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Metals and molecular carcinogenesis

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Abstract

Many metals are essential for living organisms, but at higher doses they may be toxic and carcinogenic. Metal exposure occurs mainly in occupational settings and environmental contaminations in drinking water, air pollution and foods, which can result in serious health problems such as cancer. Arsenic (As), beryllium (Be), cadmium (Cd), chromium (Cr) and nickel (Ni) are classified as Group 1 carcinogens by the International Agency for Research on Cancer. This review provides a comprehensive summary of current concepts of the molecular mechanisms of metal-induced carcinogenesis and focusing on a variety of pathways, including genotoxicity, mutagenesis, oxidative stress, epigenetic modifications such as DNA methylation, histone post-translational modification and alteration in microRNA regulation, competition with essential metal ions and cancer-related signaling pathways. This review takes a broader perspective and aims to assist in guiding future research with respect to the prevention and therapy of metal exposure in human diseases including cancer.

Introduction

Metals are major components of the earth's crust, and many of them are essential elements for life maintaining homeostasis in metabolic and physiologic processes. However, an excess intake usually by chronic exposure to metals and their compounds can induce cancer in humans and animals. Metals can drive tumorigenesis by damaging cellular organelles and other cellular components, disrupting metabolic enzymes that support detoxification, causing imbalanced cellular redox homeostasis and uncontrolled oxidation, dysregulation in cell cycle and cell growth, disrupting DNA repair pathways and causing DNA damage, and affecting cell apoptosis and autophagy, etc. (1).

Metal pollution is a global problem. In the last several decades, there has been a striking increase of metal usage in industries, agriculture, pharmaceutical and technology applications. Metals are widely used for synthesizing alloys, smelting and in commercial products, which also increase hazards of occupational exposures. Industrial products and processes, such as chrome plating baths, chrome containing anti-rust agents for cooling, and oil drilling, has resulted in high levels of chromate in human drinking water globally. The carcinogenic form of chromium is hexavalent chromate, which is rarely found naturally, and is usually a result of human activities. Contamination of the environment with metals has been a great concern for both ecology and global public health, since metal exposure imposes serious health risks to humans and other organisms (2). This review provides a summary of the molecular mechanisms of the Group 1 metal carcinogens, including arsenic (As), beryllium (Be), cadmium (Cd), chromium (Cr) and nickel (Ni).

Arsenic

Arsenic is a naturally occurring metalloid with properties similar to a metal. A worldwide contamination of drinking water with arsenic has been recognized as a major human health problem, which is mostly non-man made but naturally occurring from the geological formations in the earth's crust. Many epidemiological studies have provided strong evidence that arsenic exposure is related to an increased risk in human cancers, including lung, bladder, skin, liver and prostate cancer (3). Studies have also indicated that As exposure-induced anchorage independent growth in cultured diploid human fibroblasts (4).The carcinogenic mechanism of arsenic has been investigated in numerous studies. In fact, there are more published studies on arsenic toxicity than all the other carcinogenic metals combined.

Arsenic does not bind to DNA and form DNA adducts or cause mutations directly, but it is able to induce genotoxicity by interfering with DNA repair and inducing chromosomal

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Abbreviations

ERα	estrogen receptor-α
GSH	glutathione
ROS	reactive oxygen species
SLBP	stem-loop-binding protein

instability in the cell (3,5). Inhibition of DNA repair by direct binding or affecting the expression of DNA repair genes is an important mechanism for arsenic-induced genotoxicity (6), resulting in the mutation of tumor suppressor genes such as p53 (7). Arsenic can directly inhibit different repair pathways including nucleotide excision repair, base excision repair and mismatch repair (8), and the mechanisms involve its ability to displace zinc from zinc fingers consisting of three or four cysteines in poly(ADP-ribose) polymerase-1 and xeroderma pigmentosum complementation group A (9–11). Arsenic also induces double-strand breaks, which leads to chromosome aberrations (5,12). Several studies have demonstrated that chronic exposure to arsenic in drinking water increased incidence of chromosome aberrations, sister chromatid exchange and micronucleus formation in human cells (13–17). The chromosomal instability caused by arsenic is often seen at the centromeres, resulting in the formation of acentric chromosomes or the fusion of centromeres, resulting in aneuploidy and micronuclei formation (12,18).

Arsenic induces oxidative stress in the cell by increasing the formation of reactive oxygen species (ROS) such as peroxyl radicals, hydroxyl radicals, hydrogen peroxide and dimethylarsenic radicals, which contributes to oxidative DNA damage (19,20). One mechanism is thought to be due to the activation of reduced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, an enzyme complex consisting of different membrane-associated and cytosolic subunits (21). It was reported that arsenic exposure upregulated NADPH-oxidase components as well as oxidative stress-related proteins, while an inhibition of NADPH-oxidase blocked ROS production by arsenic (22). Moreover, arsenic interferes with antioxidants. It depletes glutathione (GSH), a major cellular oxidative defence, and inhibits GSH activity by binding and converting it into glutathione disulphide during metabolism, resulting in increased ROS level and cellular oxidative stress (23,24). The ROS induced by arsenic can react with DNA and form oxidative DNA adducts such as 8-oxo-guanine, and DNA–protein cross-links in the cell, leading to increased DNA strand breaks events during excision repair (25,26). Studies have reported that high levels of oxidative DNA damage in the urine of arsenic-exposed humans and formation of oxidative DNA damage using *in vitro* systems (20,27,28).

Arsenic induces epigenetic alterations in DNA methylation, histone modification and non-coding RNA expression. Arsenic exposure caused global DNA hypomethylation in both human and animal studies (29–32). Arsenic has been found to inhibit the expression of DNA methyltransferases, leading to reduced methylation levels at target sites (33,34). Conversely, arsenic exposure is associated with hypermethylation at the promoter region of specific genes such as tumor suppressor genes p53 and p16 (35,36), DNA repair genes ERCC2 and replication protein A1 (RPA1), and Wnt pathway genes c-MYC and Wnt family member 2B (37). In general, DNA methylation is thought to regulate long-term silencing of gene expression, and it is a critical determinant of chromatin structure. Thus, altered DNA methylation status not only affects the transcription of key genes such as those regulating cell differentiation, proliferation and development, but also causes chromosomal defects and genetic instability (38–40). Many studies have reported arsenic's effect on histone methylation and acetylation of lysine residues in different tissues, such as increased H3 lysine 9 dimethylation (H3K9me2), H3 lysine 4 trimethylation (H3K4me3) and reduced H3 lysine 27 trimethylation (H3K27me3) (41,42). A reduction of H3K9 and H4K16 acetylation by chronic arsenic exposure was observed in some studies (43–45). However, many inconsistent conclusions have been reported and this might be due to factors such as exposure time, the chemical form of arsenic used and arsenic metabolism rates in different cell types (42). Moreover, arsenic was also found to induce phosphorylation of H3 by inhibiting protein phosphatase and activating JNK and p38/MPK2 kinase, leading to upregulation of c-Fos and c-Jun oncogenes (46). MicroRNAs (miRNAs) are small non-coding RNAs that destabilize and silence the translation of target mRNAs that encode for genes. It was reported that arsenic-induced global changes in miRNA expression (47). Many cancer-related miRNAs or onco-miRNAs were found dysregulated by arsenic exposure including miR-21 associated which was associated with skin cancer (48), let-7c associated with prostate cancer (49), miR-27a associated with breast cancer (50), miR-143 associated with prostate cancer (51), miR-222 associated with lung cancer (52), miR-200a and miR-200b associated with skin cancer (48,53) and miR-205 associated with urothelial cancer (54).

However, despite many studies suggesting that arsenic appears to be a potent and broad acting human carcinogen, it does not induce cancers in experimental animal unless there is a 'whole life' exposure, for example, mice will develop cancers when exposed to arsenic during embryonic development and continuously for 2 years after that, which represents the average life span of a mouse (55). In some studies, arsenic was believed to be a cocarcinogen because it synergistically increases skin basal cell carcinoma induced by UV irradiation (56). It was reported that cells became resistant to DNA damage repair and cell apoptosis with increased cell proliferation following low-dose treatment; and with increased survival, the living cells contained significant amounts of unrepaired DNA lesions induced by UV radiation, enhancing the overall carcinogenicity (28,57).

Recent studies revealed a novel mechanism by which arsenic caused an imbalanced proportion of histone variants in chromosomes by promoting the degradation and epigenetic silencing of the stem-loop-binding protein (SLBP) (58–60) (Figure 1). Canonical histones are expressed in a replication-dependent manner during S phase, and unlike most other genes, the mRNA of canonical histones lacks a poly(A) tail at the 3′ end of its mRNA, but instead has a 3′ stem-loop structure where the pre-mRNA processing complexes can bind to (61). SLBP is one component of this processing complex and arsenic targets SLBP for degradation, causing a default aberrant polyadenylation of canonical histone mRNAs (62,63). Polyadenylated mRNAs are more stable and this polyadenylation results in overproduction of canonical histone proteins such as histone H3.1 (58). The histone composition of the chromosome is important because it determines its structure and epigenetic features (64). Arsenic increased histone H3.1 protein expression, which displaced the non-canonical histone H3.3 (they differ from canonical histone H3.1 by only five amino acids) on chromosomes at active promoters, enhancers and insulator regions, resulting in transcriptional deregulation and chromosome instability (65). This effect may apply to the carcinogenic mechanisms of other metals, since it was found that Cd and Ni also caused SLBP depletion by a similar mechanism as arsenic (66).

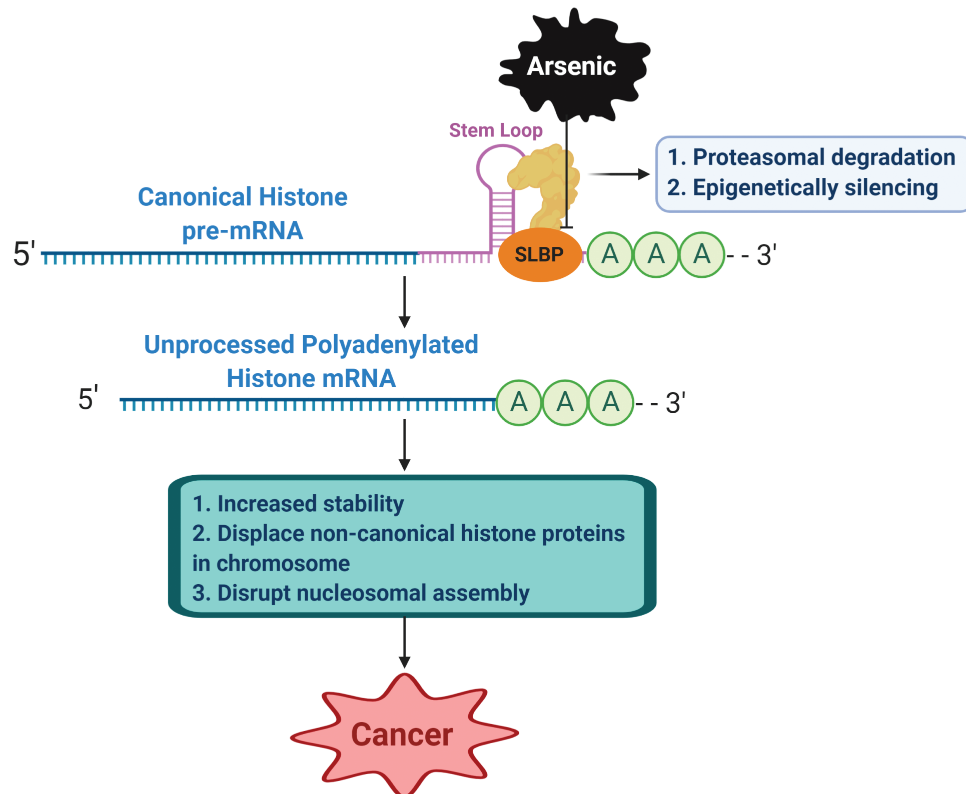

Figure 1. Arsenic reduced SLBP level and subsequent aberrant polyadenylation of canonical histone mRNA, leading to carcinogenesis. Canonical histone pre-mRNA is processed by a cleavage complex containing SLBP. Arsenic downregulates SLBP by promoting proteasomal degradation and epigenetically silencing SLBP gene, causing the polyadenylation of pre-mRNA of canonical histone mRNAs and resulting in increased stability. Polyadenylated canonical histones make more protein causing an imbalanced proportion of histone variants and displace non-canonical histone in the chromosome, leading to aberrant nucleosomal assembly and chromosome instability. A, poly-A tail. Figures are created with Biorender.com.

Beryllium

Beryllium (Be) is mainly used as a component of alloys in combination with other metals such as Cu and Al. Occupational exposure to Be and its compounds by inhalation causes chronic beryllium diseases (67). Berylliosis is an allergic type of lung disease featured by the formation of inflammatory granulomas within tissues and organs including lung, skin, subcutaneous tissues and liver, followed by scarring and gross thickening of deep lung tissues (68). This is caused by a delayed-type hypersensitivity reaction when Be sensitizes T cells and promotes production of cytokines such as interleukin-2 and interferon-γ to activate macrophage, and an aggregation of CD4+ helper T cells, macrophages and plasma cells in the lung, leading to non-caseating inflammatory nodules and fibrosis of the lung (69). Studies also suggested that skin exposure is another possible route for Be-induced chronic beryllium disease or Be sensitization (70). Susceptibility to Be was found to be determined by the types of HLA-DP allele (71). HLA is a receptor that presents peptides onto the cell surface for recognition by T cells and production of immune responses. The polymorphic sequence coding for HLA-DP was investigated and a lysine to glutamic acid change in the fourth variable domain D of the β-chain of HLA-DP (HLA-DP Glu69) was identified as a Be susceptible variant (71). This result was supported by a cohort study demonstrating that subjects with berylliosis had a much higher frequency of HLA-DP Glu69 compared with those not having this sequence (72). It was previously believed that Be is recognized as a specific HLA class II restricted antigen by T cells (69). Whereas later it was shown that Be can bind with HLA, altering the properties of the molecule (73,74). This revealed that HLA-DP Glu69 allele as a susceptibility marker, since it exhibited higher affinity for Be by creating an acidic domain that is readily favors Be^{2+} binding (69). It is now possible to screen workers who might be susceptible to chronic beryllium disease and prevent their exposure to Be in industrial operations.

Animal studies, including monkeys, rabbits and rats, have proven that Be is toxic and carcinogenic (75,76). Several epidemiology studies have related Be exposure to the increased incidence of lung cancer (77). Although the association between lung cancer and Be exposure has been disputed (78,79), Be and its compounds are classified as a Group 1 carcinogen by International Agency for Research on Cancer (IARC). Beryllium was suggested to be a mutagen, since it was reported to decrease the fidelity of DNA polymerase and cause single base substitutions by directly binding with the DNA polymerase enzyme (80). However, these experiments were conducted *in vitro* using a purified DNA polymerase and naked DNA. There is concern that this may not occur in intact cells or *in vivo*. Scientists also suggested this unique mechanism be considered for screening of potential mutagenic carcinogens; however, since this screen was done outside of a cell with purified DNA polymerase, it may not be as relevant as mutation assays done in intact cells. Gene mutations were observed in mammalian cells treated with $BeCl_2$ (81) and $BeSO_4$ (82) and clastogenic alterations were found in cells treated with $Be(NO_3)_2$ (83). However, contradictory results suggested that metallic Be is non-genotoxic to the cell by multiple assays including bacterial reverse mutagenicity assay, unscheduled DNA synthesis assay, mammalian cell gene mutation

assay and chromosome aberration assay (79). In fact, it has been proposed that the soluble Be compounds generate more cytotoxicity and genotoxicity than insoluble Be particles (84,85). However, the dose of soluble Be used in many studies was high and likely caused artificial production of ROS which would not occur at doses relevant to human exposed (86). Further assays on morphological cell transformation and impaired DNA repair were positive (79), but more investigations are required to understand the of genotoxicity and carcinogenicity mechanism of Be and its compounds. Research should also focus on the bioavailability of the Be compound in each of these assays.

Cadmium

Cadmium (Cd) is a relatively rare metal in the earth's crust and is released into the environment due to anthropogenic activities. The biological function for Cd has been characterized in a diatom that utilize the Cd-enzyme, carbonic anhydrase, for living in the marine environment (87), but Cd is very unlikely to have any essential role in humans. In fact, Cd is considered as highly toxic metal, and Cd and its compounds are classified by IARC as a Group 1 carcinogen (88). Studies also indicate an association between the exposure to Cd and the risk of other human cancers such as prostate, renal, liver bladder and stomach cancers (88–91).

Similar to arsenic, Cd is not a direct mutagen and weakly binds to DNA (92). Cd induces DNA damage by generating ROS and inhibiting DNA repair (93,94). In fact, Cd induces ROS such as lipid peroxidation, but not via the Fenton-type of reaction (94). Cd likely displaces Fenton-type metals from their binding sites and the displaced redox-active metal generates ROS to attack DNA (95). Although Cd was also found to impact antioxidant defence by depleting GSH, exacerbating the cellular oxidative defence status (96); however, this is not considered a major mechanism of Cd-related carcinogenesis because it requires relatively high dose and causes a significant portion of the cells to undergo apoptosis (97). In fact, Cd-induced oxidative stress such as lipid peroxidation can occur by the inhibition of antioxidant enzymes such as superoxide dismutase and GSH peroxidase (98,99). Cd has been found to inhibit GSH peroxidase in many organisms (100–102). In addition, it was suggested that selenium (Se) in the peroxidases can protect against Cd-induced toxicity (103).

Cd is one of the best studied metalloestrogens, which are small ionic metals or metalloids that can activate the estrogen receptor in the absence of estradiol (104). Cadmium exposure has been associated with breast cancer in human studies (105). Both *in vitro* and *in vivo* studies demonstrated Cd activation of the estrogen receptor-α (ERα) stimulating the proliferation of estrogen-dependent breast cancer cells and induced the expression of estrogen-regulated genes such as the progesterone receptor (106–109). However, the estrogenic response to Cd is affected by culture media composition, animal species, age, hormonal status, target tissue and the dose and route of exposure to Cd (104). It was suggested that bivalent cationic metalloestrogens like Cd can activate ERα by mimicking Ca and mediate the cross-talk between growth factors/cytokines and the ligand-binding domain of ERα (104). There is evidence to support that Cd competes with Ca for binding to the ligand-binding domain of ERα and Cd requires the same amino acids as Ca to bind and activate the receptor (110–112).

In many instances, toxic metals compete with essential metals and disrupt their actions. In addition to competing with Ca, Cd has been found to displace Zn ion in many proteins with Zn-finger structures, since Cd/Zn have many similarities in their physical and chemical properties (113,114) (Figure 2). The toxic effect of Cd was found to be antagonized by excessive Zn treatment, and Zn also reduced Cd-induced tumor formation (90). Ca is less effective in reducing the carcinogenic effect of Cd replacement as compared with Zn (90). Studies reported that Zn inhibited the carcinogenic effects induced by Cd in the lung, testes and at local injection sites in rodents, and Zn deficiency increased Cd sensitivity and carcinogenic responses at injection sites (90,115). Zn-finger structures are commonly seen in transcription factors and DNA repair proteins that are key regulators in mediating DNA–protein and protein–protein interactions, and important for cell biochemical processes and functions. Thus, this substitution of Cd for Zn in zinc fingers has been examined in many studies and it is believed to be a leading mechanism of Cd carcinogenicity, since it alters the domain structure as well as the activity of the proteins (116–121). Interestingly, it was found in some cases that the substitution of Cd at Zn-binding site of the protein inhibited the binding of the protein to its cognate DNA without affecting the domain structure (120), or changed the structure of the protein without affecting its DNA-binding activity (122), demonstrating the DNA-binding domain exhibited flexibility in metal-binding capacity.

Epigenetic mechanisms also play an important role in Cd-mediated carcinogenesis. Cd is able to modify DNA methylation status, causing both global and gene-specific promoter hypermethylation such as at the p16 promoter and DNA repair genes ERCC1 and XRCC1, and it also increases DNA methyltransferase activity (123–126). However, during early time interval of exposure, it was shown that Cd caused DNA hypomethylation and inhibited DNA methyltransferase (123). Cd exposure was also found to increase methylation at H3K4me3 and H3K9me2, which was associated with cell transformation of

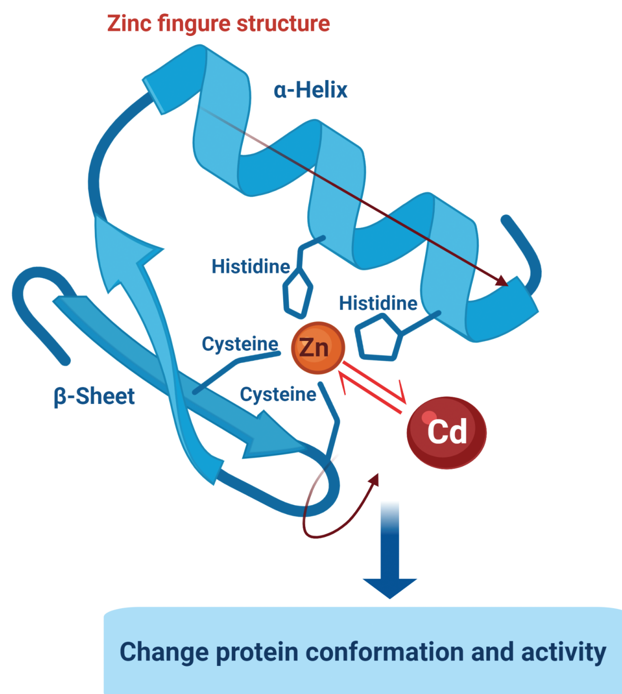

Figure 2. Cd displaces Zn in the Zn-finger structure of a protein leading to altered protein conformation and activity. Cd can displace Zn due to their similarities in physical and chemical properties. Cd displaces Zn at the Zn-figure structure that contain two cysteines and two histidines. Altered orientation of the secondary structure will antagonize the activity of the wild-type protein. Cd, cadmium; Zn, zinc. Figures are created with Biorender.com.

lung epithelial cells (127). In fact, the protein levels of the H3K4 and H3K9 demethylases were not affected by the Cd exposure, but the activity was inhibited (127). Histone demethylases such as lysine demethylase 5A (KDM5A) and KDM3A are Zn-finger enzymes (128,129), and thus it was suggested that Cd displaced Zn at the binding site, leading to impaired activity of the histone demethylases and increased global methylation.

Chromium

Chromium (Cr) is an abundant mineral in the earth's crust. Elementary Cr is not absorbed by the body and has no nutritional value (130). Trivalent chromium (Cr(III)) is the most stable form of Cr found in nature and it is believed to be a nutritional supplement affecting lipid, carbohydrate and protein metabolism (131). However, it has relatively low reactivity and absorption rate by gastrointestinal system (132). The toxicity of Cr is primarily caused by the hexavalent form of chromium (Cr(VI)), which is almost entirely of industrial origin in our environment. There is very little naturally occurring Cr(VI) and most instances of toxicity are a result of intentional dumping of this toxic and carcinogenic agent. The exposure to Cr(VI) also occurs from occupational inhalation of Cr(VI) particles in chrome plating or welding. Cr(VI) is a strong oxidant and unlike Cr(III), it can easily cross cell membrane by riding on the sulfate and phosphate cell transporters, and subsequently reacting with protein components and nucleic acids when reduced to Cr(III) inside the cell (Figure 3) (133). Measurement of Cr(VI) exposure requires isolation of red blood cells or white blood cells to measure the Cr content inside the cell, since only Cr(VI) but not Cr(III) enters cells. However, once present inside the cells, it is in the Cr(III) form. Cr(VI) has been classified as Group 1 carcinogen by IARC and epidemiological studies have associated the occupational exposure of Cr(VI) with a high incidence of lung cancer among industrial workers (134,135). The U.S. National Toxicology Program (NTP) reported a 2-year study demonstrating that ingested Cr(VI) was carcinogenic to rats (tongue cancers) and mice (small intestinal cancers) (136). There are now several human epidemiological studies showing that chromate can induce other types of cancer, including liver, kidney, prostate, bladder, skin, brain and stomach cancer (137). Studies also reported that Cr(VI) compounds induced anchorage independent growth and mutation to 6-thioguanine resistance in cultured diploid human foreskin fibroblasts (4). It was suggested that Cr(VI) compounds are 1000 times more effective on a concentration basis at inducing cytotoxicity and mutation to 6-thioguanine resistance (138). In addition, lead chromate was found to induce focus formation, anchorage independent growth and tumorigenicity without inducing mutation to ouabain resistance in C3H/10T1/2 C1 8 mouse embryo fibroblasts (139).

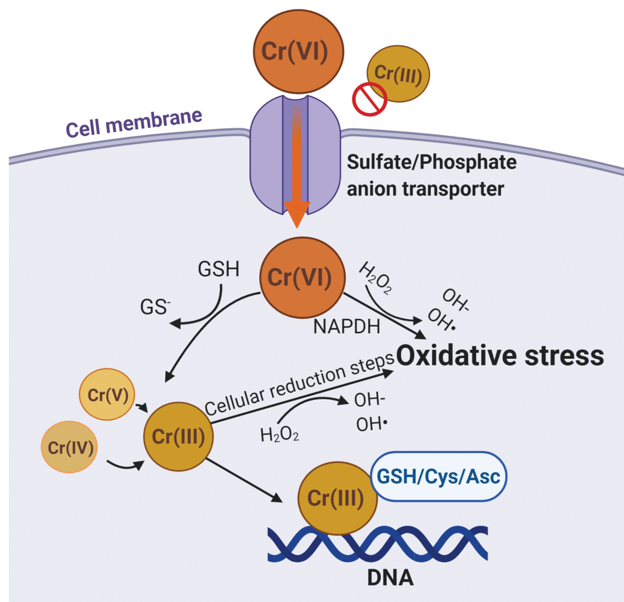

Figure 3. Cr(VI) reduction to Cr(III) in the cell will form Cr-DNA adducts. Cr(VI) is delivered into the cell via sulphate or phosphate anionic channels, and then reduced to intermediates Cr(V) and Cr(IV), and finally accumulates as Cr(III), the most stable form, which is able to form bulky DNA adducts with ligands such as GSH, cysteine and ascorbic acid to cause genotoxicity. Asc, ascorbic acid; Cr, chromium; Cys, cysteine. Figures are created with Biorender.com.

Cr(VI)-induced genotoxicity and DNA damage are considered a primary mechanism of its carcinogenicity. GSH and vitamin C are important antioxidants that mediate the reduction Cr(VI) in the stomach and in the cell (140). Extracellular reduction of Cr(VI) to Cr(III) is a protective mechanism, since Cr(III) does not enter the cell well (141). In contrast, in purely *in vitro* studies, low dose of intracellular Cr(III) has been shown to increase the binding and processivity of polymerases to DNA, which enhanced the rate of DNA replication with decreased fidelity, subsequently this mechanism was proposed as a way that Cr(III)-induced mutagenesis in cells (142–145). Higher levels of intracellular Cr(III) reduced from Cr(VI) were found to decrease the polymerase processivity (146). Cr(III) can form both ionic and coordinate complexes with DNA (Cr-DNA) favoring the phosphodiester backbone with some nucleic acid base binding (147,148). The ternary complexes are coupled with ligands such as GSH, ascorbate, cysteine and histidine, generating bulky DNA adducts such as GSH-Cr-DNA, Asc-Cr-DNA, Cys-Cr-DNA and His-Cr-DNA (149), which likely increase errors during DNA replication and cause a variety of DNA lesions, including DNA and RNA polymerase arrest and mutagenesis, leading to chromosomal abnormalities (150–155). One type of DNA lesion produced by Cr(III) is DNA interstrand cross-links, which interferes with DNA replication processes to cause DNA polymerase arresting lesions and fork collapse, resulting in cytotoxicity (150,156,157). A study suggested that the ionic Cr-DNA binding is responsible for increased DNA replication, while the coordinate covalent interaction is probably the main cause of DNA lesions that impede the replication processes and induce mutagenesis (146). In addition to Cr-DNA adducts, a variety of genetic lesions including oxidation of the bases, abasic sites and DNA strand breaks were caused by the metabolic reduction of Cr(VI) (155,156,158–161).

It is believed that the toxicity of Cr(VI) also originates from the oxidative DNA damage (162). It has been demonstrated that chronic exposure of low-dose Cr(VI) contaminated drinking water can induce oxidative stress in mice, which led to cytotoxicity and focal or diffused hyperplasia in the target tissue (163). Cr(VI) can react with GSH and hydrogen peroxide to produce ROS directly in the cell (164–168). Cr(VI) is reduced by GSH, generating the GSH-derived thiyl radical ($GS^{\cdot}$) (168). Cysteine or penicillamine was also found to react with Cr(VI) and generate thiyl radicals (165). Cr(VI) reacting with hydrogen peroxide or with $O_2^{\cdot-}$ radicals to produce $^{\cdot}OH$ and OH^- is similar to Fe(II)-mediated Fenton and Haber–Weiss reaction (166,167,169,170). The highly reactive intermediates such as Cr(V) and Cr IV are generated from one electron reductions of Cr(VI) and these intermediates further exacerbate DNA damage and cellular toxicity (171). On the other hand, Cr(VI) stimulates cell reactions by activating the signal transduction pathways such as the

NADPH-oxidase to generate ROS (172,173). Moreover, NF-κB and AP-1 are important oxidant response proteins found to be activated by Cr(VI)-induced ROS (174–177). It was also suggested that ROS produced by Cr(VI) might serve as a second messenger in initiating signaling responses by inhibition of tyrosine phosphatases and increased tyrosine phosphorylation (178,179). In addition, the dioxygenase enzymes which require vitamin C for activity can be inhibited by chromate depletion of reduced vitamin C in tissue culture systems where the levels of this vitamin are very low (50 μM), since the only source is from FBS and not from exogenously added vitamin C to the culture media. However, *in vivo* the levels of this vitamin are high, and this may not be an operative mechanism of toxicity.

Numerous studies have found epigenetic changes induced by Cr(VI), which is another important mechanism in Cr-induced carcinogenicity (180,181). An increased DNA methylation was reported at the p16 tumor suppressor promoter in lung cancer workers exposed to Cr(VI) by inhalation (182). Silencing of other genes such as MLH1 (mismatch repair gene), APC (tumor suppressor gene), WIF1(tumor suppressor gene) and MGMT (DNA methyltransferase) genes (183–185) by hypermethylation at the promoter region was identified in lung cancers of chromate workers. However, a global hypomethylation was observed among chromate workers without tumors and human cells acutely exposed to Cr(VI) (186,187). Histone modifications were also altered by Cr(VI) exposure, such as global decreased H3K27me3 and H3R2me2, and increased H3K4me3, H3K9me2 and H3K9me3 in human lung A549 cells (185,188). It was suggested that the induced expression of histone methyltransferase G9a by Cr(VI) might be the mechanism contributing to the increased H3K9me2 in cells (189). Moreover, Cr(VI) exposure caused decreased histone acetylation, thereby downregulating biotinidase and increased histone biotinylation (190,191).

Nickel

Nickel (Ni) is believed to be an important metal that existed in hot oceans at the beginning of life as a metal cofactor in the metabolism of methanogenic archaea (192,193). It is an essential element for bacteria and plant in biosynthesis of enzymes such as the hydrogenases, ureases and carbon monoxide dehydrogenases (194,195). It has no essential role in humans except for the microbiome. However, pathogenic bacteria such as *Helicobacter pylori*, which cause stomach cancer, requires Ni ions for the activity of urease to colonize in the acidic environment within the stomach (196). Ni exposure poses many health concerns in humans, such as Ni allergy, hematogenous contact eczema and systemic allergy syndrome (197).

Ni compounds are classified as Group 1 carcinogen by IARC, since studies have shown that workers in Ni refineries under chronic exposure of a heterogeneous mixture of Ni compounds exhibited increased risk of lung and nasal sinus cancer (198). Studies have shown that samples of Ni refinery dust-induced strong morphological transformation in cultured C3H/10T1/2 Cl 8 mouse embryo cells (199). It is believed that Ni compounds with low water solubility, such as crystalline Ni compounds—NiS and Ni_3S_2, and Ni oxide (NiOx), are more potent carcinogens (200,201). Studies indicate that insoluble Ni compounds, including crystalline NiS, Ni_3S_2 and green and black Ni oxide, induced focus formation, anchorage independence and tumorigenicity in cultured C3H/10T1/2 Cl 8 mouse embryo fibroblasts (202). Cell lines derived from transformed foci induced by crystalline NiS and green NiO have amplification of proto-oncogene Ect-2, and overexpression of Ect-2 mRNA and protein (203). Similar to Cr(VI), insoluble Ni(II) compounds were also found to induce anchorage independence and mutation to 6-thioguanine resistance in cultured diploid human foreskin fibroblasts (4). The uptake of Ni compounds by the cell and intracellular concentration of Ni is critical to its carcinogenetic activity (204–206). This was supported by the study showing that amorphous NiS was poorly taken up into cells and it failed to cause cell transformation (204). The model of different Ni compounds entering the cell is illustrated in Figure 4 (207–209). Water-soluble Ni compounds—$NiCl_2$ and $NiSO_4$ $(H_2O)_6$—were not carcinogenic to animals or humans by *in vivo* studies (205,206). The clearance rate of water-soluble Ni^{2+} by lung is much faster than that of Ni particles, since the water-soluble Ni^{2+} was rapidly mobilized away from the lung (210). However, numerous *in vitro* studies have demonstrated that soluble Ni exposure can also modulate gene expression globally and lead to cell transformation (211,212).

Unlike other metals that induce oxidative stress in the cell, Ni creates a hypoxic cellular environment, which is an important mechanism for Ni-induced carcinogenesis (213). Hypoxia-inducible factor-1 (HIF-1) is a transcription factor that regulates hundreds of genes in mediating cell survival and adaptation to hypoxic conditions (214,215). Its molecular mechanisms in oxygen detection, angiogenesis promotion and cancer biology have been studied and characterized by scientists Willian G. Kaelin Jr., Sir Peter J. Ratcliffe and Gregg L. Semenza that have been awarded the Nobel Prize in Medicine 2019. HIF-1 stability is mainly regulated by prolyl-hydroxylase (PHD), a Fe-dependent enzyme and a cellular oxygen sensor (216). Ni was found to displace Fe from the active site of a number of dioxygenase enzymes which all have the same active site consisting of two histidines and a carboxylic acid facial triad (217). As a result, studies showed that Ni inhibits HIF-PHD activity by displacing Fe from the enzyme, and the lack of prolyl hydroxylation prevented von Hippel–Lindau from binding to HIF which

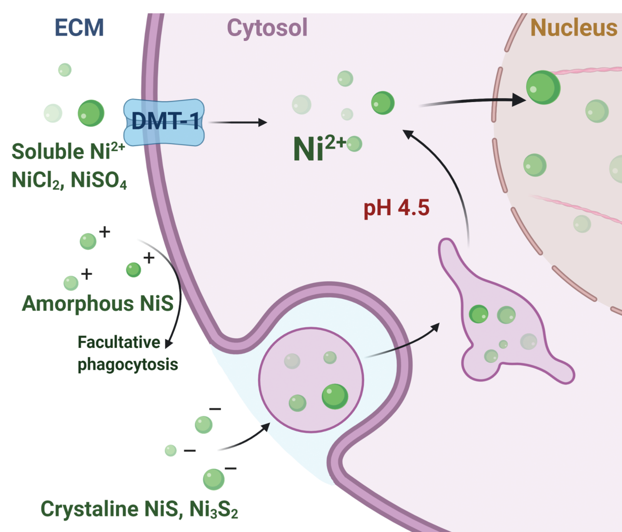

Figure 4. Transport of particulate Ni compounds into the cell and delivery of Ni ions into the nucleus. Particulate Ni compounds (crystalline NiS and Ni_3S_2) enter cells by phagocytosis and subsequently release water-soluble Ni^{2+} ions within intracellular vacuoles. When vacuoles fused with lysosomes and acidified, Ni^{2+} ions are released into cytoplasm and then enter the nucleus to exert its toxic and carcinogenic effect. Water-soluble Ni compounds enter cells via active transport aided by surface metal transport proteins such as DMT-1. Amorphous Ni (NiS) is not taken by the cell due to its positive charge but changing its charge to negative will result in uptake and carcinogenesis. DMT-1, divalent metal transporter 1; Ni, nickel. Figures are created with Biorender.com.

suppressed proteasomal degradation, resulting in the accumulation of HIF-1α protein and activation of HIF signaling pathway (Figure 5) (207). In addition, it was proposed that Ni compound-mediated activation of PI-3 kinase signaling pathway could be another mechanism of inducing HIF-1 (218).

Ni also promotes tumorigenesis through epigenetic mechanisms including DNA methylation, histone post-transcriptional modifications and non-coding RNA regulation. Ni is a weak mutagen (219) and inactivates gpt transgene expression in a transgenic gpt+ Chinese hamster cell line (G12) without mutagenesis of the transgene (220). It has been demonstrated that Ni-induced chromatin condensation and heterochromatinization because of the unique gpt integration site in G12 cells. Addition of $NiCl_2$ to nuclei from G12 cells (gpt gene is located near heterochromatin) but not G10 cells (gpt gene is distant from heterochromatin) prevented degradation of gpt gene by DNase I through chromatin condensation, resulting in a *de novo* NDA methylation and gene silencing (220,221).

Histone modification was suggested to be another mechanism by which Ni induces cell transformation, resulting in altered expression of oncogenes or tumor suppressor genes (212,222). It was found that Ni produced a telomeric silencing in yeast where there is no DNA methylation (223). Then Ni was shown to inhibit acetylation of histone H4 globally in both yeast and mammalian cell (224,225). A chromosome immunoprecipitation analysis further supported the deacetylation of H4 and H3, and methylation of H3 lysine 9 by Ni exposure (226). Moreover, chronic Ni exposure was found to cause phosphorylation of H3 serine 10, and ubiquitination of histones H2A and H2B (219,227). Recently, many studies have investigated the modulation of non-coding RNA expression by Ni exposure in inducing cell transformation, such as MEG-3, NRG1, miR-152, miR-203, miR-4417, miR-222 and miR-210 (228). This pathway might be regulated by activating DNA methyltransferases and histone deacetylases following Ni exposure (229–231), or other pathways, for example by inducing HIF-1α to regulate miR-210 (232). In addition, MEG-3 is an upstream regulator for HIF-1α, providing another possible way that Ni-induced HIF-1α activation through epigenetic mechanisms (229).

Conclusion and future direction

Metal and metal compounds have been identified as causing human cancers by association in epidemiology studies. Current studies have been conducted to unveil the mechanisms by which metal induces genotoxicity and carcinogenicity with many still not well elucidated. The dose, exposure time, target tissues or cells, culture conditions and many experimental factors are needed to be considered if the metal exerts different effect under varied conditions.

A comprehensive understanding of the pathways mediated by the metals will be helpful in the prevention and therapy of the metal-induced diseases and cancers. The metals discussed in this review share some common mechanisms in tumorigenesis, but also have their unique pathways. For example, most metal carcinogens are found to produce ROS and increase oxidative stress. Antioxidative phytochemicals and chelating agents will be of importance in the prevention of the genotoxicity induced by oxidative stress-related metals. However, Ni is mainly found to activate hypoxia-induced signaling pathways, which is mediated by competing with Fe in prolyl-hydroxylase. Other metals such as arsenic and Cd are also found to compete or displace essential metals such as Zn and Ca in proteins as their major mechanism of genotoxicity and cytotoxicity in the cell. Recent studies have indicated a role of selenium in antagonizing As and Cd toxicity by sequestration and activation of Se-dependent antioxidant enzymes (103). In addition, heavy metals such as arsenic and Cd are found to suppress cell autophagy (233,234), a process that plays an important role in tumor suppression (235). Studies have reported that arsenic caused overexpression of interleukin-6, which antagonized autophagic states, thereby promoting cancer cell survival and tumor progression (236). Cd-transformed Beas2B cells acquired autophagy deficiency, which caused overexpression of p62 and Nrf2 and further induced antiapoptotic signals to assist in cancer cell survival and proliferation (237). This suppression of autophagy is emerging as a new mechanism in metal-induced carcinogenesis, and it will be a promising area for future research, since the ability to restore autophagy flux, which is inhibited by carcinogenic metals, might be a potential therapeutic strategy for metal-induced carcinogenesis. Chemicals such as sulforaphane and curcumin are indicated as autophagy inducers as they were found to repair autophagy impairment in metal-transformed cancer cells and prevent carcinogenesis (237–239).

It is also possible that metals induce tumorigenesis through a combination of their effects, since the exposure of a mixture of different metals is more relevant to what humans' experience in the real world. The carcinogenic mechanisms induced by multiple factors will be much more complicated than simply adding up the effects induced by each metal but studies of mixtures should also be addressed in the future.

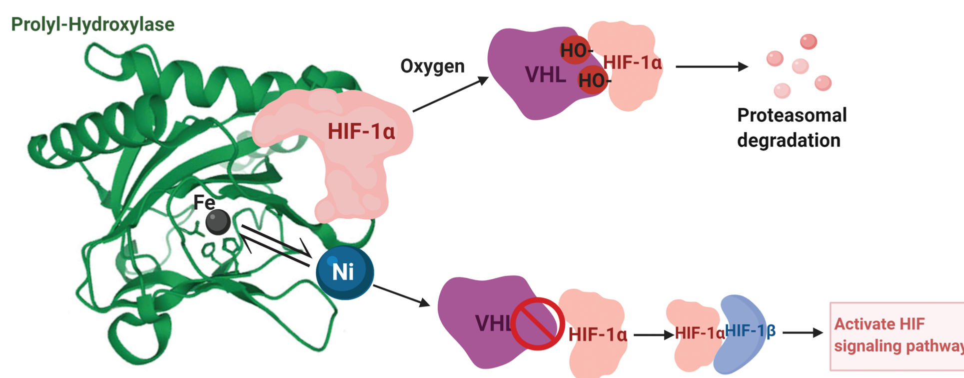

Figure 5. Ni displacing Fe in prolyl-hydroxylase and activating HIF signaling pathway. HIF can be hydroxylated by a class of prolyl-hydroxylase to be targeted for proteasomal degradation mediated by VHL. Ni can replace Fe from the enzyme and inhibit its activity, subsequently stabilizing HIF-1α and activating HIF signaling pathway. Fe, iron; Ni, nickel; VHL, von Hippel–Lindau. Figures are created with Biorender.com.

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