Georgian Scientists
ქართველი მეცნიერები
Vol. 8 Issue 4(1), 2026
https://doi.org/10.52340/gs.2026.08.04(1).107



FROM INFECTION TO ORGAN FAILURE: MITOCHONDRIAL DYSFUNCTION IN THE PATHOGENESIS OF SEPSIS

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Background:

Sepsis is a life-threatening syndrome caused by a dysregulated host response to infection and remains a major cause of multiple-organ dysfunction and mortality. Despite advances in antimicrobial therapy and intensive care, the mechanisms responsible for the transition from infection to progressive organ failure are not fully understood. Growing evidence suggests that mitochondrial dysfunction plays a central role in this process by linking inflammation, oxidative and nitrosative stress, immune dysregulation, endothelial injury, and impaired cellular bioenergetics.

Objective:

To discuss the role of mitochondrial dysfunction in the pathogenesis of sepsis and its potential importance in the development of organ dysfunction and biologically distinct host-response states.

Main concepts:

During sepsis, pathogen-associated and damage-associated molecular signals activate inflammatory pathways and stimulate excessive production of reactive oxygen and nitrogen species. These processes may impair the mitochondrial electron transport chain, disturb mitochondrial membrane potential, reduce ATP production, and increase mitochondrial ROS generation. Mitochondrial damage may also promote the release of mitochondrial DNA and other danger-associated signals, further amplifying innate immune responses through pathways involving NF-κB and the NLRP3 inflammasome.

Alterations in mitochondrial dynamics, mitophagy, and mitochondrial biogenesis may additionally compromise mitochondrial quality control. The resulting bioenergetic imbalance can affect immune cells, vascular endothelium, and metabolically active organs, contributing to

immune dysfunction, endothelial barrier impairment, microcirculatory abnormalities, and progressive failure of the heart, lungs, kidneys, liver, and other organs.

Importantly, mitochondrial dysfunction in sepsis is heterogeneous and may differ between patients and across the course of disease. Integration of mitochondrial parameters with inflammatory, redox, immune, endothelial, and metabolic markers may therefore help to define distinct biological endotypes and trajectories of sepsis.

Conclusion:

Mitochondrial dysfunction represents a critical interface between infection-induced inflammation and organ failure in sepsis. Better understanding of mitochondrial bioenergetics, redox imbalance, and mitochondrial quality-control mechanisms may improve patient stratification and support the development of personalised, host-directed therapeutic approaches.

Keywords: sepsis; mitochondrial dysfunction; organ failure; oxidative stress; bioenergetics; mitochondrial ROS; mtDNA; NLRP3 inflammasome; endotypes.