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Mitochondrial Dysfunction in Kidney Transplantation: A Mechanistic Link Between Ischemic Injury and Chronic Allograft Damage

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ABSTRACT
Kidney transplantation remains the preferred treatment for end-stage kidney disease, yet ischemia–reperfusion injury continues to compromise early graft recovery and long-term allograft survival. The concept of mitochondrial dysfunction has come to play a key role in the understanding of the relationship between peri-transplant ischemic injury and chronic allograft damage. Warm and cold ischemia leads to impaired oxidative phosphorylation, ATP depletion, calcium imbalance and metabolic disruption that destabilize renal tubular cells and endothelial cells. Excessive generation of ROS, membrane depolarization, permeability transition, defective mitophagy, and activation of apoptosis, necroptosis and ferroptosis are further exacerbated during reperfusion. CGAS–STING activation, activation of the NLRP3 inflammasome, endothelial inflammation, recruitment of leukocytes, and alloimmune responses are also promoted by damaged mitochondria releasing mitochondrial DNA and other damage associated molecular patterns. The lack of mitochondrial homeostasis can perpetuate tubular and endothelial dysfunction, promote maladaptive reparative response, induce fibroblast activation and present a risk of interstitial fibrosis, tubular atrophy, microvascular rarefaction, delayed graft function, and chronic allograft dysfunction. New mitochondrial biomarkers such as circulating and urinary mitochondrial DNA, metabolic signatures and respiratory parameters could help to better evaluate the graft and to better stratify the risk. There are several promising strategies to protect the graft such as those using antioxidants targeted to the mitochondria, metabolic modulators, mitophagy-directed therapies, and machine-perfusion strategies. Targeting mitochondrial dysfunction may therefore provide an integrated strategy to reduce ischemic injury and preserve long-term kidney allograft function.

Keywords: kidney transplantation; mitochondrial dysfunction; ischemia–reperfusion injury; delayed graft function; chronic allograft dysfunction; mitophagy

1. Introduction

Kidney transplantation is the optimal renal replacement therapy for those who are suitable for the procedure and offers better survival, quality of life, and long-term clinical outcomes compared with maintenance dialysis. Although there have been significant advances in surgical technique, immunosuppressive therapy, donor–recipient matching and perioperative management, maintaining long-term allograft function continues to be a significant challenge. Ischemia-reperfusion injury (IRI) is one of the earliest and most important non-immunological injuries of transplanted kidneys, which is caused by the process of organ procurement and preservation, the period of transplantation, and re-establishment of blood flow. Donor factors, warm and cold ischemia times, preservation conditions and recipient factors all affect the degree of ischemic damage. IRI activates a chain of events that includes depletion of cellular energy, oxidative stress, endothelial dysfunction, inflammation, and programmed cell death, which affects the immediate success of the graft, as well as the repair process in the tissue following surgery [1].

Although reperfusion is essential for restoring oxygen and nutrient delivery, the abrupt reintroduction of oxygen to previously ischemic tissue can paradoxically intensify cellular injury. This effect is especially important in renal transplantation since metabolic demands of the transplanted kidney are very high and oxidative phosphorylation is crucial for tubular transport processes. Severe IRI has been associated not only with acute impairment of graft function but also with reduced long-term graft survival, emphasizing that the consequences of peri-transplant injury may extend well beyond the immediate postoperative period [2]. Persistent cellular abnormalities following ischemic injury may promote maladaptive repair, chronic inflammation, microvascular injury, and progressive fibrotic remodeling, thereby establishing a biological connection between early graft injury and later chronic dysfunction [3].

The mitochondria are located in the middle of this pathogenic continuum. Mitochondria are especially abundant in renal tubular epithelial cells since they have

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to produce adenosine triphosphate continuously as they are involved in reabsorptive and secretory activities. Under ischemic conditions, oxygen deficiency causes disturbances in the oxidative phosphorylation, loss of cellular energy stores, changes of mitochondrial membrane potential and disturbances of calcium and redox homeostasis. This can lead to excessive production of reactive oxygen species (ROS) in mitochondria during the following reperfusion, that can cause membrane permeabilization, dysfunctional mitochondrial dynamics, impaired mitophagy, activation of multiple cell-death pathways. These alterations can amplify inflammatory signaling while reducing the capacity of renal cells to recover normal metabolic function. There is therefore growing evidence that mitochondrial dysfunction plays a significant part in the severity and duration of transplant-associated IRI [4].

In the clinic, the most common example of a severe peri-transplant injury is delayed graft function (DGF), which is associated with the need for dialysis within the first few days after transplantation. The implications of DGF for patient management and its link to high risk of graft failure and acute rejection make this an important factor to consider [5]. These are also corroborated by more recent, long-term evidence that DGF can be used to predict chronic allograft dysfunction, which further suggests that the acute injury that occurs around transplantation can have long-term implications for graft integrity [6].

Accordingly, mitochondrial dysfunction may represent a mechanistic bridge connecting early ischemic injury with progressive chronic allograft damage. Revealing the interplay of mitochondrial energetics, redox balance, quality control, cell death signaling, inflammation and tissue repair after transplantation could provide clinically relevant biomarkers and therapeutic targets. Therefore, this review discusses the changes in mitochondrial function during renal IRI, their role in immune-inflammatory activation and maladaptive repair mechanism, and how they could contribute to chronic allograft dysfunction, also highlighting emerging mitochondria-directed strategies to enhance long-term kidney transplantation outcomes.

2. Mitochondrial Homeostasis in the Kidney

The kidney is one of the most metabolically active organs of the body and has a particularly high requirement for mitochondrial oxidative phosphorylation for ATP production. A significant amount of energy is needed by renal tubular epithelial cells to drive the reabsorption of solutes, the transport of ions, and maintenance of the electrochemical gradients. The proximal tubular cells are particularly rich in mitochondria, as they have little capacity for glycolysis and are highly dependent on fatty acid oxidation and mitochondrial respiration. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is an important regulator of renal mitochondrial metabolism which regulates oxidative phosphorylation, fatty acid oxidation and cellular energy homeostasis [7].

Maintaining a sufficient number of functional mitochondria and the ability of renal cells to respond to alterations in metabolic requirements depends on mitochondrial biogenesis. PGC-1α switches on transcription programmes for mitochondrial replication, respiratory chain activity and antioxidant defence. The impaired PGC-1α signaling may lead to decreased mitochondrial mass, ATP-producing capacity, and increased mitochondrial sensitivity to oxidative injury. On the other hand, mitochondrial biogenesis restoration could promote metabolic recovery after renal stress, which could be a key factor in renal cellular resilience [8].

Coordinated mitochondrial fission, fusion and selective mitochondrial clearance are essential for maintaining mitochondrial integrity. Mitochondrial fusion enables exchange of mitochondrial contents, whereas fission segregates damaged components for subsequent removal through mitophagy. The imbalance causes dysfunctional mitochondria to accumulate, excessive production of ROS and poor bioenergetics [9]. In the acute kidney injury/acute repair stage, the proper function of mitophagy protects against mitochondrial injury and promotes tubular repair [10]. Mitochondrial homeostasis also requires coordinated redox control, calcium handling, proteostasis, and organelle turnover, disturbances of which can promote senescence, inflammation, and progressive renal dysfunction [11]. Tubular and endothelial cells are particularly vulnerable during transplantation because ischemia rapidly compromises ATP production and microvascular function. Therefore, good mitochondrial quality control will prevent the persistence of damaged organelles and further graft damage [12].

3. Ischemia–Reperfusion Injury and the Initiation of Mitochondrial Dysfunction

In the early events of kidney transplantation, ischemia–reperfusion injury is a crucial process that directly impairs mitochondrial structure and function. Oxygen deprivation during procurement and preservation, followed by abrupt restoration of oxygenated blood, produces metabolic instability in tubular and endothelial cells. The dysfunction of mitochondria plays a prominent role in the severity of renal IRI and the recovery of grafts, due to their role in the regulation of respiration, redox balance, calcium handling, and cell-death signaling [13].

3.1 Mitochondrial Changes during Warm and Cold Ischemia

Warm ischemia begins when renal blood flow is interrupted while the organ remains at physiological temperature, whereas cold ischemia develops during hypothermic preservation before implantation. Oxygen deficiency inhibits mitochondrial oxidative phosphorylation, leading to a rapid decline in ATP synthesis, and promoting renal cells to switch to less efficient anaerobic metabolism. ATP depletion leads to decreased activity of membrane ion pumps, alteration of ionic gradients, intracellular acidosis, and accumulation of calcium and metabolic intermediates. Mitochondrial respiratory-chain components also become increasingly reduced during ischemia, creating conditions that predispose the organelles to increased electron leakage when oxygen is restored [14]. Extended cold ischemia may worsen the integrity of the respiratory chain and

the antioxidant capacity. Thus, strategies aimed at preventing oxidative damage to the mitochondria have been suggested as a possible strategy to prevent renal injury during the preservation and reperfusion period [15].

3.2 Reperfusion-Induced Oxidative Stress and Calcium Overload

Reperfusion restores oxygen, but also produces a surge of mitochondrial reactive oxygen species (ROS). This process can be significantly accentuated by impaired mitochondrial antioxidant defenses. Loss of mitochondrial NADP+-dependent isocitrate dehydrogenase, which helps to regulate mitochondrial redox balance, has been linked with increased oxidative damage, mitochondrial dysfunction, and renal cellular damage after ischemia–reperfusion [16]. Succinate accumulated during ischemia represents another important metabolic driver of reperfusion injury. It rapidly oxidizes in presence of oxygen which is favorable for reverse electron transport and overproduction of mitochondrial ROS. Pharmacological inhibition of succinate dehydrogenase (SDH) with malonate compounds has therefore been found to decrease renal ischemia–reperfusion injury [17]. At the same time, deficiencies in ATP and changes in ion transport lead to increased loading of calcium into the cytosol and mitochondria, further impairing respiratory function and promoting oxidative stress.

3.3 Loss of Mitochondrial Membrane Potential and Permeability Transition

These excessive ROS and calcium levels disrupt the inner mitochondrial membrane leading to decreased mitochondrial membrane potential and less ATP production. With continued mitochondrial stress, the mitochondrial permeability transition pore may open, leading to dissipation of the proton gradient, swelling of the matrix, disruption of the mitochondrial membrane and liberation of pro-death mediators. Experimental data suggest that preservation of mitochondrial structure and function can limit renal IRI damage: for example, treprostinil has been found to limit mitochondrial damage in experimental renal IRI [18]. Additionally, in transplantation, a reduction in hypoxic mitochondrial damage during preservation might also benefit recovery of the transplanted organ. Oxygen supplementation during hypothermic machine perfusion has therefore emerged as a strategy to support mitochondrial metabolism and reduce the adverse consequences of ischemia before reperfusion [19]. All of these events together, indicate mitochondrial dysfunction as an initiating mechanism for ischemia-reperfusion injury, which can impact immediately as well as with later allograft outcomes.

4. Molecular Mechanisms of Mitochondrial Injury in Kidney Allografts

Kidney allograft mitochondrial injury is a multi-layered process involving a complex interplay between perturbations of redox balance, organelles, mitochondrial quality control, inflammatory signaling and programmed cell death. Following ischemia and reperfusion, these mechanisms can reinforce one another, converting initially reversible metabolic stress into sustained tubular and endothelial injury. Therefore, the extent to which mitochondrial integrity is restored influences whether renal cells recover normally or progress toward persistent dysfunction and maladaptive remodeling.

4.1 Reactive Oxygen Species and Oxidative Damage

Reperfusion causes a rapid rise in the production of mitochondrial ROS that results from the reintroduction of oxygen into a respiratory chain modified during ischemia. The ROS overproduced further disrupt the electron transport and the ATP production by oxidizing mitochondrial proteins, membrane lipids and nucleic acids. This forms a vicious cycle that leads to further mitochondrial injury by oxidative stress and further oxidative stress by mitochondrial dysfunction. A protective response that is important is selective elimination of damaged mitochondria. In the kidney, activation of the PINK1-PRKN/PARK2 mitophagy pathway has been shown to maintain mitochondrial integrity and minimize renal cellular injury during renal ischemia–reperfusion [20].

4.2 Mitochondrial Dynamics and Organelle Crosstalk

Mitochondrial fission and fusion allow renal cells to adapt organelle structure to metabolic stress. Fusion preserves bioenergetic competence through exchange of mitochondrial contents, whereas fission segregates damaged regions for subsequent clearance. This balance is disrupted under ischaemia–reperfusion, with fragmentation, impairment of respiration and increased dysfunctional mitochondria. During hypoxic stress, BNIP3-induced mitophagy can rescue renal cells from damage by eliminating damaged mitochondria [21] and HIF-1α activates BNIP3 to further maintain the quality of renal tubular mitochondria [22].

Mitochondrial behavior is also influenced by endoplasmic reticulum contact sites that regulate calcium transfer, lipid metabolism, redox signaling, and organelle morphology. Disruption of this crosstalk can aggravate calcium dysregulation and oxidative injury during renal ischemia–reperfusion [23]. Therefore, altered mitochondrial dynamics and impaired organelle communication may inhibit restoration of normal bioenergetic function following ischemic injury.

4.3 Impaired Mitophagy and Mitochondrial Quality Control

Maintaining a viable mitochondrial population is crucial after ischemic injury during transplantation, which requires efficient mitophagy. If the damage to mitochondria is too great to be repaired by quality-control pathways, depolarized mitochondria with the ability to produce ROS are retained within tubular epithelial cells. This sustained mitochondrial dysfunction may then lead to a lack of metabolic recovery and to an extended cellular stress. Defective clearance also permits damaged organelles to act as signaling platforms for inflammatory and cell-death pathways. For instance, translocation of RIP3 into the mitochondria leads to breakdown of mitofilin, a protein associated with the structure of the mitochondria,

causing the mitochondria to become disrupted, inflammation to be aggravated, and kidney injury after ischemia–reperfusion [24].

4.4 Mitochondrial DNA Damage and DAMP Release

Mitochondrial DNA (mtDNA) is also very vulnerable to oxidative damage because it is near the electron transport chain. If the mitochondria are severely damaged, they can release mtDNA and other components of the mitochondria into the cytosol or outside the cell where they act as damage-associated molecular patterns (DAMPs). These signals can lead to activation of innate immune pathways and persistent sterile inflammatory response in the allograft. In addition to membrane-associated pathways that exacerbate cellular injury, damage to the mitochondria has been observed and ferroptosis caused by pannexin 1 has been shown to be a significant factor in renal ischemia–reperfusion damage [25]. Mitochondrial damage may occur alongside membrane-associated pathways that intensify cellular injury; pannexin 1-mediated ferroptosis has been identified as an important contributor to renal ischemia–reperfusion damage [25]. Endoplasmic reticulum–mitochondrial communication also links organelle stress with inflammation, as XBP1-dependent regulation of mitochondrial crosstalk can influence NLRP3 activation during renal IRI [26]. Altered calcium trafficking across mitochondria-associated membranes provides an additional mechanism through which mitochondrial and endoplasmic reticulum stress become interconnected [27].

4.5 Mitochondria-Mediated Cell Death Pathways

Persistent mitochondrial dysfunction can ultimately shift cellular responses from adaptation toward regulated cell death. Rupture of mitochondrial membrane, oxidative stress, calcium dysregulations and metabolic failure can be involved in inducing apoptosis and may interact with necroptotic and ferroptotic pathways. Renal ischemia/reperfusion triggers dynamic activation of Necroptosis, which may play a role in tubular injury, inflammatory amplification in situations of intense stress [28]. Ferroptosis is characterized by iron-dependent lipid peroxidation and is particularly relevant in the oxidant-rich environment of reperfused renal tissue. Recently, ferroptosis-related genes that are linked to renal ischemia–reperfusion injury were identified using analysis and shown to be relevant to kidney transplantation [29]. Collectively, oxidative damage, disturbed mitochondrial dynamics, defective mitophagy, DAMP-associated inflammatory signaling, and regulated cell death form an integrated mechanistic network through which early mitochondrial injury can persist beyond reperfusion and promote subsequent allograft deterioration.

5. Mitochondrial Dysfunction and Immune–Inflammatory Activation

Mitochondrial dysfunction after IRI does not only cause metabolic alterations but plays a role in sterile inflammation and immune activation in the kidney allograft. Mitochondrial DNA (mtDNA), reactive oxygen species, ATP, and other mitochondrial components act as damage associated molecular patterns (DAMPs) that are released by damaged mitochondria. mtDNA is structurally similar to bacterial DNA and when released into the cytosol or extracellular space can trigger innate immune receptors and induce inflammatory cytokine biosynthesis. Mitochondrial injury has been shown to perpetuate the inflammatory effect of the initial ischemic insult, causing acute kidney injury and also leading to chronic renal damage, as a result of persistent mtDNA-mediated signaling [30].

One important pathway linking mitochondrial DAMPs with innate immunity is the cyclic GMP–AMP synthase–stimulator of interferon genes (cGAS–STING) axis. mtDNA in the cytosol can be sensed by cGAS and induce cGAS-dependent signaling and production of type I interferons and other inflammatory mediators. In transplantation, over-activation of this pathway can aggravate ischemia–reperfusion injury and boost the immune-mediated injury of the graft, suggesting cGAS–STING as a therapeutic target to enhance transplantation outcomes [31].

Mitochondrial stress is also tightly linked to activation of NLRP3 inflammasome. Overproduction of mitochondrial ROS, loss of membrane potential, ion imbalance and oxidized mtDNA release can contribute to inflammasome assembly and activation of caspase-1 and maturation of interleukin-1β and interleukin-18. The interaction between defective mitophagy and inflammasome signaling is particularly important because insufficient removal of damaged mitochondria allows inflammatory stimuli to persist and intensify renal injury [32].

The renal microvasculature is also damaged in an inflammatory amplification process. Endothelial activation leads to increased expression of adhesion molecules and promotes recruitment of leukocytes to the post-ischemic tissue. Experimental data suggest a role for inflammatory mediators like LIGHT in the development of persistent renal damage after ischemia–reperfusion (I/R), and LIGHT deficiency in the dampening of renal progression towards acute kidney disease (AKD) [33]. On the other hand, preservation of mitochondrial integrity can dampen inflammatory signaling, such as the ability of fibroblast growth factor 2 has been shown to attenuate mitochondrial damage and proinflammatory responses during renal ischemia–reperfusion injury [34].

Alloimmune responses can also augment innate inflammatory processes through antigen presentation, leukocyte recruitment and activation of adaptive immune responses. Mitochondrial-encoded gene expression patterns in peripheral blood have been shown to differentiate acute renal allograft rejection, directly linking mitochondrial biology with transplant-specific immune responses [35]. Mitochondrial DAMP signaling, inflammasome activation, endothelial inflammation, and alloimmune responses may therefore cooperate to sustain graft inflammation and promote chronic injury.

Figure 1 illustrates how mitochondrial damage and mtDNA/DAMP release activate cGAS–STING and NLRP3 inflammasome signaling, promoting inflammatory and immune responses that contribute to tubular and endothelial allograft injury.

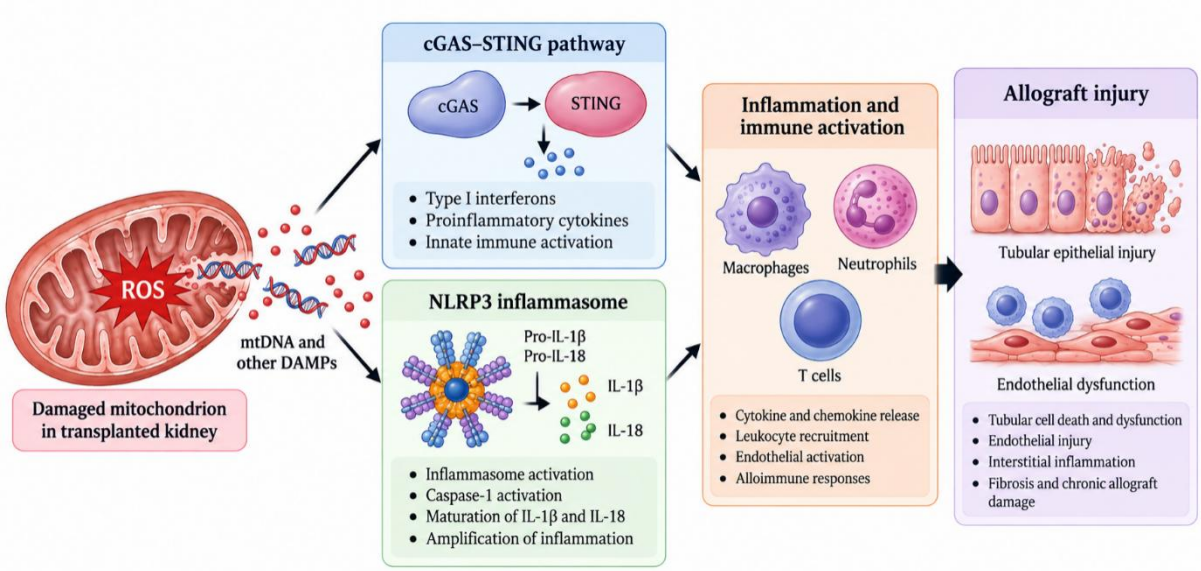

Figure 1. Mitochondrial DAMP-mediated activation of inflammatory and immune pathways in kidney allograft injury.

6. From Acute Mitochondrial Injury to Chronic Allograft Damage

The transition from acute ischemic injury to chronic allograft damage is increasingly understood as a continuum rather than as two independent pathological stages. When mitochondrial recovery after ischemia–reperfusion remains incomplete, renal tubular cells, endothelial cells, and interstitial compartments may enter a state of persistent metabolic and inflammatory stress. This prolonged dysfunction can drive maladaptive repair, extracellular matrix accumulation, vascular rarefaction, and progressive loss of functioning nephron mass.

6.1 Delayed Graft Function and Incomplete Metabolic Recovery

Delayed graft function may reflect incomplete metabolic recovery following severe peri-transplant injury. Damaged mitochondria can fail to restore oxidative phosphorylation, fatty acid oxidation, and ATP production, while impaired biogenesis and inadequate mitochondrial clearance prolong tubular energetic deficiency. The transition from AKI to CKD occurs by similar mechanisms, where ongoing mitochondrial dysfunction results in inability to restore structure and function [36]. Therefore, a potential early connection between acute injury of the graft and chronic deterioration may be through mitochondrial signaling [37].

6.2 Persistent Tubular and Endothelial Mitochondrial Dysfunction

Mitochondrial dysfunction leads to impaired tubular transport and to oxidative and inflammatory stress. Endothelial mitochondrial dysfunction also decreases the efficiency of the microvasculature and adds to endothelial activation. Structural injury is sustained in the tissues by tubular and vascular abnormalities, which together cause tissue hypoxia, and establish a metabolic environment that promotes further structural damage.

6.3 Maladaptive Repair and Fibroblast Activation

Acute injury recovery is a complex process that involves coordinated tubular regeneration, inflammation resolution and restoration of microvascular integrity. When these processes fail, repair becomes maladaptive. Tubular epithelial cells may adopt a persistent stress-associated phenotype and release profibrotic mediators that activate interstitial fibroblasts and promote their differentiation into matrix-producing myofibroblasts. Cellular senescence, mitochondrial dysfunction, inflammatory signaling, and defective metabolic reprogramming can reinforce this process. Modern AKI-to-CKD models thus suggest that improper epithelial repair, and the activation of fibroblasts, are central drivers of the transition from AKI to CKD [38].

6.4 Interstitial Fibrosis, Tubular Atrophy, and Microvascular Rarefaction

Progressive extracellular matrix deposition results in interstitial fibrosis, while unresolved epithelial injury promotes tubular atrophy. The pathological changes of the kidneys, which are relevant to kidney transplantation, are highly interesting because early ischemic events may be important in shaping the course of fibrosis after transplantation. For deceased-donor kidney recipients, interstitial fibrosis during the first year after transplant was linked to delayed graft function, suggesting that it is associated with structural remodeling later in the course of the disease [39]. Concurrent microvascular rarefaction can compromise oxygen delivery, causing tissue hypoxia and worsening mitochondrial dysfunction, sustain a vicious cycle of metabolic stress and fibrosis.

6.5 Progression toward Chronic Allograft Dysfunction

With time, chronic mitochondrial stress, inflammation, fibrosis, tubular damage and vascular damage together decrease the allograft functional reserve. Chronic allograft dysfunction reflects a multifactorial process involving both immune and non-immune mechanisms,

with ischemic injury contributing to progressive fibrotic remodeling and declining graft function [40]. Alloimmune pathways also can interact with ischemia: Anti-LG3 antibodies have been shown to aggravate renal ischemia–reperfusion injury and worsen long-term renal allograft dysfunction [41]. In a broader context, transcriptomic studies have been performed in each of the transplanted organs have revealed common molecular signatures of allograft dysfunction, such as immune activation, tissue remodeling, stress response and fibrosis pathways [42]. Collectively, these findings support a mechanistic model in which unresolved mitochondrial injury after transplantation promotes maladaptive repair and creates a sustained biological pathway from delayed graft recovery to chronic allograft deterioration.

Table 1 presents the major mitochondrial alterations that connect ischemia–reperfusion injury with persistent cellular stress, inflammatory activation, maladaptive repair, and chronic kidney allograft damage.

Table 1. Major Mitochondrial Mechanisms Linking Ischemia–Reperfusion Injury to Chronic Kidney Allograft Damage

Mitochondrial alteration	**Principal mechanism**	**Immediate cellular consequence**	**Downstream allograft effect**
ATP depletion and impaired oxidative phosphorylation	Oxygen deprivation during warm and cold ischemia suppresses mitochondrial respiration	Ion-pump failure, metabolic acidosis, cellular energy deficit	Delayed recovery and increased susceptibility to reperfusion injury
Excess mitochondrial ROS	Rapid oxidation of accumulated metabolites and electron leakage during reperfusion	Oxidative damage to proteins, lipids, mtDNA, and respiratory complexes	Persistent tubular injury and inflammatory amplification
Calcium overload and membrane depolarization	Disrupted ion homeostasis and mitochondrial Ca^{2+} accumulation	Loss of membrane potential, permeability transition, impaired ATP synthesis	Cell death and reduced graft functional reserve
Fission–fusion imbalance	Excessive fragmentation and inadequate mitochondrial network recovery	Reduced bioenergetic efficiency and accumulation of damaged organelles	Persistent metabolic dysfunction
Defective mitophagy	Inadequate clearance of depolarized or ROS-generating mitochondria	Prolonged oxidative stress and inflammatory signaling	Maladaptive repair and chronic injury
mtDNA/DAMP release	Damaged mitochondria release mtDNA and other mitochondrial components	cGAS–STING and inflammasome activation	Sterile inflammation and alloimmune amplification
Regulated cell death	Activation of apoptosis, necroptosis, and ferroptosis	Tubular and endothelial cell loss	Fibrosis, tubular atrophy, and progressive allograft dysfunction
Incomplete mitochondrial recovery	Failure of biogenesis and metabolic normalization	Persistent tubular and endothelial stress	Microvascular rarefaction, fibrosis, and chronic allograft deterioration

Figure 2 illustrates the proposed mechanistic continuum linking ischemia–reperfusion injury and persistent mitochondrial dysfunction with maladaptive repair and chronic allograft damage.

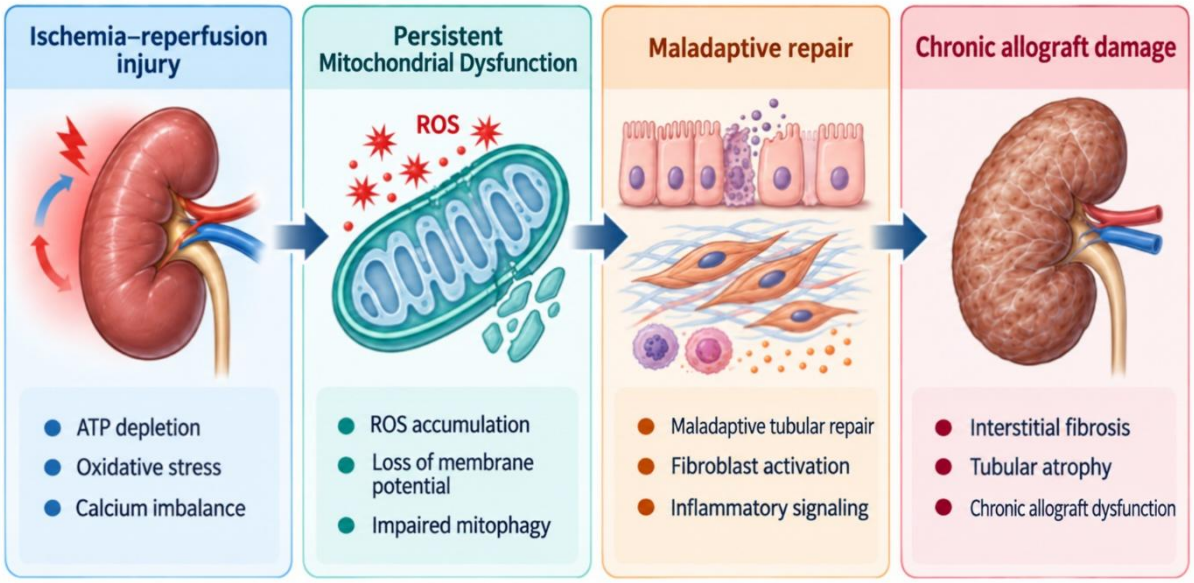

Figure 2. Mechanistic continuum from ischemia–reperfusion injury to chronic allograft damage through persistent mitochondrial dysfunction and maladaptive repair

7. Mitochondrial Biomarkers in Kidney Transplantation

Mitochondrial biomarkers are increasingly being investigated as indicators of early graft injury, organ viability, and subsequent transplant outcomes. Mitochondrial disruption can occur quickly after ischaemia–reperfusion injury and may occur before conventional markers of functional deterioration, such as serum creatinine. Cell-free mitochondrial DNA (cf-mtDNA) is one of the more researched candidates that can be released into the bloodstream after damage to the mitochondrial membrane. In kidney transplant recipients, circulating cf-mtDNA measured during the early postoperative period has shown clinical relevance as a marker of peri-transplant tissue injury and graft recovery [43].

Another promising non-invasive biomarker is urinary mitochondrial DNA (mtDNA) which can be liberated directly into the urinary compartment from damaged tubular or renal parenchymal cells. A higher urinary mtDNA level has been shown to be correlated with delayed graft function post renal transplantation, which suggests its potential use as a marker for more severe ischemia–reperfusion injury [44]. More recent studies of living donor transplantation also suggest that urinary mtDNA is correlated with allograft function, suggesting that urinary mitochondrial markers may be able to offer information of allograft injury and recovery without using invasive biopsy procedures [45].

In addition to mtDNA, other parameters measured to assess mitochondrial function may include oxidative stress markers, respiratory markers, ATP-producing capacity, and metabolic signatures. During ex vivo normothermic machine perfusion, mitochondrial function and oxygen consumption can provide information on kidney viability and complement conventional perfusion parameters [46]. The molecular mitochondrial signatures may also be useful to predict delayed graft function and long-term outcomes [47].

However, there is a need to standardize sampling time, assay methodology, biological matrices and diagnostic thresholds for clinical application. To assess the value of these approaches beyond the current measures of graft function, further prospective large studies are required.

Table 2 summarizes the principal mitochondrial biomarkers and functional measurements that may support non-invasive graft injury assessment, organ viability evaluation, and prediction of post-transplant outcomes.

Table 2. Mitochondrial Biomarkers with Potential Utility in Kidney Transplantation

Biomarker/assessment	Sample or setting	Biological information reflected	Potential clinical utility
Circulating cell-free mtDNA	Blood	Systemic mitochondrial damage and tissue injury	Early postoperative assessment of graft injury and recovery
Urinary mtDNA	Urine	Renal tubular and parenchymal mitochondrial injury	Non-invasive identification of delayed graft function risk
Mitochondrial oxygen consumption	Ex vivo perfused kidney	Respiratory competence and mitochondrial functional integrity	Assessment of organ viability before transplantation
Respiratory efficiency/ATP-generating capacity	Perfusion or tissue	Bioenergetic recovery and mitochondrial performance	Complementary measure of graft metabolic fitness

	assessment		
Oxidative stress indicators	Blood, urine, tissue, or perfusate	Redox imbalance and reperfusion-associated injury	Injury stratification and treatment-response monitoring
Mitochondrial molecular/metabolic signatures	Molecular profiling	Distinct patterns of mitochondrial stress and recovery	Prediction of delayed graft function and longer-term graft outcomes

8. Mitochondria-Targeted Strategies for Allograft Protection

This central role of mitochondrial dysfunction to ischemic–reperfusion injury of the kidneys has led to an interest in mitochondria integrity preservation during and after kidney transplantation. The aim of these approaches is that of reducing oxidative stress, stabilizing mitochondrial metabolism, and improving the quality-control pathways, and increasing the recovery of the graft. Their therapeutic potential is based on their ability to intervene at the early stages of the injury prior to the development of ongoing mitochondrial damage that can lead to chronic allograft dysfunction, fibrosis, and inflammation.

8.1 Donor Preservation and Machine Perfusion

Improved organ preservation is an important strategy for limiting mitochondrial injury before implantation. Normothermic machine perfusion keeps the kidney near-physiologic and enables the uninterrupted supply of oxygen and nutrients and the evaluation and possibly repair of substandard kidneys. This method could decrease the metabolic deterioration due to static cold storage and help to recover the mitochondria before transplantation [48]. There is also a low-temperature oxygenated perfusion that incorporates low-temperature preservation with active oxygen delivery. Randomized clinical evidence has shown the clinical potential of hypothermic oxygenated perfusion as a measure to reduce preservation injury in extended-criteria donor kidneys [49]. The extended organ assessment and intervention prior to transplantation using a prolonged normothermic perfusion platform is also emerging as a viable option [50].

8.2 Mitochondria-Targeted Antioxidants

Mitochondria-targeted antioxidants accumulate in mitochondria where they act directly to eliminate excessive and harmful ROS at their major intracellular production site. In renal ischemia–reperfusion injury, Mitoquinone has shown to be protective by maintaining mitochondrial homeostasis via a Sirt3-dependent pathway, minimizing oxidative damage and maintaining mitochondrial function [51]. These agents can be especially useful for reperfusion, as it is a period where ROS are rapidly created and can cause irreversible damage to the membranes and to the respiratory chain.

8.3 Modulation of Mitochondrial Dynamics and Mitophagy

Persistent mitochondrial injury following ischemia–reperfusion could be prevented by therapeutic modulation of mitochondrial dynamics and mitophagy. Activation of PINK1-PRKN/PARK2, BNIP3 and HIF-1α–BNIP3 pathways allow the removal of impaired mitochondria and tubular survival [20–22]. This may, in turn, result in more rapid recovery and less oxidative and inflammatory signaling, thus, strategies that restore balanced mitochondrial turnover will improve recovery. Careful optimization of the time and intensity of the treatment will be required for clinical translation, in order to prevent either excessive or insufficient mitochondrial clearance.

8.4 Promotion of Mitochondrial Biogenesis and Metabolic Recovery

Also, recovery of oxidative metabolism is essential for the long-term success of the graft. ZLN005 has been shown to protect against ischemia–reperfusion-induced renal injury by reducing oxidative stress and restoring mitochondrial fatty acid oxidation [52]. Enhancement of mitochondrial biogenesis, respiratory capacity, and substrate utilization may therefore help injured tubular cells regain sufficient ATP production and avoid maladaptive metabolic reprogramming.

8.5 Emerging Pharmacological and Regenerative Approaches

Dimethyl malonate is a succinate dehydrogenase inhibitor that is able to protect renal and mitochondrial function following ischemia-reperfusion [53]. Future approaches may combine metabolic modulation, mitochondrial antioxidants, mitophagy regulators, regenerative therapies, and organ-directed delivery during machine perfusion. These strategies may allow for treatment prior to implantation and potentially enhance the early recovery from the graft and long-term allograft outcomes.

Table 3 outlines major mitochondria-targeted strategies for allograft protection, ranging from oxygenated machine perfusion and antioxidant therapy to metabolic modulation, mitophagy regulation, and restoration of mitochondrial biogenesis.

Table 3. Mitochondria-Targeted Strategies for Kidney Allograft Protection

Strategy	Mitochondrial target	Expected protective effect	Translational status/potential
Normothermic machine perfusion	Cellular metabolism and oxygen delivery	Supports mitochondrial respiration, graft assessment, and	Clinically advancing preservation platform

		metabolic recovery	
Hypothermic oxygenated perfusion	Oxygenation during cold preservation	Limits hypoxic metabolic deterioration and preservation injury	Supported by emerging clinical evidence
Mitoquinone	Mitochondrial ROS and Sirt3-dependent homeostasis	Reduces oxidative injury and preserves mitochondrial integrity	Preclinical renal IRI evidence
Mitophagy modulation	PINK1-PRKN/PARK2, BNIP3 and related quality-control pathways	Enhances clearance of damaged mitochondria and limits oxidative stress	Promising experimental approach
ZLN005	Mitochondrial fatty acid oxidation and metabolic recovery	Restores oxidative metabolism and reduces cellular stress	Experimental pharmacological strategy
Dimethyl malonate	Succinate dehydrogenase	Reduces succinate-driven ROS generation during reperfusion	Strong mechanistic/preclinical potential
Mitochondrial biogenesis enhancement	PGC-1α-related pathways	Restores mitochondrial mass, respiratory capacity, and ATP production	Emerging therapeutic direction
Perfusion-based targeted delivery	Mitochondrial metabolism and repair pathways	Enables organ-specific treatment before implantation	Promising precision-transplant strategy

9. Future Perspectives

Identifying the injury to the mitochondria before the condition progresses to irreversible injury to the graft, will be important for future progress in kidney transplantation. Circulating and urinary mtDNA, respiratory parameters, oxidative stress indicators, and metabolic signatures may complement conventional measurements of graft function and improve risk stratification.

Machine perfusion offers a valuable platform in which to integrate mitochondrial monitoring with organ assessment and intervention. However, for clinical adoption, protocols need to be standardized, viability endpoints validated, and evidence of long-term benefit is needed [54]. There also needs to be a consensus on the type of perfusion device, length of treatment, and how the results are measured [55].

The possibility of developing therapies against ROS production, succinate metabolism, permeability transition, mitophagy, mitochondrial dynamics, and biogenesis directed towards the mitochondria is further worth consideration in the context of translation. Optimal time, dose, safety and compatibility with immunosuppressive therapy should be determined in future trials.

Eventually, preservation of the grafts by precision may combine donor properties, ischemic exposure, mitochondrial markers, metabolic data obtained from perfusion and molecular signatures in order to ensure personalised intervention and to enhance long-term allograft preservation.

10. Conclusion

The transplanted kidney is exposed to ischemic, metabolic, inflammatory, and immune stresses, in which mitochondrial dysfunction plays a central role. Decreased oxygen and ATP levels disrupt mitochondrial respiration, ionic balance and cellular homeostasis during warm and cold ischemia. Reperfusion then intensifies injury through reactive oxygen species generation, calcium overload, membrane depolarization, permeability transition, and activation of regulated cell-death pathways. When mitochondrial quality-control mechanisms, including fission–fusion balance, mitophagy, and biogenesis, fail to restore organelle integrity, injured tubular and endothelial cells may remain metabolically compromised and continue to generate inflammatory signals.

These chronic abnormalities are significant to the link between early ischemia–reperfusion injury and chronic allograft damage. Mitochondrial DAMP release and inflammasome activation may lead to endothelial dysfunction, maladaptive tubular repair, fibroblast activation, interstitial fibrosis, tubular atrophy and microvascular rarefaction, creating a scenario that can ultimately lead to progressive deterioration of the transplanted kidney. Delayed graft function may thus be

not only the early clinical manifestation of ischemic injury, but also a reflection of incomplete metabolic recovery, and thus may have implications for long-term graft survival.

The mitochondrial biomarkers and interventions that target mitochondria provide some important opportunities for interrupting this continuum. The combination of circulating or urinary mitochondrial markers with machine-perfusion assessment could help to select organs, classify injury, and predict early graft recovery. Likewise, therapies targeting oxidative stress, succinate metabolism, mitophagy, mitochondrial dynamics, and biogenesis may enhance graft resilience. Therefore, a mitochondria-centered framework serves as a unified framework for understanding kidney allograft injury and for devising strategies to maintain long-term graft function. Validation of biomarkers, standardisation of preservation protocols and trials involving the correlation of mitochondrial protection with patient-centred transplant outcomes will be needed for clinical translation.

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