Oops I Did it Again: Integrative Pathways of Injury, Proliferation, and Cell Death in Polycystic Kidney Disease and Relations to Oncogenesis

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Introduction

Polycystic kidney disease (PKD) is a genetically inherited disorder most often caused by mutations in the PKD1 or PKD2 genes, which encode the proteins polycystin-1 (PC1) and polycystin-2 (PC2), respectively. These proteins are essential for maintaining the structural and functional integrity of renal tubular epithelial cells, particularly through their regulation of intracellular calcium (Ca^{2+}) signaling and mitochondrial activity (1, 2). In healthy nephrons, PC2 localizes to the endoplasmic reticulum (ER)-mitochondria interface, facilitating Ca^{2+} transfer and supporting normal metabolic function. Mutations that disrupt PC1 or PC2 impair calcium signaling and mitochondrial homeostasis, leading to metabolic reprogramming and the formation of fluid-filled cysts throughout the kidney parenchyma. This relentless cystogenesis gradually compromises renal function and frequently culminates in end-stage renal disease.

While much of PKD research has focused on genetic and metabolic triggers of cyst formation, growing evidence emphasizes the critical role of crystal-induced injury in accelerating disease progression. Metabolic imbalances common in PKD, such as hyperoxaluria and hypocitraturia, favor the intratubular formation of calcium oxalate (CaOx) and calcium phosphate crystals (3). These crystals adhere to the tubular epithelium, inflicting injury and initiating a cascade of mechanical, oxidative, and inflammatory stress. Crystal-induced mechanical stretching rapidly activates signaling pathways such as mTOR and STAT3, promoting compensatory tubular dilation. Simultaneously, mitochondrial stress marked by upregulation of TOMM20 drives excessive reactive oxygen species (ROS) production and activates pro-inflammatory mediators including NF-κB and the NLRP3 inflammasome (1, 4).

The resulting inflammatory milieu further compromises epithelial integrity. Dysregulated expression of integrin α6β4 and hyperactivation of Src kinase weaken cell-basement membrane adhesion, while amplifying proliferative signaling through ErbB2 and the B-Raf/MEK/ERK pathways (5, 6). These molecular events establish a permissive environment for unchecked cyst expansion, tissue remodeling, and progressive kidney damage.

Notably, the signaling pathways activated in PKD - such as STAT3, mTOR, and MAPK/ERK - mirror those implicated in tumorigenesis, including disruptions in cell adhesion, metabolic rewiring, and cell death regulation (7, 8). Central to this process is the STAT3 → cadherins → GPX4 axis, which integrates proliferative, adhesive, and death-related signals in cyst-lining cells. Sustained STAT3 activity suppresses E-cadherin expression and reduces ferroptosis resistance by downregulating GPX4. Meanwhile, chronic injury also triggers apoptosis and necroptosis pathways. Dissecting how these interconnected mechanisms respond to crystal-induced injury offers valuable insight into the pathogenesis of PKD and reveals promising therapeutic targets for slowing or reversing disease progression.

Crystal Accumulation and Tubular Injury

Crystal accumulation within renal tubules represents a critical early event that accelerates the pathogenesis of PKD. Metabolic disturbances such as hyperoxaluria, hypocitraturia, and altered urinary pH create a biochemical environment conducive to the formation and retention of CaOx and calcium phosphate crystals (3). Compounding these conditions, PKD patients often exhibit reduced excretion of natural crystallization inhibitors like citrate, further promoting crystal nucleation and growth. These crystals adhere tenaciously to the apical surface of tubular epithelial cells, especially in regions where cyst expansion or architectural distortion disrupts tubular flow.

The initial interaction between crystals and the tubular epithelium causes significant injury. Mechanical stretching and microtrauma from crystal impaction directly damage epithelial cells, triggering a rapid compensatory response. This response involves the activation of mechanosensitive pathways such as mTOR and STAT3, which mediate acute tubular dilation in an effort to clear the obstruction (9). However, in PKD, impaired PC1 and PC2 function compromises the tubule's ability to regulate diameter and repair damage, leading to persistent dilation and the initiation of new cysts (1, 2).

Beyond mechanical damage, crystal-induced injury initiates a cascade of bioenergetic and inflammatory changes that destabilize the epithelium. CaOx crystals disrupt mitochondrial dynamics, as evidenced by increased TOMM20 expression - a marker of mitochondrial stress and mass (1). Mitochondrial dysfunction then drives excessive production of reactive oxygen species (ROS), which act as signaling molecules to activate pro-inflammatory pathways, including NF-κB and the NLRP3 inflammasome (4). This activation leads to the release of cytokines such as IL-1β and IL-18, which recruit immune cells, amplify inflammation, and perpetuate epithelial damage.

A key component of this injury response is the activation of Src kinase, which is hyperactive in PKD. Src phosphorylates integrin α6β4, a laminin-5 receptor that is abnormally overexpressed in cyst-lining cells (5, 10). This phosphorylation weakens cell-basement membrane adhesion, increasing susceptibility to tubular dilation and cystic transformation. In parallel, the integrin α6β4-Src signaling axis activates downstream proliferative pathways through ErbB2 and MAPK, closely resembling oncogenic networks (6). These pathways drive compensatory hyperplasia and disrupt epithelial polarity, initiating epithelial-to-mesenchymal transition (EMT), as indicated by decreased E-cadherin and increased vimentin expression (11).

The consequences of crystal-induced injury are both immediate and long-term. Acutely, activation of the NLRP3 inflammasome and necroptosis contributes to necroinflammation, while EMT primes the tissue for fibrotic remodeling. Chronically, sustained oxidative and inflammatory stress promotes ongoing apoptosis, ferroptosis, and extracellular matrix (ECM) remodeling. These processes culminate in interstitial fibrosis and the expansion of cystic lesions (12). Thus, crystal accumulation is not a passive byproduct of PKD but an active driver of the molecular and cellular mechanisms that underlie disease progression, amplifying both proliferative and cell death pathways central to cystogenesis.

The STAT3 → Cadherins → GPX4 Axis in Cystic Transformation

The STAT3 → Cadherins → GPX4 axis is a core molecular pathway in PKD that links upstream injury signals to downstream disruptions in cell adhesion, oxidative stress response, and cell fate.

In healthy renal tubules, PC1 tightly regulates STAT3 activity to maintain a balance between proliferation and survival, supporting tissue homeostasis. However, in PKD, loss-of-function mutations in PKD1 disrupt this regulation, leading to aberrant and sustained STAT3 activation, particularly in cyst-lining epithelial cells (7, 13). This chronic activation is further amplified by upregulated signals in the PKD microenvironment - including EGF/EGFR, HGF/c-Met, and Src kinase - that converge to phosphorylate and activate STAT3 (7, 14).

Once phosphorylated, STAT3 translocates to the nucleus and induces the transcription of genes that promote cell proliferation, survival, and inflammation. One of the most consequential outcomes of persistent STAT3 signaling is the downregulation of E-cadherin, a key cadherin protein essential for tight cell-cell adhesion and epithelial polarity (7). The loss of E-cadherin weakens adherens junctions and compromises epithelial barrier function, promoting EMT, which increases the proliferative and migratory capacity of cyst-lining cells and enhances their susceptibility to tissue remodeling and transformation - paralleling oncogenic mechanisms (7, 14).

Disruption of cadherin-mediated adhesion, compounded by oxidative and metabolic stress within the cystic microenvironment, increases cellular vulnerability to ferroptosis - a regulated form of cell death driven by iron-dependent lipid peroxidation. Glutathione peroxidase 4 (GPX4), a central enzyme that detoxifies lipid hydroperoxides, normally prevents ferroptosis. In PKD, transcriptional changes driven by STAT3, along with E-cadherin loss, correlate with reduced GPX4 expression or activity, rendering cystic epithelial cells highly susceptible to ferroptotic damage (15, 16). Elevated levels of reactive oxygen species (ROS) and impaired mitochondrial metabolism further accelerate lipid peroxidation, amplifying cell death and tissue injury.

This axis also contributes to broader pathological remodeling. Persistent STAT3 activation promotes the secretion of cytokines and growth factors, which in turn recruit and activate fibroblasts, stimulate ECM deposition, and foster a pro-fibrotic environment (17). This chronic inflammatory and fibrotic milieu exacerbates cyst expansion and progressively compromises renal function.

Together, sustained STAT3 activation, E-cadherin loss, and GPX4 suppression create a self-reinforcing feedback loop that drives unchecked proliferation, impaired epithelial integrity, and increased cell death. This molecular circuit closely mimics pathways seen in cancer biology and has emerged as a promising therapeutic target for PKD. Interventions aimed at inhibiting STAT3 signaling, restoring E-cadherin expression, or protecting against ferroptosis are currently under active investigation (7, 15, 16).

Cell Death Mechanisms in Crystal-Associated PKD

Crystal-associated PKD involves not only unchecked cell proliferation but also the dysregulation of multiple regulated cell death pathways, particularly apoptosis, ferroptosis, and necroptosis. These mechanisms are intricately tied to cellular stress from CaOx and phosphate crystal deposition, and their interplay drives both cyst formation and progressive kidney damage.

Apoptosis, the classical form of programmed cell death, maintains homeostasis in healthy kidneys by removing damaged or unneeded cells without inciting inflammation. In PKD, this process becomes pathological. Crystal-induced oxidative stress, mitochondrial dysfunction - exacerbated by TOMM20 upregulation - and chronic inflammation activate pro-apoptotic

signaling in both cyst-lining epithelial cells and the surrounding parenchyma (18, 19, 20). This effect is magnified by the hyperactivation of mTOR and STAT3, which can paradoxically drive both proliferation and apoptosis depending on context. Sustained apoptotic signaling compromises epithelial integrity, accelerates nephron loss, and creates a pro-cystic, fibrotic microenvironment (18).

Ferroptosis, a distinct form of regulated cell death, is driven by iron-dependent lipid peroxidation. In PKD, cystic epithelial cells exhibit impaired antioxidant defenses - chiefly due to GPX4 downregulation, which limits their ability to neutralize lipid hydroperoxides (15, 16, 20). Mitochondrial dysfunction and sustained ROS production further shift the cellular redox balance toward ferroptosis. Recent studies indicate that ferroptosis plays a key role not only in acute kidney injury but also in chronic kidney diseases like PKD, where it triggers inflammation and may even initiate necroptosis (20, 21). Notably, suppression of ferroptosis can increase susceptibility to apoptosis or necroptosis, revealing a compensatory network among these death pathways (21).

Necroptosis, an inflammatory and regulated form of necrosis, is mediated by RIPK1, RIPK3, and the executioner MLKL. In renal tubule cells, it typically arises from sustained injury such as chronic crystal exposure, ischemia, or unresolved inflammation (22, 23). Unlike apoptosis, necroptosis leads to membrane rupture and the release of damage-associated molecular patterns (DAMPs), which intensify inflammation, attract immune cells, and amplify tissue damage. In both acute and chronic kidney models, necroptosis sustains a destructive cycle of inflammation and fibrosis that promotes cyst expansion and renal decline (22, 23). Inhibiting necroptosis experimentally has been shown to increase apoptosis, again highlighting the adaptive interplay among these cell death mechanisms (23).

Together, apoptosis, ferroptosis, and necroptosis shape the renal response to crystal-induced stress in PKD. Their dysregulation accelerates cystogenesis, inflammation, fibrosis, and renal failure. Clarifying how upstream events - such as STAT3 hyperactivation, E-cadherin loss, and GPX4 suppression - modulate these pathways may uncover therapeutic strategies aimed at preserving nephron integrity and halting disease progression (3, 20, 22).

Proliferative Signaling and Cancer Parallels

A key discovery in PKD research is the striking overlap between the molecular pathways driving cystic epithelial proliferation and those fueling tumorigenesis in cancer. Both diseases exhibit a breakdown in growth regulation, resulting in uncontrolled cell proliferation, loss of differentiation, and extensive tissue remodeling. This convergence stems from a shared dependence on conserved signaling networks that, when dysregulated, transform healthy tissue architecture into either cystic or neoplastic lesions (24, 25).

At the center of this network is the mammalian target of rapamycin (mTOR) pathway. In PKD, disrupted PC1/PC2 signaling causes chronic mTOR activation, promoting protein synthesis, cell growth, and proliferation in cyst-lining epithelial cells (26). This role closely mirrors mTOR's oncogenic function in many cancers, where its overactivation marks malignant transformation and disease progression. The MAPK/ERK cascade is similarly upregulated in PKD, often due to dysregulated cAMP, calcium, and B-Raf/Src signaling. Typically activated by growth factors like

EGF, this pathway drives cell cycle progression in cancer and contributes to the hyperproliferative phenotype of cystic epithelia (19, 26).

Notch signaling, widely implicated in both development and cancer, is also pathologically activated in PKD. Notch3 is consistently upregulated in cyst-lining cells and correlates with proliferative markers such as PCNA in both mouse models and human PKD tissue. Inhibition of this pathway reduces cyst burden and cellular proliferation, highlighting its critical role in cystogenesis and its mechanistic parallels to cancer (25). Additional developmental pathways - including Wnt/β-catenin and Hedgehog - are similarly co-opted, reinforcing the notion that cystic epithelia adopt a dedifferentiated, invasive, and proliferative phenotype reminiscent of neoplastic transformation (24).

These mechanistic parallels carry therapeutic significance. Inhibitors of mTOR, MAPK/ERK, Notch, and other proliferative pathways have shown efficacy in preclinical PKD models, echoing their use in oncology (25, 26). This translational overlap between PKD and cancer not only deepens our understanding of cystic disease but also accelerates therapeutic innovation. The convergence of these signaling pathways underscores the utility of applying oncologic frameworks to PKD and confirms that the cellular mechanisms underlying cyst expansion mirror those driving tumor growth. This insight supports ongoing efforts to repurpose anti-cancer strategies as treatments for PKD, offering a promising path to slow disease progression and preserve kidney function (24, 25).

Potential Therapeutic Interventions

Advances in understanding the molecular pathways driving PKD - particularly the roles of crystal-induced injury, proliferative signaling, and cell death - have ushered in a new era of targeted therapeutic development. The most established disease-modifying treatment to date is tolvaptan, a vasopressin V2 receptor antagonist. By inhibiting vasopressin-mediated cAMP production, tolvaptan suppresses cyst epithelial proliferation and fluid secretion, significantly slowing cyst growth and preserving kidney function in adults with autosomal dominant PKD (ADPKD) who are at risk for rapid progression (27, 28). In addition to pharmacologic treatment, supportive strategies such as increased water intake to reduce endogenous vasopressin and careful blood pressure management remain foundational to delaying disease progression (27).

Beyond vasopressin antagonism, several promising therapies are under investigation. Somatostatin analogues inhibit cAMP signaling and have shown potential to reduce cyst burden. Inhibitors of the mTOR and MAPK/ERK pathways - key drivers of proliferation in both PKD and cancer - are being evaluated in preclinical and early clinical trials (26, 29). Other investigational drugs target tyrosine kinase receptors (such as EGFR and Src), NF-κB, and epigenetic regulators, reflecting a shift toward precision medicine and pathway-specific intervention. Many of these strategies leverage mechanistic parallels between PKD and cancer, enabling researchers to repurpose oncology drugs for cystic kidney disease (24).

The most innovative frontiers in PKD therapy lie in gene and molecular interventions. Approaches currently in preclinical or early clinical development include CRISPR-Cas9 gene editing, antisense oligonucleotides targeting pathogenic microRNAs (such as miR-17), and gene delivery systems designed to restore or enhance PKD1/PKD2 function (30). In parallel, small molecules aimed at stabilizing mitochondrial function, protecting against ferroptosis through

GPX4 activation, or modulating the STAT3 → Cadherins → GPX4 axis are being actively explored. Additionally, advances in understanding extracellular vesicles as biomarkers and therapeutic delivery vehicles may enhance disease monitoring and treatment specificity (31).

Although kidney replacement therapies - including dialysis and transplantation - remain essential for patients with end-stage disease, the expanding pipeline of targeted and molecular treatments offers real hope for altering the natural history of PKD. Integrating insights from cancer biology, cell death regulation, and crystal-induced injury is accelerating the translation of bench research into clinical practice. With continued interdisciplinary collaboration and active patient participation in clinical trials, the future of PKD therapy is increasingly promising—offering the potential not just to slow, but eventually to halt or reverse cystic progression (27, 31, 32).

Conclusion

Polycystic kidney disease is now recognized as a multifactorial disorder driven by the interaction of genetic mutations, metabolic imbalances, and environmental insults - particularly crystal-induced injury. Disease initiation begins with the accumulation of CaOx and phosphate crystals in renal tubules, a process accelerated by metabolic abnormalities inherent to PKD. These crystals cause mechanical disruption, impair mitochondrial homeostasis, and activate oxidative and inflammatory signaling pathways. The result is an unstable epithelial environment characterized by increased TOMM20 expression, elevated ROS, and NLRP3 inflammasome activation - setting the stage for tissue remodeling and cyst formation.

This early injury converges on key molecular pathways that drive disease progression. Persistent STAT3 activation - stimulated by upstream signals such as EGF/EGFR, Src kinase, and integrin α6β4 - induces transcriptional changes that impair cell adhesion and polarity. E-cadherin downregulation compromises epithelial integrity and promotes EMT, while reduced GPX4 expression increases susceptibility to ferroptosis, especially within the kidney's oxidative microenvironment. Simultaneously, activation of the mTOR, MAPK/ERK, and Notch pathways fuels unchecked proliferation, loss of cellular differentiation, and cyst expansion. These molecular mechanisms strongly parallel those found in cancer biology, reinforcing the view of PKD as a neoplastic-like condition and validating the use of oncologic models to understand and treat the disease.

The downstream effects of these intersecting pathways are severe. Dysregulated cell death - including apoptosis, ferroptosis, and necroptosis - drives nephron loss and cyst enlargement while perpetuating chronic inflammation and fibrosis, hastening renal function decline. Yet, these insights have opened new therapeutic possibilities. The introduction of tolvaptan and other pathway-specific inhibitors represents a significant advance in clinical management. Meanwhile, emerging gene-editing and molecular therapies targeting the STAT3 → Cadherins → GPX4 axis, mitochondrial function, and regulated cell death offer the potential for more durable interventions. As research continues to integrate cancer-based frameworks into PKD biology and clinical trials broaden the treatment landscape, the future for PKD patients grows increasingly hopeful. Multidisciplinary collaboration and sustained patient engagement will be essential to translating these scientific breakthroughs into clinical success - redefining PKD from a relentlessly progressive condition into one that is manageable, and potentially curable.

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