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Review

Mitochondrial Bioenergetics in Acute Tubular Injury: Metabolic Plasticity, Cell Fate, and Translational Opportunities

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Abstract

Acute tubular injury (ATI), often called acute tubular necrosis in clinical practice, is a major tissue-injury pattern in acute kidney injury (AKI), although necrosis is variable. Tubular transport places a high demand on mitochondrial ATP production. Ischemia-reperfusion, sepsis, and nephrotoxins disrupt this supply through respiratory dysfunction, calcium and redox imbalance, and mitochondrial DNA stress. The consequences depend on the nephron segment, cause of injury, and timing. This narrative review uses those differences to connect mitochondrial quality control and metabolic adaptation with cell fate, biomarkers, and therapeutic opportunities. We distinguish changes in gene expression or metabolite abundance from measured pathway function, and experimentally supported mechanisms from human associations and clinical intervention results. Human renal physiology, tissue studies, organ-perfusion experiments, and small randomized trials provide useful translational evidence. However, an increase in circulating NAD+ or an encouraging biomarker signal does not establish improved kidney outcomes. The proposed phase-based framework is therefore a guide to testing mechanisms and treatment windows, not a universal sequence from early adaptation to late harm. Clinical translation requires evidence that an intervention reaches its renal target, acts within a relevant window, and benefits patients beyond current supportive care.

Keywords: acute kidney injury; acute tubular injury; acute tubular necrosis; mitochondria; oxidative phosphorylation; fatty-acid oxidation; mitophagy; ferroptosis; biomarkers

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1. Introduction

Acute kidney injury (AKI) is a heterogeneous clinical syndrome defined by an abrupt change in kidney function. It is common in hospitalized and critically ill patients and is associated with short-term complications, mortality, prolonged hospitalization, and an increased risk of chronic kidney disease (CKD). Despite substantial mechanistic progress, no pharmacologic therapy reliably reverses established AKI; contemporary care therefore centers on treating the precipitating disorder, optimizing hemodynamics and volume status, avoiding additional nephrotoxins, adjusting drug doses, and providing kidney replacement therapy when indicated [1,2].

The term acute tubular necrosis (ATN) is widely used for intrinsic AKI caused by ischemia, sepsis, or nephrotoxins, but it can overstate what is seen in human tissue. Kidney

biopsies frequently show a spectrum of acute tubular injury (ATI)—epithelial simplification, loss of brush border, luminal dilation, casts, and focal cell detachment—with relatively little overt necrosis. Clinical–pathologic correlation is also imperfect, and biopsy is generally reserved for diagnostically uncertain or atypical cases. Accordingly, this review uses ATI for the tissue process and retains ATN when referring to the conventional clinical label. This distinction matters: a large fall in glomerular filtration can coexist with focal structural change because tubular transport failure, altered tubuloglomerular feedback, microvascular dysfunction, and inflammation contribute to the functional phenotype [3,4].

A bioenergetic framework helps connect these observations. Renal tubular epithelia maintain steep ion gradients and reabsorb filtered solutes continuously. The proximal tubule, in particular, contains abundant mitochondria and derives much of its ATP from oxidative metabolism. When oxygen delivery, substrate handling, or mitochondrial integrity is disturbed, ATP production can fall rapidly; polarity and transport fail before extensive cell loss is apparent. Mitochondria also integrate redox balance, calcium handling, innate immune signaling, and cell-death decisions. They are therefore both targets of injury and active determinants of recovery [5,6].

The initiating mechanism remains important. Ischemia–reperfusion imposes oxygen and substrate limitation followed by a burst of redox stress. Nephrotoxins may concentrate within tubular cells and directly affect the respiratory chain, mitochondrial membranes, or mitochondrial DNA (mtDNA). Sepsis-associated AKI is not simply global renal hypoperfusion: microcirculatory heterogeneity, inflammatory signaling, endothelial dysfunction, altered oxygen utilization, and adaptive metabolic downshifting all contribute, sometimes with limited histologic cell death. A single linear model therefore cannot explain all clinical ATI [7,8].

Existing reviews already cover mitochondrial dysfunction, quality-control pathways, and mitochondrial-directed therapies in AKI [9–11]. Here, we bring these topics together by asking where the injury occurs, what causes it, when a response is measured, and whether that response identifies a plausible treatment window. Table 1 separates directly tested timing effects from interpretations drawn across studies. Tables 2–4 then distinguish cell-death mechanisms, human evidence, and therapeutic readiness. This organization is the contribution of the review; it does not establish a new pathway or a universal transition from adaptive to harmful metabolism.

2. Review Approach

This narrative review combines the existing bibliography with a targeted supplementary PubMed search performed on 29 October 2026. Four Boolean queries addressed mitochondrial injury, human mitochondrial or NAD+ findings, named interventions in renal clinical testing, and human glucose or lactate metabolism. The exact strings and retrieval counts are provided in Supplementary File S1. PubMed was the only bibliographic database used for this documented update. The searches were restricted to English-language publications through 29 October 2026, with no clinically selected lower publication-year cutoff (the technical date range began on 1 January 1800). Up to 100 records per query were retrieved using the requested relevance ranking: 394 records before deduplication and 338 unique records. Titles were reviewed for relevance, followed by selected abstracts and accessible primary reports. This was a focused narrative update, not exhaustive or independently duplicated systematic screening.

Selection favored primary studies that addressed a central mechanism, measured function rather than expression alone, or supplied human physiologic, tissue, interventional, or organ-perfusion evidence. Foundational background references were retained, and human studies without a demonstrated renal benefit were included alongside positive

experimental findings. Discordant observations were considered in relation to the model, nephron segment, timing, assay, and specificity of the intervention. ClinicalTrials.gov records linked to selected trials and the cited FDA prescribing information were checked separately on 29 October 2026; this was not a comprehensive registry search. No formal risk-of-bias score, meta-analysis, or claim of systematic completeness is made.

3. Segmental Bioenergetics and Renal Vulnerability

3.1. Transport Work and Fuel Preference

The kidney receives a high fraction of cardiac output, yet renal oxygen consumption is dominated by tubular sodium transport rather than by filtration itself. Basolateral Na+/K+-ATPase maintains the electrochemical gradient that drives apical solute entry, linking transport demand to ATP consumption. Proximal tubules reclaim most filtered sodium and bicarbonate and nearly all filtered glucose and amino acids under physiologic conditions. Their elongated basolateral membrane, dense mitochondrial population, and close peritubular capillary supply reflect this sustained energetic workload [5,12].

Healthy proximal tubular cells have limited capacity to generate ATP through glycolysis and rely predominantly on oxidative phosphorylation (OXPHOS), using fatty acids, glutamine, lactate, and other substrates in a flexible, segment-dependent manner. Fatty-acid β-oxidation supplies acetyl-CoA to the tricarboxylic-acid cycle and reducing equivalents to the electron-transport chain (ETC). Glucose handling in the proximal tubule should not be equated with a highly glycolytic phenotype: filtered glucose is largely reabsorbed for systemic use, while local glucose oxidation and glycolytic capacity vary along the nephron [6,13].

3.2. Oxygen Gradients and Nephron-Segment Heterogeneity

Renal oxygen delivery and demand are spatially mismatched. Cortical blood flow is high, whereas the outer medulla receives less oxygen and supports substantial transport work in the S3 proximal segment and medullary thick ascending limb. Countercurrent oxygen shunting and local microvascular architecture can further constrain medullary oxygen availability. The outer medulla therefore operates close to a hypoxic threshold and is vulnerable to reductions in perfusion or increases in transport demand [5,12].

This vulnerability is not metabolically uniform. Proximal tubular cells are highly oxidative and have limited glycolytic reserve, whereas thick ascending limb cells possess greater glycolytic capacity. Contemporary spatial transcriptomic and metabolomic maps of the human kidney reinforce the importance of regional and cell-type-specific metabolic programs. Experimental results from one segment should therefore not be generalized automatically to the entire tubule. This segmental organization and regional vulnerability are summarized in Figure 1 [5,14].

Recent work also links this spatial view to human material. Arnoux et al. combined experimental metabolic profiling with human kidney-allograft analyses and identified outer-medullary thick ascending limb vulnerability. Higher propofol exposure in transplant recipients was associated with impaired oxidative metabolism and poorer renal outcomes; that observational association does not establish a causal clinical drug effect [15].

Nephrotoxic exposure adds another level of segment specificity. Experiments in isolated human proximal tubules support basolateral cisplatin uptake involving organic cation transporter 2 (OCT2), whereas apical megalin-mediated uptake is important for aminoglycoside toxicity and can also contribute to uptake of other nephrotoxic drugs [16,17]. In an immortalized mouse proximal-tubule segment model, platinum agents were more toxic to S3 than S1 or S2 cells, but greater platinum accumulation did not explain that difference; cadmium did not reproduce the same sensitivity pattern [18]. These findings support

compound- and model-specific vulnerability, not a universal S3-only rule for cisplatin or an identical map for aminoglycosides. Uptake localization should be established before attributing a segmental mitochondrial phenotype to intrinsic metabolic susceptibility alone.

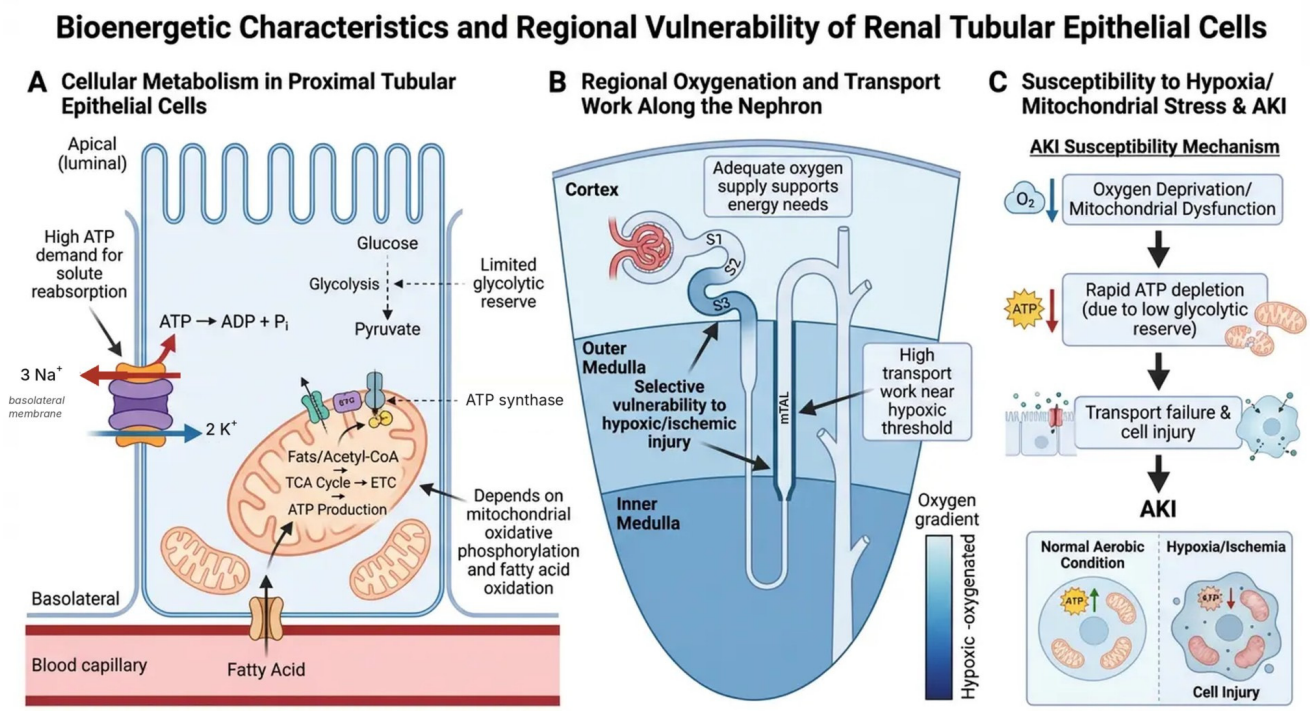


Figure 1. Bioenergetic architecture and regional vulnerability of renal tubular epithelial cells. Panel (**A**) emphasizes the oxidative, fatty-acid-supported phenotype of the proximal tubule; panel (**B**) depicts the corticomedullary oxygen gradient and vulnerable S3 and medullary thick ascending limb regions; panel (**C**) links oxygen or mitochondrial limitation to ATP-dependent transport failure. Fuel preference and glycolytic capacity differ among nephron segments. In panel A, the Na+/K+-ATPase on the lateral (basolateral) membrane moves three Na+ out of the cell in exchange for two K+ moved in; panel B labels the medullary thick ascending limb (mTAL). Created in BioRender. Tousif, M. (2026) https://BioRender.com/f3lydle (accessed on 1 November 2026). Upward and downward arrows indicate increases and decreases, respectively.

4. Mitochondrial Injury and Quality-Control Responses

4.1. Convergent Mitochondrial Stress Across Different Insults

Interruption of oxygen supply limits complex IV activity and stalls electron transport. The proton-motive force and mitochondrial membrane potential ($\Delta\psi m$) decline, oxidative phosphorylation becomes inefficient, and ATP production falls. Reperfusion restores oxygen but can also increase electron leak and mitochondrial reactive oxygen species (mtROS). Nephrotoxins produce partially overlapping phenotypes through compound-specific mechanisms: cisplatin, for example, accumulates in proximal tubular cells and perturbs mtDNA, antioxidant defenses, respiratory proteins, and membrane integrity. Sepsis can produce a more heterogeneous state of altered mitochondrial respiration and metabolic downregulation rather than uniform anoxic necrosis [9,19].

A more specific reperfusion mechanism involves ischemic succinate accumulation followed by rapid oxidation by succinate dehydrogenase (SDH). The resulting reduced coenzyme Q pool and high proton-motive force can favor reverse electron transport (RET) at complex I and ROS generation [20,21]. Renal experiments demonstrated succinate accumulation in mouse and pig kidneys and in declined human kidneys studied ex vivo; malonate-ester inhibition around reperfusion reduced injury in mice. The dimethyl mal-

onate regimen was beneficial when delivered around reperfusion but not before ischemia, providing a concrete example of an experimentally constrained intervention window [20]. This mechanism does not establish that RET dominates every septic or nephrotoxic mitochondrial ROS signal, nor that SDH inhibition is effective in patients with established AKI.

ATP depletion has immediate functional consequences. Na+/K+-ATPase activity and other transport processes become unsustainable; intracellular sodium and water rise; actin architecture, tight-junction organization, and apicobasal polarity are disturbed; and detached cells or debris can contribute to luminal obstruction. Increased cytosolic calcium, impaired mitochondrial calcium buffering, and pathologic opening of the mitochondrial permeability transition pore (mPTP) amplify depolarization and swelling. These changes can cause transport failure before extensive epithelial cell death is demonstrable [4,12].

mtROS are signaling molecules at physiologic concentrations, but excessive production can oxidize proteins, phospholipids, and nucleic acids. Damage to mitochondrial transcription factor A (TFAM) and mtDNA maintenance creates a feed-forward loop of respiratory dysfunction and oxidative stress in experimental ischemic AKI. Oxidized or mislocalized mtDNA can also function as a damage-associated molecular pattern. Cytosolic mtDNA activates cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) signaling, while extracellular or endosomal mtDNA may engage pattern-recognition receptors such as Toll-like receptor 9. These pathways connect organelle damage to local and systemic inflammation, although their contribution depends on model, tissue compartment, and timing [22–24].

4.2. Mitochondrial Dynamics

Mitochondria form a dynamic network controlled by fission, fusion, transport, and turnover. Dynamin-related protein 1 (DRP1) promotes fission; mitofusins 1 and 2 (MFN1/2) regulate outer-membrane fusion; and optic atrophy protein 1 (OPA1) coordinates inner-membrane fusion and crista architecture. Ischemic and toxic AKI models commonly show early mitochondrial fragmentation, sometimes before conventional evidence of apoptosis. Experimental inhibition of excessive DRP1 activity or preservation of fusion has reduced injury in selected models, supporting a causal contribution rather than a purely morphologic association [10,25].

Fission and fusion are not intrinsically harmful or beneficial. They contribute to mitochondrial distribution, damage segregation, and turnover, so morphology alone cannot determine whether a response is adaptive. The protective effects of selected genetic or pharmacologic interventions support involvement in injury in those models, but do not establish that every fragmented mitochondrion is causally injurious or that continuous fission inhibition is desirable. Dynamic measurements and functional perturbation are needed to distinguish a damaged network from an active quality-control response [10,25].

4.3. Mitophagy, Biogenesis, and Redox Repair

Mitophagy removes damaged mitochondria and can limit organelle-derived ROS and inflammatory signaling. PTEN-induced kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin mediate one route, while receptor-mediated programs include hypoxia-inducible factor-1α (HIF-1α) and BCL2-interacting protein 3 (BNIP3). Genetic and functional experiments support protective PINK1-Parkin and HIF-1α-BNIP3 responses in the cited cisplatin and ischemia-reperfusion models, respectively [26,27]. However, an increase in pathway-protein abundance or mitochondria-containing autophagosomes does not by itself measure completed mitophagic flux. Increased clearance should not be labeled harmful without evidence of impaired function, inadequate replacement, or a detrimental effect of experimentally modifying that clearance.

Recovery nevertheless requires replacement of cleared organelles. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) coordinates transcriptional programs involving nuclear respiratory factors and TFAM, thereby supporting mitochondrial biogenesis, oxidative metabolism, and antioxidant capacity. Tubular PGC-1α expression falls during inflammatory and ischemic AKI, while restoration of this axis promotes functional recovery in experimental settings. Inflammation can directly suppress PGC-1α, as shown for tumor necrosis factor-like weak inducer of apoptosis (TWEAK), providing a mechanistic bridge between cytokine signaling and prolonged energetic insufficiency [28–30].

AMP-activated protein kinase (AMPK) senses cellular energy stress and can support fatty-acid oxidation, autophagy, and mitochondrial homeostasis. Sirtuin 3 (SIRT3), a mitochondrial NAD+-dependent deacetylase, regulates antioxidant enzymes and respiratory proteins. Experimental loss or inactivation of these pathways worsens injury, whereas AMPK–SIRT3 activation improves mitochondrial function in several models. These nodes are attractive because they integrate energy sensing with repair, but their broad biologic effects also create potential off-target and timing-dependent consequences. Figure 2 summarizes the convergence of mitochondrial injury, quality-control responses, and divergent repair trajectories [31–33].

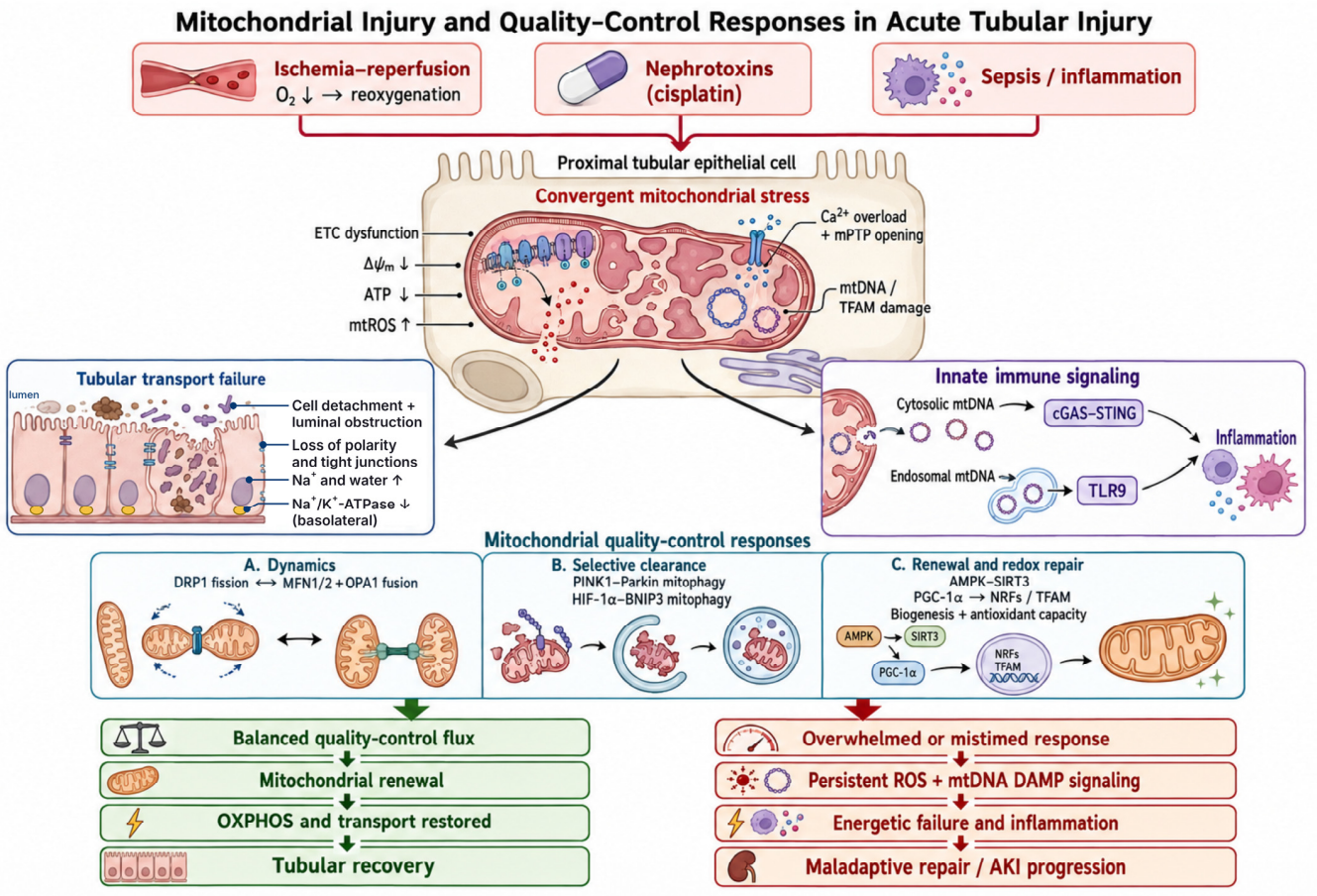


Figure 2. Convergent mitochondrial injury and quality-control responses in ATI. Distinct insults can impair electron transport and OXPHOS, dissipate Δψm, increase mtROS, and promote calcium-dependent mPTP opening. Balanced dynamics, mitophagy, biogenesis, and redox repair support recovery; persistent injury or inadequate repair favors energetic failure, mtDNA-triggered innate immune signaling, cell death, and maladaptive repair. Effects are segment-, insult-, and time-dependent. In the transport-failure inset, the Na+/K+-ATPase is shown on the basolateral membrane of the tubular cells, where its activity falls. Upward and downward arrows indicate increases and decreases,

respectively. Red boxes identify injurious stimuli and adverse outcomes; green boxes and arrows indicate recovery-associated responses; and purple outlines identify innate immune signaling. Other colors distinguish schematic components and do not represent quantitative measurements. Created in BioRender. Tousif, M. (2026) https://BioRender.com/fvnqgkd (accessed on 1 November 2026).

5. Metabolic Plasticity: Adaptive Bridge or Maladaptive State?

5.1. Suppression of Fatty-Acid Oxidation and Lipid Stress

Reduced fatty-acid oxidation (FAO) is one of the most reproducible metabolic features of injured proximal tubules. ETC dysfunction limits oxidative substrate use, while inflammatory and stress pathways suppress transcriptional regulators of FAO. The resulting decline in ATP production is especially consequential in a cell with high transport demand and limited glycolytic reserve. Lipid uptake and synthesis may then exceed oxidation and export, producing intracellular lipid droplets and potentially toxic lipid intermediates [6,34].

Evidence linking defective tubular FAO to fibrosis includes reduced FAO-related programs in human fibrotic kidney samples and functional perturbation or rescue in experimental systems [35]. In selected AKI models, peroxisome proliferator-activated receptor α (PPARα) ligands and farnesoid X receptor (FXR) activation preserved fatty-acid handling and reduced injury [36,37]. The human association does not by itself prove that restoring FAO reverses acute injury. Lipid droplets can also buffer excess fatty acids, and neutral lipid accumulation does not establish lipotoxicity without identifying the relevant lipid species and functional consequences. Segment, oxygen availability, and injury phase remain important interpretive variables [38].

5.2. Glycolysis and the Importance of Time

A glycolytic transcriptional response is not equivalent to an increase in usable glycolytic capacity. In the mouse cecal ligation and puncture model, proximal tubular oxygen consumption was suppressed at 4 h, whereas by 24 h respiratory capacity was higher despite lower tissue ATP and mitochondrial-content markers. Glycolytic-enzyme expression increased at 24 h, but functional measurements showed lower glycolytic capacity, reserve, and compensatory glycolysis [19]. Thus, this primary study supports a time-dependent metabolic disturbance and a mismatch between expression and function, rather than a general claim that early proximal-tubule glycolysis necessarily compensates for oxidative failure.

The adaptive-versus-maladaptive interpretation must therefore be conditional. Healthy proximal tubules have limited glycolytic reserve, and increased glucose uptake, enzyme expression, lactate abundance, or extracellular acidification should not be treated as interchangeable measurements of pathway flux [6,19]. An adaptive interpretation requires evidence that the measured change preserves energy balance or viability in that setting. Conversely, persistence of a glycolytic expression pattern during failed repair does not by itself prove that glycolysis causes fibrosis. The literature links altered oxidative metabolism, differentiation, and fibrotic remodeling, but it does not establish one obligatory metabolic sequence across ischemic, septic, and toxic ATI [35,39,40]. Table 1 separates directly tested timing from this proposed integrative interpretation.

Human physiology provides a complementary perspective. Using renal arteriovenous measurements, Legouis et al. found impaired glucose production and lactate clearance during AKI. Related metabolic abnormalities were associated with mortality in critically ill patients [41]. These findings concern renal gluconeogenesis and whole-organ substrate handling; they do not directly demonstrate increased glycolytic ATP flux or prove that manipulating glycolysis improves survival.

Table 1. Conditional phase map linking experimental observations, segment or insult, and proposed intervention windows.

Injury Phase	Setting and Measured Response	Evidence and Adaptive or Harmful Interpretation	Intervention Window and Limits
Initiation or ischemia	Oxidative proximal tubules have limited glycolytic reserve [6]. Succinate accumulated during ischemia in mouse, pig, and declined human kidney experiments [20].	Established physiology plus experimental metabolite measurements. Accumulation is not evidence that glycolysis provides sufficient compensatory ATP.	Restoring oxygen delivery and limiting exposure remain context-specific priorities. No universal human metabolic rescue interval is established here.
Extension or reperfusion	Renal succinate oxidation and ROS increased on reperfusion; SDH inhibition reduced injury in mice [20,21].	Functional animal intervention evidence supports a harmful reperfusion-associated process; human organ observations do not establish therapeutic efficacy.	Dimethyl malonate was protective with delivery around reperfusion, not before ischemia in the tested mouse regimen [20]. This is a demonstrated model-specific timing effect.
Maintenance during sepsis	Mouse proximal tubules: suppressed oxygen consumption at 4 h; greater respiratory capacity but lower ATP and mitochondrial markers at 24 h. Glycolytic enzymes rose while functional capacity fell [19].	Time-resolved measurements, not proof that a glycolytic switch is protective early and harmful late. Expression and functional reserve diverged.	Selecting treatment from expression alone is not supported. The 4 h and 24 h samples are model time points, not clinical phase boundaries.
Recovery	PGC-1α supported recovery after systemic inflammation in mice [28]. Protective mitophagy was shown in separate cisplatin and ischemia models [26,27].	Functional model evidence for specific pathways. These separate experiments do not prove one obligatory clearance-then-biogenesis sequence.	Coordinating organelle clearance with replacement is a proposed strategy requiring flux and functional testing, not a validated human regimen.
Persistent injury or failed repair	Human fibrotic tissue and experimental studies link reduced FAO programs with fibrosis; metabolic remodeling is also described during AKI-to-CKD transition [35,40].	Human association plus experimental support for selected mechanisms. Neither persistent glycolytic markers nor lipid droplets alone establish causation.	Restoring oxidative differentiation after adequate oxygenation is a hypothesis to test. Timing, reversibility, and patient selection remain unresolved.

Phases overlap and need not follow a fixed order, especially in septic or mixed-cause AKI. This table combines studies rather than reconstructing one longitudinal human trajectory. Only the explicitly tested animal dosing comparison establishes a treatment-timing effect.

5.3. NAD+ Metabolism and Metabolic Readouts in Humans

Nicotinamide adenine dinucleotide (NAD+) supports redox reactions and stress-response enzymes. Experimental work links PGC-1α to de novo NAD+ biosynthesis and renal protection [42]. Human urinary quinolinate-to-tryptophan ratio (uQ/T) findings are consistent with impaired de novo NAD+ biosynthesis in AKI, but do not directly measure compartment-specific tubular NAD+ flux. A small phase 1 cardiac-surgery nicotinamide (NAM) trial demonstrated changes in circulating metabolites and exploratory renal signals; it was not designed to establish definitive AKI efficacy [43].

Small randomized studies extend this work into established AKI. Simic et al. tested nicotinamide riboside with pterostilbene (NRPT) in 24 hospitalized patients, most with

stage 1 AKI. Whole-blood NAD+ increased during short-term dosing, but the study assessed exposure and tolerability rather than kidney recovery or survival [44].

More recently, 42 patients hospitalized with coronavirus disease 2019 (COVID-19) and AKI were randomized to MIB-626, a β-nicotinamide mononucleotide (NMN) formulation, or placebo. Blood NAD+ rose, but creatinine, cystatin C, and kidney-injury markers did not differ significantly between groups [45]. This distinction between biochemical response and renal benefit is central to interpreting NAD+-directed therapies.

Experimental urinary metabolomics also identifies altered metabolites during cisplatin nephrotoxicity, as demonstrated in a mouse study [46]. These model findings require separate clinical validation. Human biofluid signatures are additionally affected by systemic metabolism, nutrition, medications, and kidney handling; concentrations cannot by themselves establish production, oxidation, or clearance rates. Paired tissue–biofluid measurements and flux studies are therefore needed to test the proposed interpretations. Figure 3 presents the metabolic themes, with the evidence boundaries summarized in Table 1.

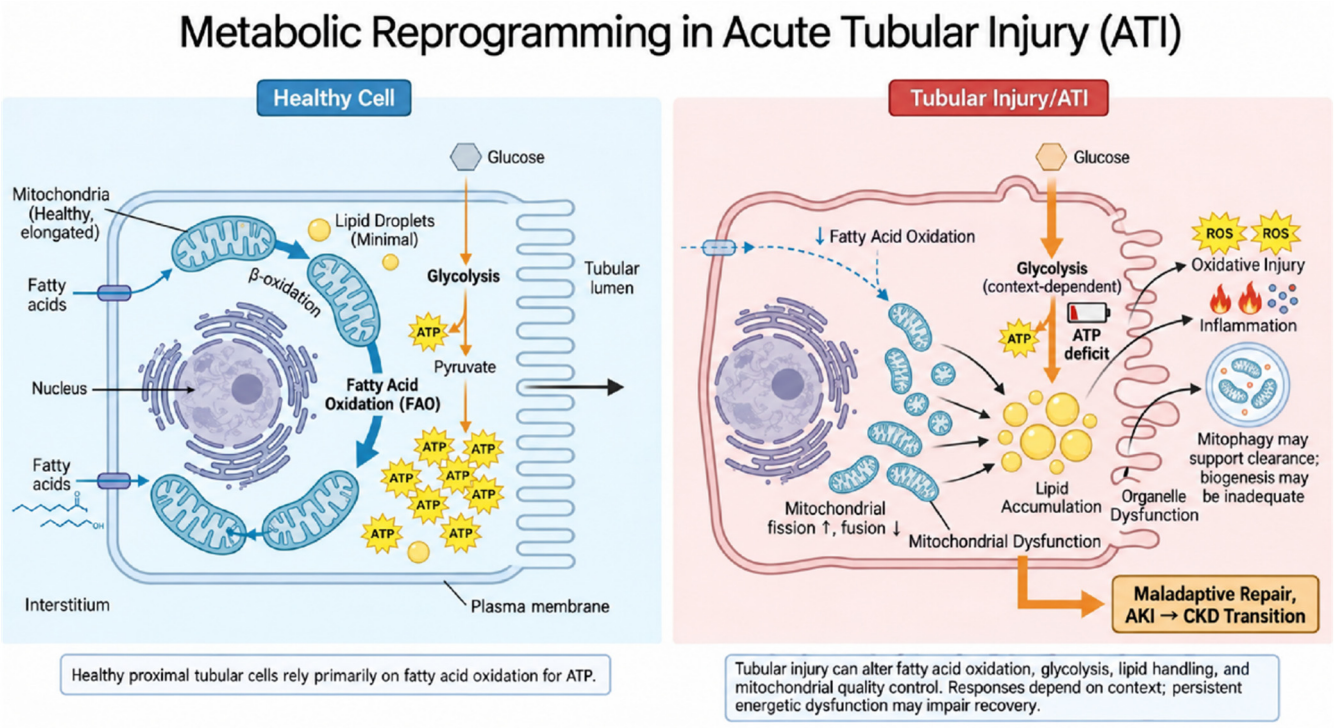


Figure 3. Metabolic reprogramming after acute tubular injury (ATI). Injury can suppress oxidative metabolism and alter glycolytic programs, lipid handling, and mitochondrial quality control. Glycolytic markers do not establish increased flux or a protective effect. Mitophagy is protective in selected experimental settings, while an imbalance between clearance and replacement is a proposed mechanism requiring functional confirmation. The relative contribution of these responses depends on segment, insult, and phase; the schematic is not evidence for a universal temporal sequence. Created in BioRender. Tousif, M. (2026) https://BioRender.com/ekwu0ba (accessed on 1 November 2026).

6. Bioenergetics and Cell Fate

Necrotic morphology does not identify a single execution pathway. Severe energetic failure may culminate in membrane rupture, but mitochondrial permeability transition can also participate in regulated necrosis, as shown by cyclophilin D-dependent experiments in renal ischemia-reperfusion [4,47]. Intrinsic apoptosis is more directly defined by BCL2-associated X protein (BAX)/BCL2 antagonist/killer 1 (BAK)-dependent mitochondrial outer-membrane permeabilization and cytochrome-c release [48]. Ferroptosis, necroptosis,

and pyroptosis have different execution machinery; mitochondrial metabolism or stress can modulate them without being an equivalent obligate executor in every setting [49].

Ferroptosis is executed through iron-dependent phospholipid peroxidation when defenses including glutathione peroxidase 4 (GPX4) fail. Synchronized tubular injury and acute renal failure after Gpx4 inactivation provide strong experimental evidence, and acyl-CoA synthetase long-chain family member 4 (ACSL4) deficiency protects in selected models [50–53]. Mitochondrial substrate use and redox state can influence susceptibility, but ferroptosis should not be equated with BAX/BAK-mediated mitochondrial apoptosis or assumed to have identical mitochondrial dependence across triggers. The cited model interventions do not establish efficacy of ferroptosis-directed treatment in human AKI.

Necroptosis is executed through receptor-interacting protein kinase 3 (RIPK3) and mixed-lineage kinase domain-like pseudokinase (MLKL); pyroptosis involves inflammatory caspases and gasdermin membrane pores. RIPK3-MLKL signaling has been implicated in experimental AKI-to-CKD progression, and gasdermin D (GSDMD) contributes to cisplatin injury in mice [54,55]. Mitochondrial ROS or mtDNA may influence these inflammatory responses, but those upstream links are not equivalent to a universally required mitochondrial execution step. Model, timing, genetic evidence, and inhibitor specificity must be considered before assigning pathway dominance [49,56]. Table 2 makes these distinctions explicit.

Table 2. Cell-death mechanisms, mitochondrial involvement, and the model level of the cited evidence.

Pathway or Phenotype	Execution Mechanism	Mitochondrial Relationship	Primary Evidence and Model	Human or Clinical Boundary
Necrotic morphology	Membrane failure and release of cell contents	Energetic collapse can contribute, but morphology does not identify the executor.	Histopathologic and mechanistic synthesis [4]; not one experimental execution pathway.	Does not by itself identify a druggable cause in human ATI.
Permeability-transition-driven necrosis	Cyclophilin D-associated mitochondrial permeability transition	A regulated mitochondrial process, distinct from simply labeling all necrosis unregulated.	Genetic/pharmacologic renal ischemia-reperfusion experiments in mice [47].	Model-specific causation; no clinical efficacy conclusion from this study.
Intrinsic apoptosis	BAX/BAK-dependent outer-membrane permeabilization and caspases	Mitochondria participate directly in execution.	Global and proximal-tubule-specific Bax/Bak knockout mice with ischemic AKI [48].	Relative contribution and treatment effect in human ATI require separate testing.
Ferroptosis	Iron-dependent phospholipid peroxidation when GPX4-related defenses fail	Metabolism and redox state modulate susceptibility; not an equivalent BAX/BAK execution step.	In vitro and mouse in vivo tubular studies; Gpx4 inactivation and selected interventions [50–53].	The cited studies do not establish human AKI treatment efficacy.
Necroptosis	RIPK3-MLKL-dependent membrane injury	Mitochondrial stress may modulate signaling; dependence is context-specific.	Mouse AKI-to-CKD and cell experiments implicating RIPK3-MLKL [54].	No clinical pathway dominance or therapeutic efficacy established by this study.
Pyroptosis	Inflammatory caspase activation and gasdermin pores	mtROS or mtDNA can influence upstream inflammation; gasdermin pores execute membrane injury.	Cisplatin-exposed cell and mouse experiments involving GSDMD [55].	Human pathway contribution and effects on host defense remain translational questions.

7. Biomarkers of Tubular and Bioenergetic Injury

Serum creatinine and urine output remain central to AKI diagnosis and staging, but neither identifies etiology or directly measures tubular energetics. Creatinine rises only after a sufficient reduction in filtration and is affected by baseline muscle mass, fluid balance, drug effects on tubular secretion, and non-steady-state kinetics. It is therefore better viewed as a functional marker than as an early readout of mitochondrial injury [1,57].

Tubular injury and stress markers provide complementary information. Urinary or plasma neutrophil gelatinase-associated lipocalin (NGAL), urinary kidney injury molecule-1 (KIM-1), interleukin-18, and the product of urinary tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 ([TIMP-2]·[IGFBP7]) can rise before or without a large creatinine change. [TIMP-2]·[IGFBP7] reflects cell-cycle stress and was discovered and validated for risk prediction in critically ill adults. These markers improve detection or prognostication in defined contexts, but they do not specify whether the primary mechanism is ischemic, toxic, inflammatory, or bioenergetic [58,59].

Urinary cell-free mtDNA is a plausible organelle-proximal marker. Higher concentrations have been associated with renal dysfunction and AKI in human cohorts, including surgical critical illness. Nonetheless, urinary mtDNA is not exclusively derived from tubular epithelial cells; may be affected by leukocytes, urinary tract pathology, preanalytical handling, urine concentration, and nuclease activity; and lacks a harmonized assay [60,61].

Metabolic and proteomic approaches may support molecular subphenotyping. uQ/T is a candidate indicator of NAD+ biosynthetic stress rather than a validated mitochondria-specific diagnostic [43]. In a 2024 plasma-proteomics study, 156 proteins were associated with histologic ATI severity among 434 participants with biopsy-confirmed kidney disease, not 434 participants all proven to have ATI. The investigators also examined associations in the Kidney Precision Medicine Project ($n = 44$), Atherosclerosis Risk in Communities study ($n = 4610$), and COVID-19 Host Response and Clinical Outcomes study ($n = 268$). This supports tissue-anchored human association and biomarker development, not direct proof of mitochondrial causation or therapeutic target engagement [62].

Functional measures, tubular stress markers, and candidate organelle-associated markers answer different questions. Creatinine and urine output support clinical diagnosis and staging; [TIMP-2]·[IGFBP7] has human risk-prediction evidence, while urinary mtDNA and uQ/T remain investigational mechanistic candidates [1,43,58,60,61]. A temporal multimodal panel is a proposed strategy, not a validated mitochondrial diagnostic. Prediction, diagnosis, treatment selection, and pharmacodynamic monitoring require separate validation. Figure 4 presents the intended biomarker layers; Table 3 distinguishes selected human observations, early interventions, and ex vivo organ experiments.

Table 3. Selected human renal studies and a registered trial relevant to mitochondrial translation.

Study and Setting	Design and Exposure or Measurement	Main Observation	Evidence Category and Interpretive Boundary
Poyan Mehr et al., 2018 [43] Human metabolic observations	Cardiac-surgery nested comparison (6 with and 6 without AKI); ICU urine analysis in 215 participants, including 51 with incident AKI.	Higher uQ/T was associated with subsequent AKI and adverse outcomes.	Human observational/mechanistically consistent evidence. Does not directly measure tubular NAD+ flux or establish a therapeutic effect.

Table 3. *Cont.*

Study and Setting	Design and Exposure or Measurement	Main Observation	Evidence Category and Interpretive Boundary
Poyan Mehr et al., 2018 [43] Cardiac-surgery NAM pilot	Randomized, single-blind, placebo-controlled phase 1 study; 41 participants. Perioperative oral NAM.	Circulating NAD+-related metabolites increased; safety assessments yielded exploratory renal signals.	Early clinical testing in a perioperative setting, not definitive AKI efficacy. Primary focus was metabolite exposure. Published registration: NCT02701127.
Saad et al., 2017 [63] Renal artery stenosis and revascularization	Randomized blinded phase 2a pilot: 14 patients; elamipretide 6 versus placebo 8, administered around angioplasty/stenting.	Procedure-associated oxygenation, blood-flow, and renal-function signals favored further investigation.	Early clinical testing in a selected renal-vascular procedure, not a general established-AKI treatment trial. Published registration: NCT01755858.
Whitaker et al., 2015; Hu et al., 2017 [60,61] Cardiac surgery and surgical critical illness	Human observational urinary mtDNA analyses; the Whitaker study also used experimental ischemic injury for tissue comparisons.	Urinary mtDNA was associated with renal dysfunction or AKI-related trajectories in the reported cohorts.	Human biomarker association, not a validated mitochondria-specific companion diagnostic or proof of treatment responsiveness.
Schmidt et al., 2024 [62] Biopsy-anchored proteomics	434 participants with biopsy-confirmed kidney disease and graded ATI; additional analyses in cohorts of 44, 4610, and 268.	156 plasma proteins associated with ATI severity; additional cohorts tested related AKI associations.	Human tissue-anchored observational evidence. Not all discovery participants had ATI, and the signature is not specific proof of mitochondrial dysfunction.
Hamed et al., 2021 [64] Declined human donor kidneys	Ex vivo preservation and blood reperfusion with or without MitoQ; study also included pig kidneys.	A human-organ perfusion signal was observed; the reported urine-output difference was not statistically significant.	Human ex vivo intervention, not treatment of living recipients or evidence of graft survival or clinical AKI benefit.
Arnoux et al., 2025 [15] Human kidney allografts	Spatial and functional profiling with experimental models and human transplant material.	Segment-specific metabolic vulnerability and an association with propofol exposure.	Human tissue association with experimental support. Not a randomized test of sedation strategy.
Legouis et al., 2020 [41] Renal glucose and lactate handling	Human renal arteriovenous measurements, clinical observations, and complementary models.	Impaired glucose production and lactate disposal in AKI.	Human functional and observational evidence; not direct measurement of glycolytic ATP flux or treatment efficacy.
Simic et al., 2020 [44] Hospitalized patients with AKI	Randomized, blinded short-term dose-escalation study; 24 participants. NRPT versus placebo.	Whole-blood NAD+ increased during dosing.	Exposure and tolerability study, not renal-efficacy confirmation. NCT03176628.
Pencina et al., 2025 [45] COVID-19 with AKI	Randomized placebo-controlled NMN trial; 42 randomized. MIB-626 for 14 days.	Blood NAD+ increased without significant differences in measured renal markers.	Published early clinical testing; no demonstrated renal benefit. NCT05038488.
NCT07013591 [65] Cardiac surgery	Registered randomized NMN study; estimated enrollment 90. Primary endpoint: myocardial NAD+.	Postoperative AKI is a secondary outcome; no posted results at access.	Protocol only. Registry listed recruiting on 29 October 2026; not efficacy evidence.

This is a selective synthesis, not a complete inventory of human studies or trials. Registration status was checked on 29 October 2026. The registered cardiac-surgery protocol is separated from published results; its primary endpoint is myocardial, not renal. Human associations, ex vivo effects, circulating target responses, and clinical kidney benefit answer different questions.

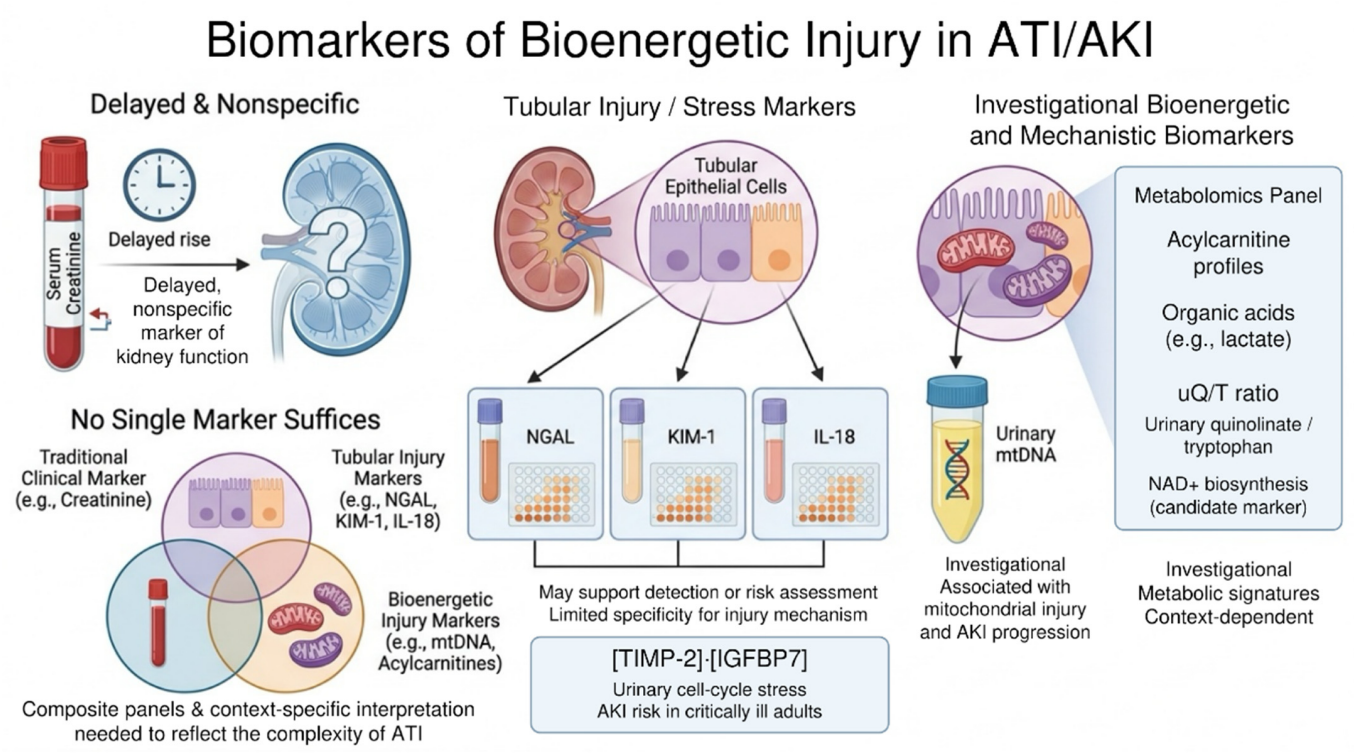


Figure 4. Candidate biomarker layers for acute tubular injury (ATI) and bioenergetic dysfunction. Creatinine is a delayed functional marker; NGAL, KIM-1, IL-18, and [TIMP-2]·[IGFBP7] report tubular injury or stress but are not mitochondria-specific. Urinary mtDNA, uQ/T, acylcarnitines, and broader metabolomics remain investigational mechanistic measures and require assay harmonization and validation for defined clinical uses. Created in BioRender. Tousif, M. (2026) https://BioRender.com/7taf1nx (accessed on 1 November 2026).

8. Therapeutic Opportunities and Translational Readiness

8.1. Mitochondrial Membrane and Cardiolipin-Directed Strategies

Elamipretide (SS-31) is a mitochondria-targeting tetrapeptide associated with cardiolipin-directed membrane effects. In rodent ischemia-reperfusion and cisplatin studies, treatment preserved mitochondrial or renal injury measures, supporting further mechanistic investigation [66–68]. A randomized phase 2a pilot involved 14 patients with atherosclerotic renal artery stenosis undergoing stent revascularization (elamipretide, $n = 6$; placebo, $n = 8$). Procedure-associated hypoxia, renal blood flow, and renal-function signals were encouraging, but this small selected-population study did not establish efficacy for heterogeneous established AKI [63].

The 2025 U.S. prescribing information documents accelerated approval of FORZINITY (elamipretide) to improve muscle strength in adults and pediatric patients with Barth syndrome weighing at least 30 kg. This is a non-AKI indication and does not establish renal efficacy [69]. Renal dosing, treatment timing, target engagement, and efficacy must be evaluated specifically for an AKI application.

8.2. Restoring Energy Sensing, Biogenesis, and NAD+

PGC-1α, AMPK, SIRT3, and NAD+ metabolism connect energy sensing with repair. Experimental interventions in these pathways can improve mitochondrial function and recovery in selected AKI models [28,33,42]. The clinical question is whether a feasible dose restores the relevant renal compartment soon enough to influence injury. The NAM, NRPT, and NMN studies summarized in Section 5.3 show why changes in circulating metabolites must be distinguished from kidney outcomes [43–45]. NCT07013591 is a registered

randomized NMN cardiac-surgery trial that includes postoperative AKI as a secondary outcome; its primary endpoint is myocardial NAD+. The registry listed recruitment and no posted results when checked on 29 October 2026 [65].

8.3. Mitochondrial Quality Control and Controlled Uncoupling

Protective mitophagy in selected models supports testing quality-control interventions, but the direction and duration of treatment cannot be inferred from pathway abundance alone [26,27]. A possible strategy would coordinate removal of damaged organelles with recovery of mitochondrial mass and oxidative function. This is a proposed sequence, not a validated clinical regimen or proof that continued mitophagy is necessarily harmful. Measurements of flux, replacement, and functional recovery are needed together [10].

Mild mitochondrial uncoupling can reduce membrane potential-dependent ROS production at the cost of lower coupling efficiency. The experimental uncoupler BAM15 improved survival and kidney injury in a mouse model of sepsis, linking tubular injury, mtDNA, and neutrophil responses. This is provocative preclinical evidence, not a recommendation for clinical uncoupling; safety margins, thermogenesis, tissue selectivity, and hemodynamic effects require careful evaluation [70].

8.4. Fuel Utilization, Redox Control, and Regulated Cell Death

PPARα- and FXR-directed interventions preserve FAO-related function in selected experimental injury models [36,37]. Whether stimulating oxidative substrate use is beneficial during severe oxygen limitation requires direct testing rather than assumption. Likewise, redox therapy should aim at a relevant compartment or source of injurious signaling, not elimination of all ROS. The rationale for mitochondria-targeted antioxidants remains distinct from demonstrated clinical AKI efficacy [71].

MitoQ protected mice when administered before renal ischemia-reperfusion, a prevention design that does not demonstrate rescue of established injury [72]. In declined human kidneys, MitoQ delivered during preservation improved an ex vivo perfusion measure; this was not a trial in living transplant recipients [64]. A comparative study found concentration-dependent protection with MitoTEMPO and SkQ1 in cell experiments and greater protection with MitoTEMPO in the tested mouse renal ischemia model; higher SkQ1 concentrations were cytotoxic [73]. These findings support model- and dose-specific redox effects, not a uniform antioxidant class benefit. SkQ1 should also not be conflated with related SkQR compounds.

SGLT2 inhibitors also warrant agent-specific interpretation. In cisplatin-exposed HK-2 cells and mice, canagliflozin-associated protection involved AMPK/autophagy signaling; inhibition experiments supported pathway involvement but do not eliminate inhibitor off-target effects. In that cell model, dapagliflozin and empagliflozin did not reproduce the protective effect [74]. Another experimental study implicated reduced cisplatin uptake and Akt signaling [75]. These observations do not establish that all SGLT2 inhibitors restore mitochondrial ATP production or treat established clinical cisplatin-associated AKI. Changes in toxin exposure, transport workload, and cellular signaling must be distinguished from direct mitochondrial rescue.

Ferroptosis inhibition is protective in selected experimental toxic and ischemic models, but renal efficacy and pathway-specific target engagement remain to be established in patients [49,52,53]. Necroptosis and pyroptosis interventions face similar questions about the dominant injury pathway and effects on host defense. Table 4 uses explicit evidence categories and separates human exploratory observations from preclinical protection; Figure 5 maps the proposed intervention points.

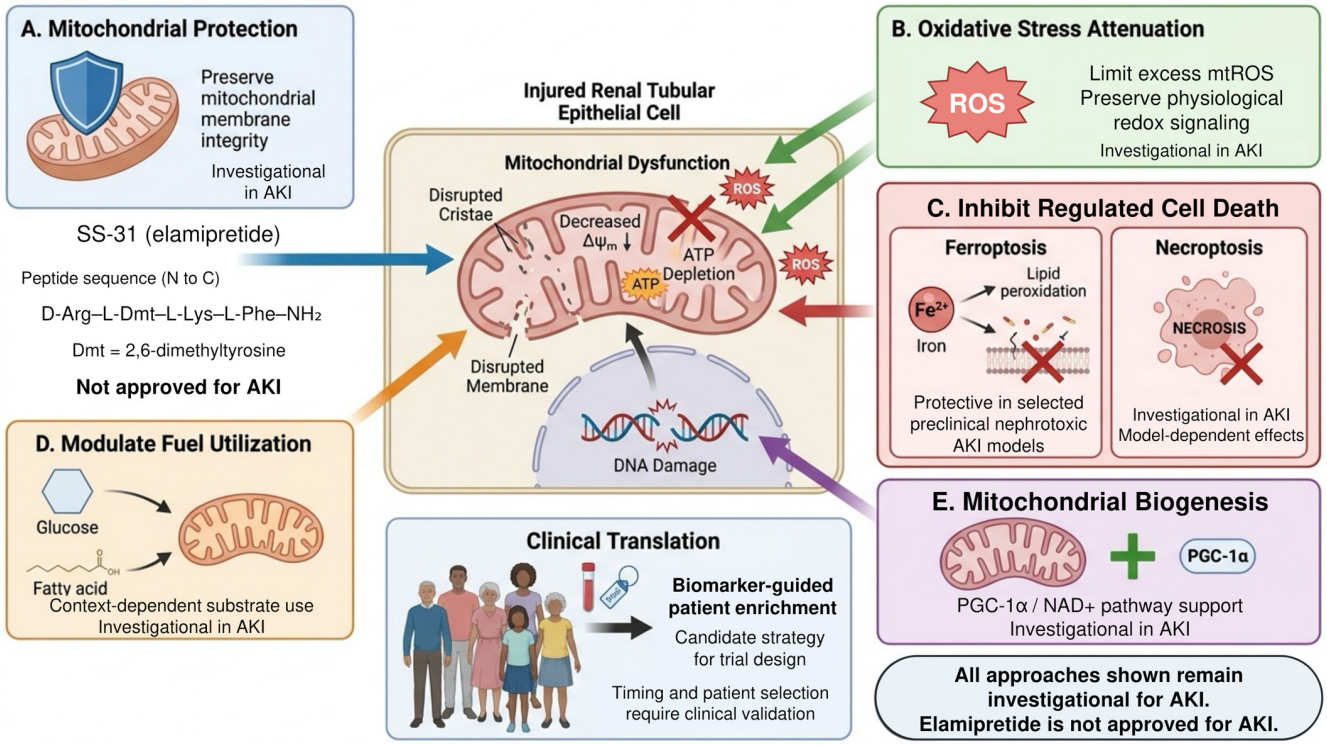


Figure 5. Mechanism-based therapeutic opportunities in acute tubular injury (ATI). Proposed approaches include mitochondrial protection (**A**), redox modulation (**B**), regulated cell-death inhibition (**C**), fuel modulation (**D**), and mitochondrial biogenesis (**E**). All AKI applications remain investigational; elamipretide is approved for Barth syndrome, not AKI. Arrows indicate targets, not treatment order. Created in BioRender. Tousif, M. (2026) https://BioRender.com/e5wsj7u (accessed on 1 November 2026).

Table 4. Mitochondrial and metabolic intervention strategies with explicit evidence categories and clinical boundaries.

Strategy	Evidence Category and Model	Interpretation of the Reported Findings	Principal Translational Boundary
Elamipretide (SS-31)	Preclinical: rodent ischemia/toxin injury [66,67]. Early clinical: renal-revascularization pilot [63].	Mitochondrial and renal signals support further testing. Non-AKI accelerated approval is documented for Barth syndrome [69].	No established efficacy for heterogeneous clinical AKI. Non-AKI approval is not renal efficacy.
PGC-1α/NAD+ support	Preclinical mechanisms [28,42]; human NAM, NRPT, and NMN testing [43–45].	Circulating metabolic responses can be achieved; the NMN AKI trial did not demonstrate renal benefit.	Renal compartment exposure, timing, and adequately powered clinical outcomes remain unresolved.
AMPK-SIRT3 activation	Preclinical: genetic and pharmacologic AKI studies [31,33].	Energy-sensing and mitochondrial repair pathways are experimentally modifiable.	Pleiotropy, inhibitor specificity, tissue pharmacodynamics, and human efficacy require study.
Mitophagy or dynamics modulation	Preclinical: cisplatin and ischemia models [25–27].	Selected functional perturbations support protective quality-control responses.	Flux and replacement must be measured; a universal treatment direction or sequence is not established.
FAO preservation	Preclinical AKI interventions [36,37]; human fibrotic tissue association and experimental fibrosis work [35].	Selected interventions preserve substrate-handling programs and reduce model injury.	Oxygen supply, lipid species, model, and phase matter; human association is not acute treatment efficacy.

Table 4. *Cont.*

Strategy	Evidence Category and Model	Interpretation of the Reported Findings	Principal Translational Boundary
MitoQ	Preclinical mouse ischemia pretreatment [72]; human ex vivo preservation/perfusion [64].	Protection or improved perfusion in the tested settings.	Pretreatment and ex vivo organ results do not demonstrate rescue of established clinical AKI.
MitoTEMPO and SkQ1	Preclinical cell oxidative-stress and mouse renal ischemia comparisons [73].	Dose- and agent-dependent benefit; higher SkQ1 concentrations were cytotoxic.	Do not infer a uniform antioxidant class effect, clinical superiority, or patient efficacy.
Canagliflozin	Preclinical HK-2 and mouse cisplatin studies [74,75].	AMPK/autophagy, toxin uptake, and Akt pathways were implicated; other SGLT2 agents did not reproduce all cell findings.	Agent-specific experimental protection is not class-wide direct mitochondrial rescue or established clinical AKI efficacy.
Ferroptosis inhibition	Preclinical: selected toxic/ischemic models and genetic studies [50–53].	Lipid-peroxidation-related cell death is experimentally tractable.	Human pathway enrichment, pharmacology, and efficacy require validation.
BAM15 and mild uncoupling	Preclinical: mouse sepsis [70].	Renal injury and survival improved in the reported model.	Therapeutic window, tissue selectivity, systemic safety, and human renal efficacy remain uncertain.

9. Clinical Translation and Future Directions

9.1. Improve Model Fidelity and Human Anchoring

Many interventions are tested in young, otherwise healthy rodents exposed to one timed insult, whereas clinical AKI often involves aging, CKD, diabetes, infection, repeated exposures, and treatment after injury is recognized. Experimental age and sex effects illustrate why this difference matters: aged versus young rats showed greater mitochondrial apoptotic responses after ischemia-reperfusion, while a mouse/cell study linked estrogen-associated SIRT3 responses to sex-related differences in injury and mitochondrial dynamics [76,77]. These model findings do not establish a uniform age or sex effect on treatment response in humans. Translation should test both sexes, relevant ages and comorbidities, delayed dosing, and supportive-care cointerventions, with prespecified reporting of differential responses.

Cell systems also require scrutiny. Immortalized cells grown in high-glucose medium and atmospheric oxygen can adopt a glycolytic phenotype that poorly represents primary proximal tubular bioenergetics. Primary human tubular cells, precision-cut kidney slices, organoids, microphysiologic kidney-on-chip systems, and ex vivo human tissue can improve relevance, although none fully reproduces blood flow, filtration, immune interactions, or whole-organ oxygen gradients. Spatial omics, electron microscopy, respirometry, and stable-isotope tracing should be integrated where feasible to distinguish mitochondrial abundance from function and metabolite concentration from flux [6,14].

Human kidney tissue is difficult to obtain during AKI, but tissue anchoring is essential. Clinically indicated biopsies, transplant implantation or protocol biopsies, nephrectomy-adjacent tissue, and rapid autopsy programs can be linked to plasma and urine. The proteomic study of biopsy-confirmed ATI demonstrates the value of this approach. Prospective biobanking should record time from insult, vasopressor exposure, nephrotoxins, nutrition, fluid balance, and kidney support because each can alter bioenergetic measurements [62].

9.2. Resolve Timing, Heterogeneity, and Target Engagement

A temporal framework is useful only when it distinguishes measured trajectories from hypotheses. The glycolytic-expression/function mismatch in experimental sepsis, protective mitophagy perturbations, and reperfusion-timed SDH inhibition illustrate different kinds of evidence rather than a single common clock [19,20,26,27]. Serial measurements of substrate use, organelle turnover, mitochondrial replacement, and tissue function are needed to test which response is adaptive in a given setting. Enrollment across mechanistically different phases could obscure a treatment signal, but phase-based treatment selection itself remains to be validated.

Etiology should also be treated as a mechanistic variable rather than a simple covariate. Ischemic postoperative AKI, septic AKI, aminoglycoside or cisplatin toxicity, pigment nephropathy, and mixed intensive-care AKI differ in timing, cell targets, inflammatory context, and reversibility. Consensus phenotypes and molecular subphenotypes should be prespecified, while acknowledging that many patients have more than one insult [7,8].

Demonstrating target engagement is a prerequisite for efficacy testing. For a cardiolipin-directed agent, this might include a validated measure of mitochondrial membrane or respiratory recovery; for NAD+ therapy, restoration of the relevant NAD+ pool and downstream enzymatic activity; for ferroptosis inhibition, a lipid-peroxidation signature. Serum creatinine alone cannot establish that a mitochondrial mechanism was modified.

9.3. Design Trials Around Actionable Windows

Prevention trials may be feasible when the injury window is predictable, as in selected cardiac surgery, transplantation, or scheduled nephrotoxin exposure. Established AKI requires rapid recognition and may demand a different intervention than the recovery phase. Adaptive platform designs could allow biomarker-defined enrollment and test mechanism-specific therapies under a common protocol. Early-phase studies should emphasize safety, renal and systemic pharmacokinetics, tissue-relevant target engagement, and trajectory-based endpoints before relying on major adverse kidney events.

The mitochondrial-directed strategies summarized here do not yet establish an effective treatment for heterogeneous clinical AKI. Human renal observations and small interventional studies provide a translational basis, not a substitute for adequately powered efficacy trials [11,43,63,78]. The next step is to define an eligible population, a measurable mechanism, and an experimentally justified treatment window. Figure 6 summarizes these research priorities rather than an established clinical sequence.

9.4. Limitations of the Review and Proposed Framework

Study selection was interpretive, without a formal risk-of-bias assessment or pooled effect estimate. The supplementary update was limited to English-language PubMed records and capped at 100 results per query, so relevant studies may have been missed. Selective retrieval of accessible full texts and publication bias toward positive experiments may also affect the synthesis. Many mechanisms are supported mainly by cells and animals. Human associations, ex vivo responses, and small trials add clinical relevance, but they cannot be treated as equivalent evidence of treatment benefit. Expression, metabolite abundance, respiration, and organelle turnover measure different processes. The phase-based framework combines studies rather than following one human injury trajectory, and it does not validate a universal treatment window. Mixed insults, segmental differences, age, sex, and comorbidity further limit extrapolation. The human-evidence table and registry checks are selective.

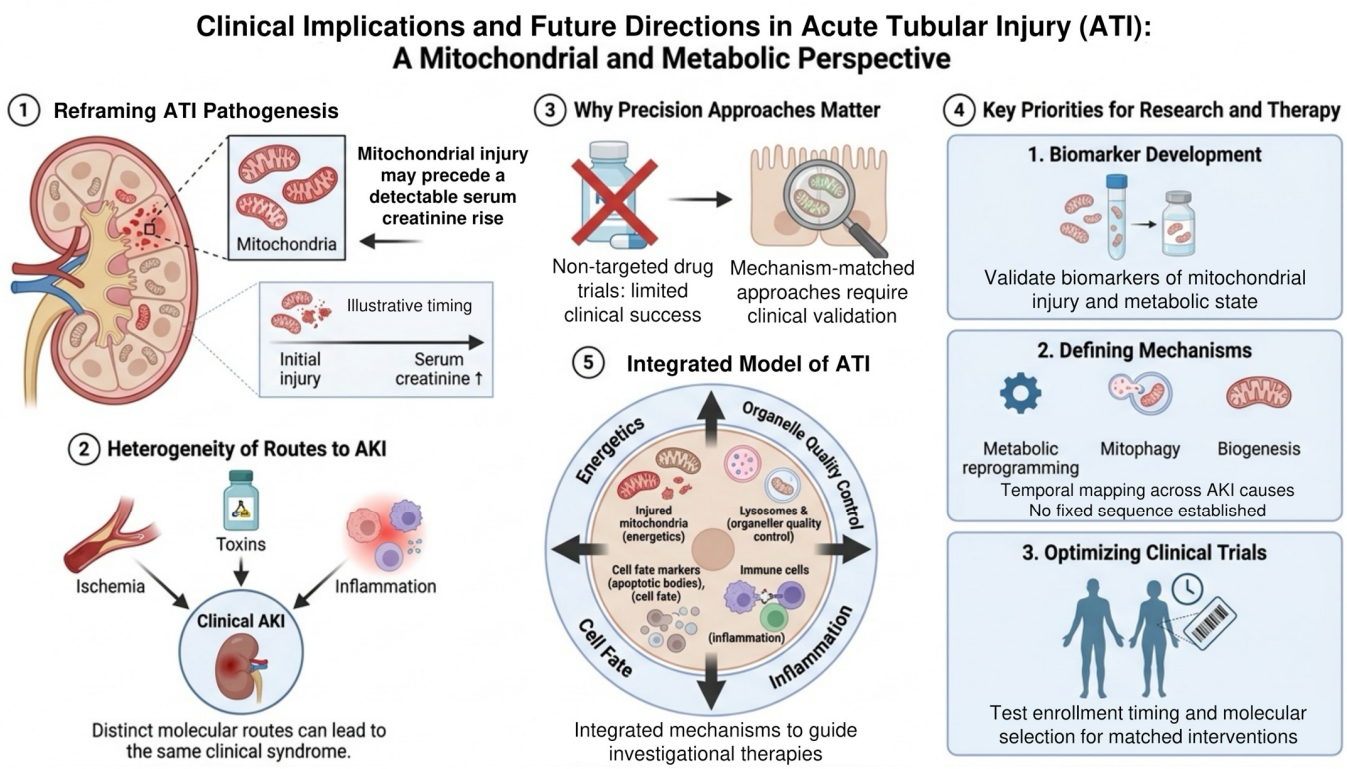


Figure 6. Clinical implications and research priorities in acute tubular injury (ATI). Mitochondrial and tubular stress may precede a detectable rise in serum creatinine, while ischemic, toxic, and inflammatory routes can converge on the clinical AKI phenotype. Priorities include deployable mechanistic biomarkers, temporal mapping of overlapping metabolic and quality-control responses, and molecularly enriched trials. Timing and treatment selection require validation; no universal sequence is implied. Created in BioRender. Tousif, M. (2026) https://BioRender.com/w0gminj (accessed on 1 November 2026).

10. Conclusions

ATI encompasses transport dysfunction and variable structural injury rather than uniform tubular necrosis. Renal segmental physiology is well established, while experimental studies support multiple causal mitochondrial and metabolic contributions under defined conditions. Their importance varies with insult, segment, assay, and time. The temporal framework proposed here organizes those differences but does not establish a universal shift from adaptive to harmful glycolysis or mitophagy.

Human studies now connect metabolic disruption with renal physiology, tissue injury, and circulating biomarkers, and early trials show that NAD+ exposure can be modified. The next step is not simply to demonstrate another biochemical response, but to establish renal target engagement and a meaningful benefit for patients. Cardiolipin stabilization, NAD+ support, quality-control modulation, substrate handling, targeted redox approaches, and cell-death interventions remain investigational renal strategies. Trials should test a defined mechanism and treatment window in a clinically characterized population, alongside current supportive care.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cimb48111210/s1, Supplementary File S1. Supplementary literature search record flowchart of the search and selection process, complete PubMed search strategies, search dates, retrieval counts and targeted clinical trial registry checks performed for the revision contains the documented PubMed search update and targeted trial-registry checks performed for this revision. References [15,41,44,45] are cited in the supplementary materials.

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Abbreviations

The following abbreviations are used in this manuscript:

Abbreviation	Definition
ACSL4	Acyl-CoA synthetase long-chain family member 4
ADP	Adenosine diphosphate
AKI	Acute kidney injury
AKT	Protein kinase B (Akt)
AMPK	AMP-activated protein kinase
ATI	Acute tubular injury
ATN	Acute tubular necrosis
ATP	Adenosine triphosphate
BAK	BCL2 antagonist/killer 1
BAX	BCL2-associated X protein
BCL2	B-cell lymphoma 2
BNIP3	BCL2-interacting protein 3
cGAS	Cyclic GMP-AMP synthase
CKD	Chronic kidney disease
COVID-19	Coronavirus disease 2019
Dmt	Dimethyltyrosine
DNA	Deoxyribonucleic acid
DRP1	Dynamin-related protein 1
ETC	Electron-transport chain
FAO	Fatty-acid oxidation
FDA	U.S. Food and Drug Administration
FXR	Farnesoid X receptor
GPX4	Glutathione peroxidase 4
GSDMD	Gasdermin D
HIF-1α	Hypoxia-inducible factor 1α
HK-2	Human kidney 2 proximal tubular cell line
ICU	Intensive care unit
IGFBP7	Insulin-like growth factor-binding protein 7
IL-18	Interleukin-18
KIM-1	Kidney injury molecule-1
MFN1/2	Mitofusins 1 and 2
MLKL	Mixed-lineage kinase domain-like pseudokinase
mPTP	Mitochondrial permeability transition pore
mTAL	Medullary thick ascending limb
mtDNA	Mitochondrial DNA
mtROS	Mitochondrial reactive oxygen species

NAD+	Oxidized nicotinamide adenine dinucleotide
NAM	Nicotinamide
NFRs	Nuclear Respiratory Factors
NGAL	Neutrophil gelatinase-associated lipocalin
NLRP3	NLR family pyrin domain-containing 3
NMN	Nicotinamide mononucleotide
NRPT	Nicotinamide riboside with pterostilbene
OCT2	Organic cation transporter 2
OPA1	Optic atrophy protein 1
OXPHOS	Oxidative phosphorylation
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1α
PINK1	PTEN-induced kinase 1
PPARα	Peroxisome proliferator-activated receptor α
RET	Reverse electron transport
RIPK3	Receptor-interacting protein kinase 3
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase
SGLT2	Sodium-glucose cotransporter 2
SIRT3	Sirtuin 3
SS-31	Szeto-Schiller peptide 31 (elamipretide)
STING	Stimulator of interferon genes
TCA	Tricarboxylic acid
TFAM	Mitochondrial transcription factor A
TIMP-2	Tissue inhibitor of metalloproteinases-2
[TIMP-2]·[IGFBP7]	Product of urinary TIMP-2 and IGFBP7
TLR9	Toll-like receptor 9
TWEAK	Tumor necrosis factor-like weak inducer of apoptosis
uQ/T	Urinary quinolinate-to-tryptophan ratio
Δψm	Mitochondrial membrane potential

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