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Research Advances in the Molecular Biological Mechanisms of Depleted Uranium–Induced Renal Injury

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Abstract: Against the backdrop of the development of nuclear energy technologies and the application of uranium-containing weapons, the health effects induced by depleted uranium (DU) have attracted increasing attention. As the primary organ for DU accumulation in the human body, the kidney is highly susceptible to DU-induced toxicity. The mechanisms underlying DU-induced renal injury mainly involve oxidative stress, mitochondrial structural and functional dysfunction, and cell death. However, detailed elucidation of these pathogenic mechanisms remains insufficient. Therefore, this review systematically summarizes the molecular biological mechanisms of DU-induced renal injury, with the aim of providing a theoretical basis for subsequent animal experiments and population-based epidemiological studies.

1. Introduction

Uranium is an important radioactive resource. After purification and enrichment, the abundance of ^{235}U can be increased from less than 1% in natural uranium to approximately 2%–4%. The resulting product is referred to as enriched uranium, which serves as an important raw material for nuclear weapons. Correspondingly, in the residual product generated during the enrichment process, the abundance of ^{235}U typically decreases to 0.2%–0.3%. This form of uranium is referred to as depleted uranium (DU)[1].

During the mining, production, and application of uranium, the dust and particulate matter generated can enter the human body through the respiratory tract, skin, or gastrointestinal tract. After entering the body, uranium is primarily transported in the form of the uranyl ion (UO_2^{2+}) and accumulates in the kidneys via the blood circulation. The kidneys are not only the main organs responsible for the excretion of uranium and its compounds but also the principal target organs for their accumulation in vivo.

Short-term intake of large amounts of uranium can lead to excessive accumulation in the kidneys, thereby inducing renal functional impairment. This is mainly manifested by increased levels of urinary protein, serum creatinine (SCr), and blood urea nitrogen (BUN). Pathological examination reveals dilation of the cortical and papillary tubules, as well as tubular cast formation and interstitial hemorrhage in the renal cortex, medulla, and papillary regions. In severe cases, these alterations may progress to acute renal failure[2,3].

At present, numerous animal experiments and epidemiological studies have been conducted worldwide to investigate DU-induced renal injury. However, the underlying molecular biological mechanisms have not yet been fully elucidated, and certain discrepancies remain in the current understanding.

In view of this, the present study systematically reviews the research progress on the molecular biological mechanisms underlying DU-induced renal injury, with particular emphasis on the potential signaling pathways involved, in order to provide a theoretical reference for subsequent animal experiments and epidemiological investigations.

2. Pathological and Epidemiological Basis of Depleted Uranium–Induced Renal Injury

2.1. Pathological Studies of Renal Injury

Uranium is a heavy metal element that possesses both radiological and chemical toxicity, and the pathological characteristics of uranium exposure–induced renal injury have become a major focus of research. Animal studies have demonstrated that DU-induced renal injury exhibits clear dose- and time-dependent characteristics and is associated with multi-level pathological alterations in renal tissues.

Acute uranium exposure primarily induces marked renal dysfunction and structural damage to renal tissues. Studies have shown that short-term uranium exposure can rapidly lead to renal impairment; for example, after 48 h of DU exposure in rats, urinary creatinine, BUN, and glucose levels are significantly elevated[4]. At the histological level, uranium can selectively target renal tubular structures, manifesting as marked dilation of renal tubules in the cortical and papillary regions, accompanied by chronic inflammatory cell infiltration in the interstitium and fibrotic proliferation[5]. At the cellular level, renal tubular epithelial cells represent the primary cellular targets of uranium toxicity. Characteristic lesions include loss of the brush border, cytoplasmic swelling and vacuolization, and delayed cellular regeneration, ultimately leading to disorganization of cellular arrangement and cell death[6]. Ultrastructural observations further confirm that uranium can directly damage intracellular organelles, manifested by mitochondrial swelling, reduction or disappearance of cristae, as well as uneven distribution of nuclear heterochromatin and invagination of the nuclear membrane[7].

Compared with acute exposure, the progression of renal pathological alterations induced by chronic DU exposure is relatively insidious. In the early stage of chronic exposure, the kidneys of mice mainly exhibit glomerular swelling, inflammatory cell infiltration, widening of the intercellular spaces of renal tubular epithelial cells, and swelling and necrosis of some epithelial cells. In the later stage of exposure, marked renal interstitial fibrosis can be observed[8]. Notably, long-term chronic uranium exposure may, to some extent, induce adaptive changes in the kidneys, thereby enhancing their tolerance to injury. For example, under repeated uranium exposure at a relatively low dose (0.25 mg/kg/day), the gene expression of the early biomarker of renal injury, clusterin (CLU), is downregulated, and renal function indicators can return to normal levels, suggesting that the kidneys possess a certain compensatory capacity[2]. In addition, when mice previously subjected to chronic DU exposure are subsequently challenged with acute uranyl nitrate (UN), the gene expression level of the uranium-induced renal injury marker kidney injury molecule-1 (KIM-1) is significantly lower than that in the group exposed to acute UN alone, with an approximately 3.7-fold reduction in expression ($P < 0.05$), accompanied by a corresponding attenuation of renal injury[9].

2.2. Epidemiological Evidence in Human Populations

Epidemiological studies indicate that acute uranium exposure events reported in the 20th century

primarily affected human health through two major routes: gastrointestinal intake and occupational exposure. Studies have shown that When the uranium intake reaches 0.15 mg/kg, conventional renal function indicators, including SCr and BUN, in exposed individuals remain within the normal reference range[10]. However, in cases involving markedly higher ingestion doses, when uranium intake reaches 89 mg/kg, abnormalities can be observed in multiple indicators, including SCr, BUN, albumin, urine volume, and urinary glucose. These findings suggest that high-dose acute uranium exposure can lead to significant renal functional impairment.

With regard to occupational exposure, uranium hexafluoride (UF_6) exposure incidents occurring during nuclear facility accidents represent cases of particular research value. In one uranium hexafluoride (UF_6) leakage accident, two exposed workers not only sustained chemical burns to the skin but also had a history of inhalational exposure to uranium compounds. Urinalysis during the acute phase revealed abnormalities in renal tubular injury markers, including proteinuria and the presence of urinary casts. Follow-up results showed that transient casts appeared 18 days after the accident, after which renal function indicators gradually returned to baseline levels, suggesting that renal injury induced by acute uranium exposure exhibits a certain degree of dose dependence and potential reversibility[11].

Compared with acute exposure, chronic uranium exposure involves a broader population, primarily including residents in areas with high uranium concentrations in drinking water, Gulf War veterans, and occupationally exposed populations. Long-term uranium intake from drinking water is significantly positively correlated with urinary uranium levels. For every 1 μg increase in daily uranium intake, urinary uranium concentration increases by 0.21 ng/mmol Cr, with a 95% confidence interval (confidence interval, CI) of 0.19–0.24. Moreover, a significant exposure–response relationship has been observed between uranium exposure from drinking water and the risk of moderate chronic kidney disease. Compared with individuals consuming drinking water containing <2 μg/L uranium, those exposed to ≥15 μg/L uranium in drinking water for three years or longer show a 14% increased risk of chronic kidney disease (95% CI, 5%–25%). Among Gulf War veterans, follow-up studies conducted between 2009 and 2019 observed changes in several indicators, including SCr, uric acid, urinary glucose, urinary albumin, and total protein. However, only a mild increase in urinary interleukin-18 (IL-18) levels was detected in 2019, and the overall levels remained close to the normal range. Therefore, current evidence is still insufficient to determine whether uranium exposure–related renal injury is present, and longer-term follow-up observations are required[12-15].

With increasing cumulative absorbed doses of uranium in the body, the mortality risks of kidney stones, renal cancer, chronic kidney disease, and multiple myeloma show an upward trend [16,17]. However, some studies have reported contrasting findings[18], according to standardized mortality ratio (SMR) analyses, uranium miners appear to be protected against mortality from renal diseases, all-cause mortality, cardiovascular diseases, or diabetes as a result of uranium exposure.

In summary, epidemiological evidence suggests that DU exposure is associated with renal injury. Its health effects may manifest as acute and potentially reversible renal dysfunction, alterations in early biomarkers of renal tubular injury under chronic exposure conditions, and, in populations with long-term high cumulative exposure, an increased risk of kidney-related diseases and mortality.

3. Molecular Biological Mechanisms of Depleted Uranium–Induced Renal Injury

3.1. Oxidative Stress

Oxidative stress is considered one of the important mechanisms underlying DU-induced renal injury and plays a key role in the initiation and progression of both acute and chronic kidney damage. Under conditions of oxidative stress, excessive production of reactive oxygen species (ROS) and

reactive nitrogen species (RNS) can induce oxidative damage to lipids, proteins, and DNA, and may mediate cellular oxidative injury by regulating the expression of apoptosis-related genes[19,20]. DU-induced oxidative stress can lead to injury and necrosis of renal tubular epithelial cells, accompanied by a series of pathological alterations, including glomerulosclerosis, apoptosis, inflammatory cell infiltration, and tubulointerstitial fibrosis[1,21].

Both acute and chronic DU exposure can induce significant alterations in total oxidant status (TOS), total antioxidant status (TAS), and the oxidative stress index (OSI) in renal tissues and serum. Moreover, these indicators exhibit dose-dependent changes with increasing DU levels in the body[19]. In acute exposure models, rats treated with DU exhibit significantly elevated levels of the oxidative stress end-product malondialdehyde (MDA) indicating that DU can markedly enhance lipid peroxidation[1,21,22].

At the level of molecular regulation, DU can influence oxidative stress through multiple mechanisms. On the one hand, DU can inhibit the activities of aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1 (ADH1), thereby inducing carbonyl stress and reducing the metabolism of reactive aldehydes[23]; On the other hand, DU can suppress the signaling pathway of nuclear factor erythroid 2–related factor 2 (Nrf2), a key transcription factor in the renal antioxidant defense system. Under conditions of medium- and high-dose DU exposure, its cytoplasmic chaperone protein Kelch-like ECH-associated protein 1 (Keap1) is inhibited, resulting in reduced accumulation and nuclear translocation of Nrf2. This subsequently downregulates the expression of the downstream antioxidant gene glutamate–cysteine ligase catalytic subunit (GCLC), thereby aggravating the oxidative stress response[24].

In chronic DU exposure models, the expression of antioxidant enzymes and ion transport proteins associated with oxidative stress responses is also altered. For example, the expression of superoxide dismutase 1 (SOD1) is upregulated, while the expression of sodium-dependent phosphate cotransporter II (NaPi-II) and its encoding gene SLC34A1 is also increased[25]. It has been suggested that NaPi-II may enhance the accumulation of DU in renal tubules and mediate its cytotoxic effects by promoting the reabsorption of DU from primary urine and reducing its excretion in urine[26].

DU can also induce oxidative stress through the coordinated activation of multiple signaling pathways. Among these, the Hedgehog (Hh) signaling pathway plays an important role in DU-induced oxidative stress. Studies have shown that mice orally administered 100 mg/kg DU every two days for four consecutive weeks exhibit significantly decreased expression of antioxidant enzymes in renal tissues, including heme oxygenase-1 (HO-1), superoxide dismutase 2 (SOD2), and catalase (CAT). In contrast, knockout of Gli2, a key effector of the Hh signaling pathway, markedly upregulates the levels of these antioxidant enzymes, reduces renal ROS production, and improves renal tissue structure as well as renal function indicators[6]. On the other hand, as a heavy metal element, DU can directly promote the generation of ROS during its metabolic processes in vivo. Previous studies have indicated that a mutually reinforcing relationship exists between ROS production and the Hh signaling pathway. Specifically, ROS can activate the Hh signaling pathway, while activation of the Hh pathway further promotes ROS generation, thereby forming a positive feedback amplification effect[27,28].

In addition, DU exposure can enhance the conversion of linoleic acid to arachidonic acid (AA) in human renal proximal tubular epithelial cells (HK-2). AA can promote the excessive generation of ROS through multiple pathways. On the one hand, AA can activate Ca^{2+} channels on the cell membrane, facilitating Ca^{2+} influx and activating NADPH oxidase, thereby inducing ROS production[29]; On the other hand, AA can also promote ROS generation through the overactivation of receptor-interacting protein 1 (RIP1) [30]. Furthermore, during the metabolic processes of AA via the cyclooxygenase (COX) and lipoxygenase (LOX) pathways, the oxidative stress response can be further amplified.

In summary, DU can induce oxidative stress in the kidneys through multiple pathways. These mechanisms include increasing the oxidative burden in vivo, suppressing the Nrf2/Keap1-mediated antioxidant defense system, and activating the Hedgehog (Hh) signaling pathway and arachidonic acid metabolism. Together, these processes contribute to a sustained and amplified oxidative stress state, ultimately leading to renal cell injury, inflammatory responses, and pathological alterations such as renal interstitial fibrosis.

3.2. Mitochondrial Structural and Functional Dysfunction

Mitochondria are the central organelles responsible for intracellular energy metabolism. In addition to mediating ATP synthesis, they also participate in the regulation of multiple important biological processes, including apoptosis, autophagy, and Ca^{2+} homeostasis. DU exposure can reduce the number of mitochondria in renal cells and induce structural abnormalities such as mitochondrial swelling, vacuolization, and impaired membrane integrity. These alterations lead to mitochondrial dysfunction, which is mainly characterized by decreased mitochondrial membrane potential (MMP), reduced ATP synthesis, increased ROS generation, aggravated lipid peroxidation, and enhanced mitophagy[22,31,32].

MMP is an important indicator reflecting mitochondrial membrane integrity and metabolic function, and its decline or collapse is considered a critical trigger of cellular necrosis and apoptosis [33,34]. In an acute DU exposure model, rats treated with 10 mg/kg DU for 72 h exhibited a significant decrease in mitochondrial MMP in renal cells, whereas intervention with the mitochondrial protective agent melatonin (melatonin, Mel) partially restored MMP levels and improved mitochondrial and renal function[22].

Mechanistic studies have shown[35] that DU can induce the translocation of the pro-apoptotic protein BCL2-associated X protein (Bax) to the outer mitochondrial membrane, where it cooperates with the abnormally opened mitochondrial permeability transition pore (MPTP), leading to a decline in MMP. The translocation of Bax to the mitochondrial outer membrane not only disrupts mitochondrial membrane potential but also promotes the release of multiple mitochondria-derived apoptotic signaling molecules into the cytoplasm, thereby inducing apoptosis of renal cells [36]. In addition, persistent opening of the MPTP can facilitate the release of proteins such as cytochrome c and apoptosis-inducing factor (AIF), further activating downstream apoptotic cascades [36,37]. Blocking the abnormal opening of the MPTP has been demonstrated to significantly alleviate DU-induced mitochondrial dysfunction and renal injury.

Inhibition of the mitochondrial oxidative respiratory chain by DU is considered one of the direct causes of energy metabolism disorders. In vivo, DU mainly exists in the form of the redox-active uranyl ion (UO_2^{2+}), which can markedly increase intracellular ROS levels. Excessive ROS attack the polyunsaturated fatty acids abundant in the mitochondrial inner membrane, triggering lipid peroxidation and subsequently leading to structural defects or even disruption of the mitochondrial inner membrane[38]. Once the integrity of the mitochondrial inner membrane is compromised, the enzyme complexes of the oxidative respiratory chain lose their stable anchoring, thereby impairing the overall function of the respiratory chain.

In addition, DU can directly inhibit the activity of mitochondrial enzyme complexes II, III, IV, and V[39,40]. In particular, inhibition of complexes IV and V leads to the accumulation of highly reactive intermediates upstream of complexes I–III. These intermediates can reduce molecular oxygen to superoxide anion ($O_2^{\cdot -}$), which is subsequently converted into various ROS. Continuous accumulation of ROS within mitochondria can disrupt oxidative phosphorylation, resulting in decreased ATP synthesis, collapse of MMP, and ultimately damage to the integrity of the mitochondrial outer membrane. Half-maximal inhibitory concentrations (IC_{50}) of DU for complexes

IV and V are comparable to the dose threshold that induces nephrotoxicity, suggesting that these enzyme complexes may represent key molecular targets of DU-induced nephrotoxicity. Notably, the organism may partially compensate for this functional inhibition by upregulating the gene expression of the relevant enzyme complexes [38].

Recent studies have shown that downregulation of mitochondrial persulfide dioxygenase ETHE1 is closely associated with DU-induced nephrotoxicity. DU exposure can decrease ETHE1 expression, leading to the accumulation of hydrogen sulfide (H_2S) and its derivatives (such as thiosulfate) in vivo. High concentrations of H_2S may inhibit mitochondrial respiratory function, whereas exogenous supplementation of ETHE1 can significantly alleviate DU-induced mitochondrial dysfunction and oxidative stress injury, suggesting that the ETHE1/Nrf2 signaling axis plays an important regulatory role in DU-induced nephrotoxicity [22,41].

However, other studies have proposed a different perspective[23] , suggesting that H_2S may exert protective effects on mitochondrial and renal function by enhancing the activation and nuclear translocation of Nrf2, thereby reversing the DU-induced downregulation of aldehyde-metabolizing enzymes and reducing the generation of reactive aldehydes, ultimately lowering oxidative stress levels.

In addition, recent studies have found that DU can induce ferroptosis in renal cells by downregulating ETHE1 expression. DU exposure leads to mitochondrial dysfunction, and excessive accumulation of ROS activates the P38-MAPK stress signaling pathway. This pathway further promotes ferritinophagy mediated by nuclear receptor coactivator 4 (NCOA4). This cascade results in intracellular Fe^{2+} overload and lipid peroxidation, ultimately triggering ferroptosis [42].

In summary, DU-induced mitochondrial injury in the kidneys represents a multi-level process involving the coordinated action of multiple pathways. DU not only directly disrupts mitochondrial structure—such as mitochondrial swelling and inner membrane damage—and impairs key mitochondrial functions, including ATP synthesis and maintenance of mitochondrial membrane potential (MMP), but also promotes mitochondrial-dependent apoptosis mediated by the Bax/MPTP pathway. In addition, downregulation of ETHE1 further amplifies oxidative stress, together forming a cascade of "structural damage–functional impairment–cell death." The recently proposed ETHE1/Nrf2 regulatory axis provides a new integrative perspective for understanding the mitochondrial mechanisms underlying DU-induced renal injury.

3.3. Cell Death

Cell death can occur through several forms, including apoptosis, pyroptosis, and necrosis [43]. Studies have shown that DU exposure can significantly increase the level of apoptosis in renal tissues, and typical apoptosis-like pathological alterations can be observed in renal tubular epithelial cells [44-46]. Current evidence suggests that DU-induced apoptosis of renal cells mainly occurs through three pathways: the intrinsic apoptotic pathway, the extrinsic apoptotic pathway, and the endoplasmic reticulum stress–related apoptotic pathway.

The intrinsic apoptotic pathway is a form of programmed cell death triggered by intracellular stress signals and primarily involves key molecular events such as regulation by the Bcl-2 protein family, release of cytochrome c, and activation of the Caspase cascade, ultimately leading to apoptosis. Studies have shown that DU exposure can induce intrinsic apoptosis through both DNA damage and mitochondrial pathways[47].

DU binds to DNA molecules in the form of UO_2^{2+}, catalyzing hydrolysis of DNA strands and interfering with DNA replication, transcription, and repair processes. Impairment of DNA synthesis and repair is considered one of the major triggers of apoptosis in renal cells [48].Uranium can covalently interact with oxygen atoms in the phosphate backbone of DNA or with nitrogen and

oxygen atoms within nucleobases, forming uranium–DNA adducts. One study reported that after cells were treated with 300 μM uranium for 48 h, approximately eight uranium atoms were detected per 1000 phosphate groups on average [49]. These findings suggest that uranium exposure may initiate the intrinsic apoptotic program by inducing direct DNA damage in renal cells.

DU can catalyze the production of highly reactive hydroxyl radicals from H_2O_2 through a Fenton-like reaction, which subsequently attack DNA molecules. Compared with iron, the conventional catalyst in Fenton reactions, DU exhibits approximately sixfold higher catalytic efficiency. DU exposure significantly increases the levels of DNA oxidative damage markers, including 8-hydroxydeoxyguanosine (8-OHdG) and thymidine glycol, and the extent of DNA damage shows a dose-dependent relationship with DU concentration[50]. Application of the ROS scavenger sodium azide markedly suppresses the formation of 8-OHdG, further suggesting that DU indirectly damages DNA by promoting oxidative stress, thereby initiating the intrinsic apoptotic pathway.

In addition, DU can induce cell death through the mitochondrial-dependent apoptotic pathway. Increased mitochondrial membrane permeability promotes the release of cytochrome c into the cytoplasm, where it binds to Apaf-1 to form the apoptosome, subsequently activating Caspase-9 and Caspase-3[51]. In the kidneys of uranium-exposed rats, the expression of the pro-apoptotic protein Bax is significantly upregulated, and the expression level of Caspase-3 increases markedly with increasing DU concentrations[35,36], indicating that uranium exposure can induce intrinsic apoptosis in renal cells through the mitochondrial apoptotic pathway.

Extrinsic apoptosis is a form of programmed cell death mediated by extracellular death signals. This process is typically initiated by the binding of cell-surface death receptors—such as Fas and tumor necrosis factor receptors (TNFRs)—to their corresponding ligands[48]. Following ligand–receptor interaction, a death-inducing signaling complex (DISC) is formed, which subsequently activates initiator Caspases such as Caspase-8 and Caspase-10. These initiator Caspases further activate downstream effector Caspases, including Caspase-3 and Caspase-7, ultimately leading to apoptosis[52].

In DU-exposed HK-2 cells, the expression level of sFasL (Fas ligand) is significantly upregulated, with an increase of approximately 400%, accompanied by a marked elevation in Caspase-3 expression[36] These findings suggest that DU may participate in renal cell apoptosis through the Fas-mediated extrinsic apoptotic pathway. In addition, the Fas-mediated apoptotic signaling pathway involves activation of multiple downstream molecules, including ERK/JNK MAPKs, JNK, and p38-K, which can further regulate the apoptotic process. Among these pathways, the MAPK signaling pathway appears to play a particularly important role. Gene Ontology (GO) analysis has shown that in HK-2 cells exposed to 800 μM DU, the MAPK signaling pathway ranks among the most significantly enriched pathways [48]. These results suggest that DU may induce extrinsic apoptosis in HK-2 cells through activation of the MAPK signaling pathway.

DU-induced endoplasmic reticulum (ER) stress–related apoptosis is primarily mediated through inhibition of the Nrf2 signaling pathway. Reduced Nrf2 activity can trigger ER stress responses, which subsequently activate Caspase-12 and Caspase-3, thereby initiating the apoptotic program. DU exposure significantly suppresses the nuclear translocation of Nrf2 in renal cells and downregulates the expression of proteasome subunits α type-6 and β type-7. This reduction decreases the assembly of the 20S proteasome complex, and impairment of proteasome function interferes with the clearance of misfolded or unfolded proteins within the ER, ultimately inducing ER stress[53].

ER stress can further promote apoptosis through activation of multiple signaling pathways involved in the unfolded protein response (UPR). DU exposure has been shown to significantly decrease the expression of UBL5, a protein associated with ER stress[48]. Previous studies indicate that downregulation of UBL5 can activate multiple cell death pathways, thereby inducing apoptosis[54]. These findings suggest that DU may disrupt downstream apoptotic signaling by

activating ER stress pathways and suppressing UBL5 expression, ultimately leading to cell apoptosis.

In addition, the ER serves as the primary intracellular reservoir for Ca^{2+}. Disruption of ER Ca^{2+} homeostasis or depletion of ER Ca^{2+} can trigger ER stress responses[55]. Inositol 1,4,5-trisphosphate receptors (IP3Rs) are ligand-gated channels that mediate Ca^{2+} release from the ER into the cytoplasm. DU exposure significantly upregulates the expression of IP3Rs in renal cells[56], resulting in substantial Ca^{2+} release from the ER into the cytoplasm. This process subsequently activates the ER stress–associated cysteine protease Caspase-12, which further activates Caspase-3 and ultimately induces apoptosis in renal cells [57].

Moreover, excessive ROS generated in the kidneys following DU exposure can markedly upregulate the expression of the key transcription factor C/EBP homologous protein (CHOP) involved in ER stress–mediated apoptosis[53], Through oxidative stress, DU triggers the UPR and activates Caspase-12, thereby initiating the apoptotic cascade. Administration of the ROS scavenger N-acetylcysteine (NAC) has been shown to significantly alleviate renal cell apoptosis induced by DU exposure.

Pyroptosis is an inflammatory form of programmed cell death mediated by inflammasomes and is characterized by activation of Caspase-1. Activated Caspase-1 cleaves Gasdermin D (GSDMD), which forms pores in the cell membrane, leading to cell swelling, membrane rupture, and the release of mature pro-inflammatory cytokines IL-1β and IL-18, thereby triggering a strong inflammatory response[58]. DU exposure can induce excessive generation of reactive oxygen species (ROS) in renal tubular epithelial cells, which subsequently activates the key NLRP3 inflammasome. The activated NLRP3 inflammasome recruits and cleaves pro-Caspase-1, generating the active form, cleaved Caspase-1. On the one hand, cleaved Caspase-1 cleaves GSDMD, resulting in membrane pore formation and leakage of lactate dehydrogenase (LDH); on the other hand, it processes the precursors of IL-1β and IL-18, promoting their maturation and release, ultimately inducing pyroptosis in renal cells[58,59]. AKT, an important downstream signaling molecule in this pathway, plays a key role in promoting cell survival and inhibiting cell death during heavy-metal-induced cellular injury [53,60]. DU exposure significantly reduces AKT expression in renal cells, whereas treatment with NaHS upregulates AKT expression and markedly reduces the level of renal cell pyroptosis. These findings suggest that endogenous H_2S can effectively alleviate DU-induced renal cell pyroptosis [61], and the development of novel H_2S donors may represent a potential therapeutic strategy.

In summary, DU exposure can synergistically induce apoptosis and pyroptosis in renal cells through multiple signaling pathways. These mechanisms include intrinsic apoptosis mediated by direct DNA damage and oxidative stress, extrinsic apoptosis mediated by death receptors and the MAPK signaling pathway, endoplasmic reticulum stress–related apoptosis triggered by inhibition of the Nrf2 pathway and disruption of ER Ca^{2+} homeostasis, as well as pyroptosis mediated by activation of the NLRP3/Caspase-1 signaling pathway.

4. Conclusion and Perspectives

Comprehensive evidence from animal experiments, epidemiological investigations, and molecular mechanism studies indicates that DU exposure can exert adverse effects on the kidney, which is considered one of the primary target organs of DU toxicity. The proximal renal tubules are the main sites of injury, manifested by renal functional abnormalities, structural alterations in renal tissue, and activation of multiple forms of cell death. At the molecular level, oxidative stress, mitochondrial structural and functional dysfunction, and cell death processes play critical roles in DU-induced renal injury.

Although significant progress has been made in recent years in elucidating the mechanisms of DU-induced nephrotoxicity, several issues remain to be addressed. First, most current mechanistic studies

are still based on animal models and in vitro cell experiments, and uncertainties remain when extrapolating these findings to scenarios of long-term, low-dose exposure in human populations. Second, although epidemiological studies have observed changes in renal tubular injury biomarkers, their biological significance and causal relationship with clinical outcomes remain unclear. Third, under different exposure doses, exposure routes, and exposure durations, the boundary between adaptive renal responses and toxic effects induced by DU requires further clarification.

Future studies should focus on several key aspects. First, long-term prospective cohort studies in exposed populations should be conducted, combined with highly sensitive biomarkers of renal injury, to clarify the health risks associated with chronic DU exposure and their progression patterns. Second, further investigations are needed to elucidate the key regulatory nodes linking oxidative stress, mitochondrial structural and functional dysfunction, and cell death signaling pathways, in order to identify molecular targets with potential therapeutic value. Third, emerging mechanisms—such as the ETHE1/Nrf2 axis, H_2S signaling pathways, and inflammasome regulation—should be explored to clarify their roles in DU-induced nephrotoxicity and to provide a theoretical basis for the development of preventive and therapeutic strategies.

In summary, DU-induced renal injury is a complex, multilevel process involving the coordinated action of multiple mechanisms. Its toxic effects evolve from early molecular events to cellular damage and ultimately to histopathological alterations. A systematic elucidation of these mechanisms will not only deepen the understanding of uranium toxicology but also provide an important scientific basis for assessing human health risks and developing effective protective measures.

References

[1] Yang X, Liu J, Yin Y, et al. MSC-EXs inhibits uranium nephrotoxicity by competitively binding key proteins and inhibiting ROS production. Ecotoxicol Environ Saf, 2025, 289: 117654

[2] De Castro L, Manoury A, Claude O, et al. Renal toxicity and biokinetics models after repeated uranium instillation. Sci Rep, 2023, 13(1): 4111

[3] Zhong D, Wang R, Zhang H, et al. Induction of lysosomal exocytosis and biogenesis via TRPML1 activation for the treatment of uranium-induced nephrotoxicity. Nat Commun, 2023, 14(1): 3997

[4] Zhang H, Wang Y, Wang R, et al. TRPML1 agonist ML-SA5 mitigates uranium-induced nephrotoxicity via promoting lysosomal exocytosis. Biomed Pharmacother, 2024, 181: 117728

[5] Chen X, Dai C M, Zhang B, et al. RGD hydrogel-loaded ADSC extracellular vesicles mitigate uranium-induced renal injury via TLR4/NF-kappaB pathway inhibition. J Nanobiotechnology, 2025, 23(1): 114

[6] Xie X, Fu G, Liu Y, et al. Hedgehog pathway negatively regulated depleted uranium-induced nephrotoxicity. Environ Toxicol, 2024, 39(7): 3833-3845

[7] Li J, Li Y, Zhao Y, et al. Mitigation of depleted uranium-induced mitochondrial damage by ethylmalonic encephalopathy 1 protein via modulation of hydrogen sulfide and glutathione pathways. Arch Toxicol, 2025, 99(3): 1133-1141

[8] Zhu G, Xiang X, Chen X, et al. Renal dysfunction induced by long-term exposure to depleted uranium in rats. Arch Toxicol, 2009, 83(1): 37-46

[9] Bontemps-Karcher A, Magneron V, Conquet L, et al. Renal adaptive response to exposure to low doses of uranyl nitrate and sodium fluoride in mice. J Trace Elem Med Biol, 2021, 64: 126708

[10] Pavlakis N, Pollock C A, Mclean G, et al. Deliberate overdose of uranium: toxicity and treatment. Nephron, 1996, 72(2): 313-317

[11] Kathren R L, Moore R H. Acute accidental inhalation of U: a 38-year follow-up. Health Phys, 1986, 51(5): 609-619

[12] Grau-Perez M, Domingo-Relloso A, Garcia-Barrera T, et al. Association of single and joint metals with albuminuria and estimated glomerular filtration longitudinal change in middle-aged adults from Spain: The Aragon workers health study. Environ Pollut, 2023, 318: 120851

[13] Medgyesi D N, Mohan S, Bangia K, et al. Long-Term Exposure to Uranium and Arsenic in Community Drinking Water and CKD Risk Among California Women. Am J Kidney Dis, 2025, 86(2): 222-235.e1

[14] Mcdiarmid M A, Gaitens J M, Hines S, et al. The U.S. Department of Veterans' Affairs depleted uranium exposed cohort at 25 Years: Longitudinal surveillance results. Environ Res, 2017, 152: 175-184

[15] Jenny-Burri J, Blanc A, Aubert R, et al. Uranium exposure of the Swiss population based on 24-hour urinary excretion. Swiss Med Wkly, 2020, 150: w20207

[16] Zhao H, Fang L, Chen Y, et al. Associations of exposure to heavy metal mixtures with kidney stone among U.S. adults: A cross-sectional study. Environ Sci Pollut Res Int, 2023, 30(42): 96591-96603
[17] Yiin J H, Anderson J L, Bertke S J, et al. Dose-response relationships between internally-deposited uranium and select health outcomes in gaseous diffusion plant workers, 1948-2011. Am J Ind Med, 2018, 61(7): 605-614
[18] Horvit A M, Molony D A. A systematic review and meta-analysis of mortality and kidney function in uranium-exposed individuals. Environ Res, 2024, 248: 118224
[19] Yang Y, Dai C, Chen X, et al. Role of uranium toxicity and uranium-induced oxidative stress in advancing kidney injury and endothelial inflammation in rats. BMC Pharmacol Toxicol, 2024, 25(1): 14
[20] Nguyen T T, Mazzucco G, Kyriacou E, et al. Oxidative stress at telomeres triggers internal DNA loops, TRF1 dissociation, and TRF2-dependent R-loops. Nucleic Acids Res, 2025, 53(7): gkaf285
[21] Hu S, Zhang Q, Zhou Q, et al. Effect of polysaccharides and saponins from Polygonatum kingianum against uranium-induced renal injury in rats. Int J Biol Macromol, 2025, 307(Pt 2): 141984
[22] Liu S, Wang S, Zhao Y, et al. Depleted uranium causes renal mitochondrial dysfunction through the ETHE1/Nrf2 pathway. Chem Biol Interact, 2023, 372: 110356
[23] Liu J L, Wang M, Zhang R, et al. Hydrogen Sulfide Alleviates Lipid Peroxidation-Mediated Carbonyl Stress in Uranium-Intoxicated Kidney Cells via Nrf2/ARE Signaling. Biomed Environ Sci, 2025, 38(4): 484-500
[24] Banday A A, Priyamvada S, Farooq N, et al. Effect of uranyl nitrate on enzymes of carbohydrate metabolism and brush border membrane in different kidney tissues. Food Chem Toxicol, 2008, 46(6): 2080-2088
[25] Taulan M, Paquet F, Argiles A, et al. Comprehensive analysis of the renal transcriptional response to acute uranyl nitrate exposure. BMC Genomics, 2006, 7: 2
[26] Muller D, Houpert P, Cambar J, et al. Role of the sodium-dependent phosphate co-transporters and of the phosphate complexes of uranyl in the cytotoxicity of uranium in LLC-PK1 cells. Toxicol Appl Pharmacol, 2006, 214(2): 166-177
[27] Thauvin M, Matias De Sousa R, Alves M, et al. An early Shh-H2O2 reciprocal regulatory interaction controls the regenerative program during zebrafish fin regeneration. J Cell Sci, 2022, 135(6): jcs259664
[28] Liu X, Miao J, Wang C, et al. Tubule-derived exosomes play a central role in fibroblast activation and kidney fibrosis. Kidney Int, 2020, 97(6): 1181-1195
[29] Fiorio Pla A, Genova T, Pupo E, et al. Multiple roles of protein kinase a in arachidonic acid-mediated Ca2+ entry and tumor-derived human endothelial cell migration. Mol Cancer Res, 2010, 8(11): 1466-1476
[30] Kim S, Dayani L, Rosenberg P A, et al. RIP1 kinase mediates arachidonic acid-induced oxidative death of oligodendrocyte precursors. Int J Physiol Pathophysiol Pharmacol, 2010, 2(2): 137-147
[31] Mousa D, Rezk M M, Osman A, et al. Therapeutic Potential of Phycocyanin in Attenuating Uranium-Induced Neurophysiological Alterations in Adult Male Albino Rats. J Appl Toxicol, 2026, 46(4): 1207-1221
[32] Huang L, Sun G, Xu W, et al. Uranium uptake is mediated markedly by clathrin-mediated endocytosis and induce dose-dependent toxicity in HK-2 cells. Environ Toxicol Pharmacol, 2023, 101: 104171
[33] Xing Y, Ge J, Wang Y, et al. Mitochondrial HKDC1 suppresses oxidative stress and apoptosis by regulating mitochondrial function in goose fatty liver. Int J Biol Macromol, 2024, 282(Pt 4): 137222
[34] Morse P T, Arroum T, Wan J, et al. Phosphorylations and Acetylations of Cytochrome c Control Mitochondrial Respiration, Mitochondrial Membrane Potential, Energy, ROS, and Apoptosis. Cells, 2024, 13(6): 493
[35] Shaki F, Hosseini M J, Ghazi-Khansari M, et al. Toxicity of depleted uranium on isolated rat kidney mitochondria. Biochim Biophys Acta, 2012, 1820(12): 1940-1950
[36] Hao Y, Ren J, Liu C, et al. Zinc protects human kidney cells from depleted uranium-induced apoptosis. Basic Clin Pharmacol Toxicol, 2014, 114(3): 271-280
[37] Li J Y, Sun X A, Wang X, et al. PGAM5 exacerbates acute renal injury by initiating mitochondria-dependent apoptosis by facilitating mitochondrial cytochrome c release. Acta Pharmacol Sin, 2024, 45(1): 125-136
[38] Armant O, Gombeau K, Murat El Houdigui S, et al. Zebrafish exposure to environmentally relevant concentration of depleted uranium impairs progeny development at the molecular and histological levels. PLoS One, 2017, 12(5): e0177932
[39] Shaki F, Hosseini M J, Ghazi-Khansari M, et al. Depleted uranium induces disruption of energy homeostasis and oxidative stress in isolated rat brain mitochondria. Metallomics, 2013, 5(6): 736-744
[40] Yu L, Li W, Chu J, et al. Uranium inhibits mammalian mitochondrial cytochrome c oxidase and ATP synthase. Environ Pollut, 2021, 271: 116377
[41] Hao Y, Huang J, Liu C, et al. Differential protein expression in metallothionein protection from depleted uranium-induced nephrotoxicity. Sci Rep, 2016, 6: 38942
[42] Huang F, Li W, Li J, et al. Depleted uranium exposure induced ferroptosis in renal cells via the ETHE1/P38-MAPK pathway. Arch Toxicol, 2026, 100(2): 465-474
[43] Jiao Y, Cao F, Liu H. Radiation-induced Cell Death and Its Mechanisms. Health Phys, 2022, 123(5): 376-386
[44] Gao N, Huang Z, Liu H, et al. Advances on the toxicity of uranium to different organisms. Chemosphere, 2019, 237: 124548

[45] Sano K, Fujigaki Y, Ikegaya N, et al. The roles of apoptosis in uranyl acetate-induced acute renal failure. Ren Fail, 1998, 20(5): 697-701
[46] Shu C, Li J, Liu S, et al. Depleted uranium induces thyroid damage through activation of ER stress via the thrombospondin 1-PERK pathway. Chem Biol Interact, 2023, 382: 110592
[47] Kashyap D, Garg V K, Goel N. Intrinsic and extrinsic pathways of apoptosis: Role in cancer development and prognosis. Adv Protein Chem Struct Biol, 2021, 125: 73-120
[48] Wang Z, Huang Y, Zhang Y, et al. Toxicological Mechanisms of Uranium-Induced Apoptosis in HK-2 Cells: A Proteomics and Metabolomics Study. Toxics, 2025, 13(8): 699
[49] Stearns D M, Yazzie M, Bradley A S, et al. Uranyl acetate induces hprt mutations and uranium-DNA adducts in Chinese hamster ovary EM9 cells. Mutagenesis, 2005, 20(6): 417-423
[50] Miller A C, Stewart M, Brooks K, et al. Depleted uranium-catalyzed oxidative DNA damage: absence of significant alpha particle decay. J Inorg Biochem, 2002, 91(1): 246-252
[51] Mcarthur K, Whitehead L W, Heddleston J M, et al. BAK/BAX macropores facilitate mitochondrial herniation and mtDNA efflux during apoptosis. Science, 2018, 359(6378): eaao6047
[52] Hu L, Lu J, Fan H, et al. FAS mediates apoptosis, inflammation, and treatment of pathogen infection. Front Cell Infect Microbiol, 2025, 15: 1561102
[53] Yi J, Yuan Y, Zheng J, et al. Hydrogen sulfide alleviates uranium-induced kidney cell apoptosis mediated by ER stress via 20S proteasome involving in Akt/GSK-3beta/Fyn-Nrf2 signaling. Free Radic Res, 2018, 52(9): 1020-1029
[54] Wang W, Hawkridge A M, Ma Y, et al. Ubiquitin-like protein 5 is a novel player in the UPR-PERK arm and ER stress-induced cell death. J Biol Chem, 2023, 299(7): 104915
[55] Hu Q, Zheng J, Xu X N, et al. Uranium induces kidney cells apoptosis via reactive oxygen species generation, endoplasmic reticulum stress and inhibition of PI3K/AKT/mTOR signaling in culture. Environ Toxicol, 2022, 37(4): 899-909
[56] Ondrias K, Sirova M, Kubovcakova L, et al. Uranyl acetate modulates gene expression and protein levels of the type 2, but not type 1 inositol 1,4,5-trisphosphate receptors in mouse kidney. Gen Physiol Biophys, 2008, 27(3): 187-193
[57] Kopacek J, Ondrias K, Sedlakova B, et al. Type 2 IP(3) receptors are involved in uranyl acetate induced apoptosis in HEK 293 cells. Toxicology, 2009, 262(1): 73-79
[58] Zheng J, Hu Q, Zou X, et al. Uranium induces kidney cells pyroptosis in culture involved in ROS/NLRP3/caspase-1 signaling. Free Radic Res, 2022, 56(1): 40-52
[59] Cruz C M, Rinna A, Forman H J, et al. ATP activates a reactive oxygen species-dependent oxidative stress response and secretion of proinflammatory cytokines in macrophages. J Biol Chem, 2007, 282(5): 2871-2879
[60] P S V, P D R, A B A. Role of PI3K-Akt and MAPK Signaling in Uranyl Nitrate-Induced Nephrotoxicity. Biol Trace Elem Res, 2019, 189(2): 405-411
[61] Hu Q, Zhang R, Zheng J, et al. Hydrogen sulfide attenuates uranium-induced kidney cells pyroptosis via upregulation of PI3K/AKT/mTOR signaling. J Biochem Mol Toxicol, 2023, 37(1): e23220