Review

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Cadmium-induced Carcinogenesis in Respiratory Organs and the Prostate: Insights from Three Perspectives on Toxicogenomic Approach

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Cadmium (Cd) exposure primarily occurs through inhalation, either by smoking or occupational exposure to contaminated air. Upon inhalation, Cd ultimately reaches the prostate through the bloodstream. In this review, we investigate the carcinogenic potential of Cd in both respiratory organs and the prostate. Specifically, this review examines cellular metabolism, comprehensive toxicity, and carcinogenic mechanisms by exploring gene ontology, biological networks, and adverse outcome pathways. In the respiratory organs, Cd induces lung cancer by altering the expression of *IL1B* and *FGF2*, causing DNA damage, reducing cell junction integrity, and promoting apoptosis. In the prostate, Cd induces prostate cancer by modifying the expression of *EDN1* and *HMOX1*, leading to abnormal protein activities and maturation, suppressing tumor suppressors, and inducing apoptosis. Collectively, this review provides a comprehensive understanding of the carcinogenic mechanisms of Cd in two different organs by adopting toxicogenomic approaches. These insights can serve as a foundation for further research on cadmium-induced cancer, contributing to the establishment of future cancer prevention strategies.

Key Words Cadmium, Carcinogenesis, Computational biology, Toxicogenetics, Adverse outcome pathways

INTRODUCTION

Cadmium (Cd) is a naturally occurring heavy metal that is artificially emitted into the atmosphere through human activities such as smoking and industrial processes. Humans are primarily exposed to Cd through inhalation, ingestion, and skin contact [1]. In scenarios of dietary intake, only about 5% of the ingested amount is absorbed through the gastrointestinal tract [2]. Cd exposure via skin contact is rare, with this exposure route accounting for only approximately 0.5% of Cd absorption [3]. However, Cd uptake through inhalation is quite high, with up to 90% of the inhaled dose being deposited in the lungs [4].

The inhalation of Cd scenario which is the most significant route of absorption in the human body can be divided into two cases. For the general case, smoking is the primary route of Cd exposure [5]. For occupational case, Cd fume emitted from industrial activities such as the production of nickel-Cd batteries, metal coatings, and pigments [6,7] is a kind of causes [8]. Cd exposure through smoking or polluted air can have serious adverse effects including lung cancer. Cd can induce lung cancer, which has already been widely recognized through numerous research studies. Numerous reports have found that cadmium inhalation leads to respiratory cancers including tracheal cancer, bronchus cancer and lung cancer [9-11]. Additionally, occupational exposure to Cd is known to have adverse effects on the prostate [12,13]. Cd absorbed through the respiratory system can circulate through the bloodstream and reach the prostate (Fig. 1) [14-16]. The mechanisms underlying the onset of prostate cancer due to Cd are not fully understood, so the need for further research is increasing.

Public databases such as the Gene Expression Omnibus (GEO) provide recently detailed biological data, including

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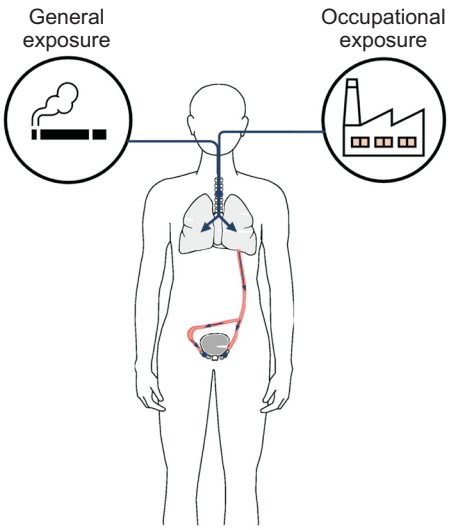

Figure 1. The route through which inhaled cadmium passes the respiratory organs and circulates in the bloodstream to reach the prostate.

experimental design, methodology, and sample attributes for high-throughput gene expression studies [17]. Here, we reviewed studies on Cd exposure in human respiratory organs and the prostate from the GEO database and compiled a list of differentially expressed genes (DEGs) associated with Cd exposure in each organ.

This review used three different toxicogenomic approaches including gene ontology (GO), biological network, and adverse outcome pathways (AOPs). The GO serves as an inclusive platform for categorizing genes according to their biological process (BP), cellular component (CC), molecular function (MF) [18], thereby offering comprehensive insights into the biological functions affected by differential gene expression at the cellular and molecular levels. Given the abundance of biological data in databases [19], the ability of researchers to effectively find the desired information has become crucial. Biological network is an effective approach for gaining an extensive understanding of heavy metal-induced carcinogenesis, diseases, and identification of central genes. Moreover, the direct relations between central genes, cell processes, and diseases enhances the ability to predict protein markers specific to carcinogenesis. AOP provides a comprehensive overview of the mechanisms underlying the carcinogenic effects of Cd. AOP is a biological mechanism consisting of a series of cellular and molecular events required to demonstrate adverse outcomes (AOs) when an organism is exposed to a noxious substance such as Cd [20].

This review reports our current understanding of the toxic mechanisms underlying the toxicity of Cd. Especially, its carcinogenic effects on the respiratory organs and prostate by exploring using toxicogenomic approaches. We provide biological understanding of respiratory organs and prostate cancer induced by cadmium. This understanding can contribute to the prevention and treatment of these cancers.

ADVERSE EFFECTS OF Cd EXPOSURE IN RESPIRATORY ORGANS

Respiratory toxicity of Cd from the perspective of GO

To gain insights into the toxicity of Cd inhalation in respiratory organs, we examined gene expression data (GSE128263) from human bronchial epithelial cells (BEAS-2B) exposed to Cd. The top 10 BPs, CCs, and MFs from the Cd exposure study (adjusted *P*-value < 0.05) were identified respectively (Table 1). For the activated ontologies within the BPs, most gene ontologies were related to Cd metabolism and protective effects such as 'detoxification of inorganic compound,' 'stress response to metal ion,' and 'response to Cd ion.' Among the suppressed ontologies, 'negative regulation of pathway-restricted suppressor of mothers against decapentaplegic (SMAD) protein phosphorylation' likely plays a protective role against carcinogens. The SMAD protein is phosphorylated by TGF-β, activin, or bone morphogenetic proteins, thereby regulating target gene expression [21,22]. Souchelnytskyi et al. [23] demonstrated down-regulation of the SMAD protein phosphorylation as indication of abnormal transcription of its target genes. SMAD proteins are components of the TGF-β family signaling pathways [24], and dysfunction of TGF-β family signaling pathways causes bronchopulmonary diseases [25]. The suppression of 'negative regulation of cellular response to growth factor stimulus' can be interpreted as a healing effect. Because growth factors play a key role in tissue interactions, normal lung development, homeostasis [26], tissue repair and tissue regeneration [27]. When considering the integrated activation and suppression of BPs, there was a clear increase in Cd metabolism, whereas defense against carcinogens, bronchial homeostasis, recovery, and regeneration in bronchial tissue decreased.

In the activated CCs, most gene ontologies are related to cell junctions. 'Cell-cell junction,' 'apical junction,' and 'desmosome' are involved in cell junctions, with 'desmosome' being the major intercellular adhesive junctions [28]. 'Basal plasma membrane' is also related to cell junctions because the differentiation of the apical plasma membrane from the basal plasma membrane is mediated and controlled by lateral cell-cell adhesion junctions [29]. Cell junctions are linked to cell permeability, and as cell junctions tighten, cell permeability decreases [30]. This can be understood as a protective measure against Cd by decreasing cell permeability.

Among activated MFs, 'cell adhesion mediator activity' plays a crucial role in reducing cell permeability as described in the CCs. 'Sterol transporter activity' and 'sterol binding' are intricately linked to both homeostasis and immune functions [31]. This can be interpreted as a defense against Cd, down-regulating cell permeability and up-regulating immune functions.

Table 1. Gene ontology classification of the DEGs from Cd exposed respiratory cells

Ontology category	Activated ontology	-log (adjusted *P*-value)	Suppressed ontology	-log (adjusted *P*-value)
Biological processes	Regulation of lipid biosynthetic process	3.7	Response to virus	3.7
	Detoxification of inorganic compound	3.7	Defense response to virus	3.2
	Stress response to metal ion	3.6	Defense response to symbiont	3.2
	Cellular zinc ion homeostasis	3.1	Negative regulation of pathway-restricted SMAD protein phosphorylation	2.4
	Regulation of steroid metabolic process	3.1	Viral life cycle	2.3
	Response to Cd ion	3.1	Negative regulation of cellular response to growth factor stimulus	1.7
	Zinc ion homeostasis	3.0	Viral process	1.6
	Regulation of steroid biosynthetic process	3.0	Regulation of viral process	1.6
	Negative regulation of neuron projection development	3.0	Negative regulation of viral process	1.6
	Cellular transition metal ion homeostasis	2.7	Wound healing	1.6
Cellular components	Neuronal cell body	4.0	-	-
	Cell-cell junction	3.2		
	Apical junction complex	3.1		
	Basal plasma membrane	3.0		
	Basal part of cell	3.0		
	Presynapse	2.7		
	Main axon	2.5		
	Basolateral plasma membrane	2.5		
	Exocytic vesicle	2.4		
	Desmosome	2.1		
Molecular functions	Sterol transporter activity	3.4	-	-
	Protein binding involved in heterotypic cell-cell adhesion	1.8		
	Alcohol binding	1.8		
	Efflux transmembrane transporter activity	1.8		
	Cell adhesion mediator activity	1.8		
	Phospholipid binding	1.8		
	Cell-cell adhesion mediator activity	1.8		
	Transmembrane receptor protein kinase activity	1.6		
	Amyloid-beta binding	1.6		
	Steroid binding	1.6		

DEGs, differentially expressed genes; Cd, cadmium; SMAD, suppressor of mothers against decapentaplegic.

After considering the overall GO of Cd on respiratory cells, we were able to discern how cells interact with Cd and manifest toxic effects at the cellular level. In respiratory cells, Cd appears to prompt cells to strengthen intercellular junctions as a defense mechanism against Cd permeation. The activation of Cd metabolism and immune functions aims to protect against Cd toxicity. However, the suppression of defense against carcinogens, homeostasis, cellular regeneration, and cell recovery suggests that these are the key molecular mechanism through which Cd exerts its toxic effects.

Comprehensive evaluation of the respiratory toxicity of Cd through biological network

In order to gain a comprehensive understanding of the toxic mechanisms of Cd inhalation in respiratory organs, we constructed a biological network using Pathway Studio version 12.5.0.2 (Elsevier). The biological network including gene-gene interactions, cell processes, primarily inflammation response and lung cancer shows toxic effects in the respiratory system by Cd inhalation (Fig. 2A). Apart from cancer and inflammation, respiratory diseases encompass ‘pulmonary edema,’ ‘asthma,’ ‘adult respiratory distress syndrome,’ ‘pulmonary fibrosis,’ and ‘nasal polyp.’ To identify central genes

in the Cd respiratory toxicity network, each gene in the gene-gene interaction network was assessed based on two parameters: edge degree and betweenness centrality. *IL1B*, *FGF2*, *ABCA1*, and *ZEB1* displayed high significance in the network.

A central network was constructed using these genes, cell processes, and diseases that exhibit a relationship with these central genes (Fig. 2B). The interactions between the central genes and Cd ion were confirmed on the Pathway Studio database, suggesting that the central genes could serve as potential biomarkers for respiratory diseases caused by Cd inhalation. *IL1B* is a potent pro-inflammatory cytokine secreted by numerous cell types, which plays a crucial protective role against infection and injury [32]. *FGF2* possesses broad mitogenic and angiogenic activities, playing key roles in diverse BPs such as wound healing and tumor growth [33]. Wu et al. [34] demonstrated that *ABCA1* mediates the transmembrane transport of free intracellular cholesterol and phospholipids to apolipoprotein, maintaining the normal metabolism of intracellular cholesterol. In addition, *ABCA1* serves as the main efflux channel of intracellular cholesterol, indirectly affecting proliferation, metastasis, and invasion of various cancer cells by regulating intracellular cholesterol levels [34]. *ZEB1* participates in the transcriptional repression of interleukin-2 [35]. Zhang et al. [36] expressed that *ZEB1* is crucial for transformation, promoting tumorigenesis, and its overexpression is associated with cancer malignancy in various cancer cells.

In brief, we constructed a biological network to gain a comprehensive understanding of the adverse effects of Cd (Fig. 2A). Cd poisoning is associated with 'inflammatory response,' 'DNA damage,' 'apoptosis,' and 'oxidative stress.' (Fig. 2B) Additionally, numerous respiratory diseases were found to be linked to Cd poisoning. Importantly, the identified central genes could serve as potential biomarkers for respiratory cancer caused by Cd inhalation.

Table 2. Gene ontology classification of the DEGs from Cd exposed prostate cells

Ontology category	Activated ontology	-log (adjusted *P*-value)	Suppressed ontology	-log (adjusted *P*-value)
Biological processes	Response to endoplasmic reticulum stress	4.5	Response to oxidative stress	1.9
	Response to topologically incorrect protein	4.5	Protein processing	1.7
	Cellular response to topologically incorrect protein	4.0	Protein maturation	1.7
	Response to unfolded protein	3.5	Regulation of mRNA processing	1.7
	Endoplasmic reticulum unfolded protein response	3.0	Regulation of mRNA metabolic process	1.6
	Cellular response to unfolded protein	3.0	Protein nitrosylation	1.4
	Regulation of transcription from RNA polymerase II promoter in response to stress	2.5	Peptidyl-cysteine S-nitrosylation	1.4
	Cellular response to hypoxia	2.5	Negative regulation of JUN kinase activity	1.4
	Cellular response to decreased oxygen levels	2.5	-	-
	Regulation of DNA-templated transcription in response to stress	2.5		
Cellular components	Endoplasmic reticulum lumen	5	Peroxisome	1.6
	Endoplasmic reticulum chaperone complex	2.4	Microbody	1.6
	Melanosome	2.1	Cell-substrate junction	1.4
	Pigment granule	2.1	SWI/SNF superfamily-type complex	1.4
	-	-	Intrinsic component of external side of plasma membrane	1.4
			ATPase complex	1.4
			Vacuolar lumen	1.4
			Focal adhesion	1.4
			Golgi apparatus subcompartment	1.4
Molecular functions	Chaperone binding	1.7	Ubiquitin-like protein ligase binding	1.3
	Receptor ligand activity	1.7	Ubiquitin protein ligase binding	1.3
	Signaling receptor activator activity	1.7	NAD binding	1.3
	Misfolded protein binding	1.7	-	-

DEGs, differentially expressed genes; Cd, cadmium.

Putative AOP of respiratory organ exposed to Cd

To explore the specific toxic mechanism of Cd in respiratory cells, we constructed a putative AOP based on central genes specific to the respiratory (Fig. 2C). This review makes use of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway to construct putative AOP. The putative AOP for Cd exposure to the respiratory cell encompasses the MAPK signaling pathway. The putative AOP reveals that the expression of *IL1B* and *FGF2* undergo alterations upon Cd exposure. The binding of *IL1B* to Interleukin 1 receptor type 1 is considered a putative molecular initiating event (MIE). This putative MIE results in changes in *MAP3K7* expression, NF-κB expression, and the activation of the Wnt signaling pathway. These three events are regarded as putative key events (KEs). The altered expression of NF-κB by *MAP3K7* causes proliferation, inflammation, and anti-apoptosis, whereas the Wnt signaling pathway results in increased cell growth. The theses generated by NF-κB and the Wnt signaling pathway are considered putative AOs. The other MIE involves *FGF2* binding to fibroblast growth factor receptor 1. Following this MIE, the RAS signaling pathway is initiated, leading to SRF and JNK binding to DNA. These three events are considered KEs, with SRF and JNK binding to DNA causing proliferation and differentiation, and JNK binding to DNA inducing apoptosis.

Through this putative AOP, we observed that Cd exposure leads to alterations in the expression levels of *IL1B* and *FGF2*, resulting in abnormalities in parts of the MAPK signaling pathway. Specifically, dysregulation in the functions of Wnt signaling, NF-κB, and RAS signaling occurs. These KEs contribute to cancer-related cellular processes in cell growth, differentiation, inflammation, and apoptosis.

In summary, by interpreting the results acquired from the GEO database, we identified DEGs derived from the transcriptome of Cd-exposed respiratory cells. Our interpretation was approached from three perspectives: understanding at

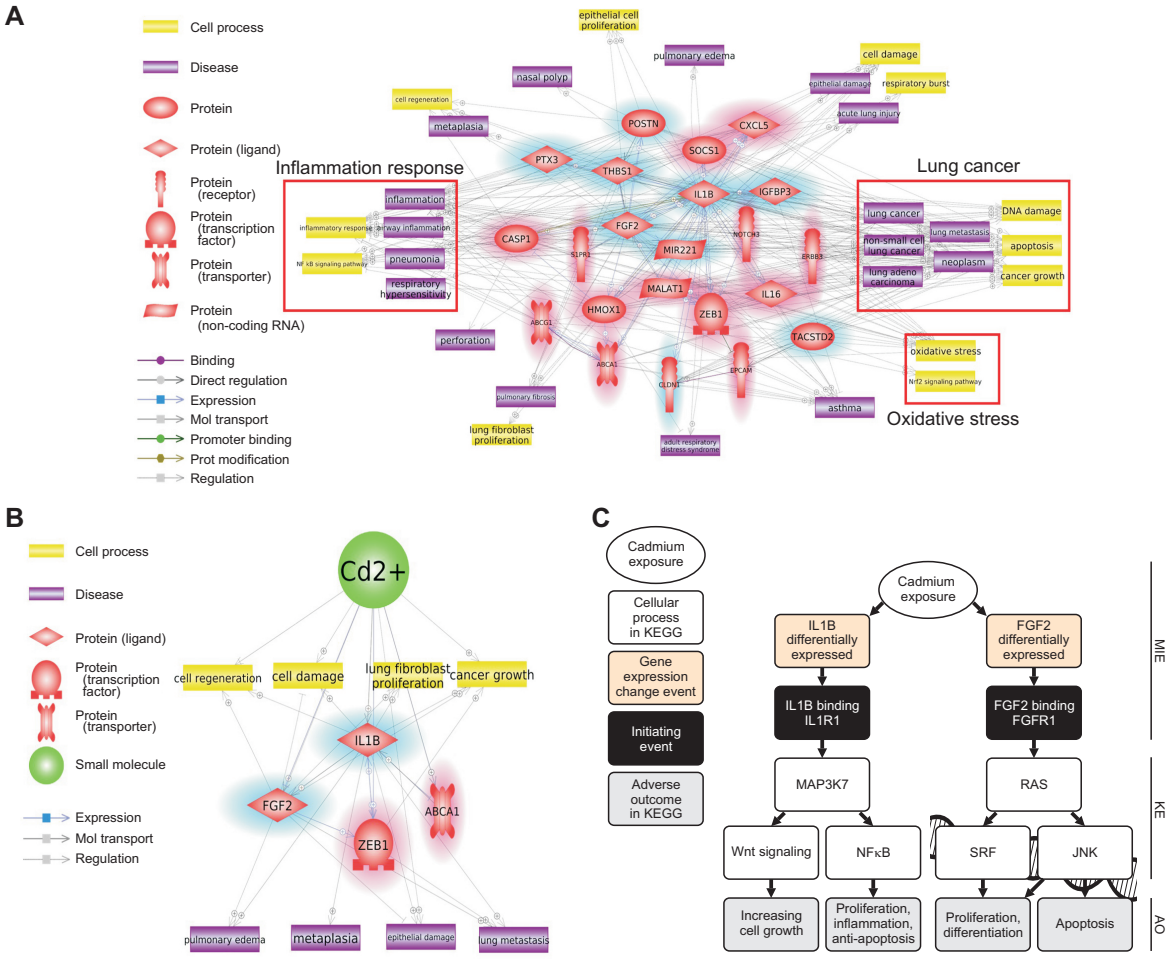

Figure 2. Inclusive understanding about cadmium (Cd) exposure in respiratory organs. (A) Comprehensive molecular network for the differentially expressed genes (DEGs) with cell process and diseases. (B) Condensed network containing hub genes. (C) Potential adverse outcome pathways (AOPs) for cadmium carcinogenicity in bronchial epithelium. KEGG, Kyoto Encyclopedia of Genes and Genomes; MIE, molecular initiating event; KE, key event; AO, adverse outcome.

the cellular level using GO, comprehensive understanding through biological network, and mechanistic insights through the putative AOP. We identified alterations in cell junctions, homeostasis, and the inflammatory response in respiratory cells due to Cd exposure, leading to potential diseases including inflammatory-related diseases and lung cancer. The putative AOP revealed that Cd induces changes in the expression of *IL1B* and *FGF2*, potentially causing AOs, such as cancer-related alterations in cell growth, differentiation, inflammation, and apoptosis.

ADVERSE EFFECTS OF Cd EXPOSURE ON PROSTATE

Toxicity of Cd in the prostate from the perspective of GO

Finding GO were conducted using a gene expression dataset (GSE9951) from the GEO database. The dataset was obtained from an experiment in which normal prostate epithelial cells (NPrEC) were exposed to Cd. To understand an interpretation of the changes in the expression of genes related to Cd toxicity, we identified the ontology of each DEGs. The top 10 gene ontologies (adjusted *P*-value < 0.05) within the BP, CC, and MF categories were identified in the Cd-exposed prostate cells (Table 2).

In the activated BPs, endoplasmic reticulum stress has been previously linked to inflammation [37]. Among the suppressed BPs, we detected 'response to oxidative stress,' 'protein maturation,' and 'negative regulation of JUN kinase activity.' The down-regulation of genes associated with oxidative stress suggests genetic damage in the prostate due to Cd-induced oxidative stress [38]. Moulis and Thévenod [39] presented that Cd can directly affect protein maturation by blocking transporter. The JNK signaling pathway related to JUN regulates growth control, transformation, and apoptosis [40-42]. Considering the extensive activation and suppres-

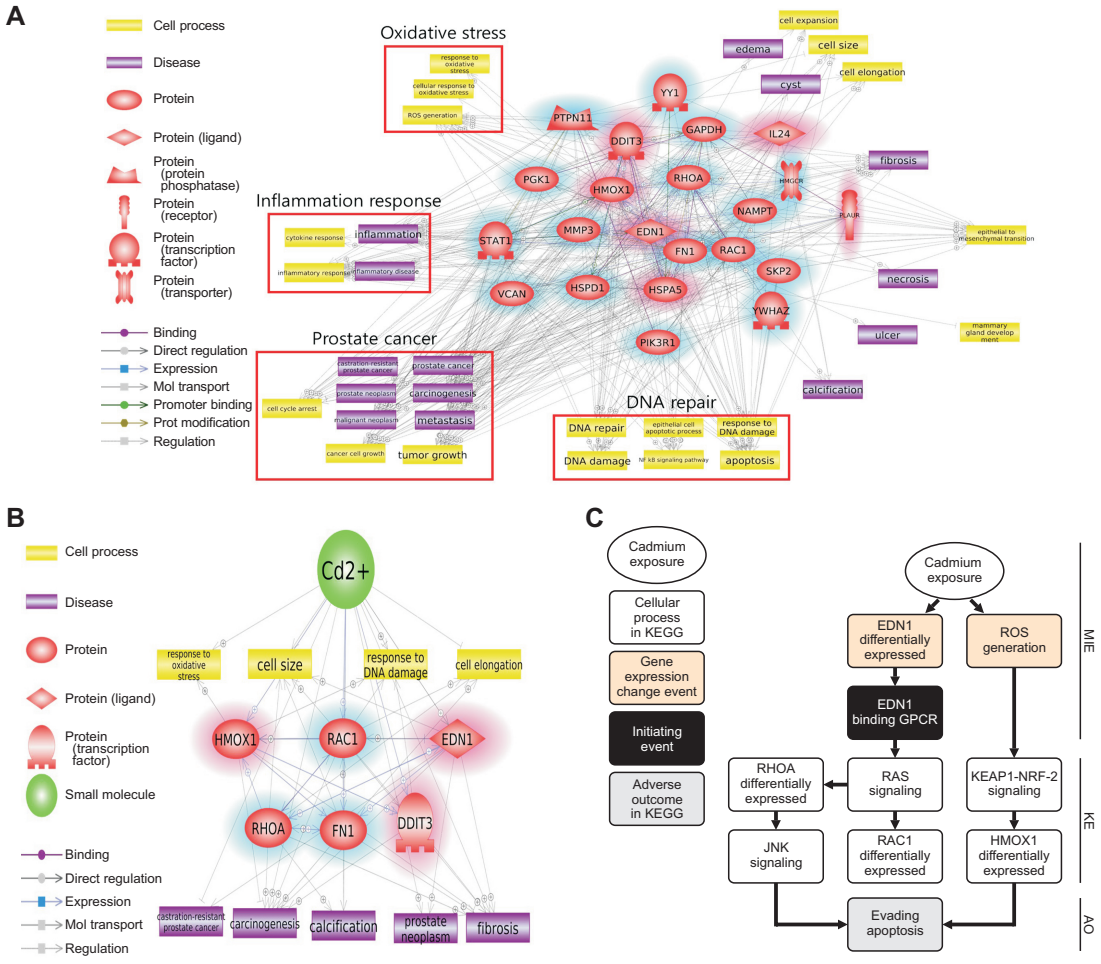

Figure 3. Inclusive understanding about cadmium (Cd) occupational exposure in prostate. (A) Comprehensive molecular network for the differentially expressed genes (DEGs) with cell process and diseases. (B) Condensed network containing hub genes. (C) Potential adverse outcome pathways (AOPs) for Cd carcinogenicity in prostate epithelium. KEGG, Kyoto Encyclopedia of Genes and Genomes; ROS, reactive oxygen species; MIE, molecular initiating event; KE, key event; AO, adverse outcome.

sion of BPs, it is evident that Cd suppresses protein structure, induces protein dysfunction and abnormal maturation, and promotes transcription in prostate cells under stress.

The activated CCs were primarily related to cellular secretion. Reactive oxygen species (ROS) can be generated by peroxisomes in response to Cd exposure [43]. Mittal and Roberts [44] found that the SWI/SNF superfamily is a chromatin-remodeling complex with a role in tumor suppression. These activated and suppressed CCs can be understood as prostate cells increasing the secretion of factors, weakening cell-substrate junctions, and suppressing tumor suppressor genes.

The activated MFs, including 'receptor ligand activity' and 'misfolded protein binding,' indicate abnormal protein binding and function. The suppressed MFs, including 'ubiquitin protein ligase binding,' suggest decreased protein degradation [45]. These findings indicate abnormal protein binding and degradation due to Cd.

Through every GO of DEGs from Cd exposed prostate cells, Cd appears to have a significant impact on proteins in prostate cells. It affects protein activities such as function, maturation, binding, and degradation. Furthermore, it increases the likelihood of prostate cancer development by inhibiting the activity of the tumor suppressor SWI/SNF superfamily.

Comprehensive exploration of the mechanisms of Cd toxicity in the prostate through biological network

To understand the toxic effects of Cd in the prostate comprehensively, a biological network was constructed using the Pathway Studio. In the biological network (Fig. 3A), prostate cancer, inflammation, and DNA damage are the main detected toxicity. Each gene in the central network (Fig. 3B) was assessed based on edge degree and betweenness centrality to identify central genes in the network. Heme oxygenase-1 (*HMOX1*), Ras-related C3 botulinum toxin substrate 1 (*RAC1*), homolog family member A (*RHOA*), fibronectin 1 (*FN1*), DNA damage inducible transcript 3 (*DDIT3*), and endothelin 1 (*EDN1*) were selected as central genes of the central network. The interactions between the central genes and Cd were confirmed on the Pathway Studio database, suggesting that the central genes could be potential biomarkers of prostate cancer caused by Cd. It was reported that *HMOX1* was overexpressed in androgen-dependent prostate cancer cells [46]. *RAC1* was also differentially expressed in Cd-treated prostate cells using cohort data [47] and is related to tumor metastasis [48]. *RHOA* is associated with cytoskeleton regulation [49] and angiogenesis in prostate cancer [50]. *FN1* codes for fibronectin protein, a major component of the extracellular matrix [51], and is down-regulated in the prostate cell line PC-3 cells [52]. *DDIT3* is linked to endoplasmic reticulum stress, and its mRNA and protein levels are increased in PC-3 cells [53]. *EDN1* is a potent vasoconstrictor [54] and is up-regulated in Cd-exposed NPrEC [55].

In brief, we presented a comprehensive biological network (Fig. 3A) to elucidate the extensive carcinogenic properties of Cd. Cd toxicity exhibits significant associations with central BPs such as 'inflammatory response,' 'DNA repair,' 'cell cycle,' and 'oxidative stress.' Furthermore, biological networks revealed a correlation between Cd poisoning and the manifestation of various diseases in the prostate. The identified potential central genes could serve as potential biomarkers of prostate cancer induced by Cd exposure. The biological networks contribute to a comprehensive understanding of the molecular interactions underlying Cd toxicity.

Putative AOP of prostate exposed to Cd

The putative AOP of Cd exposure in the prostate (Fig. 3C) were constructed based on "pathways in cancer" in the KEGG pathway. The alteration of *EDN1* gene expression leads to the generation of ROS after Cd exposure in the prostate. The change of *EDN1* expression results in abnormal binding between *EDN1* and endothelin receptor type A. These two events are considered MIE. This MIE triggers RAS signaling, followed by the differential expression of *RAC1* and *RHOA*. The *RHOA* expression change induces JNK signaling. These four events are regarded as KEs. After KEs, JNK signaling regulates the apoptosis [56]. Another MIE is ROS generation. After MIE, KEAP1-NRF2 signaling is activated and *HMOX1* is differentially expressed. They could be considered KEs. The change in *HMOX1* expression affects apoptosis [57]. Oxidative stress caused by Cd can lead to DNA damage [58], and apoptosis resulting from DNA damage could be influenced by Cd exposure.

Through the putative AOP, we anticipate that Cd exposure in prostate leads to changes in the expression of *EDN1*, *HMOX1*, *RHOA*, and *RAC1*. These result in abnormalities in parts of the cancer pathway. Specifically, the functions of RAS signaling and KEAP1-NRF2 signaling were dysregulated, leading to the inhibition of apoptosis and the onset of cancer.

In summary, we obtained DEGs from the transcriptome of Cd-exposed prostate cells in GEO database. We approached the interpretation from three perspectives: understanding at the cellular level using GO (Table 2), comprehensive understanding through biological network (Fig. 3A and 3B), and mechanistic insights through putative AOP (Fig. 3C). We identified abnormal protein activities, down-regulated tumor suppressor genes in prostate cells due to Cd exposure. These toxic effects could lead to inflammatory-related diseases and prostate cancer. Through putative AOP, we demonstrate that Cd induces changes in the expression of *EDN1*, *HMOX1*, *RAC1*, and *RHOA*. Thes central genes potentially cause cancer-related alterations such as apoptosis inhibition.

CONCLUSION

In this review, we discussed the inhalation route as the most

prominent scenario for Cd absorption in the human body through three toxicogenomic approach. These approaches provide a comprehensive understanding of the toxicity of Cd in respiratory organs and prostate, particularly its carcinogenicity. We revealed the cellular responses that occur upon exposure to Cd using GO, in addition to providing a comprehensive overview of the carcinogenic toxicity of Cd through biological network, presenting each potential biomarker for respiratory organs and prostate exposed Cd, and exploring the potential carcinogenic mechanisms of Cd using a putative AOP. This review was prepared using only limited public data, so more genomic data need to be integrated. The potential biological networks, potential biomarkers, and putative AOPs that we have proposed will require experimental validation in further research. Investigating the toxic effects of Cd from various perspectives constitutes a promising approach to understanding the complex mechanisms of Cd-induced cancer and diseases.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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