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Epigenetic mechanisms in metal carcinogenesis

Luka Manić [a], David Wallace [b], Pinar Uysal Onganer [c], Yasmeen M. Taalab [d,e], Ammad Ahmad Farooqi [f], Biljana Antonijević [a], Aleksandra Buha Djordjevic [a,*]

[a] Department of Toxicology "Akademik Danilo Soldatović", Faculty of Pharmacy, University of Belgrade, Belgrade, Serbia
[b] School of Biomedical Science, Oklahoma State University Center for Health Sciences, Tulsa, United States
[c] Cancer Research Group, School of Life Sciences, University of Westminster, London, UK
[d] Institute of Forensic and Traffic Medicine, University of Heidelberg, Voßstraße 2, 69115 Heidelberg, Germany
[e] Forensic Medicine and Clinical Toxicology Department, Faculty of Medicine, Mansoura University, Dakahlia Governate 35516, Egypt
[f] Laboratory for Translational Oncology and Personalized Medicine, RLMC, Lahore, Pakistan

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ABSTRACT

Many metals exhibit genotoxic and/or carcinogenic effects. These toxic metals can be found ubiquitously – in drinking water, food, air, general use products, in everyday and occupational settings. Exposure to such carcinogenic metals can result in serious health disorders, including cancer. Arsenic, cadmium, chromium, nickel, and their compounds have already been recognized as carcinogens by the International Agency for Research on Cancer. This review summarizes a wide range of epigenetic mechanisms contributing to carcinogenesis induced by these metals, primarily including, but not limited to, DNA methylation, miRNA regulation, and histone posttranslational modifications. The mechanisms are described and discussed both from a metal-centric and a mechanism-centric standpoint. The review takes a broad perspective, putting the mechanisms in the context of real-life exposure, and aims to assist in guiding future research, particularly with respect to the assessment and control of exposure to carcinogenic metals and novel therapy development.

1. Introduction

Metal carcinogenicity is undoubtedly a well-known topic in toxicology. Carcinogenicity was measured and discussed as early as the 1930s [1,2]. In 1956 Oppenheimer et al. suggested that subcutaneous embedding of metals, e.g., silver, vitallium (an alloy of cobalt, chromium, and molybdenum), tantalum, and stainless steel (an alloy of iron and chromium) in rats could be associated with cancer [3], while in 1962 a carcinogenesis mechanism involving cadmium was proposed [4]. Since then, arsenic, cadmium, chromium, nickel, and many more metals have been identified as carcinogens [5]. Today, IARC (WHO) recognizes many of these as human carcinogens. However, it was not until the 1980s that the epigenetic role of metals was discussed more extensively and until 1995, when the effects of nickel were linked to carcinogenesis [6,7]. Numerous epigenetic mechanisms have been proposed since the mid-1990s, with varying amounts of evidence in support of epigenetic changes. Prominent epigenetic phenomena include DNA methylation, histone posttranslational modifications, gene silencing, X chromosome inactivation, paramutation, position-effect variegation, genomic imprinting, and the silencing of paternal chromosomes [8].

While DNA damage is likely the most widely known carcinogenesis mechanism, other mechanisms of carcinogenesis, such as epigenetic changes, referred to as "field cancerization", were also mentioned as early as 1953. Although the exact nature of these alterations was unclear at the time, it was suggested that premalignant epithelial tissue had been preconditioned by an unknown process, predisposing it to cancer development [9]. Numerous studies examining tumors in vivo and neoplastic tissues in vitro concluded there was evidence that most mutations existed in cells with high genome instability before the onset of terminal clonal expansion [10,11]. Epigenetic mechanisms, some linked to exposure to certain metals, have been increasingly researched in the past years and the understanding of these mechanisms has been recognized as an important step towards understanding the development of pathological conditions and consequently could help develop diagnosis and treatment options for those conditions [12–17].

Whether the existing gene mutations will cause a visible defect is mainly dependent on their expression, which is where the epigenetic mechanisms come into play. Silent, methylated oncogenes become

* Correspondence to: Department of Toxicology "Akademik Danilo Soldatović", Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia.
E-mail address: Aleksandra.Buha@pharmacy.bg.ac.rs (A. Buha Djordjevic).

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aberrantly expressed when methylation is lost. Conversely, the hypermethylation of tumor suppressor genes results in the loss of their expression. CpG (CG) islands (regions of DNA strands with frequent CpG sites – sequences of cytosine followed by guanine in 5′ to 3′ direction) are especially prone to succumbing to epigenetic changes resulting in differential gene expression, e.g., when methylated or demethylated. Similar alterations of histones such as methylation, acetylation, phosphorylation, etc., also affect gene expression, making histone modifications an important epigenetic mechanism capable of contributing to the onset and progression of carcinogenesis. Since there are other proteins, e.g., HMGA2, that are involved in chromosome architecture, their modification could be considered an epigenetic mechanism, too, as well as changes in microRNA (miRNA) expression.

The goal of this review is to provide a comprehensive summary of the common and well-established epigenetic mechanisms in metal carcinogenesis and bring to the forefront several recently proposed mechanisms. The choice of metals ranges from well-known to newly established carcinogens, to illustrate the principles of epigenetics translated across different metals' reported carcinogenicity. An effort has also been made to include metals with varying genotoxicity. Arsenic and chromium are genotoxic, while cadmium is weakly genotoxic [18]. On the other hand, nickel is not considered genotoxic [18]. The review is divided into two sections, one elaborating on mechanisms themselves and the other describing how the mechanisms fit into the carcinogenicity profiles of individual metals. A summary of cancer treatments related to epigenetics is given afterward.

2. Epigenetic mechanisms in carcinogenesis

Epigenetic changes are a collective term referring to DNA, histone, or other changes that result in altered gene expression without changing the DNA sequence. Environmental factors, including diet, xenobiotics, and the total living environment, all affect the epigenome. Epigenetic changes can affect the cells in which they occur, but can also affect the subsequent cell generations. Currently, the mechanisms of these transgenerational effects in mammals are unclear [8,19]. An important consideration was made in The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals concerning transgenerational effects – a study conducted on pregnant female F0 generation should at least assess the effects in F3 generation. The argument behind the recommendation is that if F1 generation was exposed prenatally to an agent, the precursors of their ova – the future F2 generation – have been exposed, as well. Thus, to be truly transgenerational, the effect should at least be transferred to F3 generation [20]. Although known as carcinogens for a relatively long time, toxic metals have been increasingly examined recently to elucidate their involvement in epigenetically mediated carcinogenesis mechanisms [19].

2.1. DNA methylation in gene promoter regions

DNA methylation refers to the bonding of methyl groups to DNA, specifically to position 5 of cytosine residues. These methylated sites containing 5-methylcytosine (5mC) occur as part of CpG dinucleotides. In mammalian cells, 60–90% of the sites are methylated, and the methylation coincides with long-term transcriptional silencing – genomic imprinting, X chromosome inactivation, suppression of repetitive DNA silencing, and the silencing of lineage-specific genes. The extent to which DNA is methylated is not permanent but rather changes with time to maintain genomic stability. While the methylation of promoter regions is usually associated with repressed transcription, the methylation of gene body is associated with the activation of transcription. DNA methyltransferases (DNMTs) catalyze cytosine methylation. Methyl residues can be removed through passive demethylation via a gradual shortage of DNMTs during replication over time. Intense cell division thus favors demethylation. An active demethylation mechanism has also been proposed – 5mC oxidized by ten-eleven translocation (TET) methylcytosine dioxygenase, iron, oxygen, and 2-oxoglutarate yield 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxylcytosine (5caC), that are removed by activation-induced cytidine deaminase (AID) or thymine DNA glycosylase (TDG) and base excision repair system (Fig. 1). This mechanism is assumed to involve the reprogramming of the DNA methylation profile in primordial germ cells and paternal pronuclei of zygotes. The methylated regions in gene promoters obstruct activation, while long-term suppression can be achieved via proteins with methyl-binding domains (MBD) – MeCP2, MBD1, MBD2, MBD3, and MBD4. MBD proteins mobilize corepressors, e.g., HDACs, and other enzymes modifying chromatin to form compact, repressive heterochromatin (Fig. 2) [21].

2.2. Posttranslational histone modifications

In eukaryotic cells, histones and DNA form a dynamic structure – chromatin. Depending on the degree of condensation, one can observe heterochromatin, the tightly condensed form, with little access to DNA and thus little transcription, and euchromatin, the loose form mostly available for transcription. The steric availability of DNA does not only affect transcriptional activity, highlighted in this review, but also affects replication, repair, and recombination. Chromatin is comprised of nucleosomes, hank-like structures containing approximately 147 base pairs wrapped around an octamer protein core – two sets of H2A, H2B, H3, and H4 histones each. N-terminal tails of histones protrude from nucleosomes and can be chemically modified.

It is these protruding tails that are substrates for modifications such as acetylation, methylation, sumoylation, ubiquitination, and biotinylation, characteristic for lysine residues, while others like citrullination and ADP-ribosylation are characteristic for arginine, serine, and threonine. Proline, on the other hand, is prone to cis-trans isomerization. Histone acetyltransferases (HATs) are involved in transferring acetyl groups to histones, while histone deacetylases (HDACs) are involved in removing the groups from the proteins. Certain modifications are found more often than others in specific DNA regions. In that regard, dimethylated and trimethylated lysine 9 on histone H3 (H3K9) is associated with gene repression, and while trimethylated K3K9 (H3K9me3) is found in heterochromatic regions, dimethylated lysine 9 (H3K9me2) is found in euchromatic regions of silenced genes. Gene activation is associated with methylated H3K4, while H3K27 modification is repressive, and methylated H3K36 is associated with transcription elongation. Lysine methyltransferases (KMTs) contain a Set domain and use S-adenosyl methionine (SAM) as a methyl donor. On the other hand, lysine demethylases (KDMs) can be lysine-specific (LSD1), targeting H3K4 and H3K9, while the others are dioxygenases containing JmjC-domain and can remove up to three methyl groups from lysine residues [21].

2.3. MicroRNA activity

MicroRNAs (miRNAs) are short, single-stranded noncoding RNAs that regulate gene expression in a sequence-specific manner, mostly

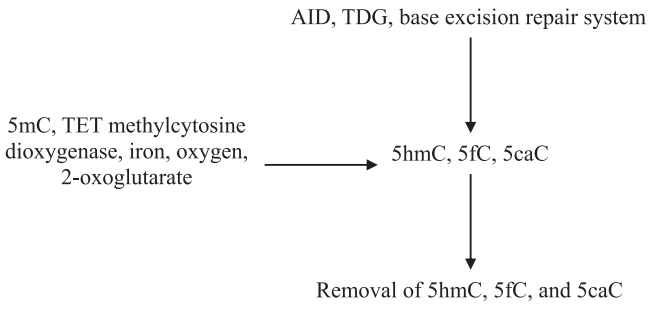

Fig. 1. A proposed mechanism of active demethylation.

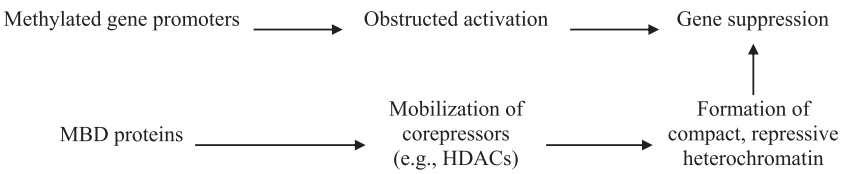

Fig. 2. A proposed mechanism of long-term gene suppression.

negatively. miRNAs bind to complementary sequences in either 3′ or 5′ untranslated regions, as well as coding regions, which results in mRNA degradation and the inhibition of protein synthesis. More than two thousand miRNAs in the human genome have been noted in the miRbase, actively influencing major processes such as cell proliferation, differentiation, metabolism, and apoptosis [21]. In their review published in 2013, Sun, Shamy, and Costa mentioned that dysregulated miRNA profiles may be associated with cancer initiation and progression [21]. The role of miRNAs in xenobiotic toxicity as well as their potential role as biomarkers has been profoundly studied recently [22]. Furthermore, since mature miRNA bind to numerous partially complementary regions, the number of the affected mRNAs is relatively high even for a single miRNA [21].

3. Metals

A substantial body of evidence confirming carcinogenic effects of heavy metals has been collected. Some of these metals exhibit toxicity even when exposure levels are very low [23]. The International Agency for Research on Cancer has included many of these metals in its classification as known, potential, or possible carcinogens for humans. Although certain metals are genotoxic and may damage DNA e.g., through induction of oxidative stress, some can also induce epigenetic changes. The summary of this evidence has been published recently by Wallace and Buha Djordjevic [24]. Most of the evidence concerns well-established carcinogenesis mechanisms, e.g., arsenic facilitating oxidative stress and DNA damage, cadmium altering mitochondrial function, or chromium exerting mutagenic effects, but little is known about the epigenetic effects, that are increasingly gaining prominence in cancer research.

3.1. Arsenic

Arsenic and its compounds have been used in pharmaceuticals, wood preservatives, chemicals used in agriculture, semiconductors, metallurgy, mining, and glass production. IARC lists workers in smelters, coal power plants, and timber treatment, glass production, battery assembly, and electronics plants as the ones who may be at risk of occupational arsenic exposure. Strictly occupational exposure cannot be assumed, however, bearing in mind that the major exposure route for humans is through contaminated food and water. Inhalation is a minor exposure route according to the data presented by IARC but transdermal exposure may be of importance in population with significant occupational exposure, e.g., workers that treat timber with chromated copper arsenate [18].

According to IARC, arsenic is a group 1 human carcinogen. IARC has also classified arsenic compounds – its inorganic compounds are group 1 human carcinogens, while dimethylarsinic acid and monomethylarsonic acid are group 2B human carcinogens. In comparison, arsenobetaine and other organic arsenic compounds that are not metabolized in humans are group 3 human carcinogens [18]. Arsenic is already known to produce reactive oxygen species and indirectly damage DNA through oxidative stress. Overexpression of antioxidant enzymes leads to desensitization to apoptosis, allowing cell transformation and carcinogenesis to occur [25].

3.1.1. Epigenetic mechanisms in arsenic carcinogenesis

Not only may arsenic contribute to carcinogenesis through well-established conventional mechanisms, but it has also been linked to the epigenetic phenomena that are involved in carcinogenesis, as well. The mechanism of arsenic excretion, methylation by S-adenosylmethionine (SAM), depletes SAM and reduces the number of methyl group donors in a cell, thus favoring hypomethylation as fewer methyl group donors are available [26]. However, arsenic can be found in cells in amounts of several μM, while in contrast, there is approximately 80 μM of SAM in cells, plus an additional reserve [25]. Hypermethylation may occur globally or at a specific gene location. Arsenic exposure was found to induce the hypermethylation of tumor suppressor genes such as p53 and p16 [27]. Methylation of transposable elements, such as LINE-1, which correlates to arsenic exposure and multiple human diseases – colon cancer, beta-thalassemia, and oculomotor apraxia, was also observed [28,29].

Histone kinases mediate posttranslational histone modifications: nuclear-mitogen and stress-activated protein kinase 1 (MSK1), both activated following arsenic exposure [30]. MSK1 activation favors H3K9 demethylation, which increases transcriptional activity, and H3S10 phosphorylation, which induces proto-oncogenes, such as c-fos and c-jun [31,32].

Recently, a link between arsenic-induced defects in alternative splicing and cancer development has been suggested (alternative splicing occurs in 95% of multiexon genes) [33,34]. Alternative splicing defects are already associated with angiogenesis, carcinogenesis, and epithelial-mesenchymal transition, all related to cancer development and progression [35–37]. Moreover, exon selection is dependent on DNA methylation and histone posttranslational modifications, both possibly affected by arsenic exposure [38,39]. Consequentially, exon selection can indirectly be influenced by arsenic. It is also suggested that arsenic exposure could affect miRNA expression, which leads to irregular gene expression and genome instability, both conditions related to carcinogenesis [39–41].

Increased DNA methylation at CpG sites was associated with arsenic exposure, including tumor suppressor p16 and DAPK genes. The exposure also led to a decrease in H4K16 acetyltransferase, possibly leading to less intensive gene activation. In human bladder epithelial cells, the effect was dose- and time-dependent, suggesting that effects originating from chronic exposure could be intensive enough to contribute to carcinogenesis. In human lung carcinoma cells exposed to arsenic, H3K9me2 was increased, while H3K27me3 was decreased, suggesting a role in lung carcinogenesis, as well [42–44].

3.2. Cadmium

The primary route of cadmium exposure in the general population is ingestion of contaminated food, while water, ambient air, and dust make up minor exposure routes. Tobacco leaves naturally accumulate cadmium in large amounts, making tobacco smokers inherently exposed to cadmium. IARC states that according to the present data, approximately 10% of cadmium that smokers are exposed to is inhaled while smoking. When cadmium is used in multiple manufacturing processes, occupational exposure may be a significant route of exposure. IARC also reported a general drop in occupational cadmium exposure since the 1970 s due to changes in manufacturing processes. Yet, cadmium remains a persistent toxicant, and IARC has recognized cadmium and its

compounds as group 1 human carcinogens [18].

Cadmium is known to induce oxidative stress, attenuate apoptosis, and inhibit DNA repair mechanisms – that is how it causes genotoxic and mutagenic effects [45,46]. Cadmium is also an endocrine disruptor and can target steroid hormone receptors as an agonist or modulator, possibly due to the presence of zinc finger motifs [47–49]. Some studies suggest that cadmium inhibits methyltransferases, resulting in methyltransferase upregulation and DNA hypermethylation after long-term exposure to cadmium [49–51]. On the other hand, brief exposure to cadmium would result in hypomethylation: methylated DNA would be lost without active methyltrasferases due to passive demethylation: the enzyme preserves parent strand methylation in daughter strands [25]. As mentioned, chronic exposure to cadmium leads to the elevation of DNMT1 activity and hypermethylation [52]. Increased DNMT1 activity and hypermethylation can then lead to the reduced expression of RASSF1A and P16 tumor suppressor genes [25,53].

Short-term exposure to cadmium has been associated with reduced DNA methylation, possibly through DNMT1 inhibition [50,51]. The study that linked short-term exposure to cadmium to reduced DNA methylation also linked long-term exposure to cadmium to DNMT1 enhancement and increased DNA methylation [50]. Several additional studies associated cadmium exposure with increased DNA methylation (44,46−48). Researchers found that cadmium exposure may lead to oncogene activation, e.g., c-myc, c-jun, and c-fos, as well as the suppression of tumor suppressor genes p 53 and p27 [54,55]. A connection between cadmium exposure and chronic myelogenous leukemia K562 cell proliferation was implied; however, no mechanism was suggested. A similar relationship was made when 3.5 times higher cadmium levels were observed in breast cancer tissue compared to healthy breast tissue [56]. Based on promoter-specific DNA and histone methylation, cadmium could modulate the expression of genes involved in carcinogenesis through altering epigenetic marks in these gene regions [57].

3.2.1. *Epigenetic mechanisms in cadmium carcinogenesis*

Initial exposure to cadmium has been associated with hypomethylation at promoter sites, while hypermethylation has been associated with long-term exposure to cadmium. An increase in p-Ras, p-Raf-1, p-MEK-1, and p-ERK-1 levels was observed, suggesting a boosted Ras signaling cascade in cells exposed to cadmium. Cadmium exposure has also been associated with aberrant miRNA expression, such as upregulated miRNA 146, which is linked to downregulated NF-κB and increased tumor growth in pancreatic ductal adenocarcinoma [58]. Whether these epigenetic alterations can be inherited remains inconclusive and requires further research. These mechanisms have been thoroughly laid out in 2017 in a review by Buha et al. [59].

In a review on cadmium epigenetic carcinogenesis, Wang et al. [19] described three major paths of cadmium-induced DNA methylation: (1) increased global DNA methylation, (2) increased methylation of specific genes, and (3) the influence on DNMT activity. In one of the reviewed papers, the promoters of RASSF1A and p16 genes were hypermethylated after ten weeks of cadmium exposure [60]. Genes corresponding to DNA repair mechanisms, such as hMSH2, ERCC1, XRCC1, and hOGG1, were found hypermethylated in another study that also observed decreased mRNA levels – a characteristic of elevated miRNA levels, as well. In the same study, cells exposed to cadmium were also treated with a DNA demethylating agent, 5-aza-2′-deoxycytidine, time-dependently reversed the hypermethylation and silencing of hMSH2, ERCC1, XRCC1, and hOGG1 [61]. Rat liver cells were found to have reduced DNMT activity following only a week of exposure to cadmium [62]. In another study, the findings have been confirmed in human prostate epithelial cells and embryo lung fibroblasts [52]. Cadmium was also characterized as a hypomethylating agent when it was observed that increased DNMT expression occurred in HT-29 cells after 24-hour exposure to cadmium chloride solution [63]. A study examining the effects of cadmium exposure on histone modifications concluded that the exposure to cadmium alone did not cause increased histone modification. However, the combination of cadmium exposure and gamma radiation made the effects of radiation (increased histones) more pronounced [64]. Recently, cadmium was found to increase CpG demethylation in the promoter regions of oncogenic methyltransferases PRMT5 and EZH2, consequentially increasing their expression in vitro [65]. Indirect damage to mitochondria linked to cadmium exposure, resulting in epigenetic alterations has also been suggested [66]. Another study suggested the association of cadmium with the development of breast cancer through epigenetic regulation of Wnt and metabolic signaling pathways, with TXNRD1 and CCT3 identified as critical genes [67]. A summary of the studies examining cadmium effects on miRNA was published recently by Wallace et al. in 2020 [68].

An approach to assessing toxicant effects has centered on determining toxicant levels in disease-stricken compared to healthy neighboring tissue has been developed in the recent years. This new approach aims to consider direct, and systematic effects of toxicants. The goal is to account for cell damage due to toxicants delivered to the damaged site, but also damage on-site or originating from neighboring cells. The approach could ease the differentiation between systematic and on-site toxic effects. Studies of pancreatic and breast cancer that take cadmium tissue levels in cancerous and healthy neighboring tissue into account have been conducted recently [56,69].

3.3. *Nickel*

The main route of exposure to nickel is primarily through contaminated food and drinking water. Lesser exposure to nickel occurs through inhalation and transdermal absorption. Workers who manufacture nickel alloys, weld, grind, or cut materials containing nickel, as well as those who are involved in electroplating and electrowinning are at risk of occupational exposure to nickel, according to IARC, while inhalation may be a significant exposure route in this population. Metallic nickel is a group 2B human carcinogen according to IARC, while nickel compounds are classified as group 1 human carcinogens [18].

Nickel mimics gene expression patterns like hypoxia, a condition commonly found in tumors. Nickel also inhibits HIF-prolyl and -asparaginyl hydroxylases and promotes the stabilization of HIF-alpha proteins and HIF-1-dependent transcription. Nickel-induced, hypoxia-like state with normal oxygen levels could thus be a mechanism for promoting cancer development [70–73]. Nickel ions inhibit other dioxygenases, other than prolyl hydroxylase, by displacing iron ions from the active site. Nickel ions are bound to the same ligands as iron (two histidines and a carboxylate facial triad), except that iron is pentacoordinated, while nickel is hexacoordinated, which means that there is no space left for oxygen to bind [74–77]. Nickel is not highly toxic, with most cells tolerating nickel exposure up to 1 mM for 24 h with little toxicity [74]. Low lethality of nickel exposure has also been suggested by Wallace et al. [78]. Global and gene-specific hypermethylation is notably seen in nickel carcinogenesis. DNA methylation and gpt inactivation were first shown in Chinese hamster ovary cells - gpt is found near heterochromatin in G12 cells, while in G10 cells it can be dounf in the vicinity of euchromatin. After nickel exposure, gpt was silenced in G12 but not in G10 cells, suggesting that nickel induces heterochromatin spreading – heterochromatin condenses and pulls in the nearby genes, resulting in their silencing. A hypothesis exists that nickel can displace magnesium ions in heterochromatic complexes, triggering chromatin condensation [79]. When tumor suppressor genes are silenced, a window is opened for carcinogenesis (17,71,72). Histone hypoacetylation is also found in cells exposed to nickel, inducing alpha-helical conformation in histone H4 N-terminal tails in some studies, while others observed histone acetylation after long-term exposure to nickel [80–82]. Nickel affects miRNA regulation, as well – upregulated miRNAs were found in lung, stomach, colon, and ovary. Nickel-induced lung cancer differentially expressed miR-152, -222, and -223 which are all among the miRNAs associated with cancer. miRNA-222 is a significant regulator of p27, p57, and PTEN, all important tumor suppressor genes, which further strengthens

the hypothesis that nickel carcinogenicity may as well be miRNA-mediated to a certain extent [83–85].

3.3.1. Nickel intake

One study has shown that insoluble nickel compounds are 'trapped' inside cells and can remain there longer than soluble nickel compounds [86]. The proposed intake mechanism includes phagocytosis and dissolution in acidic vacuoles, with subsequent deposition of nickel (II) ions in the nucleus. Also, particles with negative surface charge are phagocytized more easily. Additionally, nickel (II) ions can enter cells through DMT1 transporter. Once in the vicinity of nucleus, nickel (II) ions bind to proline hydroxylase domain proteins, which degrade hypoxia-inducible factor-1 alpha through hydroxylation and Von-Hippel-Lindau E3 ubiquitin ligase complex binding. Nickel (II) ions inhibit enzymes by replacing iron as a catalyzing metal in the complex [87]. Interestingly, nickel particles were often observed in the vicinity of nuclear membrane but never inside the nucleus [88].

The same mechanism is proposed to describe the inhibition of H3K9 demethylases. Members of this family of enzymes are markers of DNA methylation and long-term gene silencing. Other enzymes, such as JHDM2A/JMJD1A, were also inhibited when nickel ions replaced ferrous iron ions in the enzymes' catalytic centers [89,90]. Nickel-mediated enzyme inhibition resulted in decreased expression of CD3EAP, a DNA-dependent RNA polymerase, and ILI2B, a cytokine related to immune response, with an accumulation of H3K9me2 silencing mark. On the other hand, the accumulation of H3K4me3 in NRDG1 and CA9, hypoxia-inducible genes with a role in nickel carcinogenesis, cell migration, and invasion, was associated with the increased gene expression [91–95].

3.3.2. Epigenetic mechanisms in nickel carcinogenesis

Low mutagenicity, well-documented in prokaryotic tests, may suggest that nickel contributes to carcinogenesis in mammalian cells through epigenetic mechanisms rather than mutations [50]. Knowing that nickel exposure is associated with gene silencing, a question arises regarding the mechanisms causing silencing and whether heterochromatization has a role in it. Sun et al. [21] have summarized experiments examining heterochromatization following nickel exposure which has resulted in two conclusions: (1) the vicinity of the gpt gene to heterochromatin was associated with the silencing induced by nickel and sensitization of cells to nickel-induced gene silencing, and (2) nickel could induce of chromatin condensation near heterochromatic regions and inactivation of nearby genes, such as gpt or tumor suppressor genes, leading to the development of cancer. Sun et al. also described the major epigenetic mechanisms of nickel-induced carcinogenesis described until 2013 [21].

One of the major epigenetic mechanisms is the induction of local DNA methylation. It was observed in vivo in p53 heterozygous mice implanted with nickel sulfide that developed malignant fibrous histiocytomas along with the hypermethylation of the promoter of tumor suppressor p16 gene. The same effect was observed with the promoters of RARβ2, RASSF1A, and p16 in Wistar rats injected with nickel subsulfide that acquired muscle tumors [96,97].

Another epigenetic mechanism concerns histone modifications – most prominently acetylation, associated with gene activation, and methylation, associated with gene inactivation. In vitro, nickel inhibited both HAT and histone acetylation. Interestingly, the addition of antioxidants diminished these acetylation effects, while hydrogen peroxide augmented acetylation [98,99]. Additionally, nickel can bind H4 tails to form a structure like acetylated lysine – possibly preventing further acetylation [100]. Methylated promoters associated with gene repression were found in nickel-exposed cells [101]. Nickel inhibited demethylases containing JmjC-domain, an iron-binding motif with a higher affinity for nickel (II) than iron. A downstream target JMJD1A, a H3K9me2 demethylase, was silenced because of long-term nickel exposure, favoring anchorage-independent growth [67,81,92].

Another mechanism involved in nickel-induced malignant transformation was observed - miRNAs, e.g., upregulated miR-222 that was associated with rhabdomyosarcoma in rats. There are numerous miRNAs that target several tumor suppressor genes, including p27, p57, and PTEN, each associated with numerous cancers in humans. Both p27 and p57 are considered negative cell cycle regulators. Therefore, repressed p27 and p57 would favor intensive cell growth in tumors and transformed cells [102]. Eight different miRNAs levels were found to be partially regulated by nickel in cultured BEAS-2B cells, most prominently miR-4417. The effects of miR-4417 levels were then assessed in BEAS-2B and A549 cells, resulting in evidence supporting the hypothesis that miR-4417 specifically mediates nickel-induced fibronectin expression without affecting E-cadherin expression. Downregulated TAB2 and upregulated fibronectin were among 37 genes potentially targeted by miR-4417 in cells exposed to nickel [103]. Epigenetic mechanisms could also overlap and intertwine – DNA methylation in certain promoter regions could downregulate miR-152, a tumor suppressor miRNA targeting DNMT1, thus further affecting DNA methylation, as observed in cells treated with nickel sulfide. As DNMT1 levels increased, DNA methylation would increase further in miR-152 promoter, completing the cycle, but would also increase in MeCP2 as well [84]. Thus, epigenetic mechanisms could collectively affect increased cell proliferation and favor carcinogenesis.

3.3.3. Additional considerations

Jose et al. [104] identified three types of differentially expressed genes in nickel-exposed cells: (1) transiently upregulated and transiently downregulated genes, whose expression returned to normal once the cells were no longer exposed to nickel, (2) genes whose expression remained unaltered during exposure to nickel, but altered only after the exposure ended, and (3) genes that were differentially expressed during exposure to nickel and retained the increased or decreased expression after the exposure ended. H3K4me3 histone modification, associated with the activation of transcription, was found across the entire genome, coinciding with gene expression occurring after the exposure. Interestingly, most of the genes whose upregulation was permanent displayed an increase in expression only after nickel exposure, but not during the exposure itself. When genes were permanently upregulated during nickel exposure, no difference in H3K4me3 levels was observed between the exposed, washed out, and untreated cells, however, when the upregulation occurred following nickel exposure, a significant increase in H3K4me3 levels was observed in washed out cells compared to the other two. In most cases, gene expression was altered after exposure to nickel. Permanently downregulated genes displayed similar trends: (1) gene expression was mostly downregulated following exposure to nickel (2) when downregulation occurred during the exposure, cells displayed similar H3K4me3 levels, and (3) washed out cells displayed significantly lower H3K4me3 levels when downregulation occurred after the exposure [104].

The same group of authors made another note – a persistent increase in gene expression during the exposure was associated with the loss of H3K27me3, a modification associated with gene repression. Permanent downregulation, however, was not associated with an increase in H3K27me3. The study results highlight an important issue in epigenetic toxicology studies – it is important to assess the effects occurring after the exposure instead of focusing solely on those that occur during the exposure. Also, if a trend is observed, an analogous but opposite trend may not occur when the conditions change in the opposite direction [104].

3.4. Chromium

IARC has recognized metallic chromium and chromium (III) compounds as group 3 human carcinogens, certain chromium alloys have been classified as group 2B, while chromium (VI) compounds have been classified as group 1 human carcinogens. Hexavalent chromium is a

strong mutagen, unlike arsenic, cadmium, or nickel. Also, unlike nickel, hexavalent chromium is highly cytotoxic, a trait that is still actively researched [105]. DNA damage was considered the primary mechanism of chromium genotoxic and carcinogenic effects; however, dichromate ions have also been found to induce DNA methylation and gene silencing, suggesting that epigenetic mechanisms may be involved, as well. Additionally, exposure to chromate ions was found to increase H3K9 dimethylation in the promoter region of MLH1, a gene involved mismatch repair [57].

Chromium can be easily dispersed in bodies of water; additionally, inhalation is considered another main route of exposure for the general population [18]. Although chromium itself is considered non-mutagenic and nonreactive in respect to biomolecules, the detoxication process it undergoes produces compounds that may lead to DNA lesions, tumor development, and cytotoxicity. Chromium is often reduced from chromium (VI) to chromium (III) outside the cell, rendering it less capable of entering cells, and supporting the hypothesis that its toxic effects do not originate directly from chromium ions. Chromate ions, being similar to sulfate and phosphate ions, can easily pass through cell membrane, through anion transporters. Most of cell damage induced by chromium comes from the generated ROS. Exposure to chromium is associated with changes in histone marks, as well. Chromium was further suggested to be part of a positive feedback loop along with several molecules, resulting in MLH1 differential expression: chromium induced the expression of histone methyltransferase G9a, thus increasing post-translational methylation of H3K9. H3K9Me2 was detected in A549 cells exposed to chromium (VI), which resulted in heterochromatic DNA state and decreased MLH1 expression, limiting DNA repair capacity of the cell [106]. In another study, it was observed that chromium induced global changes in histone modifications – an increase in H3K9 dimethylation in MLH1 gene promoter coincided with decreased mRNA expression, supporting the positive feedback loop hypothesis [107].

3.4.1. *Epigenetic mechanisms in chromium carcinogenesis*

Since 2002 when it was reported that chromium (VI) induces DNA methylation and silences gpt transgene in G12 Chinese hamster lung cells [108], studies have observed various chromium-related epigenetic effects. Epigenetic changes following chromium (VI) exposure include global DNA hypomethylation as well as promoter-specific DNA methylation – a phenomenon to genomic instability and gene silencing in numerous cancer types and human diseases [106]. It was found that CpG sites on p16 gene were significantly more methylated than controls and that p16 mRNA expression negatively correlated with the amount of chromium exposure in human bronchial epithelial cells (16HBE), following chromium (VI) exposure [109]. Similarly, in lung tumor samples obtained from workers exposed to chromate in Japan, methylation of two DNA repair genes, hMLH1 (28%) and MGMT (20%), and tumor suppressor gene APC (86%), were detected using nested methylation-specific PCR [110]. In lung cancer not associated with chromate exposure, hMLH1 methylation was not detected, while APC methylation was detected in 44% of the samples.

It was also reported that exposure to acute high doses of chromium (VI) in vitro induced histone modifications, including an increase in global histone 3 lysine 9 (H3K9) and histone 3 lysine 4 (H3K4) di- and trimethylation, and decreased global histone 3 lysine 27 (H3K27) trimethylation and histone 3 arginine 2 (H3R2) demethylation [106]. Chromium (VI) was also shown to inhibit JHDM2A, an H3K9 demethylase, by reducing the availability of ascorbic acid [111]. After the intracellular reduction of chromium (III), ascorbic acid reserve needed for JHDM2A demethylase activity was particularly depleted, which subsequently contributed to elevated H3K9me2 levels. Chromium (VI) is not only suggested to interfere with histone methyltransferase and demethylase activity but is also suggested to participate in HDAC1-DNMT1 crosslink to the Cyp1A1 promoter. Total HDAC1 activity after chromium (VI) was shown to be unaffected by chromium (VI), yet local deacetylase activity was sufficient to impact histone acetylation levels in Cyp1A1 [112]. In addition to HDAC1, both HDAC2 and HDAC3 expression in 16HBE cells was increased following 24-hour exposure to chromium (VI). Correspondingly, global H3 and H4 acetylation decreased [113]. Similarly, global and gene-specific alterations in histone acetylation were observed after 24-hour exposure to chromium (VI) in the case of 16HBE cells. Specifically, biotinidase expression was downregulated [114].

Compared to DNA methylation and histone posttranslational modifications, there is insufficient information about chromium (VI) effects on microRNAs. In human lung cancer cells, miR-143 was downregulated in chromium (VI)-transformed cells [115]. Repression of miR-143 could induce cell transformation and angiogenesis via insulin-like growth factor-1 receptor (IGF-IR) and insulin receptor substrate-1 (IRS1) upregulation. IGF-IR/IRS1 was found to upregulate interleukin-8 (IL-8) and activate downstream ERK/HIF-1a/NF-kB signaling pathway, inducing cell transformation and tumor angiogenesis. Concurrent downregulation of miRNA gene targets, mus309 and mus312, acon, and pyd, involved in DNA repair, oxidation-reduction processes, and stress-activated MAPK cascade, respectively, were also reported. A significant dose-dependent increase in miR-21 and dose-dependent decrease in mRNA and protein expression of its target tumor suppressor gene, PDCD4, was also observed [116]. Oncogenic c-MYC and uPAR, targets of b-catenin/TCF4-dependent transcription, were increased in a dose-dependent manner, and chromatin immunoprecipitation analysis showed their association with both uPAR and c-MYC promoters. uPAR expression has been shown to enhance tumor growth and metastasis, and has been associated with cancer stem cell-like properties in small cell lung cancer [117].

4. Possible treatment options

Epigenome-targeted therapy is a promising strategy for the treatment of cancer. However, two factors ought to be considered: (1) the complexity of cancer and (2) the influence of epigenetic alterations on cancer development, such as the expression of oncogenes, tumor suppressor genes, and signal transduction resulting in enhanced cancer growth, invasion, and metastasis. Some cancers depend on specific epigenetic alterations and can be sensitive to this regulation. Therefore, the first step would be to determine the most specific epigenetic alterations to particular types of cancer. Thus far, epigenetic therapy has obtained impressive results in hematological malignancies but not in solid tumors, possibly because of different cell properties of hematological cancers and solid tumor cancers.

Certain small-molecule drugs can reverse a distinctive cellular phenotype, a characteristic making them prospective anticancer drug candidates. HDAC, HAT, and DNMT inhibitors are such drugs that could theoretically normalize epigenetic processes within a cell. TSA, an HDAC inhibitor, attenuates gene silencing in yeast and mammalian cells – it can reactivate silenced genes, e.g., gpt [8,21]. Another group of such small molecule drugs are deoxycytidine analogs, which prevent the release of DNMTs. Henikoff and Greally (2016) made an important note regarding these drugs interfering in epigenetic processes – HDACs, HATs, and DNMTs have a significant number of substrates apart from histones. Possible side effects to consider are: (1) a significant increase in acetyl group retention caused by HDAC inhibitors, which would lead to lower intracellular pH, (2) inhibitors preventing proteins from binding to acetylated histone lysine that also inhibit the binding of transcription factors, e.g., p53, suggesting alternative modes of action, and (3) drugs already in use, such as doxorubicin and anthracyclines, that cause major nucleosome eviction, an effect not directly related to their mode of action.

Since epigenetic alterations can affect the sensitivity of small molecule targeted therapy, chemotherapy, or radiotherapy, epigenome-targeted treatment seems to be an essential possible adjunctive therapy option to consider for development. The combination of epigenome-targeted therapy and immunotherapy has also been considered and

investigated [118–121]. To date, optimized treatment options, including combination therapies, are still undiscovered. The effects of these drugs should be carefully considered, as these epigenetic drugs have the potential not only to return cancer cells' phenotype to their original healthy state but also to damage chromatin in any rapidly dividing cell. The patients' overall well-being comes first, and the risk-benefit ratio must be carefully assessed when considering the safety of epigenome-targeted therapy [8].

4.1. Recent miRNA application in cancers

Many clinical trials in the field of miRNA-based therapeutics have been initiated to positively impact patients' outcomes, such as MiRNA Therapeutics (NASDAQ: MIRN) and a miRNA mimic, MRX34. MiR-34 is a well-characterized tumor suppressor downregulated in many cancers [122]. MRX34 was delivered as a double-stranded RNA encapsulated into a liposome-formulated nanoparticle. Preclinical studies were promising when used in several cancer types, such as renal cell carcinoma, acral melanoma, and hepatocellular carcinoma [123]. However, the FDA halted their phase 1 clinical trial when many immune-related serious adverse events, some leading to death, were registered. MiRagen Therapeutics is actively developing MRG-106, also known as Cobomarsen, an LNA antagomiR that targets miR-155. This miRNA is involved in the differentiation and proliferation of blood and lymphoid cells. Cobormarsen has been involved in phase 1 (Identifier NCT02580552) and phase 2 clinical trials (Identifier NCT03713320), to treat certain types of lymphoma and leukemia [124].

5. Conclusion

Epigenetic mechanisms play an essential role in metal-induced carcinogenesis. Therefore, it is no surprise that various epigenetic pathways are being researched more frequently regarding metal-induced carcinogenesis. Undoubtedly, remarkable progress has been made in understanding epigenetic mechanisms and how they contribute to carcinogenesis. However, further large-scale epigenetic profiling, interdisciplinary collaboration together with the carefully developed public communication regarding epigentic risk is essential. Today, with the growing awareness of the toxic metals – arsenic, cadmium, chromium, nickel, and more – it is important that the understanding of the development and progression of cancer is broadened as much as possible. Further research in this field warrants a strong foundation for future improvements in cancer prevention, and epigenome-targeted therapy.

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Declaration of competing interest

The authors declare no conflict of interest.

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