless, many of these "acute-phase" animal models, particularly those using cecal slurry or non-resected CLP protocols with antibiotic therapy, partly mirror the clinical scenario of ICU patients with intra-abdominal or polymicrobial infections who receive source control through antimicrobials alone. While retaining the necrotic focus could sustain systemic inflammation beyond the acute phase, this may also reflect the real-world situation in patients where surgical control is delayed, incomplete, or unavailable. The applicability of such interventions to the PSS, which manifests weeks to months after the initial insult and

Table 3 Linking mitochondrial dysfunction to the persistent inflammatory phenotype of post-sepsis syndrome (PSS)

Author (Ref ID)	Mitochondrial mechanism identified	Cell type/tissue	How this drives persistent inflammation	Study type/model
Patoli D et al., 2020 [31] (○)	LPS/IFN-γ → STAT1→ casp-1/-11–mediated PINK1 degradation → PINK1/Parkin mitophagy ↓ → mitochondrial burden & ΔΨm ↑ → mROS ↑ → HIF-1α–dependent classical activation	In vitro: RAW 264.7 macrophages and murine bone-marrow–derived macrophages (BMDMs). In vivo (CLP sepsis in mice): peritoneal macrophages and circulating Ly6C^hi inflammatory blood monocytes	→ HIF-1α stabilization → sustained classical activation (↑TNF-α, ↑IL-6, ↑iNOS) → NO inhibits→ mROS further ↑ (feed-forward loop) → glycolytic shift sustaining the inflammatory program (OCR ↓, ECAR ↑) → persistence of inflammation; blunted by MitoTEMPOL (mROS scavenger) or echinomycin (HIF-1α inhibitor)	In vitro + mouse CLP ; mdivi-1 (50 mg/kg, −24 h) & Pink1$^{-/-}$ chimeras ; 10-day survival
Li S et al., 2019 [32] (★)	↑ Mitochondria-derived DAMPs (mtDNA, TFAM, succinate, cardiolipin, ATP, cytochrome c, N-formyl peptides) → ↑ activation of TLR9 / cGAS–STING / NLRP3 (inflammasome)	Multiorgan tissues; CLP models & septic patients	TLR9 / cGAS–STING / NLRP3 activation → NF-κB & IRF3 signaling + caspase-1 → ↑ pro-inflammatory cytokines (TNF, IL-6, IL-1β/IL-18) + type I IFNs → cytokine storm; in parallel → immune paralysis → tissue injury & impaired mitophagy → continued mtDAMP release → feed-forward loop sustaining inflammation	Narrative review
Shi Y et al., 2025 [33] (★)	Inflammation ↑ → mTOR/HIF-1α ↑ and AMPK ↑ → glycolysis ↑ (Th1/Th17); OXPHOS + FAO ↑ (Treg/Tmem)	CD4 + T-cell subsets (Th1, Th17, Treg, Tmem) – human & murine evidence	Teff/Treg metabolic imbalance sustains pro-inflammatory cytokine production; in parallel, long-term OXPHOS/FAO programming favors the persistence of Treg/Tmem, fueling a cycle of chronic inflammation and immune dysfunction	Narrative review of T-cell metabolism in inflammatory disease
Bomans K et al., 2018 [34] (★)	12-week post-CLP survivors → glycolytic flux ↑ in bone marrow monocytes (consistent with trained-immunity metabolic reprogramming)	Bonemarrow monocytes	Long-lasting pro-inflammatory priming of bone marrow monocytes (trained immunity), with increased glycolysis and amplified TNF/IL-6 upon restimulation; predisposes to exaggerated responses to later triggers, without evidence of persistent systemic inflammation	CLP without source control/antibiotics; 12-weeks follow-up; ex vivo LPS, Seahorse, RNAseq
Denstaedt SJ et al., 2021 [35] (★)	S100A8/A9 ↑ → TLR4/NF-κB ↑ (inference; causal role not directly tested in this study) → amplified cytokine burst (TNF, IL-1β) & lung injury	Ly6C^hi monocytes & macrophages in lung; CLP mouse survivors (3 wk) + plasma from sepsis/Acute Respiratory Distress Syndrome (ARDS) survivors	Mice (3 wk post-CLP) → intranasal LPS → BAL protein ↑, IgM ↑, BAL neutrophils ↑; sRAGE ↑ (72 h); trend toward ↑ 72-h mortality; Ly6C^hi monocyte Tnf mRNA ↑. Humans (≤180 d post-sepsis) → plasma S100A8/A9 ↑ at multiple time points, consistent with ongoing inflammation → supports biomarker/therapeutic-target potential for late pulmonary complications	Low-mortality CLP (imipenem/cilastatin + fluids; septic focus left in situ); intranasal LPS at 3 weeks; readouts to 72 h; longitudinal survivor cohorts (mice/humans) with serial plasma S100A8/A9 ≤180 days

involves a remodeled mitochondrial population, remains largely unexplored. Moreover, if a large proportion of the mitochondrial population is dysfunctional, fusion-fission processes may risk propagating dysfunction across the network, potentially compromising otherwise functional organelles. This concern is consistent with Hu et al. [54], who document content exchange and the association between dynamic imbalance and stress, but do not provide direct evidence of propagation of injury. This raises the testable concern that a therapy aiming to protect or even introduce healthy mitochondria could, in principle, result in their functional deterioration through contact with a heavily compromised mitochondrial pool.

To address this issue, we propose a dual-intervention approach ("mitochondrial flush"), which involves the coordinated clearance of dysfunctional mitochondria alongside stimulation of mitochondrial biogenesis. This synchronized strategy, potentially via PGC-1α activation, may promote balanced mitochondrial renewal and support metabolic stability in stressed tissues [10, 54, 57, 64, 76]. Notably, the biogenesis component is already supported by an accumulating body of preclinical evidence in sepsis, including AMPK-PGC-1α signaling and NAD^+ replenishment [54, 59]. In contrast, selective removal of senescent mitochondria remains a more exploratory field, with a growing interest but limited translational validation. Targeted compounds are still needed, and further studies are required to define precise mechanisms and ensure specificity. Although this concept has not yet been systematically explored in the context of PSS, it may offer a novel framework for addressing persistent mitochondrial pathology.

Yet, critical questions remain unanswered. Does the host retain sufficient regenerative capacity to support this process, particularly in the immediate aftermath of severe sepsis? Can mitochondrial biogenesis be induced

Table 3 (continued)

Author (Ref ID)	Mitochondrial mechanism identified	Cell type/tissue	How this drives persistent inflammation	Study type/model
Zhang Z et al., 2021 [36] (o)	Exogenous mitochondria 2 h post-CLP → maximal mitochondrial respiration (OCR) ↑ → IL-6/IL-1β ↓ & bacterial clearance ↑	CLP mouse; i.v. muscle-derived mitochondria; multiorgan assessment	24 h: plasma IL-6/IL-1β ↓, CFU ↓, organ injury scores ↓; 7 day survival ↑75% vs37% → blunts escalation toward persistent post sepsis inflammation	Mouse polymicrobial CLP (no antibiotics); tail-vein injection of muscle-derived mitochondria; endpoints at 24 h (OCR, CFU, cytokines, organ injury) and 7 days (survival)
Li J et al., 2023 [37] (o)	NOX4↑ → ROS↑ → mitochondrial damage (swelling/cristae loss, ATP↓) with a fission bias (↑DRP-1, ↓MFN-1/OPA-1) → NF-κB p65 activation; NOX4 inhibition reverses these effects. Note: In this study, NOX4 acts detrimentally in renal tubular epithelial cells during sepsis-AKI and is context-dependent ("double-edged sword") across AKI models	Mouse renal tubular epithelial cells (RTECs) & TCMK-1 line	NOX4↑ → ROS↑ → mitochondrial damage (creating a secondary ROS source) → NF-κB p65 activation → sustained TNF-α/IL-6/IL-1β/MCP-1 transcription, locking the kidney in an inflammatory loop; RTEC-NOX4^KO, siNOX4, or GKT137831 disrupt this ROS↔mitochondria↔NF-κB feed-forward loop, restore ATP, and reduce cytokines	In vivo / in vitro: Sepsis models (LPS/CLP) in WT vs. RTEC-NOX4^KO mice, ± GKT137831; LPS-challenged TCMK-1 cells with NOX4 gain/loss of function or GKT137831

AKI – acute kidney injury, AMPK – AMP-activated protein kinase, ARDS – acute respiratory distress syndrome, ATP – adenosine triphosphate, BAL – bronchoalveolar lavage, BMDM – bone marrow–derived macrophages, casp-1 – caspase-1, casp-11 – caspase-11, CD4 – cluster of differentiation 4, cGAS-STING – cyclic GMP–AMP synthase–stimulator of interferon genes, CFU – colony-forming units, CLP – cecal ligation and puncture, Cyt c – cytochrome c, DAMPs – damage-associated molecular patterns, DRP-1 – dynamin-related protein 1, ECAR – extracellular acidification rate, FAO – fatty acid oxidation, GKT137831 – a dual NADPH oxidase (NOX) 1 and 4 inhibitor, HIF-1α – hypoxia-inducible factor 1-alpha, IFN-I – type I interferons, IFN-γ – interferon gamma, IgM – immunoglobulin M, IL-1β – interleukin-1 beta, IL-18 – interleukin-18, IL-6 – interleukin-6, iNOS – inducible nitric oxide synthase, IRF3 – interferon regulatory factor 3, i.v. – intravenous, KO – knockout, LPS – lipopolysaccharide, Ly6C^hi – Ly6C-high monocyte subset, MCP-1 – monocyte chemoattractant protein-1, mdivi-1 – mitochondrial division inhibitor 1, MFN-1 – mitofusin 1, mROS – mitochondrial reactive oxygen species, mtDNA – mitochondrial DNA, mTOR – mammalian target of rapamycin, NF-κB – nuclear factor kappa B, NLRP3 – NOD-, LRR-, and pyrin domain-containing protein 3 inflammasome, NO – nitric oxide, NOX4 – NADPH oxidase 4, OCR – oxygen consumption rate, OPA-1 – optic atrophy 1, OXPHOS – oxidative phosphorylation, p65 – NF-κB p65 (RelA) subunit, Parkin – ubiquitin E3 ligase mediating mitophagy, PINK1 – PTEN-induced kinase 1, Pink1–/– – Pink1 gene knockout, RNAseq – RNA sequencing, ROS – reactive oxygen species, RTECs – renal tubular epithelial cells, S100A8/A9 – S100 calcium-binding proteins A8/A9, siNOX4 – siRNA targeting NOX4, siRNA – small interfering RNA, STAT1 – signal transducer and activator of transcription 1, TCMK-1 – Transformed C3H Mouse Kidney-1, TFAM – mitochondrial transcription factor A, Th1/Th17 – T helper 1/T helper 17 cells, TLR4 – Toll-like receptor 4, TLR9 – Toll-like receptor 9, Tmem – memory T cells, TNF – tumor necrosis factor, Treg – regulatory T cells, WT – wild type, ΔΨm – mitochondrial membrane potential. Study-type codes: Exp-in vivo – original animal sepsis model with mechanistic readouts. ★ – strong evidence for post-sepsis syndrome & mitochondrial dysfunction. o – partial evidence for post-sepsis syndrome & mitochondrial dysfunction (partial evidence = biologically valid but not correlated with persistent clinical manifestations of post-sepsis syndrome)

rapidly enough to prevent energy collapse in vulnerable cell populations? What are the long-term implications of pharmacologically altering mitochondrial turnover rates in such a delicate context?

Because pathological signalling remains chronically active in PSS, there is concern that newly formed mitochondria may also become senescent despite prior clearance efforts. This possibility points to the need for a broader systemic reset, one that not only targets existing damage but also modifies the pro-inflammatory and oxidative environment that perpetuates mitochondrial dysfunction.

These uncertainties highlight the need for robust pre-clinical studies and carefully designed translational models. Many existing sepsis models focus primarily on short-term survival and fail to reflect the chronic mitochondrial dysfunction observed in PSS. Improved in vivo and organoid-based systems will be necessary to explore the long-term dynamics of mitochondrial quality control. A further limitation is that most pre-clinical sepsis work still relies on static ATP colorimetry or luminescence, techniques that cannot resolve coupling efficiency, spare respiratory capacity or proton-leak kinetics. Integrating high-resolution respirometry (e.g., Oroboros O2k) or extracellular-flux analysis (Seahorse XF) would allow real-time measurement of oxygen-consumption states, reserve capacity and Phosphate to Oxygen Ratio (P/O) ratios, thereby clarifying whether a mitochondrial flush truly restores oxidative phosphorylation rather than merely expanding nucleotide pools. Accordingly, future studies must combine transplantation (or clearance-plus-biogenesis) with high-resolution functional assays, yielding a definitive mechanistic readout of mitochondrial recovery. Available in vivo data on MuSC dysfunction following sepsis currently derive primarily from the murine CLP model, in which the necrotic cecum is typically left in place. This sustained intra-abdominal inflammation may exaggerate deficits in muscle regeneration. CLP variants with cecal resection or lavage lessen this bias, but rodent physiology still differs markedly from humans. Porcine and ovine sepsis models better replicate human hemodynamics, drug handling, and muscle composition, allowing implementation of intensive care interventions comparable to those used in clinical settings. A tiered

approach that uses rodents for mechanistic screening and large animals for validation, alongside a strict separation of pre-clinical and clinical findings, will strengthen translational hypotheses such as the mitochondrial flush. To enhance clinical relevance, we recommend employing large-animal models (porcine, ovine), with specific measurements including neuromuscular function (electromyography, muscle force and structure analysis via MRI or biopsy), inflammatory biomarkers (IL-6, IL-10, TNF-α), immune dysfunction markers (Tregs, MDSCs, PD-1/PD-L1, monocyte HLA-DR), mitochondrial function parameters (high-resolution respirometry, circulating mitochondrial DNA, oxidative stress markers), and standard organ function indicators (renal, hepatic, and intestinal permeability markers).

The success of this approach will depend on several factors, including timing relative to the acute illness, the extent of mitochondrial impairment across tissues, and the patient's baseline regenerative potential. The therapeutic window may be narrow and highly individualized, requiring precise biomarkers to guide administration and monitor response. Moreover, the inherent risk of disturbing mitochondrial networks essential for cell survival reinforces the need for highly selective elimination strategies.

Identifying candidates for a mitochondrial flush requires biomarkers that reflect not only mitochondrial injury itself but also its downstream metabolic, immune, and inflammatory consequences. Based on the mechanistic framework discussed in this manuscript, we propose a multi-dimensional panel including circulating mitochondrial DNA and oxidized cardiolipin as markers of mitochondrial membrane disruption and innate immune activation through TLR9 and NLRP3. Depressed spare respiratory capacity and reduced P/O ratios in PBMCs or muscle-derived cells indicate impaired bioenergetic reserve. Low monocyte HLA-DR expression and elevated PD-1 or PD-L1 levels on lymphocytes reflect sustained immunoparalysis linked to mitochondrial reactive oxygen species. Persistently high levels of S100 Calcium-Binding Proteins A8/A9 (S100A8/A9) and inflammatory cytokines such as IL-6 and IL-1β may indicate mitophagy failure and ongoing inflammasome activation. Reduced expression or activity of mitochondrial quality control regulators such as PINK1, Parkin, PGC-1α, or TFAM in immune or muscle cells may further confirm persistent organelle dysfunction. Together, these biomarkers can define a post-septic state characterized by unresolved mitochondrial stress and may support patient stratification for future mitochondrial-targeted interventions.

Although our model centers on mitochondrial dysfunction, we recognize the contribution of other systems, including epigenetic reprogramming, hormonal imbalances, and persistent microbiome disruption. These may interact with mitochondrial health and collectively shape the clinical course of PSS. Rather than proposing a single cause, we outline an integrative framework that places mitochondrial energetics at the intersection of immune and metabolic regulation, which may help explain failed recovery in some sepsis survivors [55, 77].

Conclusion

While the idea that mitochondrial dysfunction contributes to PSS is not entirely new, our aim is to reinforce this concept and take it a step further by proposing a focused therapeutic framework. We introduce the concept of a "mitochondrial flush", which combines the targeted elimination of irreversibly impaired mitochondria with concurrent support for mitochondrial regeneration, offering a new approach to addressing this persistent dysfunction.

The persistent symptoms observed in PSS suggest that recovery is not merely a matter of surviving the acute event, but of resolving deeper, ongoing biological processes. Among these, mitochondrial dysfunction stands out not only as a marker of cellular stress but as a potential contributor to long-term physiological disruption.

Based on the synthesis of current evidence, we propose that post-sepsis syndrome (PSS) be defined as a state of persistent mitochondrial dysfunction, sustained by chronic oxidative stress and impaired mitochondrial quality control mechanisms. Depending on the severity of mitochondrial injury resulting from the acute phase of sepsis, this dysfunction may remain subclinical or progress toward persistent, clinically evident manifestations.

By focusing on mitochondrial quality and turnover, we aim to redirect attention toward the underlying mechanisms that may actively sustain the post-septic state. Our therapeutic proposal is not a definitive solution, but a conceptual starting point for further research. Future work should determine whether the host retains sufficient regenerative capacity after sepsis, how rapidly mitochondrial biogenesis can be safely induced, and which biomarkers can guide optimal timing and patient selection.

What remains clear is that improving outcomes for sepsis survivors will likely require strategies that go beyond managing symptoms, addressing instead the fundamental processes that limit full recovery. Mitochondria may not be the only piece of the puzzle, but understanding their role could bring us closer to solving it.

Abbreviations

AAV	Adeno-Associated Virus
ADP	Adenosine Diphosphate
AKI	Acute Kidney Injury
Akt	Protein Kinase B
AMPK	AMP-Activated Protein Kinase
AP-1	Activator Protein 1
ARDS	Acute Respiratory Distress Syndrome
Atrogin-1	Muscle Atrophy F-box protein
ATP	Adenosine Triphosphate
BAL	Broncho-Alveolar Lavage
BMDM	Bone-Marrow–Derived Macrophages
BNIP3	BCL2 Interacting Protein 3
cGAS–STING	Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes pathway
CD4	Cluster of Differentiation 4
CD80/CD86	Co-Stimulatory Molecules CD80 and CD86
CD274	Gene Encoding PD-L1
CFU	Colony-Forming Units
CLP	Cecal Ligation and Puncture
Complex I–V	Individual oxidative phosphorylation complexes 1 to 5
CoQ	Coenzyme Q
COX-2	Cyclooxygenase-2
CSA	Cross-Sectional Area
CT	Computed Tomography
CTLA-4	Cytotoxic T–Lymphocyte–Associated Protein 4
Cyt c	Cytochrome c
DAMPs	Damage-Associated Molecular Patterns
Drp1	Dynamin-Related Protein 1
E. coli	Escherichia coli
EDL	Extensor Digitorum Longus
ERK (ERK1/2)	Extracellular Signal–Regulated Kinase
ETC	Electron Transport Chain
FAO	Fatty Acid Oxidation
$FAD/FADH_2$	Flavin Adenine Dinucleotide (oxidized/reduced)
fMet	N-formylmethionine
Foxp3	Forkhead Box P3
FUNDC1	FUN14 Domain Containing 1
FVIIa	Activated Factor VII
FX/XI/XII	Factor X, XI, XII
GA	Gastrocnemius
GKT137831	Dual NADPH Oxidase (NOX) 1/4 Inhibitor
GMP	Granulocyte-Monocyte Progenitor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GSDMD	Gasdermin D
H^+	Proton
H_2O	Water
H_2O_2	Hydrogen Peroxide
HIF-1α	Hypoxia-Inducible Factor-1 Alpha
HLA-DR	Human Leucocyte Antigen-DR Isotype
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit-Acquired Weakness
IFN-α/β/γ/I	Interferon α, β, γ, Type I
IFNs	Interferons
IκB	Inhibitor of NF-κB
IKK	IκB Kinase complex
IL	Interleukin
IL-1β/4/6/10/17/18/33/37	Interleukin 1β, 4, 6, 10, 17, 18, 33, 37
IL-1Ra	Interleukin-1 Receptor Antagonist
IL-8 (CXCL8)	Interleukin-8
iNOS	Inducible Nitric Oxide Synthase
IRAK1/4	Interleukin-1 Receptor-Associated Kinases 1 & 4
IRF3/7	Interferon Regulatory Factor 3/7
JAK/STAT	Janus Kinase / Signal Transducer and Activator of Transcription
JNK	c-Jun N-terminal Kinase
KO	Knockout
L6	L6 rat myoblast cell line
LPS	Lipopolysaccharide
Ly6C^hi	Ly6C^hi Monocyte subset
M1	M1 macrophage phenotype (pro-inflammatory)
M2	M2 macrophage phenotype (alternatively activated)
M2-like	M2 macrophage phenotype (pro-repair/ anti-inflammatory)
MAPKs	Mitogen-Activated Protein Kinases
MCP-1	Monocyte Chemoattractant Protein-1
Mdivi-1	Mitochondrial division inhibitor 1
MFN1	Mitofusin 1
MDSCs	Myeloid-Derived Suppressor Cells
miR-223	MicroRNA-223
MnSOD	Manganese Superoxide Dismutase
MODS	Multiple Organ Dysfunction Syndrome
MPO	Myeloperoxidase
MKK (MEK; MAP2K)	Mitogen-Activated Protein Kinase Kinase
mROS	Mitochondrial Reactive Oxygen Species
mTOR	Mechanistic Target of Rapamycin
MSC	Mesenchymal Stem Cell
mtDAMPs	Mitochondria-Derived DAMPs
mtDNA	Mitochondrial DNA
mtOCR	Mitochondrial Oxygen-Consumption Rate
MuRF1	Muscle RING-Finger Protein 1
MuSC	Muscle Satellite Cell
MyD88	Myeloid Differentiation Primary Response 88
$NAD^•/NADH$	Nicotinamide Adenine Dinucleotide (oxidized/ reduced)
Ndufs4	NADH dehydrogenase [ubiquinone] iron-sulfur protein 4
NETs	Neutrophil extracellular traps
N-GSDMD	N-Terminal fragment of Gasdermin D
NF-κB	Nuclear Factor κ-Light-Chain-Enhancer of Activated B Cells
NLRP3	NOD-, LRR- and Pyrin-Domain-Containing Protein 3
NMN	Nicotinamide Mononucleotide
NO	Nitric Oxide
NOX	NADPH Oxidase family
NOX1/2/4	NADPH Oxidase 1/2/4
O_2	Molecular Oxygen
O_2^{-}·,O_2^{-}	Superoxide
O2k	Oroboros Oxygraph-2k (O2k) high-resolution respirometer

OCR	Oxygen-Consumption Rate
$ONOO^-$	Peroxynitrite
OPA1	Optic Atrophy 1
OR	Odds Ratio
OXPHOS	Oxidative Phosphorylation
P	Phosphorylated Residue (Phosphate Modification)
P/O	Phosphate-to-Oxygen Ratio
Pro-IL-1β/18	Pro-interleukin-1 beta/18
PAMPs	Pathogen-Associated Molecular Patterns
Parkin	E3 Ubiquitin ligase in mitophagy
PBMC	Peripheral Blood Mononuclear Cell
PD-1	Programmed Cell Death Protein 1
PD–L1	Programmed Death-Ligand 1
PGE_2	Prostaglandin E_2
PGC-1α/1β	Peroxisome Proliferator-Activated Receptor-Gamma Coactivator 1-Alpha/1β
PI3K	Phosphoinositide 3-Kinase
PICS	Persistent Inflammation, Immunosuppression and Catabolism Syndrome
PINK1	PTEN-Induced Kinase 1
Pink1-/-	Pink1 gene knockout
PSS	Post-Sepsis Syndrome
PSGL-1	P-Selectin Glycoprotein Ligand-1
RAGE	Receptor for Advanced Glycation End Products
RIP	Receptor-Interacting Protein kinase
RIPK1	Receptor-Interacting Serine/Threonine-Protein Kinase 1
RNA-seq	RNA sequencing
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RTECs	Renal Tubular Epithelial Cells
S1PR2	Sphingosine-1-Phosphate Receptor 2
S100A8/A9	S100 Calcium-Binding Proteins A8/A9
SCFAs	Short–Chain Fatty Acids
Seahorse XF	Agilent Seahorse XF extracellular flux analyzer
SHP1/2	Src homology 2 domain-containing phosphatase 1 and 2
siNOX4	siRNA Targeting NOX4
siRNA	Small Interfering RNA
SMI	Skeletal Muscle Index
SS-31	Elamipretide (Cardiolipin-Targeted Peptide)
STAT1/3/6	Signal Transducer and Activator of Transcription 1/3/6
TA	Tibialis Anterior
TAK1	Transforming Growth Factor-β-Activated Kinase 1
TBK1	TANK-Binding Kinase 1
TCA	Tricarboxylic Acid cycle
TCMK-1	Transformed C3H Mouse Kidney-1
TGF-β	Transforming Growth Factor-Beta
TF	Tissue Factor
TFAM	Mitochondrial Transcription Factor A
TF–FVIIa	Tissue Factor-Factor VIIa Complex
Th1/2/17	T-Helper 1/2 /17 Cell
TIM-3	T-cell Immunoglobulin and Mucin-Domain Containing 3
TLR4/9	Toll-Like Receptor 4/9
Tmem	Memory T Cells
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor-Alpha
TNFR (1)	Tumor Necrosis Factor Receptor (1)
TRADD	TNF Receptor-Associated Death Domain
TRAF2/5	TNF Receptor-Associated Factor 2/5
TRAF6	TNF Receptor-Associated Factor 6
Tregs	Regulatory T Cells
Ub	Ubiquitin
VDAC	Voltage-Dependent Anion Channel
vs.	versus
WPB	Weibel-Palade Bodies
WT	Wild-Type
ΔSMI	Standardized Change in Skeletal Muscle Index
ΔΨm	Mitochondrial Membrane Potential
p38	p38 Mitogen-Activated Protein Kinase
p65	NF-κB p65 (RelA) Subunit
p65/p50	NF-κB subunits p65 and p50
e^-	Electron

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