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REVIEW ARTICLE

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Role of renal tubular programed cell death in diabetic kidney disease

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Abstract

The pathogenic mechanism of diabetic kidney disease (DKD) is involved in various functions; however, its inadequate characterisation limits the availability of effective treatments. Tubular damage is closely correlated with renal function and is thought to be the main contributor to the injury observed in early DKD. Programed cell death (PCD) occurs during the biological development of the living body. Accumulating evidence has clarified the fundamental role of abnormalities in tubular PCD during DKD pathogenesis. Among PCD types, classical apoptosis, autophagic cell death, and pyroptosis are the most studied and will be the focus of this review. Our review aims to elucidate the current knowledge of the mechanism of DKD and the potential therapeutic potential of drugs targeting tubular PCD pathways in DKD.

KEYWORDS

apoptosis, autophagy, diabetic kidney disease, programed cell death, pyroptosis, review

Xiaojun Zhou and Chunmei Xu have contributed equally to this work and share first authorship.

1 | INTRODUCTION

Normal kidney structure and function involve the coordination of several different cell types, such as tubular epithelial cells, endothelial cells, mesangial cells, and podocytes. Renal tubules are the prominent executors of reabsorption and comprise four major segments, the proximal tubule, Henle's loop, the distal tubule, and the collecting duct (Figure 1). Each segment consists of a layer of epithelial cells specifically suitable for exerting unique transport functions. The proximal tubule maintains blood glucose levels and metabolic balance by reabsorbing filtered glucose to produce new glucose.[1] Tubular epithelial cells (TECs) are the most common cell type in renal tubule and perform various regulatory functions under different pathophysiological conditions.

Diabetic kidney disease (DKD) is the principal cause of the end-stage renal disease (ESRD) and has become a public issue that seriously threatens human health. In recent years, although the development of clinical therapies for DKD has made considerable advances, the progression of DKD still cannot be effectively controlled, and its exacerbation of renal failure needs urgent attention.[2] When the kidney is exposed to a high glucose (HG) environment, TECs are the initial site of injury and are vulnerable to metabolic disturbances that can induce oxidative stress and the secretion of a variety of cytokines,[3,4] which contribute to interstitial inflammation and renal fibrosis. Considering the initial site of injury, renal tubules are regarded not only as a target tissue that suffers from injury but also as a driving force for the induction of kidney diseases.[5]

2 | TUBULAR INJURY PRECEDES GLOMERULAR ABNORMALITY IN DKD

The traditional theory of DKD pathogenesis emphasises that the glomerulus acts as the major renal compartment where the injury is induced by hyperglycaemia, whereas tubulo-interstitial injury is a secondary or later lesion. During the last decade, the significance of tubulopathy in early DKD has been increasingly recognised as a critical component of DKD progression.

Microalbuminuria is considered an early diagnostic marker for DKD that can regress or remain unchanged, indicating the limitation of glomerular damage in predicting renal function in DKD.[6] Other evidence from urinary biomarker data indicates that proximal tubular injury contributes primarily rather than secondarily to early DKD in human beings.[7] Tubular damage markers appear before microalbuminuria in early DKD.[8,9] In turn, accumulative proteinuria stimulates inflammatory responses and oxidative stress in TECs, contributing to changes in TECs morphology and function, epithelial-mesenchymal transition, epithelial cell detachment, and apoptosis. Exfoliation and apoptosis of TECs ultimately result in renal fibrosis and ESRD occurrence and progression.[10]

Owing to emerging evidence supporting a role for tubular injury in DKD, interest has shifted to the proximal tubule, which may function as an initiator, driver, or contributor in the early pathogenesis of kidney disease under diabetic conditions. Diabetic tubulopathy is a real entity that may possess separate pathophysiology from other renal lesions. The mechanisms underlying tubular injury in DKD are complex, and understanding the mechanisms of tubular damage could contribute to new therapeutic interventions for DKD. Therefore, the purpose of this review is to briefly summarise the current knowledge of the pathogenesis of DKD caused by TEC damage from the perspective of programed cell death (PCD) and offer a comprehensive update of therapeutic strategies targeting tubular death in DKD.

3 | CELL DEATH UNDER NORMAL AND ABNORMAL CONDITIONS

Programed cell death (PCD) occurs during the biological development of an organism. When a cell is subjected to stimuli from internal and external environments, the protective behaviours of PCD are

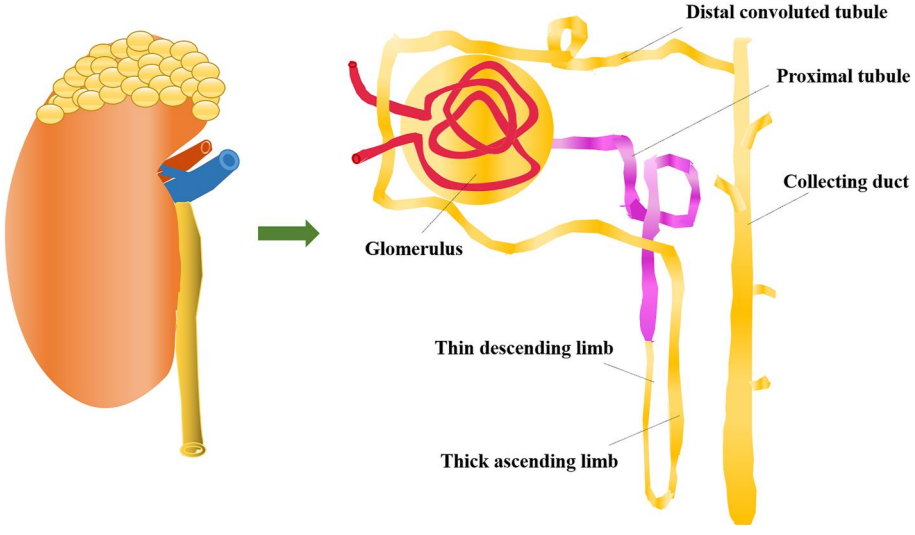

FIGURE 1 Normal kidney structure

initiated to remove injured cells. The Nomenclature Committee on Cell Death (NCCD) uncovered 12 distinct cell death types and execution modes in 2012.[11] Among these PCD types, classical apoptosis, autophagic cell death, and pyroptosis are the most studied cell death modes relevant to the topic of this review. The differences between the three cell death types are displayed in Table 1, and in this section, the characteristics and biological functions of these forms of PCD are discussed.

Apoptosis was first described by Kerr and Wyllin in 1972[12] as a physiological and programed suicidal behaviour of cells. When exposed to certain endogenous and exogenous stimuli, cells receive the apoptotic signal, and then apoptotic regulatory molecules interact with each other to activate the cell death pathway. This is accompanied by the activation of proteolytic enzymes, including caspase-9 and caspase-3, and programed apoptosis and continuous reactions occur under the control of specific genes.

Autophagy was described by Duve and Wattiaux, who discovered lysosomes in 1966.[13] When confronted with abnormally stimulated factors, such as external and internal stimuli including tissue damage and oxidative stress, normal cells induce autophagy; proteins and organelles are encased in autophagic vesicles that are transported into lysosomes for degradation, resulting in inflammation and dysfunction.

Pyroptosis was first described by Cookson and Brennan in 2001[14] as a novel type of PCD when cells are exposed to classical microbial infection. The execution of its function primarily relies on caspase-1, which is accompanied by the release of several pro-inflammatory factors. Pyroptosis is widely implicated in infectious, atherosclerotic, and nervous system diseases, whereas pyroptosis is relatively infrequent in DKD onset and development.

The cell death modes of renal tubular epithelial cells under HG are summarised in Figure 2, and the specific contents of pathogenic mechanism of renal tubular epithelial cells in DKD will be elaborated in the next part.

4 | APOPTOSIS OF RENAL TUBULAR CELLS IN DKD

Under normal conditions, apoptosis and cell division maintain the total number of cells in the human body. In DKD, many factors can attack cells and promote stronger apoptosis in cells than proliferation, leading to structural changes, including tubular atrophy and tubulointerstitial fibrosis and aggravating renal function failure. Accumulating evidence confirm the fundamental role of TEC apoptosis in DKD pathogenesis. Apoptotic cells have been discovered in the tubular epithelium of human and experimental diabetic kidneys,[15,16] demonstrating that apoptosis may participate in the loss of tubular cells in DKD. Studies have revealed that apoptosis is associated with decreased Bcl-2 expression and increased Bax protein expression.[17,18] Apoptosis of TECs is not only a significant characteristic of DKD but also a reliable predictor and hallmark of DKD.[19] Hence, elucidating the mechanism of tubular apoptosis and targeting TEC apoptosis may be beneficial in treating DKD.

4.1 | Mitochondrial damage is involved in TEC apoptosis

Apoptosis is commonly caused by mitochondria-related pathways. Under normal conditions, the dicarboxylate carrier (DIC) and 2-oxoglutarate carrier (OGC) act as principal membrane carriers and mediate the transport of glutathione to the mitochondrial matrix. However, stable upregulation of DIC and OGC in DKD promotes a reduction in mitochondrial nephrotoxic S-(1,2-dichlorovinyl)-L-cysteine-induced apoptosis in TECs.[20] Furthermore, HG-induced apoptosis in the HK-2 human proximal tubular cell line, which manifested as the upregulation of fragmented DNA and apoptosis molecules in the cells.[21] Moreover, sirtuin-1 (SIRT1) is

TABLE 1 Summary of three programed cell death types, including classical apoptosis, autophagy, and pyroptosis

Types	Initially proposed	Morphological characteristics	DNA damage	Key genes involved	Regulatory pathways	Reference
Apoptosis	In 1972 by Kerr, Wyllie, and Currie	Cell shrinkage, membrane blebbing but preserved initially, phosphatidylserine externalisation, nuclear condensation	√	Caspase-1, caspase-3/6/7, caspase-8/9/10, Fas, Bcl2, cytochrome C, p53	Mitochondrial pathway, death receptor pathway, endoplasmic reticulum pathway	[12]
Autophagy	In 1966 by Christian de Duve	Three distinct cellular processes—macroautophagy(cell are enclosed in double-membrane vesicles referred to as autophagosomes.), microautophagy and chaperone-mediated autophagy	×	ATG-3/5/7, LC3 II, beclin 1, vps34	mTOR, AMPK, cAMP-dependent PKA signalling, JNK2, TLR4 signalling	[13]
Pyroptosis	In 2001 by Cookson and Brennan	Rapidly lose cell membrane integrity, increase in size, and have smaller nuclei	√	Caspase-1, gasdermin D (GSDMD), caspase-11/4/5, NLRP3, ELAV1	Inflammasome, IL-1β, damage-associated molecular patterns	[14]

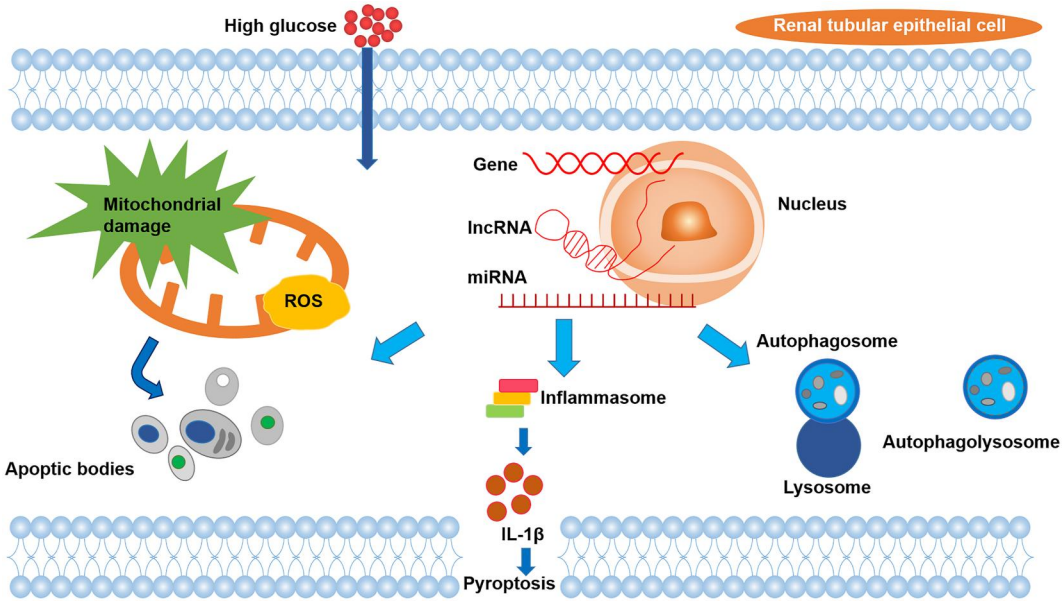

FIGURE 2 Cell death of renal tubular epithelial cells under high glucose

involved in tubular apoptosis in DKD by regulating mitochondrial function.[22]

4.2 | HG increases apoptosis in TECs through enhanced reactive oxygen species generation

Enhanced oxidative stress caused by increased reactive oxygen species (ROS) production promotes apoptosis in proximal tubular epithelial cells (PTECs) through multiple caspase pathways.[23] In addition to caspase signalling pathways, ROS can contribute to the activation of NF-κB under hyperglycaemic conditions, which mediates the induction of apoptosis.[24] Another study revealed that MAPK/NF-κB activation is involved in HG-induced tubular dysfunction and apoptosis in DKD.[25] The interaction between thioredoxin-interacting protein (TXNIP) and thioredoxin (TRX) is a vital regulatory mechanism in DKD progression.[26] Forkhead box protein O1 (FOXO1)/TXNIP-TRX plays a productive role in activating HG-mediated tubular apoptosis by alleviating ROS generation, which may provide new insights into therapeutic targets for DKD pathogenesis.[27] Furthermore, the role of SIRT1 in inhibiting oxidative stress and protecting kidney cells from apoptosis was revealed by Dong et al.[22]

The generation of peroxynitrite (ONOO-), a powerful oxidant, was augmented in PTECs, which further contributed to caspase-mediated apoptosis, whereas ebselen, a scavenger of ONOO-, prevented PTECs from HG-induced apoptosis, indicating that ONOO- is a proapoptotic ROS implicated in early DKD.[23] Overexpression of catalase, an enzyme involved in ROS generation in PTECs, was also shown to mitigate tubular apoptosis in db/db mice.[15] These studies indicate the vital role of ROS in TEC apoptosis in DKD.

4.3 | Small non-coding RNAs mediate TEC apoptosis in DKD

Among the transcribed human genomes, only 2% of the transcripts code for proteins, whereas others are known as non-coding RNAs. Small non-coding RNAs (sncRNA) are a kind of non-coding RNAs that contain about 21 nucleotides and function to induce mRNA cleavage and inhibit the translation of target mRNAs.[4] Different sncRNAs execute various functions during TECs damage. Research studies showed that inhibiting the expression of miRNA, such as miR-218[28] and miR-125b,[29] could mitigate tubular damage and achieve a reduction in TEC apoptosis. Furthermore, inhibition of microRNA-148b-3p can reduce TEC apoptosis by suppressing tumour necrosis factor receptor 2 (TNFR2).[30] In contrast, the upregulation of miR-140-5p suppressed the Toll-like receptor 4 (TLR4)/NF-κB signalling pathway and inhibited apoptosis in TECs.[31] Additionally, upregulation of miR-25 could improve HG-induced PTEC apoptosis by activating the PTEN/AKT pathway in DKD.[32]

4.4 | Other molecules and signalling pathways involved in TEC apoptosis in DKD

Other potential molecules and related pathways that participate in tubular apoptosis during DKD development are summarised in Table 2. Studies have shown that the apoptosis of TECs is tightly correlated with a decrease in full-length cell adhesion molecule 1,[33] 3-hydroxy-3-methylglutaryl reductase degradation protein,[34] electron transfer flavoprotein β,[35] C-X-C chemokine receptor type 4,[36] vitamin D,[37] autophagy protein 5 (Atg5),[2] netrin-1,[38] stearoyl-CoA desaturase-1,[39] Rap1b,[40] and mitoQ,[41] which further exacerbate

TABLE 2 Other molecules and signalling pathways are involved in TECs apoptosis in the development of DKD

Molecule	Role in TECs apoptosis	Regulatory mechanism	Reference
FL-CADM1	Decrease of FL-CADM1 induced tubular apoptosis	Exacerbated renal tubular injuries in the development of DKD	33
HRD1	Upregulation of HRD1 alleviated the apoptosis of TECs	Inducing the ubiquitination and degradation of eIF2α in DKD	34
ETFβ	Decreased expression of ETFβ was associated with TECs apoptosis in DKD	Promoted renal injury in DKD	35
CXCR4	Upregulation of CXCR4 blocked apoptosis of renal tubule cells in DKD	Inhibiting SDF-1- augmented phosphorylation of the pro-survival kinase in DKD	36
Vitamin D	Blockade of vitamin D metabolism was involved in tubular apoptosis	Loss of function during DKD	37
Atg5	Suppression of Atg5 in GECs apoptosis of TECs	Increased proteinuria in DKD	2
Netrin-1	Overexpression of netrin-1 suppressed TECs apoptosis in DKD	Suppression of COX-2/PGE2 pathway in DKD	38
SCD1	SCD1 protected TECs from apoptosis	Increasing the production of lipid droplet and inhibiting ER stress in DKD	39
Rap1b	Rap1b ameliorated tubular apoptosis	Modulation of C/EBP-β/PGC-1α signalling in DKD	40
MitoQ	MitoQ protected against HG-induced TECs apoptosis	Suppressing Nrf2/PINK signalling in DKD	41
Nox4	Upregulation of Nox4 mediated TEC apoptosis	Controlling Notch pathway and contributed to TECs injury in DKD	36
CYP24A1	Increased activity of CYP24A1 leads to apoptosis of TECs in DKD	Increasing expression and activation of caspase-3 during progression of DKD	37
Agt	Overexpression of Agt promoted TEC apoptosis	Renin-angiotensin system blocker inhibited the apoptosis of TECs in DKD via upregulating ACE2 expression	42
PRMT1	PRMT1 induced TECs apoptosis	Activating PERK and ATF6 which exerted regulatory function in ER stress	43
ANG II	ANG II induced TECs apoptosis	Binding AT1 and AT2 receptors, accompanied with the increased generation of TGF-β, and upregulation apoptotic factors such as Fas, FasL, and Bax under HG ambience	44
Calpain 10	Inhibition of expression in mitochondrial calpain 10 promoted TECs apoptosis	Activation of cleaved procaspase 3	45
MIOX	MIOX mediated the abnormal apoptosis of TECs	Inhibition of PINK	46
AGEs	AGEs enhanced apoptosis of TECs	Lowering the klotho expression and elevating HAVCR1 production in DKD	47
Bim	Overexpression of Bim contributed to the initiation of TECs apoptosis	Controlling the transcript factors FOXO3A and FOXO1 under HG condition	48
AOPPs	AOPPs induced TECs apoptosis	Activating CD36/β-Catenin pathway in DKD	49
p66Shc	The activation and phosphorylation of p66Shc aggravated the apoptosis of TECs	Enhancing Mfn1-Bak interactions under HG	50

(Continues)

TABLE 2 (Continued)

Molecule	Role in TECs apoptosis	Regulatory mechanism	Reference
Uric acid	The high level of uric acid increased the permissiveness of TECs to apoptosis	Triggering NADPH oxidase signalling pathway and URAT1 transport in DKD	51
Oxidised lipoproteins	Promoted tubular apoptosis	Upregulating NADPH oxidase-mediated ROS production and increased pro-inflammatory factors levels, such as IL-6 and TNF-α, which were secreted by TECs	52

Abbreviations: ACE2, angiotensin-converting enzyme 2; AGEs, advanced glycation end-products; Agt, angiotensinogen; ANG II, angiotensin II; AOPPs, advanced oxidation protein products; AT1, ANG II type 1; AT2, ANG II type 2; ATF6, activating transcription factor 6; Atg5, autophagy protein 5; Bak, Bcl-2 homologous antagonist/killer; Bax, apoptosis regulator BAX; Bcl-2, bcl2-associated agonist of cell death; Bim, Bcl-2 interacting mediator; C/EBP-β, CCAAT/enhancer-binding protein beta; COX-2, cyclooxygenase-2; CXCR4, C-X-C chemokine receptor type 4; CYP24A1, cytochrome P450 family 24 subfamily A member 1; DKD, diabetic kidney disease; eIF2α, eukaryotic initiation factor; ER, endoplasmic reticulum; ETFβ, electron transfer flavoprotein β; FasL, Fas ligand; FL-CADM1, full-length cell adhesion molecule 1; FOXO1, forkhead box protein O1; FOXO3A, forkhead box protein O3a; GECs, glomerular endothelial cells; HAVCR1, hepatitis A virus cellular receptor 1; HG, high glucose; HRD1, 3-hydroxy-3-methylglutaryl reductase degradation protein; IL-6, interleukin-6; Mfn1, mitofusin-1; MIOX, myo-inositol oxygenase; Nox4, NADPH oxidase 4; Nrf2, NF-E2-related factor 2; PERK, protein kinase R-like ER kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGE2, prostaglandin E2; PINK, PTEN-induced putative kinase 1; PRMT1, protein arginine methyltranferase-1; Rap1b, ras-related protein Rap-1b; ROS, reactive oxidative species; SCD1, stearoyl-CoA desaturase-1; SDF-1, stromal cell-derived factor 1; TECs, tubular epithelial cells; TGF-β, transforming growth factor beta; TNF-α, tumour necrosis factor α; URAT1, solute carrier family 22 member 12.

renal tubular injuries during the development of DKD. Several studies have also reported potential molecules and mechanisms that promote TEC apoptosis. The upregulation of NADPH oxidase 4,[36] cytochrome P450 family 24 subfamily A member 1,[37] angiotensinogen,[42] protein arginine methyltranferase-1,[43] angiotensin II,[44] calpain 10,[45] myo-inositol oxygenase (MIOX),[46] advanced glycation end products (AGEs),[47] Bcl-2 interacting mediator (Bim),[48] advanced oxidation protein products,[49] p66Shc,[50] and high levels of uric acid[51] and fatty acids[52] can lead to TEC apoptosis in DKD. The exact mechanism and the role of TEC apoptosis during the development of DKD remain active areas of the study.

4.5 | Pharmacological effects on TEC apoptosis in DKD

Understanding the mechanisms underlying TECs apoptosis and investigating its therapeutic targets are vital for the prevention of tubular injury and failure that are associated with DKD. The pharmacological effects of various drugs on TEC apoptosis are summarised in Table 3. AGEs promote apoptosis in tubular cells,[47] which are disrupted by treatment with irbesartan.[53] Metformin has been reported to play a vital role in the prevention of tubular injury in DKD. Ishibashi et al. revealed that metformin blocked AGE-induced PTECs apoptosis by activating AMP-activated protein kinase (AMPK) and inhibiting ROS generation by downregulating advanced glycation end product receptor (RAGE) expression.[54] Furthermore, the nephroprotective benefits of combination of metformin and irbesartan in patients with DKD were also observed.[54]

The deterioration of apoptosis is caused by glucose overload in the kidneys. The SGLT2 inhibitors, tofogliflozin and empagliflozin, have anti-apoptotic properties and protect against tubular injury in DKD by inhibiting the glycer-AGE/RAGE axis.[55] Additionally, dapagliflozin, the first approved SGLT2 inhibitor for the treatment of T2DM, was reported to alleviate tubular apoptosis and injury in DKD.[56] Liraglutide, a human incretin GLP-1 analogue, was shown to prevent apoptosis in DKD rats by increasing GLP-1R expression.[57] Finally, the c-peptide cleavage product of pro-insulin and insulin exhibited a protective potential in DKD by reducing tumour necrosis factor α (TNF-α)-induced apoptosis by activating NF-κB.[58]

In addition to these antihyperglycemic therapies, lipid-reducing drugs can reverse tubular damage in DKD. Pravastatin blocked AGE-induced apoptosis in PTECs by inhibiting geranylgeranyl pyrophosphate generation, indicating that the protective effect of pravastatin on the DKD tubule occurs by disrupting the AGE/RAGE axis.[59] Moreover, taurine, an amino acid that exerts antioxidant properties, alleviates HG-induced PTEC apoptosis through the suppression of ROS, suggesting that it is a potential therapeutic target for DKD.[18]

In addition to chemical compounds, traditional Chinese medicine (TCM) and natural compounds have also shown the protective role of DKD tubules. Methylglyoxal, a metabolite of glucose metabolism, was implicated in the pathogenesis of DKD through the formation of

TABLE 3 Pharmacological effects of drugs and therapy on the TECs apoptosis and autophagy

Drug or therapy	Introduction	Pharmacological effects on the TECs damage	Regulatory pathway and involved mechanism	Author and year
Metformin	Antihyperglycemic drug by activation of AMPK	Block AGEs-induced human PTECs apoptosis in vitro	Activation of AMPK and inhibiting the generation of ROS	Ishibashi et al. in 2012 [54]
Liraglutide	Antihyperglycemic drug as human incretin GLP-1 analogue	Ameliorate of renal tubular apoptosis in STZ-induced rats and human PTECs apoptosis	Increase in GLP-1 receptor expression	Zhao et al. in 2015 [57]
Tofogliflozin	Antihyperglycemic drug as SGLT2 inhibitors	Prevent AGEs-elicited apoptosis of HG-exposed human PTECs in vitro	Inhibition of the glycer-AGE/RAGE axis and oxidative stress	Ishibashi et al. in 2016 [55]
Dapagliflozin	Antihyperglycemic drug as SGLT2 inhibitors	Alleviate the tubular apoptosis in Fr-STZ-induced diabetes in rats	Unknown	Oraby et al. in 2019 [56]
C-peptide	A cleavage product originated from pro-insulin and insulin	Reduce the TNF-α-induced apoptosis of opossum kidney PTECs	Activation of NF-κB	Al-Rasheed et al. in 2006 [58]
Pravastatin	Lipid-lowering drug	Block the AGEs-induced human PTECs apoptosis	Disrupt the AGEs/RAGE axis via inhibition of geranylgeranyl pyrophosphate generation	Ishibashi et al. in 2012 [59]
Taurine	An amino acid	Alleviate HG-induced human PTECs apoptosis	Through anti-oxidation and suppression of oxidative stress	Verzola et al. in 2002 [18]
Baicalin and chrysin mixture	Natural compounds of traditional Chinese medicine	Methylglyoxal-induced rat TECs apoptosis and n STZ-induced diabetic rats	Unknown	Singh et al. in 2017 [61]
Akebia saponin D	Ingredients of herb, Dipsaci Radix	Ameliorate the apoptosis of human TECs and STZ-induced diabetic mice	Activation of Nrf2/HO-1 and inactivation of NF-κB pathway	Lu et al. in 2020 [63]
Apigenin	A natural compound extracted from fruits and vegetables	Disrupt human TECs apoptosis	Increase the expression of Nrf2 and HO-1	Zhang et al. in 2019 [64]
Astragaloside IV	An active component in the medicinal plant Astragalus membranaceus	Alleviate ER stress-induced TECs apoptosis of STZ-induced diabetic rats	Suppression the p-PERK, ATF4 and CHOP	Ju et al. in 2019 [65]
Anthocyanins	Natural phenols present in numerous fruits and vegetables	Suppress human TECs apoptosis in vitro and tubular apoptosis in db/db mice in vivo	Increase thioredoxin 2 expression and the biological activity of thioredoxin	Wei et al. in 2018 [66]
Erianin	A major bibenzyl present in D. chrysotoxum	Protect rat TECs against apoptosis	Inhibit activation of JNK/p38-MAPK and NF-κB signalling	Chen et al. in 2019 [67]
Sulodexide	A highly purified glycosaminoglycan	Inhibit TECs apoptosis of STZ-induced rats	Upregulate the expression of klotho	Liu et al. in 2017 [47]
Resveratrol	SIRT1 activator	Attenuate human TECs apoptosis and STZ-induced rats	Increase SIRT1 expression	Wang et al. in 2016 [21]
Hepatocyte growth factor	A type of growth factor	Inhibit human PTECs apoptosis	Reduction in the expression of TGF-β1	Mou et al. in 2010 [68]
Genipin	Inhibitor of UCP2	Exacerbate rat TECs apoptosis	Downregulation of UCP2	Chen et al. in 2014 [69]
Combination of prostaglandin E1 and ACE inhibitor	Combination treatment	Decrease the apoptosis of tubule in DKD rats	Unknown	Mou et al. in 2018 [70]
Prostaglandin E1	A 20-carbon unsaturated fatty acid	Protect PTECs against HG-apoptosis in DKD rats and human PTECs	Inhibit JNK/Bim signalling pathway	Zhang et al. in 2020 [72]
Calcium dobesilate	A vascular protective compound of TCM	Prevent human PTECs from HG-induced apoptosis	Inhibit the Bim expression	Cai et al. in 2017 [73]

(Continues)

TABLE 3 (Continued)

Drug or therapy	Introduction	Pharmacological effects on the TECs damage	Regulatory pathway and involved mechanism	Author and year
Salidroside	An active component isolated from *Rhodiola rosea*	Suppress the PTECs apoptosis in DKD rats and human PTECs	Suppress the Bim expression	Guo et al. in 2018 [74]
Experimental knockout of SGLT2	Inhibition of SGLT2	Upregulate autophagic flux	Enhance activation of SIRT1 and AMPK	Packer et al. in 2020 [90]
Fenofibrate	A fibric acid derivative	Induce TECs autophagy in high-fat diet-fed mice	AMPK activation and upregulation of FAO enzymes	Sohn et al. in 2017 [93]

Abbreviations: ACE, angiotensin converting enzyme; AGEs, advanced glycation end products; AMPK, adenosine monophosphate activated protein kinase; ATF4, activating transcription factor 4; Bim, Bcl-2 interacting mediator; CHOP, C/EBP-homologous protein; ER, endoplasmic reticulum; FAO, fatty acid oxidation; Fr, fructose; GLP-1, glucagon-likepeptide-1; HG, high glucose; HO-1, hemeoxygenase-1; JNK, c-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; Nrf2, nuclear factor erythroid-2 related factor 2; p-PERK, phospho-protein kinase R-like ER kinase; PTECs, proximal tubular epithelial cells; RAGE, advanced glycation end product receptor; ROS, reactive oxygen species; SGLT2, sodium-glucose co-transporter 2; SIRT1, sirtuin-1; STZ, streptozotocin; TCM, traditional Chinese medicine; TGF-β1, transforming growth factor β1; TNF-α, tumor necrosis factor α; UCP2, uncoupling protein-2.

AGEs.[60] In contrast, baicalin and chrysin were shown to have a protective effect against methylglyoxal-induced TEC apoptosis in DKD.[61] Akebia saponin D (ASD) is found in the herb Dipsaci Radix and possesses various pharmacological effects.[62] Lu et al. revealed that ASD ameliorated apoptosis in DKD mice by activating NF-E2-related factor 2 (Nrf2)/hemeoxygenase-1 (HO-1) and inactivating the NF-κB pathway.[63] Furthermore, apigenin, a natural compound extracted from vegetables, was shown to disrupt TEC apoptosis and exert beneficial effects on HG-induced renal injury by increasing the expression of Nrf2 and HO-1.[64] Astragaloside IV (AS-IV) is an active component of the medicinal plant *Astragalus membranaceus* that alleviates apoptosis induced by endoplasmic reticulum (ER) stress by suppressing phosphorylated protein kinase R-like ER kinase, activating transcription factor 4 and C/EBP-homologous protein, indicating a novel theoretical application of AS-IV as a treatment for DKD.[65] Furthermore, anthocyanins, the natural phenols present in many fruits and vegetables, suppressed TEC apoptosis by increasing thioredoxin 2 expression and stabilising the biological activity of thioredoxin, indicating protective effects against TEC apoptosis in DKD.[66] Another study revealed that erianin, the major bibenzyl present in *Dendrobium chrysotoxum*, protects TECs against injury by ameliorating apoptosis by inactivating c-Jun N-terminal kinase (JNK)/p38-MAPK and NF-κB signalling, suggesting it has a protective role in DKD.[67] Liu et al. reported that sulodexide, a highly purified glycosaminoglycan, can also inhibit TEC apoptosis and prevent the progression of DKD by upregulating the klotho enzymes.[47] Treatment with resveratrol (RSV), a SIRT1 activator, significantly attenuated the expression of apoptosis indicators, which were further eliminated by *SIRT1* silencing, indicating a potential role for RSV in DKD through the upregulation of SIRT1.[21]

Research revealed that the application of hepatocyte growth factor could inhibit PTEC apoptosis and contribute to the prevention of tubular damage in an HG environment.[68] Furthermore, uncoupling protein-2 (UCP2), a mitochondrial membrane protein, has been implicated in tubular apoptosis. Genipin, an inhibitor of UCP2, exacerbated TEC apoptosis and was accompanied by caspase-3 activation, which revealed that UCP2 activation is a candidate target for DKD therapy.[69] Additionally, Mou et al. revealed that the apoptosis of tubules was significantly decreased by a combination of prostaglandin E1 and angiotensin-converting enzyme (ACE) inhibitors, which showcased the remarkable protective effect prostaglandin E1 and ACE inhibitors have on renal function in DKD.[70]

Zhang et al.[71] reported that different sulfonylurea compounds could mediate PTEC apoptosis by closing the K_{ATP} channel at different binding selectivity and reversibility. A therapeutic effect of gliclazide on the inhibition of PTEC apoptosis was also observed, which benefited the preservation of functional PTEC mass.[71]

In terms of Bim-mediated PTEC apoptosis, our team investigated a series of therapeutic drugs,[72–74] and their related mechanisms are summarised in Figure 3. By developing a DKD rat model and HG-treated PTECs in vitro, we found that prostaglandin E1 reduced the expression of JNK, Bim, Bax, and caspase-3 and prevented apoptosis in PTECs. Further application of a JNK activator and inhibitor indicated the nephroprotective role of prostaglandin E1 through the inhibition of the JNK/Bim signalling pathway.[72] We also revealed that TCM and the active components of herbs protected TECs from apoptosis; in addition to vascular protection, calcium dobesilate was shown to protect PTECs from HG-induced apoptosis by inhibiting Bim expression, suggesting its potential significance in DKD treatment.[73] Furthermore, salidroside isolated from *Rhodiola rosea* was also found to have therapeutic efficacy in DKD. These data showed that salidroside effectively suppressed tubular injury by inhibiting Bim-mediated PTEC apoptosis in DKD.[74]

5 | AUTOPHAGY OF RENAL TUBULAR CELLS IN DKD

Autophagy affects various renal cell types to maintain renal pathophysiology and homoeostasis in humans. Under normal conditions, functional cells can mitigate the oxidative and ER stresses produced in the diabetic kidney by promoting autophagic flux such that renal

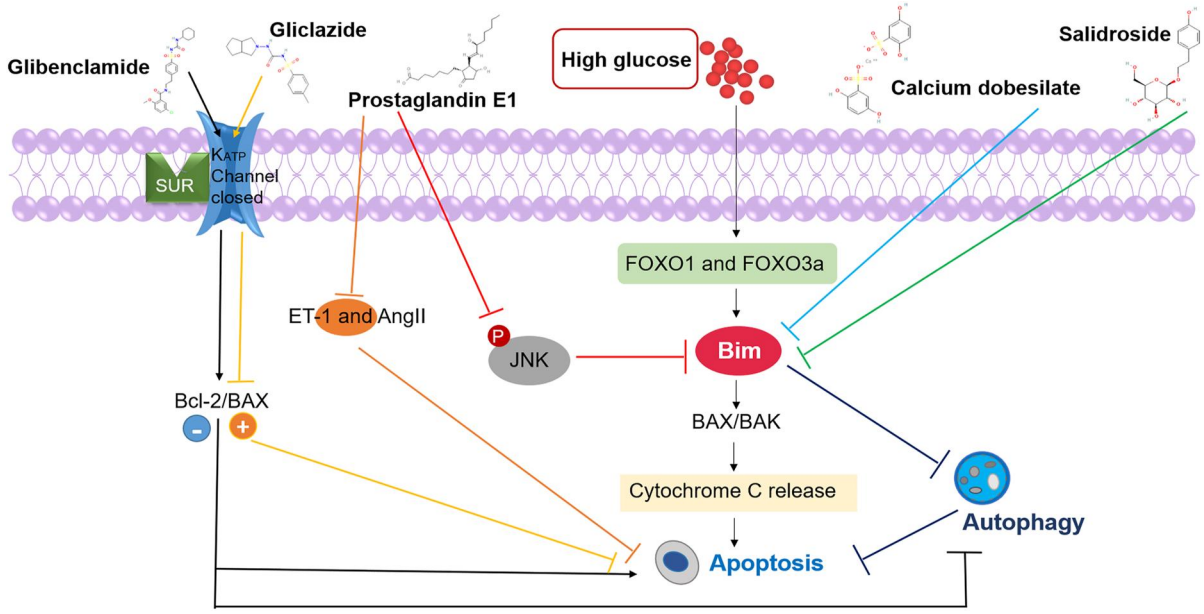

FIGURE 3 Pharmacological effects targeting Bim protein and related pathways on the TECs apoptosis and autophagy in DKD. High glucose induced the upregulation of transcription factors, FOXO1 and FOXO3a, and then Bim expression was increased and initiated BAX/BAK-mediated mitochondria-dependent apoptosis, which further inhibited the autophagy of TECs (black arrows in the middle). The inhibitory effect of prostaglandin E1 on the TECs apoptosis involved two pathways. On one hand, prostaglandin E1 reduced the ET-1 and Ang II levels to suppress the apoptosis (orange line). On the other hand, prostaglandin E1 attenuated high glucose-induced Bim expression by inhibiting phosphorylated JNK (red line). Calcium dobesilate exerted the protective function against TECs apoptosis by downregulating the expression of Bim (light blue line). Salidroside inhibited the apoptosis of TECs by targeting Bim protein (green line). Glibenclamide aggravated TECs apoptosis by inhibiting Bcl-2 and upregulating Bax and suppressed autophagy (black line on the left side). In contrast, the therapeutic effect of gliclazide on the inhibition of TECs apoptosis was achieved by increasing Bcl-2 expression and suppressing Bax expression (yellow line). The 2D structure of drug was acquired from PubChem database. TECs: tubular epithelial cells; ET-1: endothelin-1; Ang II: angiotensin II; JNK: c-Jun N-terminal kinase; FOXO1: forkhead box protein O1; FOXO3a: forkhead box protein O3a; Bim: Bcl-2 interacting mediator

tubules can sustain their structural and functional integrity.[75] Under adverse conditions, proximal tubular cells are exposed to multiple stimuli, including oxidative stress, ER stress, hypoxia, nutrient and energy depletion, and mitochondrial damage, which can all activate autophagy. The regulation of autophagy in renal tubular cells is reduced in diabetes, significantly contributing to the severity of the renal injury. Impaired autophagic activity is involved in the pathogenesis of DKD; therefore, the study of the mechanisms of renal tubular injury caused by abnormal tubular autophagy is a core area in the study of DKD tubulopathy. Mechanistic evidence of cellular autophagy was first proposed in a streptozotocin-induced diabetes rat model in the 1990s, which revealed that the number and volume of autophagic vacuoles were markedly reduced in the proximal tubules.[76,77] Improving tubular autophagy inhibited oxidative stress in TECs and ameliorated renal tubular injury in a diabetic mouse model.[78] These studies provide evidence that suggests a pivotal role for autophagy during cellular remodelling and renal tubule homoeostasis.

5.1 | Molecules and signalling pathways involved in TEC autophagy impairment in DKD

Liu et al.[79] reported that Atg5 deficiency in the proximal and distal tubules contributes to serious tubular injury and dysfunction. However, only distal tubules-specific-Atg5 knockout mice exhibited the integrity of renal function and maintenance of tubular structure.[79] These findings revealed that autophagy is crucial for the integrity of proximal tubule function. In contrast, distal tubules depend less on autophagy to maintain homoeostasis, presumably because their function requires minimal energy.

Jiang et al.[80] observed an increase in the expression of soluble epoxide hydrolase (sEH) and damaged autophagy flux in PTECs from db/db diabetic mice under HG conditions. The inhibition of sEH notably alleviated tubular damage injury and improved autophagic flux of PTECs in DKD, indicating that the suppression of sEH played a protective role in proximal tubular injury in DKD and that there is a potential capacity for targeting sEH-mediated TEC autophagy as a treatment of DKD.[80]

Under HG conditions, autophagy in HK-2 cells was promoted and accompanied by an increased expression of Beclin-1 and LC3 II, as well as serum and glucocorticoid-induced kinases (SGK1).[81] Inhibiting autophagy signalling using the SGK1 inhibitor GSK650394 protected PTECs against HG-induced injury by activating PI3K/AKT/mTOR signalling, demonstrating that SGK1 could act as an effective therapeutic target for DKD.[81] Evidence suggests that PI3K/AKT/mTOR signalling is part of the modulation of autophagy. The upregulation of KCa3.1 participated in tubular autophagy dysfunction in DKD through the activation of the PI3K/AKT/mTOR pathway.[82] In

contrast, the inhibition of PI3K/AKT/mTOR signalling initiated autophagic activity and protected against tubular epithelial injury.[83]

Wang et al. reported that HG promoted miR-155 expression in HK-2 cells, which was accompanied by the upregulation of p53 and the downregulation of SIRT1 and autophagy-associated proteins and suggested that p53/miR-155/SIRT1 signalling in the autophagic process may be vital in the pathogenesis of DKD renal tubular injury.[84]

Huang et al. demonstrated that the inhibition of mitophagy induces tubular injury via activation of TXNIP/mTOR/BCL2 interacting protein 3 signalling in DKD mice, and suppression of TXNIP effectively alleviates TEC autophagy and renal dysfunction in DKD.[85] In addition to the induction of aberrant apoptosis, Zhan et al.[86] found that increased MIOX expression was associated with defective autophagy in the tubules of diabetic mice. Inhibition of MIOX partially reversed autophagic abnormalities, indicating that MIOX contributes to the regulation of autophagy during DKD.[86]

5.2 | Other harmful factors that impair TEC autophagy in DKD

In addition to HG, obesity-mediated autophagic deficiency in DKD could be a vital factor evoking the vulnerability of PTEC under diabetic conditions. A study revealed that obesity-mediated autophagy impairment involves the induction of mTORC1 hyperactivation during renal tubular damage.[87] Moreover, oxidative stress provoked by AGE-RAGE interactions not only trigger the apoptosis of PTECs, but play a fundamental role in autophagic abnormalities. For example, AGEs induce lysosomal membrane permeabilisation and lysosomal dysfunction, contributing to autophagic inactivation in PTECs.[88]

The profibrogenic cytokine, transforming growth factor β1 (TGF-β1), is involved in renal dysfunction and progression of DKD. Research has shown that TGF-β1 stimulation in renal tubules promotes tubular autophagy and may represent a novel insight into tubular disruption in DKD.[89]

5.3 | Pharmacological effects that improve abnormal autophagy in TECs

The pharmacological influence on abnormal autophagy of TECs is also summarised in Table 3. The dominant drivers of autophagy that function as signalling molecules under nutrient deprivation include SIRT1, AMPK, and hypoxia-inducible factors (HIF-1α and HIF-2α), which play a protective role in increasing autophagic flux in the kidneys.[90] Under hyperglycaemic conditions, suppression of SIRT1 and AMPK significantly decreases autophagic flux in tubules and renal injury deterioration.[91] Additionally, SGLT2 downregulation helps reduce glomerular filtration pressure by suppressing proximal reabsorption of glucose. Research has shown that the experimental knockout of SGLT2 in PTECs upregulates autophagic flux by enhancing SIRT1 and AMPK,[90] indicating tubular SGLT2 may be a promising target for therapeutic interventions in DKD.

Fenofibrate is a fibric acid derivative widely used in the clinic to treat dyslipidaemia. AMPK is the crucial mediator of autophagy in TECs and plays a critical role in fenofibrate-mediated amelioration of renal injury during lipotoxicity in db/db mice.[92] Furthermore, fenofibrate treatment induced renal autophagy in DKD mice via AMPK activation and the upregulation of fatty acid oxidation enzymes. This indicates that fenofibrate can alleviate DKD injury by improving tubular autophagic dysfunction.[93]

6 | THE ROLE OF PYROPTOSIS IN DKD

Unlike apoptosis and autophagy, pyroptosis is a pro-inflammatory type of PCD. In response to abnormal signals, immune cells in the body release numerous pro-inflammatory mediators, such as cytokines that further attract more immune cells, induce the secretion of cytokines, and form a perpetuating inflammatory cascade in the kidney that contributes to the induction of cell swelling and cell death. Pyroptosis is characterised by plasma membrane rupture mediated by the NOD-like receptor pyrin-containing receptor 3 (NLRP3) inflammasome, caspase-1, and secretion of pro-inflammatory cytokines.[94] Activation of the NLRP3 inflammasome and caspase-1 is a critical step for the execution of pyroptosis. Upon danger signal stimulation, inflammatory caspase-1 is cleaved, and gasdermin D (GSDMD) is activated to generate the active form GSDMD-N and the self-inhibited form GSDMD-C. GSDMD-N induces the formation of protein pores by specifically binding to lipids in the cell membrane and mediating cell swelling. When the swollen cells are activated by danger signals, cell pyroptosis is observed. It results in cell membrane damage and the release of cytoplasmic contents and pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-18 (IL-18).[95,96]

Several reports have shown that pyroptosis of TECs is a required process in acute kidney injury (AKI),[97] indicating that pyroptosis contributes to the progression of tubulopathy in kidney diseases. However, few studies have focussed on the role of pyroptosis in DKD TECs. Pyroptosis is reportedly evoked by hyperglycaemia and exerts its function by forming a multiprotein complex known as the supramolecular pyroptosome, which mainly contains caspase-1.[98] The formation of pyroptosomes further results in the activation of the pyroptosis-related proteins ELAV-like protein 1 (ELAVL1) and NLRP3, which destroys cells and tissues. Evidence has shown that pyroptosis is implicated in DKD via its activation of NLRP3 inflammasomes that further mediate DKD progression.[99,100] Therefore, pyroptosis in tubular cells plays a vital role in DKD, and the underlying mechanism requires further exploration.

6.1 | Molecular signalling pathways involved in pyroptosis impairment in TECs in DKD

TLR4 is a member of the TLRs family that plays a vital role in activating the immune response. TLR4 has been implicated in the pathogenesis of acute and chronic renal disorders, such as AKI, DKD, and

renal fibrosis.[101] Wang et al.[102] proposed that overexpressed TLR4 participates in tubular injury induced by enhanced pyroptosis, and the inhibition of TLR4/NF-κB signalling could reverse PTEC pyroptosis and the release of IL-1β, accompanied by increased expression of GSDMD-NT under HG conditions. Therefore, these findings suggest that the TLR4/NF-κB signalling pathway contributes to the increased GSDMD-related pyroptosis observed in DKD.

Another study showed that an A1 adenosine receptor (A1AR) deletion increased caspase-1/IL-18 expression, megalin loss, and albuminuria.[103] The upregulation of A1AR successfully reversed proximal tubular megalin loss-associated albuminuria by interrupting pyroptosis-related caspase-1/IL-18 signalling in DKD, indicating a protective role for A1AR in DKD renal injury.[103]

6.2 | Abnormal TEC pyroptosis is mediated by non-coding RNA in DKD

Emerging evidence indicates that long non-coding RNAs (lncRNAs), which are endogenous non-coding RNAs of over 200 nucleotides that lack protein-coding functions, play crucial roles in the pathological processes of diabetes and diabetes-related complications.[104] After treatment with HG, HK-2 cell pyroptosis was markedly induced, accompanied by increased lncRNA-antisense non-coding RNA in the INK4 locus (ANRIL), TXNIP expression, and decreased miR-497 expression. Further research revealed that miR-497 mimics inhibited caspase-1-dependent pyroptosis, whereas co-overexpression of TXNIP blocked its activity in HG-treated HK-2 cells. In other words, upregulation of ARNIL in DKD promotes PTEC pyroptosis by sponging miR-497 to activate TXNIP/NLRP3/caspase-1 signalling, and this axis could serve as an effective therapeutic target for DKD.[105]

Another study demonstrated that lncRNA metastasis-associated lung adenocarcinoma transcript-1 (MALAT1) was involved in the development of DKD, and that downregulating MALAT1 could inhibit TEC pyroptosis by decreasing its interaction with the transcription factor FOXO1 to activate *SIRT1* transcription.[106] Furthermore, upregulated MALAT1 induced NLRP3-mediated TEC pyroptosis by inhibiting miR-30c from targeting *NLRP3*, providing another potential mechanistic model for ceRNA-mediated pyroptosis in DKD pathogenesis.[107] In addition to sponging miR-30c, the lncRNA MALAT1 also acts as an endogenous sponge of miR-23c to remove the suppression of the target gene *ELAVL1*, which further leads to the activation of the downstream protein NLRP3 and subsequent pyroptosis.[108]

Other lncRNAs have also been confirmed to participate in the pyroptosis of TECs in DKD. Overexpression of the lncRNA GAS5 alleviated HG-induced pyroptosis of TECs by downregulating miR-452-5p expression.[109] Additionally, the downregulation of lncRNA KCNQ1OT1 inhibited pyroptosis in HG-induced PTECs by removing the inhibition of its downstream miR-506-3p.[110] This evidence elucidates the promising therapeutic benefits of lncRNAs for DKD treatment.

In addition to lncRNAs functioning as regulators of TEC pyroptosis in DKD, the critical role of circRNAs in HG-induced pyroptosis in PTECs has been recently reported by Wen et al. They identified circACTR2, which upregulated HG-induced PTEC pyroptosis, inflammation, and fibrosis, indicating a potential novel target for DKD therapy in the future.[111]

7 | INTERACTION AMONG THE THREE PCD PATTERNS IN TECS IN DKD

Although the three PCD patterns that contribute to executioner activation have been identified independently, there is considerable evidence of significant interactions among the three patterns. Autophagy has been found to cross-regulate apoptosis,[112] mostly in an inhibitory manner. As a mediator of abnormal apoptosis, Bim inhibition restored the defective autophagic activity in TECs that was induced by HG.[48] Furthermore, autophagy inhibitor, which was used in Bim-downregulated TECs, could trigger apoptosis again, indicating that the relationship between apoptosis and autophagy was inhibitory on each other in TECs.[48] The targeted intervention of Bim had dual effects on the inhibition of apoptosis and restoration of autophagy in TECs. Kimura et al. developed a proximal tubule-specific autophagy-knock out mouse model. They found that ubiquitin-positive inclusion bodies, damaged mitochondria, and misfolded protein aggregates markedly accumulated in autophagy-deficient TECs, which manifested an obvious increase of apoptosis in TECs.[113] Thus, autophagy activation suppresses the apoptosis of TECs and activation of the apoptosis couples the inhibition of autophagy.

Interaction between pyroptosis and apoptosis also exists in DKD tubules. TLR4 could aggravate tubular injury via the GSDMD-mediated pyroptosis in DKD.[114] The upregulation of GSDMD induced pyroptosis and suppressed apoptosis, which might participate in the switch mechanism between pyroptosis and apoptosis that was mediated by TLR4 during DKD tubular injury.[114] Moreover, activation of caspase-3, an executor of intrinsic and extrinsic apoptosis, induced pyroptosis by cleaving gasdermin E in DKD tubules.[115] These findings suggest that the pyroptosis and apoptosis interact closely in the TECs of DKD. Pyroptosis and autophagy theoretically interact with each other; however, few studies report a relationship between pyroptosis and autophagy in DKD tubular injury. Thus, investigating the interaction between pyroptosis and autophagy in TECs is essential to determine the underlying mechanisms of DKD.

8 | CONCLUSION

The programed cell death (PCD) of TECs is vital to hyperglycaemia-mediated renal damage in DKD. By studying the mechanisms of apoptosis, autophagy, and pyroptosis of TECs in DKD, many mediators and signalling pathways were identified, and their potential

pharmacological effects on the prevention of tubular damage in DKD were further investigated. The mechanism of programed TECs death involved in the pathogenesis of DKD is complicated, and new advancements in the field show promise as novel therapeutic targets for DKD.

AUTHOR CONTRIBUTIONS

XZ did the scientific literature search. CX wrote the first draft of the report. JD and LL contributed to the critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

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CONFLICT OF INTEREST

We declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Not applicable.

PEER REVIEW

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