

Anaerobic Bioenergetics in Nephron Regeneration: Metabolic Mechanisms, Cellular Adaptations, and Therapeutic Opportunities

Liu Zeng*, Li Wang, Jiang Li

State Key Laboratory of Hybrid Rice, Hubei Hongshan Laboratory, College of Life Sciences, Wuhan University, Wuhan, Hubei 430072, China

*Corresponding author:

Liu Zeng, State Key Laboratory of Hybrid Rice, Hubei Hongshan Laboratory, College of Life Sciences, Wuhan University, Wuhan, Hubei 430072, China, E-mail: liu.z@whu.edu.cn

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Abstract

Acute kidney injury (AKI) remains a significant contributor to morbidity and mortality worldwide because of its rapid onset and its capacity to disrupt nephron structure and function. Although the kidney possesses an intrinsic ability to repair damaged tubular epithelium, the efficiency of regeneration depends on tightly coordinated metabolic adaptations that sustain cellular survival and tissue remodeling during periods of limited oxygen availability. Emerging evidence indicates that anaerobic bioenergetics, particularly glycolysis and associated metabolic pathways, serves as a critical energy source that supports nephron repair by maintaining ATP production, preserving cellular integrity, and regulating stress-responsive signaling networks. These metabolic adjustments influence epithelial dedifferentiation, proliferation, migration, and redifferentiation, thereby facilitating structural and functional recovery following injury. In parallel, anaerobic metabolic intermediates participate in cellular communication, immune modulation, angiogenic responses, and extracellular matrix remodeling, collectively shaping the regenerative microenvironment. Advanced experimental systems, including zebrafish, kidney organoids, and single-cell multi-omics technologies, have substantially expanded current understanding of the spatial and temporal metabolic changes that accompany nephron regeneration, overcoming several limitations associated with conventional mammalian models. These platforms have revealed dynamic interactions between metabolic reprogramming, mitochondrial function, hypoxia-responsive pathways, and renal progenitor populations that govern successful tissue restoration. Furthermore, pharmacological strategies targeting metabolic plasticity have emerged as promising therapeutic approaches for enhancing renal recovery while minimizing maladaptive fibrosis and progression to chronic kidney disease. This review examines the molecular mechanisms underlying anaerobic bioenergetics during nephron regeneration, discusses cellular adaptations that coordinate tissue repair, evaluates insights gained from contemporary experimental models, and highlights emerging therapeutic opportunities aimed at optimizing metabolic regulation to improve renal regeneration and long-term kidney function.

Keywords: Acute kidney injury; Nephron regeneration; Anaerobic bioenergetics; Glycolysis; Metabolic reprogramming; Renal repair; Hypoxia signaling; Cellular plasticity; Mitochondrial adaptation; Kidney organoids; Zebrafish model; Therapeutic strategies.

INTRODUCTION

The nephron is the fundamental structural and functional unit of the kidney, responsible for filtration, solute transport, and maintenance of systemic homeostasis. During acute kidney injury (AKI), tubular epithelial cells experience oxygen deprivation, oxidative stress, and ATP depletion, leading to impaired cellular function and structural damage. Because mitochondrial oxidative phosphorylation becomes inefficient under hypoxic conditions, injured nephron cells undergo metabolic reprogramming toward anaerobic glycolysis to maintain minimal energy production. Although glycolysis generates substantially less ATP than aerobic respiration, it provides a rapid and oxygen-independent mechanism for sustaining essential cellular processes during the early stages of injury. This metabolic transition is coordinated through the activation of hypoxia-responsive transcription factors, glucose transporters, glycolytic enzymes, and stress-associated signaling pathways that collectively preserve cell viability (1).

Beyond ATP generation, anaerobic metabolism contributes to the production of metabolic intermediates that serve as substrates for nucleotide synthesis, amino acid metabolism, and membrane biogenesis, all of which are necessary for cellular repair. The metabolic flexibility exhibited by renal epithelial cells enables them to adapt to fluctuating oxygen availability while maintaining intracellular homeostasis. Crosstalk between glycolysis, mitochondrial metabolism, and redox regulation determines whether injured cells survive, undergo apoptosis, or initiate regenerative responses. Consequently, understanding the metabolic basis of anaerobic bioenergetics provides critical insight into the mechanisms governing nephron regeneration and establishes a framework for developing metabolism-based therapeutic interventions (2).

Cellular Adaptations Driving Nephron Repair Following Injury

Successful nephron regeneration depends on coordinated cellular adaptations that restore tubular architecture and renal function. Following injury, surviving tubular epithelial cells undergo transient dedifferentiation, characterized by the loss of mature epithelial features and acquisition of a proliferative phenotype. This reversible process allows cells to migrate toward damaged regions, replace lost epithelial populations, and subsequently redifferentiate into specialized nephron cells. These regenerative events require substantial metabolic support, making anaerobic glycolysis an important contributor during the early repair phase when oxygen delivery remains compromised (3).

In addition to epithelial plasticity, multiple renal cell populations participate in tissue repair. Endothelial cells promote vascular restoration, fibroblasts regulate extracellular matrix remodeling, and resident immune cells coordinate inflammatory responses that influence regeneration. Macrophages exhibit functional heterogeneity throughout kidney repair, initially facilitating debris clearance before transitioning toward reparative

phenotypes that promote tissue remodeling. Metabolic signaling also regulates communication among these cell populations through cytokines, growth factors, and extracellular vesicles. Simultaneously, mitochondrial quality-control mechanisms—including mitophagy, mitochondrial biogenesis, and antioxidant defense systems—limit oxidative injury and facilitate recovery of aerobic metabolism once tissue oxygenation improves. Together, these cellular adaptations establish a dynamic regenerative microenvironment that supports nephron reconstruction while minimizing irreversible fibrosis (4).

Molecular Mechanisms Linking Anaerobic Metabolism and Renal Regeneration

Nephron regeneration is orchestrated by an extensive network of molecular signaling pathways that integrate metabolic status with cellular repair programs. Hypoxia-inducible factors (HIFs) serve as central regulators by sensing oxygen availability and activating genes involved in glucose transport, glycolysis, angiogenesis, and cell survival. HIF-mediated metabolic reprogramming enables injured renal cells to maintain ATP production while simultaneously reducing mitochondrial oxygen consumption and reactive oxygen species generation (5).

Additional signaling pathways, including PI3K/Akt, AMPK, mTOR, Wnt/ β -catenin, Notch, TGF- β , and MAPK cascades, coordinate cellular proliferation, differentiation, inflammation, and extracellular matrix remodeling during regeneration. Energy-sensing molecules such as AMP-activated protein kinase maintain metabolic homeostasis by balancing anabolic and catabolic activities under nutrient-limited conditions. Epigenetic regulation further modulates regenerative capacity through DNA methylation, histone modifications, and non-coding RNAs that influence gene expression without altering genomic sequences. Recent investigations have demonstrated that microRNAs and long non-coding RNAs regulate glycolytic enzymes, mitochondrial function, and inflammatory mediators, thereby influencing nephron repair outcomes. The integration of these signaling networks highlights the complexity of metabolic regulation and identifies numerous molecular targets for therapeutic intervention.

Experimental Models and Emerging Technologies for Investigating Nephron Regeneration.

Advances in experimental models have substantially enhanced understanding of metabolic regulation during nephron repair. Traditional rodent models remain indispensable for investigating renal physiology and disease progression; however, limitations related to intravital imaging, nephron accessibility, and species-specific differences restrict comprehensive analysis of dynamic regenerative events. Consequently, complementary experimental systems have become increasingly valuable (6).

The zebrafish has emerged as an important vertebrate model because its transparent embryos permit direct visualization of nephron development, injury responses, and cellular regeneration in living organisms. The zebrafish pronephros shares significant

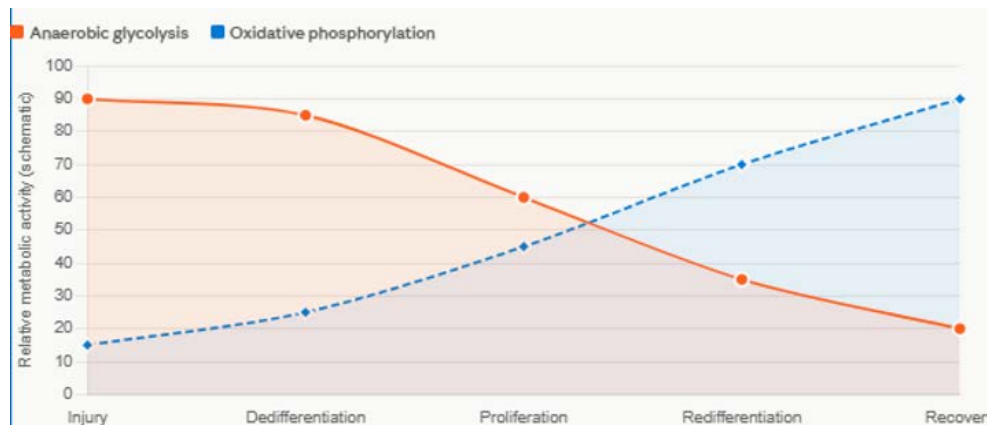


Figure 1: Schematic metabolic shift during nephron regeneration.

structural and genetic similarities with mammalian nephrons, allowing investigators to examine metabolic adaptations with high temporal and spatial resolution. Kidney organoids derived from pluripotent stem cells further provide human-relevant platforms for studying nephron differentiation, metabolic remodeling, and drug responses under controlled laboratory conditions. Advances in single-cell RNA sequencing, spatial transcriptomics, metabolomics, proteomics, and high-resolution live-cell imaging now enable comprehensive characterization of metabolic heterogeneity among regenerating renal cells. Integration of these technologies with computational modeling and artificial intelligence has accelerated identification of novel metabolic regulators and therapeutic targets involved in kidney repair (7).

Recognition of anaerobic bioenergetics as a fundamental component of nephron repair has stimulated the development of therapeutic strategies aimed at modulating cellular metabolism to enhance renal regeneration. Pharmacological activation of hypoxia-responsive signaling, controlled stimulation of glycolytic pathways, preservation of mitochondrial integrity, and enhancement of cellular antioxidant defenses have demonstrated promising experimental outcomes in reducing tissue injury and improving functional recovery. Likewise, interventions targeting inflammatory metabolism, extracellular matrix remodeling, and angiogenesis may further optimize the regenerative microenvironment while limiting progression toward chronic kidney disease.

Emerging regenerative approaches combine metabolic modulation with stem cell therapy, extracellular vesicle delivery, biomaterial scaffolds, and gene-editing technologies to promote durable renal repair. Personalized medicine strategies based on metabolic biomarkers, genetic profiling, and multi-omics analyses may facilitate patient-specific therapeutic selection and improve clinical outcomes. Nevertheless, translating these discoveries into routine clinical practice requires further validation through carefully designed preclinical studies and large-scale clinical trials to determine long-term safety, efficacy, and optimal treatment timing. Continued integration of molecular biology, systems metabolism, regenerative medicine, and precision therapeutics

is expected to expand opportunities for restoring nephron structure and preserving kidney function in patients with acute and chronic renal diseases (8).

Methods

This review was developed through a structured and comprehensive evaluation of published literature focusing on anaerobic bioenergetics and nephron regeneration. Peer-reviewed articles published in English between 2005 and 2026 were identified from major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. Search terms included combinations of acute kidney injury, nephron regeneration, anaerobic metabolism, glycolysis, hypoxia-inducible factor, renal tubular repair, mitochondrial function, kidney organoids, zebrafish kidney model, metabolic reprogramming, and renal fibrosis. Additional references were retrieved through manual screening of bibliographies from relevant review articles and original research publications (9).

Studies were considered eligible if they investigated molecular mechanisms of nephron repair, metabolic adaptations during renal injury, hypoxia-mediated signaling, experimental models of kidney regeneration, or therapeutic interventions targeting cellular metabolism. Both experimental and translational studies involving mammalian models, zebrafish, kidney organoids, and human clinical observations were included. Publications lacking mechanistic relevance, duplicate records, conference abstracts without complete datasets, and non-English articles were excluded. Information from selected studies was synthesized narratively to compare molecular pathways, cellular responses, experimental findings, and therapeutic strategies. Particular emphasis was placed on identifying common mechanisms linking anaerobic bioenergetics with renal epithelial regeneration, mitochondrial adaptation, inflammatory regulation, and functional recovery following kidney injury (10).

DISCUSSION

The collected evidence consistently demonstrates that anaerobic bioenergetics represents a critical adaptive mechanism supporting

nephron survival and regeneration following acute kidney injury. During ischemic or hypoxic stress, renal tubular epithelial cells undergo metabolic reprogramming characterized by increased glycolytic activity and reduced dependence on mitochondrial oxidative phosphorylation. This transition preserves intracellular ATP levels, limits oxidative damage, and enables injured cells to maintain essential physiological functions while tissue oxygen availability remains restricted. Activation of hypoxia-inducible factors and associated glycolytic enzymes emerged as a central regulatory mechanism coordinating these metabolic adaptations.

Analysis of experimental studies further revealed that metabolic remodeling is closely associated with epithelial dedifferentiation, proliferation, migration, and subsequent redifferentiation, which collectively restore nephron architecture. Crosstalk between glycolytic metabolism, mitochondrial quality-control pathways, antioxidant defense mechanisms, and inflammatory signaling was consistently observed across multiple experimental systems. Investigations using zebrafish and kidney organoid models provided valuable real-time insights into cellular behavior during nephron regeneration, highlighting spatial and temporal changes in metabolic activity that are difficult to visualize in conventional mammalian models. Single-cell sequencing and metabolomic analyses additionally identified substantial metabolic heterogeneity among regenerating renal cell populations, suggesting that repair responses vary according to cell type and injury severity.

The reviewed studies also indicate that therapeutic modulation of cellular metabolism has significant potential for improving renal recovery. Pharmacological activation of hypoxia-responsive signaling pathways, enhancement of glycolytic efficiency, preservation of mitochondrial integrity, and regulation of inflammatory metabolism demonstrated protective effects in numerous preclinical investigations. These interventions reduced tubular injury, promoted vascular recovery, attenuated extracellular matrix deposition, and limited progression toward chronic kidney disease. Despite these promising findings, translation into clinical practice remains limited because of incomplete understanding of metabolic timing, tissue-specific responses, and long-term safety. Collectively, the available evidence supports anaerobic metabolic regulation as a fundamental determinant of successful nephron regeneration and a promising target for future regenerative therapies.

CONCLUSION

Anaerobic bioenergetics has emerged as an essential component of nephron regeneration by enabling renal cells to adapt to hypoxic stress while maintaining the energy required for tissue repair. Metabolic reprogramming toward glycolysis supports cellular survival, regulates proliferative and differentiation processes, minimizes oxidative injury, and coordinates communication among epithelial, endothelial, immune, and stromal cell populations involved in renal recovery. Advances

in experimental platforms, including zebrafish models, kidney organoids, single-cell transcriptomics, metabolomics, and spatial imaging technologies, have considerably expanded current understanding of the metabolic mechanisms governing nephron repair.

Although substantial progress has been achieved in identifying molecular pathways linking anaerobic metabolism with kidney regeneration, several mechanistic questions remain unresolved, particularly regarding long-term metabolic regulation, intercellular communication, and translational applicability in human disease. Future research integrating systems biology, precision medicine, and metabolism-targeted therapeutics will be essential for developing interventions capable of enhancing renal regeneration while preventing fibrosis and chronic kidney disease progression. A deeper understanding of anaerobic bioenergetics is expected to facilitate the development of innovative therapeutic strategies that improve functional recovery and long-term outcomes in patients with acute and chronic kidney disorders.

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