An Overview of Carcinogenic Heavy Metal: Molecular Toxicity Mechanism and Prevention

REVIEW

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Almost all heavy metals are serious toxicants as carcinogens. However, due to their chemical and physiological properties, heavy metals are useful in industrial areas including alloy, smelting and production of commercial products. Such applications increase the opportunity for heavy metal exposure. Waste from industrial processes is also a major source of environmental contamination and accumulation in the human body. Arsenic, cadmium, chromium, and nickel are classified as group 1 carcinogens by the International Agency for Research on Cancer, and are utilized commercially. In this review, we used molecular pathway analysis to understand the toxicity and carcinogenic mechanisms of these metals. Our analyzed data showed that above-mentioned metallic substances induce oxidative stress, DNA damage, and cell death processes, resulting in increase the risk of cancer and cancer-related diseases. Thus, we might think phytochelatin molecules and antioxidative phytochemical substances are helpful for prevention of heavy metal-induced cancer.
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Key Words: Carcinogenic heavy metals, Molecular mechanism, Pathway analysis, Cancer prevention

INTRODUCTION

Most heavy metals are one cancer-inducing agents.[1] Although several heavy metals, including copper (Cu) and zinc (Zn), serve as enzymes that are essential for intracellular processes and have DNA-binding domains, almost all heavy metals induce various cancers and diseases.[2-4] Oxidative stress caused by reactive oxygen species (ROS) is a well-known mechanism of heavy metal-induced damages.[1,5] Despite such serious toxicity, heavy metals are utilized in various industrial products; they are found in batteries, paints, and vehicle emissions. Furthermore, heavy metals are used in pigments that are then used in consumer products like children's jewelry and toys.[6] Electronic waste from heavy metal-containing batteries is an important source of heavy metal contamination in the environment through erosion by rain and groundwater flow to soil, rivers and the sea. Dissolved forms of toxic heavy metals can be magnified via circulation in the bio-system, including the food chain, and finally end up in very high concentrations in humans.[1,5,7]

Arsenic (As), cadmium (Cd), chromium (Cr), and nickel (Ni) are category 1 heavy metals according to the International agency for Research on Cancer.[8] Various reports have found that exposure to these compounds leads to disruptions in tumor suppressor gene expression, damage repair processes, and enzymatic activities concerned in metabolism via oxidative damage.[5,9] Some studies have indicated that the risk of heavy metal exposure is interrelated with the contamination source.[10,11] For example, recent studies found an increased risk of occupational disease and cancer in workers in heavy metal-using industrial areas.[12,13]

Nowadays, massive floods of biological data are available because of increased attention to health and biology, so the importance of data-mining techniques is a main issue. The Pathway

Studio database can help to understand the gene/chemical-specific complex pathways as it provides pathway drawings using data from multitude of sources.[14] Using pathway analysis is one way to provide a comprehensive view of heavy metal-induced carcinogenesis, disease, and marker proteins. In addition, direct connectivity between marker proteins and cellular processes contributes to the prediction of carcinogenesis-specific protein markers.

Various intracellular chelation processes and antioxidants are involved in the prevention and detoxification of heavy metal-induced damage. Chelating agents in plants called phytochelatins (PCs) combine with metal ions and provide resistance to metal poisoning.[15,16] Antioxidant molecules interact with free radicals and protect from oxidative damage.[17] Consumption of phytochemicals from antioxidant substances from plants can assist in the antioxidant-related detoxification process.[18]

In this review, we will explain the toxicity and carcinogenicity of heavy metals like As, Cd, Cr, and Ni by providing a comprehensive understanding their toxicological mechanisms with using molecular pathway analysis. In addition, we present the cancer prevention properties of PCs and antioxidant such as phytochemicals.

ARSENIC (As)

1. Contamination source

As is a metalloid that exists in inorganic and organic compound forms. Inorganic As is more harmful than the organic form. Pentavalent inorganic compounds of As solubilize in water to weak acid forms and produce salts called arsenate.[19] Arsenate induces ground water contamination that affects many people.[20,21] Recently, As has been used for the isotope labeling in cancer research, instead of radioactive elements, and is mainly used for industrial purposes, including the manufacture of car batteries and alloyed semiconductor materials, and pigments.[19,22,23] Mining and ore smelting for industrial purposes are related to As poising in humans, but the major source of As exposure is from natural sources, such as contaminated water.[20,21] Arsenates in the soil can dissolve easily in groundwater and flow to rivers and the sea. As accumulates in aquatic organisms, where it is converted to its organic compound form. In addition, As-contaminated groundwater may be taken up by crop plants including rice, and therefore highly accumulate in individuals who eat rice as a staple food.[24,25] Thus, consumption of crops grown in As-contaminated groundwater contributes to the As accumulation in humans and increases the risk of poisoning.

2. Toxicity and carcinogenic mechanism

The major mechanism of As-related damage is oxidative stress.[26,27] It can cause numerous diseases which disrupt cellular signaling pathways. In an in vitro cell line study, arsenical compounds led to genotoxicity in mice leucocytes and human.[28-30] The methylated form of arsenic inhibits DNA repair processes and also produces ROS in spleen and liver as metabolic products.[31,32] Accumulation of free radicals from ROS results in cell death via abnormal gene expression and lesions of cellular components including DNA, lipids, and proteins.[33] Chemical residues of As can bind to DNA-binding proteins and increase the risk of carcinogenesis via disruption of DNA repair processes. For example, As binds methyl-transferase and induces suppression of tumor suppressor gene-coded DNA with methyl-transferase.[34] Recent studies uncovered the reasons for tissue toxicity of As accumulation. Methylated metabolites of As cause urinary bladder cancer by ROS generation in As-exposed rats.[35,36] Hepatic function is also disrupted by As toxicity because of cross-linking with enzymes and oxidative DNA damage in rats.[37]

In order to understand the carcinogenic mechanism of As, we conducted the pathway analysis with Pathway Studio ver. 11.1.0.6 (Elsevier, Amsterdam, Netherlands) (Fig. 1). Figure 1 showed that As poisoning was mainly associated with apoptosis, cell damage, oxidative stress, cell cycle, and DNA damage response. We found genomic interactions among tumor protein 53 (TP53), interferon gamma, catalase, etc. Those genes are also related to As. We also discovered that cancers of skin, liver, prostate, kuffer cell were associated with As poisoning. This result may provide aid to comprehensive understanding of As-related mechanisms.

CADMIUM (Cd)

1. Contamination source

Cd is rare in the natural in environment. It generally comes from environmental pollution from industrial and agricultural waste.[38] Although it is fatally toxic, Cd is used in batteries and electroplating.[39,40] In addition, it is a component of paint for plastic products and chalk pastels, acrylic colors, and watercolor pigments.[41] Recently, in laboratory experiments, Cd with helium was shown to be a common component of blue-ultraviolet light in fluorescence microscopes.[42] In agriculture, some fertilizers which contain Cd cause an increase of Cd concentration in the soil. Farmland near industrial areas becomes contaminated.[38,43] The major source of human Cd exposure is food intake. Itai-itai disease, for instance, is caused by Cd in crop plants that were
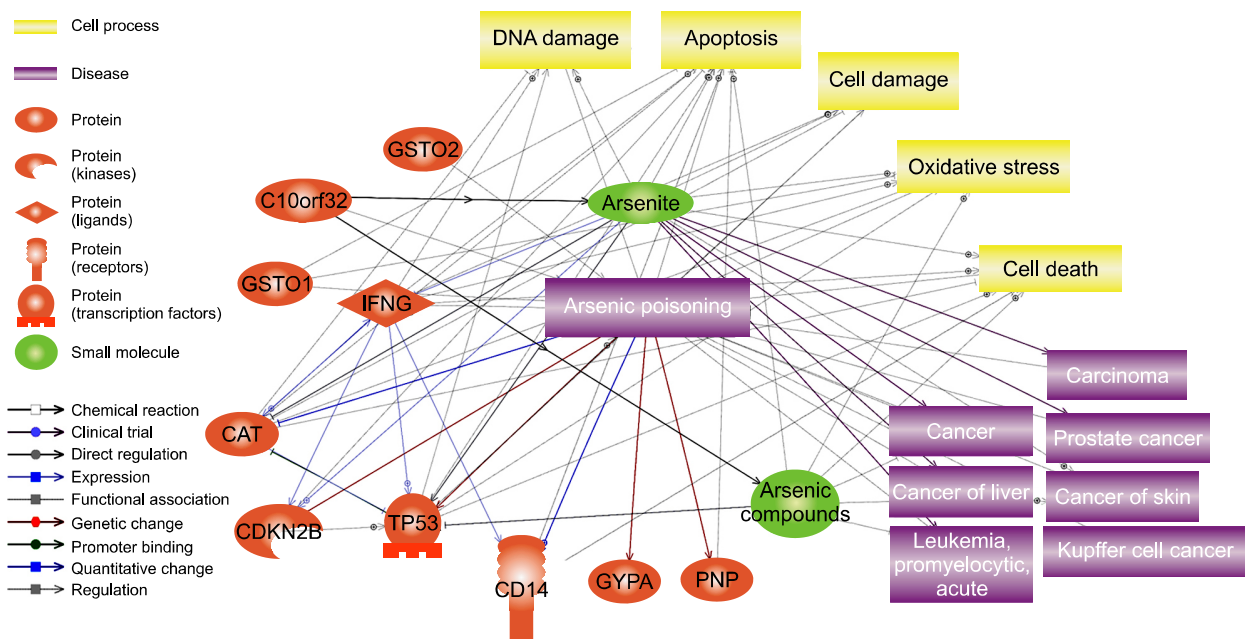
Figure 1. Pathway analysis of arsenic toxicity. The analyzed data showed the potentials of genomic interaction, cellular processes, and diseases induced by exposure of arsenic. Ten proteins, 5 cellular processes, 8 diseases and 2 small molecules appeared in figure. GSTO, glutathione-S-transferase omega; C10orf32, chromosome 10 open reading frame 32; IFNG, interferon gamma; CAT, catalase; CDKN2B, cyclin-dependent kinase 4 inhibitor 2B; TP53, tumor protein 53; CD14, monocyte differentiation antigen CD14; GYPA, glycophorin-A; PNP, purine nucleoside phosphorylase.

grown with Cd-contaminated water.[44] Plants in non-industrial areas contain less Cd, but animals that live in such areas contains high levels of Cd because of biomagnification through the food chain via Cd dissolved in groundwater and rivers exposed to Cd-contaminated soil. Furthermore, Cd flowed from rivers to the sea and accumulated in marine organisms.[45,46] Hence, humans, the apex predators, are exposed to the risk of Cd poisoning.

2. Toxicity and carcinogenic mechanism

The most well-documented reason for Cd-related toxicity is oxidative stress. Research on chronic exposure to Cd in a rat model showed that liver and kidney toxicity are induced via inhibition of components of the cellular antioxidant system.[47-49] Oxidative stress following Cd exposure accelerates of transcriptional activity of the metallothionein (MT) coding gene. MT is a ubiquitous protein in most bodily organs. It can form a complex with metal elements such as Cd.[50] When chronic Cd exposure occurs, a complex form of Cd and MT called Cd-MT is found, especially in the kidney. It accumulates in tubules via a reuptake process and causes conformational change of renal tubular cell as well as degradation of glomerular cell function. These functional problems disrupt calcium metabolism and augment the calcium load in the kidney, thereby resulting in an increase of kidney stones and cancer.[51,52] Moreover, disruption of calcium metabolism causes bone damage. Increasing the Cd concentration in

the kidney means high excretion of calcium in the urine and is significantly related to calcium concentration decrease in bones. It results in bone pain, osteomalacia, osteoporosis, and itai-itai disease.[53-55] Cd is also an as endocrine disrupter, especially of reproductive hormones.[56,57] Cd mimics Zn's divalent chemical state, so it can interfere with the DNA Zn binding site. It disrupts the ovarian steroidogenic pathway, production of progesterone and testosterone, and mimics endogenous estrogen, thus increasing the risk of ovarian cancer and breast cancer.[56,58,59]

In order to understand the carcinogenic mechanism of Cd, we did pathway analysis with Pathway Studio (ver. 11.1.0.6) (Fig. 2). Figure 2 showed that Cd poisoning is mainly associated with apoptosis, oxidative stress, and DNA damage response. In addition, genomic interactions between B cell lymphoma 2 protein (BCL2)-associated X protein (BAX), mitogen-activated protein kinase 1, huntingtin, etc. were presented. Those genes are also connected with Cd. Correlation of PC, MT, and Cd ion were shown. We also discovered that numerous diseases in bone and kidney were associated with Cd poisoning. This figure may provide help to comprehensive understanding of Cd-related toxicity mechanisms.

CHROMIUM (Cr)

1. Contamination Source

Cr is abundant in the earth's crust, and its toxicity depends on
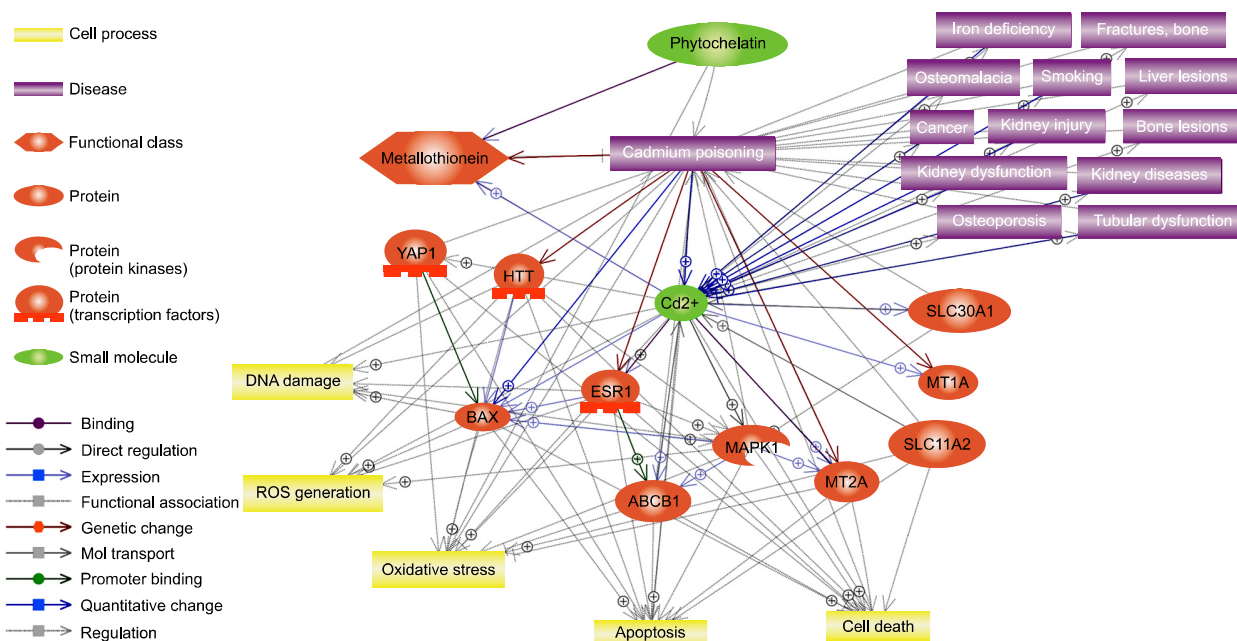
Figure 2. Pathway analysis of cadmium toxicity. The analyzed data showed the potentials of genomic interaction, cellular processes, and diseases induced by exposure of cadmium. Ten proteins, 5 cellular processes, 13 diseases, 2 small molecules and 1 functional class appeared in figure. YAP1, yes-associated protein 1; HTT, huntingtin; BAX, B cell lymphoma 2 protein-associated X protein; ROS, reactive oxygen species; ESR1, estrogen receptor 1; MAPK1, mitogen-activated protein kinase 1; ABCB1, aTP-binding cassette sub-family B member 1; MT2A, metallothionein 2A; SLC11A2, solute carrier family 11, member 2; MT1A, metallothionein 1A; SLC30A1, solute carrier family 30, member 1.

its chemical state.[60] It exists in divalent to hexavalent compounds, but only the trivalent and hexavalent compounds have significant biological toxicity.[61-63] Cr compounds are usually found in industrial purposes such as chromite ore mining, pigment production, tanning of leather, formation of wood preservatives, and anticorrosive agents in cooking goods. Paint is a significant source of hexavalent Cr but is still used for industrial applications.[64,65] The salt form of trivalent and hexavalent Cr compounds, called chromate, are produced through mining, smelting, roasting and extraction. Chromates generate the toxic dust during manufactural processes. Several studies had investigated that toxicity about Cr dust in chromate production workers.[65,66] Furthermore, industrial wastes from Cr manufacturing are known as significant source of the soil and water pollution.[67,68]

## 2. Toxicity and carcinogenic mechanism

The carcinogenicity of Cr dust has been studied since the 1980s. In a case study, lung cancer occurred more often in workers in the chromate-producing industry.[65-67,69] Trivalent compounds included in Cr dust are water-insoluble, but can enter cells in ionized form via a specific membrane transport system. High concentrations of trivalent Cr can lead to cellular damage.[62] Hexavalent Cr is also a strong toxicant as it produces reactive

hydroxyl radicals. In blood vessels, for example, Cr compounds are reduced from hexavalent to trivalent and reactive hydroxyl radicals are produced during the process. Thus, high levels of hexavalent Cr in the bloodstream cause blood cell damage by oxidation and functional degradation of the liver and kidney.[70-72] If hexavalent Cr compounds are reduced to the pentavalent form, they can bind DNA and interrupt cellular processes.[62,71,73] Furthermore, Cr in soil and water involve skin damage by absorption.[74]

In order to understand the carcinogenic mechanisms of Cr, we investigated molecular pathway analysis using Pathway Studio (ver. 11.1.0.6) (Fig. 3). Figure 3 showed that Cr and Cr compounds were mainly induce apoptosis, oxidative stress and DNA damage. We found Cr-related genomic interactions among nuclear factor (erythroid-derived 2)-like 2 (NFE2L2, Nrf2), TP53, BAX etc. Association between MT, which was mentioned with Cd toxicity, and Cr was also investigated. In addition, we also discovered that considerable diseases including lung cancer, skin allergy with dermatitis, and kidney diseases were induced by Cr and Cr compounds. These results may aid to comprehensive understanding of Cr-related toxicity mechanisms.
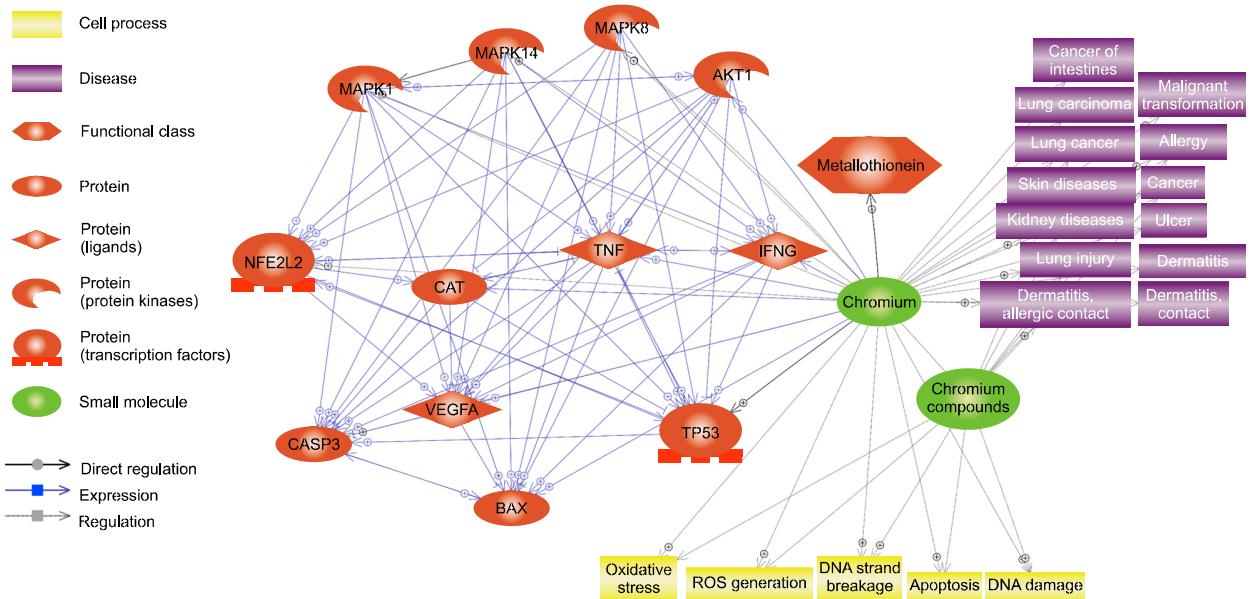
Figure 3. Pathway analysis of chromium toxicity. The analyzed data showed the potentials of genomic interaction, cellular processes, and diseases induced by exposure of chromium. 12 proteins, 5 cellular processes, 13 diseases, 2 small molecules and 1 functional class appeared in figure. MAPK, mitogen-activated protein kinase; AKT1, V-akt murine thymoma viral oncogene homolog 1; NFE2L2, nuclear factor, erythroid 2-like 2; CAT, catalase; IFNG, interferon gamma; CASP3, caspase 3, apoptosis-related cysteine peptidase; VEGFA, vascular endothelial growth factor A; TP53, tumor protein 53; BAX, B cell lymphoma 2 protein-associated X protein; ROS, reactive oxygen species.
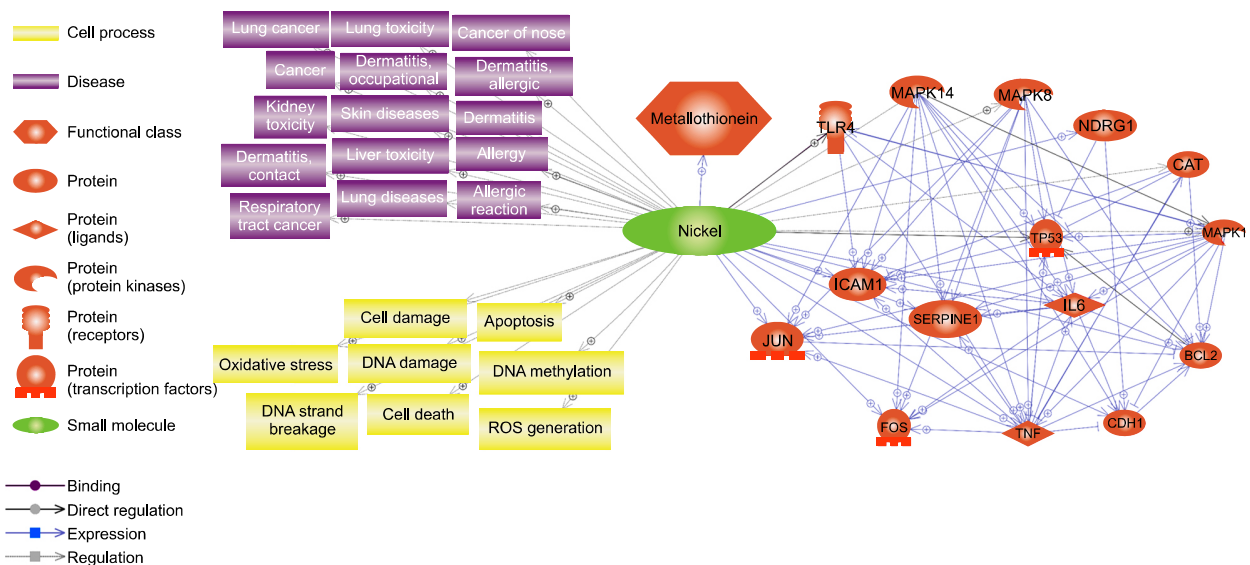
Figure 4. Pathway analysis of nickel toxicity. The analyzed data showed the potentials of genomic interaction, cellular processes, and diseases induced by exposure of nickel. 15 proteins, 8 cellular processes, 15 diseases, 1 small molecule and 1 functional class appeared in figure. ROS, reactive oxygen species; TLR4, toll-like receptor 4; MAPK, mitogen-activated protein kinase; NDRG1, N-myc downstream regulated 1; CAT, catalase; TP53, tumor protein 53; ICAM1, Intercellular adhesion molecule 1; JUN, Jun proto-oncogene; SERPINE1, serine peptidase inhibitor, clade E, member 1; IL, interleukin; BCL2, B cell lymphoma 2 protein; FOS, Finkel-Biskis-Jinkins murine osteosarcoma viral oncogene homolog; CDH1, cadherin 1.

NICKEL (Ni)

1. Contamination source

Ni is widely used for industrial purposes because of its physicochemical properties. It is utilized in alloys and various products including rechargeable batteries, coins, electroplates, pigments, and stainless steel.[75,76] Ni is a remarkable alloying agent for various metals including Cr, lead, and Cu; this is a major source of Ni exposure.[77] Ni-plated pipe and faucets, Ni-containing stainless cookers, and products that are colored with Ni-based

pigment are introduced into the soil and cause water pollution with Ni compound. Waste water and dust from mining and smelting processes of Ni production also contaminate the environment. Because of this, people are often exposed to Ni by inhalation, direct skin contact, and oral consumption.[78]

2. Toxicity and carcinogenic mechanism

Skin contact with Ni compounds through contaminated water, air, and children's toys result in dermatitis and allergy.[79,80] Oral exposure to Ni also induces skin and oral epithelium damage.[81-83] Industrial dust from Ni refineries contains water-insoluble Ni compounds including Ni_3S_2 and NiO, which are carcinogenic. Breathing in Ni-contaminated dust from Ni smelting, mining and tobacco smoking leads to significant damage to lungs and nasal cavities, resulting in occupational diseases such as lung cancer and nasal cancer in Ni refinery workers.[13,78,84,85] Although the molecular carcinogenic mechanisms of Ni toxicity are not clear, several studies suggest that Ni exposure induces oxidative stress via a reduction in expression of antioxidant enzymes and DNA single- and double-strand breaking.[86-88]

In order to understand the carcinogenic mechanisms of Ni, we analyzed molecular pathway using Pathway Studio (ver. 11.1.0.6) (Fig. 4). Figure 4 showed that Ni induce apoptosis, oxidative stress, DNA methylation, and DNA damage. We investigated

Ni-related genomic interactions among TP53, TNF, BCL2, etc. We also discovered that various toxicity in lung, nose, skin, kidney and liver were induced by Ni. Interaction of MT and Ni was also investigated. This result may aid to comprehensive understanding of Ni-related toxicity mechanisms.

REDUCTION AND PREVENTION OF CANCER BY HEAVY METAL DETOXIFICATION

Metal ions in living organisms can bind with other specific ligand molecules in a phenomenon called chelation.[89] PCs are protein ligand molecules in plants which chelate metal ions when plants are exposed to heavy metals.[15,16,90,91] Various studies investigated that PCs are synthesized from glutathione (GSH) by the enzyme PC synthetase,[92,93] and end up forming GSH oligomers. Metallic ion-bound PCs are transported into vacuoles and successfully isolated from cellular proteins,[92] and reduce heavy metal ion-induced damage (Fig. 5A).

A major factor in heavy metal-induced carcinogenesis is inhibition of DNA repair and DNA crosslinking with proteins via ROS generation.[94] ROS, which include the hydroxyl radical (HO), the superoxide radical (O_2^-), and hydrogen peroxide (H_2O_2), leads to an imbalance in homeostasis between antioxidant and
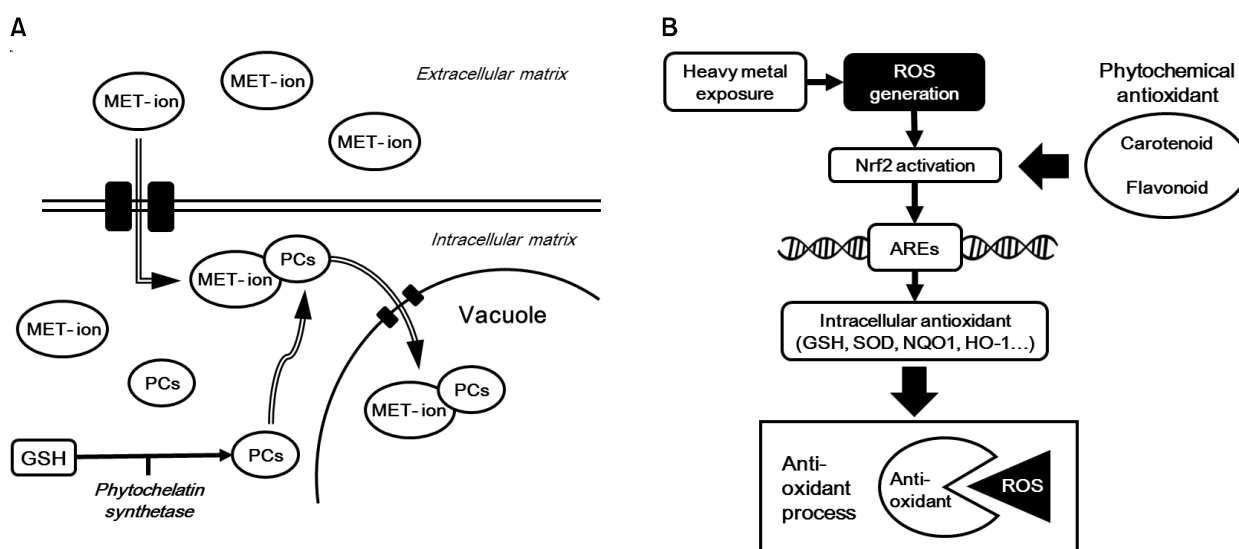
Figure 5. Mechanism of heavy metal detoxification via phytochelatin (PC) and antioxidants. (A) Schematic diagram of the PC pathway. Ionized forms of heavy metals are in bold circles marked as 'MET-ion'. PCs molecules are in bold circles marked as 'PCs'. A double-lined arrow indicates import direction. A bold arrow indicates the PCs synthesis process. Enzymes are written in an italicized bold font. (B) Schematic diagram of heavy metal-induced antioxidant processes. ROS generation by heavy metal exposure activates Nrf2, which is a transcription factor for antioxidant response elements (AREs). Phytochemicals contribute to antioxidative process via stimulation of the Nrf2 pathway. Various antioxidants are activated and remove ROS. GSH, glutathione; ROS, reactive oxygen species; SOD, superoxide dismutase; NQO1, NAD(P)H: quinone acceptor oxidoreductase 1; HO-1, heme oxygenase 1.

pro-oxidant molecules and results in oxidative stress-related damage to cellular components such as proteins, DNA, and lipids.[9,17,95] Intracellular antioxidant agents inhibit such process by removing ROS by being oxidized themselves and interacting with free radicals in ROS.[17] There are various types and complex systems of intracellular antioxidants, including GSH, heme oxygenase 1 (HO-1), superoxide dismutase (SOD), NAD(P)H: quinone acceptor oxidoreductase 1 (NQO1), and catalases.[17,18,95] Also, the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein is well known as a regulator of antioxidant elements in reaction to oxidative stress. Nrf2 is activated by ROS and act as transcription factor that stimulates antioxidative genes through binding to antioxidant response element, which in the promoter region of antioxidative gene.[96] Phytochemical substances, which include carotenoids and flavonoids, are also important antioxidants. They are found abundantly in vegetables and fruits; thus, regularly ingestion of those foods helps reduce damage from oxidative stress.[18,97,98] We might conclude that above-mentioned antioxidant processes contribute to oxidative stress-induced cancer following heavy metal exposure (Fig. 5B).

CONCLUSIONS

Some heavy metals are significant toxicants and carcinogens.[1] We discussed the major sources of exposure, toxicity, and carcinogenic mechanisms of four heavy metals in this review. Industrial development increases a risk of heavy metal exposure via production and consumption of commercial products containing heavy metal compounds.[1,5-7] Direct or indirect exposure of heavy metals induces disruption of intracellular processes via complex pathway. In pathway analysis, we found some genes and processes that are common to the toxic effects of As, Cd, Cr, and Ni. These processes might be candidates for markers of heavy metal-induced carcinogenesis. In particular, oxidative stress-mediated pathways are common to toxicity of As, Cd, Cr, and Ni. We might suggest that antioxidative phytochemicals and chelating agents including PCs will be helpful for prevention of heavy metal-induced cancers. Furthermore, comprehensive understanding of these complex mechanisms by pathway analysis will be beneficial to research on the heavy metal-induced cancers and diseases.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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