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Commentary
https://doi.org/10.63501/6m5jt258

Immuno-metabolic Reprogramming in Perioperative Medicine: A New Determinant of Surgical Outcomes

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ABSTRACT:

The perioperative period represents a critical physiological window during which surgical stress, anesthesia, and host immune responses interact to shape short- and long-term patient outcomes. Traditionally, perioperative physiology has been interpreted through isolated frameworks of inflammation, metabolism, and organ dysfunction. However, growing evidence supports a unified paradigm of immuno-metabolic reprogramming in which immune cell function is tightly regulated by cellular metabolic pathways.

Immunometabolism governs immune cell activation, differentiation, and effector function. Surgical trauma induces a rapid shift toward glycolysis in innate immune cells, enabling immediate ATP production and pro-inflammatory cytokine release. While adaptive in the acute phase, persistent metabolic dysregulation can sustain inflammation and contribute to postoperative complications, including acute kidney injury, neurocognitive dysfunction, respiratory failure, and sepsis.

Central metabolic pathways such as glycolysis, oxidative phosphorylation, fatty acid oxidation, and mitochondrial signaling regulate immune responses. Metabolites, including lactate and succinate, function as signaling mediators that amplify inflammation through hypoxia-inducible factor-1α and related pathways. Concurrently, mitochondrial dysfunction and reactive oxygen species generation promote inflammasome activation and cellular injury.

Understanding immuno-metabolic signaling provides a foundation for precision perioperative medicine. Pharmacologic, anesthetic, and nutritional interventions targeting metabolic pathways may modulate immune responses rather than nonspecifically suppress them. This narrative review synthesizes current evidence on immuno-metabolic reprogramming in perioperative medicine and explores its implications for surgical outcomes and therapeutic innovation.

INTRODUCTION:

Surgical trauma triggers a complex systemic response involving neuroendocrine activation, inflammation, and metabolic stress. While these responses are essential for wound healing and host defense, excessive or prolonged activation contributes to organ dysfunction and postoperative complications (1).

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Historically, immune activation and metabolism were studied as separate entities. However, contemporary immunology has established that immune cell function is fundamentally metabolically programmed. Activated immune cells undergo metabolic reconfiguration that determines their phenotype, cytokine profile, and survival (2).

In the perioperative setting, hypoxia, tissue injury, and anesthetic exposure further modulate immune metabolism. Dysregulated immuno-metabolic responses have been implicated in postoperative delirium, acute kidney injury, and systemic inflammatory complications (3).

This review synthesizes current evidence on immuno-metabolic reprogramming in perioperative medicine and highlights its relevance to surgical outcomes and therapeutic strategies.

Literature Search Strategy

This narrative review was conducted using PubMed/MEDLINE and Google Scholar databases. Literature from 2005 to 2025 was evaluated.

Search terms included:

- immunometabolism
- perioperative inflammation
- surgical stress response
- mitochondrial dysfunction anesthesia
- immune metabolic reprogramming

Studies were selected based on relevance to perioperative or translational immunometabolism research. No formal inclusion/exclusion criteria, systematic screening, or PRISMA methodology was applied. Literature was synthesized qualitatively based on thematic relevance and mechanistic contribution.

Immuno-Metabolic Mechanisms in Perioperative Inflammation

Glycolysis and Pro-Inflammatory Immune Activation

Activated immune cells such as macrophages and neutrophils undergo a metabolic shift toward aerobic glycolysis, resembling the Warburg effect (2). This transition supports rapid ATP production and biosynthesis of inflammatory mediators.

Beyond energy production, glycolysis generates metabolites with signaling roles. Lactate and succinate stabilize hypoxia-inducible factor-1α (HIF-1α), promoting transcription of pro-inflammatory cytokines such as IL-1β (4). This creates a feed-forward inflammatory loop that amplifies perioperative immune responses.

Importantly, persistent glycolytic dominance is associated with exaggerated systemic inflammation and impaired resolution of injury.

Mitochondrial Dysfunction and Oxidative Stress

Mitochondria are central regulators of immune cell fate and inflammatory signaling. In homeostatic or reparative states, immune cells rely on oxidative phosphorylation and fatty acid oxidation for energy efficiency and anti-inflammatory programming (5).

During surgical stress, mitochondrial dysfunction leads to impaired electron transport, ATP depletion, and excessive production of reactive oxygen species (ROS). ROS activate redox-sensitive pathways and the NLRP3 inflammasome, contributing to tissue injury and systemic inflammation (6). Thus, mitochondrial integrity serves as a key determinant of perioperative immune balance.

Metabolites as Immune Signaling Molecules

Metabolites are not passive intermediates but active regulators of immune responses. Succinate promotes inflammatory signaling via HIF-1α stabilization, while itaconate acts as an endogenous anti-inflammatory metabolite by activating NRF2 pathways (7). This metabolite-driven regulation

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highlights metabolism as an instructive component of immune signaling rather than a supportive process.

Immuno-Metabolism in the Perioperative Context

Surgical Stress and Immune Rewiring

Surgical trauma induces rapid systemic immune activation characterized by cytokine release, neuroendocrine stress, and metabolic reprogramming (1). Immune cells shift toward glycolysis to sustain immediate inflammatory demands. Although essential for defense and tissue repair, excessive or prolonged activation contributes to endothelial dysfunction, capillary leak, and organ injury.

Anesthesia and Immuno-Metabolic Modulation

Anesthetic agents significantly influence immune metabolism. Volatile anesthetics modulate mitochondrial respiration and can alter inflammatory signaling pathways through effects on oxidative phosphorylation and ROS generation.

Intravenous agents such as propofol exhibit antioxidant properties that may attenuate mitochondrial oxidative stress. Experimental evidence suggests that anesthetic choice may influence postoperative immune trajectory, although clinical translation remains under investigation. These findings suggest anesthetic agents may function as metabolic modulators rather than purely sedative drugs.

Organ-Specific Immuno-Metabolic Dysfunction

Brain

Postoperative neurocognitive disorders, including delirium and cognitive dysfunction, are increasingly linked to neuroinflammation driven by metabolic dysregulation. Microglial activation, mitochondrial dysfunction, and impaired energy metabolism contribute to synaptic dysfunction and cognitive decline (3).

Kidney

Acute kidney injury (AKI) in the perioperative setting is strongly associated with mitochondrial dysfunction, ischemia-reperfusion injury, and metabolic stress. Tubular epithelial cells exhibit ATP depletion and oxidative injury, amplifying inflammatory signaling pathways and worsening renal dysfunction (9).

Lung

Pulmonary complications following surgery are increasingly recognized as consequences of immuno-metabolic imbalance. Alveolar macrophages undergo glycolytic reprogramming during acute lung injury, leading to cytokine overproduction and impaired gas exchange. Mitochondrial dysfunction further exacerbates epithelial injury and inflammatory infiltration.

Clinical Implications

Biomarkers of Immuno-Metabolic Dysfunction

Emerging biomarkers include:

- Lactate (glycolytic activation marker)
- Mitochondrial DNA (damage-associated molecular pattern)
- Succinate and other metabolic intermediates

These biomarkers may assist in perioperative risk stratification and early detection of inflammatory complications.

Therapeutic Targeting of Immuno-Metabolism

Targeted modulation of metabolic pathways represents a novel therapeutic approach:

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- **Metformin**: activates AMPK, suppresses excessive glycolysis, and reduces inflammatory signaling
- **Dimethyl itaconate**: enhances NRF2-mediated antioxidant and anti-inflammatory pathways
- **Nicotinamide riboside**: supports mitochondrial NAD^+ metabolism and improves oxidative phosphorylation

Additional strategies include modulation of perioperative glucose control, oxygen delivery, and anesthetic selection to maintain metabolic homeostasis.

Discussion

Immuno-metabolic reprogramming represents a central mechanism linking surgical stress to immune activation and postoperative outcomes. The perioperative immune response is not solely inflammatory but is fundamentally metabolically determined.

Metabolic switching between glycolysis and oxidative phosphorylation determines whether immune responses are pro-inflammatory or reparative. Dysregulation of this balance contributes to organ dysfunction and postoperative complications.

Anesthetic agents and perioperative interventions may modulate this metabolic landscape, offering opportunities for precision perioperative medicine. Future research integrating metabolomics, immune profiling, and clinical outcomes is essential to translate these findings into practice.

Conclusion

Immunometabolic reprogramming provides a mechanistic link between surgical stress and postoperative outcomes. By integrating metabolic and immunologic pathways, this framework advances a systems-level understanding of perioperative physiology. Targeting immunometabolic pathways offers a promising avenue for precision perioperative medicine to reduce organ dysfunction and improve recovery.

Ethical Approval: Not applicable (no new human or animal subjects were involved; this narrative is based on published data).

Conflict of Interest: None

Declaration of AI Use: This letter was drafted and revised with the assistance of an AI language model (ChatGPT, GPT-5, OpenAI) for grammar refinement, structural reorganization, and clarity enhancement. All intellectual content, interpretation, and final approval of the text are solely the responsibility of the authors.

Funding: None

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