# Pyruvate dehydrogenase kinase 4 in acute kidney injury and the acute kidney injury-to-chronic kidney disease transition: A key metabolic regulatory hub and potential therapeutic target (Review)

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**Abstract.** Acute kidney injury (AKI) is a common and heterogeneous clinical syndrome characterised by a rapid decline in renal function and caused by a range of insults, including ischaemia-reperfusion injury, sepsis, nephrotoxic drugs, hypovolaemia, major surgery and transplantation-related injury. AKI is prone to progression to chronic kidney disease (CKD), and no effective treatment is currently available. Pyruvate dehydrogenase kinase 4 (PDK4), a regulator of mitochondrial metabolism, phosphorylates the E1α subunit of the pyruvate dehydrogenase (PDH) complex, thereby suppressing PDH enzymatic activity and limiting pyruvate oxidation. In renal tubular epithelial cells and other renal cell types, increased PDK4 mRNA expression and/or PDK4 protein abundance has been associated with enhanced inhibitory signalling through the PDK4-PDH complex axis, typically reflected by increased phosphorylation of the PDH E1α subunit, reduced total PDH complex activity and suppressed mitochondrial pyruvate oxidation. These changes contribute to metabolic reprogramming, mitochondrial dysfunction, oxidative stress, inflammatory activation and cell death. Accumulating evidence suggests that PDK4-mediated metabolic dysregulation contributes to tubular injury and maladaptive repair during AKI and the AKI-to-CKD transition, although its effects remain dependent on disease context and biological stage. The present review summarises the molecular regulation of PDK4, its pathological relevance in experimental AKI and the potential implications of PDK4 for therapeutic intervention and biomarker development. Moreover, the limited evidence supporting PDK4 as a candidate biomarker in AKI and the AKI-to-CKD transition is discussed. Although PDK4 protein is biologically linked to tubular metabolic stress and renal injury, its clinical biomarker performance has not yet been validated and further studies are required to determine its diagnostic and prognostic utility.

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## 1. Introduction

Acute kidney injury (AKI) is a common and clinically heterogeneous syndrome characterised by an abrupt decline in renal function. The incidence of AKI remains high worldwide, particularly among hospitalised and critically ill patients, and it is associated with notable short-term mortality and a high risk of progression to chronic kidney disease (CKD) and end-stage renal disease (1-5). AKI can arise from a range of aetiologies, including ischaemia-reperfusion injury (IRI), sepsis, nephrotoxic drugs, hypovolaemia, major surgery and transplantation-related injury, each of which may involve partially distinct pathogenic mechanisms and patterns of tubular stress (6,7). Among these phenotypes, IRI-associated AKI has been particularly well studied in the context of kidney transplantation, major cardiovascular surgery and haemodynamic instability, whereas cisplatin-induced AKI and sepsis-associated AKI (SA-AKI) represent two additional experimental and translational settings in which metabolic dysfunction has emerged as a key pathogenic feature (2,7-9). Accordingly, AKI should not be viewed as a single disease

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entity, but rather as a syndrome encompassing multiple injury contexts with shared and distinct molecular mechanisms.

Increasing evidence indicates that metabolic disturbances are a shared feature of multiple AKI phenotypes (10,11). Within this framework, pyruvate dehydrogenase kinase 4 (PDK4) has attracted attention as a stress-responsive regulator that may influence mitochondrial adaptation and tubular cell vulnerability under ischaemic, toxic and inflammatory conditions (12-14). However, the strength of evidence supporting a pathogenic role for PDK4 differs across AKI phenotypes: Mechanistic evidence is currently strongest in ischaemia-reperfusion models, whereas data in cisplatin-induced AKI and SA-AKI remain comparatively limited or context-dependent (11-15). Therefore, the present review discusses PDK4 in AKI within a phenotype-specific framework, with separate sections devoted to IRI, cisplatin nephrotoxicity and SA-AKI, followed by the role of PDK4 in maladaptive repair and the AKI-to-CKD transition.

The kidney is an energy-demanding organ, with proximal tubular epithelial cells predominantly relying on mitochondrial oxidative phosphorylation (OXPHOS) to produce ATP (16,17). Metabolic perturbation has emerged as a central hallmark of renal injury, manifested by mitochondrial dysfunction, altered substrate preference and maladaptive metabolic reprogramming (18,19). PDK4 may serve as a modulator of mitochondrial metabolism by phosphorylating the E1α subunit of the pyruvate dehydrogenase PDH complex, thereby inhibiting PDH complex activity and redirecting cellular carbon flux away from mitochondrial pyruvate oxidation (15,20). As a potential metabolic switch, PDK4 is co-ordinately regulated at multiple levels by: i) Hypoxia-inducible factor (HIF) signalling; ii) nuclear receptors, including peroxisome proliferator-activated receptors (PPARs) and the oestrogen-related receptor (ERR)/PPARγ coactivator-1α (PGC-1α) axis; and iii) nutrient- and hormone-responsive pathways, including insulin-Forkhead box O (FOXO) signalling, glucocorticoids and thyroid hormones (21-26). Mechanistically, increased PDK4 mRNA expression and/or PDK4 protein abundance and, where directly examined, increased PDK4 enzymatic activity can enhance inhibitory phosphorylation of the PDH E1α subunit, reduce total PDH complex activity and redirect glucose-derived carbon away from mitochondrial oxidation towards glycolytic metabolism (15,20). In studies that did not directly measure PDK4 kinase activity, elevated PDH E1α phosphorylation should be interpreted as evidence of enhanced inhibitory signalling through the PDK4-PDH complex axis rather than direct proof of increased PDK4 enzymatic activity (27,28).

Under ischaemic, hypoxic and inflammatory stress conditions, PDK4 mRNA expression, protein abundance or both are frequently upregulated in renal tissue, particularly in renal tubular epithelial cells. Depending on the study design, this upregulation has been associated with increased phosphorylation of the PDH E1α subunit, reduced total PDH complex activity and downstream mitochondrial dysfunction, oxidative stress and endoplasmic reticulum stress (ERS) (15,20). Although previous studies have validated the involvement of PDK4 in metabolic reprogramming, inflammatory cascades and fibrotic pathogenesis in diabetic nephropathy and renal cell carcinoma, the precise function of PDK4 in AKI and the transition from AKI to CKD remains largely uncharacterised (29-35). Outstanding questions primarily concern the cell-type-specific roles of PDK4 across distinct renal compartments, its crosstalk with mitochondrial impairment and regulated cell death pathways, including ferroptosis, and its potential therapeutic value in halting AKI-to-CKD progression.

In the present narrative review, current knowledge of PDK4 in systemic metabolic disorders and kidney diseases is first summarised, with emphasis on its expression patterns, temporal dynamics and regulatory roles in experimental AKI models and chronic renal disorders. Given the aetiological heterogeneity of AKI, PDK4 is discussed in a phenotype-specific manner. The available evidence in ischaemia-reperfusion-induced AKI, cisplatin-induced AKI and SA-AKI is evaluated separately, with explicit distinction between direct evidence from established renal AKI models and indirect or hypothesis-generating observations derived from non-AKI renal diseases, AKI-to-CKD models or extra-renal injury systems. How PDK4-associated metabolic remodelling may influence AKI through interconnected processes involving mitochondrial dysfunction, oxidative stress, ERS, inflammation and regulated cell death pathways is then discussed. In addition, PDK4 has been implicated in several chronic disease-associated metabolic complications, such as vascular calcification. Subsequently, how sustained PDK4 activation may drive the transition from AKI to CKD by disrupting the renal repair microenvironment, promoting interstitial fibrosis, altering cell fate and exerting systemic metabolic effects, such as skeletal muscle dysfunction, is discussed. Existing and emerging therapeutic strategies targeting PDK4 as a candidate therapeutic target are also reviewed, including small-molecule inhibitors and nanotechnology-based delivery systems, and recent progress on the potential of PDK4 as a diagnostic and prognostic biomarker is highlighted. Finally, current controversies are summarised and future research directions are outlined, aiming to provide a comprehensive framework for understanding and targeting PDK4 in AKI and the AKI-to-CKD transition.

## 2. Physiological role of the PDK4-PDH complex axis

*Structure and function of the PDK4-PDH complex axis.* PDK4 is an inducible mitochondrial kinase whose mRNA and protein expression are regulated by multiple stress and hormonal signals. PDK4 belongs to the PDK family, which consists of four isoforms, PDK1-PDK4, all of which are localized in the mitochondrial matrix. The PDH complex is a critical regulator of mitochondrial metabolism, linking glycolysis to the tricarboxylic acid (TCA) cycle (36). This metabolic linkage can be disrupted by increased PDK4 mRNA and/or PDK4 protein expression, together with enhanced PDK4-dependent phosphorylation of the PDH E1α subunit, leading to a series of downstream metabolic disturbances, including reduced pyruvate oxidation, impaired mitochondrial ATP production and increased reliance on glycolysis (37). Experimental inhibition or genetic deletion of PDK4 has been shown to reduce PDH E1α phosphorylation, restore total PDH complex activity and partially normalize mitochondrial oxidative metabolism in specific models, such as renal ischemia-reperfusion

injury (12). The PDK family regulates cellular glucose metabolism by phosphorylating the E1 subunit of the PDH complex, thereby inhibiting its activity and regulating OXPHOS during cellular glycolysis (38). Unlike PDK2, which is widely expressed, PDK3, which has a limited tissue distribution and PDK1 (38,39), which primarily regulates cardiac energy metabolism, PDK4 is an inducible isoenzyme. The expression of PDK4 is markedly upregulated in response to stress conditions such as fasting, diabetes, hypoxia and inflammation. PDK4 is predominantly expressed in skeletal muscle and brown adipose tissue, where it participates in the regulation of gluconeogenesis and thermogenesis (39).

As a critical metabolic checkpoint in the mitochondrial network, PDK4 regulates specific metabolic processes during stress by inhibiting PDH complex activity and disrupting the link between glycolysis and the TCA cycle. Notably, inducible PDK4 expression is not random, but is precisely controlled by various stress and hormonal signals. Inhibition of PDK4 expression may represent a potential therapeutic strategy for improving related pathological damage.

*Regulation of PDK4 expression*

*Regulation by the HIF-1α pathway*. HIF-1α is an upstream transcriptional regulator of the PDK4 gene. Under normoxic conditions, the HIF-1α subunit is degraded, preventing transcriptional activation of the PDK4 gene. However, under hypoxic conditions or in the presence of HIF activators, HIF-1α is stabilised and translocates to the nucleus, where it binds to the hypoxia response element in the promoter region of the PDK4 gene, thereby activating PDK4 transcription and increasing PDK4 protein abundance (21,40). The increase in PDK4 protein abundance promotes inhibitory phosphorylation of the PDH E1α subunit, thereby reducing total PDH complex activity and limiting pyruvate conversion to acetyl-CoA. This inhibits the TCA cycle and OXPHOS, redirecting glucose metabolism from mitochondrial oxidative pathways to cytosolic glycolysis. This 'metabolic switch' mechanism enables cells to adapt to hypoxic stress by compensating for the reduced efficiency of the mitochondrial respiratory chain under hypoxic conditions and enhancing glycolysis to maintain cellular energy homeostasis (21,41). Moreover, enhanced glycolysis reduces reactive oxygen species (ROS) production, thereby alleviating oxidative stress and improving the survival of tumour cells, cardiomyocytes and other cells under hypoxic conditions (21). In summary, HIF-1α directly induces PDK4 transcription and represents a major upstream regulator of PDK4 under ischaemic and hypoxic stress conditions.

*Regulation by the nuclear receptor PPAR family*. PDK4 transcription is directly regulated by the PPAR family, including PPARα, PPARβ/δ and PPARγ, and this regulation is tissue- and species-specific. PPARα is a key adaptive regulator during prolonged fasting and its agonists markedly upregulate PDK4 transcription and increase PDK4 protein expression in multiple tissues, including the heart, skeletal muscle, liver and kidneys (24,42). In rodent liver and kidneys, retinoid X receptor agonists and PPAR agonists can induce PDK4 transcription through a PPARα-dependent pathway, although this effect is not observed in human liver cells or rabbit liver cells (42). In skeletal muscle, liver X receptor enhances PPARα-mediated regulation of PDK4 transcription. Additionally, in the human renal tubular epithelial cell line HK-2, PDK4 has been identified as a direct target gene of PPARα agonists and PDK4 transcription is closely associated with PPARα activation, making PDK4 a potential early biomarker of PPARα agonist activity (22). PPARβ/δ is also a key regulator of the PDK4 gene. The promoter region of the human PDK4 gene contains two PPAR response elements, to which PPARβ/δ can bind with its co-activator proteins to directly regulate PDK4 transcription. PPARβ/δ agonists can regulate PDK4 expression and may also indirectly influence PDK4 expression by inducing FOXO1 expression (25). PPARγ is highly expressed in adipose tissue and its agonist, rosiglitazone, specifically increases PDK4 protein levels in white adipose tissue, with no effect on liver or muscle tissues (24,43). In 293 cells, PPARγ ligands can also regulate PDK4 mRNA expression. Free fatty acids and their derivatives, as endogenous PPAR ligands, can enhance PDK4 transcription. Long-chain fatty acids can directly induce PDK4 mRNA expression in skeletal muscle and hepatocellular carcinoma cells. Lipoprotein lipase and hepatic lipase, through indirect fatty acid supply, synergise with PPARα and PPARβ/δ to upregulate PDK4 expression (24,25). In summary, the PPAR family subtypes form a core network that regulates PDK4 transcription through tissue- and species-specific mechanisms involving direct and indirect binding. Endogenous fatty acids and metabolism-related enzymes further participate in and reinforce this regulatory pathway.

*Insulin/FOXO pathway regulation*. The insulin/FOXO signalling pathway is a central regulator of PDK4 transcription and its regulatory effect is influenced by insulin levels and insulin sensitivity. When insulin signalling is active, insulin activates Akt, which subsequently phosphorylates FOXO proteins, thereby inhibiting PDK4 transcription. However, when insulin levels are reduced or under conditions of insulin resistance, FOXO proteins, primarily FOXO1 and FOXO3, bind to the insulin response elements of the PDK4 gene and induce PDK4 transcription. The human PDK4 gene contains three insulin response sequences, which serve as binding sites for FOXO1 and FOXO3. Constitutively active FOXO1/3 enhances both basal and dexamethasone-induced PDK4 transcription, whereas mutation of these binding sites abolishes this enhancement (44,45). In addition, FOXO proteins can interact with ERRs, glucocorticoid receptors, PPARs and other nuclear hormone receptors to jointly regulate PDK4 transcription (44,46-48). Factors such as nutrient deprivation and CD36-mediated fatty acid uptake in muscle can indirectly promote PDK4 transcription through FOXO activation (44,46). Precise regulation of this pathway is essential for integrating metabolic signals and maintaining cellular energy homeostasis.

*Other regulatory factors and pathways*. The regulation of PDK4 transcription involves a complex network of multiple signalling pathways and nuclear receptor factors. Core regulatory mechanisms centre on the binding of specific elements in the gene promoter region. Glucocorticoids directly bind to their corresponding response elements to induce PDK4 transcription and this process acts synergistically with FOXO proteins. However, the insulin pathway antagonises this process (44). Orphan nuclear receptors, including ERRα and ERRγ, cooperate with PGC-1α to activate PDK4 transcription independently of PPARα. In addition, thyroid hormones,

growth hormones and Kruppel-like factor 15 can regulate PDK4 transcription through their respective receptors or signalling pathways (47-52). The adiponectin-AMP-activated protein kinase (AMPK) pathway shows context-dependent effects on PDK4 transcription, with the direction of regulation varying according to the physiological or pathological state (24,26,53,54). For example, in skeletal muscle myotubes derived from obese or obese diabetic individuals, adiponectin stimulation or pharmacological AMPK activation with 5-amin oimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) decreased PDK4 gene expression (53). By contrast, under conditions of energy stress such as hypoxia or in the presence of elevated fatty acids, AMPK activation by hypoxia or AICAR synergistically increased PDK4 expression, promoting a metabolic shift away from glucose oxidation (54). These findings indicate that the effect of adiponectin-AMPK signalling on PDK4 transcription is influenced by the cellular metabolic environment and the accompanying nutrient and hormonal signals. The coordinated and antagonistic actions of these pathways and factors ensure precise regulation of PDK4 transcription, thereby helping to maintain energy homeostasis under different metabolic states. Collectively, the aforementioned regulatory pathways enable rapid transcriptional induction of PDK4 during ischaemic, inflammatory and toxic stress, providing the biochemical basis for the subsequent involvement of PDK4 in AKI. The major upstream regulatory pathways controlling PDK4 expression are summarised in Fig. 1.

*Metabolic consequences of the PDK4-PDH complex axis.* Increased PDK4 protein abundance, together with enhanced inhibitory signalling through the PDK4-PDH complex axis, can markedly reshape cellular energy metabolism. As aforementioned, PDK4 phosphorylates the E1α subunit of the PDH complex, thereby inhibiting PDH complex activity and limiting the conversion of pyruvate into acetyl-CoA. Consequently, carbon flux from glycolysis into the TCA cycle is reduced, mitochondrial OXPHOS is impaired and ATP production declines. To compensate for reduced mitochondrial energy generation, cells undergo metabolic reprogramming characterised by enhanced glycolysis and increased lactate production (15,55). Although this adaptive metabolic shift may transiently preserve cellular viability under nutrient deprivation or hypoxia, prolonged reliance on glycolysis compromises mitochondrial bioenergetics and metabolic flexibility.

In metabolically active renal tubular epithelial cells, sustained suppression of PDH complex activity after PDK4 activation further disrupts mitochondrial homeostasis by altering TCA-cycle metabolite flux and promoting succinate accumulation, thereby impairing mitochondrial function (12). The resulting imbalance between electron transport and oxygen utilisation promotes excessive ROS accumulation, mitochondrial membrane depolarisation and defective mitochondrial quality control. Increased oxidative stress subsequently damages mitochondrial DNA, proteins and membrane lipids, establishing a vicious cycle in which mitochondrial dysfunction further aggravates oxidative injury and metabolic impairment (20). In addition, ATP depletion caused by sustained suppression of OXPHOS compromises multiple energy-dependent cellular processes, including ion transport, cytoskeletal maintenance, protein folding and intracellular repair mechanisms (56,57), rendering renal tubular epithelial cells particularly susceptible to injury.

Beyond its effects on mitochondrial metabolism, sustained suppression of PDH complex activity through the PDK4-PDH complex axis reduces mitochondrial pyruvate oxidation and may increase pyruvate availability for lactate production, contributing to lactate accumulation and intracellular acidification (13-15). In kidney disease research, lactate is increasingly recognised not only as a metabolic intermediate but also as a signalling metabolite involved in protein lactylation and inflammatory regulation (58-60). However, robust data confirming a direct functional PDK4-lactate-lactylation signalling axis across AKI subtypes remain lacking (60,61). Therefore, lactate-dependent lactylation as a potential mediator of PDK4-associated renal tubular injury should currently be regarded as a hypothetical mechanism that requires validation in dedicated renal AKI models.

Overall, current evidence indicates that PDK4-associated metabolic remodelling may contribute to ATP depletion, oxidative stress and mitochondrial dysfunction (13,14). However, the relative contribution of each downstream pathway across different AKI phenotypes remains incompletely defined (18). Following PDK4-mediated suppression of PDH complex activity, pyruvate flux may be redirected towards lactate synthesis. Increased lactate accumulation may further contribute to intracellular acidosis, inflammatory activation and pathological metabolic remodelling (62). Although multiple renal studies support lactate-mediated signalling through lactylation, whether and to what extent PDK4 signalling initiates this cascade in distinct AKI phenotypes remains unclear and requires further experimental validation (14,18,58,59).

Therefore, activation of the PDK4-PDH complex axis represents a metabolic regulatory event linking reduced glucose oxidation with downstream mitochondrial dysfunction and metabolic stress. This metabolic shift provides a mechanistic framework for understanding the context-dependent roles of PDK4 in experimental AKI, including IRI, cisplatin nephrotoxicity and maladaptive repair during the AKI-to-CKD transition.

*Biological role of the PDK4-PDH complex axis in kidney injury.* Renal tubular epithelial cells, particularly proximal tubular epithelial cells, have among the highest mitochondrial densities in the kidney and rely predominantly on OXPHOS for ATP generation (16). During ischaemia, cisplatin exposure or sepsis, mitochondrial oxidative metabolism declines, and these stresses are frequently accompanied by increased PDK4 mRNA expression and PDK4 protein abundance in renal tubular epithelial cells. In several models, these changes are associated with increased PDH E1α phosphorylation and reduced total PDH complex activity, consistent with enhanced inhibitory signalling through the PDK4-PDH complex axis (14,20). Although transient increases in PDK4 protein abundance or transient enhancement of PDK4-dependent inhibitory signalling towards the PDH complex may initially support metabolic adaptation, sustained activation of the PDK4-PDH complex axis may suppress glucose oxidation and promote maladaptive metabolic remodelling, thereby

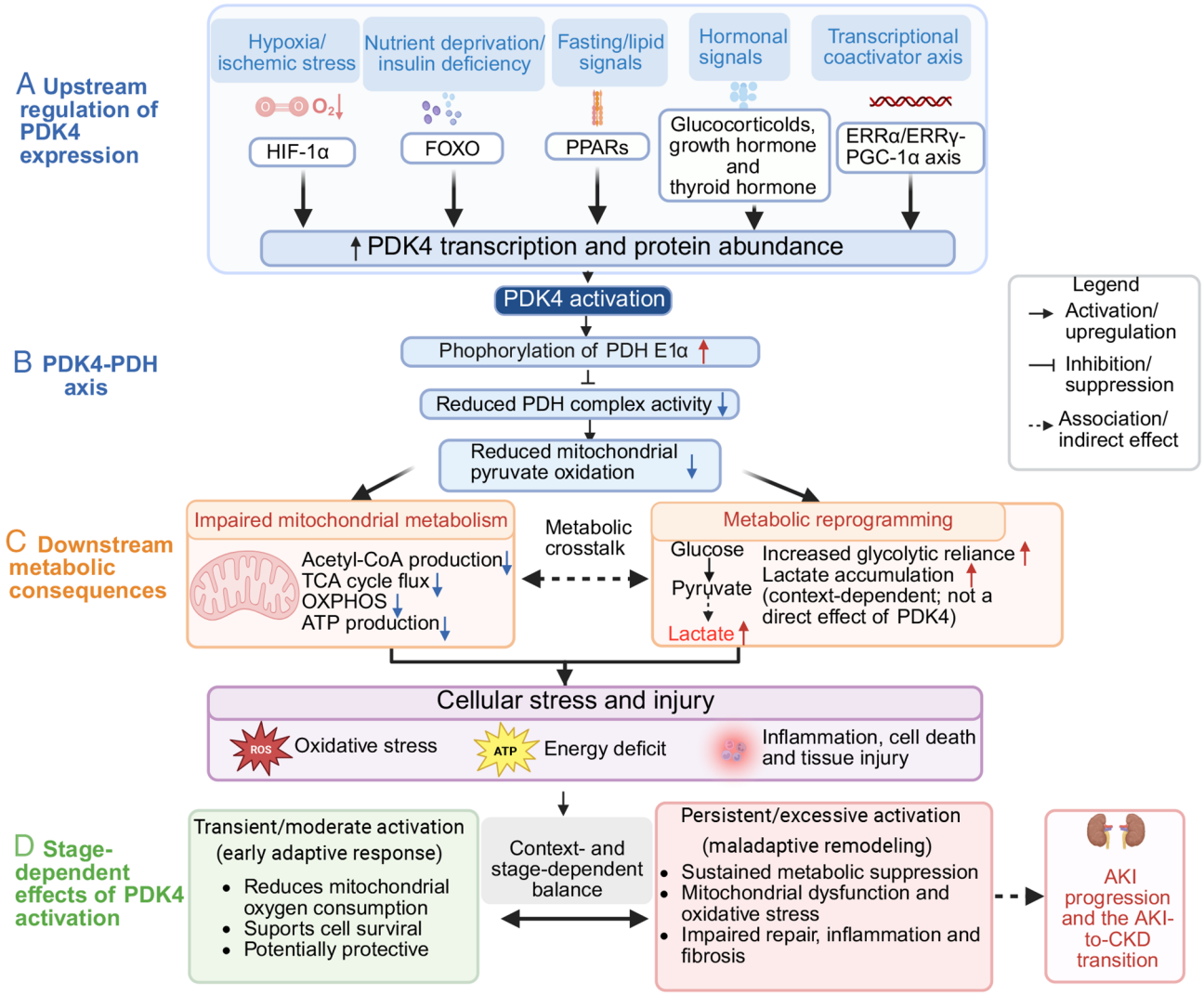



Figure 1. Regulation of PDK4 expression and metabolic consequences of PDK4 activation. (A) Upstream regulation of PDK4 expression by metabolic, hormonal and stress-responsive pathways, including hypoxia/ischemic stress, nutrient deprivation or insulin deficiency, fasting/lipid signals, hormonal signals, and the ERR/PGC-1α transcriptional coactivator axis. (B) PDK4-mediated inhibition of the PDH complex through phosphorylation of PDH E1α, resulting in reduced PDH complex activity and mitochondrial pyruvate oxidation. (C) Downstream metabolic consequences of PDK4 activation, including impaired mitochondrial metabolism, reduced acetyl-CoA production, TCA cycle flux, OXPHOS and ATP production, together with metabolic reprogramming and increased glycolytic reliance. (D) Context- and stage-dependent effects of PDK4 activation, with transient or moderate activation potentially supporting early adaptive responses, whereas persistent or excessive activation may contribute to sustained metabolic suppression, mitochondrial dysfunction, oxidative stress, impaired repair, inflammation and fibrosis, thereby contributing to AKI progression and the AKI-to-CKD transition. Created in BioRender. Zhao, Y. (2026). https://BioRender.com/gqwirgq. AKI, acute kidney injury; CKD, chronic kidney disease; ERR, oestrogen-related receptor; FOXO, forkhead box O; HIF-1α, hypoxia-inducible factor-1α; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; PGC-1α, peroxisome proliferator-activated receptor g coactivator 1-α; PPARs, peroxisome proliferator-activated receptors; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle.

contributing to tubular injury and impaired renal repair (15). These biochemical characteristics provide the mechanistic basis for the role of PDK4 in experimental AKI discussed in the following sections.

## 3. PDK4 in experimental AKI

PDK4 has been implicated in several renal pathological processes, although its functional significance varies according to disease context and experimental setting. Current evidence regarding PDK4 in kidney injury differs notably in source and strength. As AKI is aetiologically heterogeneous, evidence for PDK4 should be interpreted within specific AKI phenotypes rather than generalised across all forms of AKI. In the present review, findings from established renal AKI models are considered the primary evidence supporting the role of PDK4 in AKI pathogenesis. AKI-associated insults, including ischaemia/reperfusion injury, nephrotoxic exposure and systemic inflammatory conditions, converge on stress-responsive signalling pathways that may induce PDK4 activation and subsequent metabolic and cellular injury responses (Fig. 2). Mechanistic observations from models of AKI-to-CKD transition, CKD, other non-AKI renal disorders or non-renal injury models are discussed as supportive, hypothesis-generating or potentially relevant evidence rather than as established AKI-specific mechanisms. The reported

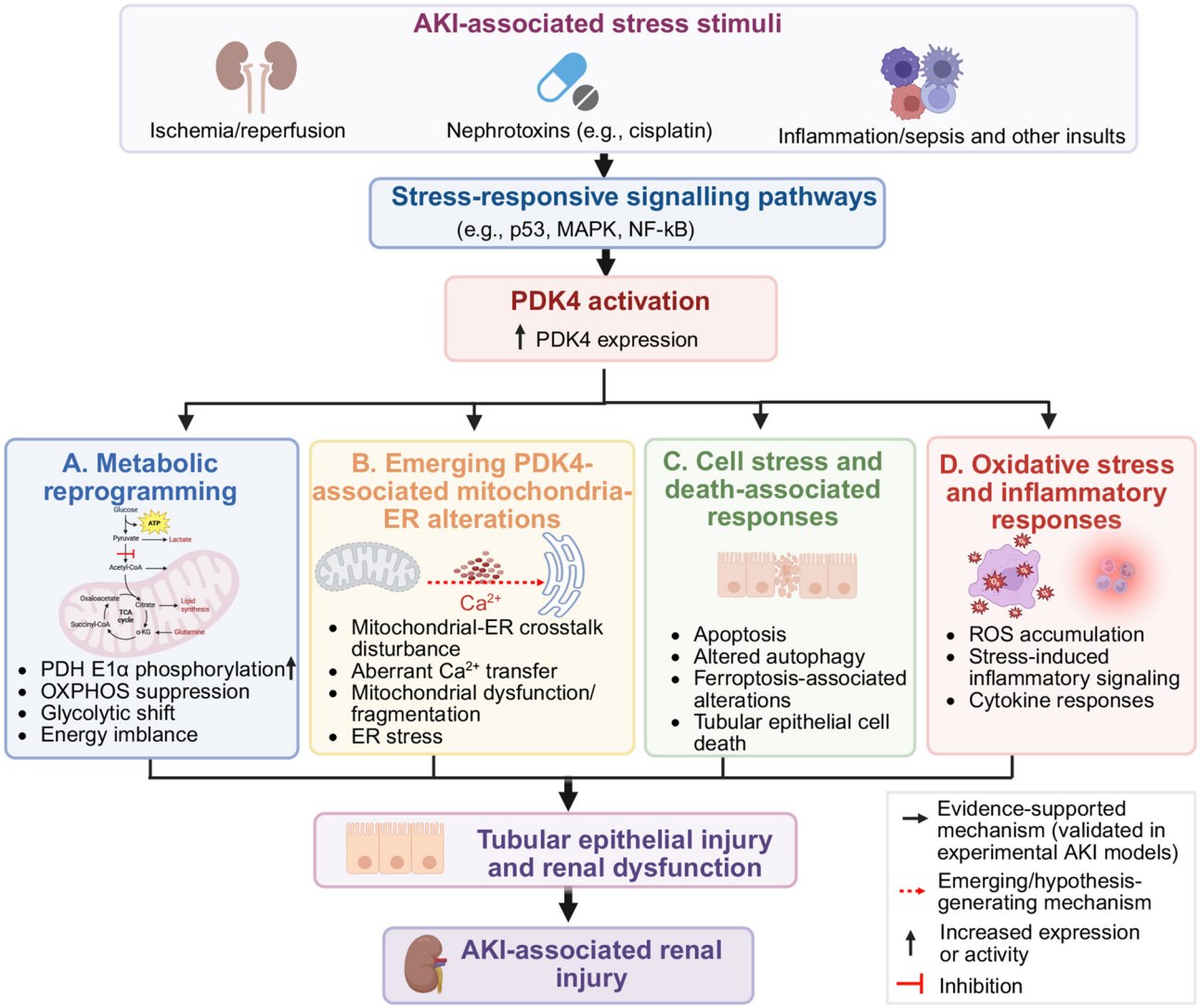



Figure 2. Integrated mechanisms linking AKI-associated stress stimuli to PDK4 activation and tubular injury. AKI-associated insults, including ischemia/reperfusion, nephrotoxic agents and inflammatory/septic conditions, activate stress-responsive signalling pathways, leading to increased PDK4 expression and activation. (A) Metabolic reprogramming associated with PDK4 activation, including increased PDH E1α phosphorylation, suppression of OXPHOS, a glycolytic shift and energy imbalance. (B) Emerging PDK4-associated mitochondria-ER alterations, including disrupted mitochondrial-ER crosstalk, aberrant $Ca^{2+}$ transfer, mitochondrial dysfunction/fragmentation and ER stress. (C) Cell stress- and death-associated responses, including apoptosis, altered autophagy, ferroptosis-associated alterations and tubular epithelial cell death. (D) Oxidative stress and inflammatory responses, including ROS accumulation, stress-induced inflammatory signalling and cytokine responses. These downstream alterations ultimately contribute to tubular epithelial injury and renal dysfunction. Created in BioRender. Zhao, Y. (2026). https://BioRender.com/4rfuzvk. AKI, acute kidney injury; ER, endoplasmic reticulum; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PDK4, pyruvate dehydrogenase kinase 4; ROS, reactive oxygen species.

expression patterns, mechanistic characteristics and representative experimental evidence of PDK4 across different AKI models and other kidney diseases are summarised in Table I. Tables SI and SII summarize reported mechanistic functions and representative findings of PDK4 across kidney diseases, including key molecular pathways and experimental contexts.

*PDK4 in IRI-AKI*. IRI is a well-established cause of AKI, particularly in clinical settings such as kidney transplantation, major cardiovascular surgery, haemorrhagic shock and severe hypotension (63-65). Abrupt interruption of renal blood flow causes oxygen and nutrient deprivation, whereas subsequent reperfusion can exacerbate tissue injury through excessive ROS generation, calcium overload, mitochondrial dysfunction and inflammatory activation. As renal proximal tubular epithelial cells contain abundant mitochondria and rely predominantly on OXPHOS to meet their high energy demands, they are particularly vulnerable to ischaemic metabolic stress (6,66,67). Accordingly, metabolic reprogramming has been recognised as a component of IRI, with the PDK4-PDH complex axis emerging as a potential regulatory node involved in metabolic adaptation and mitochondrial dysfunction.

*Induction of PDK4 during ischemia-reperfusion*. Experimental studies consistently demonstrate that renal PDK4 mRNA expression and PDK4 protein abundance increase rapidly after IRI, predominantly in renal tubular epithelial cells (12,68). Under ischaemic conditions, HIF-1α, p53, FOXO transcription factors and inflammatory signalling pathways have been reported to contribute to PDK4 transcriptional induction and

Table I. Expression patterns, major mechanisms and representative evidence for PDK4 across experimental AKI models and other kidney diseases.

| Disease | PDK4 expression | Major mechanism | Major consequence | Evidence level | Representative model | (Refs.) |
|---|---|---|---|---|---|---|
| IRI-AKI | Early induction with sustained activation during persistent injury | PDH inhibition; mitochondrial dysfunction; oxidative stress; ERS | Metabolic reprogramming; ATP depletion; tubular injury; apoptosis | Strong | Mouse IRI models; HK-2 and primary tubular epithelial cells | (12,68,75) |
| Cisplatin-induced AKI | Early and sustained upregulation in proximal tubules | p53/MAPK signalling; PDH inhibition; mitochondrial dysfunction-ER stress crosstalk | Metabolic shift toward glycolysis; mitochondrial dysfunction; apoptosis; tubular injury | Strong | Mouse cisplatin-AKI models; HK-2 cells | (8,13,20) |
| SA-AKI | Putative induction reported in experimental sepsis models | Proposed activation of the PDK4-PDH axis; inflammatory metabolic reprogramming | Putative lactate accumulation; mitochondrial dysfunction; inflammatory injury | Limited | LPS- or CLP-induced sepsis models | (14,96,97) |
| CKD | Elevated in advanced CKD | Uremic metabolite-AHR-PDK4 axis | Impaired glucose oxidation; skeletal muscle metabolic dysfunction | Moderate | Mouse models of CKD; skeletal muscle cells | (124,125) |
| Diabetic kidney disease | Dysregulated (context-dependent) | Keap1-Nrf2-PDK4; miR-15b-5p/PDK4; TRIM65/PDK4 | Oxidative stress; ferroptosis/apoptosis; podocyte and tubular injury; fibrotic remodelling | Moderate | db/db mice; high-glucose-treated podocytes and HK-2 cells | (30,31,62) |
| ccRCC | Aberrant expression in tumour tissue | VHL-HIF-PDK axis; metabolic reprogramming | Enhanced glycolysis; tumour progression; immune-associated molecular signatures | Moderate | TCGA-KIRC cohorts; ccRCC cell lines | (126,127) |
| MN | Identified as a ferroptosis-related hub gene | Ferroptosis-associated pathways | Podocyte injury; immune dysregulation | Limited | Patient samples; experimental MN models | (128) |

Representative mechanisms are summarised from the studies cited in the present review and highlight the principal findings currently supported by experimental evidence. Evidence level reflects the extent of experimental support linking PDK4 to disease pathogenesis. 'Strong' indicates multiple kidney-specific experimental studies; 'Moderate' indicates consistent evidence from renal disease models but limited mechanistic validation and 'Limited' indicates preliminary or indirect evidence requiring further confirmation. AKI, acute kidney injury; IRI-AKI, ischemia-reperfusion-induced AKI; SA-AKI, sepsis-associated AKI; CKD, chronic kidney disease; ccRCC, clear cell renal cell carcinoma; MN, membranous nephropathy; PDK4, pyruvate dehydrogenase kinase 4; PDH, pyruvate dehydrogenase; ERS, endoplasmic reticulum stress; HIF-1α, hypoxia-inducible factor-1α; AHR, aryl hydrocarbon receptor; TCGA-KIRC, The Cancer Genome Atlas Kidney Renal Clear Cell Carcinoma; TRIM65, tripartite motif-containing protein 65; Keap1, Kelch-like ECH-associated protein 1; Nrf2, nuclear factor erythroid 2-related factor 2; VHL, von Hippel-Lindau; LPS, lipopolysaccharide; CLP, cecal ligation and puncture.

increased PDK4 protein abundance (21,24,28). In parallel, phosphorylation of the PDH E1α subunit increases and total PDH complex activity declines under ischaemic conditions, consistent with enhanced inhibitory signalling through the PDK4-PDH complex axis (12,20,69). Initially, this PDK4-associated metabolic adaptation limits pyruvate oxidation, reduces mitochondrial oxygen consumption and may partially preserve cellular viability during oxygen deprivation. Such transient metabolic remodelling may therefore represent an adaptive response that enables tubular epithelial cells to survive acute ischaemic stress (21,28,70). However, sustained activation of the PDK4-PDH complex axis during reperfusion may become maladaptive. Persistent suppression of PDH complex activity reduces the conversion of pyruvate to acetyl-CoA, thereby limiting carbon entry into the TCA cycle and decreasing mitochondrial ATP production (12,28,70). Consequently, renal tubular epithelial cells progressively lose metabolic flexibility and become increasingly dependent on glycolysis despite restored oxygen availability (12,71,72). This persistent metabolic shift may represent a mechanism linking unresolved ischaemic stress to mitochondrial dysfunction and subsequent tubular injury.

*PDK4 promotes mitochondrial dysfunction and metabolic reprogramming*. Mitochondrial dysfunction is widely recognised as a hallmark of ischaemia-reperfusion-induced AKI and accumulating evidence suggests that PDK4 contributes to this process (73). In addition to limiting glucose oxidation, increased PDK4-dependent inhibitory signalling towards the PDH complex may alter mitochondrial substrate utilisation and promote maladaptive metabolic reprogramming, characterised by enhanced glycolysis and reduced OXPHOS (12,71).

Using ischaemia-reperfusion models, Oh *et al* (12) demonstrated that genetic deletion of PDK4 or pharmacological inhibition of PDK4 ameliorated renal injury. PDK4 deficiency or pharmacological inhibition of PDK4 was associated with reduced inhibitory signalling through the PDK4-PDH complex axis, improved PDH-dependent mitochondrial glucose oxidation, decreased ischaemic succinate accumulation, preservation of mitochondrial respiratory function and improved renal functional recovery. When examined individually, these effects were accompanied by reduced PDH E1α phosphorylation or restoration of total PDH complex activity in injured renal tissue (12,20). Together, these findings suggest that PDK4-associated metabolic remodelling contributes to succinate-associated mitochondrial dysfunction during IRI.

*Oxidative stress and inflammatory amplification*. Persistent mitochondrial dysfunction associated with sustained increases in PDK4 protein abundance and continued inhibitory signalling through the PDK4-PDH complex axis may contribute to oxidative stress during reperfusion (15,73). Impaired electron transport chain activity can increase electron leakage and ROS production, resulting in oxidative damage to mitochondrial DNA, membrane lipids and respiratory chain proteins (74). Progressive oxidative damage further compromises mitochondrial integrity, thereby establishing a self-amplifying cycle of mitochondrial dysfunction and ROS accumulation.

In addition to direct oxidative injury, ROS function as intracellular signalling molecules that activate inflammatory pathways. Increased oxidative stress can activate inflammatory pathways, including nuclear factor-κB (NF-κB) and MAPK signalling, and enhance the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 (15,74). These inflammatory mediators further aggravate tubular epithelial cell injury and recruit inflammatory cells into the injured kidney, amplifying local tissue damage. Experimental approaches targeting PDK4 activity or PDK4-dependent metabolic signalling have been associated with reduced ROS accumulation, decreased inflammatory cytokine production and attenuation of renal histological injury, supporting a link between PDK4-associated metabolic remodelling and oxidative-inflammatory responses during IRI (12,68).

*ERS and mitochondria-ER crosstalk*. Previous evidence suggests that PDK4-associated metabolic remodelling may influence mitochondria-ER communication during ischaemic AKI (75,76). In renal ischemia-reperfusion models, increased PDK4 abundance has been associated with ER stress and renal injury (75), whereas in obese skeletal muscle models, increased PDK4 activity enhances mitochondria-associated ER membrane (MAM) formation, ER-to-mitochondria calcium transfer and mitochondrial dysfunction (76). Excessive mitochondrial calcium accumulation may subsequently aggravate mitochondrial depolarisation, oxidative stress and ATP depletion (76).

Persistent mitochondrial dysfunction activates unfolded protein response (UPR) pathways, including activating transcription factor 6 (ATF6)-associated signalling, in renal tubular epithelial cell models of ischaemic injury (76,77). *In vitro* studies using HK-2 cells further suggest that increased PDK4 expression may modulate MAM organisation and ER-mitochondria calcium exchange, thereby potentially contributing to ERS (75,76). However, the causal relationships among PDK4 abundance, PDH complex phosphorylation status and global UPR activation remain insufficiently validated in *in vivo* AKI models. A recent *in vivo* study has shown that extracellular vesicles (EVs) derived from human umbilical cord mesenchymal stem cells alleviate IRI by delivering microRNA (miR)-148b-3p, which directly targets PDK4 and is associated with reduced ERS during reperfusion (75). These findings support the possibility that PDK4-associated metabolic remodelling represents a potential link between mitochondrial dysfunction and ERS during ischaemic AKI.

*Regulation of tubular cell death and autophagy*. The combined effects of mitochondrial dysfunction, oxidative stress and ERS ultimately converge on multiple regulated cell death pathways. Sustained ATP depletion and ROS accumulation can activate the intrinsic mitochondrial apoptotic pathway through Bax translocation, cytochrome c release and sequential activation of caspase-9 and caspase-3 (78,79). Upstream stress-responsive pathways should also be considered. For example, activation of the JNK/c-Jun pathway may function as an upstream regulator of PDK4 expression under pathological conditions rather than as a downstream mediator of PDK4-induced apoptosis (80). Meanwhile, accumulating data from renal injury studies and extra-renal damage models suggest that PDK4-associated metabolic remodelling may interact with ferroptosis-related processes, including lipid peroxidation and impaired antioxidant defence (31,81,82). However, direct evidence showing that PDK4 drives tubular ferroptosis in AKI remains limited (83). Accordingly, the

putative crosstalk between PDK4 and ferroptosis in ischaemic AKI should be considered a potentially relevant but incompletely validated mechanism that requires direct experimental verification using renal AKI models.

Autophagy, an essential adaptive mechanism responsible for removing damaged mitochondria and maintaining intracellular homeostasis, is also influenced by PDK4-associated metabolic remodelling. Moderate autophagic activation during the early phase of ischaemia may exert protective effects by eliminating dysfunctional mitochondria (73). However, sustained metabolic stress and persistent activation of the PDK4-PDH complex axis may impair autophagic flux and mitochondrial quality control, leading to the accumulation of dysfunctional mitochondria and further aggravation of tubular injury (73,84,85). Collectively, dysregulation of apoptosis, ferroptosis and autophagy associated with persistent metabolic remodelling contributes to progressive tubular epithelial cell loss after ischaemia-reperfusion.

*Therapeutic implications of targeting PDK4*. The emerging contribution of PDK4 to ischaemic AKI has made PDK4 a potential therapeutic target. In mouse models of renal ischemia-reperfusion injury, pharmacological inhibition of PDK4 has been shown to improve mitochondrial function, reduce ischaemic succinate accumulation, attenuate oxidative stress and enhance renal functional recovery (12,15). Similarly, pharmacological approaches targeting the PDK4-PDH complex axis have shown renoprotective effects in several experimental models, accompanied by decreased inflammatory responses, reduced tubular apoptosis and improved mitochondrial function (12,15,68). In a mouse model of renal IRI, pharmacological inhibition of PDK4 reduced succinate accumulation during ischemia and preserved mitochondrial function during reperfusion, thereby attenuating renal injury (12). In diabetic mice subjected to renal IRI, PDK4 inhibition reduced oxidative stress and inflammatory responses and alleviated renal injury (15). Furthermore, treatment with an enzyme-mimicking ROS scavenger targeting PDK4 reduced oxidative stress and inflammation, and ameliorated IRI-induced acute kidney injury (IR-AKI) (68). These findings suggest that restoration of PDH complex activity may represent a potential strategy for modulating ischaemia-induced metabolic reprogramming.

Nevertheless, complete and sustained inhibition of PDK4 may not always be beneficial. Moderate induction of PDK4 expression during the initial ischaemic phase appears to facilitate metabolic adaptation by limiting mitochondrial oxygen consumption under severe hypoxia (21,28). Therefore, the biological effects of PDK4 are likely to be stage-dependent and therapeutic interventions may require precise temporal regulation rather than continuous suppression throughout the entire course of AKI.

In summary, current experimental evidence supports a functional contribution of PDK4 to ischaemia-reperfusion-induced AKI through regulation of metabolic adaptation, mitochondrial homeostasis and cellular stress responses. Rather than acting through a single downstream pathway, PDK4-associated metabolic alterations appear to interact with multiple stress responses that collectively influence tubular epithelial cell survival and renal recovery. Through inhibition of PDH complex activity, activation of the PDK4-PDH complex axis promotes metabolic reprogramming, which disrupts mitochondrial energy metabolism and subsequently contributes to oxidative stress, ERS, inflammatory activation and regulated cell death. Consistent renoprotective effects following genetic deletion of PDK4 or pharmacological targeting of the PDK4-PDH complex axis support its potential as a therapeutic target for ischaemic AKI. However, most available evidence is derived from rodent models and cultured tubular epithelial cells, and whether these mechanisms are fully conserved in human AKI remains unclear. Moreover, current studies have largely investigated individual downstream pathways separately, whereas the integrated interactions among mitochondrial dysfunction, stress responses and cell death pathways require further clarification. Future studies should therefore establish a unified mechanistic framework and validate the translational relevance of PDK4 targeting in human AKI.

*PDK4 in cisplatin-induced AKI*. Cisplatin remains one of the most effective chemotherapeutic agents for treating a wide range of solid malignancies. However, the clinical use of cisplatin is notably limited by dose-dependent nephrotoxicity, and cisplatin exposure remains a major cause of drug-induced AKI (69,78,86). Renal proximal tubular epithelial cells are particularly susceptible to cisplatin, partly due to preferential intracellular accumulation mediated by transporters such as organic cation transporter 2 and copper transporter 1 (69). Although DNA damage, oxidative stress and inflammation are well-recognised contributors to cisplatin nephrotoxicity, emerging evidence suggests that metabolic remodelling associated with the PDK4-PDH complex axis may represent an additional mechanism contributing to mitochondrial dysfunction and tubular injury (20,28).

*Dynamic induction of PDK4 during cisplatin nephrotoxicity*. Experimental studies indicate that cisplatin nephrotoxicity is associated with dynamic activation of inhibitory signalling through the PDK4-PDH complex axis in renal tubular epithelial cells (20,87). During the early phase of injury, renal cortical and/or tubular PDK4 mRNA expression increases in parallel with mitochondrial stress. In later phases, increased PDK4 protein abundance has been observed in renal tubular epithelial cells, together with elevated phosphorylation of the PDH E1α subunit and reduced total PDH complex activity. These findings suggest sustained suppression of PDH-dependent glucose oxidation during cisplatin nephrotoxicity (28). However, unless directly measured, increased phosphorylation of the PDH E1α subunit should be interpreted as evidence of enhanced PDK4-mediated inhibition of the PDH complex rather than as direct proof of increased PDK4 enzymatic activity. Sustained cisplatin exposure is associated with persistent elevation of PDK4 expression, accompanied by prolonged suppression of PDH complex activity and glucose oxidation. Consequently, pyruvate utilisation may be reduced, with decreased acetyl-CoA production and impaired mitochondrial ATP synthesis. This persistent metabolic shift may promote a glycolysis-dependent energy profile while reducing metabolic flexibility, thereby contributing to maladaptive metabolic remodelling and progressive tubular injury.

*PDK4-associated mitochondrial dysfunction and oxidative stress*. In cisplatin-induced AKI models, increased PDK4 expression and PDH E1α phosphorylation have been associated with impaired mitochondrial oxidative metabolism, reduced ATP production and increased mitochondrial ROS generation in renal tubular epithelial cells (20,28). Genetic deletion or pharmacological inhibition of PDK4 has been shown to attenuate mitochondrial injury and oxidative stress, and to improve renal function in cisplatin-treated models (20,88). These findings suggest that PDK4-associated metabolic dysregulation may contribute to mitochondrial dysfunction and oxidative stress during cisplatin nephrotoxicity.

*ERS and apoptotic signalling*. In addition to mitochondrial dysfunction, emerging evidence suggests that PDK4-associated metabolic remodelling may influence ERS responses during cisplatin nephrotoxicity (77,89). In cisplatin-induced AKI models, PDK4-associated metabolic dysregulation has been linked to ERS, mitochondrial dysfunction and tubular epithelial cell apoptosis. A recent study showed that pharmacological suppression of PDK4 attenuated cisplatin-induced ERS, mitochondrial dysfunction and apoptosis in renal tubular epithelial cells, supporting the possibility that PDK4-associated metabolic remodelling links metabolic dysfunction with programmed cell death (13).

*Experimental evidence supporting PDK4-targeted therapeutic strategies*. Experimental evidence suggests that PDK4 contributes to cisplatin-induced AKI through metabolic dysregulation. A pioneering study by Oh *et al* (20) demonstrated that genetic deletion of PDK4 markedly attenuated cisplatin-induced renal injury, accompanied by reduced tubular apoptosis, preservation of mitochondrial integrity and improved renal function. These findings support a functional contribution of PDK4 to cisplatin nephrotoxicity, rather than indicating that it serves merely as a biomarker.

Pharmacological inhibition of the PDK4-PDH complex axis has yielded similarly encouraging results. In cisplatin-induced AKI models, inhibition of PDK activity with dichloroacetate (DCA) reduces inhibitory phosphorylation of the PDH E1α subunit and restores total PDH complex activity, thereby enhancing mitochondrial pyruvate oxidation and ATP production (80,90). In cisplatin models, these metabolic effects have been associated with reduced mitochondrial oxidative stress, attenuated tubular apoptosis and improved renal function (88). These findings suggest that metabolic correction through restoration of PDH complex activity may represent a promising strategy for preventing cisplatin-induced nephrotoxicity.

In summary, current evidence indicates that PDK4 is a regulator of metabolic remodelling during cisplatin-induced AKI. Persistent activation of inhibitory signalling through the PDK4-PDH complex axis may suppress mitochondrial glucose oxidation, promote oxidative stress, enhance ERS and contribute to tubular epithelial cell apoptosis, thereby aggravating renal injury. Experimental studies demonstrate that genetic deletion of PDK4 or pharmacological targeting of PDK activity can ameliorate cisplatin nephrotoxicity by preserving mitochondrial function and restoring metabolic homeostasis. These findings support the potential of PDK4-targeted strategies for cisplatin-induced AKI, while also highlighting the need to develop isoform-selective inhibitors and kidney-specific drug delivery strategies to facilitate future clinical translation.

*PDK4 in SA-AKI*. SA-AKI is among the most severe and complex forms of AKI in critically ill patients, with high incidence and mortality rates in intensive care units (91,92). Unlike ischaemia-reperfusion or nephrotoxin-induced AKI, SA-AKI is characterised by multifactorial pathophysiology involving a systemic inflammatory response, microcirculatory dysfunction, mitochondrial injury and notable metabolic reprogramming (73,91,92). Increasing evidence suggests that metabolic dysregulation in renal tubular epithelial cells plays a role in the pathogenesis of SA-AKI (14,71). In this context, the PDK4-PDH complex axis has been implicated as a key metabolic regulator that may link inflammatory stress with mitochondrial dysfunction and impaired cellular energy metabolism.

*Metabolic reprogramming and PDK4 induction during sepsis*. During sepsis, circulating endotoxins such as lipopolysaccharide and pro-inflammatory cytokines, including TNF-α and IL-6, activate multiple stress-responsive signalling pathways, including HIF-1α, NF-κB and aryl hydrocarbon receptor (28,91-95). Evidence suggests that inflammatory and hypoxic signalling pathways during sepsis may induce PDK4 mRNA and protein expression in metabolically active tissues (55). In renal tubular epithelial cells and sepsis-related experimental systems, enhanced inhibitory signalling through the PDK4-PDH complex axis has been associated with increased PDH E1α phosphorylation, reduced total PDH complex activity, suppressed pyruvate oxidation and impaired mitochondrial ATP production (14,96,97). However, the extent to which these observations reflect kidney-specific mechanisms in established SA-AKI models remains incompletely defined, as direct mechanistic evidence is limited. Consequently, suppression of mitochondrial pyruvate oxidation may impair OXPHOS, reduce ATP production and promote greater reliance on glycolytic metabolism. Although this metabolic shift may initially represent an adaptive response to inflammatory stress by limiting mitochondrial oxygen consumption, persistent upregulation of PDK4 expression and sustained inhibitory signalling through the PDK4-PDH complex axis may contribute to maladaptive metabolic remodelling and progressive energy failure in renal tubular epithelial cells during prolonged sepsis.

*PDK4-driven lactate accumulation and immunometabolic dysregulation*. A hallmark of sepsis-associated metabolic reprogramming is robust lactate overproduction (96,98). Enhanced inhibitory signalling through the PDK4-PDH complex axis suppresses total PDH complex activity and limits mitochondrial pyruvate oxidation, thereby redirecting pyruvate flux towards lactate production (98-100). In experimental sepsis systems, elevated lactate levels have been associated with exaggerated inflammatory responses and widespread immunometabolic dysfunction (101).

Nevertheless, mechanistic extrapolation of these observations to the kidney requires caution. Most available data linking lactate to immunometabolic remodelling, protein lactylation and inflammatory phenotypes derive from

non-renal sepsis models, isolated immune cell cultures or extra-renal injury studies rather than kidney-specific SA-AKI models (14,100,102). Accordingly, these findings suggest that PDK4-mediated lactate accumulation may influence the intrarenal inflammatory milieu during SA-AKI, but such links remain hypothetical rather than confirmed kidney-specific mechanisms and require rigorous validation in dedicated renal SA-AKI models.

Excess lactate may also aggravate intracellular acidosis, potentially compromising mitochondrial bioenergetics and promoting oxidative stress, thereby contributing to a feed-forward cycle of metabolic dysfunction and inflammatory injury (62).

*Mitochondrial dysfunction, oxidative stress and tubular injury*. Mitochondrial dysfunction is a central event in SA-AKI and available evidence suggests that PDK4-associated metabolic remodelling may contribute to this process (28,73). Persistent inhibitory signalling through the PDK4-PDH complex axis may reduce mitochondrial substrate oxidation and compromise respiratory efficiency. This metabolic disturbance can increase oxidative stress and promote secondary damage to mitochondrial components, thereby further impairing tubular cell function.

Renal tubular epithelial cells are dependent on mitochondrial ATP production for solute transport and cellular homeostasis. Therefore, energy depletion can rapidly result in loss of polarity, cytoskeletal disruption and cellular dysfunction. In addition, ROS-mediated activation of inflammatory signalling pathways, including NF-κB and MAPK, may further amplify cytokine production and leukocyte infiltration, thereby aggravating tubular injury (74,94). Although direct experimental evidence linking PDK4 to SA-AKI remains limited compared with ischaemia-reperfusion or cisplatin-induced AKI, available data from sepsis-related organ injury models suggest that PDK4 may participate in immunometabolic dysregulation and mitochondrial dysfunction under systemic inflammatory stress (96,97,100,103). These findings are informative but should not be interpreted as direct evidence of a renal AKI-specific mechanism.

*Emerging evidence and translational implications*. Although the role of PDK4 in SA-AKI has not been as extensively characterised as in other AKI subtypes, indirect evidence from experimental models of sepsis and inflammatory organ injury suggests that modulation of the PDK4-PDH axis may influence mitochondrial metabolism, lactate handling and inflammatory responses under systemic inflammatory stress.

Given the systemic nature of sepsis, therapeutic targeting of PDK4 should consider both renal and extra-renal metabolic effects. Although inhibition of PDK4 may improve mitochondrial function and energy metabolism in renal tubular epithelial cells, excessive systemic suppression could potentially disrupt physiological metabolic adaptation in other organs. Therefore, strategies aimed at tissue-specific or temporally controlled modulation of the PDK4-PDH complex axis may represent a more rational approach for future therapeutic development in SA-AKI.

Collectively, available evidence suggests that increased PDK4 expression and enhanced inhibitory signalling through the PDK4-PDH complex axis may contribute to metabolic remodelling during SA-AKI. By contrast, downstream cascades linking this metabolic shift to protein lactylation, intrarenal immune microenvironment remodelling and inflammatory rewiring remain unconfirmed in renal SA-AKI and require rigorous verification using kidney-specific experimental models. The interplay between metabolic and inflammatory disturbances associated with the PDK4-PDH complex axis may contribute to tubular epithelial injury and renal dysfunction under septic stress. Although dedicated mechanistic studies focused on SA-AKI remain scarce, available evidence suggests that the PDK4-PDH complex axis may participate in sepsis-associated metabolic dysfunction. Further kidney-specific experimental studies and clinical investigations are required to determine whether targeting this pathway represents a viable therapeutic strategy for SA-AKI.

In summary, accumulating evidence from experimental models indicates that PDK4 participates in AKI pathogenesis through regulation of mitochondrial metabolism, oxidative stress, inflammatory responses and tubular epithelial cell injury. However, the biological effects of PDK4 activation appear to be context-dependent and may vary according to the type of injury and disease stage. The established and emerging mechanisms linking PDK4 activation to AKI pathogenesis and subsequent maladaptive repair are summarized in Fig. 3.

## 4. PDK4 in maladaptive repair and AKI-to-CKD transition

*Physiological tubular repair after AKI and the requirement for metabolic recovery*. Following AKI, surviving tubular epithelial cells initiate a coordinated repair programme aimed at restoring nephron integrity and renal function. This adaptive repair process generally involves transient dedifferentiation of injured tubular epithelial cells, proliferation of surviving cells, replacement of lost epithelium and subsequent redifferentiation to re-establish tubular polarity and transport capacity (73,104,105). Of note, successful repair is determined not only by structural regeneration, but also by the timely restoration of mitochondrial function and metabolic homeostasis (16,73). As proximal tubular epithelial cells are dependent on OXPHOS for ATP production, reactivation of mitochondrial glucose oxidation and normalisation of energy metabolism are essential for effective tubular repair. The balance between adaptive repair and maladaptive remodelling after AKI, and the potential contribution of persistent PDK4-associated metabolic dysregulation to this transition, are illustrated in Fig. 4.

Under physiological repair conditions, metabolic reprogramming after AKI should be transient. As oxygen and nutrient delivery recover, surviving tubular epithelial cells are expected to progressively restore mitochondrial glucose oxidation, re-establish ATP production and regain metabolic flexibility (73,106). In this setting, an early stress-induced increase in PDK4 mRNA and/or protein expression may represent an adaptive metabolic response that would be expected to resolve as tubular repair proceeds, although direct temporal evidence remains limited (12). Failure of this normalisation may represent a critical metabolic checkpoint that diverts post-injury repair from adaptive recovery towards maladaptive remodelling.

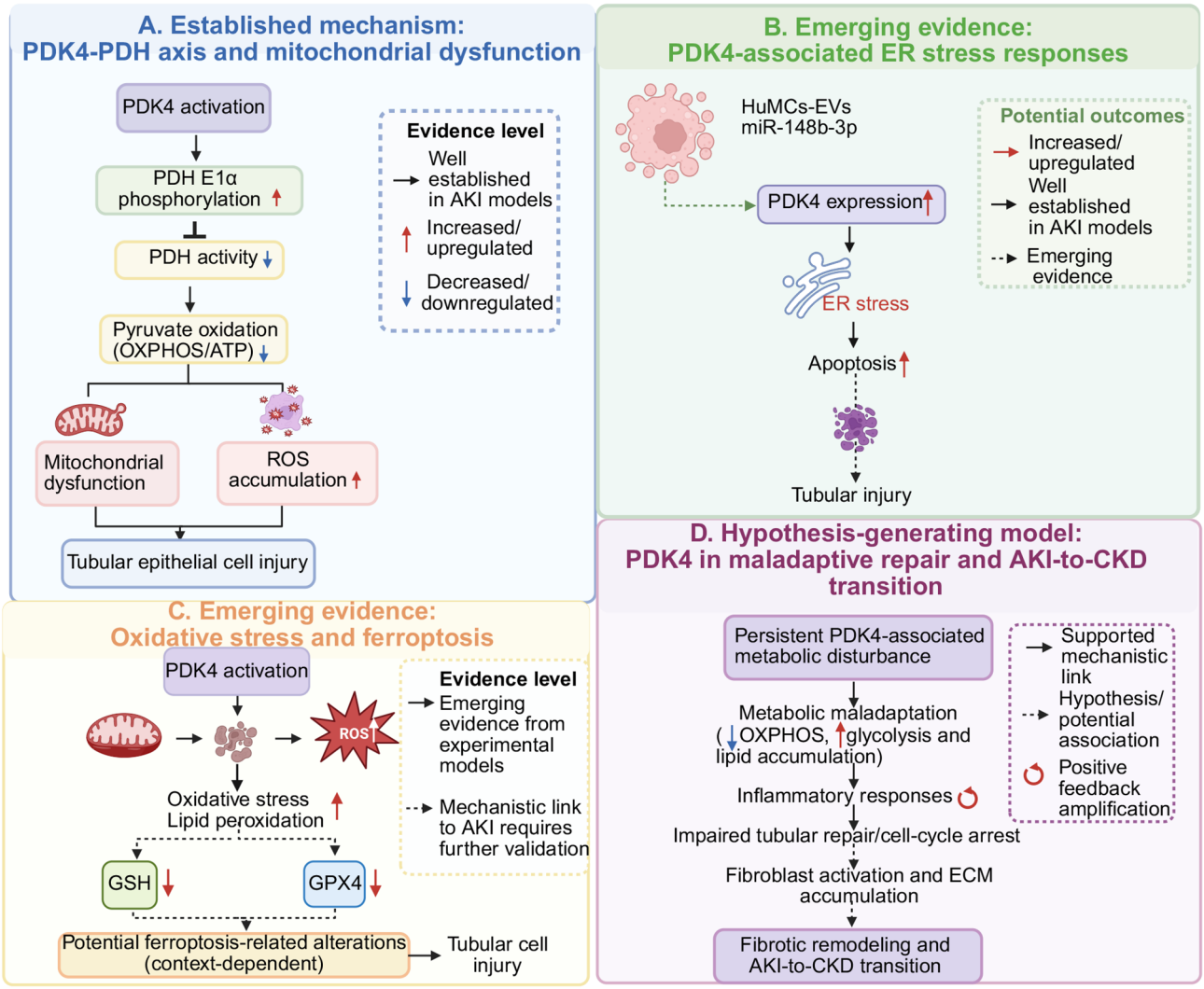



Figure 3. Established and emerging mechanisms linking PDK4 activation to AKI and AKI-to-CKD transition. (A) Established mechanism: PDK4-PDH axis and mitochondrial dysfunction. PDK4 activation promotes inhibitory phosphorylation of the PDH E1α subunit, resulting in reduced PDH complex activity and impaired mitochondrial pyruvate oxidation. This metabolic alteration contributes to mitochondrial dysfunction, ROS accumulation and tubular epithelial cell injury. (B) Emerging evidence: PDK4-associated ERS responses. Experimental studies suggest that PDK4 may participate in ERS-associated pathways, including regulation of apoptosis-related responses, thereby contributing to tubular injury. However, the mechanistic relationship between PDK4 activation and ERS requires further validation. (C) Emerging evidence: Oxidative stress and ferroptosis-related alterations. PDK4 activation has been associated with increased oxidative stress, lipid peroxidation and alterations in antioxidant defence systems, including reduced GSH availability and GPX4 expression. These findings suggest a potential involvement of PDK4 in ferroptosis-related processes; however, the contribution of PDK4 to ferroptosis in AKI remains context-dependent and requires further investigation. (D) Hypothesis-generating model: PDK4 in maladaptive repair and AKI-to-CKD transition. Persistent PDK4-associated metabolic disturbances may promote metabolic maladaptation, including reduced OXPHOS, altered glycolytic metabolism and lipid metabolic imbalance. These changes may contribute to sustained inflammatory responses, impaired tubular repair, cell-cycle arrest, fibroblast activation and ECM accumulation, potentially facilitating maladaptive renal remodelling and AKI-to-CKD progression. Created in BioRender. Zhao, Y. (2026). https://BioRender.com/ywluv9l. AKI, acute kidney injury; CKD, chronic kidney disease; ECM, extracellular matrix; ERS, endoplasmic reticulum stress; GPX4, glutathione peroxidase 4; GSH, glutathione; HuMCs-EVs, high glucose-treated mesangial cell-derived extracellular vesicles; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase complex; PDK4, pyruvate dehydrogenase kinase 4; ROS, reactive oxygen species.

By contrast, when metabolic recovery remains incomplete after the acute insult, the repair programme may deviate from adaptive regeneration towards maladaptive remodelling (73,105,106). Persistent suppression of mitochondrial oxidative metabolism limits ATP availability, compromises tubular cell proliferation and redifferentiation and favours sustained stress signalling within the post-injury microenvironment (73,106). In this context, sustained inhibitory signalling through the PDK4-PDH complex axis is of particular interest, as it may prevent recovery of mitochondrial pyruvate oxidation and maintain renal tubular epithelial cells in a metabolically inefficient state characterised by impaired OXPHOS, enhanced glycolysis and reduced metabolic flexibility. These abnormalities provide the metabolic basis for failed repair, tubular atrophy and the subsequent transition from AKI to CKD.

*Stage-dependent roles of PDK4 during post-AKI repair.* Emerging evidence suggests that the biological role of PDK4 during the AKI-to-CKD transition is stage-dependent rather than uniformly deleterious. During the acute phase of ischaemic, toxic or inflammatory injury, transient induction of

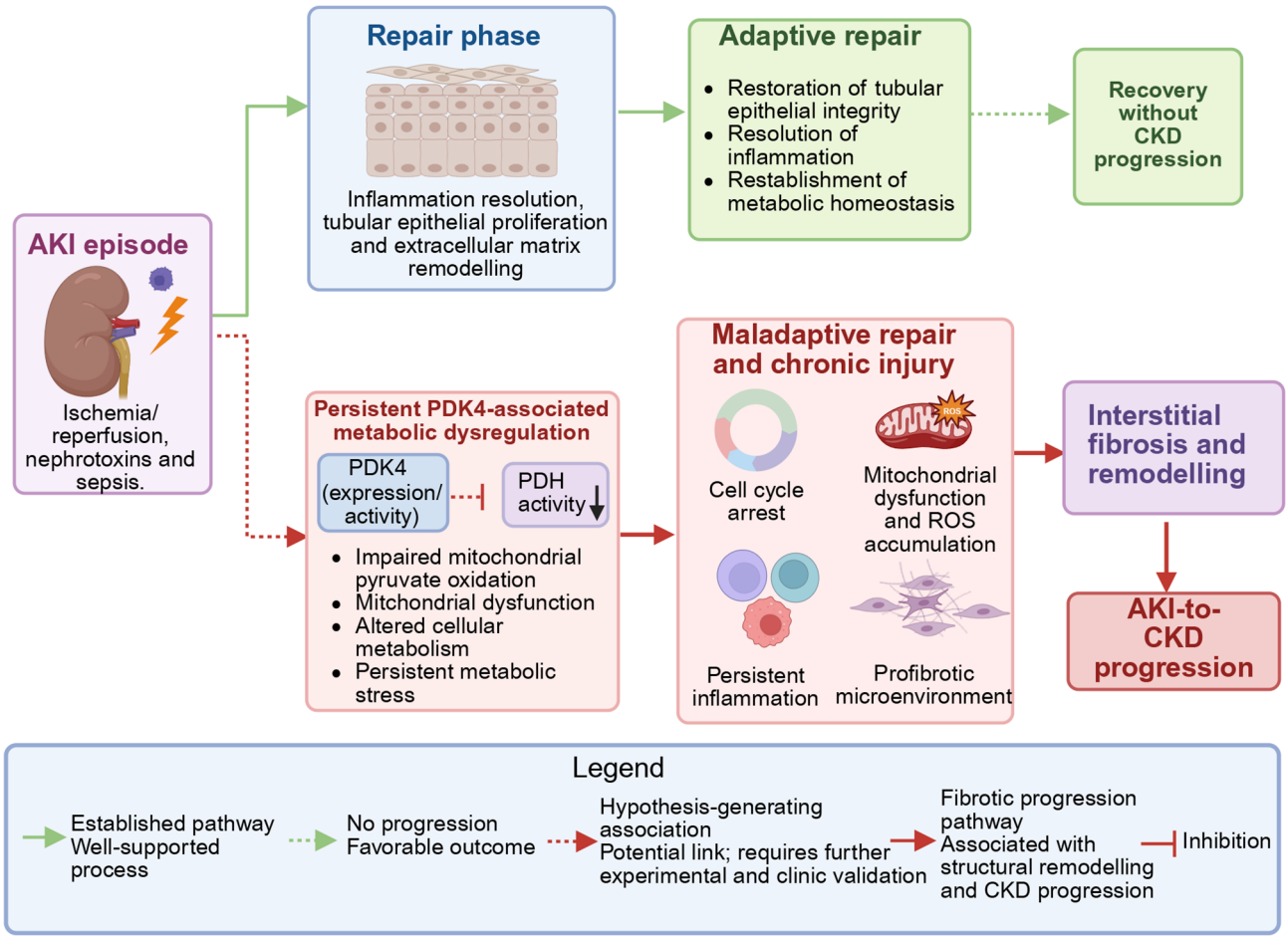



Figure 4. A proposed model of PDK4-associated metabolic regulation during adaptive repair and AKI-to-CKD transition. Following AKI, renal repair can proceed through adaptive or maladaptive pathways depending on the extent of metabolic recovery. During adaptive repair, transient metabolic reprogramming supports tubular epithelial regeneration, resolution of inflammation and restoration of metabolic homeostasis, resulting in recovery without CKD progression. By contrast, persistent PDK4-associated metabolic dysregulation may impair recovery of mitochondrial oxidative metabolism through sustained inhibition of the PDK4-PDH complex axis. This metabolic disturbance may contribute to reduced OXPHOS, impaired cellular energy metabolism, persistent stress signalling and defective tubular repair. These abnormalities may promote cell-cycle arrest, mitochondrial dysfunction, oxidative stress, inflammatory activation and a profibrotic microenvironment, ultimately contributing to interstitial fibrosis and AKI-to-CKD transition. Although accumulating evidence supports an association between persistent PDK4 activation and maladaptive renal remodelling, the precise temporal regulation, cell-type specificity and causal contribution of PDK4 during the AKI-to-CKD progression requires further experimental validation. Created in BioRender. Zhao, Y. (2026). https://BioRender.com/68cd7ge. AKI, acute kidney injury; CKD, chronic kidney disease; ECM, extracellular matrix; PDH, pyruvate dehydrogenase complex; PDK4, pyruvate dehydrogenase kinase 4; OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species.

PDK4 mRNA and/or protein expression may serve as an adaptive metabolic response (12,21). In this setting, moderate inhibitory signalling through the PDK4-PDH complex axis may help injured tubular epithelial cells survive the initial insult.

At present, the precise temporal window during which PDK4 signalling shifts from adaptive to maladaptive remains incompletely defined. Nevertheless, available evidence from studies of AKI repair suggests that this transition is most likely to occur during the early repair phase, when restoration of oxygen delivery is accompanied by recovery of mitochondrial oxidative metabolism required for tubular proliferation, redifferentiation and structural repair (73,105,106). In this context, persistent inhibitory signalling through the PDK4-PDH complex axis may become harmful by delaying metabolic recovery despite resolution of the initial insult. This concept has therapeutic implications, as it raises the possibility that PDK4 inhibition may be beneficial during the repair phase, even if transient PDK4 induction was initially adaptive during the acute injury stage.

However, this adaptive response is likely to be beneficial only if it is transient. Once the acute injury begins to resolve, successful tubular repair requires restoration of mitochondrial OXPHOS, ATP production and metabolic flexibility (73). If sustained inhibitory signalling through the PDK4-PDH complex axis persists during the repair phase, continued inhibition of the PDH complex prevents recovery of pyruvate oxidation, sustains glycolytic dependence and locks tubular epithelial cells into a metabolically inefficient state (12,73). Therefore, the pathogenic effect of PDK4 in the AKI-to-CKD transition may depend less on whether it is induced and more on whether inhibitory signalling through the PDK4-PDH complex axis fails to be appropriately terminated during post-injury repair.

One major consequence of sustained metabolic dysfunction is failure of tubular epithelial redifferentiation. Instead of returning to a mature epithelial phenotype, a subset of injured tubular cells remains in a dedifferentiated and

stress-responsive state, with reduced proliferative capacity and impaired functional recovery (107). In parallel, chronic mitochondrial dysfunction and energy depletion promote persistent oxidative stress and inflammatory signalling, thereby maintaining a pro-injury microenvironment that further interferes with repair (15,73). Persistent activation of the PDK4-PDH complex axis may impair autophagic flux and mitochondrial quality control, potentially hindering the clearance of damaged mitochondria and further compromising tubular homeostasis (73,84,85).

Another feature of maladaptive repair is cell-cycle arrest. Increasing evidence from AKI-to-CKD research indicates that tubular epithelial cells arrested in the G2/M phase acquire a profibrotic secretory phenotype characterised by the production of TGF-β, connective tissue growth factor and other mediators that activate interstitial fibroblasts (106,108). Although direct evidence specifically linking PDK4 to tubular cell-cycle arrest in the AKI-to-CKD transition remains limited, its established role in sustaining mitochondrial dysfunction, ATP depletion and cellular stress supports the possibility that sustained inhibitory signalling through the PDK4-PDH complex axis contributes to this maladaptive repair phenotype (12). In this setting, PDK4 may function not merely as a metabolic enzyme, but as a determinant of post-AKI repair outcome by preventing restoration of normal epithelial cell metabolism. These observations support a model in which sustained inhibitory signalling through the PDK4-PDH complex axis may influence post-AKI repair outcomes by linking mitochondrial dysfunction with impaired epithelial recovery, cell-cycle disturbance and chronic stress signalling.

*PDK4 and fibrogenic remodelling*. A defining feature of maladaptive repair is progressive fibrogenic remodelling of the tubulointerstitium. Current evidence does not support the view that PDK4 functions as a classical profibrotic molecule that directly triggers extracellular matrix (ECM) production in the same manner as canonical fibrogenic mediators such as TGF-β (109). Instead, the contribution of PDK4 to fibrosis is more plausibly explained by its association with sustained metabolic dysfunction, mitochondrial injury, oxidative stress and inflammatory remodelling within injured tubular epithelial cells (12,15,73). Through these effects, sustained inhibitory signalling through the PDK4-PDH complex axis may contribute to a renal microenvironment that favours fibroblast activation, ECM deposition and progression from AKI to CKD.

First, sustained inhibitory signalling through the PDK4-PDH complex axis may indirectly amplify canonical profibrotic pathways by maintaining oxidative stress and inflammatory signalling in injured tubular epithelial cells. ROS and inflammatory mediators stimulate TGF-β/Smad signalling, which is widely regarded as a central pathway in renal fibrosis (109). Activation of this pathway promotes fibroblast proliferation, myofibroblast differentiation and the synthesis of ECM components such as collagen and fibronectin. Persistent NF-κB activation may further amplify chronic inflammatory responses and cooperate with TGF-β signalling to sustain fibrogenesis (72). Thus, in this setting, PDK4 may be viewed as an upstream metabolic amplifier of TGF-β-associated fibrogenic signalling rather than as a direct matrix-inducing effector.

Second, injured tubular epithelial cells that fail to redifferentiate can themselves become a source of profibrotic mediators (72,106,110). Rather than serving merely as passive targets of injury, these maladaptively repaired tubular cells secrete TGF-β and other paracrine signals that stimulate interstitial fibroblasts and promote ECM accumulation (72,111). Although epithelial-to-mesenchymal transition has historically been proposed as a contributor to renal fibrosis, current evidence more strongly supports a model in which injured tubular cells primarily act as profibrotic signalling hubs rather than fully converting into matrix-producing fibroblasts (111,112). Therefore, in the context of the AKI-to-CKD transition, the contribution of PDK4 could be understood as promoting a persistent profibrotic tubular phenotype driven by metabolic dysfunction and failed repair. This distinction suggests that the fibrogenic effect of PDK4 may be mediated primarily through persistence of an injured tubular secretory phenotype, rather than through direct transdifferentiation of epithelial cells into matrix-producing fibroblasts.

Third, sustained inhibitory signalling through the PDK4-PDH complex axis may exacerbate lipid metabolic abnormalities during the post-AKI repair phase. Impaired mitochondrial substrate utilisation and abnormal fatty acid handling favour lipid accumulation and lipotoxic stress within tubular epithelial cells, which can further aggravate inflammation, mitochondrial dysfunction and fibrogenic signalling (110,113). Through these combined effects, persistent inhibitory signalling through the PDK4-PDH complex axis may facilitate the transition from acute tubular injury to chronic tubulointerstitial fibrosis, thereby establishing a potential mechanistic link between AKI and CKD progression. Whether these lipid metabolic abnormalities are directly controlled by PDK4 in post-AKI tubular cells or arise secondarily from broader mitochondrial dysfunction remains to be clarified.

*Current evidence linking PDK4 to AKI-to-CKD progression and remaining limitations*. Taken together, current evidence supports a model in which persistent inhibitory signalling through the PDK4-PDH complex axis may act as a metabolic determinant of maladaptive repair following AKI. By sustaining mitochondrial dysfunction, impairing oxidative metabolism and being associated with oxidative stress and a profibrotic tubular phenotype, PDK4 may contribute to failed tubular recovery and progressive tubulointerstitial fibrosis (12,15,106,110). Experimental studies showing that genetic deletion or pharmacological inhibition of PDK4 alleviates renal injury, improves mitochondrial homeostasis and reduces fibrotic remodelling further support a potential pathogenic contribution of PDK4 in the AKI-to-CKD continuum (12,20).

Nevertheless, several mechanistic questions remain unresolved regarding PDK4-mediated regulation of the AKI-to-CKD transition. First, the temporal dynamics of PDK4 expression, PDH complex phosphorylation status and downstream metabolic consequences during the shift from adaptive repair to maladaptive renal remodelling have not been fully characterised. Transient induction of PDK4 mRNA and/or protein expression in the acute phase of renal injury may serve as an adaptive endogenous response to tissue hypoxia and

mitochondrial stress (21,28,70). In this context, non-selective early inhibition of the PDK4-PDH complex axis could theoretically abrogate this protective metabolic compensation (114). By contrast, targeted modulation of the PDK4-PDH complex axis during the repair phase may confer renoprotective benefits by restoring PDH complex activity, facilitating mitochondrial glucose oxidation and halting progressive maladaptive renal remodelling. Although this stage-specific therapeutic paradigm requires direct experimental validation, it challenges the oversimplified notion that sustained PDK4 suppression is uniformly beneficial throughout the entire course of AKI, highlighting the need for precise temporal intervention strategies.

Second, the cell-type-specific functions of PDK4 during AKI-to-CKD progression remain poorly defined and require systematic elucidation. Existing data suggest that tubular epithelial PDK4 may contribute to maladaptive repair by inhibiting mitochondrial oxidative metabolism, exacerbating oxidative stress and impairing tubular recovery (75). However, the functional role of PDK4 in renal interstitial fibroblasts remains largely uncharacterised. It remains unclear whether PDK4 directly modulates fibroblast activation and ECM deposition or whether fibrotic activation is a secondary consequence of tubular-derived inflammatory and profibrotic cues after AKI (106). Additionally, while emerging immunometabolic studies in multiple organs have established PDK4 as a critical regulator of immune cell metabolism and cytokine secretion, the specific contribution of immune cell-intrinsic PDK4 to persistent renal inflammation and subsequent fibrotic progression after AKI remains insufficiently explored. Moreover, current evidence regarding PDK4 function in podocytes is predominantly derived from diabetic nephropathy and chronic glomerulopathy models, which cannot be directly extrapolated to post-AKI remodelling or the AKI-to-CKD transition.

Third, the causal relationship among PDK4 expression, PDK4-PDH complex axis signalling and renal fibrosis requires cautious interpretation. Rather than serving as a direct profibrotic effector, PDK4 may function as an upstream metabolic regulator that shapes the pathological post-AKI repair microenvironment. Persistent inhibitory signalling through the PDK4-PDH complex axis may sustain mitochondrial dysfunction and oxidative stress, trigger renal inflammatory responses and disrupt tubular epithelial repair, collectively contributing to tubulointerstitial fibrosis and chronic renal deterioration. This mechanistic interpretation aligns well with current experimental evidence and may explain the context-, stage- and cell-type-dependent pathogenic roles of PDK4 in renal disease progression.

## 5. Therapeutic strategies targeting PDK4

PDK4 has emerged as a therapeutic candidate in kidney injury due to its role in regulating glucose oxidation, mitochondrial homeostasis and maladaptive stress responses. However, most currently available PDK4-related interventions remain at the preclinical stage. Accumulating experimental evidence suggests that pharmacological or biological modulation of the PDK4-PDH complex axis may alleviate renal injury by restoring PDH activity, improving mitochondrial function, reducing oxidative stress and attenuating inflammatory or profibrotic signalling (12,15,20,68). However, the extent to which these effects reflect direct and selective inhibition of PDK4 varies notably among available interventions. Alongside conventional small-molecule inhibitors, emerging approaches, including kidney-targeted nanodelivery systems and EV-mediated miRNA strategies, have broadened the experimental landscape of PDK4-related intervention (68,75). Nevertheless, these approaches remain proof-of-concept and have not yet been clinically validated in AKI. Current therapeutic approaches targeting the PDK4-PDH complex axis in kidney injury are therefore predominantly preclinical and have primarily been developed to restore PDH complex activity and correct PDK4-associated metabolic dysregulation. As summarised in Table II, these representative interventions vary considerably in their target specificity, mechanistic basis, renoprotective effects, advantages, limitations and stage of clinical translation. The following sections first summarise currently available PDK4-targeted or PDK-related pharmacological inhibitors, followed by emerging drug delivery and nanotechnology-based therapeutic strategies.

### *Existing PDK4-targeted or related inhibitors*

*DCA*. DCA inhibits PDK activity and thereby reduces inhibitory phosphorylation of the PDH E1α subunit, leading to partial restoration of PDH complex activity and enhanced mitochondrial glucose oxidation. The biological effects of DCA are cell-type dependent. In tumour models, including glioblastoma and breast cancer, DCA restores mitochondrial oxidative metabolism and may increase intracellular ROS generation, thereby promoting apoptosis and enhancing antitumour activity (70,114). By contrast, in experimental AKI models and normal renal tubular epithelial cells, DCA-mediated inhibition of the PDK-PDH complex axis has been associated with reduced oxidative stress, preservation of mitochondrial OXPHOS and improved renal function (12,15,20). Therefore, the effects of DCA on ROS production should be interpreted in a cell-type-specific context rather than generalised across different biological systems. DCA is a pan-PDK inhibitor rather than a PDK4-selective compound and the pharmacological effects of DCA are likely to reflect simultaneous inhibition of multiple PDK isoforms. Accordingly, although DCA has demonstrated renoprotective effects in experimental kidney injury models, these benefits should be interpreted as modulation of the broader PDK-PDH complex axis rather than evidence of selective pharmacological inhibition of PDK4.

In preclinical cisplatin-induced AKI models, DCA exerts renoprotective effects by suppressing tubular apoptosis and ameliorating renal dysfunction. Mechanistically, DCA blocks PDK-mediated inhibitory phosphorylation of the PDH E1α subunit, which rescues suppressed PDH complex activity and restores defective mitochondrial pyruvate oxidation. Improved mitochondrial metabolic function further reduces cisplatin-induced oxidative stress and indirectly counteracts the apoptotic cascade driven by mitochondrial metabolic collapse in renal tubules (20). These protective effects have been linked to suppression of the JNK/14-3-3/Bax/caspase-9 pathway and inhibition of caspase-8 activation via cellular FAS-associated death domain-like IL-1β-converting enzyme inhibitory protein in renal tubular cells (80). However, the renoprotective profile of DCA remains incompletely characterised and its effects

Table II. Current and emerging PDK4-targeted therapeutic strategies for AKI and the AKI-to-CKD transition.

| Strategy | PDK4 specificity | Main mechanism | Experimental model | Translation stage | Advantages | Limitations and safety concerns | (Refs.) |
|---|---|---|---|---|---|---|---|
| DCA | Non-selective PDK inhibitor | Activates pyruvate dehydrogenase by inhibiting PDK activity | Cisplatin-AKI; IRI-AKI models | Preclinical renal evidence | Inexpensive; extensive experimental validation | Lack of PDK4 specificity; neuropathy and systemic metabolic effects | (80,114,115) |
| GM-10395 | PDK4-selective | Allosteric inhibition of PDK4 | IRI-AKI; fibrosis models | Preclinical only | High target specificity | Limited pharmacokinetic data; long-term safety unknown | (12,95) |
| 4-PBA | Indirect | Endoplasmic reticulum stress attenuation; reduces PDK4 expression | Cisplatin-AKI | Approved for other indications; renal studies preclinical | Clinical experience; multi-target protection | Not a direct PDK4 inhibitor; renal-specific safety unclear | (13,106,118,119) |
| curcumin analogue-loaded poly-dopamine nanoparticles | Indirect | Kidney-targeted reactive oxygen species scavenging and PDK4 downregulation | IRI-AKI | Early preclinical | Targeted delivery | Complex formulation; biodistribution/toxicity unclear | (68) |
| MSC-EVs/ miR-148b-3p | Gene regulation | Suppresses PDK4; improves mitochondrial function | IRI-AKI | Preclinical | High molecular specificity | Manufacturing and long-term safety issues | (75) |
| MSC-EVs/ miR-15b-5p | Gene regulation | miRNA-mediated PDK4 suppression | DKD models | Proof-of-concept preclinical | Molecular specificity | Mainly validated in DKD; translation to AKI unclear | (30) |

Representative therapeutic strategies are summarised. Unless otherwise indicated, the available evidence is derived predominantly from experimental animal or cellular studies and none have been clinically validated for the treatment of AKI or prevention of the AKI-to-CKD transition. AKI, acute kidney injury; DCA, dichloroacetate; DKD, diabetic kidney disease; IR-AKI, ischemia-reperfusion-induced AKI; miRNA, microRNA; MSC-EVs, mesenchymal stem cell-derived extracellular vesicles; PDK4, pyruvate dehydrogenase kinase 4; 4-PBA, sodium 4-phenylbutyrate.

on oxidative and inflammatory signalling may vary across experimental settings. Nevertheless, the translational value of DCA in AKI is limited by several factors including: i) Lack of isoform selectivity; ii) absence of intrinsic kidney-targeted delivery; and iii) the possibility of systemic adverse effects associated with broad metabolic modulation (114,115). In addition, to the best of our knowledge, no kidney-specific clinical trials evaluating DCA as a PDK-targeting metabolic therapy for AKI are currently available. Therefore, DCA should presently be regarded as a proof-of-concept metabolic modulator of the PDK-PDH complex axis rather than an established PDK4-selective therapeutic agent for kidney disease. Outside the kidney field, nanoparticle-based formulations of DCA have been explored to improve drug stability and systemic delivery in non-renal disease models, including a breast carcinoma model (116). However, these studies do not constitute direct evidence for AKI therapy and are mentioned only to illustrate the broader feasibility of formulation-based optimisation for pan-PDK inhibitors.

*GM-10395*. GM-10395 is a small-molecule allosteric inhibitor reported to preferentially target PDK4 in preclinical studies. However, current evidence for the efficacy and safety of GM-10395 remains limited to experimental models. A preclinical study suggests that GM-10395, a pharmacological inhibitor with preferential activity against PDK4, may attenuate renal injury-associated phenotypes and reduce inflammation- and fibrosis-related responses in experimental models, although direct evidence supporting its efficacy in established AKI models remains limited (12). In addition, GM-10395 has shown anti-inflammatory activity in a murine colitis model, where it reduces ER-mitochondrial calcium transfer and inhibits T cell activation (95). Mechanistically, GM-10395 disrupts the interaction between PDK4 and septin 2, thereby reducing MAM formation and limiting pathological ER-to-mitochondria calcium transfer. These changes are associated with attenuation of ERS and preservation of mitochondrial homeostasis, providing a mechanistic basis for the potential renoprotective effects of GM-10395 (95). However, these findings should be regarded as supportive mechanistic evidence rather than direct evidence for AKI therapy. Although GM-10395 is of mechanistic interest because it represents a more selective pharmacological strategy targeting the PDK4 pathway, its translational development remains preliminary. At present, to the best of our knowledge, no kidney-targeted formulation, human renal data or registered clinical trials evaluating GM-10395 in AKI are available. Moreover, the available safety data remain limited to preclinical assessment. Therefore, further studies are required to define the pharmacokinetic profile, renal delivery efficiency, long-term safety and therapeutic efficacy of GM-10395 in clinically relevant AKI models before clinical translation can be considered.

*Sodium 4-phenylbutyrate (4-PBA) and emerging strategies for PDK-targeted drug development*. 4-PBA is a chemical chaperone approved for the treatment of urea cycle disorders and should not be regarded as a validated direct PDK4 inhibitor (13,117). A previous study suggests that, in cisplatin-induced AKI models, 4-PBA alleviates renal injury in association with reduced PDK4 mRNA and/or protein expression, improved mitochondrial function and partial restoration of cellular energy metabolism (106). These findings suggest that modulation of PDK4-associated signalling may contribute to the nephroprotective effects of 4-PBA. In addition, 4-PBA alleviates ERS and improves mitochondrial homeostasis, indicating that its renoprotective effects are likely mediated by multiple convergent mechanisms rather than by selective pharmacological inhibition of PDK4 alone (118,119). Unlike DCA or GM-10395, 4-PBA does not directly inhibit PDK4. Instead, 4-PBA functions as a chemical chaperone that alleviates ERS downstream of PDK4-associated metabolic dysfunction by improving protein folding capacity and suppressing UPR activation (119). Consequently, the renoprotective effects of 4-PBA primarily target the ERS pathway rather than the PDK4 kinase itself, thereby complementing metabolic correction through downstream stress modulation. At present, evidence supporting 4-PBA-related modulation of the PDK4 axis in AKI is primarily derived from cisplatin-induced AKI models and comparable evidence in other AKI subtypes, including IRI and SA-AKI, remains limited. In addition, kidney-specific human data and AKI-focused clinical trials evaluating 4-PBA through a PDK4-related therapeutic framework are currently lacking.

Nevertheless, the currently available evidence has several limitations. Although the nephroprotective effects of 4-PBA are associated with reduced PDK4 protein expression, the molecular mechanism responsible for PDK4 downregulation remains unclear. Furthermore, direct binding of 4-PBA to PDK4 or inhibition of PDK4 kinase activity has not been experimentally demonstrated. Similarly, whether 4-PBA directly regulates phosphorylation of the PDH E1α subunit or PDH complex activity remains to be established (13). Taken together, 4-PBA should currently be interpreted as an indirect PDK4-related renoprotective modulator rather than as a selective PDK4-targeted therapeutic agent.

As direct PDK4-selective inhibitors remain unavailable, recent studies have focused on structure-based drug discovery to improve isoform selectivity (114,120). Structure-based virtual screening has accelerated the development of isoform-selective PDK inhibitors. A recently identified structure-guided inhibitor, Compound 1, exhibits improved isoform selectivity among PDK family members and demonstrates favourable pharmacological activity in preclinical cancer models, including A549 lung cancer cells (114,120). Although Compound 1 is not PDK4-specific and has not been evaluated in kidney injury models, its development illustrates the feasibility of structure-guided optimisation for improving isoform selectivity among PDK inhibitors. These findings may provide a useful conceptual framework for the future development of PDK4-selective compounds relevant to renal disease.

Current research strategies for renoprotective agents primarily focus on targeting the PDK-PDH complex axis and developing high-potency PDK inhibitors through structure-based virtual screening and systematic pharmacological evaluation. A recent comprehensive review has summarised the major structural features, druggable binding pockets and structure-activity relationships of mainstream PDK inhibitors, including inhibitors targeting the pyruvate-binding, CoA-binding, lipoamide-binding and ATP-binding pockets. Most classical PDK inhibitors, including DCA, AZD7545 and Pfz3, are pan-PDK inhibitors with limited isoform selectivity and lack specific targeting of PDK4, which may contribute

to potential off-target effects and limited renoprotective efficacy (114). Through structure-based rational optimisation and molecular hybridisation strategies, novel PDK inhibitors, including GM-10395, with improved potency, isoform selectivity, metabolic stability and *in vivo* biosafety have been developed (12,95). Collectively, these advances demonstrate that rational structure-based optimisation can notably improve inhibitor potency, isoform selectivity, metabolic stability and biosafety. Although no selective PDK4 inhibitor has yet entered clinical development for kidney diseases, these studies provide useful structural templates for future drug discovery rather than direct evidence of near-term translational readiness in AKI.

*Targeted delivery systems*

*Curcumin analogue-loaded polydopamine nanoparticles (CF@PDA).* To address the challenge of renal delivery, a preclinical kidney-targeted nanoparticle platform consisting of CF@PDA has been developed for experimental modulation of PDK4-related signalling in IR-AKI. These nanoparticles comprise a polydopamine (PDA) matrix loaded with a curcumin analogue (CF) and are further surface-modified with pH-responsive moieties to facilitate renal accumulation and enhance uptake by proximal tubular epithelial cells (68). According to the original study, this platform exerts combined antioxidant effects and suppresses renal PDK4 expression in injured kidneys. Mechanistically, CF@PDA was reported to suppress renal PDK4 expression, reduce oxidative stress and attenuate inflammatory injury, while the antioxidant properties of PDA and CF may additionally contribute to ROS scavenging. In a mouse model of renal ischaemia-reperfusion AKI, CF@PDA decreased renal ROS levels and improved renal function (68). However, since this platform integrates delivery-related, antioxidant and PDK4-associated effects, the specific contribution of PDK4 suppression to the overall renoprotective phenotype remains to be clarified. The nanoparticle system also exhibits imaging capability and preliminary biocompatibility in animal experiments (68). However, these findings should be interpreted cautiously, as human pharmacokinetic data, long-term toxicity data and clinical trial evidence are currently unavailable. By enhancing kidney-targeted delivery of PDK4-modulating agents, this nanoplatform may improve mitochondrial metabolic homeostasis, reduce oxidative stress and minimise systemic off-target effects. These properties may contribute to enhanced therapeutic efficacy while reducing adverse effects associated with non-specific drug distribution. Thus, CF@PDA should currently be regarded as a proof-of-concept kidney-targeted nanodelivery platform that ameliorates experimental IR-AKI through combined modulation of oxidative stress, inflammation and PDK4-associated signalling, rather than as a clinically validated therapeutic strategy for kidney disease.

*Mesenchymal stem cell-derived EVs (MSC-EVs) carrying miR-148b-3p.* MSC-EVs represent an emerging biological delivery strategy for modulating PDK4-related signalling in kidney injury. In IR-AKI, human umbilical cord MSC-EVs delivered miR-148b-3p to renal tubular epithelial cells, directly targeting PDK4 and suppressing its protein expression, thereby reducing ERS, improving mitochondrial function and attenuating tubular apoptosis following IRI (75). However, current evidence remains limited to experimental AKI models. Further studies are required to determine EV pharmacokinetics, renal targeting efficiency, long-term safety and translational feasibility before clinical application.

*MSC-EVs carrying miRNA-15b-5p.* MSC-EVs carrying miRNA-15b-5p have been reported to protect podocytes in diabetic nephropathy models by targeting the PDK4-VEGFA signalling axis. MSC-EVs were used to deliver miR-15b-5p, which reduced PDK4 expression, attenuated podocyte apoptosis and mitigated VEGFA-related injury (30). Mechanistically, EV-mediated delivery of miR-15b-5p directly targets the 3'-untranslated region of PDK4, suppressing PDK4 mRNA and protein expression and subsequently downregulating VEGFA, thereby attenuating podocyte apoptosis and inflammation (30). However, this evidence derives from diabetic nephropathy rather than AKI and should therefore be regarded as supportive evidence for the broader therapeutic relevance of PDK4-related EV-miRNA modulation, rather than as direct evidence for AKI treatment. Overall, EV-mediated delivery of miR-15b-5p illustrates the possibility that upstream RNA-based regulation may modulate PDK4-associated signalling in renal disease. Nevertheless, this strategy remains preclinical, has not been validated in AKI and currently lacks human renal data, clinical trials and standardised safety evaluation.

## 6. Biomarker potential and current translational limitations

Activation of the inhibitory PDK4-PDH complex axis is mechanistically linked to several biological processes that are relevant to AKI, including mitochondrial dysfunction, oxidative stress, metabolic reprogramming and maladaptive tubular repair. Since these processes are central to tubular injury and post-AKI remodelling, altered PDK4 expression has attracted interest as a potential biomarker candidate (12-15,20). However, currently available evidence does not support describing PDK4 as a validated clinical biomarker for AKI diagnosis, prognosis or prediction of AKI-to-CKD transition (121). Instead, existing data should be interpreted as preliminary and hypothesis-generating.

At present, most studies concerning PDK4 in kidney injury have evaluated its mRNA and/or protein expression in experimental AKI models, cultured renal tubular epithelial cells or renal tissue specimens (12-15,20). Accordingly, the strongest evidence currently supports PDK4 as a tissue-level mechanistic marker associated with renal metabolic stress and tubular injury. By contrast, evidence from clinically accessible biospecimens remains limited. It is unclear whether PDK4 can be robustly and reproducibly measured in blood, urine or urine-derived cells in patients with AKI, and no consensus exists regarding the most appropriate sample type for clinical biomarker development (9,106). Therefore, although renal tissue expression data suggest biological relevance, the translational applicability of PDK4 as a non-invasive biomarker remains unestablished.

Current evidence is also insufficient to support the use of PDK4 for early AKI diagnosis (121,122). To date and to the best of our knowledge, no well-established clinical studies have shown that circulating or urinary PDK4 levels can detect AKI earlier than conventional functional criteria or established

tubular injury biomarkers. Likewise, no standardised clinical validation cohorts have defined reference ranges, diagnostic cut-off values, assay reproducibility, sensitivity, specificity or receiver operating characteristic (ROC) performance for PDK4-based AKI detection (9,106). As a result, it remains unknown whether PDK4 provides incremental diagnostic value beyond serum creatinine, urine output or currently available renal injury markers.

The prognostic role of PDK4 in the transition from AKI to CKD is similarly unresolved (5,106). From a mechanistic perspective, persistent activation of the PDK4-PDH complex axis may contribute to maladaptive repair, sustained mitochondrial dysfunction and fibrogenic remodelling after AKI, providing a biological rationale for considering PDK4 as a prognostic candidate marker (12,104,106). Nevertheless, direct clinical evidence remains lacking. Prospective human cohort studies demonstrating that PDK4 measured during or after AKI predicts long-term CKD progression, renal fibrosis or incomplete renal recovery have not yet been reported (106). Therefore, any prognostic role of PDK4 in AKI-to-CKD transition should currently be regarded as speculative rather than clinically established.

Another translational limitation is the lack of head-to-head comparisons with established renal biomarkers. Existing studies have not systematically compared PDK4 with clinically used or clinically investigated AKI biomarkers, such as neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, cystatin C or the cell-cycle arrest biomarkers tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 (121,122). Similarly, there are currently no robust data indicating whether PDK4 improves risk stratification when added to these established markers, either alone or as part of a multimarker panel. In the absence of such comparative analyses, it is premature to position PDK4 as a clinically competitive biomarker for AKI or AKI-to-CKD progression.

Taken together, the current literature supports PDK4 expression primarily as a biologically plausible candidate biomarker reflecting renal metabolic stress and tubular injury, rather than as a validated biomarker ready for clinical application (9,12-15,20,106,121,122). Future studies should focus on several priorities: i) Determining whether PDK4 can be reliably measured in clinically accessible specimens, such as blood, urine, urinary EVs or urine-derived cells; ii) establishing standardised assays and defining reference ranges and diagnostic thresholds; iii) evaluating diagnostic sensitivity, specificity and ROC-area under the curve performance in well-phenotyped AKI cohorts; iv) testing whether PDK4 provides early diagnostic or prognostic value beyond established biomarkers; and v) performing prospective longitudinal studies to determine whether PDK4 can predict maladaptive repair and AKI-to-CKD transition. Until such data become available, PDK4 should be described cautiously as a candidate biomarker rather than a validated biomarker in AKI and AKI-to-CKD transition.

## 7. Controversies and future perspectives

Although notable progress has been made in elucidating the role of PDK4 in AKI, translating these mechanistic findings into clinical applications remains challenging. Current evidence suggests that PDK4 is a promising but still preliminary therapeutic target, particularly in IR-AKI. However, whether these findings can be generalised to other forms of AKI remains uncertain, as available evidence is derived predominantly from experimental models. The role of PDK4 in AKI also does not appear to be uniformly detrimental, but rather stage- and context-dependent. During the early phase of injury, moderate PDK4 induction may support metabolic adaptation and cellular compensation, whereas sustained upregulation under persistent stress conditions may aggravate mitochondrial dysfunction, inflammation and fibrotic remodelling. These findings indicate that PDK4 should not be regarded simply as a harmful molecule and that therapeutic strategies targeting PDK4 are likely to require precise temporal control.

Most conclusions regarding the stage-dependent effects of PDK4 are currently derived from animal models, whereas evidence from human AKI remains limited. Moreover, differences in injury models, intervention timing and outcome assessment among published studies make direct comparisons difficult. These factors may partly explain apparent discrepancies in the reported effects of PDK4-associated metabolic regulation and underscore the need for standardised experimental designs and clinical validation. Several bioinformatics-based studies have also identified potential PDK4-associated regulatory networks and downstream pathways in renal injury (83,123). Related studies have also described PDK4-associated alterations in CKD, clear cell renal cell carcinoma and membranous nephropathy (124-129). However, these findings remain largely hypothesis-generating and require further validation through functional experiments and disease-relevant models.

Another unresolved issue is the cell type-specific function of PDK4 in the injured kidney. Although growing evidence supports a role for PDK4 in renal tubular epithelial cells, its functions in podocytes, fibroblasts and immune cells remain insufficiently characterised. Whether PDK4 participates in immune-cell metabolic reprogramming and thereby modulates the inflammatory microenvironment during AKI has not been fully clarified. Addressing this question is essential for a more comprehensive understanding of PDK4-mediated pathogenesis and for the rational design of cell-specific therapeutic interventions. Future studies integrating single-cell transcriptomics, spatial transcriptomics, metabolomics and lineage-tracing approaches may help clarify the dynamic and cell type-specific functions of PDK4 during renal injury and repair. Determining whether PDK4 directly regulates fibroblast activation or immune-cell metabolism, rather than indirectly affecting these populations through tubular injury, is critical for defining its therapeutic relevance.

A further limitation of the current literature is the heterogeneity of available evidence. Existing studies differ notably in AKI aetiology, experimental species, disease severity, intervention timing and evaluated endpoints. Consequently, although most reports support a pathogenic role for PDK4, the strength and consistency of evidence vary across AKI models. Future investigations using standardised experimental protocols and direct comparisons among ischaemic, septic and nephrotoxic AKI models are required to define the generalisability of PDK4-mediated mechanisms. Metabolic

disturbances, inflammatory responses and mitochondrial injury differ notably among ischaemic, septic and nephrotoxic AKI, and the biological effects of PDK4 may therefore not be identical across AKI subtypes.

From a translational perspective, developing selective PDK4 inhibitors is a priority, although several obstacles remain. This challenge is largely attributable to the high degree of structural similarity among PDK family members, which complicates the development of truly PDK4-specific inhibitors. First, PDK isoforms share notable structural homology, particularly within the catalytic and ATP-binding regions, making it difficult for currently available small-molecule inhibitors to selectively target PDK4 without affecting other family members. Such off-target isoform inhibition may compromise specificity and limit therapeutic utility. Second, since PDK4 is broadly involved in systemic energy metabolism in tissues such as skeletal muscle, liver and heart, systemic inhibition may disrupt metabolic homeostasis and increase the risk of adverse effects, including altered glucose utilisation, impaired lipid metabolism and reduced adaptive responses to metabolic stress. Stronger inhibition may therefore not necessarily translate into improved therapeutic outcomes. Third, even when candidate compounds show activity *in vitro*, insufficient delivery efficiency and limited accumulation at renal injury sites remain barriers to *in vivo* efficacy and clinical translation. These challenges suggest that successful clinical translation will require more selective PDK4 modulators, optimisation of treatment timing and kidney-specific delivery strategies.

Building on these mechanistic insights, future translational research should focus on several priorities. First, single-cell transcriptomics, spatial transcriptomics and metabolomics should be integrated to define the dynamic expression patterns, activity status and functional heterogeneity of PDK4-associated signalling across renal cell types and disease stages, thereby identifying the optimal therapeutic window. Second, drug development efforts should move beyond conventional broad enzyme inhibition towards isoform-selective precision modulation. Structure-based drug design, computer-assisted screening and identification of allosteric binding sites unique to PDK4 may provide feasible approaches for improving subtype selectivity. Third, kidney-targeted delivery systems, including nanoparticle-based carriers, prodrug strategies and tubular-targeting molecular modifications, may enhance local drug accumulation while minimising systemic exposure. Finally, prospective clinical studies are needed to evaluate the diagnostic and prognostic value of PDK4 in AKI and clarify its contribution to AKI-to-CKD progression, particularly in relation to persistent inflammation and fibrotic remodelling. Multicentre prospective studies with standardised sampling procedures and outcome definitions are also essential for evaluating the clinical applicability of PDK4 across different AKI populations.

In conclusion, although PDK4 has been proposed as a candidate biomarker for AKI and AKI-to-CKD progression, clinical validation remains insufficient. Studies evaluating PDK4 levels in blood or urine samples, establishing standardised detection methods and determining diagnostic or prognostic thresholds are still lacking. Collectively, current evidence supports PDK4 as a regulator that may contribute to mitochondrial dysfunction, metabolic reprogramming and maladaptive renal repair in AKI, although its precise pathogenic role and therapeutic value remain to be fully established. Numerous challenges remain before these findings can be translated into clinical practice: i) Limited human validation; ii) incomplete understanding of cell-specific and stage-dependent functions; iii) uncertainty regarding isoform-selective targeting; iv) potential systemic metabolic consequences of PDK4 inhibition; and v) the absence of clinically validated biomarkers. Addressing these issues through integrated mechanistic, translational and clinical investigations is essential for determining whether modulation of the PDK4-PDH complex axis can improve outcomes in patients with AKI and prevent progression to CKD.

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**Authors' contributions**

YZ, SZ and LS contributed to the conception and design of the review, the literature search, data collection, manuscript drafting and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

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Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Use of artificial intelligence tools**

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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