Cell death-related molecules and targets in the progression of urolithiasis (Review)

LIPING WU[1*], XIAOYAN XUE[1*], CHENGWU HE[2], YONGCHANG LAI[2,3] and LINGFEI TONG[4]

[1]Department of Pharmacy, Ganzhou People's Hospital, Ganzhou, Jiangxi 341099, P.R. China; [2]Department of Urology, The Eighth Affiliated Hospital of Sun Yat-sen University, Shenzhen, Guangdong 518033, P.R. China; [3]Department of Pharmaceutical Management, School of Medical Business, Guangdong Pharmaceutical University, Guangzhou, Guangdong 510006, P.R. China; [4]Department of Pharmacy, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi 330006, P.R. China

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Abstract. Urolithiasis is a high-incidence disease caused by calcium oxalate (mainly), uric acid, calcium phosphate, struvite, apatite, cystine and other stones. The development of kidney stones is closely related to renal tubule cell damage and crystal adhesion and aggregation. Cell death, comprising the core steps of cell damage, can be classified into various types (i.e., apoptosis, ferroptosis, necroptosis and pyroptosis). Different crystal types, concentrations, morphologies and sizes cause tubular cell damage via the regulation of different forms of cell death. Oxidative stress caused by high oxalate or crystal concentrations is considered to be a precursor to a variety of types of cell death. In addition, complex crosstalk exists among numerous signaling pathways and their key molecules in various types of cell death. Urolithiasis is considered a metabolic disorder, and tricarboxylic acid cycle-related molecules, such as citrate and succinate, are closely related to cell death and the inhibition of stone development. However, a literature review of the associations between kidney stone development, metabolism and various types of cell death is currently lacking, at least to the best of our knowledge. Thus, the present review summarizes the major advances in the understanding of regulated cell death and urolithiasis progression.

Correspondence to: Professor Lingfei Tong, Department of Pharmacy, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, 152 Patriotism Road, Yu Zhang Street, Donghu, Nanchang, Jiangxi 330006, P.R. China
E-mail: tonglingfei@ncmc.edu.cn

*Contributed equally

Abbreviations: CaOx, calcium oxalate; COM, calcium oxalate monohydrate; AKI, acute kidney injury; ROS, reactive oxygen species; ER, endoplasmic reticulum; Nrf2, nuclear factor erythroid 2-related factor; GPX4, glutathione peroxidase 4; TNF, tumor necrosis factor; UPEC, uropathogenic *Escherichia coli*; TNFR, tumor necrosis factor receptor; ERS, endoplasmic reticulum stress; SOCE, store-operated Ca^{2+} entry; Mp, macrophage polarization; lncRNA, long non-coding RNA; SIRT, sirtuin; GSDM, gasdermin; GSH, glutathione; PUFAs, polyunsaturated fatty acids; ACSL4, acyl coenzyme A synthase long-chain family member 4; DHA, dihydroxyadenine; TFEB, transcription factor EB; TCA, tricarboxylic acid; α-KG, α-ketoglutaric acid; NF-κB, nuclear factor κB; HO-1, heme oxygenase-1

Key words: kidney stone, apoptosis, ferroptosis, kidney injury, pyroptosis, necroptosis

Contents

1. Introduction

As a common disease of urinary system, urolithiasis mainly manifests by the formation of stones in the renal pelvis and calyces. The incidence of urolithiasis is ~15%, and its occurrence may be associated with dietary habits, inflammation, oxidation/antioxidant imbalances, angiogenesis, lifestyle factors (e.g., reduced physical activity), purine metabolism and urea cycle disorders (1). Symptoms of kidney stones include lower back pain, hematuria, difficulty urinating and, in severe cases, the stones may lead to kidney failure. By stone composition, urolithiasis can be divided into calcium oxalate (CaOx; main), uric acid, calcium phosphate, struvite, apatite, cystine and other types (2). The key processes of kidney stone formation are supersaturation, nucleation, crystal growth and adhesion retention in cells, as well as renal tubular cell damage caused by high concentrations of oxalate and other factors, which facilitate crystal adhesion and growth (3).

Based on functional differences, cell death can generally be classified as accidental, triggered by unexpected injurious stimuli, or regulatory, characterized by structured signaling cascades involving effector molecules (4,5). Common forms of

cell death include apoptosis, lysosomal cell death, necroptosis, pyroptosis, NETosis, immunogenic cell death, entosis, ferroptosis, autosis, oxeiptosis, cuproptosis and disulfidptosis (4,6,7). Cell death plays key roles in the pathogenesis and treatment of a variety of uropathies, including cancer, urinary tract infections and urolithiasis (8). Apoptosis, necroptosis, pyroptosis and ferroptosis induce acute kidney injury (AKI) or chronic kidney injury, which is associated with nephrolithiasis (9,10).

Cell death is a complex pathological process that can be affected by crystal shape and structure, as well as other physical and chemical properties; however, studies on the roles of crystal characteristics in the mode of cell death are limited (11). For example, calcium oxalate monohydrate (COM) nanoparticles adhere more readily to injured Vero cells than do CaOx dehydrate nanoparticles, although both particle types aggravate Vero cell injury (12). In addition, the same stimulus can induce different forms of regulatory cell death, depending on its intensity or the presence of co-stimulatory factors; these forms are characterized by multiple layers of interconnection, including common triggers, molecular components and protective mechanisms (13). The present review summarizes the major advances made in the understanding of regulated cell death and the progression of kidney stones.

2. Key factors for renal stone formation

Oxalate is a non-essential metabolic end product that can cause hyperoxaluria, and renal cells exposed to oxalate stress produce reactive oxygen species (ROS), ultimately promoting the formation of CaOx stones (14). In a previous study, the examination of a spatially anchored transcriptome map of the human renal papillae revealed the upregulation of a variety of cell damage pathways in patients with stone-related disease, characterized by immune activation, the oxidative stress response and extracellular matrix tissue remodeling; matrix metalloproteinase 7 and matrix metalloproteinase 9 were found to be associated with active stones and mineralization (15). Thus, oxidative stress and inflammatory responses are key factors in CaOx crystal-induced kidney injury (16). The underlying causes of kidney stone formation are multifactorial, including environmental, dietary, hormonal and genetic factors, leading to an imbalance in crystallization inhibitors and promoters (17). There are inhibitors (e.g., citrate, magnesium and pyrophosphate) and promoters (Randall's plaques, cell injury, bacterial products and slow urinary flow) of nephrolithiasis (18). In addition to their ability to inhibit crystallization, citrate and magnesium can also prevent the crystallization of CaOx by reducing its supersaturation (19). Among various theories about the urolithiasis formation mechanism, the papillary calcification of Randall's plaque is considered to be the origin of CaOx stone formation (20). It has recently been reported that the deficiency of pyrophosphate, a calcification inhibitor, predisposes to cardiovascular and renal papillary calcification, which can lead to the development of kidney stones (21). In fact, the oral administration of pyrophosphate inhibits connective tissue calcification (22). In addition to pyrophosphate, the dissolution effect of hexametaphosphate on CaOx stones is 12-fold greater than that of citrate (23). Predisposing factors of urolithiasis include a low urine volume, hypocitraturia, hypercalciuria, hyperoxaluria, a low urinary pH (uric acid or cystine stones), medullary sponge kidney, polycystic kidney disease and hyperuricosuria (18,24).

The renal tubules are the main kidney components injured by hypoxia, proteinuria, toxins, metabolic disorders, aging, stone obstruction, silica, cholesterol, and calcium oxalate (25,26). AKI is an epidemic syndrome characterized by a rapid decline in kidney function (27). Recovery from crystalline or obstruction-induced chronic kidney disease, on the other hand, is characterized by remaining tissue damage, fibrosis and nephron loss, rather than being reflected by standard measures of kidney function (28). In addition, the pathogenesis of crystalline nephropathy involves various forms of cell death in the processes of tubule crystal deposition, tubule obstruction and urinary tract infection.

Urinary tract obstruction caused by calculi is another common symptom that induces mechanical stretching, oxidative stress and inflammation that may lead to tubular cell death and kidney injury via the key processes of apoptosis, necroptosis and autophagy (8,29,30). Following ureteral obstruction, renal tubule pyroptosis mediated by tumor necrosis factor (TNF)-α/caspase 3/gasdermin (GSDM)E signaling triggers the release of high mobility group box 1 and the activation of inflammasomes, ultimately leading to tubule injury and promoting the development of hydronephrosis, inflammatory responses and renal fibrosis (31). The ferroptosis inhibitor liproxstatin-1 reduces lipid peroxidation and inhibits the downregulation of glutathione peroxidase 4 (GPX4) expression, the ferroptosis of renal tubular epithelial cells induced by ureteral obstruction, and the paracrine activity of profibrotic factors in human proximal renal tubular cells, thereby alleviating renal fibrosis in a mouse model (32).

During a urinary tract infection, invading bacteria can promote or prevent host cell death by interfering with cell death pathways (8). Microorganisms, such as bacteria may be involved in kidney stone formation through hyperoxaluria and CaOx supersaturation, biofilm formation and crystal binding to promote aggregation, urothelial injury and inflammation (33). Uropathogenic *Escherichia coli* (UPEC), for example, can promote the formation of CaOx stones by enhancing oxidative damage and inflammation regulated by polyphosphate kinase 1/flagellin and activating the nuclear factor κB (NF-κB)/p38 pathway (34). Within the urinary microbiome, the role of urease-producing bacteria (i.e., *Proteus mirabilis*) in stone formation is well-established (33).

Hyperuricemia or uric acid crystals can induce pyroptosis by activating the NLR family pyrin domain containing 3 (NLRP3) inflammasome and promoting the release of a number of pro-inflammatory molecules within the cells, thereby playing a critical role in kidney disease (35). Cystine crystals can also activate the NLRP3 inflammasome through the inducion of ROS production, increase the expression of CD44 and osteopontin in HK-2 cells, and promote cell apoptosis and crystal adhesion (36). The antioxidant, L-ergothioneine, prevents cystine stones in solute carrier family 7 (Slc7)a9$^{-/-}$ mouse models by increasing urinary cystine solubility and restoring renal glutathione (GSH) metabolism and mitochondrial function (37). As a common component of most CaOx stones and the core of Randall's plaques, hydroxyapatite crystals cause oxidative stress, decrease cell viability and mitochondrial membrane potential, and lead to cell swelling

and necrosis (38). In addition to being caused by programmed pathway activation (i.e., apoptosis, necroptosis and pyroptosis), cell death can also be caused by imbalances resulting from the loss of cytoplasmic or cell membrane integrity, the accumulation of misfolded proteins, excitatory toxicity, oxidative stress and lipid peroxidation (39). Thus, the pathogenesis of crystalline nephropathy involves various forms of cell death in the processes of tubule crystal deposition, tubule obstruction and urinary tract infection.

3. The various forms of cell death and urolithiasis

Apoptosis and urolithiasis. Apoptosis can be triggered by the intrinsic mitochondrial (BCL-2) pathway, which is regulated by pro-apoptotic and anti-apoptotic members of the BCL-2 protein family, or by the extrinsic death receptor pathway, which is activated by ligands of members of the TNF receptor (TNFR) superfamily with intracellular death domains (4). Overall, apoptosis is performed by caspase-3 and caspase-7, which are activated by upstream extrinsic apoptosis-related caspase-8 and intrinsic stress-related caspase-9 molecules, respectively (40). Endoplasmic reticulum (ER) stress, oxidative stress, growth factor withdrawal and microtubular alteration are intrinsic lethal stimuli for the apoptotic pathway, and FASL/FAS, TNF/TNFR1 and TRAIL/TRAIL receptors are the main extrinsic apoptotic drivers and activators of inflammation (5). The level of ER stress (ERS) is closely associated with the degree of HK-2 cell injury and apoptosis induced by CaOx crystals, and the latter can be reduced significantly by inhibiting the former (41).

Ions, amino acids and their transporters and channels, calcium-sensitive receptor signaling pathways, and the metabolic pathways of vitamin D, oxalic acid, cysteine, purine and uric acid are considered to play key roles in the etiology of kidney stones (42). CaOx stones formed due to hyperoxaluria account for approximately two-thirds of all kidney stones (43). In HK-2 cells, oxalate activates ERS/ROS via NF-κB-dependent pathways, causing autophagy, apoptosis and mitochondrial damage (44). The ER affects protein and lipid synthesis, Ca^{2+} homeostasis regulation and subcellular organelle crosstalk, and disruptions in homeostasis can cause toxic protein and lipid accumulation and Ca^{2+} homeostasis disorders, leading to cell damage and death and thereby promoting the development of kidney disease (45). Hyperoxaluria causes ERS, which leads to an unfolded protein response in rat kidney tissue and to altered sigma-1 receptor protein expression in mitochondria-associated ER membranes, resulting in mitochondrial dysfunction, cell apoptosis, kidney injury and CaOx crystal deposition (46). Oxalate poisoning can directly induce the expression of the ERS markers, glucose-regulated protein 78 and CHOP, upregulate transforming growth factor β-1, activate ERS-mediated apoptosis, and induce renal fibrosis (14).

Idiopathic hypercalciuria is another key risk factor for the formation of calcium-containing kidney stones (47). By activating Ca^{2+}-sensing receptors, melamine can increase intracellular Ca^{2+} concentrations, promote ROS production, activate the apoptosis and necroptosis of renal epithelial cells, lead to renal tubular cell injury, inflammation and fibrosis, and promote the formation of kidney stones (48). Under co-exposure to melamine and oxalate, the antioxidant capacity of nuclear factor erythroid 2-related factor (Nrf2) decrease and the levels of DNA oxidative damage in HK-2 cells and kidney tissues, renal tubule cell apoptosis, tubule atrophy and interstitial fibrosis increase (49). In a previous study, more calcium deposits were detected in the medullae of male mice than in those of female and castrated male mice, and testosterone was found to induce renal tubular epithelial cell apoptosis and necrosis via the hypoxia-inducible factor 1α/BCL-2 interacting protein 3 pathway (50). Crystal internalization causes the transformation from receptor-operated Ca^{2+} entry to store-operated Ca^{2+} entry (SOCE), and the prevention of SOCE can antagonize crystal-induced ERS and proximal tubular cell death, thereby reversing pathological outcomes, including cardiovascular calcification, in crystal-induced environments (51).

Macrophages can clear CaOx crystals to a certain extent; however, exosomes derived from macrophages via CaOx crystal pretreatment can accelerate HK-2 cell apoptosis by increasing autophagy, suggesting that they have an important function in CaOx-induced injury to human proximal tubule cells (52). Idiopathic CaOx stones frequently feature Randall's plaques on renal papillae surfaces; these plaques are composed of calcium phosphate crystals mixed with a protein- and lipid-rich organic matrix, associated with the presence of classically activated pro-inflammatory M1 macrophages and the downregulation of anti-inflammatory M2 macrophages in the surrounding renal tissue (53). Medulla macrophages in renal medullary tubules were recently found to spontaneously form protrusions, penetrate epithelial cells to 'sample' urine contents depending on integrin β1, and even migrate to the lumen and carry particles out with urine, suggesting that urine flushing is not the only mechanism of urinary tract particle removal (54). By inhibiting the activation of NADPH oxidase, the production of ROS, and the phosphorylation of p38 MAPK, M2 macrophages reduce oxidative stress damage and apoptosis in HK-2 cells, thereby reducing the formation of kidney stones (55). Rosiglitazone, a macrophage polarization (Mp) regulator, can significantly inhibit oxidative stress and inflammation through the Nrf2/heme oxygenase-1 (HO-1) pathway and promote M2Mp, thereby reducing renal tubule injury, apoptosis, and crystal adhesion (56).

Long non-coding RNAs (lncRNAs) play crucial roles in the regulation of CaOx crystal-induced kidney stone formation and deposition. The expression of LINC01197 and sirtuin (SIRT)3 is downregulated in patients with kidney stones, and LINC01197 knockdown promotes CaOx-induced cell adhesion and apoptosis via the miR-516b-5p/SIRT3/forkhead box (FOX)O1 signaling pathway (57). The overexpression of SIRT3 may lead to the activation of the NRF2/HO-1 signaling pathway in HK-2 cells, reduce oxidative stress and apoptosis induced by CaOx crystals in renal tubular epithelial cells, and reduce crystal adhesion on cell surfaces, thereby inhibiting the formation of kidney stones (58). miR-200a mimics can reduce COM-induced cell injury, apoptosis, inhibit proliferation and changes in epithelial-mesenchymal transition, and lncRNA-ATB can participate in the regulation of CaOx crystal-induced kidney injury and apoptosis through sponge adsorption by the miR-200 family (59). miR-21 can facilitate CaOx-induced renal tubular cell damage by targeting PPAR-α, and its inhibition can enhance the proliferation of HK-2 cells

and reduce apoptosis and lipid accumulation following COM exposure and *in vivo*, suggesting that it is a therapeutic target for kidney stones (60).

Esophageal cancer-related gene 4, a tumor suppressor gene originally described in the esophagus, has recently been proven to be associated with apoptosis, cell senescence, cell migration and inflammation, and its loss may ameliorate CaOx-induced nephropathy (61). Enhancer of zeste homolog 2 (EZH2) inhibition can restore cell viability, inhibit lactate dehydrogenase release and intracellular ROS production via the regulation of the JNK/FOXO3a pathway, and significantly reduce renal CaOx crystal deposition and oxidative and inflammatory damage induced by hyperoxaluria *in vivo* (62). Sodium butyrate may partially reverse the oxidative stress, inflammation and apoptosis induced by CaOx crystallization or nephrolithiasis by inhibiting CYP2C9 (63). FKBP prolyl isomerase 5, regarded as a predictor of kidney damage, promotes cell-crystal adhesion, apoptosis, stone aggregation and kidney injury in cells and mice (64). Nox4-derived ROS induced by high calcium-protein kinase C levels cause oxidative stress injury and the apoptosis of renal tubular epithelial cells, as well as abnormal activation of bone morphogenetic protein 2 through the MAPK signaling pathway, thereby promoting calcium salt deposition and kidney stone formation (65).

Glutamine can induce the transcriptional and proteomic reprogramming of mouse renal tubular epithelial cells, thereby reducing neutrophil recruitment, improving mitochondrial function and oxidative phosphorylation, and reducing endogenous apoptosis of mitochondria to alleviate kidney injury (66). The adhesion of crystals to cells is a key initial step in kidney stone formation; ATPase Na^+/K^+ transporting subunit alpha 1 (ATP1A1) is involved in renal crystal formation via the Src/ROS/p38 signaling pathway, and the specific suppression of the ATP1A1/Src complex with pNaKtide mitigates crystal-cell adhesion, apoptosis, inflammation and oxidative stress (67). Resveratrol, a well-known antioxidant, inhibits crystal deposition and kidney cell injury by increasing the expression of SIRT1 (68). Thus, ROS-associated ERS, inflammatory macrophage phenotype switching, and various other factors induced by high oxalate, calcium and/or crystal levels are involved in apoptosis.

Pyroptosis and urolithiasis. In contrast to ferroptosis and apoptosis, pyroptosis is a pro-inflammatory form of cell death with unique morphological and mechanistic characteristics; it involves the release of the inflammatory cytokines IL-1β and IL-18 by gasdermin family members (69). Whereas caspase-3/7 are involved in apoptosis, inflammatory caspase-1/4/5/11 mediate pyroptosis by cracking GSDMD (40). Various pathogenic microorganisms and endogenous harmful substances can activate the NLRP3 inflammasome, which can assemble the intracytoplasmic innate immune complex, activate the cysteine protease caspase-1, and then lyse GSDMD, eventually leading to pyroptosis (70,71). As a sensor required for inflammasome formation, NLRP3 plays a key role in oxalate-associated renal failure (72). The NLRP3-GSDMD pathway is involved in oxalate-induced pyroptosis in HK-2 cells, and the inhibition of ROS production or silencing of NLRP3 can prevent NLRP3 inflammasome formation, thereby reducing oxalate-induced damage to membrane integrity and ultrastructural changes (73).

In cell and animal models, IL-22 has been shown to reduce the sodium oxalate-induced NLRP3 inflammasome and mature IL-1β expression in kidney tissue and ROS accumulation, mitochondrial damage, and renal tubular epithelial cell death by decreasing the serum levels of IL-1β, IL-18, TNF-α and other cytokines (74). Hyperuricemia induces a pro-inflammatory microenvironment with increased serum levels of IL-1β, IL-6 and TNF-α, elevates renal expression of NLRP3 and cleaved caspase-1, and leads to microstructural kidney disorders in mice; Simiao San alleviates hyperuricemia and renal inflammation by inhibiting the NLRP3 inflammasome and the JAK2/STAT3 signaling pathway (75).

Cytoplasmic and mitochondrial ROS production induced by CaOx crystals can promote the initiation and activation of the NLRP3 inflammasome, thereby stimulating the maturation and activation of IL-18/1β; polydatin can reduce the resulting inflammatory kidney damage and renal epithelial cell injury by decreasing ROS production (16). CaOx crystals can induce the expression of caspase-1, GSDMD-N, IL-1β and IL-18 in renal tubular cells, thereby promoting pyroptosis, and miR-141-3p can inhibit NLRP3-mediated pyroptosis by inhibiting the expression of NLRP3, thereby protecting against renal tubular cell injury (76). Vitexin can also inhibit GSDMD-related pyroptosis, which is involved in nephrolithiasis (77). The expression of the lncRNA LINC00339 has been found to be elevated in HK-2 cells treated with COM, and LINC00339 has been found to regulate the expression of NLRP3 by sponging miR-22-3p, which contributes to pyroptosis (78).

Human recombinant relaxin 3 can act on the transmembrane receptor, relaxin family peptide receptor 1, to produce cAMP, and then inhibit the NLRP3 inflammasome activated by CaOx crystals through the consumption of ATP, thereby reducing CaOx-induced inflammatory pyroptosis in the kidneys (79). In addition to CaOx lithiasis, the NLRP3-mediated inflammasome and oxidative stress damage play important roles in ceftriaxone calcium crystal-induced urinary lithiasis, thereby promoting acute kidney injury (80). Similar to CaOx and ceftriaxone calcium, cystine crystals are endogenous inflammasome activators; thus, sodium urate, calcium phosphate, and other crystals can be inferred to cause kidney damage through NLRP3-mediated inflammation (72). NLRP12 is another key cytosolic sensor in the activation of the inflammasome, the PANoptosome, and cell death driven by heme plus PAMPs or TNF, whose deletion protects mice from AKI and death (81).

Necroptosis and urolithiasis. Unlike apoptosis, necroptosis is morphologically involved in cell swelling, membrane rupture, and the release of cytoplasmic contents. It is a regulated inflammatory cell death mechanism mediated by the cascade phosphorylation-induced activation of receptor-interacting serine/threonine-protein kinase (RIPK)1, RIPK3 and mixed lineage kinase domain like pseudokinase (MLKL) (14). Extrinsic apoptosis-inducing molecules, such as FASL/FAS can activate caspase-3/7 by promoting the activity of caspase-8 to trigger apoptosis; when caspase-8 is inhibited, the same cell death-inducing factors trigger its oligomerization and membrane destruction via RIPK/MLKL, leading to necroptosis (40). Intratubular crystal deposition may result in tubular cell injury, obstruction, interstitial inflammation, and crystal-induced renal colic, which are driven in part by the

NLRP3 inflammasome and necroptosis (82). Both necroptosis and pyroptosis can cause kidney damage directly or through the recruitment of immune cells and stimulation of an inflammatory response (13).

As a novel RIPK3 inhibitor, compound 42 alleviates CaOx crystal-induced renal tubular epithelial cell damage by inhibiting necroptosis and inflammation, while improving impaired renal function and reducing intrarenal crystal deposition in mice with renal calcification; thus, it achieves a better inhibition of necroptosis than does the classical RIPK3 inhibitor dabrafenib (83). Tubastatin A, an HDAC6 inhibitor, can inhibit acute oxalate nephropathy by modulating kidney tubule IL-1β secretion and RIP kinase-mediated necroptosis (84). 6,7-Dihydroxycoumarin was shown to inhibit the phosphorylation of MLKL, protecting cells from CaOx crystal–induced necroptosis, both *in vitro* and *in vivo* (85). TNFR signaling is essential for intrarenal crystallization-induced inflammation and kidney cell necroptosis, and may influence CaOx crystal adhesion to the renal tubule lumen by modulating the expression of the crystal adhesion molecules CD44 and annexin II (86). Thus, various inhibitors of RIPK/MLKL signaling have urolithiasis-inhibiting effects.

Ferroptosis and urolithiasis. Ferroptosis is a non-apoptotic form of cell death characterized by abnormal iron homeostasis, lipid metabolism and redox system regulation that plays crucial roles in organ injury and degenerative diseases (87). It has been observed in various forms of AKI, such as sepsis, ischemia, and folate cisplatin, and oxalate nephropathies; it not only is a mechanism of renal injury, but also alters the course of AKI and inhibits recovery (10). Ferroptosis, a novel iron- and ROS-dependent form of programmed cell death, can be induced by various drugs (e.g., erastin, cisplatin, sorafenib, artemisinin, and statins) through various mechanisms (88).

Under ferroptosis regulation, renal tubular epithelial cell damage has been found to significantly increase with the ferroptosis level and vice versa, suggesting that ferroptosis is essential for the injury caused by CaOx crystals (89). The significant activation of ferroptosis has been observed in patients with kidney stones and in hyperoxaluric mice, and this activation can be inhibited by p53 deacetylation, thereby mitigating CaOx crystal-induced renal fibrosis (90). Oxalate has been found to induce ferroptosis in HK-2 cells by activating NCOA4-mediated autophagy (91). Ferrostatin-1, a ferroptosis inhibitor, can mitigate oxalate-induced kidney tubular epithelial cell damage, fibrosis, and CaOx lithogenesis by suppressing ferroptosis (92). It can also regulate abnormal kidney lipid metabolism enzymes in AKI (93).

GPX4 is an antioxidant enzyme that uses GSH as a cosubstrate to reduce lipid hydroperoxides, and GSH may replace cysteine or homocysteine as a GPX4 cofactor in the evolution of aerobic metabolism (94). AKI repair ability differs significantly between males and females, as GPX4 knockout leads to increased renal tubular epithelial cell injury and ferroptosis in male, but not female, mice (95). OTU deubiquitinase 5 (OTUD5), a protein that interacts with GPX4, can promote ferroptosis resistance during ischemia/reperfusion injury by stabilizing GPX4 expression; in turn, hypoxia/ischemia-induced OTUD5 autophagy can destabilize GPX4, leading to ferroptosis-dependent kidney injury (96). Vitexin has been found to increase GPX4 expression by activating the NRF2/HO-1 pathway, inhibit the ferroptosis of renal tubule epithelial cells, and significantly reduce renal tubule injury, interstitial fibrosis, and renal inflammation in mice with unilateral ureteral obstruction (97).

SLC7A11, a cellular transmembrane protein that makes up the light chain of system Xc-, is a key pathway for REDOX homeostasis, transporting extracellular cysteine into cells for cysteine production and GSH biosynthesis and thereby maintaining cellular GSH levels to antagonize cellular oxidative stress and inhibit ferroptosis (98). SOX4 promotes ferroptosis in CaOx crystal-induced kidney injury by modulating EZH2/H3K27Me3-mediated SLC7A11 inhibition. Ankyrin repeat domain 1 is involved in CaOx kidney stone formation via the activation of p53/SLC7A11-mediated ferroptosis (99). Von Hippel-Lindau, a critical renal tumor suppressor gene, interacts with BICD2 and weakens system Xc^--mediated ferroptosis processes, which can be disrupted by a BRAF inhibitor during severe ferroptosis and nephrotoxicity (100).

Polyunsaturated fatty acids (PUFAs) are the main targets of lipid peroxidation, and their incorporation into phospholipids, a key event in lipid hydroperoxide-induced ferroptosis, is dependent on acyl coenzyme A synthase long-chain family member 4 (ACSL4) (101). Instead of causing ferroptosis, PUFAs have been shown to reduce the COM-induced apoptosis of HK-2 cells and diminish kidney tubular damage in a renal-stone mouse model via the miR-93-5p/Pknox1 axis (102). Yes-associated protein can enhance ACSL4 expression, thereby inducing ferroptosis and increasing CaOx crystal-induced renal fibrosis (103). FSP1-dependent non-canonical vitamin K, a naphthoquinone group that includes methylnaphthoquinone and phylloquinone, has powerful anti-ferroptosis properties and can protect cells from detrimental lipid peroxidation (104).

NRF2 regulates several genes that are critical; for ferroptosis, including GPX4 (105). In erastin- or oxalate-induced HK-2 cells, schizandrin B modulates the expression of ferroptosis-related proteins and reduces ferroptosis-related cellular Fe^{2+} accumulation and lipid peroxidation by facilitating Nrf2 nuclear translocation (106). Drugs and substances, such as gallic acid (107), curcumin (108) and dimethyl fumarate (109), significantly ameliorate CaOx crystal-induced renal injury via Nrf2 pathway regulation, which involves antioxidant and antiapoptotic effects and the inhibition of autophagy and inflammation to prevent nephrolithiasis. Oxidative stress may promote and increase renal crystal formation through the Keap1-Nrf2 pathway (110). Thus, Nrf2 is associated with apoptosis, autophagy and ferroptosis through its numerous effects (i.e., antioxidant effects).

Melatonin can increase the total antioxidant capacity of HK-2 cells and decrease the ERS and apoptosis induced by oxalate in a dose-dependent manner, depending partly on 5' adenosine monophosphate-activated protein kinase (AMPK) activation (111). It may also alleviate oxalate-induced renal injury via the PTEN induced kinase 1/AMPK pathway to restore mitophagy and subsequently inhibit ferroptosis (112). Exosome Ambra1 can be secreted by HK-2 cells damaged by supersaturated oxalate, inducing mitochondrial and ferroptosis-related autophagy in normal HK-2 cells, which contributes to the occurrence of kidney stones (113). In the context of nephropathy induced by adenine and 8-dihydroxyadenine (DHA)

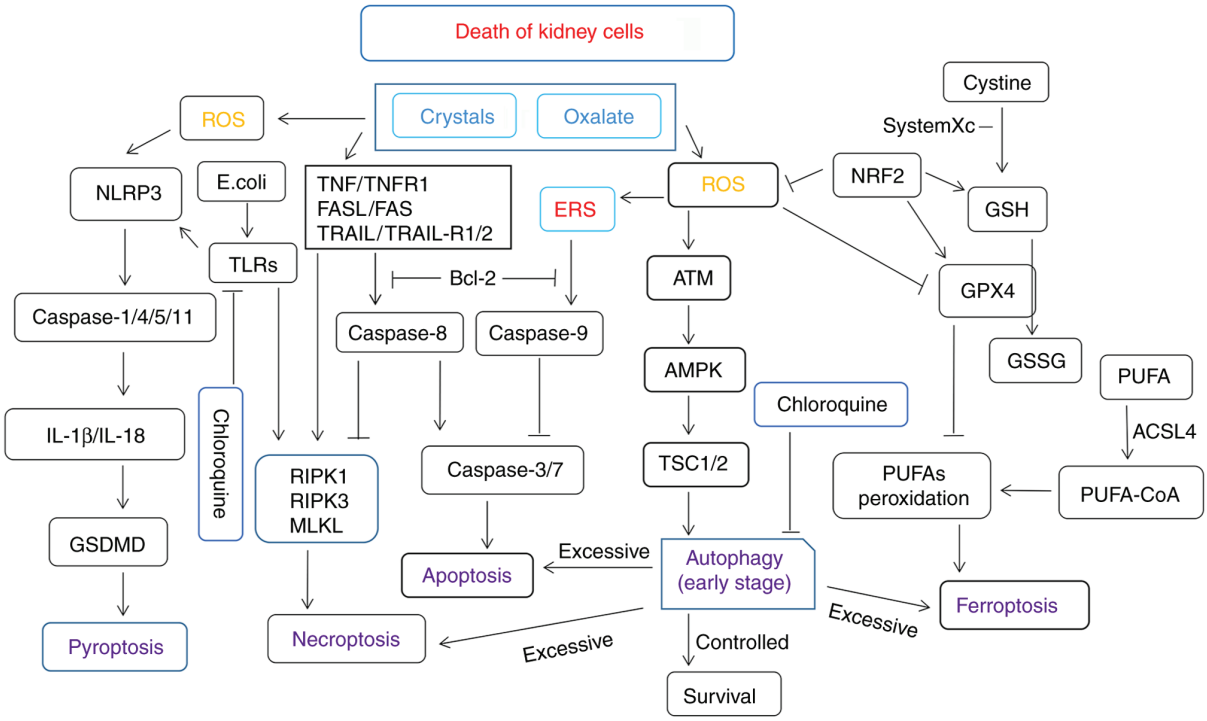

Figure 1. A simplified summary of apoptosis-, necroptosis-, pyroptosis-, ferroptosis-, and autophagy-related signaling pathways and crosstalk among them. Kidney cell injury induced by high oxalate, crystal, and *Escherichia coli* concentrations or other bacteria may promote the production of ROS and various forms of cell death. Nrf2, nuclear factor erythroid 2-related factor; GPx, glutathione peroxidase; GSH, glutathione; PUFAs, polyunsaturated fatty acids; ROS, reactive oxygen species; NLRP3, NLR family pyrin domain containing 3; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; ERS, endoplasmic reticulum stress; GSDMD, gasdermin D; ACSL4, acyl coenzyme A synthase long-chain family member 4; TLRs, Toll-like receptors; ERS, endoplasmic reticulum stress; RIPK, receptor-interacting serine/threonine-protein kinase; MLKL, mixed lineage kinase domain like pseudokinase; TSC1/2, tuberous sclerosis proteins 1 and 2; AMPK, 5' adenosine monophosphate-activated protein kinase; GSSG, glutathione disulfide; CoA, coenzyme A.

crystals, ferroptosis is the main mode of proximal tubular epithelial cell necrosis, and baicalein is a potential therapeutic tool for ferroptosis-related crystalline (e.g., DHA or oxalate) nephropathy (114). Thus, a number of ferroptosis-related molecules (e.g., GPX4 and NRF2) can affect certain steps of urolithiasis and may participate in apoptosis, autophagy, and other forms of cell death. A simplified summary of apoptosis-, necroptosis-, pyroptosis-, ferroptosis- and autophagy-related signaling pathways and their crosstalk in kidney cells is shown in Fig. 1.

Autophagy and lysozyme cell death in urolithiasis. Autophagy is a process through which cells maintain homeostasis by degrading and recycling organelles and their proteins. Autophagy often has a protective effect; however, the disruption of its mechanisms or excessive autophagic flux induces cell death; indeed, autophagy is involved in the regulation of almost all cell death in various diseases (115). Such death can be autophagy-dependent (or autophagic, i.e., ER-phagy, mitophagy and autosis) or mediated (i.e., apoptosis, necroptosis and ferroptosis) (115). Autophagy is considered to be an enhancer that promotes ROS-dependent ferroptosis by regulating iron-dependent lipid peroxidation, and excessive autophagy and lysosomal activity can also promote ferroptosis through iron accumulation (116). Thus, there are many different types of molecular signaling crosstalk between autophagy and various forms of cell death.

Autophagy and mitophagy play critical roles in cell survival by preventing nutrient deprivation and regulating oxidative stress; however, they can be dysregulated, leading to cell death, by oxidative stress caused by sustained kidney injury (117). The autophagy antagonist, chloroquine, can significantly reduce oxalate-induced autophagy activation and oxidative and mitochondrial damage in renal tubule cells *in vitro* and *in vivo*, and inhibit hyperoxaluria-induced renal CaOx crystal deposition, reflecting the roles of autophagy in the regulation of oxalate-induced renal oxidative damage and CaOx crystal deposition (118). ERS can mediate excessive autophagy and regulate cell damage and apoptosis through the PERK-eIF2α pathway, and the inhibition of ERS-mediated autophagy can effectively protect renal function and prevent renal cell apoptosis and kidney stone formation (119). The enhancement of superoxide dismutase activity by atorvastatin can reduce the autophagy-ERS response and CaOx kidney stone formation, and thus may be an option for the prevention and treatment of nephrolithiasis (120).

Mitochondrial ROS and IL-10 are involved in oxalate-induced metabolism and immune response impairment via the disruption of monocyte and macrophage function (121). CaOx crystals significantly induce lysosomal injury and subsequent transcription factor EB (TFEB) activation in proximal renal tubule epithelial cells, whereas tubule injury, renal function impairment, the expression of the lysosome damage marker Gal-3, and cell apoptosis were significantly increased in TFEB-deficient mice treated with oxalates for 48 h, suggesting that TFEB activation can alleviate subsequent tissue damage by promoting lysosomal damage repair (122). Resveratrol reduces oxalate-induced renal inflammation,

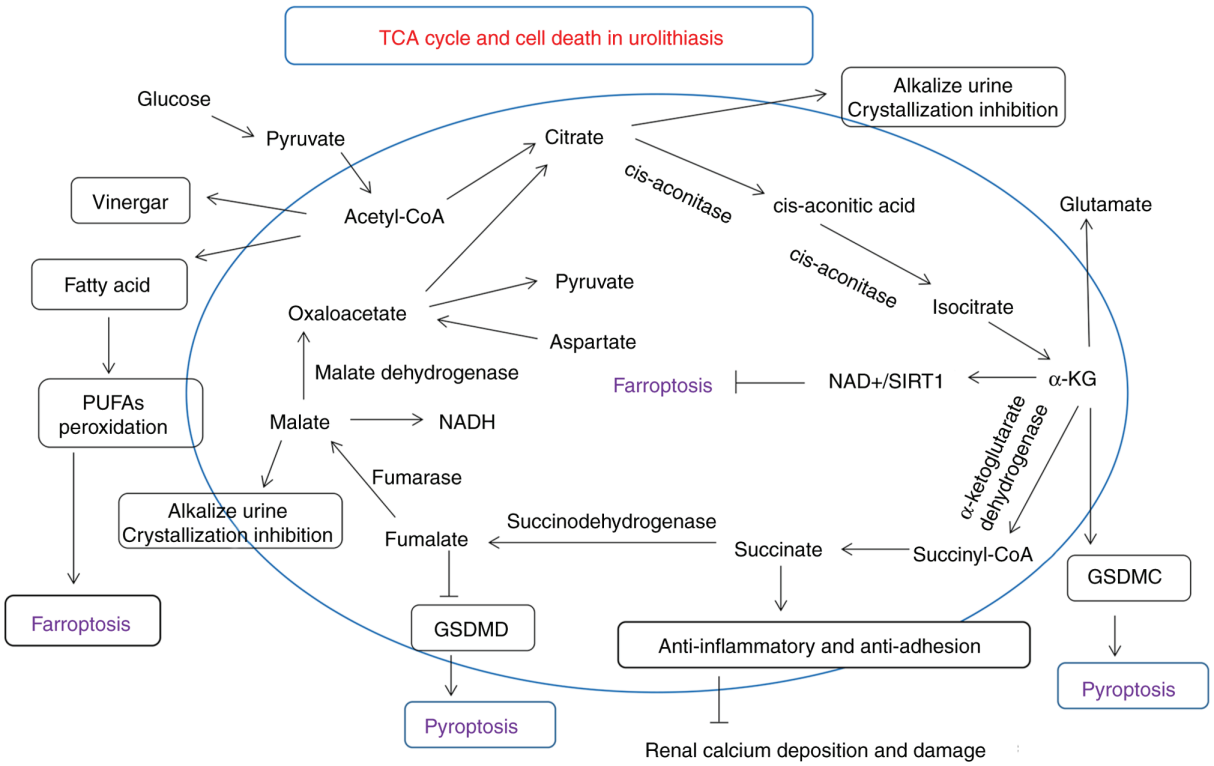

Figure 2. Roles of small organic acids, TCA cycle-related molecules (i.e., citric acid, malate, fumarate and succinate), and cell death in urolithiasis are described in detail. Various molecules involved in the TCA cycle, particularly citrate, which is considered to be a stone-inhibiting substance, may regulate molecules associated with kidney cell damage and cell death. GSDMD, gasdermin D; GSDMC, gasdermin C; PUFAs, polyunsaturated fatty acids; TCA, tricarboxylic acid; α-KG, α-ketoglutaric acid.

oxidative damage and CaOx crystal deposition by activating TFEB-induced autophagy (123). Trimethylamine N-oxide, a metabolite derived from gut microbes, not only plays a key role in the pathogenesis of atherosclerosis, diabetes and chronic kidney disease, but also exacerbates kidney damage and renal tubule cell autophagy, apoptosis and inflammation, and promotes hyperoxaluria-induced CaOx crystal deposition by triggering the PERK/ROS pathway (124).

Other forms of cell death and urolithiasis: NETosis, cuproptosis and disulfidptosis. Recent research has demonstrated that NETosis, a unique neutrophil death mechanism that can cause various inflammatory and autoimmune conditions, is also involved in the development and progression of kidney disease (125). Increased neutrophil infiltration and NETosis have been found to differentiate patients with brushite and CaOx stones, potentially explaining the apparent increases in scarring and inflammation in the papillae in the former, although the role of neutrophil activation in the increased incidence of brushite stone formation needs to be investigated further (126). Recent studies have also shown that ferroptosis in renal parenchymal cells initiates neutrophil migration to injury sites through C-X-C chemokine receptor type 4, a surface receptor that binds to the metformin-iron-NGAL complex, causing NETosis to aggravate AKI, and that a reduction in iron concentration may protect against kidney damage (127).

Malireddi *et al* (128) described PANoptosis as an inflammatory programmed cell death type with key features of pyroptosis, apoptosis and/or necroptosis that cannot be characterized as any one of these death modes alone. As previously demonstrated, NLRP12 drives the activation of the inflammasome and PANoptosome, and its loss in a hemolysis model protected mice from AKI and death (81). It has been mentioned previously that urolithiasis-related processes can cause pyroptosis, apoptosis, and necroptosis; whether they are associated directly with PANoptosis requires further investigation. Other regulatory pathways of non-apoptotic cell death (i.e., parthanatos, lysozincrosis and disulfidptosis) have also been found to exist (129), although their roles in kidney stone progression remain to be determined.

4. Oxalate metabolism and the tricarboxylic acid cycle in cell death

Oxalic acid is a toxic end-metabolite with no known physiological function in humans (130). The metabolic precursors of oxalic acid *in vivo* include glyoxylate, aromatic amino acids glyoxal and vitamin C (131). Oxalic acid in human blood comes from diet, ascorbic acid degradation and liver synthesis (132). Therefore, the causes of hyperoxaluria include the excessive intake of oxalic acid in the daily diet, intestinal diseases leading to the excessive absorption of oxalic acid in the intestine and the intestinal excretion of oxalic acid, and metabolic disorders of the liver, leading to abnormal increases in endogenous oxalates, such as primary hyperoxaluria (133). A low urine volume and dehydration are common risk factors for all types of stones, while hyperoxaluria, high-calcium urea and low-citrate urea are the main risk factors for calcium-containing stones (130). The increased excretion of

urine citrate, a molecule involved in the tricarboxylic acid (TCA) cycle, reduces the risk of stone development by inhibiting calcium crystallization and complexing (134).

Metabolites in the TCA cycle include malate, fumarate, pyruvate, alpha-ketoglutarate, succinate and citrate/isocitrate, while low urinary TCA circulating organic anions, particularly low methylmalonic acid, ethyl malonic acid and citrate/isocitrate, are potential biomarkers of renal damage in early diabetic nephropathy (135). By reducing Cu^{2+} to Cu^{+}, ferredoxin-1 promotes the abnormal oligomerization of copper-dependent fatty acylated proteins in the TCA cycle and reduces Fe-S cluster protein levels, leading to protein aggregation, toxic stress, and ultimately, to cuproptosis (136). Fumarate, an intermediate in the TCA cycle, succinacylates GSDMD and GSDME at specific cysteine sites, inhibiting the formation of oligomers and thereby preventing pyroptosis (137). Succinate also reduces renal calcium deposition and damage in an ethylene glycol-induced rat model via anti-inflammatory effects and the inhibition of cell adhesion and osteogenic differentiation (138). The TCA cycle also affects ferroptosis by participating in the production of O_2·and NAD(P)H (139). However, the direct role of cuproptosis in kidney stone development, particularly via the TCA cycle, remains to be determined.

In a previous study, the preliminary analyses of metabolic profiles in urine from 110 patients with kidney stones and 106 healthy controls revealed that glycine, serine and threonine metabolism, the TCA cycle, glyoxylate and dicarboxylate metabolism, and phenylalanine metabolism were four metabolic pathways closely related to the presence of kidney stones (140). Citric acid and malate, two TCA cycle molecules, can also alkalize urine, particularly for uric acid stone formation (141,142). Vinegar can affect urinary citrate and calcium excretion through epigenetic regulation, thereby preventing the formation of calcium crystals in the kidney (143). The metabolite α-ketoglutaric acid (α-KG) can promote GSDMC-dependent pyroptosis via the death receptor 6-activated caspase-8, and its pyroptosis inducing efficiency depends on the acidity of the environment (144). In addition to affecting REDOX homeostasis and cytokine signaling, oxalate can also impair macrophage metabolism, leading to a reduced antimicrobial response and increased infection (145). UPEC can use a novel UPEC-associated two-component signaling system to facilitate the utilization of the metabolite α-KG to adapt to life in the urinary tract (146). However, in cardiomyocytes α-KG inhibits ferroptosis and alleviates myocardial cell injury by upregulating NAD+ levels and activating the SIRT1 signaling pathway (147). The roles of small organic acids, TCA cycle-related molecules (i.e., citric acid, malate, fumarate and succinate), and cell death in urolithiasis are illustrated in Fig. 2. In total, the main targets or molecules that have signaling crosstalk with cell death and urolithiasis are mainly oxidative stress (e.g., NRF2), inflammatory (e.g., NLRP3), adhesive (e.g., succinate), aggregation (e.g., citrate) or metabolic genes (α-ketoglutarate).

5. Conclusion and future directions

Numerous types of urinary calculus are related to cell death, whose progression commonly causes renal tubular cell damage, often mediated by apoptosis, pyroptosis, necroptosis and ferroptosis, are related to oxidative stress, inflammation and lipid peroxidation molecular signals caused by high oxalate and calcium crystal aggregation and precipitation. In addition, the roles of cell death-related metabolic disorders and non-unique cell death (e.g., PANoptosis) in urolithiasis processes remain to be explored. However, there are still limitations as the changes in *in vitro* experiments and animal models of CaOx-induced kidney injury cannot always represent the actual situation of the real stone formation in human.

The understanding of cell death was initially limited to apoptosis, and various types of cell death (i.e., necroptosis, pyroptosis and ferroptosis) and their mechanisms and evolution are increasingly being explored. Specific biomarkers are required to identify cell death types, and the exploration of cell death physiology and pathology and their roles in urolithiasis is essential. Elucidation of the regulatory mechanisms of renal inflammatory injury, renal cell death, and related crosstalk is important for the prevention and treatment of kidney stone-related diseases. Bioinformatic technology, metabolomics, intestinal flora, spatial transcription analysis, artificial intelligence and other methods are developing rapidly and will be increasingly used to study the urine composition and environment in patients with kidney stones, which can open new avenues for the exploration of urolithiasis (15). In addition, the application of organoids and other new models, which can simulate the pathological conditions of human urinary calculi is anticipated to be used to explore the corresponding mechanisms of the disease in future.

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Authors' contributions

All authors (LW, XX, CH, YL and LT) contributed to the conception and design of the study. The first draft of the manuscript was written by LW, XX and LT. YL and CH contributed to the literature search and the preparation of the figures. All authors commented and critically revised on previous versions of the manuscript. All authors have read and agreed to the final version of manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

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

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