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Epigenetics in metal carcinogenesis: Nickel, Arsenic, Chromium and Cadmium

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Summary

Although carcinogenic metals have been known to disrupt a wide range of cellular processes the precise mechanism by which these exert their carcinogenic effects is not known. Over the last decade or two, studies in the field of metal carcinogenesis suggest that epigenetic mechanisms may play a role in metal-induced carcinogenesis. In this review we summarize the evidence demonstrating that exposure to carcinogenic metals such as nickel, arsenic, chromium, and cadmium can perturb DNA methylation levels as well as global and gene specific histone tail posttranslational modification marks. We also wish to emphasize the importance in understanding that gene expression can be regulated by both genetic and epigenetic mechanisms and both these must be considered when studying the mechanism underlying the toxicity and cell-transforming ability of carcinogenic metals and other toxicants, and aberrant changes in gene expression that occur during disease states such as cancer.

Introduction

Over the last decade we have learned that gene expression is not determined solely by DNA base sequence, but also depends upon dynamic chromatin states. Today, it is strongly believed by many who study the mechanisms of transcriptional regulation that just as the field of genetics has become an integral part of modern medicine, the new field of epigenetics will also have an enormous impact on medicine. The rapidly evolving field of epigenetics focuses on the study of heritable alterations in gene expression that occur in the absence of changes in genome sequences. The two main categories of epigenetic mechanisms known to affect mammalian gene expression at the chromatin level are DNA methylation and histone posttranslational modifications. Future research efforts in both fields, genetics and epigenetics, promise to provide insights in the understanding of the mechanisms by which gene expression is transcriptionally regulated.

In DNA, methylation is the most common and best understood epigenetic modification. DNA methylation is a naturally occurring modification that involves the addition of a methyl group to the 5′ position of the cytosine ring in the context of CpG dinucleotides to form 5-methylcytosine (5-MeC).[1] In general, methylation in the promoter region of a gene leads to its transcriptional repression.2 The predominant role of DNA methylation appears to be involved over aspects of development, tissue-specific gene expression, expression of imprinted genes, and silencing of transposable elements.3 In histones, epigenetic information is stored by posttranslational modifications at well-conserved amino acid residues of its N- and C-terminal tails. Histone posttranslational modifications include lysine acetylation, arginine and lysine methylation, serine phosphorylation, lysine ubiquitylation, among others. Acetylation of

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histone lysines is generally associated with transcriptional activation but the functional consequences of methylation of lysine and arginine residues depend on the residue and specific site of the residue within the histone tail.4–7 For example, methylation of histone H3 at lysine 4 is closely linked to transcriptional activation, whereas methylation at histone H3 at lysine 9 or lysine 27, and histone H4 at lysine 20 is associated with transcriptional repression.5–7 An emerging model, the "histone code" hypothesis, proposes that specific histone modifications on the same or different tails can act sequentially or in combination to confer the overall expression status of a region of chromatin.8 For instance, methylated promoter regions are often coupled with regional histone deacetylation, suggesting that these two mechanisms may act in concert to accomplish transcriptional silencing.[9] The enzymes involved in "writing" and "erasing" the reversible marks on DNA and histone tails include DNA methyltransferases (DNMT), the methyl binding domain protein MECP2, histone acetylases, histone deacetylases (HDAC), histone methyltransferases and demethylases, and histone ubiquitinating enzymes and deubiquitinating enzymes.[10]

Due to the emerging extensive role that epigenetics has been shown to play in controlling gene expression, there is an increasing interest in its potential role in various human diseases including cancer, neurological disorders and diabetes.[11–12] Indeed, perturbations in patterns of DNA methylation and histone modifications have been linked to congenital disorders and pediatric symptoms or predispose people to acquired disease states such as sporadic cancers, neurodegenerative and neuropsychiatric disorders, atherosclerosis, and immunity disorders. [13] Today, cancer is the disorder most commonly associated with aberrant DNA methylation. [14] DNA methylation patterns in tumor tissues characteristically exhibit a decrease in global methylation levels accompanied by some increased methylation in selected regions.[14] A common finding in cancers is increased methylation in promoter regions of tumor suppressor genes, associated with its transcriptional silencing, whereas activation of oncogenes is brought about by DNA hypomethylation.[15–18] So far, little is known about the patterns of histone modifications disrupted in human tumors. Promoter hypermethylation in cancer cells is known to be associated with: deacetylation of histones H3 and H4, loss of histone H3 lysine 4 trimethylation, and gain of H3K9 methylation and H3K27 trimethylation.[19–21] Global loss of monoacetylation and trimethylation of histone H4 has also been implicated as a common hallmark of human tumor cells.[22–23] Today, few epigenetic therapies, such as DNA demethylating agents and histone deacetylase inhibitors, are used and several are currently being studied in clinical trials.[13]

Epidemiological, cell culture, and animal experimental studies have shown an increased cancer incidence associated with chronic exposure to certain metals such as nickel, chromate, arsenite, and cadmium.24–27 Sources of potential exposure to carcinogenic metals include occupational exposure, the massive growth of manufacturing activities in industrialized countries, large consumption of nonferrous metals, and creation of large toxic Superfund sites in the U.S. due to the high volume utilization and poor practices in the disposal of metal-containing waste products.[28] Although it is known that carcinogenic metals can disrupt a wide range of cellular processes, such as, signaling pathways, induce DNA damage via both oxidative and nonoxidative mechanisms, and induce a variety of toxic effects; the mechanism(s) for their cell transforming ability is still poorly understood. Because carcinogenic metals are typically weak mutagens, with the exception of chromium that does form DNA adducts, recent developments in the field of metal carcinogenesis suggest that epigenetic mechanisms may play a role in activating or silencing the expression of genes critical for driving the metal-induced carcinogenicity.

Here, we review the evidence that suggest that epigenetic mechanisms play a role in the toxic and carcinogenic effects exerted by nickel, arsenic, chromium and cadmium metals. We also wish to highlight the importance in understanding that mutagenesis is not the sole mechanism

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underlying heritable alterations. Instead, it is appropriate to consider both genetics and epigenetics when studying the mechanisms that regulate gene expression.

Nickel

Nickel is a nonessential metal of great environmental concern because it is widely used in the production of coins, jewelry, stainless steel, batteries, medical devices, carbon particles as well as in Ni refinery, plating and welding.[28] Although, epidemiological, animal, and cell culture studies have found nickel compounds to be carcinogenic, the mechanism(s) of nickel carcinogenesis require additional research.[29–32] Since the mutagenic activity of nickel compounds in mutation assays from *Salmonella* to mammalian cells *in vitro* has been low it has been suggested that nickel-induced mutagenic activity is not the underlying mechanism in nickel induced carcinogenesis.[33–36] Instead, numerous studies have implicated structural alterations in chromatin and epigenetic changes as the primary events in nickel carcinogenesis.

First, phagocytized nickel sulphide particles were shown to selectively target heterochromatin.[37] These effects of nickel compounds on heterochromatin led to the discovery that nickel compounds could silence genes by inducing DNA methylation. Changes in DNA methylation leading to the inactivation of gene expression following exposure to nickel compounds were initially found using the Chinese hamster G12 cell line which possess a copy of the bacterial *gpt* transgene near the telomere of chromosome 1.[38] Changes in DNA methylation have also been observed *in vivo* in nickel-induced tumors of wild type C57BL/6 mice and mice heterozygous for the tumor suppressor p53 gene injected with nickel sulfide. The promoter of the tumor suppressor gene p16 was found hypermethylated in all tumors of these mice.[39] Although the mechanisms by which nickel induces DNA hypermethylation is presently unknown, a proposed model includes the ability of nickel to substitute for magnesium in the phosphate backbone of DNA; Ni^{2+} may be better at condensing heterochromatin than Mg^{2+} ions, increasing chromatin condensation and triggering *de novo* DNA methylation of critical tumor suppressor or senescence genes that can become incorporated into heterochromatin because of their proximity to this type of chromatin.[38] The reason that nickel ions target heterochromatin is not known but may be because of the higher concentration of Mg^{2+} present in the phosphate backbone of DNA in heterochromatin than euchromatin. An additional possibility included the fact that heterochromatin forms the inside lining of the interface nucleus and with this location it encounters toxins entering the nucleus before they reach euchromatin.[40–42]

In addition to gene silencing by DNA methylation, other nickel-induced epigenetic changes include the loss of histone acetylation in H2A, H2B, H3, and H4, increases in H3K9 dimethylation, and increases in the ubiquitylation of H2A and H2B at a global level.[43–50, 38] A decrease in histone acetylation and H3K4 methylation and increase in H3K9 dimethylation and DNA methylation was also observed in the promoter of the *gpt* transgene in the G12 cells that is silenced by nickel.46, 38, 51 Furthermore, pretreatment of mouse PW cells and human cells with the histone deacetylase inhibitor trichostatin A (TSA) significantly inhibited the ability of nickel to induce cell transformation suggesting that gene silencing mediated by histone modification may play a role in nickel-induced cell transformation.52 It has been reported that the mechanism by which Ni exposure decreases histone acetylation is by inhibition of histone acetyltransferase activity, but has no effect on histone deacetylase activity.53 A role for chromatin damage in nickel-induced carcinogenesis has also been hypothesized.101 Supporting this hypothesis, the ability of Ni (II) to bind to specific motifs on histone H3 and H2A could potentially disrupt the structure and function of the nucleosome.96–101 Ni (II) binding to H3 and H2A may cause several lesions including oxidative DNA damages via Fenton-like mechanisms and disrupt gene expression resulting in carcinogenicity.101

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In support of an epigenetic mechanism for nickel carcinogenesis, it has been recently reported that nickel ions inhibit a novel class of histone H3K9 demethylases that depend upon iron and -2-oxoglutarate for their enzymatic activity and as a result cause a significant increase in global H3K9 dimethylation.46 The JmjC domain of these dioxygenases contains the catalytic activity of the enzyme, which includes the His/His/carboxylic facial triad that binds iron and is a characteristic of all dioxygenases.[54] It is estimated that the affinity constant of Ni (II) binding to this iron-binding motif is at least three orders of magnitude greater than that of iron.[55] Based on this estimation, it can be predicted that nickel ions will effectively compete with iron ions for binding to this motif, and that iron ions will not be able to replace nickel ions once nickel ions bind to this motif.56 Nickel ion inhibition of the activity of H3K9 demethylases will prevent demethylation of H3K9, resulting in global increase in H3K9 dimethylation.46 Because there is supporting evidence that H3K9 methylation is important for DNA methylation and long-term gene silencing the observed increase in DNA methylation after nickel exposure is likely to be a result of nickel-induced effect on H3K9 methylation.46, [57] The enzymatic activity of other members of this iron-and 2-oxoglutarate-dependent dioxygenase family, including HIF-prolyl hydroxylase PHD2 and DNA repair enzyme ABH3, has also been shown to be sensitive to nickel ion inhibition.[56]

Taken together, numerous data suggest that epigenetic changes contribute more to nickel-induced toxic and carcinogenic effects than mutagenic effects.

Arsenic

Arsenic is an environmental contaminant, which can be found in the soil, water, and airborne particles. Epidemiological studies have shown that chronic, low dose exposure to arsenic is associated with skin, bladder, lung, kidney and liver cancer.[58] Exposure to Arsenic (As) occurs generally in the form of either arsenite [As (III)] or arsenate [As (VI)]. The increased cancer risk is attributed to arsenite rather than the less toxic arsenate. Although proposed mechanisms for the carcinogenicity of arsenic include oxidative stress, inhibition of DNA repair, perturbation of signal transduction pathways, and chromosomal aberrations, the mechanism for the carcinogenicity of arsenite remains unclear.[59–61]

Due to the observed widespread disruption in global gene expression in spite of its low mutagenic activity, a large body of evidence has accumulated suggesting that arsenite-induced carcinogenesis may be mediated by epigenetic mechanisms.[62] Indeed; various studies have reported that arsenite exposure induces both DNA hypo and hypermethylation. Low dose chronic As treatment of a rat liver epithelial cell line resulted in a reduction of *S*-adenosyl-methionine levels, an increase in global DNA hypomethylation levels and decreased DNA methyltransferase activity.[63] Consistently, As was also shown to deplete *S*-adenosyl-methionine in human HaCat keratinocytes, repress the expression of the DNA methyltransferase genes DNMT1 and DNMT3 and induce global DNA hypomethylation.[64] The metabolism of As requires the methyl donor *S*-adenosyl-methionine and converts arsenite into mono- and dimethylated metabolites.[65] Both hypo and hypermethylation of different genes was found in human kidney cells treated with arsenite *in vitro*.[66] Arsenic was also associated with hypermethylation of the promoter of the tumor suppressor genes, *RASSF1A* and *RPSS3* in a population-based study of bladder cancer.[67] Consistent with the Marsit et al. study, higher rates of methylation in CpG islands within the tumor suppressor genes *p16(INK4a)* and *RASSF1A* with decreased expression of both these genes was observed in As-exposed A/J mice.[68] Hypermethylation and lower protein expression of *death-associated protein kinase (DAPK)* was also detected in As-treated SV40-immortalized human uroepithelial cells.[69] The promoter region of the p53 tumor suppressor gene was also found hypermethylated as a result of arsenic exposure in a tissue culture model system and in arsenic-induced skin cancer patients.[70–71] Clearly, the results of various studies demonstrate that As can disrupt DNA methylation

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and suggest that As-induced disruption of DNA methylation may be important in carcinogenesis. The As-induced global levels of DNA hypomethylation and promoter specific hypermethylation of tumor suppressor genes is consistent with the fact that cancer cells often exhibit promoter hypermethylation simultaneously with wide spread loss of methylation.[72]

In addition to DNA methylation, recently it was reported that arsenite alters global histone methylation levels in human lung carcinoma A549 cells.[62] It was found that arsenite increased both dimethylated H3K9 and H3K4 trimethylation levels and decreased the repressive mark trimethylated H3K27. The increase in dimethylated H3K9 was attributed to an increase in the histone methyltransferase G9a mRNA and protein levels.[62] The observed effects on arsenite-induced global and gene specific changes in DNA methylation and alteration in global histone methylation levels strongly suggest that epigenetic mechanisms contribute to arsenite-induced aberrant gene expression.

Chromium

Hexavalent chromium [Cr (VI)] is widely used in many industries such as chromate manufacturing, chrome plating, ferrochrome production, and stainless steel welding. Environmental exposure likely impacts millions of people drinking Cr-contaminated water who reside in the vicinity of numerous toxic sites or use Cr containing products. Recent epidemiological risk-assessment studies revealed a high incidence of lung cancer following occupational exposure to Cr (VI).73 However, the precise mechanism(s) of Cr (VI) carcinogenicity is not well understood. It has been suggested that Cr (VI) mediates a majority of its cytotoxic and genotoxic effects by inducing oxidative stress, forming stable-Cr-DNA adducts, protein-DNA crosslinks, and DNA single and double-strand breaks.74–75 Cr (VI) induced DNA-damage can affect DNA replication, transcription, and translation resulting in altered gene expression.76

Until recently, changes in gene expression mediated by DNA damage were considered the key mechanism underlying the genotoxic and carcinogenic activities of Cr (VI). However, several studies have highlighted the potential epigenetic effects of Cr (VI) and how these may contribute to its toxicity and carcinogenicity. First, potassium dichromate was able to induce DNA methylation and silence the transgene expression of a cell line expressing a bacterial *gpt* reporter gene.[77] Furthermore, potassium dichromate was shown to induce an increase in genome-wide cytosine-hypermethylation in the CCGG-DNA sequence in the *Brassica napus L*. plants.[78] DNA methylation was also found increased in the promoter region of the tumor suppressor gene p16 and the DNA mismatch repair (hMLH1) gene in chromate induced human lung cancers.[79–80] In addition, chromium was found to cross link the histone deacetylase 1-DNA methyltransferase 1 complexes to the chromatin of the *Cyp1a1* promoter and inhibit histone marks induced by AHR-mediated gene transactivation, including phosphorylation of histone H3 Ser-10, trimethylation of H3 Lys-4, and various acetylation marks in histones H3 and H4.81 Most recently, it was observed that exposure of human lung carcinoma A549 cells to potassium chromate was able to induce global changes in various histone tail modifications. 82 Interestingly, chromate exposure induced an increase in H3K9 dimethylation in the promoter of the MLH1 gene promoter with a decrease in its mRNA expression.[82] Therefore, various studies suggest that, other than genotoxic effects, epigenetic modifications may contribute to the carcinogenicity of Cr (VI) compounds.

Cadmium

Cadmium (Cd) is a toxic nonessential transition metal classified as a human carcinogen by the National Toxicology Program.[27] Sources of human exposure to cadmium include employment in metal industries, production of certain batteries, some electroplating processes and consumption of tobacco products.27, 83 Cadmium poses a great health risk to humans because

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the body has limited capacity to respond to cadmium exposure, as the metal cannot undergo metabolic degradation to less toxic species and is poorly excreted.84 Multiple studies have linked occupational exposure to cadmium with pulmonary cancer, as well as prostate, renal, liver, hematopoietic system, urinary bladder, pancreatic, and stomach cancers.[85–89, 27] However, the potential mechanism(s) of cadmium carcinogenesis is unknown. Although cadmium does not form adducts with DNA it can still produce some oxidative stress that could indirectly attack DNA but does not do this by participation in Fenton type chemical reactions.[90–92] Suggested mechanisms for Cd-carcinogenesis include include aberrant gene activation and signal transduction, suppressed apoptosis and disruption of E-cadherin-mediated-cell-cell adhesion, and/or altered DNA repair.84

Since cadmium is poorly mutagenic it may well act as an epigenetic or indirect genotoxic carcinogen.[27, 88] Three independent studies have reported cadmium-induced changes in global and gene specific DNA methylation levels. First, acute exposure (1 week) of TRL 1215 rat liver cells to cadmium inhibited DNA methyltransferase activity and induced global DNA hypomethylation while prolongued exposure (10 week) resulted in DNA hypermethylation and enhanced DNA methyltransferase activity.[93] Another group confirmed these results and showed that a 10-week exposure to cadmium, induced malignant transformation associated with DNA hypermethylation at the global level, overexpression of DNMT3b DNA methyltransferase and increased DNMT activity, promoter hypermethylation and reduced expression of the *RASSF1A* and *p16* tumor suppressor genes.[94] However, another group reported that Cd induced global DNA hypomethylation and suggested this to be the potential facilitator of Cd-stimulated cell proliferation in the chronic myelogenous leukemia K562 cell line.[95] The relation between the alteration of DNA methyltransferase activity and cell proliferation induced by Cd remain to be studied.[95] To the best of our knowledge, no studies have reported an effect of cadmium on histone tail posttranslational modifications. Based on the promoter specific effects on DNA methylation and histone methylation status observed with both nickel and chromium treatment it is likely that cadmium regulates the expression of genes important for carcinogenesis by “writing” and “erasing” epigenetic marks on the promoters of these genes.[82, 46, 38, 53] However, studies that investigate whether cadmium can alter histone tail posttranslational modifications at a global level or induce changes in gene expression by modification of histone tails at gene specific promoters are necessary.

The evidence described above demonstrates that exposure to carcinogenic metals can perturb DNA methylation levels as well as global and gene specific histone posttranslational modification marks and highlights the importance of considering epigenetics as a possible mechanism underlying the toxicity and cell-transforming ability of carcinogenic metals. As is the case with any toxicant, we wish to emphasize that we are not suggesting that an epigenetic mechanism is the “one and only” force driving the toxic and carcinogenic effects of the metals discussed above. Instead, we want to demonstrate the importance for applying to the study of metal carcinogenesis, and potentially other toxicological research, the understanding that mutagenesis is not the sole mechanism underlying changes in gene expression leading to carcinogenicity. Instead, it is appropriate to consider that heritable alterations in phenotype may have an epigenetic basis as well. It’s possible that in the near future well characterized epigenetic modifications may promise to aid in the molecular diagnosis of a variety of cancers and other disorders.

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