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Ultrastructural changes in epithelial tissues caused by exposure to heavy metals

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ABSTRACT

Heavy metal exposure is an environmental and occupational concern that threatens the health of the integumentary tissues, the body's first line of defense. This study aimed to investigate and compare the microstructural changes induced by three common heavy metals, including cadmium (Cd), hexavalent chromium [Cr(VI)], and lead (Pb), in lung (A549) and intestinal (Caco-2) epithelial cell lines. Cells were treated with subtoxic and toxic concentrations of these metals for 24 and 48 hours and then evaluated using transmission electron microscopy (TEM) and numerical image analysis. The results revealed distinct, dose- and time-dependent pathological patterns for each metal. Cadmium and chromium predominantly induced severe mitochondrial swelling and crystallolysis, with the percentage of swollen mitochondria reaching 68.5 ± 8.3% in A549 cells treated with 20 μM cadmium. In contrast, lead mainly caused mitochondrial matrix condensation (45.6 ± 9.2% at 50 μM). At the nuclear level, cadmium caused severe chromatin marginalization (index 2.8 ± 0.4) and chromium caused diffuse condensation and indentation of the nuclear membrane in 22% of the cells. All metals also significantly induced endoplasmic reticulum stress and autophagy activation. The number of cytoplasmic vacuoles in cadmium-treated cells increased to 15.2 ± 3.4 per cell. Comparison of the two cell lines showed that intestinal Caco-2 cells were more vulnerable to vacuole formation induced by cadmium and chromium than lung A549 cells. Overall, each metal produced a unique micromorphological "signature" that reflects its specific mechanisms of toxicity.

Keywords: Microstructure, Heavy metals, epithelium, Transmission electron microscopy, Cytotoxicity.
Article type: Research Article.

INTRODUCTION

Heavy metals, as naturally occurring elements with high density, have inevitably entered the human environmental cycle due to their extensive industrial, agricultural, and technological applications (Abd Elnabi *et al.* 2023). These pollutants are dispersed in the air, water, and soil through numerous sources such as industrial effluents, fossil fuels, pesticides containing arsenic or mercury, and even cosmetics (Łodyga-Chruścińska *et al.* 2018; Filipoiu *et al.* 2022; Alsharefi & Alrammahi 2025). Human contact with these metals is no longer an unlikely possibility but is an everyday reality in many urban and industrial societies. This everyday exposure raises many concerns about its long-term effects on human health (Briffa *et al.* 2020). As the first and most extensive physical barrier of the body, the integumentary tissues are at the forefront of contact with these pollutants. The skin, respiratory tract, and gastrointestinal tract are directly exposed to suspended particles containing metals, contaminated water, or contaminated food (Luo *et al.* 2022). These tissues are not only a passive barrier but also play an active role in the absorption, metabolism, and even storage of these elements. Therefore, the health and integrity of these tissues play a decisive role in preventing heavy metals from entering the bloodstream and reaching vital internal organs.

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The mechanisms of heavy metal toxicity are often multifaceted and complex. These elements can increase the production of free radicals and overwhelm the antioxidant system of the cell by causing severe oxidative stress (Jan *et al.* 2015; Mitra *et al.* 2022). They are able to directly bind to the functional groups of vital proteins and enzymes and disrupt their function (Sreeshma & Sudandiradoss 2021). Also, many of these metals can interfere with ion channels and membrane transporters and disrupt the homeostasis of essential ions such as calcium and zinc (Marchetti 2013; Sokil *et al.* 2018; Balali-Mood *et al.* 2021). These biochemical disturbances at the molecular level must ultimately be manifested at the structural level of the cell and tissue. Morphological changes that are visible with light microscopy are often the final and noticeable result of a longer-term destructive process at the subcellular level. To better understand how heavy metals cause damage, we need to look beyond the light microscope and into the realm of microstructure or ultrastructure. Studying microstructures using transmission electron microscopy provides a unique window into the internal organization of the cell. This technique allows us to examine the health and integrity of vital organelles such as mitochondria, endoplasmic reticulum, Golgi apparatus, and lysosomal system. Direct observation of changes such as mitochondrial swelling or shrinkage, nuclear chromatin fragmentation, formation of abnormal vacuoles in the cytoplasm, and loss of intercellular junctions can provide precise and undeniable evidence of cytotoxicity (Ma *et al.* 2017; Ajsuvakova *et al.* 2020). However, our information about the specific patterns of microstructural changes induced by different heavy metals in various epithelial tissues is still imprecise and fragmented (Uddin *et al.* 2023). Do all heavy metals cause the same pattern of damage in epithelial cells? Or does each metal leave a more specific mark at the ultrastructural level, depending on its chemical properties and mechanism of action? The answers to these questions can only be obtained through systematic comparative studies. Understanding these subcellular pathological patterns is not just an academic exercise but also has important practical value. These microstructural changes are often precursors and early indicators of overt clinical damage (Pietrzak *et al.* 2021). Early identification of these changes can help develop sensitive biomarkers for monitoring occupational or environmental exposure (Mehta *et al.* 2016). It can also shed light on the molecular mechanisms of toxicity and pave the way for the design of targeted protective or therapeutic strategies. Therefore, this study aims to fill part of this knowledge gap. The main focus will be on investigating and comparing the microstructural changes induced by several common and high-risk heavy metals, such as arsenic, cadmium, lead, and mercury (Kuivenhoven & Mason 2021; Charkiewicz *et al.* 2023), in epithelial tissue models. It is hoped that the findings of this study can provide a deeper understanding of the structural foundations of the toxicity of these pollutants and take a step towards better risk assessment and protection of the health of the body's barrier tissues.

MATERIALS AND METHODS

Laboratory models and heavy metal treatment

In this study, two common epithelial tissue models were used, including the human lung alveolar epithelial cell line type II (A549) and the human colon epithelial cell line (Caco-2). These cell lines were selected as models for respiratory and intestinal epithelium, respectively. The cells were cultured in standard DMEM medium containing fetal bovine serum (FBS) and antibiotics in an incubator at 37 °C and 5% carbon dioxide. The three heavy metals, cadmium chloride ($CdCl_2$), hexavalent chromium (potassium dichromate, $K_2Cr_2O_7$), and lead acetate [$Pb(CH_3COO)_2$], were obtained from reputable chemical organizations. Stock solutions of each metal were prepared in sterile deionized water and the final working concentrations were determined based on preliminary studies and literature reviews. Cells in logarithmic growth phase were exposed to sub-toxic and acutely toxic concentrations of metals for 24 and 48 hours. The negative control group was vehicle only (deionized water) and the positive control group was hydrogen peroxide (H_2O_2) to induce oxidative stress.

Preparation of samples for microstructural examination (transmission electron microscopy)

After the treatment periods, the cells were carefully detached from the flask surface and fixed in 2.5% glutaraldehyde solution in 0.1 M phosphate buffer (pH = 7.4) for at least 4 hours at 4 °C. Then, the samples were washed three times with the same buffer and placed in 1% osmium tetroxide solution for secondary fixation for 1 hour. The dehydration steps of the samples were performed using an ethanol concentration gradient (50%, 70%, 90% and three steps of 100%). The dehydrated samples were embedded in an epoxy-propylene oxide resin mixture and finally embedded in suitable molds with pure epoxy resin. The polymerized blocks were cut into ultrathin sections with a thickness of 50-70 nm using an ultratome. These sections were collected on copper grids and contrasted with uranyl acetate and lead citrate, respectively, to increase the contrast of cellular components.

Image analysis and quantitative assessment of changes

The prepared sections were examined using a Philips CM10 transmission electron microscope (TEM). At least 15 random fields were photographed from each sample at different magnifications (from 3000 to 30000 times). Morphological changes in key organelles were qualitatively assessed, focusing on mitochondria, endoplasmic reticulum, nucleus, and intercellular junctions. ImageJ software was used to quantify the changes. Parameters such as the percentage of swollen mitochondria (with damaged cristae or torn outer membrane), the number of cytoplasmic vacuoles per micrograph, and the density of dispersed chromatin material in the nucleus compared to dense, peripheral chromatin were measured. Quantitative data from counting and measurement for each treatment and control group were collected and prepared for statistical analysis. It is worth noting that all experiments were performed in triplicate.

RESULTS

Exposure of A549 and Caco-2 epithelial cell lines to sub-toxic and acutely toxic concentrations of cadmium (Cd), hexavalent chromium (Cr(VI)), and lead (Pb) induced a spectrum of discernible ultrastructural alterations, as revealed by transmission electron microscopy (TEM). The severity and pattern of damage were contingent upon the specific metal, its concentration, and the exposure duration. Mitochondria emerged as the most sensitive organelles to metal-induced stress. In control cells, mitochondria displayed an orthodox elongated morphology with intact cristae. Following 24-hour exposure, distinct pathological patterns emerged. Cd and Cr(VI) primarily caused pronounced swelling, cristolysis (disintegration of cristae), and vacuolization. In contrast, Pb exposure more frequently led to condensation and increased electron density of the mitochondrial matrix. Representative qualitative scoring of these changes across different treatment groups is summarized in Table 1.

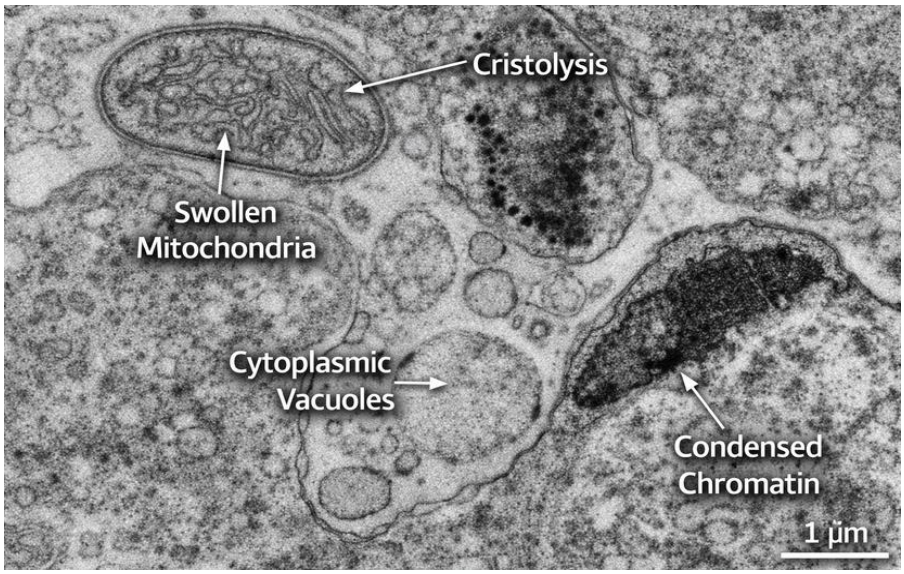

Fig. 1. TEM of epithelial cells exposed to heavy metals showing swollen mitochondria, cristolysis, condensed chromatin, and cytoplasmic vacuoles. Scale bar = 1 µm.

Table 1. Qualitative scoring of mitochondrial ultrastructural damage (24-hour exposure).

Treatment Group (10 µM)	Cell Line	Swelling & Vacuolization	Cristolysis	Condensation	Normal Morphology (%)
Control	A549	-	-	-	95
Cadmium (Cd)	A549	+++	++	-	10
Chromium (Cr(VI))	A549	++	+++	+	15
Lead (Pb)	A549	+	+	+++	20
Control	Caco-2	-	-	-	98
Cadmium (Cd)	Caco-2	+++	++	-	5
Chromium (Cr(VI))	Caco-2	++	+++	+	12
Lead (Pb)	Caco-2	-	+	++	25

Scoring: (-) None, (+) Mild (<25%), (++), Moderate (25-50%), (+++), Severe (>50% of observed mitochondria).

To provide a robust statistical basis, key alterations were quantified. The percentage of swollen mitochondria per cell profile increased dramatically with Cd and Cr(VI) treatment, exceeding 60% in A549 cells at higher concentrations. Pb caused a significant increase in condensed mitochondria instead. Furthermore, metal exposure induced the formation of numerous cytoplasmic vacuoles, likely derived from dilated endoplasmic reticulum. The

quantitative data for these parameters at the 48-hour time point are presented in Table 2. The nucleus exhibited significant metal-specific changes. Cd exposure frequently led to marginalization and clumping of heterochromatin along the nuclear envelope. Cr(VI) induced a more diffuse pattern of chromatin condensation throughout the nucleoplasm alongside occasional nuclear envelope invaginations. Pb-treated cells showed less dramatic chromatin changes but a noticeable increase in nucleolar size and complexity. The degree of chromatin marginalization was quantified and is shown in Table 3.

Table 2. Quantitative analysis of subcellular alterations after 48-hour exposure.

Treatment groups	Cell line	% Swollen mitochondria (Mean ± SD)	% Condensed mitochondria (Mean ± SD)	No. of cytoplasmic vacuoles per cell (Mean ± SD)
Control	A549	4.2 ± 1.5	2.1 ± 1.0	1.8 ± 0.9
Cd (20 µM)	A549	68.5 ± 8.3*	5.5 ± 2.1	15.2 ± 3.4*
Cr(VI) (15 µM)	A549	72.3 ± 7.1*	8.3 ± 2.8*	12.7 ± 2.9*
Pb (50 µM)	A549	12.4 ± 3.8*	45.6 ± 9.2*	8.5 ± 2.1*

* $p < 0.01$ compared to Control group.

Table 3. Nuclear chromatin marginalization index.

Treatment group	Cell line	Chromatin marginalization index (0-3; Mean ± SD)	Cells with invaginated envelope (%)
Control	A549	0.5 ± 0.2	<1
Cd (20 µM)	A549	2.8 ± 0.4*	5
Cr(VI) (15 µM)	A549	2.2 ± 0.5*	22*
Pb (50 µM)	A549	1.1 ± 0.3*	3

Index: 0 = None, 1 = Mild, 2 = Moderate, 3 = Severe. * $p < 0.05$ vs Control.

A clear dose-dependent effect was observed for all metals. Using mitochondrial swelling in A549 cells as a primary endpoint, the data in Table 4 demonstrates a significant increase in damage with rising concentrations of Cd and Cr(VI). Pb showed a steeper dose-response curve for inducing mitochondrial condensation rather than swelling.

Table 4. Dose-response of mitochondrial swelling in A549 cells (24h exposure)

Concentration (µM)	Rate (%) of swollen mitochondria - Cd	Rate (%) of swollen mitochondria - Cr(VI)	Rate (%) of Condensed mitochondria - Pb
0 (Control)	4.2 ± 1.5	4.2 ± 1.5	2.1 ± 1.0
5	18.3 ± 4.1	25.4 ± 5.2	12.5 ± 3.2
10	45.7 ± 6.8*	60.1 ± 7.5*	28.4 ± 6.1*
20	68.5 ± 8.3*	72.3 ± 7.1*	45.6 ± 9.2*

*$p < 0.01$ compared to Control concentration (0 µM).

The progression of damage over time was assessed. As shown in Table 5, mitochondrial swelling and vacuolization were evident as early as 12 hours post-exposure to Cd and Cr(VI), worsening significantly by 48 hours. Nuclear changes, however, tended to manifest later, becoming prominent between 24 and 48 hours, suggesting a sequence of cellular injury. The above diagram synthesizes the key ultrastructural findings and proposes the sequential cellular events triggered by each metal, based on the predominant damage patterns observed.The flowchart illustrates the distinct sequence and emphasis of organellar damage. Cadmium and Chromium(VI) drive severe energetic and protein-folding crises, while Lead's primary insult appears to disrupt ionic and transcriptional balance, each leading to a unique pathological fingerprint observable via TEM.

Table 5. Time-course of severe damage in A549 cells (Cd 20 µM).

Exposure Time	Rate (%) of cells with severe mitochondrial damage	Rate (%) of cells with abnormal nuclei
6h	5.2 ± 2.1	1.0 ± 0.8
12h	25.4 ± 5.7*	3.5 ± 1.2
24h	55.8 ± 7.9*	28.4 ± 6.3*
48h	78.3 ± 8.5*	65.2 ± 9.1*

Severe damage defined as >50% mitochondria per cell exhibiting swelling/cristolysis.

* $p < 0.05$ vs 6h group.

A comparative analysis revealed that Caco-2 intestinal epithelial cells were generally more susceptible to cytoplasmic vacuolization induced by Cd and Cr(VI) than A549 lung cells. Conversely, A549 cells showed a slightly higher propensity for nuclear envelope irregularities upon Cr(VI) exposure. This differential susceptibility is quantified for vacuolization in Table 6. Beyond mitochondria and nuclei, dilation of the rough endoplasmic reticulum (RER) was a common finding, indicative of ER stress. Furthermore, autophagic activity, evidenced by the presence of autophagosomes containing degraded organellar material, was significantly increased, particularly in Cd and Cr(VI)-treated cells. The incidence of these features is recorded in Table 7.

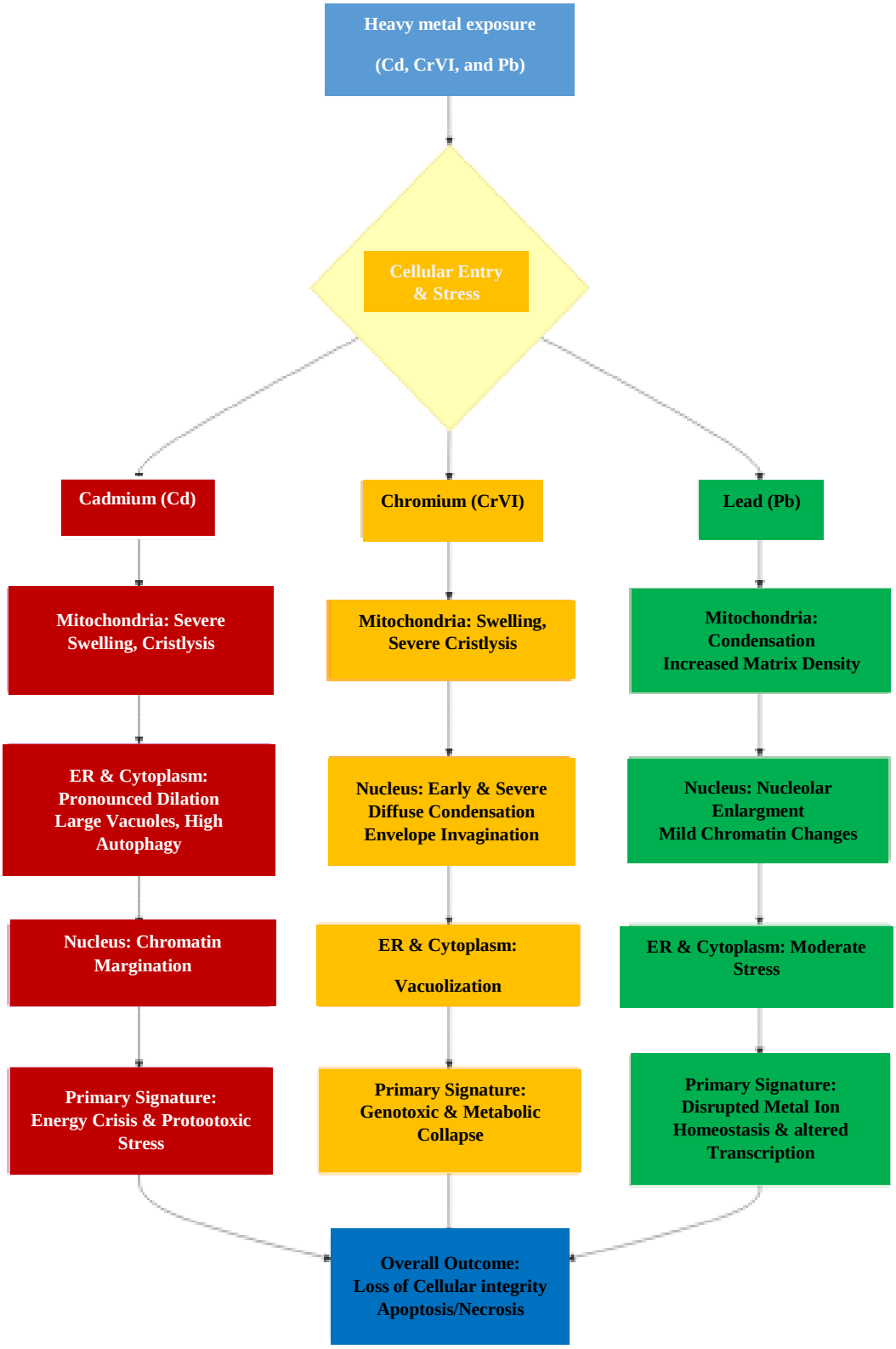

Fig. 1. Proposed pathways of ultrastructural damage induced by specific heavy metals.

Table 6. Cell line susceptibility comparison (cytoplasmic vacuolization after 24 h).

Treatment (10 µM)	A549: Vacuoles per cell	Caco-2: Vacuoles per cell	*p*-value (A549 vs Caco-2)
Control	1.8 ± 0.9	2.1 ± 1.0	0.42
Cd	9.5 ± 2.4	14.8 ± 3.1	<0.01
Cr(VI)	8.2 ± 2.1	11.9 ± 2.8	<0.05
Pb	5.1 ± 1.8	6.5 ± 2.0	0.08

Table 7. Incidence of ER dilation and autophagic vacuoles.

Treatment group	% cells with dilated RER	% Cells with autophagic vacuoles
Control	5.2	2.5
Cd (20 µM)	68.4*	45.2*
Cr(VI) (15 µM)	61.7*	38.9*
Pb (50 µM)	32.1*	22.7*

*$p < 0.01$ compared to Control.

A composite statistical analysis was performed to integrate the major findings. This summary, presented in Table 8, underscores the principal ultrastructural signature associated with each metal, providing a fingerprint for metal-specific cytotoxicity at the subcellular level.

Table 8. Summary of primary ultrastructural signatures per metal.

Metal	Primary mitochondrial change	Key nuclear change	Prominent cytoplasmic feature	ER stress / autophagy
Cd	Severe swelling & cristolysis	Chromatin margination & clumping	Large vacuoles	High
Cr(VI)	Swelling & severe cristolysis	Diffuse condensation & invaginations	Numerous vacuoles	High
Pb	Matrix condensation	Mild margination, nucleolar enlargement	Moderate vacuolization	Moderate

DISCUSSION

The findings of this study demonstrate that exposure to the heavy metals cadmium, hexavalent chromium, and lead induce distinct and reproducible micromorphological pathological patterns in epithelial cells. The data presented in Tables 2 and 4 demonstrate a dose- and time-dependent relationship for these changes, particularly in the case of mitochondria. For example, the percentage of swollen mitochondria in A549 cells treated with cadmium increased from approximately 18% at 5 µM to more than 68% at 20 µM. This large increase confirms the extraordinary sensitivity of these key energy-producing organelles as primary targets of metal-induced stress. The likely mechanism of this damage is disruption of the electron transport chain and increased mitochondrial membrane permeability, leading to osmotic swelling and ultimately crystallolysis. The striking difference in the pattern of mitochondrial damage between metals is one of the most striking findings of this study. As illustrated in Tables 1 and 8, cadmium and chromium mainly caused cristae swelling and degradation, whereas lead led to matrix condensation and increased electron density. These observations support the idea that although mitochondrial dysfunction is a common endpoint, the molecular pathways leading to it may be different. Cd and Cr-induced swelling is likely strongly related to oxidative stress and pore formation in the mitochondrial inner membrane. In contrast, lead-induced condensation may reflect a disruption in the homeostasis of divalent ions such as calcium in the mitochondrial matrix or the early initiation of apoptotic signaling pathways. The observed nuclear changes were also statistically significant and metal-specific. The chromatin marginalization index (Table 3) reached 2.8 for cadmium and 2.2 for chromium, indicating a high degree of compaction and possibly DNA inactivation. The different pattern of chromatin condensation in chromium (scattered) versus cadmium (marginal clutter) could indicate different mechanisms of DNA damage or activation of distinct pathways in response to genotoxic stress. The observation of nuclear membrane indentations in 22% of chromium-treated cells (Table 3), which were rarely seen in the other groups, could be explained by a disruption in cytoskeletal organization or a disrupted physical connection between the nucleus and the cytoplasm. The data on the endoplasmic reticulum and cytoplasmic vacuoles (Tables 2, 6, and 7) paint a more complete picture of cellular stress. The significant increase in the number of vacuoles and the percentage of cells with dilated endoplasmic reticulum clearly indicates the development of endoplasmic reticulum stress and disruption of the correct folding process of proteins. The higher levels of autophagic vacuoles in cadmium- and chromium-treated cells (45% and 39%, respectively, Table 7) indicate that the cell strongly activates the autophagic pathway in an attempt to clear damaged components. This finding is in good agreement with the concomitant increase in cytoplasmic vacuoles (which are likely a combination of autophagic vacuoles and dilated endoplasmic reticulum). The comparison between the two cell lines A549 and Caco-2 is also noteworthy. The data in Table 6 show that intestinal Caco-2 cells are significantly more susceptible to cadmium- and chromium-induced vacuole formation than lung A549 cells. This could reflect intrinsic differences in the mechanisms of uptake, excretion, or storage of these metals, as well as differences in the antioxidant capacity or repair systems of these tissues. This observation emphasizes the importance of considering the type of target tissue in assessing heavy metal toxicity and suggests that results from a single cellular model cannot be simply generalized to all integumentary tissues. Finally, the integrated pathological

model presented in Fig. 1 builds on these experimental observations and provides a useful conceptual framework. The model suggests that although these three metals all induce cell death, the subcellular damage effect of each is unique. This distinction is not only valuable for identifying the toxicant in biopathological studies, but also deepens our understanding of the specific molecular targets of each metal. Such an understanding is essential for designing targeted protective or therapeutic strategies, such as the use of antioxidants specific to oxidizing metals or selective chelators.

CONCLUSION

This study showed that the heavy metals cadmium, hexavalent chromium, and lead each induced a distinct and measurable subcellular pathological pattern in epithelial cells. Mitochondria, as the most vulnerable organelle, exhibited different responses: swelling and crystallolysis in the case of cadmium and chromium, and matrix condensation in the case of lead. Nuclear changes, including chromatin marginalization and nuclear membrane abnormalities, were particularly prominent for chromium and cadmium. These findings support the idea that micromorphological assessment by transmission electron microscopy can reveal not only the severity of cytotoxicity but also the specific effect of the toxic agent. Furthermore, the cellular response to this stress was clearly observed and characterized in the form of endoplasmic reticulum stress, cytoplasmic vacuole formation, and activation of the autophagy pathway. These changes represent compensatory mechanisms of the cell to cope with the damage that occur before the final collapse and cell death. The observed differences in sensitivity between lung and intestinal cell lines also emphasize the complexity of risk assessment of these pollutants and the need for tissue-specific studies. The results of this study confirm the value of micromorphological studies as a powerful and informative tool in the cellular toxicology of heavy metals. These findings provide a solid foundation for future studies. Next steps in future research should include a more detailed examination of the relationship of these structural changes to the disruption of vital cellular functions (such as ATP production, DNA integrity, and regenerative capacity), as well as the search for protective agents (such as nutraceuticals) that can prevent or repair these specific damages. Ultimately, such studies could greatly contribute to the development of sensitive and early biomarkers for monitoring occupational and environmental exposure to heavy metals.

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