



Cadmium toxicity and autophagy: a review

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Abstract Cadmium (Cd) is an important environmental pollutant that poses a threat to human health and represents a critical component of air pollutants, food sources, and cigarette smoke. Cd is a known carcinogen and has toxic effects on the environment and various organs in humans. Heavy metals within an organism are difficult to biodegrade, and those that enter the respiratory tract are difficult to remove. Autophagy is a key mechanism for counteracting extracellular (microorganisms and foreign bodies) or intracellular (damaged organelles and proteins that cannot be degraded by the proteasome) stress and represents a self-protective mechanism for eukaryotes against heavy metal toxicity. Autophagy maintains cellular homeostasis by isolating and gathering information about foreign chemicals associated with other molecular events. However, autophagy may trigger cell death under certain pathological conditions, including cancer. Autophagy dysfunction is one of the main mechanisms underlying Cd-induced cytotoxicity. In this review, the toxic effects of Cd-induced autophagy on different human organ systems were

evaluated, with a focus on hepatotoxicity, nephrotoxicity, respiratory toxicity, and neurotoxicity. This review also highlighted the classical molecular pathways of Cd-induced autophagy, including the ROS-dependent signaling pathways, endoplasmic reticulum (ER) stress pathway, Mammalian target of rapamycin (mTOR) pathway, Beclin-1 and Bcl-2 family, and recently identified molecules associated with Cd. Moreover, research directions for Cd toxicity regarding autophagic function were proposed. This review presents the latest theories to comprehensively reveal autophagy behavior in response to Cd toxicity and proposes novel potential autophagy-targeted prevention and treatment strategies for Cd toxicity and Cd-associated diseases in humans.

Keywords Cadmium · Autophagy · Toxic mechanism · Cell fate

Introduction

Source, species and transportation of cadmium

Cadmium (Cd) is one of the most toxic metals in the environment, and it is mainly produced through two major pathways: natural release and anthropogenic factors. Naturally produced Cd mainly occurs through volcanic eruptions, crustal movement, and vegetation combustion. Cd usually exists with other minerals in nature and forms inorganic salts, such as cadmium

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oxide (CdO), cadmium sulfide (CdS), cadmium sulfate (CdSO₄), cadmium carbonate (CdCO₃), and cadmium chloride (CdCl₂). In the atmosphere, Cd exists in aerosol form as CdO dust, CdCl₂, CdSO₄ and CdS. The chemical properties of Cd are dominated by inorganic compounds with an oxidation state of +2 (Nordberg et al. 2018). The rapid development during the human industrial revolution led to an increase in the combustion of fossil fuels and non-ferrous metal mining. Cd has been widely used in steel plating, in plastics as a stabilizer, in nickel-cadmium batteries as an electrode material, and in the production of alloys and semiconductors as a useful element. These factors have dramatically altered the biochemical life cycle of Cd in the environment, making it more mobile in ecosystems. Cd is transported through the atmosphere, which increases depositional contamination in urban, rural, and remote areas between countries, including Antarctica and the Arctic (Chiarelli et al. 2019).

With the recent rapid development of nanotechnology, an increasing number of metallic nanoparticles have been synthesized and have been adopted in multidisciplinary fields (Ghasempour et al. 2023; Sadeghzadeh et al. 2023). Although a biological function for Cd in humans has not been identified, other forms of Cd, such as CdO/CdCO₃ nanocomposites and CdS nanoparticles, have been developed as anticancer agents for drug delivery, biosensors, and bioimaging applications (Ghasempour et al. 2023; Lefojane et al. 2021). Modifying the chemical and physical characteristics of Cd can significantly change its toxicity and harmful effects, as described by Peana et al. (Peana et al. 2021).

Effects of cadmium on human health

Cd is widespread in industrially contaminated soil, water, and air, and the human body is primarily exposed to Cd through Cd-contaminated air, tobacco smoke, water, and food (Chandler et al. 2019; Ganguly et al. 2018; Satarug et al. 2003). Cd enters the body mainly through the respiratory and digestive tracts, where it is absorbed by the lungs and intestines. Cd is present in organic and inorganic (Cd²⁺) forms in human biological fluids, including blood. After acute Cd exposure, organic and inorganic Cd can be measured in the blood, and the concentration of Cd²⁺ decreases after 2–5 h (Abbasabadi and Shirkhanloo 2020). Cd can form a complex with

certain organic compounds, such as metallothionein (MT), albumin, other plasma proteins, or peptides (e.g., glutathione), and accumulates mainly in the liver and kidneys (Abbasabadi and Shirkhanloo 2020; Satarug 2018; Tinkov et al. 2018). In blood, Cd binds to molecular targets on erythrocytes as well as proteins, peptides, and amino acids; it may also be transported by anion exchangers, thereby facilitating its uptake into erythrocytes in the form of [Cd (OH) (HCO₃)₂]⁻ and [Cd (OH)(HCO₃)Cl]⁻ complexes (Lou et al. 1991). Histidine can also stimulate Cd uptake into human erythrocytes (Horn and Thoma 1996). As mentioned above, MT is an important metal-binding protein enriched in cysteine residues. Heavy metals, such as Cd, can bind to the thiol (-SH) group present in cysteine residues of the protein (Klaassen et al. 1999; Sabolic et al. 2010). Current findings on Cd target molecules have revealed that different MT isoforms I-IV are more common biomolecular targets of Cd in mammalian organs, as reviewed in detail by Hill and Gailer (Hill and Gaile 2021). The authors also summarized other possible biomolecules and mechanisms of Cd targeting in plasma and erythrocytes and provided pathways for its uptake by target organs via blood circulation in the human body.

Cd is present in the environment at extremely low levels; however, it is difficult to eliminate after absorption into the body. Cd is one of the most toxic substances known to accumulate in the body and has a biological half-life of more than 25 years (Nordberg and Nordber 2022). Once Cd is taken up by renal proximal tubule (PT) cells, it induces MT, after which, it is chelated, inactivated, and stored in the cells (Sabolic et al. 2010). Cd can damage various organ systems, including the respiratory, skeletal, reproductive, immune, and nervous systems, as well as the liver and kidneys. Available scientific evidence shows that mammals lack an effective mechanism to eliminate Cd toxicity, with most Cd ions (not bound to MT) persisting indefinitely in PT cells after filtration by the kidneys (Nordberg and Nordber 2022; Satarug 2018). In a mouse model, chronic Cd exposure resulted in its accumulation in most organs and tissues, with the kidneys being the most severely affected (Tai et al. 2022).

Epidemiological studies have shown that Cd toxicity is associated with various diseases. A positive correlation between Cd exposure and diabetes mellitus and prediabetes risk was reported in a meta-analysis

by Filippini et al. (Filippini et al. 2022), who observed that the highest and lowest Cd exposure were associated with type 2 diabetes, with relative risks (RRs) of 1.24 (95% CI: 0.96–1.59), 1.21 (95% CI: 1.00–1.45) and 1.47(95% CI:1.01–2.13)for the blood, urinary, and toenail matrices. An increased risk of prediabetes after Cd exposure was also observed based on urine and blood matrices. Furthermore, a negative correlation was reported between serum Cd levels and lung function in patients with chronic obstructive pulmonary disease (COPD) (Jiang et al. 2022). High blood Cd levels may also be associated with stroke and hypertension in the Korean population aged < 60 years (Jeong et al. 2020). Owing to the long half-life of Cd in the human body, certain organs are more vulnerable to Cd-induced carcinogenesis. Cd has been classified as a type I human carcinogen by the International Agency for Research on Cancer (IARC) (Hartwig 2013). Low-dose and long-term exposure to Cd can increase the risk of developing various cancers, including lung, liver, prostate (Waalkes 2000), oral (Satir 2022), endometrial (McElroy et al. 2017), and renal cancers (Song et al. 2015). Cd enhances the risk of lung diseases and promotes the malignant transformation and development of lung cancer, particularly in occupational populations (Humans 2012 Waalkes 2000) exposed to Cd directly through the respiratory route. Accordingly, blood Cd levels may serve as a potential marker to monitor the incidence of early lung cancer in former smokers (Lener et al. 2021). Therefore, Cd is not only closely related to toxicity in various organs and systems but also contributes to the occurrence and development of various diseases, including cancer, in humans.

Previous reviews on Cd toxicity have mainly focused on the toxicity of environmental Cd exposure to plants, crops, soil, and marine organisms, while as far as we know, few have provided assessments of the mechanism underlying Cd toxicity in the human body in terms of defense responses (Thevenod and Lee 2013). Therefore, in this review, we discuss the toxicity of Cd to specific tissues and organs after its entry into the human body and review the representative signaling pathways and molecular mechanisms involved in autophagy-Cd toxicity. The aim of this review is to explore the role of autophagy in response to Cd exposure in organisms and identify methods of better preventing and controlling Cd-induced cell and tissue damage or even cell death by monitoring

specific biomarkers in the process of autophagy. In this review, we first summarize the general information about autophagy and its regulation mechanism. We then discuss the toxic effects of Cd through the autophagic pathway in the target organs of organisms, with a focus on hepatotoxicity, nephrotoxicity, respiratory toxicity, and other systemic toxicities, including neurological and intestinal toxicities. Moreover, the characteristics of exposure to Cd in vitro and in vivo with different physicochemical conditions, such as different morphologies and concentrations, are also addressed. We then analyze the molecular defense mechanisms that induce autophagic responses that lead to cell survival, adaptive response, or death after Cd exposure.

Autophagy

Autophagy is the process in which autophagy-related genes (*ATGs*) direct cells to wrap misfolded proteins or damaged organelles in the cytoplasm to form phagocytic vesicles and fuse with lysosomes to form autophagic lysosomes that degrade the substances inside the vesicles. Autophagy is an intracellular degradation mechanism that regulates cellular metabolism and maintains intracellular homeostasis (Galluzzi et al. 2017), and it is involved in pathophysiological processes, such as cell development, senescence, starvation, hypoxia, inflammation, oxidative stress, programmed death, and immune responses (Liu and Levine 2015). Autophagy is mainly classified into three categories: macroautophagy, microautophagy, and chaperon-mediated autophagy (Mizushima et al. 2001). Among them, macroautophagy is the most extensively studied and is a highly conserved eukaryotic cellular process (Yamamoto et al. 2023). In this review, we highlight the function and signaling pathways of macroautophagy, hereafter referred to as autophagy.

Autophagy process is controlled tightly by several functional modules including the unc 51-like kinase (ULK) complex (I), the class III phosphatidylinositol 3-kinase (PI3K) complex (II), the ATG2/WD repeat domain phosphoinositide-interacting protein (WIPI) complex and the ATG9 cycling system (III), the ATG12-conjugation system (IV), and the LC3-conjugation system (V) (Keller et al. 2023). Among them, a series of *ATGs* are involved in the pre-initiation and initiation processes of autophagy, and these

processes are the most critical steps for the occurrence of autophagy in the species of *Homo sapiens* and *Saccharomyces cerevisiae* (Li, et al. 2020). Moreover, *ULK1*, *Beclin 1* and *LC3* (microtubule-associated light chain 3), *GABARAP* in *H. sapiens* are equivalent to *Atg1*, *Atg6/Vps30*, and *Atg8* respectively, in *S. cerevisiae* (Zhen, et al. 2023). *LC3B/MAP1LC3B*, one of the *Atg8* mammalian orthologs, is well-studied, owing to its role in key steps in the autophagy process. For example, receptors for selective autophagy, such as *P62/SQSTM1*, *NBR1*, and *TOLLIP*, function as connectors between *LC3/GABARAP* proteins and ubiquitinated substrates in human cells (Zellner, et al. 2021). *LC3B* is also involved in processes such as autophagosome biogenesis (Weidberg 2010), autophagosome transport, and membrane fusion process. *LC3* can be cleaved to *LC3-I* by *ATG4B*, which is then lipidated to *LC3-II* by conjugation with phosphatidylethanolamine, participating in autophagosome formation. *LC3-I* is regenerated from *LC3-II* via *ATG4B*-mediated cleavage of phosphatidylethanolamine for further membrane biogenesis (Nguyen et al. 2014). Therefore, *LC3* and its subfamily (*LC3A*, *LC3B*, and *LC3C*) are considered hallmarks reflecting canonical autophagy (Nieto-Torres et al. 2023). The initiation process of autophagy is complex. During the initiation of the autophagosome, phagophores, the pre-structures for forming autophagosomes, are formed near the ER, elongate, bend, and finally form double-membraned structures, via membrane fission, called autophagosomes (Yamamoto et al. 2023). Therefore, the ER is an important organelle for autophagosome initiation, which is the key process in controlling autophagic flux. In addition to the plasma membrane, recent studies have revealed that phagophores are also derived from lipid droplets, endosomes, contact sites between ER-mitochondria, and the Golgi endosomal membranes (Zhen et al. 2023). Most of the *ATG* family members participate in the biogenesis of phagophores, whereas the *ATG8* (homolog of *LC3*) family members *SNAP29* and *VAMP8*, along with *Syntaxin17*, are critical for autophagosome-lysosome membrane fusion in mammalian cells (Li, et al. 2020). The mammalian target of rapamycin (*mTOR*) is an also crucial signaling pathway for initiating and controlling autophagy and cellular growth under pathological conditions in humans (Panwar et al. 2023; Keller et al. 2023). Autophagosome formation

can be negatively regulated by *mTOR* signaling through AMP-activated protein kinase (*AMPK*)-*Ulk2* interactions; notably, *AMPK* is potentially involved in all stages of autophagy (Wang et al. 2022c).

Functionally, autophagy primarily serves as a cellular protective mechanism against exogenous stimuli and is considered a pro-survival mechanism (Tsapras and Nezis 2017). However, excessive autophagy or its inhibition usually results in a decreased ability to metabolically degrade foreign substances and an imbalance in cellular homeostasis, potentially resulting in cell death. Notably, various types of cell death are associated with autophagy dysfunction. Apoptosis and autophagy are considered antagonistic processes (Cong et al. 2022); the initiation of autophagy inhibits apoptosis, whereas apoptosis occurs when autophagy induction fails (Kouroumalis et al. 2023). However, excessive autophagy may also induce apoptosis. As indicated in Keller's study (Keller et al. 2023), the *Atg12-Atg5-Atg16L1* complex promotes autophagy by converting *LC3-I* to *LC3-II* to form autophagosomes. In *Atg5*-deficient mammalian cells, *Atg12* and *Atg16L1* lose the ability to interact with *Atg12* to induce autophagy (Mizushima et al. 2001). Moreover, unbound *Atg5* is cleaved by calpain to *Atg5tN*, which can mediate cytochrome C release via *Bcl-2* proteins in the mitochondria, ultimately leading to apoptosis (Lepine et al. 2011; Cong et al. 2022). In addition, *Beclin-1*, *P53*, and *Caspase*, as well as the *PI3K/AKT/mTOR* pathway play essential roles in regulating the interactions between autophagic and apoptotic processes (Cong et al. 2022; Tsapras and Nezis 2017).

Ferroptosis is a recently discovered form of cell death characterized by iron overload, lipid peroxidation, and ROS accumulation (Latunde-Dada 2017). Ferroptosis is closely related to autophagy (Chen et al. 2023; Hou et al. 2016), which is classified into selective and non-selective autophagy. As a type of selective autophagy, ferritinophagy is an autophagic degradation process of ferritin, the iron storage protein, which is essential for regulating cellular iron content. *FTL1* (ferritin light polypeptide 1) and *FTH1* (ferritin heavy polypeptide 1) belong to the ferritin family and function as intracellular iron storage proteins. Ferritin is a critical regulator for maintaining cellular iron levels (Liu et al. 2020c). Increased autophagy degrades ferritin, which increases iron levels and leads to oxidative damage. Hou et al. (Hou et al. 2016) found that knockout of *ATG5* and *ATG7*

genes can inhibit erastin (a ferroptosis inducer)-induced cell death and decrease intracellular Fe^{2+} and malondialdehyde levels, which is a typical manifestation of ferroptosis. Under *ATG5*-deficient conditions, *FTH1* was remarkably increased in PANC1 (human cancer cell line) and MEF cells (mouse embryonic fibroblasts) irrespective of erastin treatment, indicating that ferritin degradation requires *ATG5*-mediated autophagy. *NCOA4*, the cargo receptor, was identified in 2014. It is highly enriched in autophagosomes and can degrade autophagy-dependent ferritin (Mancias et al. 2014). Overexpression of *NCOA4* promotes ferroptosis via ferritin degradation (Hou et al. 2016). *NCOA4*-mediated ferritinophagy provides further evidence of the crosstalk between autophagy and ferroptosis. The discovery of multi-autophagy-dependent ferroptosis builds upon our understanding of iron-based lipid peroxidation and aberrant autophagic degradation pathways that regulate cell death (Chen et al. 2023). Defensive response mechanisms such as autophagy that balance and eliminate internal and external stimuli and adverse stress outcomes caused by excessive or inadequate autophagy, such as cellular damage, inflammation, metabolic imbalance, and even cellular death, are critical issues that require further investigation.

Cadmium and autophagy

Most living cells undergo low levels of basal autophagy to maintain cellular homeostasis under physiological conditions. When cells are subjected to stresses, such as oxidative stress, starvation, and hypoxia, autophagy adapts to changes in the internal environment by either enhancing or weakening autophagy (Phadwal et al. 2020). These dynamic changes in autophagy under different conditions can lead to different cellular outcomes. Considerable evidence indicates that autophagy is closely related to the pathogenesis of human diseases, such as cancer, cardiovascular disease, neurodegenerative disease, lung disease, kidney cancer, bone cancer, and metabolic diseases (Klionsky et al. 2021).

Mammalian cells can initiate selective autophagy to eliminate cellular damage caused by environmental pollutants, particularly industrial products, thereby maintaining cellular homeostasis and protecting cells from endogenous stress (Martinez-Garcia and Marino 2020; Rahman et al. 2023). Stress is a major factor

in the induction of autophagy, and ionized Cd can produce excessive reactive oxygen species by inducing cellular oxidative stress. Environmental pollutants, particularly industrial compounds, modulate autophagic flux by either increasing it as a protective response, blocking it, or switching its protective role toward a pro-cell death mechanism (Martinez-Garcia and Marino 2020). Under certain circumstances, exposure to low Cd concentrations induces apoptosis and autophagy; this depends on the duration of Cd exposure and autophagic signaling, which may differ in various cell types (Tuffour et al. 2023). Initially, low-dose Cd exposure may induce autophagy as a cytoprotective mechanism; however, prolonged exposure may disrupt the autophagic process and lead to apoptosis.

The relationship between cytotoxicity and the cellular stress response is one of the most important drivers of the acute exposure effects of Cd; however, this relationship remains uncertain (Man et al. 2023). Therefore, exploring the interaction between Cd and autophagy in organisms has great biological significance for understanding the molecular action in response to metal toxicity. Recent studies have shown that enhanced autophagy improves stress response and reduces genetic damage. Rahman et al. (Rahman et al. 2023) in 2023 provided a detailed review of the mechanisms of autophagy as a target of environmental pollutants and assessed current research on autophagy pathway responses and protective effects when the body is exposed to certain environmental pollutants, particularly heavy metals (including Cd) and particulate matter.

Toxic effects of Cd-induced cellular autophagy on human health

Although the mechanisms of cadmium-induced cytotoxicity remain unclear, many studies have indicated that in addition to oxidative damage and apoptosis, autophagy dysfunction is one of the main mechanisms leading to Cd cytotoxicity (Genchi et al. 2020). Numerous studies have reported that Cd-induced autophagy produces different biological effects in different organs and cells. The biological effects, pathway alterations, and pathological outcomes induced by Cd in different cells depend on the time of Cd entry into the body, duration of accumulation, dose,

and route of exposure (Guo et al. 2022). In this section, we summarize the latest research on the toxic action of Cd on its main targets (kidney, liver, lung, and others) associated with autophagy and discuss the possible role of autophagy in Cd organ-based toxicity.

Nephrotoxicity

The kidney is an important target organ of Cd, and renal proximal tubule (PT) epithelial cells are the main targets of Cd nephrotoxicity (Thevenod 2003). MTs are critical modulators of the toxicokinetics and biochemistry of essential and non-essential metals (Nordberg et al. 2018). Cd complexes bound to MTs, other plasma proteins, peptides and small organic molecules circulate through the bloodstream to the kidneys, where they are reabsorbed by PT cells via various uptake mechanisms and trigger PT cells to induce MTs (Thevenod and Wolff 2016). MT enrichment in the kidneys and liver may be partially responsible for the higher Cd concentrations in these two organs (Genchi et al. 2020; Guo et al. 2022). Approximately 30–40% of the Cd entering the body is deposited in the kidneys (Niture et al. 2021). It has been suggested that when the accumulation of Cd exceeds the ability of PT cells to synthesize MT, unbound Cd causes cellular oxidative stress, alteration of autophagic fluxes, and acute loss of cells, which exceeds the regeneration of PT cells and ultimately leads to cell death and luminal damage (Prozialeck and Edwards 2012). By using MT-null mice, Liu et al. (Liu et al. 1998) demonstrated that Cd-induced renal injury is not mediated via Cd²⁺-MT complex. Fels et al. (Fels et al. 2019) further revealed that the Cd²⁺-MT complex is likely nontoxic to tubule cells. Instead, the ligand proteins that bind with Cd²⁺ to form complexes, such as Cd²⁺-β2M (microglobulin), Cd²⁺-Alb (albumin) and Cd²⁺-Lcn2 (lipocalin-2), and are taken up by PT cells via megalin-cubilin endocytosis that eventually damages PT cells. Barrouillet et al. (Barrouillet et al. 2001) revealed potential effects of Cd speciation in renal toxicity in vitro, and showed that in cell culture media with bovine serum albumin (BSA) or fetal calf serum (FCS), both CdCl₂ and CdSO₄ had EC₅₀ value of approximately 3 × 10⁻⁵ M in porcine kidney cells (LLC-PK1). However, in protein-free cell culture media, CdSO₄ was more toxic than CdCl₂ at pH 7.4 after 24 h incubation. Notably, the amount of protein in the cell media

determines the EC₅₀ and Cd sulphate may produce more Cd²⁺ in LLC-PK1.

Autophagy is considered an early event in the onset of Cd-induced nephrotoxic effects (Lv et al. 2019). Several studies have demonstrated the involvement of autophagy in Cd-induced nephrotoxicity. Gong et al. (Gong et al. 2022) reported that Cd can induce lysosomal dysfunction and block autophagic flow, which exacerbates oxidative stress and acute kidney injury in primary rat proximal tubule cells; however, bromodomain-containing protein 4 (BRD4) blocked autophagy and lysosomal transcriptional function, which attenuated Cd damage to the kidney. Fan et al. (Fan et al. 2021) showed that Cd exposure inhibited autophagy in rat kidney and rat renal cells, and that sustained inhibition of nuclear factor erythroid 2-related factor 2 (Nrf2), an antioxidant signaling factor, led to the restoration of autophagosome-lysosome fusion, thereby attenuating Cd-induced nephrotoxicity. The outcome of Cd-induced autophagy dysfunction often determines cell fate. Chargui et al. (2011) demonstrated that in rats, Cd exposure at a subtoxic concentration enhanced autophagy and caused slight damage to proximal convoluted tubule (PCT) cells. However, the glomerular and tubular function of rat kidneys was not affected, and apoptosis was not detected in both in vivo and in vitro tests. This finding provides further evidence that upregulated autophagy could serve as an adaptive response to protect PTC cells from further damage, such as apoptosis, by environmental Cd doses. Lee et al. (Lee et al. 2017) further revealed that excessive stress triggered by Cd can lead to cell death with a disrupted autophagy flux and lysosomal instability. They also demonstrated that the ER stress pathway PERK-eIF2α was activated by Cd exposure, leading to impaired autophagy in rat kidney proximal tubule cells. The work by Lee et al. (Lee et al. 2017) was pioneering in demonstrating lysosomal dysfunction and decreased autophagosome-lysosome fusion induced by Cd. Similarly, Luo et al. (Luo et al. 2016) also demonstrated that the ER stress eIF2α-ATF4 pathway and autophagy were activated by Cd exposure in both mice kidney tissues and cultured cells. Importantly, they found that interfering with the ER stress eIF2α-ATF4 pathway can block autophagy via cyclooxygenase-2, a rate limiting enzyme for prostaglandin E2 synthesis. Research also has demonstrated that Cd exposure activates the PERK-eIF2α-ATF4-CHOP pathway and

induces ferroptosis via the PERK-autophagy pathway (Zhao et al. 2021). Lee and Oh (Lee and Oh 2021) demonstrated that Cd induces apoptosis and cellular autophagy through the P53-mediated DRAM-BAX signaling pathway. Beclin-1, a critical regulator of autophagy, can specifically interact with caspase-8 and activate autophagy to protect against Cd-induced apoptosis via Fas/FasL signaling in rat PT cells. These findings suggest that the activation or blockage of autophagy plays an important role in the degree of renal cell impairment and even cell death.

Hepatotoxicity

The liver is another important organ that is susceptible to Cd toxicity (Yuan et al. 2021). Once Cd enters the body, it is transported to the liver via blood circulation, where MTs binds to Cd and sequesters it to buffer its cytotoxic effects (Guo et al. 2022). Approximately 30% of the Cd absorbed by an organism accumulates in the liver, while the rest is distributed to other organs or tissues (Niture et al. 2021). Under physiological conditions, autophagy can maintain the stability of the intracellular environment of hepatocytes, and overactivation of autophagy can lead to damage to intracellular organelles in hepatocytes and even death. Mitophagy is a process that eliminates damaged mitochondria via selective autophagy (Ding and Yin 2012). Mitochondrial loss is a crucial event during hepatotoxicity. Pi et al. (Pi et al. 2013) revealed that exposure to Cd led to mitochondrial fragmentation /loss via the overactivation of mitophagy in normal liver L02 cells. This excessive mitochondrial loss is caused by increased dynamin 1-like (DNM1L) expression and translocation into the mitochondria. Moreover, Liu et al. (Liu et al. 2023) demonstrated that the expression of mitochondrial calcium uniporter (MCU) was upregulated in Cd-induced excessive mitophagy in HepG2 liver cells. This upregulation is attributed to increased cytosolic Ca^{2+} levels and cAMP response element binding (CREB) protein-induced MUC translocation and accumulation in the mitochondria under Cd exposure conditions. Finally, they demonstrated that VDAC1, a channel protein that mediates mitochondrial metabolism, can directly interact with MCU and overactivate mitophagy, resulting in hepatocytic death. These two studies demonstrated DNM1L and MCU as potential

molecular targets for the prevention and treatment of Cd-mediated hepatotoxicity.

Lysosomes are highly dynamic organelles that are distributed rapidly around microtubules (Cabukusta and Neeffjes 2018). Yuan et al. (Yuan et al. 2021) found that Cd can disrupt the microtubule network and downregulate the microtubule-associated proteins KIF5B, γ -tubulin, and acetylated α -tubulin in buffalo rat liver 3 A cells (BRL3A). They also demonstrated that Cd induced an increase in endosomal lysosomes by disrupting cellular microtubules, thereby blocking autophagic flux in BRL3A cells. Nrf2 is an oxidative regulator that modulates cellular redox imbalance. As previously mentioned, Cd can trigger oxidative stress and autophagy dysfunction. A recent study showed that puerarin (PU) restored Cd-induced Nrf2 inhibition, thereby preventing Cd-induced cellular autophagy and inflammatory vesicle activation (Yu et al. 2021).

The liver is the major organ involved in lipid metabolism. Autophagy can selectively target lipid droplets in the liver, namely, lipophagy (Shin 2020). Numerous studies have demonstrated that autophagy in hepatocytes is critical for lipolysis and the control of triglyceride homeostasis. In vitro studies have shown that Cd induces cholesterol redistribution from HepG2 cells to the culture medium by inhibiting the autophagy-lysosomal pathway (Rosales-Cruz et al. 2018). In vivo studies confirmed that Cd inhibits hepatic autophagic flux in mice, thereby promoting the accumulation of apolipoprotein ApoE, whereas the inhibition of low-density lipoprotein receptor expression by Cd contributed to the elevation of blood triacylglycerol levels (Liu et al. 2020b). Together, these studies demonstrate that Cd interferes with the normal physiological functions of the liver by inducing autophagy in hepatocytes. The results contribute to our understanding of the biological role of the autophagy pathway in the pathogenesis of Cd-induced hepatotoxicity.

Respiratory system

Cd is a known human carcinogen certified by the International Agency for Research on Cancer (IARC). The link between chronic exposure to Cd and the induction of malignant tumors has been well-established through animal (Waalkes et al. 2000) and epidemiological studies (Humans 2012) including

those on lung cancer (Baan et al. 2019). Long-term exposure to low-dose Cd in the respiratory system is likely to cause malignant transformation of respiratory epithelial cells (Humans 2012; Li et al. 2023a; Wang et al. 2021). However, the precise mechanism of action of the malignant transformation into lung cancer by Cd remains unclear. In vitro studies have shown that Cd exposure of human lung epithelial Beas-2B cells generates ROS, which promotes the inflammatory microenvironment, and thus facilitates the malignant transformation of Beas-2B cells. In contrast, the transformed cells exhibit a deficiency in autophagy, characterized by a state of blockage in the fusion of the autophagosome and lysosome. This blockage leads to an increase in autophagosomes and the expression of P62 proteins, which together with Nrf2, form a positive feedback mechanism leading to an increase in the expression of anti-apoptotic proteins Bcl-2 and Bcl-x1, the downstream molecules of Nrf2, thus leading to apoptosis resistance (Wang et al. 2018). Another study on ROS-dependent autophagy (Lv et al. 2018) reported that Cd (2 μ M CdCl₂) induces the proliferation, migration, and invasion of A549 cells, resulting in a significant increase in ROS levels and autophagy. ROS act as molecular signals to increase the expression of Atg4, an enzyme facilitating LC3II production, enhances cellular autophagy. Atg4 and autophagy promote proliferation, migration, and invasion of A549 cells. Atg4 expression and cellular autophagy may be valuable in preventing Cd-induced lung toxicity. In vivo experiments have also shown that respiratory Cd exposure in mice induces autophagy in B lymphocytes and promotes apoptosis in immune cells while inhibition of autophagy attenuates Cd-induced apoptosis in splenic and immune cells in mice (Gu et al. 2019).

Environmental Cd exposure is closely associated with the development of several respiratory diseases. In a case-control study, Wang et al. (Wang et al. 2022b) demonstrated that serum Cd levels were higher in patients with COPD than in the control group and the serum Cd level gradually increased with the progression of COPD. They also showed that markers of autophagy (e.g., P62, Beclin-1, LC3 II, and LC3I) and molecules of apoptosis were increased in the lungs of COPD patients. Serum Cd levels were positively correlated with autophagy and apoptosis in the lungs of patients with COPD, and in vitro experiments confirmed that Cd induces autophagy and

apoptosis in human lung epithelial cells. Surolia et al. (Surolia et al. 2015) showed that heme oxygenase-1 (HO-1) protects against Cd-induced emphysema in mice and revealed that HO-1(-/-) Cd exposed mice are more susceptible to apoptosis and emphysema. However, cell death was reduced by pretreatment of HO-1(-/-) cells with rapamycin, an autophagy activator. This indicates that the overexpression of heme oxygenase-1 induced autophagy and reduces and delays apoptosis, thereby protecting mice from the development of emphysema.

Other systems

Chronic exposure to Cd can also cause toxic effects on osteoporosis and the neurological, reproductive, and immune systems. Li et al. (Li et al. 2016) and Pi et al. (Pi et al. 2017) found that Cd impedes autophagosome-autophagy lysosome fusion and impairs lysosomal function in mouse neuroblastoma cells by decreasing the level of TFEB, which subsequently leads to neuronal cell death. Although melatonin increases TFEB expression, this study suggests that melatonin could be a potential target for exploring Cd-induced neurotoxicity by controlling the autophagy pathway.

Chronic exposure to Cd can induce human skeletal toxicity, including osteoporosis, bone atrophy, and joint pain, which mostly occurs after Cd-induced nephrotoxicity (Ma et al. 2022). RANKL (RANK) and osteoprotegerin (OPG) receptors are important molecules involved in osteoblast development and bone remodeling. In a study of chronic low-dose CdCl₂ exposure, Cd was found to act on rat mesenchymal stem cells (MSCs) through the RANKL/OPG pathway and downregulate the expression of key genes involved in the osteogenic differentiation of MSCs when CdCl₂ (1 mg/kg bw and 2 mg/kg bw) was continuously fed to rats for 38 weeks. However, Cd did not cause significant damage to the kidney, suggesting that the increased expression of proteins, including autophagy-related proteins LC3B, Beclin-1, P62, and HO-1, was the result of a renal adaptive response induced by Cd chloride (Lv et al. 2019). The toxic effects of Cd on bone may occur simultaneously with renal toxicity. Another study by Tong et al. (Tong et al. 2022) reported that puerarin attenuated Cd-induced oxidative damage in rat bones by attenuating autophagosome and lysosome fusion inhibition.

The toxic effects of Cd exposure on the reproductive system via autophagy have also been reported. For instance, Wang et al. (2020b) found that Cd-exposed testicular cells promote autophagy via the PI3K- and mTOR-independent signaling pathways, which regulate apoptosis in testicular injury and recovery. Autophagy plays a vital role in the occurrence and development of diseases as well as in defenses against the invasion of exogenous pathogens in the immune response induced by Cd. So et al. (So et al. 2018) demonstrated that Cd-induced oxidative stress triggers endoplasmic reticulum (ER) stress, which leads to the activation of Ca^{2+} proteases and subsequently activates autophagy and apoptosis, leading to immunosuppression.

Molecular mechanism of Cd-induced autophagy

Molecules and cells of living organisms perform their functions through specific signaling pathways. Similarly, Cd exerts its toxic effects through certain molecules and specific signaling pathways, and a network of these molecules has been identified. Autophagy arises from the cellular generation of stress responses, such as oxidative stress, ER stress, and Ca^{2+} disruption (Aki et al. 2013; Yorimitsu et al. 2006; Chen et al. 2008).

Among the toxicological mechanisms associated with autophagy-induced Cd, we review the literature on classical Cd-induced (1) ROS-dependent signaling pathways; (2) ER stress pathways; (3) mTOR pathways; (4) Beclin-1 and Bcl-2 families; and (5) Emerging molecules /pathways of autophagy-mediated Cd toxicity. It should be noted that these Cd-induced signaling pathways are not isolated but rather are interconnected, thus representing the main mechanisms by which Cd triggers toxicity in its target organs (kidneys, liver, lungs, skeleton and nervous system). For example, Cd exposure leads to oxidative stress in hepatocytes by generating large amounts of ROS, which in turn induces autophagy by inhibiting the AKT/mTOR signaling pathway (Niture et al. 2021). By activating or inhibiting signaling molecules at different stages of autophagy, Cd ultimately determines cell fate, that is, whether cells undergo an adaptive response without severe damage or trigger programmed or non-programmed cell death (Fig.1).

ROS-dependent signaling pathways

Oxidative stress is one of the most important mechanisms by which Cd exerts toxicity (Cuypers et al. 2010). It has long been established that Cd disrupts the electron transport chain in the mitochondria, particularly affecting complexes II/III. Cd binds to the Q0 site of cytochrome b on complex III, leading to the accumulation of semiquinones. Semi-ubiquinone is an unstable molecule that readily transfers an electron to molecular oxygen, resulting in the formation of superoxide and, thus, oxidative stress (Wang et al. 2004). Autophagy and apoptosis are triggered by various stress conditions that may be derived from exogenous factors, such as environmental pollutants, or endogenous stimuli, e.g. leakage during the mitochondrial electron transfer process (Dickinson and Chang 2011; Redza-Dutordoir and Averill-Bates 2016). Low levels of ROS are necessary for the maintenance of normal physiological states and adaptive cellular responses. Moderate levels of ROS may induce autophagy, which is considered a cell self-protection strategy (Gibson 2013). Excessive ROS may cause cell damage and activate cell survival or cell death through various signaling pathways (PI3K/Akt, MAPK, Nrf2, and ER stress) (Redza-Dutordoir and Averill-Bates 2016). In an in vivo model of Cd-exposed weaned piglets, Cd was shown to be involved in ROS-mediated autophagy and apoptosis in the liver by promoting ROS production, activating the AMPK/PPAR- γ /NF- κ B pathway, and finally inducing autophagy (increasing the expression of Beclin-1, LC3-II/LC3-I and P62) and apoptosis (increasing the expression of Bax, Bak, caspase-9, and caspase-3 and decreasing the expression of Bcl-2) (Wang et al. 2022a). Zhang et al. (Zhang et al. 2019) also reported that Cd-induced ROS activates ER stress, autophagy, and apoptosis in retinal pigment epithelial cells.

The imbalance between ROS production and restriction is a common feature of cancer cells, and ROS have the function of regulating the tumor microenvironment (Cheung and Vousden 2022). As mentioned in "Respiratory system" Section, chronic exposure to Cd leads to the malignant transformation of respiratory epithelial cells. Increased ROS expression induces ER stress in Cd-exposed prostate epithelial cells (RWPE-1), leading to defective autophagy in Cd-induced prostate carcinogenesis (Kolluru et al. 2019). Similarly, Tyagi et al. (Tyagi

Table 1 Toxic effects of Cd-induced cellular autophagy on human health

| Organ/System | Cell type | Mechanisms of toxicity | Study |
|--------------------|--|--|--------------------------------------|
| Liver | BRL3A rat hepatocytes | miR-155 promotes cadmium-induced cellular autophagy. | (Zou et al. 2021) |
| | BRL3A rat hepatocytes | Cadmium induces increased endosomal lysosomes and blocks autophagic flow. | (Yuan et al. 2021) |
| | AML12 mouse hepatocytes | Cadmium inhibits cellular autophagy, activates inflammation, and induces liver injury. | (Yu et al. 2021) |
| | Chicken embryo liver tissue/cells | Cadmium inhibits mitochondrial autophagy and induces liver damage. | (Chen et al. 2021) |
| | ICR mice | Cadmium inhibits autophagic flow, promotes upregulation of apolipoproteins, and promotes triglyceride rise. | (Liu et al. 2020b) |
| Kidney | Sprague-Dawley rat/rat proximal tubule (rPT) cells | Cadmium induces lysosomal dysfunction and impaired autophagic flow, causing oxidative stress and acute kidney injury. | (Gong et al. 2022) |
| | Sprague-Dawley rat/NRK-52E cells | Cadmium induces autophagy inhibition, and knockdown of Nrf2 attenuates cadmium-induced autophagy inhibition thereby reducing nephrotoxicity. | (Fan et al. 2021) |
| | Mouse renal mesangial MES13E cells | Cadmium exposure induces apoptosis and kidney injury via the polyUb-p62/Sirt6 autophagy pathway. | (So et al. 2021) |
| | Human proximal renal tubular cells HK2 | Cadmium induces apoptosis and cellular autophagy through the DRAM-BAX signaling pathway. | (Lee and Oh 2021) |
| | Balb/c mouse/TCMK-1 kidney cells | Cadmium induces nephrotoxicity through the MitoROS-ER stress-ferritin autophagy axis. | (Zhao et al. 2021) |
| Respiratory system | Cadmium transformed BEAS-2B cells | Cadmium induces ROS, inflammatory microenvironment, autophagy, and apoptosis in lung epithelial cells. | (Wang et al. 2018) |
| | BALB/c mouse/A549 cells | Cadmium induces cell proliferation, migration and invasion of A549 cells, leading to a significant increase in ROS levels and autophagy. | (Lv et al. 2018) |
| | Pulmonary Endothelial Cells (PECs) | Cadmium induces apoptosis thereby causing emphysema in mice. | (Surolia et al. 2015) |
| Nervous system | Mouse neuroblastoma cells (Neuro-2a cells) | Cd exposure blocks autophagic flow and reduces lysosomal function in Neuro-2a cells, subsequently leading to neuronal cell death. | (Li et al. 2016) (Pi et al. 2017) |
| Skeletal system | Rat mesenchymal stem cells (MSCs) | Chronic cadmium chloride exposure down-regulates key genes involved in osteogenic differentiation of MSCs via the RANKL/OPG pathway. | (Lv et al. 2019) |
| | Sprague-Dawley rats | Cadmium induces impaired autophagosome-lysosome fusion leading to oxidative damage in bone. | (Tong et al. 2022) |

Table 1 (continued)

| Organ/System | Cell type | Mechanisms of toxicity | Study |
|---------------------|--|--|--------------------------------------|
| Immune system | Mouse monocyte RAW264.7 ICR Mouse/Human Ramos B Cells | Cadmium-induced oxidative stress triggers ER stress and subsequent activation of autophagy and apoptosis, leading to immunosuppression. Cadmium exposure induces autophagy in B lymphocytes and promotes apoptosis in immune cells. | (So et al. 2018) (Gu et al. 2019) |
| Reproductive system | Sprague-Dawley rat/testis cell line (GC-1/ GC-2/TM3/TM4) (Cells) | Cadmium exposure promotes autophagy via the mTOR pathway, which regulates apoptosis, and the crosstalk between autophagy and apoptosis regulates cadmium-induced testicular injury/recovery via the PI3K versus mTOR pathway. | (Wang et al. 2020b) |

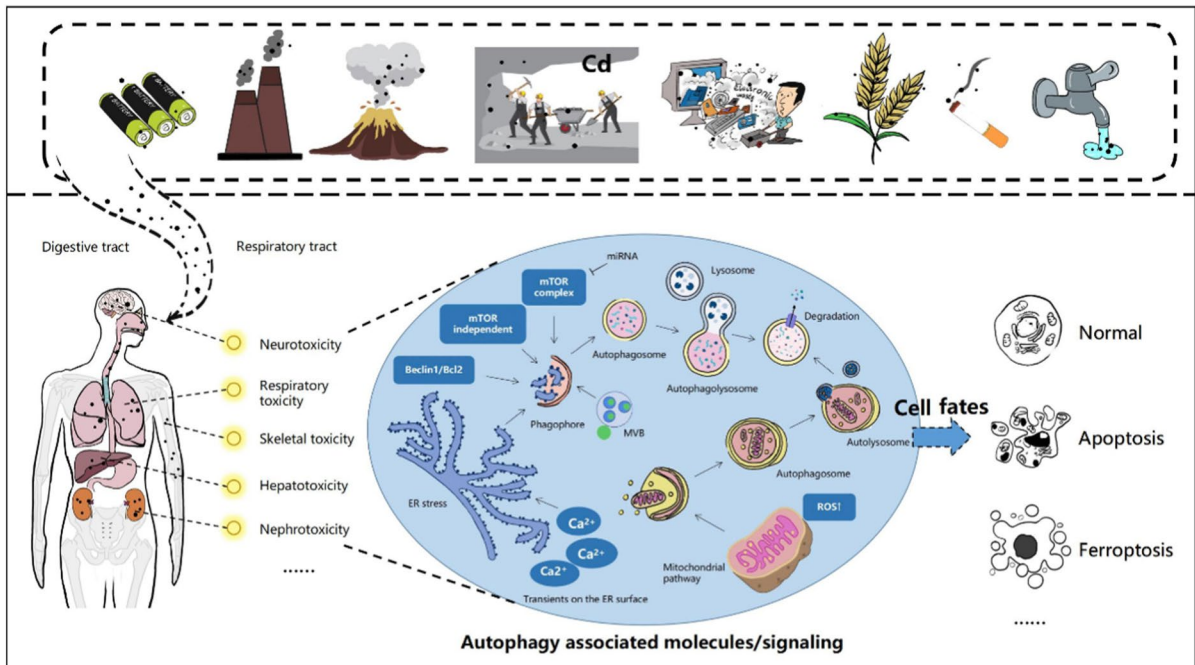


Fig. 1 Model diagram of autophagy-mediated cadmium toxicity and mechanism

et al. 2023) found that Cd exposure promotes NOX1 assembly through the activation of the cytoplasmic regulators p47phox and p67phox in RWPE-1 cells, which is essential for Cd-induced persistent ROS production and the control of ER stress-induced autophagy defects in both mice and humans. Further, Fan et al. (Fan et al. 2019) showed that ROS-dependent NUPR1-mediated autophagy plays an

important role in repetitive Cd exposure-induced cell growth, migration, and invasion of oral squamous cell carcinoma (OSCC) cells. Cd increases autophagic flux, upregulates LC3-II, and down-regulation P62 in CAL27 cells. Autophagy blockers inhibit Cd-induced cell migration and invasion, suggesting that autophagy plays an oncogenic role in Cd-treated CAL27 cells.

Endoplasmic reticulum stress pathway

The ER is a key organelle involved in protein folding, trafficking, and Ca^{2+} homeostasis maintenance. Approximately 25% ROS in cells is generated by the ER (Tu and Weissman 2004). For example, the majority of ROS in cells is produced via the electron transfer chain of protein disulfide isomerase (PDI) and endoplasmic reticulum oxidoreductin-1 (ERO1 α) during oxidative protein folding in the ER (Malhotra and Kaufman 2007). ROS generation can be further increased by the interaction of PDI with NADPH oxidases, which induces Ca^{2+} release to the mitochondria and further activates oxidative stress in the mitochondrial respiratory chain, resulting in Ca^{2+} overload and an unfolded protein response (UPR) in the ER (Gorlach et al. 2015). ER stress or persistent protein misfolding can also initiate apoptotic cascades (Malhotra and Kaufman 2007). Once ER function is disrupted, ER stress occurs through three transmembrane proteins: protein kinase R-like endoplasmic reticulum kinase (PERK), human-requiring inositolase 1 (IRE1), and activating transcription factor 6 (ATF6) (Li et al. 2023b). Activation of PERK/eukaryotic initiation factor 2 alpha (eIF2 alpha)/ATF4/C/EBP (CCAAT-enhanced binding protein) homolog (CHOP), IRE1, and ATF6 has important effects on autophagy-related gene expression and protein phosphorylation, which regulate autophagy (Cybulsky 2017). As mentioned in "Autophagy" Section, the ER is an important organelle for the initiation of phagophores, which is a pre-autophagosome structure. Moreover, ER stress triggers autophagy (Hoyer-Hansen and Jaattela 2007; Qi and Chen 2019; Yorimitsu et al. 2006) and apoptosis (Song et al. 2017). Recent studies have shown that ER stress and autophagy play dual roles in response to Cd toxicity. Mild-to-moderate ER stress or autophagy attenuates cytotoxicity and plays a protective role, whereas excessive ER stress and autophagy trigger a destructive cascade of reactions, resulting in increased cellular damage (Chou et al. 2019; Qi and Chen 2019). Liu et al. (Liu et al. 2020a) used Cd-treated rat NRK-52E cells and found that Nrf2 was activated and puerarin could reduce the damage caused by excessive ER stress; however, puerarin no longer significantly reduced ER stress after autophagy-associated protein 7 was knocked down in NRK-52E cells. This suggests that puerarin restores autophagy and reduces

endoplasmic reticulum stress by inhibiting the activation of Nrf2.

Ca^{2+} is another important signaling molecule for ER stress-induced autophagy (Hoyer-Hansen and Jaattela 2007); ER stress leads to the release of Ca^{2+} from the ER into the cytoplasm (Biagioli et al. 2008), which activates various kinases, such as mTOR and AMPK, in the autophagy signaling pathway (Hoyer-Hansen et al. 2007). Ca^{2+} transients on the outer surface of the ER membrane are closely associated with the initiation of autophagosome formation (Zheng et al. 2022). Biagioli et al. (2008) demonstrated that ER is another organelle impacted by Cd, in addition to mitochondria. They proposed that Cd induces ER stress and apoptosis by releasing Ca^{2+} and inhibiting SERCA pumps in the ER. Mitochondria and the ER may act in parallel to evoke caspase-dependent apoptosis. In testing the cytotoxic effects of Cd on Mesangial cells (MES-13), it was found that Cd induced autophagy and apoptosis by elevating cytosolic calcium (Wang et al. 2008). In addition, Cd interferes with the cycling of adhesin (CNX)/calmodulin (CRT) and triggers alterations in ER stress and autophagy-related indices in avian leg-horn male hepatoma cells. By regulating intracellular Ca^{2+} homeostasis, selenium intervention inhibits Cd-induced LDH release as well as the interplay between ER stress and autophagy (Zhang et al. 2020). Thus, the interaction between Ca^{2+} involved ER stress and autophagy is one of the main focuses of Cd toxicity research, with both processes playing dual roles in maintaining cellular homeostasis.

mTOR pathway

mTOR, a 289 kDa serine/threonine protein kinase, is a key regulator of cell growth and proliferation. mTOR participates in the convergence point of the upstream signaling cascade that regulates cellular autophagy. Aberrant regulation of the mTOR signaling pathway is closely related to cellular autophagy status (Wang and Zhang 2019). Three classes of pathways regulate mTOR activity: class I PtdIns3K-protein kinase B (PI3K/AKT), RAS proto-oncogene, and liver kinase B1-AMPK (LKB1/AMPK) pathways (Wang et al. 2012; Wang and Zhang 2019). Autophagosome formation can be suppressed by mTOR signaling, which is negatively

regulated by AMPK via LKB1 tumor suppressor kinase and Ca^{2+} /CaMKK- β (Shaw et al. 2004; Woods et al. 2005).

Cd activates the AKT/mTOR pathway and initiates autophagy, thereby inducing various diseases (Arab et al. 2022a; Sun et al. 2023; Wang et al. 2022d). Nrf2 is associated with the regulation of autophagy, as reviewed in "Nephrotoxicity", "Hepatotoxicity", "Respiratory system", "Endoplasmic reticulum stress pathway" Sections. In a study by Dong et al. (Dong et al. 2021), AMPK/AKT/mTOR was identified as a downstream pathway of Cd-induced Nrf2 in primary rat proximal tubular cell (rPT) injury. They further demonstrated that P62 accumulation due to the blockage of autophagic flux contributes to Nrf2 nuclear translocation, which further suppresses AMPK-induced AKT/mTOR signaling in Cd-exposed rPT and rat renal tubular epithelial cells. Environmental Cd exposure has been reported to reduce male fertility rates in humans and animals (Arab et al. 2022b; Ikokide et al. 2022). According to a study by Wang et al. (Wang et al. 2020b), five consecutive weeks of Cd exposure triggered reproductive toxicity in male rats, whereas at eight weeks after cessation of exposure, the toxic effects were significantly ameliorated. mTOR is a vital regulator of autophagy and apoptosis under various pathological conditions (Cayo et al. 2021; Maiese 2020; Wang et al. 2022d). The authors showed that the PI3K inhibitor 3-MA regulates apoptosis by inhibiting autophagy via an mTOR-independent pathway in Cd-treated testicular cells. Ser2448p-mTOR/mTOR protein expression did not change in any of the four testicular cell lines. Similarly, Arab et al. (Arab et al. 2022b) showed that Cd-induced testicular impairment was associated with a decline in autophagy flux with the accumulation of P62. A decrease in AMPK (Ser487) phosphorylation and an increase in the mTOR (Ser2448) phosphorylation cascade were also observed in rats. Furthermore, chronic and low concentration of Cd exposure was reported to promote both osteoclastogenesis (CdCl_2 at 0.025 and 0.050 μM in RAW264.7 cells) (Sun et al. 2023) and nephrotoxicity (CdCl_2 at 5 mg/kg/day via oral gavage in rats) (Arab et al. 2022a) by enhancing autophagy via mTOR signaling. In summary, the AKT/mTOR pathway, especially the activation of

upstream PI3K and AMPK, play an important protective role against Cd-induced cellular damage.

Beclin-1 and Bcl-2 families

Beclin-1 is a reliable autophagy marker, and Beclin-1 and its binding ligand class III phosphatidylinositol 3-kinase (PI3KCIII, also known as Vps34) are involved in autophagosome formation and regulate exogenous chemical-induced cellular autophagy (Hill et al. 2019). The Beclin-1/Bcl-2 complex is a key factor linking autophagy and apoptosis (Xu and Qin 2019). Phosphorylated Beclin-1 in the initiation complexes of autophagy can activate autophagy via Ca^{2+} /CaM (calcium/calmodulin)-DAPK (serine/threonine kinase death-associated protein kinase), triggering the dissociation of Beclin-1 from Bcl-2 (Keller et al. 2023). Another study (Arab et al. 2022b) showed that the expression of cellular Beclin-1 and the anti-apoptosis protein Bcl-2 was downregulated in Cd-exposed rat testes; however, linagliptin restored these two proteins and rescued the rebalance of autophagy and apoptosis in the testes of Cd-intoxicated rats. The relative amount of intracellular Beclin-1 and Bcl-2 bound to each other determines the level of cellular autophagy to a certain extent. In a model of duck renal tubular epithelial cells, the addition of the autophagy inhibitor 3-MA to the Cd-treated group significantly increased the rate of apoptosis; increased the mRNA expression of Caspase-3, Cyt C, Bax, and Bak-1; and decreased the mRNA expression of Bcl-2 and the ratio of Bcl-2 to Bax when compared with the control group (Wang et al. 2020a).

Stress can affect autophagy by altering Beclin1/Bcl-2 complex interactions (Lian et al. 2011). In the presence of Cd, increased Ca^{2+} release from the ER lumen leads to the dissociation of Beclin-1 from Bcl-2, thereby activating cellular autophagy. Li et al. (Li et al. 2019) found that Cd induces apoptosis and autophagy in A549 cells and Z-VAD-FMK (an apoptosis inhibitor) inhibits LC3 and Beclin1. Furthermore, they showed that the upregulation of the autophagy-inducing factor Atg4B reduced the expression of Bcl-2 protein and its localization in the mitochondria and influenced mitochondrial function. These changes promoted the dissociation of the Beclin1/Bcl-2 complex and released the autophagy protein Beclin1 to activate the autophagy pathway. The occurrence of Cd-induced cellular autophagy

is closely related to the Beclin-1 and Bcl-2 families. Exposure of cells to Cd leads to a decrease in the binding of Beclin-1 to Bcl-2, which activates cellular autophagy.

Emerging molecules and signaling pathways for Cd-induced autophagy

In addition to the classical pathways mentioned above, recent studies (Gong et al. 2022) have shown that Cd exposure can inhibit autophagy and lysosomal transcriptional function by increasing the acetylation of H4K16, which promotes the aggregation of bromodomain-containing protein 4 (BRD4), a novel epigenetic regulator, into the lysosomal gene promoter region. They also demonstrated that pharmacological (JQ1) inhibition of BRD4 can suppress Cd-induced lysosomal gene transcription and function both *in vitro* and *in vivo*, thereby inhibiting autophagy and oxidative stress-induced kidney injury. JQ1 selectively suppresses the BRD4 gene and thus, is commonly used with BRD4 for treating various cancers (Jiang et al. 2020). As mentioned above, JQ1 alone or combined with Cd were applied in Gong et al. (Gong et al. 2022) study, to investigate the potential of BRD4 as autophagy regulator on Cd-induced kidney oxidative damage. It should be noted that the link between Cd (as a potential carcinogen) and JQ1 (as anti-tumor agent) is still unclear, the combined effects of JQ1 and Cd warrant for further investigation. In addition, Zou et al. (Zou et al. 2021) reported that Cd negatively regulates the Rheb/mTOR signaling pathway by upregulating miR-155 in BRL3A cells, which induces Cd-induced autophagy in rat hepatocytes. Moreover, Rheb knockdown downregulates Cd-induced autophagy. Thus, Cd exposure may regulate autophagy through epigenetic regulatory mechanisms in both liver and renal injury. In a recent publication, Guo et al. (Guo et al. 2022) reviewed epigenetic mechanisms as key functional targets of Cd-mediated damage and covered a broad range of literature about epigenetic processes impacted due to Cd toxicity in the kidney.

In a study published in 2023 on the effects of Cd on spermatogenesis, Ali et al. (Ali et al. 2023) demonstrated that spermatozoa from 12-week Cd-contaminated mice showed aberrations, vacuolization of the sperm cytoplasm, a decrease in the production of multivesicular vesicles (MVBs) supporting the

cytoplasm, and reduction in the biological secretion of exosomes. Thus, a new mechanism by which Cd reduces the exosome-MVB pathway by over-activation of the autophagy pathway has been revealed, and it triggers sperm developmental disorders.

Summary and perspectives

Autophagy is an important regulatory mechanism that maintains homeostasis in organisms. Under physiological conditions, autophagy occurs at a low level to maintain the recycling of cellular contents. When the organism is stimulated by harmful substances such as Cd, autophagy can be activated or blocked to adapt to the alteration of the external environment. If adaptation fails to maintain homeostasis in the internal environment, then inflammation, proliferation, apoptosis, necrosis, or other defensive reactions occur, which lead to cellular injury or even organ failure.

This review summarizes and updates the literature on the origin, transport, and distribution of Cd in the external environment as well as the physicochemical characteristics of Cd distribution after entering the body through the respiratory and digestive pathways. We reviewed and discussed the basic regulatory mechanism of autophagy and the target organs and possible health effects of Cd exposure, with a focus on recently updated molecules/signaling pathways that are mediated by autophagy under Cd toxicity. Moreover, the subsequent fate of the cells following Cd exposure were described. Although the mediation of Nrf2 by the autophagy-lysosome pathway is a promising anti-toxicity molecule for Cd, the specific mechanisms of Cd-induced autophagy that cause damage to the organism are not yet fully understood. Effective therapeutic drugs, tools and sensitive biomarkers for the assessment of Cd toxicity are still lacking (Guo et al. 2022). The interactions or cascades between the reviewed molecules and signaling with autophagy as the core warrant further investigation and the correlation between autophagy and the indicators of exogenous chemical-induced organ-based toxicity and mechanism is necessary to be identified. Furthermore, prevention and treatment strategies focused on the mechanisms underlying Cd toxicity must be developed to prevent the negative effects of autophagy in pathological conditions. Last, although many studies have investigated how

Cd species are distributed and transported in the environment, such as in soil, crops and marine organisms, only few studies have focused on the effects of different Cd species on human health. More precise methods for detecting inorganic and organic forms of Cd, particularly in the human matrix, and determining the behavior of different organic complexes of Cd in the human body warrant further research.

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Declarations

Conflict of interest The authors declare no competing interests.

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