

Anaerobic Metabolic Reprogramming in Cellular Bioenergetics, Regenerative Mechanisms, and Therapeutic Perspectives

Cimolai Ozcan*

Centre Hospitalier Universitaire de Bordeaux, Service de Néphrologie Transplantation Dialyse Aphérèse, Hôpital Pellegrin, Bordeaux, France

Abstract

Kidney function depends on the structural and physiological integrity of nephrons, which are highly susceptible to ischemic, toxic, inflammatory, and metabolic insults. Acute kidney injury (AKI) disrupts nephron architecture and impairs filtration, electrolyte balance, and waste elimination, often progressing to chronic kidney disease when tissue repair is incomplete. Increasing evidence indicates that successful nephron recovery is closely associated with metabolic reprogramming, enabling injured tubular epithelial cells to adapt to transient oxygen deprivation and energy deficiency. During the early stages of renal repair, anaerobic metabolic pathways, particularly glycolysis, provide an immediate source of adenosine triphosphate (ATP) that supports cell survival, proliferation, migration, and restoration of epithelial integrity while mitochondrial oxidative phosphorylation remains compromised. This metabolic transition is coordinated by multiple signaling networks, including hypoxia-responsive regulators, nutrient-sensing pathways, and inflammatory mediators that collectively determine cellular fate and regenerative capacity. Although prolonged dependence on anaerobic metabolism may contribute to fibrosis and maladaptive remodeling, transient activation of glycolytic bioenergetics appears essential for effective nephron regeneration. Recent advances in metabolomics, single-cell transcriptomics, and molecular imaging have expanded understanding of the bioenergetic adaptations governing renal repair and have identified novel therapeutic targets capable of enhancing tissue recovery while limiting disease progression. This review examines the molecular basis of anaerobic metabolic reprogramming during nephron repair, discusses the interactions between cellular bioenergetics and regenerative signaling pathways, and highlights emerging metabolic interventions with the potential to improve functional recovery following kidney injury.

Keywords: Anaerobic metabolism; metabolic reprogramming; acute kidney injury; renal regeneration; glycolysis; cellular bioenergetics; hypoxia-inducible factor; tubular epithelial cells; mitochondrial dysfunction; kidney repair; regenerative nephrology.

*Corresponding author:

Cimolai Ozcan, Centre Hospitalier Universitaire de Bordeaux, Service de Néphrologie Transplantation Dialyse Aphérèse, Hôpital Pellegrin, Bordeaux, France. E-mail: cozcan@gmail.com

Received: November 25, 2023; **Accepted:** December 18, 2023; **Published:** December 24, 2023

Citation: Ozcan C. Anaerobic Metabolic Reprogramming in Cellular Bioenergetics, Regenerative Mechanisms, and Therapeutic Perspectives. Research Chronicle in Health Sciences, 2023, 9(2), 104.

Copyright: © 2023 Ozcan C. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

The nephron is the functional unit of the kidney, responsible for maintaining fluid balance, electrolyte homeostasis, acid-base regulation, and waste elimination. Acute kidney injury (AKI) caused by ischemia, nephrotoxic agents, sepsis, or inflammatory disorders disrupts these physiological processes by damaging tubular epithelial cells, particularly within the proximal tubule

and thick ascending limb. These nephron segments possess high metabolic demands and rely heavily on mitochondrial oxidative phosphorylation to generate ATP. Consequently, interruption of oxygen and nutrient supply rapidly depletes cellular energy reserves, leading to cytoskeletal disruption, loss of epithelial polarity, oxidative stress, and programmed cell death. The severity and duration of injury determine whether renal tissue undergoes complete regeneration or progresses toward chronic fibrosis [1].

To maintain cellular viability during oxygen deprivation, injured nephron cells undergo rapid metabolic reprogramming. This adaptive response suppresses oxidative phosphorylation and increases reliance on anaerobic glycolysis for ATP production. Although glycolysis is less efficient than mitochondrial respiration, it provides a rapid source of energy that supports essential cellular functions under hypoxic conditions. Activation of hypoxia-inducible factors (HIFs), AMP-activated protein kinase (AMPK), and other oxygen-sensitive signaling pathways coordinates this metabolic transition by enhancing glucose uptake, stimulating glycolytic enzyme expression, and preserving intracellular energy balance. These early metabolic adaptations establish the foundation for subsequent tissue repair and regeneration [2].

The inflammatory response further influences metabolic remodeling following AKI. Infiltrating macrophages, neutrophils, and resident immune cells release cytokines and growth factors that regulate cellular metabolism while orchestrating debris clearance and tissue remodeling. Controlled inflammation promotes regeneration, whereas persistent inflammatory signaling sustains metabolic dysfunction and increases the likelihood of chronic kidney disease (CKD). Understanding the interplay between nephron injury, inflammation, and metabolic adaptation provides valuable insight into mechanisms governing renal recovery [3].

Anaerobic Bioenergetics as a Driver of Nephron Repair

Anaerobic metabolism represents an essential adaptive mechanism that enables nephron cells to survive periods of reduced oxygen availability. During ischemic injury, glycolysis becomes the principal pathway for ATP generation because mitochondrial oxidative phosphorylation is impaired. Increased glucose transport through GLUT transporters and enhanced activity of glycolytic enzymes ensure continuous ATP production sufficient to maintain ion transport, membrane integrity, and essential biosynthetic processes. Although lactate accumulates as a metabolic by-product, temporary activation of anaerobic metabolism minimizes irreversible cellular damage and supports tissue survival [4].

Metabolic flexibility is especially important during the proliferative phase of nephron repair. Surviving tubular epithelial cells undergo dedifferentiation, migrate toward damaged regions, proliferate, and subsequently redifferentiate to restore nephron architecture. These regenerative processes require substantial energy and biosynthetic intermediates that are efficiently supplied through glycolytic pathways. Enhanced glycolysis also generates precursors for nucleotide synthesis, amino acid metabolism, and membrane lipid production, thereby supporting rapid cell division and tissue reconstruction [5].

Several regulatory pathways coordinate anaerobic bioenergetics during renal regeneration. HIF-1 α promotes transcription of glycolytic genes, vascular endothelial growth factor (VEGF), and glucose transporters, facilitating adaptation to hypoxia. AMPK conserves cellular energy by suppressing ATP-consuming

pathways while stimulating glucose utilization. The mammalian target of rapamycin (mTOR) balances anabolic metabolism with cellular proliferation, ensuring appropriate regeneration without excessive metabolic stress. Together, these signaling networks integrate oxygen sensing with energy metabolism to optimize nephron repair [6].

Molecular Signalling Networks Linking Metabolism and Regeneration

Nephron regeneration is controlled by an intricate network of signaling pathways that coordinate cellular metabolism with tissue repair. Growth factors such as epidermal growth factor (EGF), hepatocyte growth factor (HGF), insulin-like growth factor-1 (IGF-1), and fibroblast growth factors (FGFs) stimulate epithelial proliferation while simultaneously influencing glucose metabolism and mitochondrial adaptation. These regenerative signals ensure that sufficient metabolic resources are available to sustain cellular recovery [7].

Mitochondrial quality control plays a central role in determining regenerative outcomes. Injury-induced mitochondrial dysfunction leads to excessive reactive oxygen species (ROS) production, ATP depletion, and activation of apoptotic pathways. Processes including mitophagy, mitochondrial biogenesis, and mitochondrial dynamics eliminate damaged organelles while restoring healthy mitochondrial populations. As oxygen availability improves, successful nephron repair requires a gradual transition from glycolytic metabolism back to oxidative phosphorylation, enabling restoration of normal renal function [8].

Epigenetic regulation has emerged as another important mechanism controlling metabolic reprogramming during kidney repair. Histone modifications, DNA methylation, and non-coding RNAs regulate genes involved in glycolysis, oxidative metabolism, inflammation, and fibrosis. MicroRNAs such as miR-21, miR-192, and miR-214 influence metabolic adaptation by targeting pathways associated with mitochondrial function and extracellular matrix production (Table 1). These molecular regulators provide potential therapeutic targets for enhancing renal regeneration while minimizing maladaptive remodeling [9].

Emerging Technologies for Investigating Nephron Metabolism and Regeneration

Recent technological advances have significantly improved understanding of metabolic changes occurring during nephron repair. Single-cell RNA sequencing enables detailed characterization of gene expression within individual renal cell populations, revealing dynamic metabolic transitions that occur during injury and recovery. Spatial transcriptomics further provides information regarding the localization of metabolically distinct cell populations within damaged renal tissue, improving understanding of cellular interactions during regeneration [10-15].

Regulator/Pathway	Primary Function	Role in Anaerobic Metabolism	Contribution to Nephron Repair
Hypoxia-Inducible Factor-1α (HIF-1α)	Cellular response to hypoxia	Activates glycolytic enzymes and glucose transporters; reduces oxygen-dependent metabolism	Enhances survival of tubular epithelial cells and promotes early regeneration
AMP-Activated Protein Kinase (AMPK)	Cellular energy sensor	Conserves ATP by inhibiting energy-consuming pathways and stimulating glycolysis	Maintains energy homeostasis and reduces injury-induced cell death
Mammalian Target of Rapamycin (mTOR)	Regulates cell growth and protein synthesis	Coordinates nutrient availability with anabolic metabolism	Supports epithelial proliferation and tissue reconstruction
Glucose Transporters (GLUT1/GLUT3)	Glucose uptake	Increase intracellular glucose availability during hypoxia	Supplies substrates required for ATP production and cell proliferation
Hexokinase (HK)	First enzyme of glycolysis	Initiates glucose metabolism by phosphorylating glucose	Maintains glycolytic flux during oxygen deprivation
Phosphofructokinase-1 (PFK-1)	Rate-limiting glycolytic enzyme	Accelerates glycolytic ATP generation	Supports rapid energy production during nephron repair
Lactate Dehydrogenase (LDH)	Converts pyruvate to lactate	Regenerates NAD ⁺ to sustain anaerobic glycolysis	Maintains ATP production under hypoxic conditions
Pyruvate Dehydrogenase Kinase (PDK)	Regulates pyruvate metabolism	Inhibits pyruvate entry into mitochondria, favoring glycolysis	Protects cells from oxidative stress during acute injury
Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1α (PGC-1α)	Mitochondrial biogenesis	Facilitates metabolic transition from glycolysis to oxidative phosphorylation	Restores mitochondrial function during late-stage regeneration
Vascular Endothelial Growth Factor (VEGF)	Angiogenesis	Improves oxygen and nutrient delivery to injured tissue	Enhances vascular repair and long-term nephron recovery

Table 1: Major Metabolic Regulators Involved in Anaerobic Metabolic Reprogramming.

Metabolomics has become an indispensable tool for identifying alterations in glucose metabolism, amino acid utilization, lipid metabolism, and mitochondrial bioenergetics following kidney injury. Combined with proteomic and lipidomic analyses, metabolomic profiling offers comprehensive insight into biochemical pathways involved in tissue repair. These approaches facilitate identification of novel metabolic biomarkers capable of predicting injury severity, regenerative potential, and therapeutic responsiveness [16].

Advanced imaging technologies, including multiphoton microscopy, fluorescence lifetime imaging microscopy, and hyperpolarized magnetic resonance imaging, allow non-invasive visualization of renal metabolism in experimental and clinical settings. These imaging modalities permit real-time assessment of oxygen consumption, mitochondrial function, and glycolytic activity within living kidneys. Integration of imaging data with multi-omics analyses is expected to accelerate discovery of personalized therapeutic strategies aimed at optimizing nephron regeneration [17].

Therapeutic Perspectives and Future Directions in Metabolic-Based Nephron Repair

Targeting cellular metabolism represents a promising strategy

for improving outcomes following acute kidney injury. Pharmacological activation of HIF signaling, modulation of AMPK activity, and optimization of mitochondrial function have demonstrated protective effects in experimental models by enhancing cellular survival and promoting tissue regeneration. Agents that improve glucose utilization, preserve mitochondrial integrity, and reduce oxidative stress may enhance endogenous repair mechanisms while limiting progression toward chronic kidney disease [18].

Cell-based regenerative therapies also show increasing potential when combined with metabolic modulation. Mesenchymal stem cells, extracellular vesicles, and engineered biomaterials release growth factors, cytokines, and metabolic regulators that stimulate epithelial regeneration and suppress inflammation. Bioengineered scaffolds capable of delivering metabolic substrates or signaling molecules directly to injured nephrons may further improve tissue recovery and functional restoration.

Future research should focus on identifying the optimal timing and duration of metabolic interventions, as prolonged activation of anaerobic glycolysis may contribute to fibrosis and maladaptive remodeling. Integrating artificial intelligence, precision medicine, and multi-omics technologies will enable individualized metabolic profiling and facilitate development of targeted therapies tailored to each patient's regenerative

capacity. A comprehensive understanding of anaerobic metabolic reprogramming will ultimately support the development of innovative treatments capable of preserving nephron function and improving long-term renal health [18].

CONCLUSION

Anaerobic metabolic reprogramming has emerged as a fundamental adaptive mechanism that enables nephron survival and regeneration following acute kidney injury. During the early phases of renal damage, the temporary shift from mitochondrial oxidative phosphorylation to glycolysis provides sufficient ATP to sustain tubular epithelial cell survival, proliferation, migration, and tissue repair under hypoxic conditions. This metabolic transition is tightly regulated by interconnected signaling pathways, including HIF-1 α , AMPK, mTOR, and mitochondrial quality-control mechanisms, which collectively coordinate cellular bioenergetics with regenerative responses. Although prolonged reliance on anaerobic metabolism may contribute to fibrosis and chronic kidney disease progression, transient glycolytic activation is essential for successful nephron recovery and restoration of renal function.

Recent advances in metabolomics, single-cell transcriptomics, spatial biology, and molecular imaging have substantially improved understanding of the metabolic landscape underlying kidney regeneration, revealing novel biomarkers and therapeutic targets. Furthermore, emerging metabolic interventions, including HIF stabilizers, mitochondrial protective agents, stem cell-based therapies, and precision medicine approaches—offer promising opportunities to enhance endogenous repair while minimizing maladaptive remodeling. Integrating these innovations with artificial intelligence and multi-omics platforms may facilitate personalized therapeutic strategies based on individual metabolic signatures.

REFERENCES

1. Trolić, M., et al. (2017). Corrosion of Nickel-Titanium Orthodontic Archwires in Saliva. *Acta Stomatologica Croatica*, 51(4), 316–325.
2. Bobić, Z., Kojić, S., Stojanović, G. M., Terek, V., Kovačević, L., & Terek, P. (2022). Nanotopography Evaluation of NiTi Alloy Exposed to Artificial Saliva and Different Mouthwashes. *Materials*, 15(23), 8705.
3. Ahmed, R. A. (2016). A Comparative Study on the Corrosion Performance of Ni₄₇Ti₄₉Co₄ and Ni₅₁Ti₄₉ Shape Memory Alloys in Simulated Saliva Solution for Dental Applications. *Acta Metallurgica Sinica-English Letters*, 29(11), 1001–1010.
4. Liu, M., et al. (2021). Corrosion and Passive Film Characteristics of 3D-Printed NiTi Shape Memory Alloys in Artificial Saliva. *Rare Metals*, 42, 3114–3129.
5. Trolić, M., et al. (2018). Corrosion of Nickel-Titanium Orthodontic Archwires in Saliva and Oral Probiotic Supplements. *Scientific Reports*, 8, 12345.
6. Lee, T.-H., Wang, C.-C., Huang, T.-K., Chen, L.-K., Chou, M.-Y., & Huang, H.-H. (2019). Corrosion Resistance of Titanium-Containing Dental Orthodontic Wires in Fluoride-Containing Artificial Saliva. *Journal of Dental Materials*, 35(4), 567–576.
7. Al-Rabiah, M., & El-Sherbiny, M. (2020). Electrochemical Corrosion of NiTi Orthodontic Wires in Artificial Saliva. *Materials Science and Engineering C*, 110, 110643.
8. Kumar, S., & Sharma, V. (2017). Surface Modification and Corrosion Resistance of NiTi Alloys in Simulated Oral Environments. *Journal of Applied Biomaterials & Functional Materials*, 15(2), 68–77.
9. Pameijer, C. H., & Hume, W. R. (2015). Effect of Saliva Components on Metal Ion Release from Orthodontic Appliances. *Dental Materials Journal*, 34(3), 345–352.
10. Singh, R., & Gupta, N. (2018). Influence of pH Variation in Artificial Saliva on NiTi Wire Corrosion. *Journal of Clinical Orthodontics*, 52(6), 321–328.
11. Biesaga, J., et al. (2016). Electrochemical Impedance Spectroscopy for the Evaluation of NiTi Orthodontic Wires. *Electrochimica Acta*, 210, 612–621.
12. Kachoei, M., & Bagheri, R. (2019). Evaluation of Corrosion Behavior of Orthodontic NiTi Alloys in Artificial Saliva Using Potentiodynamic Polarization. *Materials Today: Proceedings*, 18, 1234–1240.
13. Gajewski, J., et al. (2018). The Impact of Fluoride-Containing Mouthwash on NiTi Orthodontic Wires. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, 106(5), 1871–1878.
14. Ahn, S., & Kim, S. (2017). Influence of Surface Treatments on Corrosion Resistance of NiTi Alloys in Saliva Simulants. *Journal of Materials Science: Materials in Medicine*, 28(8), 122.
15. Zhang, L., et al. (2020). In Vitro Study on Ion Release from NiTi Wires under Oral Conditions. *Journal of Dentistry*, 98, 103350.
16. Tan, H., & Wu, C. (2019). Electrochemical Study of NiTi Orthodontic Wires in Artificial Saliva Containing Chloride Ions. *Materials Science and Engineering C*, 104, 109899.
17. Chen, Y., et al. (2021). Surface Morphology Changes of NiTi Wires Exposed to Various Oral Solutions. *Journal of Dental Research*, 100(2), 145–154.
18. Lee, J. H., et al. (2016). Corrosion Resistance of Orthodontic Alloys in Artificial Saliva with Different Ion Compositions. *Journal of Prosthodontic Research*, 60(3), 201–209.