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Autophagic Punctum

The cadmium-induced death of mesangial cells results in nephrotoxicity

Liang-Yo Yang,[1,2,7,†] Kuan-Hsun Wu,[5,†] Wen-Ta Chiu,[4,6] Sheng-Hao Wang[2] and Chwen-Ming Shih[2,3,8,*]

[1]Department of Physiology; College of Medicine; [2]Graduate Institute of Medical Sciences; College of Medicine; [3]Department of Biochemistry; [4]School of Medicine; College of Medicine; Taipei Medical University; Taipei, Taiwan; [5]Department of Pediatrics; Taipei Medical University-Wan Fang Hospital; Taipei, Taiwan; [6]Department of Neurosurgery; Taipei Medical University-Shuang Ho Hospital; Taipei, Taiwan; [7]Neuroscience Research Center; [8]Traditional Herbal Medicine Research Center; Taipei Medical University Hospital; Taipei, Taiwan

[†]These authors contributed equally to this work.

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This study summarizes our most recent findings on the mechanisms underlying the cadmium-induced death of mesangial cells, which leads to nephrotoxicity. Multiple pathways participate in cadmium-induced nephrotoxicity. In the ROS-GSK-3β autophagy pathway, cadmium induces ROS most likely from the mitochondria, and the ROS consequently activate GSK-3β leading to autophagic cell death. In the calcium-ERK autophagy and apoptosis pathway, cadmium stimulates calcium release from the endoplasmic reticulum, which activates ERK leading to predominantly autophagic cell death and a minor level of apoptotic cell death. In the calcium-mitochondria-caspase apoptosis pathway, cadmium-induced elevation of calcium depolarizes the mitochondrial membrane potential and then activates caspase signaling leading to apoptosis. A proposed model for cadmium-induced autophagy and apoptosis leading to nephrotoxicity is summarized in Figure 1.

Cadmium treatment causes calcium release from the endoplasmic reticulum, and the overload of intracellular calcium consequently activates ERK and depolarizes the mitochondrial membrane potential, which in turn results in autophagy and apoptosis, respectively, leading to the death of mesangial cells. Application of cadmium to mesangial cells causes a fast increase in the intracellular calcium concentration. Pretreatment of mesangial cells with a calcium chelator, 1,2-bis (2-amino-phenoxy) ethane-N,N,N,N-tetraacetic acid (BAPTA-AM), suppresses ERK activation and attenuates apoptosis and autophagy, as manifested by the decreased formation of autophagosomes, reduced processing of microtubule-associated protein 1 light chain 3 (LC3)-I to LC3-II, and decreased acidic vesicular organelles (AVOs), further demonstrating that cadmium results in calcium-dependent autophagy and apoptosis.

*Correspondence to: Chwen-Ming Shih; Department of Biochemistry; College of Medicine; Taipei Medical University; 250 Wu-Hsing Street; Taipei 110 Taiwan; Tel.: +886.2.27361661x3151; Fax: +886.2.27356689; Email: cmshih@tmu.edu.tw

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Cadmium-induced calcium-dependent cell death comprises the calcium-ERK signaling pathway and the calcium-mitochondria-caspase signaling pathway. The expression of ERK increases significantly 1 hour following cadmium treatment, and pretreatment with PD 98059 (a MEK 1/2 inhibitor) suppresses cadmium-induced ERK expression and autophagy in mesangial cells. Similarly, pretreatment of mesangial cells with U0126 (another MEK 1/2 inhibitor) attenuates the cadmium-induced expression of ERK, autophagy and apoptosis. The results indicate that the cadmium-induced calcium-ERK signaling pathway leads predominantly to autophagy and to a lesser degree to apoptosis.

Cadmium can induce apoptosis via the calcium-mitochondria-caspase signaling pathway. In addition to the elevation of the intracellular calcium concentration, cadmium treatment depolarizes the membrane potential of mitochondria, increases the expression of caspases 9 and 3 and induces cell death in mesangial cells. Pretreatment of mesangial cells with the calcium chelator BAPTA-AM suppresses the cadmium-induced depolarization of mitochondrial membrane potential and activation of caspases 9 and 3 and attenuates cadmium-induced cell death. These findings strongly suggest that the calcium-mitochondria-caspase signaling pathway contributes significantly to the cadmium-induced death of mesangial cells.

Cadmium results in the production of ROS (including hydrogen peroxide in mesangial cells), which in turn activate GSK-3β leading to autophagy and then cell death. Suppression of GSK-3β induction by the inhibitor SB216763 or small interfering RNA (siRNA) to GSK-3β attenuates cadmium-induced autophagy. Conversely, overexpression of GSK-3β via transfection aggravates cadmium-induced autophagy. These findings demonstrate that GSK-3β plays a critical role in cadmium-induced autophagy. Moreover, N-acetylcysteine (NAC, an ROS scavenger) pretreatment prevents the cadmium-induced activation of GSK-3β and attenuates cadmium-induced autophagy. Furthermore, NAC and the antioxidant vitamin E repress both the cadmium-induced elevation of ROS and autophagy. Taken together, these findings demonstrate that cadmium induces an ROS burst, which in turn potentiates the expression of GSK-3β leading to autophagic cell death.

ROS play a pivotal role in the pathogenesis of several kidney diseases, and cadmium might act on the mitochondria to induce the release of ROS, which in turn activate GSK-3β leading to cell death,

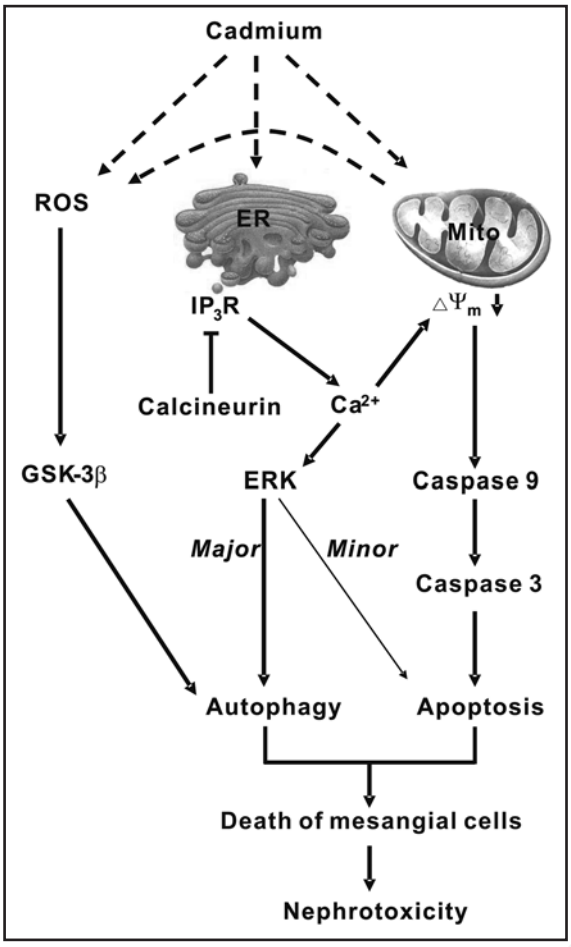

Figure 1. A proposed model for cadmium-induced nephrotoxicity. Cadmium induces nephrotoxicity via multiple pathways including the ROS-GSK-3β autophagy, calcium-ERK autophagy and apoptosis, and calcium-mitochondria-caspase apoptosis pathways. In the ROS-GSK-3β autophagy pathway, cadmium might act on the mitochondria to generate ROS, which in turn results in activation of GSK-3β leading to autophagic cell death. In the calcium-ERK autophagy and apoptosis pathway, cadmium acts on the endoplasmic reticulum to induce elevation of the cytosolic calcium concentration, which in turn activates ERK leading predominantly to autophagic cell death and a minor level of apoptotic cell death. In the calcium-mitochondria-caspase apoptosis pathway, cadmium induces the release of calcium through the inositol-1,4,5-triphosphate receptor (IP_3R) of the endoplasmic reticulum and then calcium depolarizes the membrane potential of mitochondria, which in turn activates caspases 9 and 3 leading to apoptotic cell death. ER, endoplasmic reticulum; IP_3R, inositol-1,4,5-triphosphate receptor; Mito, mitochondria; ΔΨm, mitochondrial membrane potential.

which causes nephrotoxicity. It remains unclear which organelles in the mesangial cells are the target of cadmium to generate ROS. Mitochondrial dysfunction and oxidative stress play a crucial role in the pathogenesis of neurodegenerative diseases such as Alzheimer disease (AD), Parkinson disease (PD), Friedreich ataxia (FRDA), multiple sclerosis and amyotrophic lateral sclerosis (ALS). Thus, mitochondria are one of the most likely targets of cadmium to induce the generation of ROS. Moreover, oxidative stress contributes significantly to the pathogenesis of several kidney diseases such as diabetic nephropathy, age-related ischemic kidney disease, and renal cancer. These findings together lead us to propose that the mitochondra-ROS-GSK-3β pathway leading to autophagic cell death is an important mechanism underlying cadmium-induced nephrotoxicity.

In addition to its potential effect on mitochondria, cadmium might act on the endoplasmic reticulum to induce nephrotoxicity via elevation of the cytosolic calcium concentration, which in turn activates the calcium-ERK pathway and calcium-mitochondria-caspase pathway leading to autophagic and apoptotic cell death, respectively. Endoplasmic reticulum stress and mitochondrial injury have been demonstrated to cause cell death in the glomerular and tubular epithelium of the kidney. Diabetes mellitus can often induce nephropathy. Evidence also indicates that diabetic rats show increased calcium-induced mitochondria depolarization, which is consistent with our finding that cadmium increases the intracellular calcium concentration and depolarizes the mitochondrial membrane potential leading to activation of caspases 9 and 3. In our recent study, we find that cadmium activates the calcium-ERK-autophagy and calcium-ERK-apoptosis pathways leading to the death of mesangial cells. The above findings together guide us to propose that cadmium induces nephrotoxicity via the calcium-ERK pathway and calcium-mitochondria-caspase pathway leading to autophagic and apoptotic cell death. Thus, we propose that cadmium induces nephrotoxicity via multiple pathways.

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