Review Article

EPIGENETIC MECHANISMS OF METAL CARCINOGENICITY: EXPLORING ASSOCIATED THERAPEUTIC OPTIONS FOR INDIVIDUALISED TREATMENTS

Abstract

While naturally occurring, heavy metals pose a significant global public health risk due to their extensive utilisation in industrial, residential, and agricultural activities, impacting the health of millions worldwide. Occupational and environmental exposure to these metals through contaminated sources such as food, water, and air can lead to toxic effects on organs, including the development of cancer. Arsenic, chromium, nickel, and cadmium, among others, have been classified by the International Agency for Research on Cancer (IARC) as Group 1 carcinogens, indicating a strong association with various types of cancer. Cancer, characterised by abnormal and uncontrolled cell proliferation, ranks as the second leading cause of death globally, with an estimated 9.6 million deaths attributed to it. Numerous mechanisms contribute to heavy metal-induced carcinogenesis, including oxidative stress, DNA damage, and aberrant signalling transduction pathways. Recent advancements in understanding epigenetics have unveiled the role of epigenetic alterations in cancer development. Epigenetic alterations are functionally relevant modifications which affect gene expression but do not change the DNA sequence. Three primary epigenetic mechanisms—histone modification, non-coding RNA (ncRNA)-associated gene silencing, and DNA methylation occur, which play pivotal roles in regulating gene expression and cell differentiation. Alterations in these epigenetic patterns contribute to metal-induced carcinogenicity by rendering tumour suppressor genes inactive while activating anti-apoptotic and pro-proliferative genes. Understanding the underlying epigenetic mechanisms of heavy metals holds promise for guiding future research and developing targeted therapeutic interventions. Various inhibitors, including DNA methylation inhibitors (DNMTIs), histone modification inhibitors (HMIs), histone deacetylase inhibitors (HDACIs), histone methyltransferase inhibitors, and non-coding RNA-targeted therapies, offer avenues for interfering with these mechanisms, thereby positively impacting the treatment of metal-induced cancers, mainly through individualised treatment approaches.

Keywords: Epigenetics, heavy metals, carcinogenesis, histone modifications, DNMTIs, miRNAs.

1. INTRODUCTION

The pervasive presence of heavy metals in the Earth's crust poses a global public health risk, with occupational and environmental exposure acknowledged as significant concerns [1]. Contaminated food, water, and air remain primary sources of exposure, impacting millions worldwide [2]. Industrial activities, mining operations, and residential/agricultural practices contribute to environmental contamination, exposing individuals to occupational hazards [3]. Due to their high toxicity, arsenic, cadmium, chromium, lead, and mercury are priority metals linked to various organ damage, even at low exposure levels [1][4].

Heavy metal exposure has been associated with a spectrum of toxic effects, including respiratory, gastrointestinal, renal, and hepatic issues and cancer [4][5]. Notably, arsenic, hexavalent chromium, nickel, and cadmium are classified as Group one (1) carcinogens by the International Agency for Research on Cancer (IARC) [6] with documented links to increased cancer risk [4][7].

Cancer, the second leading cause of global mortality, claimed 9.6 million lives in 2020 [8]. Despite significant advances in understanding heavy metal-induced carcinogenesis through oxidative stress, DNA damage, and abnormal signalling, recent focus has shifted towards epigenetic alterations [9][10]. Epigenetic modifications, including histone modification, non-coding RNA (ncRNA)-associated gene silencing, and DNA methylation, have become crucial contributors to metal-induced carcinogenicity [11]. While not altering the DNA sequence, these modifications regulate gene expression, pivotal in cell differentiation and function [12]. Disruptions in these well-established epigenetic patterns, as noted by Manic et al. [13], can render tumour suppressor genes inactive while activating pro-proliferative genes. By recognising the significance of both genetic and epigenetic mechanisms in metal-induced carcinogenesis, recent cancer research has intensified its focus on epigenetic variations as critical contributors to cancer onset. This review aims to synthesise insights from studies elucidating the epigenetic pathways involved in metal-induced carcinogenesis. This article explores potential epigenetic therapeutic interventions, paving the way for personalised strategies to treat metal-induced cancers.

2. BURDEN OF CANCER

Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020, or nearly one in six deaths, with one in four men and one in five women developing the disease, and one in eight men and one in eleven women dying from it [14][15]. According to WHO [8], the most common in 2020 (in terms of new cases of cancer) were breast cancer, accounting for 2.26 million cases; lung cancer, accounting for 2.21 million cases; colon and rectum cancer accounting for 1.93 million cases; prostate cancer accounting for 1.41 million cases; skin cancer (non-melanoma) accounting for 1.20 million cases; and stomach cancer accounting for 1.09 million cases. The most common causes of cancer death in 2020 were lung cancer, accounting

for about 1.80 million deaths; colon and rectum cancer, accounting for about 916 000 deaths; liver cancer, accounting for about 830 000 deaths; stomach cancer, accounting for about 769 000 deaths; and breast cancer accounting for about 685 000 deaths [8]. Globally, the burden of cancer incidence and death is increasing at a rapid pace. This increase in death and prevalence rates can be attributed to several factors, including population increase and ageing, as well as shifts in the distribution and frequency of the primary risk factors for cancer, many of which are linked to socioeconomic development [16].

Each year, approximately 400,000 children develop cancer [17]. Deaths from cancer were 5.8 million in 1990 [18]. Deaths have been increasing primarily due to longer life spans and lifestyle changes in the developing world [19]. The three most common childhood cancers are leukaemia, brain tumours and lymphomas, accounting for 34%, 23% and 12% of cases, respectively [17]. Estimates showed that about 20% of males and 17% of females will get cancer at some point in time, while 13% of males and 9% of females will die from it [20]. In addition, 43.8 million people with cancer who received a diagnosis within the previous five years were still affected in 2018. Based on projected population ageing and growth, the global burden of cancer is set to increase by more than 60% by 2040, from 18.1 million new cases in 2018 to a predicted 29.4 million cases in the year 2040 [15].

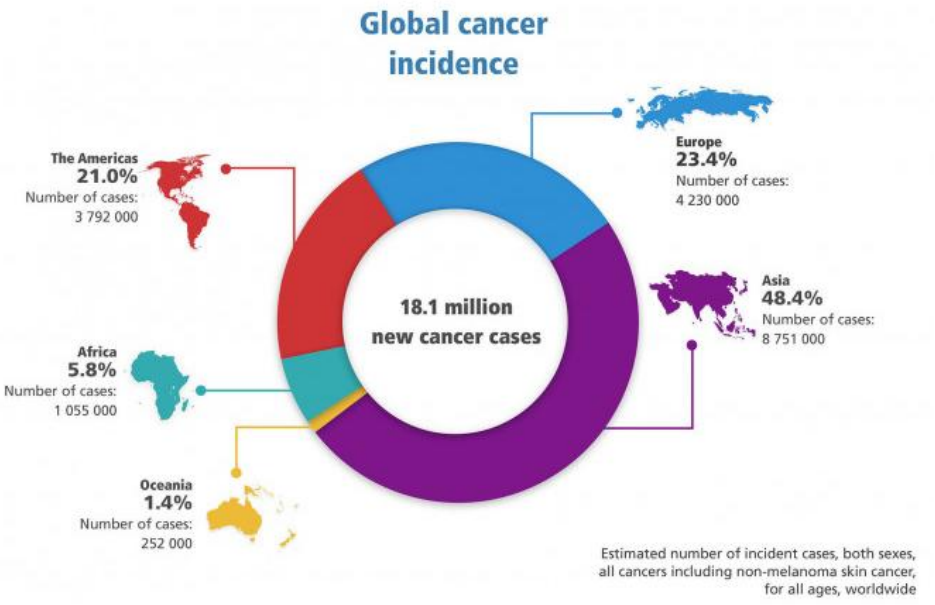

Figure 1: Global cancer incidence [21].

3. BURDEN OF HEAVY METAL EXPOSURE

Multiple industrial, domestic, agricultural, medical and technological applications of heavy metals have led to their wide distribution in the environment, raising concerns over their potential effects on human health and the environment [1]. Contamination of water, air and food by toxic metals is an environmental concern, and hundreds of millions worldwide are affected [22]. Metals, among the other environmental pollutants, may also occur naturally and remain in the environment, making human exposure to metals inevitable [1]. As a result of their high toxicity, arsenic, cadmium, chromium, lead, and mercury rank among the priority metals of public health significance. These metallic elements are considered systemic toxicants that are known to induce multiple organ damage, such as gastrointestinal and kidney dysfunction, nervous system disorders, skin lesions, vascular damage, immune system dysfunction and congenital disabilities, even at lower levels of exposure [23][24]. They are also classified as human carcinogens (known or probable) according to the International Agency for Research on Cancer [6]. While the exact mechanism is unclear, oxidative stress, abnormal signal transduction and aberrant changes in genome and gene expression are suggested as an underlying process of metal carcinogenesis. Carcinogenic metals such as arsenic, cadmium, and chromium can disrupt DNA synthesis and repair, leading to cancer formation [25][26]. Recently, studies have identified the role of epigenetics in heavy metal-induced carcinogenesis [4][13].

4. EPIGENETICS

Epigenetics refers to dynamic and heritable modifications to the chromatin without alterations in the genomic sequence; epigenetic regulations represent important mechanisms in regulating gene expression [27]. Epigenetic genome modifications commonly include DNA and RNA methylations, histone modifications, and non-coding RNAs [28]. These modifications regulate gene expression by altering the local structural dynamics of chromatin, primarily regulating its accessibility and compactness, resulting in altered gene expression without changing the DNA sequence [29]. Environmental factors, including diet, xenobiotics, and the total living environment, affect the epigenome. Epigenetic changes can affect the cells in which they occur and the subsequent cell generations - leading to germline effects. Currently, the mechanisms of

these transgenerational effects in mammals are unclear [30][31]. Unlike genomic alterations, epigenetic alterations are usually reversible and more quickly regulated. The aberrant epigenetic alterations, alone or along with widespread genetic alterations, are widely involved in cancer formation and development. 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 [30].

5. EPIGENETIC MECHANISMS

5.1. DNA Methylation/ Demethylation

DNA methylation involves adding methyl groups to cytosine at the fifth carbon position in CpG dinucleotides, resulting in 5-methylcytosine [32]. This modification, carried out by DNA methyltransferases, is crucial for gene expression control. Methylation in gene promoters leads to gene silencing, while demethylation, favoured during intense cell division, can reactivate silenced genes [32]. In mammalian cells, 60–90% of sites are methylated, associated with long-term transcriptional silencing [33].Methylation in gene bodies is linked to transcription activation [34] (E). Abnormal DNA methylation plays a vital role in cellular processes and is implicated in various diseases, particularly cancer [34]. Global DNA hypomethylation is linked to tumour initiation and progression, while site-specific changes influence oncogene and tumour suppressor expression. Aberrant DNA methylation is also associated with metal-induced carcinogenesis [4][13][35].

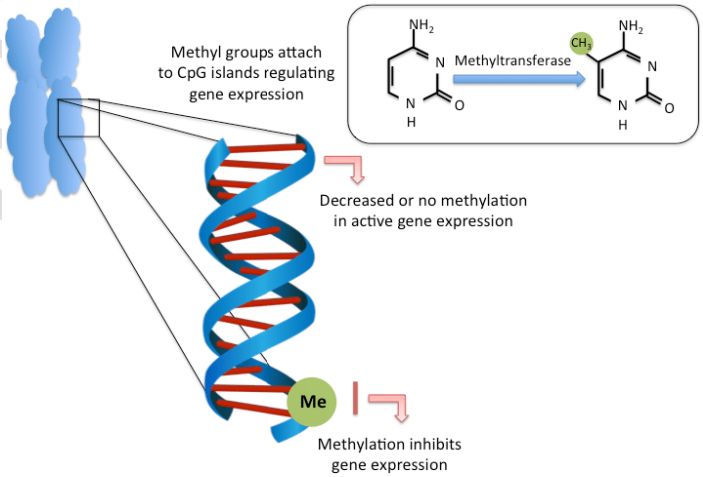

Figure 2: DNA Methylation Mechanism [35].

5.2. Post Translational Histone Modifications

Histones are DNA- binding essential proteins found in chromosomes. They contain a globular C-terminal domain and an unstructured extended N-terminal tail rich in lysine and arginine residues. They serve as spools around which DNA winds to form nucleosomes, which are structural units [36]. In turn, nucleosomes are coiled into fibres the size of 30 nanometers, which create densely packed chromatin. Histones prevent DNA from becoming tangled and protect it from DNA damage [37]. Multiple post-translational covalent modifications (PTMs) can occur to histone tails at specific amino acid residues, such as acetylation, methylation, ubiquitylation, phosphorylation, and SUMOylation [38]. By continually reorganising chromatin structures, the highly modified histone tail plays a role in controlling the expression of genes. Histone acetyltransferases (HATs) are involved in transferring acetyl groups to histones, while histone deacetylases (HDACs) are involved in removing the groups from the proteins [13].

Histone methylation is associated with active gene transcription or repressive epigenetic marks [34]. The methylation and demethylation of histones are catalysed by histone methyltransferases (HMTs) and histone demethylases (HDMTs), respectively [39]. Due to their significant involvement in controlling gene expression, the methylation process allows for several cellular functions and processes, including cell proliferation, differentiation, the cell cycle, and apoptosis [35]. Histone alterations have been linked to metal-induced carcinogenesis in an increasing number of studies conducted in recent years [4][13][40].

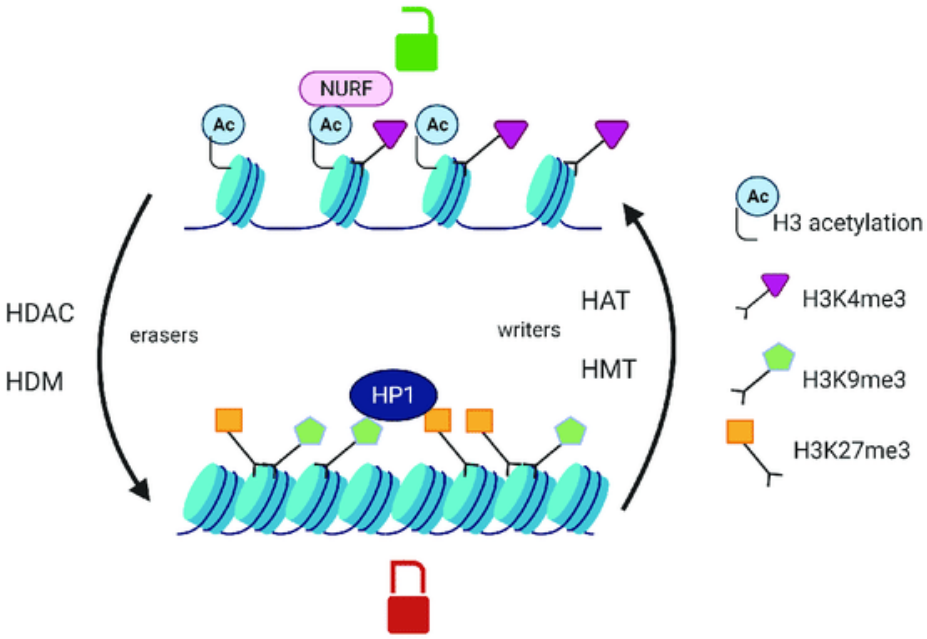

Figure 3: Post-translational histone modifications and their effects on transcription [41].

5.3. Non-coding RNA (ncRNA) Activity

Non-coding RNAs (ncRNA) are functional RNA molecules that are not translated into proteins. Transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) are common and physiologically significant forms of non-coding RNAs. Other short RNAs include microRNAs, siRNAs, piRNAs, snoRNAs, snRNAs, exRNAs, and scaRNAs, as well as long ncRNAs like Xist and HOTAIR [42]. The initiation and progression of human malignancies are significantly influenced by non-coding RNAs, specifically microRNA (miRNA), lncRNA, and circular RNA (circRNA), as they have been demonstrated to play significant roles in regulating gene expression at transcriptional or post-transcriptional levels [43].

Recent research underscores the importance of miRNA dysregulation in angiogenesis, tumour growth, and malignant cell transformation induced by metal carcinogens [4]. MicroRNAs (miRNAs) are small, non-coding RNAs that negatively regulate gene expression by inhibiting protein synthesis and degrading mRNA. They are subject to genetic and epigenetic regulation,

and dysregulated expression can result from irregular transcriptional regulation, DNA hypermethylation, and promoter region acetylation. MiRNAs play dual roles in carcinogenesis, acting as either tumour suppressors or oncogenes, and are implicated in developing drug resistance [44].

Another important RNA form is the long non-coding RNAs (lncRNAs), transcripts exceeding 200 nucleotides without protein-coding functions, which regulate gene expression through diverse mechanisms. They play pivotal roles in cellular functions, impacting cell proliferation, differentiation, apoptosis, cell cycle regulation, metabolism, migration, and invasion [45]. Dysregulation of lncRNAs, with either pro-oncogenic or tumor-suppressive effects, is implicated in cancer development [45]. For instance, LINC00152, a lncRNA, promotes non-small cell lung cancer (NSCLC) [46]. Studies suggest that heavy metal exposure disrupts lncRNA expression, and the resultant dysregulation of lncRNAs is linked to metal carcinogen-induced cancers [4][13][43].

6. EPIGENETIC MECHANISMS IN METAL CARCINOGENICITY

A substantial body of research has emerged in the contemporary scientific landscape, underscoring the pivotal role of epigenetic modifications in metal-induced carcinogenesis.

6.1. Arsenic Carcinogenicity and Associated Epigenetic Mechanisms

Arsenic, an environmental contaminant in soil, water, and airborne particles due to natural and human activities, poses health risks [47]. Epidemiological studies connect arsenic exposure to adverse effects, including diabetes, neurological issues, cardiovascular diseases, and various cancers such as skin, bladder, lung, kidney, and liver cancers [48]. Recognised as a Group 1 human carcinogen by the International Agency for Research on Cancer [6], arsenic carcinogenicity involves hypothesised mechanisms like oxidative stress, DNA repair disruption, signal transduction pathway disturbance, and chromosomal abnormalities. However, the precise mechanism behind arsenite's carcinogenicity remains unknown [44]. Recent research highlights altered epigenetic modifications contributing to tumour formation [4][13][49][50][51].

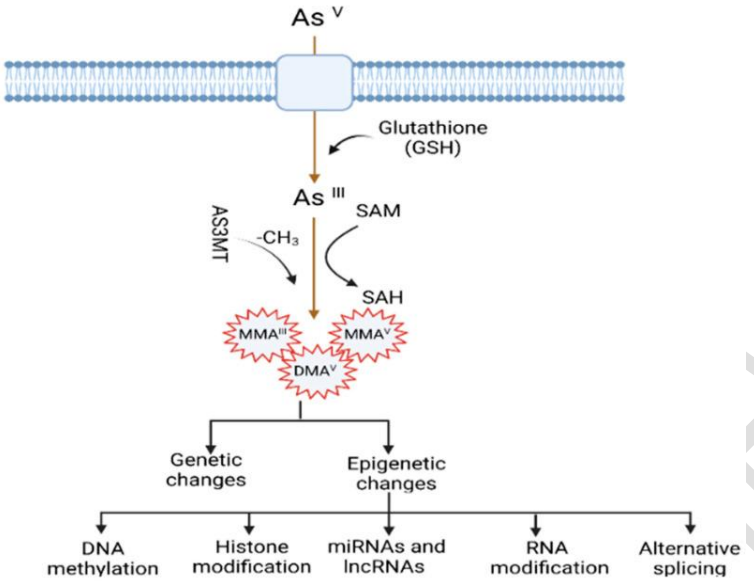

Figure 4: Mechanisms of arsenic-induced carcinogenesis [7].

Arsenic exposure transforms AsV to AsIII, facilitated by glutathione (GSH) and S-adenosylmethionine (SAM), generating highly carcinogenic organic arsenic species. Toxicity-induced alterations encompass DNA methylation, histone modification, and changes in miRNA and lncRNA expression [7]. A correlation between arsenic-induced carcinogenesis and DNA methylation is proposed due to the shared methyl donor - S-adenosylmethionine [13][50]. Prolonged arsenic exposure leads to SAM insufficiency and global DNA hypomethylation, impacting each biomethylation phase [51]. Methionine is crucial for SAM synthesis and influences arsenic's effects on DNA methylation, with dietary methyl deficiency exacerbating these effects [50]. Arsenic also interacts with transferases such as DNMTs, which causes a dose-dependent reduction in their activity [50][52]. Exposure to arsenic induces hypermethylation of tumour suppressor genes like p53 and p16 genes and transposable elements, contributing to genomic instability in cancer [53][54][55].

Methionine, an amino acid vital for S-adenosylmethionine (SAM) synthesis, influences arsenic's impact on DNA methylation, with dietary methyl deficiency potentially intensifying these effects

[50]. Arsenic not only affects SAM availability but also directly interferes with DNA methyltransferases (DNMTs), causing a dose-dependent reduction in mRNA levels and activity of DNMTs, including DNMT1 and DNMT3B, both in vitro and in vivo [50][52].

6.2. Chromium carcinogenicity and Associated Epigenetic Mechanisms

Chromium (Cr) is a naturally occurring heavy metal widely distributed in soil, rocks, and living organisms. Environmental exposure is mainly through water, air, automobile exhaust, and tobacco consumption [1]. Occupational exposure often occurs in industries such as leather tanning, smelting, welding, stainless steel production, and pigment manufacturing; the main routes of occupational exposure are inhalation or dermal absorption [56]. Environmental and occupational Cr (VI) exposures have become major public health concerns. Cr (VI) exposure can cause a series of adverse effects on the respiratory system, skin, gastrointestinal (GI) tract, kidneys and cancer [56]. studies have shown that altered epigenetic modifications and dysregulation of non-coding RNAs contribute to Cr (VI)-induced cell transformation and tumourigenesis [4][13].

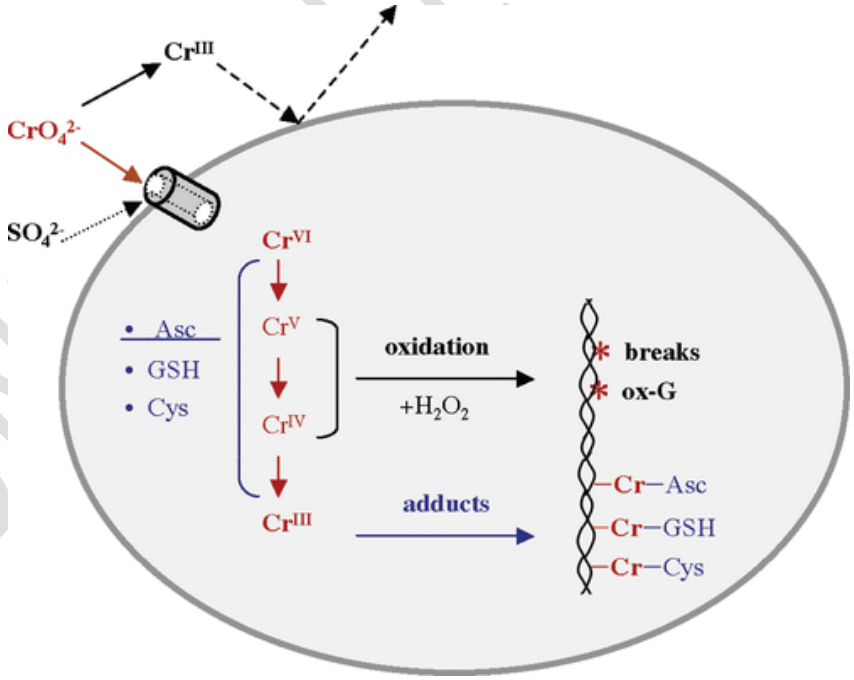

Figure 5: Schematic representation of the uptake, metabolism, and formation of DNA damage by Cr (VI) [57].

Chromium (VI) exposure is intricately linked to DNA damage and hypermethylation, leading to altered methylation status in both blood and lung cancer tissues [58]. Studies reveal that Cr exposure induces heightened DNA damage and down-regulation of the cell cycle regulator p16INK4a in 16HBE cells, while the hypermethylation of the p16INK4a promoter is implicated in Cr (VI) carcinogenesis, suppressing the DNA repair system [4][59][60]. Furthermore, DNA hypermethylation-mediated down-regulation of MLH1 expression, a DNA mismatch repair gene, is associated with Cr (VI)-induced carcinogenesis, affecting the DNA repair system [61][62][63]. Notably, Cr (VI) exposure induces significant histone modifications, globally affecting DNA expression and contributing to cancer, with specific changes observed in A549 lung cancer cells [64][65]. Dysregulated histone modification machinery, potential interference with HDAC1-DNMT1 crosslink, and epigenetic up-regulation of inflammatory factors contribute to Cr (VI)-induced carcinogenesis and cancer progression [13][66][67]. Additionally, miRNA dysregulation significantly impacts angiogenesis, carcinogenesis, and Cr (VI)-induced cell transformation, as observed in human bronchial fibroblast cells [68].

6.3. Cadmium carcinogenicity and Associated Epigenetic Mechanisms

Cadmium (Cd) and its compounds are pervasive environmental contaminants in food, drinking water, and occupational settings, presenting a significant public health concern [69] Cd exposure, notably through tobacco smoke, adversely affects various organ systems, contributing to dysfunction in the renal, digestive, respiratory, and skeletal systems [4]. Long-term exposure to Cd leads to complex alterations in DNA methylation, involving both hypermethylation at promoter regions and hypomethylation upon initial exposure, ultimately contributing to Cd-induced carcinogenesis [13]. Cd-induced changes in DNA methylation, including hypermethylation of RASSF1A and p16 gene promoters, result in the down-regulation of crucial tumour suppressors and an increase in preneoplastic lesions [70]. Additionally, histone modifications play a significant role in Cd-induced carcinogenesis, with altered histone marks influencing processes like epithelial-mesenchymal transition and lung cell transformation

[4][71]. Cd exposure induces noteworthy changes in miRNA expression, impacting cancer-associated biological processes and facilitating malignant cell transformation [72][73]. Global changes in miRNA expression, including the up-regulation of miR-370-3p and miR-124-3p, contribute to Cd-induced apoptosis by targeting the apoptosis suppressor Bcl-2 [73]. Furthermore, Cd exposure leads to the down-regulation of miR-30e, promoting epithelial-mesenchymal transition through the up-regulation of SNAIL1 [72][74]. In Cd carcinogenesis, long non-coding RNAs (lncRNAs) and dysregulated circular RNAs (circRNAs) also play significant roles, influencing cell proliferation and apoptosis, with altered expression associated with prostate cancer incidence [4][75].

6.4. Nickel Carcinogenicity and Associated Epigenetic Mechanisms

Nickel exposure primarily occurs through contaminated food and water, with additional risks for workers in industries utilising nickel for various applications, including stainless steel production and battery manufacturing [4]. While nickel exposure has been associated with cardiovascular and kidney diseases, as well as allergic dermatitis, its carcinogenic activity poses a significant global public health risk [4]. The carcinogenic potential of nickel (II) likely involves non-genotoxic pathways, suggesting the implication of epigenetic mechanisms in its role. Numerous studies highlight the involvement of epigenetic mechanisms in nickel carcinogenesis, with local DNA methylation being a prominent process mediated by nickel exposure. Synergistic interactions between MAPK activation and p16Ink4a silencing have been proposed in nickel carcinogenesis, emphasising the role of epigenetic alterations [76]. Nickel-induced alterations in gene expression without mutations have been reported, indicating the promotion of DNA methylation and chromatin condensation as contributing factors [77][78]. Epigenetic changes, such as DNA hypermethylation and altered histone modifications, contribute to reduced DNA repair and enhanced malignant transformation induced by nickel exposure. Nickel, similar to arsenic and Cr (VI), induces epithelial-mesenchymal transition (EMT) in cells, further linking epigenetic mechanisms to its carcinogenic effects [79].

Nickel's impact on histone modifications, including inhibition of histone acetyltransferase (HAT) and alterations in H3K4me3 and H3K27me3, indicates a broader influence on gene expression [13][80]. The upregulation of specific miRNAs, such as miR-222, has been associated with

nickel-induced malignant transformation, further highlighting the complexity of epigenetic regulation in nickel carcinogenesis [4][13]. These findings suggest that nickel's carcinogenic activity involves intricate interactions with the epigenetic landscape, impacting DNA methylation, histone modifications, and miRNA expression. Understanding these epigenetic mechanisms is crucial for comprehending nickel-induced carcinogenesis and developing targeted strategies for prevention and intervention in exposed populations.

7. EPIGENETIC-DERIVED THERAPEUTIC OPTIONS FOR METAL CARCINOGENICITY

Epigenome-targeted therapy poses as an effective method of treating cancer. Epigenome-targeted therapies involve small-molecule inhibitors known as 'epigenome-targeting drugs' or 'epi-drugs'. These inhibitors can reverse a particular cellular phenotype, making them promising targets for cancer treatments [13][81]. They have been developed for over 40 years [76] and recently have evidenced significant progress. Some of these epi-drugs are currently utilised in clinics and have shown promising results [76][82].

In recent years, there has been growing interest in exploring epigenetic-derived therapeutic options as novel strategies for treating different types of cancer. Epigenetic-derived therapeutic options for metal carcinogenicity involve targeting gene expression alteration caused by exposure to carcinogenic metals through epigenetic mechanisms. Targeting histone deacetylases (HDACs) and DNA methyltransferase (DNMT)/histone methyltransferase (HMT) are used as possible targets in the treatment of various types of cancer. There are FDA-approved HDAC and DNA methylation inhibitors (DNMTIs) with successful results recorded thus far. Histone methylation and ncRNA-targeted therapy have also attracted attention as potential therapeutic targets [83].

7.1 DNA Methylation Inhibitors (DNMTI)

DNA methylation is a pivotal player in cancer development, with heavy metal exposure implicated in inducing abnormal DNA methylation patterns that lead to gene silencing and oncogene activation [84]. DNA methylation inhibitors, categorised into nucleoside analogues and non-nucleoside analogues, hold promise in counteracting these metal-induced epigenetic

changes [85][86]. Nucleoside analogues like azacitidine and decitabine, approved for myelodysplastic syndrome treatment, have demonstrated potential in reactivating aberrantly methylated tumour suppressor genes. However, their efficacy in solid tumours is limited due to toxicity and low response rates. Newer nucleoside analogues, such as zebularine and guadecitabine, aim to enhance bioavailability and reduce toxicity, showing promise in reactivating silenced genes [87]. Despite zebularine's stability and low toxicity, clinical trials are required to establish its efficacy in solid tumours.

Guadecitabine, with an extended half-life and resistance to cytidine deaminase, has shown promise in solid tumour responses. Other analogues like 4′-thio-2′-deoxycytidine and 5-Fluoro-2′-deoxycytidine exhibit potential in depleting DNMT1 and inhibiting tumour growth, albeit with mutagenic risks and genomic instability [88]. Non-nucleoside analogues offer an alternative approach, overcoming bioavailability and selectivity challenges. Compounds like SGI-1027 and MC3353 exhibit demethylating effects independent of DNA incorporation [89][90][91]. Natural products such as shikonin and repurposed drugs like procainamide demonstrate demethylating effects and antitumor activity [92][93]. Diverse strategies and compounds, including psammaplin, Isofitsularin-3, epigallocatechin-3-gallate (EGCG), and the histone H3-lysine-9-methyltransferases inhibitor BIX-01294, are being explored to target DNA methylation in cancer therapy, providing hope for improved treatment outcomes.

7.2 Histone Modification Inhibitors

Various epigenetic enzymes that affect the state of histones have been detected to be deregulated, being over- or under-expressed in cancers. Histone modifications regulate transcription through various means, from directly disrupting DNA-nucleosome contacts to recruiting and binding non-histone proteins and additional histone modifiers [94]. Metal exposure can alter histone modifications, impacting chromatin structure and gene regulation. Drugs targeting histone deacetylases (HDACs) or histone methyltransferases (HMTs) can restore balanced histone modifications, influencing gene expression and potentially reversing carcinogenic effects. An extensive catalogue of histone modifications has been described, but functional understanding still needs to be improved.

More studies need to investigate histone modification inhibitors specifically for metal-induced carcinogenesis. However, general knowledge about histone modification inhibitors studied in the broader context of cancer and their potential application in metal-induced carcinogenesis can be considered.

7.3 Histone Deacetylase Inhibitors (HDACI)

Histone deacetylase (HDAC) inhibitors induce hyperacetylation in histone and non-histone proteins, affecting various processes in tumour and non-tumour cells. In cancer, hyperacetylation of histones leads to altered gene expression, inducing cell cycle arrest, apoptosis, senescence, differentiation, immunogenicity, and inhibiting angiogenesis [95]. Studies demonstrate that HDAC inhibitors effectively inhibit the proliferation of transformed cells, including lymphoma, myeloma, leukaemia, and non-small cell lung carcinoma (NSCLC), with antitumor activity observed in solid tumours and haematological malignancies, including lung cancer [96]. Clinical trials focus on cancer treatment, and HDAC inhibitors exhibit varying antitumor activity.

HDAC inhibitors can act specifically on certain HDACs or target all types (pan-inhibitors), classified based on their chemical nature. Examples include suberoylanilide hydroxamic acid (SAHA), Trichostatin A (TCA), LBH589 (panobinostat), and PXD101 (belinostat) in the hydroxymates group. Short-chain fatty acids like Valproic acid (VPA) and butyrate target class I and IIa HDACs [97][98][99]. Benzamides like MS 275 (entinostat) and FK228 (romidepsin) and depsipeptides like trapoxin (TPX) inhibit class I HDACs. TSA and Vorinostat are hydroxamate-based inhibitors. Cyclic peptides, including depsipeptide and apicidin, are structurally complex HDAC inhibitors. Aliphatic acids like butyrate, phenylbutyrate, and valproic acid are weak HDAC inhibitors. MS-275 (Entinostat) and MGCD0103 [100][101] are synthetic benzamide derivatives that are promising in clinical trials.

Numerous HDAC inhibitors, purified from natural sources or synthesised, have undergone clinical trials. FDA approval for Vorinostat, belinostat, romidepsin, tucidinostat, and panobinostat [102] as anticancer agents has spurred the development of new inhibitors. These approved agents are subjects of ongoing clinical trials, exploring their effectiveness in various neoplastic conditions, either as monotherapy or combination regimens.

7.4 Histone Methyltransferases Inhibitors

Histone methyltransferases (HMTs) are essential epigenetic regulators in gene transcription, DNA replication, and repair, catalysing methylation on specific lysine and arginine residues of histones H3 and H4. Approximately 100 histone lysine methyltransferases (KMTs) and protein arginine methyltransferases are encoded in the human genome [103], playing a significant role in diseases, including cancer, making them appealing therapeutic targets. Metals can disrupt HMT activity, contributing to abnormal histone methylation patterns implicated in cancer development. Although drugs targeting histone lysine methyltransferases are in the early stages, key enzymes like EZH2, G9a, DOT1L, and PRMTs 1 and 5 are under investigation for cancer treatment, with multiple inhibitors showing promising outcomes, particularly in inhibiting EZH2, DOT1L, G9a, and SETDB1 [104][105].

Small molecule inhibitors targeting EZH2 fall into two categories: those directly blocking enzymatic activity, including Tazemetostat (EPZ-6438), approved by the US FDA in 2020, and those disrupting the PRC2 complex and inhibiting its interaction with H3K27, such as MAK683. Additionally, a new avenue for triggering EZH2 degradation is being explored. For DOT1L, inhibitors mimicking the SAM molecule, such as EPZ-5676, EPZ004777, and SGC0946, have been developed, with EPZ-5676 validated as an 'orphan drug' for MLL-rearranged leukaemia by the US FDA in 2013[106]. G9a inhibitors, like UNC0638 and UNC0642, have demonstrated antitumor effects by blocking the H3 substrate binding site, inhibiting tumour growth, and triggering apoptosis or autophagic cell death [107].

7.5 Non-coding RNA-Targeted Therapies

Identifying non-coding RNAs (ncRNAs) as contributors to cancer development has opened novel avenues for therapy and detection [108]. The advent of RNA-based medicines, spurred by the discovery of antisense oligonucleotides (ASOs) inhibiting protein synthesis in the 1980s, gained momentum with the concept of RNA interference (RNAi) in the 2000s. RNA-based drugs, including ASOs, siRNAs, and others, have received approval and are progressing through phase III trials. Therapeutic approaches targeting ncRNAs involve altering gene expression and modulating non-coding RNA levels. Inhibitors like ASOs, antagomirs, siRNAs, and CRISPR/Cas9 are employed for in vitro and in vivo research, demonstrating efficacy in targeting various ncRNAs. ASOs, utilising RNAse-H-mediated cleavage, are crucial for specific and

efficient reduction in ncRNA levels, including miRNAs and lncRNAs. Antagomirs, particularly when conjugated to cholesterol, enhance intracellular delivery, while locked nucleic acids (LNAs) offer improved target affinity for inhibiting short RNA and DNA segments [108].

RNA interference strategies employ siRNAs, double-stranded RNA molecules that transiently silence gene expression, and shRNAs, addressing the short lifespan of synthetic siRNAs. Clinical trials for miRNA-based therapeutics, such as MiRNA Therapeutics and MRX34, a miRNA mimic, have been initiated to impact patient outcomes positively [109]. MRX34 was delivered as a double-stranded RNA encapsulated into a liposome-formulated nanoparticle. However, despite significant progress in RNA-based therapeutics, challenges persist, including limited efficacy, toxicity, specificity, delivery, and tolerability issues. Specificity concerns relate to on-target and off-target effects, while delivery hurdles involve the instability of unmodified RNA structures and the need for efficient intracellular delivery mechanisms. Alternative RNA products, such as lncRNAs and anti-miRNAs, are under clinical evaluation, while other ncRNA species are yet to be extensively targeted for therapeutic development [110].

8. CHALLENGES OF USING EPIGENETIC-DERIVED THERAPEUTIC OPTIONS FOR METAL CARCINOGENESIS

Epigenetic therapy, while theoretically profound, faces challenges that need resolution. The primary concern is the issue of selectivity, as epigenetic events are widespread in both standard and cancer cells [85]. Some cancers rely on specific epigenetic alterations, making them sensitive to regulation, while normal cells can compensate for such changes under usual regulation. Determining the most crucial epigenetic alterations for different cancers is a priority. The second challenge stems from the first, with impressive results observed in haematological malignancies but not solid tumours [85]. The distinct properties of haematological malignant cells and solid tumour cells contribute to this discrepancy.

When applying epigenome-targeted therapy to cancer, the complexity of the disease and the impact of epigenetic modifications on its development must be considered. These modifications influence tumour suppressor gene expression, oncogene expression, and signal transduction, ultimately affecting cancer invasion, growth, and metastasis. Specific cancers exhibit sensitivity

to particular epigenetic alterations, emphasising the need to identify the most precise modifications for each cancer type as an essential initial step in effective epigenetic therapy [13].

9. CONCLUSION

The pervasive environmental and occupational exposure to heavy metals poses a significant global public health threat affecting millions. A comprehensive understanding of metal carcinogenesis mechanisms is essential for preventing and treating heavy metal-induced cancers, offering tailored therapeutic options. Current research underscores the critical involvement of altered epigenetic modifications in metal carcinogenesis, opening avenues for targeted interventions using various inhibitors. By recognising the pivotal role of epigenetic mechanisms in metal-induced carcinogenesis, ongoing research is unravelling intricate pathways. While substantial progress has been made, advancing large-scale epigenetic profiling, fostering interdisciplinary collaborations, and disseminating epigenetic risk information are crucial.

Increased awareness of toxic metals like arsenic, cadmium, chromium, and nickel emphasises the need to broaden our comprehension of cancer development. Further research in this domain is critical to enhancing cancer prevention strategies and developing targeted epigenome-based therapies. Recent findings highlight the efficacy of epigenome-targeted therapy in cancer treatment, particularly addressing altered gene expression induced by carcinogenic metals through epigenetic mechanisms. Targeting HDACs, DNMTs/HMTs, histone methylation, and ncRNA pathways shows promise for diverse cancer treatment. However, more studies are warranted, especially tailored to specific heavy metal carcinogens like arsenic, cadmium, and nickel.

Despite substantial growth in studies over the past decade, only a fraction of the myriad epigenetic changes, altered non-coding RNAs, and associated therapeutic options from heavy metal exposure have been elucidated, with the significance of many remaining elusive. Therefore, further studies are imperative to enhance the diagnosis and treatment of human cancers resulting from metal carcinogen exposure, elucidating the role of epigenetic modifications and miRNAs in heavy metal carcinogenesis, angiogenesis, and targeted therapeutic modalities.

CONSENT

It is not applicable

ETHICAL APPROVAL

It is not applicable

REFERENCES

1. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. Mol Clin Environ Toxicol. 2012;101:133–164.
2. Paithankar JG, Saini S, Dwivedi S, Sharma A, Chowdhuri DK. Heavy metal associated health hazards: An interplay of oxidative stress and signal transduction. Chemosphere. 2021;262:128350.
3. He ZL, Yang XE, Stoffella PJ. Trace elements in agroecosystems and impacts on the environment. J Trace Elem Med Biol. 2005;19(2–3):125–140.
4. Zhao L, Islam R, Wang Y, Zhang X, Liu LZ. Epigenetic Regulation in Chromium-, Nickel- and Cadmium-Induced Carcinogenesis. Cancers. 2022;14(23):5768.
5. Renu K, Chakraborty R, Myakala H, Koti R, Famurewa AC, Madhyastha H, Vellingiri B, George A, Valsala Gopalakrishnan A. Molecular mechanism of heavy metals (Lead, Chromium, Arsenic, Mercury, Nickel and Cadmium)-induced hepatotoxicity—A review. Chemosphere. 2021;271:129-137.
6. International Agency for Research on Cancer (IARC): Working Group on the Evaluation of Carcinogenic Risks to Humans. Arsenic, metals, fibres, and dusts. A Review of Human Carcinogens. Lyon, France; 2012. 1-52.
7. Islam R, Zhao L, Wang Y, Lu-Yao G, Liu LZ. Epigenetic Dysregulations in Arsenic-Induced Carcinogenesis. Cancers. 2022;14(18):4502.
8. World Health Organization. Cancer. [Internet]. 2023 [cited 2023 Oct 6]. Available from: https://www.who.int/health-topics/cancer#tab=tab_1
9. Kim HS, Kim YJ, Seo YR. An Overview of Carcinogenic Heavy Metal: Molecular Toxicity Mechanism and Prevention. J Cancer Prev. 2015;20:232–240.
10. Baylin SB, Ohm JE. Epigenetic gene silencing in cancer – a mechanism for early oncogenic pathway addiction? Nat Rev Cancer. 2006;6(2):107–116.
11. Martinez-Zamudio R, Ha HC. Environmental epigenetics in metal exposure. Epigenetics. 2011;6:820–827.
12. Kanwal R, Gupta S. Epigenetic modifications in cancer. Clin Genet. 2012;81(4):303–311.

13. Manić L, Wallace D, Onganer PU, Taalab YM, Farooqi AA, Antonijević B, Djordjevic AB. Epigenetic mechanisms in metal carcinogenesis. Toxicol Rep. 2022;9:778-787.
14. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M. Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer. [Internet]. 2020 [cited 2021 Feb]. Available from: https://gco.iarc.fr/today
15. American Cancer Society. The Cancer Atlas. The Burden of Cancer. [Internet]. 2024 [cited 2024 Jan]. Available from: The Cancer Atlas website
16. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–249.
17. World Health Organization. Cancer. [Internet]. 2022 [cited 2022]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer
18. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec;380(9859):2095–2128.
19. Jemal A, Bray F, Center MM, Ferlay J, Forman D. Global cancer statistics. Cancer J Clin. 2011;61(2):69–90
20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
21. Union for International Cancer Control (UICC). Global Cancer data: GLOBOCAN 2018. [Internet]. 2018 [cited 2024 Jan]. Available from: www.uicc.org/news/global-cancer-data-globocan-2018
22. Luo L, Wang B, Jiang J, Huang Q, Yu Z, Li H, et al. Heavy metal contaminations in herbal medicines: determination. comprehensive risk assessments. Front Pharmacol. 2020;11:595–635.
23. Costa M. Review of arsenic toxicity, speciation and polyadenylation of canonical histones. Toxicol Appl Pharmacol. 2019;375:1–4.
24. Gazwi HS, Yassien EE, Hassan HM. Mitigation of lead neurotoxicity by the ethanolic extract of Laurus leaf in rats. Ecotoxicol Environ Saf. 2020;192:110–197.
25. Clancy HA, Sun H, Passantino L, Kluz T, Muñoz A, Zavadil J. Gene expression changes in human lung cells exposed to arsenic, chromium, nickel, or vanadium indicate the first steps in cancer. Metallomics. 2012;4(8):784–793.
26. Koedrith P, Kim H, Weon J-I, Seo YR. Toxicogenomic approaches for understanding molecular mechanisms of heavy metal mutagenicity and carcinogenicity. Int J Hyg Environ Health. 2013;216(5):587–598.
27. Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes Dev. 2009 Apr 1;23(7):781-3.

28. Sheudeen AA, Ben-Chioma AE, Beega GF, Simeon CA, Anthony AU, Ibioku E. Epigenetic Modulation in Breast Cancer: From Mechanisms to Therapeutic Interventions. Int Res J Oncol. 2024;7(1):1-13.
29. Allis CD, Jenuwein T. The molecular hallmarks of epigenetic control. Nat Rev Genet. 2016 Aug;17:487-500.
30. Wang B, Li Y, Shao C, Tan Y, Cai L. Cadmium and its epigenetic effects. Curr Med Chem. 2012;19:2611-20.
31. Henikoff S, Greally JM. Epigenetics, cellular memory and gene regulation. Curr Biol. 2016 Jul 25;26(14):R644-8.
32. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology. 2013 Jan;38(1):23-38.
33. Kaplun DS, Kaluzhny DN, Prokhortchouk EB, Zhenilo SV. DNA Methylation: Genomewide Distribution, Regulatory Mechanism and Therapy Target. Acta Naturae. 2022;14(4):4-19.
34. McMahon KW, Karunasena E, Ahuja N. The Roles of DNA Methylation in the Stages of Cancer. Cancer J. 2017 Sep/Oct;23(5):257-61.
35. Nevin C, Carroll M. Sperm DNA Methylation, Infertility and Transgenerational Epigenetics. J Hum Genet Clin Embryol. 2015;1.
36. Cox M, Nelson DR, Lehninger AL. Lehninger Principles of Biochemistry. W.H. Freeman; 2005.
37. Audia JE, Campbell RM. Histone Modifications and Cancer. Cold Spring Harb Perspect Biol. 2016;8:19-34.
38. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res. 2011;21:381–395.
39. Greer EL, Shi Y. Histone methylation: A dynamic mark in health, disease, and inheritance. Nat Rev Genet. 2012;13:343–357.
40. Kouzarides T. Chromatin Modifications and Their Function. Cell. 2007;128:693–705.
41. Renaude E, Marie K, Borg C, Peixoto P, Hervouet E, Loyon R, et al. Epigenetic Reprogramming of CD4+ Helper T Cells as a Strategy to Improve Anticancer Immunotherapy. Front Immunol. 2021;12:669992.
42. Morris KV (Ed.). Non-coding RNAs and Epigenetic Regulation of Gene Expression: Drivers of Natural Selection. Caister Academic Press; 2012.
43. Yan H, Bu P. Non-coding RNA in cancer. Essays Biochem. 2021;65:625–639.
44. Gao Y, Fan X, Li W, Ping W, Deng Y, Fu X. MiR-138-5p reverses gefitinib resistance in non-small cell lung cancer cells via negatively regulating G protein-coupled receptor 124. Biochem Biophys Res Commun. 2014;446:179–186.
45. Guzel E, Okyay TM, Yalcinkaya B, Karacaoglu S, Gocmen M, Akcakuyu MH. Tumour suppressor and oncogenic role of long non-coding RNAs in cancer. North Clin Istanb. 2020;7:81–86.

46. Zhang Y, Xiang C, Wang Y, Duan Y, Liu C, Jin Y, et al. lncRNA LINC00152 knockdown had effects to suppress biological activity of lung cancer via EGFR/PI3K/AKT pathway. Biomed Pharmacother. 2017;94:644–651.
47. Salnikow K, Zhitkovich A. Genetic and epigenetic mechanisms in metal carcinogenesis and cocarcinogenesis: nickel, arsenic, and chromium. Chem Res Toxicol. 2008;21(1):28–44.
48. Tchounwou PB, Centeno JA, Patlolla AK. Arsenic toxicity, mutagenesis, and carcinogenesis - a health risk assessment and management approach. Mol Cell Biochem. 2004;255:47–55.
49. Arita A, Costa M. Epigenetics in metal carcinogenesis: nickel, arsenic, chromium and cadmium. Metallomics. 2009;1(3):222–228.
50. Ren X, McHale CM, Skibola CF, Smith AH, Smith MT, Zhang L. An emerging role for epigenetic dysregulation in arsenic toxicity and carcinogenesis. Environ Health Perspect. 2011;119(1):11–19.
51. Bustaffa E, Stoccoro A, Bianchi F, Migliore L. Genotoxic and epigenetic mechanisms in arsenic carcinogenicity. Arch Toxicol. 2014;88:1043–1067.
52. Ahlborn GJ, Nelson GM, Ward WO, Knapp G, Allen JW, Ouyang M, et al. Dose-response evaluation of gene expression profiles in the skin of K6/ODC mice exposed to sodium arsenite. Toxicol Appl Pharmacol. 2008;227(3):400–416.
53. Brocato J, Costa M. Basic mechanics of DNA methylation and the unique landscape of the DNA methylome in metal-induced carcinogenesis. Crit Rev Toxicol. 2013;43:493–514.
54. Kile ML, Baccarelli A, Hoffman E, Tarantini L, Quamruzzaman Q, Rahman M, et al. Prenatal arsenic exposure and DNA methylation in maternal and umbilical cord blood leukocytes. Environ Health Perspect. 2012;120:1061-1093.
55. Paul S, Bhattacharjee P, Giri A, Bhattacharjee P. Arsenic toxicity and epimutagenesis: the new LINEage. Biometals. 2017;30:505–515.
56. den Braver-Sewradj SP, van Benthem J, Staal YCM, Ezendam J, Piersma AH, Hessel EVS. Occupational exposure to hexavalent chromium. Part II. Hazard assessment of carcinogenic effects. Regul Toxicol Pharmacol. 2021;126:105-145.
57. Salnikow K, Zhitkovich A. Chemical Research in Toxicology. 2008;21(1):28-44.
58. Feng L, Guo X, Li T, Yao C, Xia H, Jiang Z, et al. Novel DNA methylation biomarkers for hexavalent chromium exposure: An epigenome-wide analysis. Epigenomics. 2020;12:221-233.
59. Hu G, Li P, Li Y, Wang T, Gao X, Zhang W, et al. Methylation levels of P16 and TP53 that are involved in DNA strand breakage of 16HBE cells treated by hexavalent chromium. Toxicol Lett. 2016;249:15–21.
60. Hu G, Li P, Cui X, Li Y, Zhang J, Zhai X, et al. Cr(VI)-induced methylation and down-regulation of DNA repair genes and its association with markers of genetic damage in workers and 16HBE cells. Environ Pollut. 2018;238:833–843.

61. Takahashi Y, Kondo K, Hirose T, Nakagawa H, Tsuyuguchi M, Hashimoto M, et al. Microsatellite instability and protein expression of the DNA mismatch repair gene, hMLH1, of lung cancer in chromate-exposed workers. Mol Carcinog. 2005;42:150–158.
62. Tsuboi M, Kondo K, Soejima S, Kajiura K, Kawakita N, Toba H, et al. Chromate exposure induces DNA hypermethylation of the mismatch repair gene MLH1 in lung cancer. Mol Carcinog. 2020;59:24–31.
63. Ali AH, Kondo K, Namura T, Senba Y, Takizawa H, Nakagawa Y, et al. Aberrant DNA methylation of some tumour suppressor genes in lung cancers from workers with chromate exposure. Mol Carcinog. 2011;50:89–99.
64. Sun H, Zhou X, Chen H, Li Q, Costa M. Modulation of histone methylation and MLH1 gene silencing by hexavalent chromium. Toxicol Appl Pharmacol. 2009;237:258-266.
65. Zhou X, Li Q, Arita A, Sun H, Costa M. Effects of nickel, chromate, and arsenite on histone 3 lysine methylation. Toxicol Appl Pharmacol. 2009;236:78-84.
66. Xia B, Ren XH, Zhuang ZX, Yang LQ, Huang HY, Pang L, et al. Effect of hexavalent chromium on histone biotinylation in human bronchial epithelial cells. Toxicol Lett. 2014;228:241–247.
67. Ge X, He J, Wang L, Zhao L, Wang Y, Wu G, et al. Epigenetic alterations of CXCL5 in Cr (VI)-induced carcinogenesis. Sci Total Environ. 2022;838:155-137.
68. Speer RM, Meaza I, Toyoda JH, Lu Y, Xu Q, Walter RB, et al. Particulate hexavalent chromium alters microRNAs in human lung cells that target key carcinogenic pathways. Toxicol Appl Pharmacol. 2022;438:115-189.
69. Faroon O, Ashizawa A, Wright S, Tucker P, Jenkins K, Ingerman L, et al. Toxicological profile for cadmium. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); Available from: http;//www.ncbi.nlm.nih.gov/books/NBK158838/
70. Benbrahim-Tallaa L, Waterland R, Dill A, Webber M, Waalkes M. Tumour suppressor gene inactivation during cadmium-induced malignant transformation of human prostate cells correlates with overexpression of de novo DNA methyltransferase. Environ Health Perspect. 2007;115:1454–1459.
71. Liang Y, Pi H, Liao L, Tan M, Deng P, Yue Y, et al. Cadmium promotes breast cancer cell proliferation, migration, and invasion by inhibiting ACSS2/ATG5-mediated autophagy. Environ Pollut. 2021;273:116-194.
72. Tanwar VS, Zhang X, Jagannathan L, Jose CC, Cuddapah S. Cadmium exposure upregulates SNAIL through miR-30 repression in human lung epithelial cells. Toxicol Appl Pharmacol. 2019;373:1–9.
73. Yang J, Chen W, Sun Y, Xia P, Liu J, Zhang W. The role of microRNAs in regulating cadmium-induced apoptosis by targeting Bcl-2 in IEC-6 cells. Toxicol Appl Pharmacol. 2021;432:115737.
74. Wang Z, Sun Y, Yao W, Ba Q, Wang H. Effects of Cadmium Exposure on the Immune System and Immunoregulation. Front Immunol. 2021;12:695484.

75. García-Pérez J, Pérez-Abad N, Lope V, Castelló A, Pollán M, González-Sánchez M, et al. Breast and prostate cancer mortality and industrial pollution. Environ Pollut. 2016;214:394–399.
76. Govindarajan B, Klafter R, Miller MS, Mansur C, Mizesko M, Bai X, et al. Reactive oxygen-induced carcinogenesis causes hypermethylation of p16Ink4a and activation of MAP kinase. Mol Med. 2002;8(1):1-8.
77. Lee YW, Klein CB, Kargacin B, Salnikow K, Kitahara J, Dowjat K, et al. Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: A new model for epigenetic carcinogens. Mol Cell Biol. 1995;15:2547–2557.
78. Ellen TP, Kluz T, Harder ME, Xiong J, Costa M. Heterochromatinisation as a potential mechanism of nickel-induced carcinogenesis. Biochemistry. 2009;48:4626–4632.
79. Wu CH, Tang SC, Wang PH, Lee H, Ko JL. Nickel-induced epithelial-mesenchymal transition by reactive oxygen species generation and E-cadherin promoter hypermethylation. J Biol Chem. 2012;287:25292–25302.
80. Jose CC, Wang Z, Tanwar VS, Zhang X, Zang C, Cuddapah S. Nickel-induced transcriptional changes persist post-exposure through epigenetic reprogramming. Epigenetics Chromatin. 2019;12:75.
81. Lu Y, Chan YT, Tan HY, Li S, Wang N, Feng Y. Epigenetic regulation in human cancer: the potential role of epi-drug in cancer therapy. Mol Cancer. 2020;19:1-16.
82. Nepali K, Liou JP. Recent developments in epigenetic cancer therapeutics: clinical advancement and emerging trends. J Biomed Sci. 2021;28(1):1-58.
83. Kumoglu GO, Sendemir A, Tanyolac MB, Bilir B, Kucuk O, Missirlis YF. Epigenetic mechanisms in cancer. Longhua Chin Med. 2022;5:1-25.
84. Cheishvili D, Boudreau L, Szyf M. DNA demethylation and invasive cancer: implications for therapeutics. Br J Pharmacol. 2015;172(11):2705-2715.
85. Cheng Y, He C, Wang M, Ma X, Mo F, Yang S, et al. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduct Target Ther. 2019;4(1):62.
86. Zhang J, Yang C, Wu C, Cui W, Wang L. DNA Methyltransferases in Cancer: Biology, Paradox, Aberrations, and Targeted Therapy. Cancers. 2020;12:2123.
87. Cheng JC, Weisenberger DJ, Gonzales FA, Liang G, Xu GL, Hu YG, et al. Continuous zebularine treatment effectively sustains demethylation in human bladder cancer cells. Mol Cell Biol. 2004;24(3):1270-1278.
88. Parker WB, Thottassery JV. 5-Aza-4'-thio-2'-deoxycytidine, a New Orally Bioavailable Nontoxic "Best-in-Class": DNA Methyltransferase 1-Depleting Agent in Clinical Development. J Pharmacol Exp Ther. 2021;379(3):211–222.
89. Sun N, Zhang J, Zhang C, Zhao B, Jiao AO. DNMTs inhibitor SGI 1027 induces apoptosis in Huh7 human hepatocellular carcinoma cells. Oncol Lett. 2018;16(5):5799-5806.

90. Zwergel C, Fioravanti R, Stazi G, Sarno F, Battistelli C, Romanelli A, et al. Novel quinoline compounds active in cancer cells through coupled DNA methyltransferase inhibition and degradation. Cancers. 2020;12(2):447.
91. She S, Zhao Y, Kang B, Chen C, Chen X, Zhang X, et al. Combined inhibition of JAK1/2 and DNMT1 by newly identified small-molecule compounds synergistically suppresses the survival and proliferation of cervical cancer cells. Cell Death Dis. 2020;11(9):724.
92. Jang SY, Hong D, Jeong SY, Kim JH. Shikonin causes apoptosis by up-regulating p73 and down-regulating ICBP90 in human cancer cells. Biochem Biophys Res Commun. 2015;465(1):71-76.
93. Boulos JC, Rahama MS, Hegazy ME, Efferth T. Shikonin derivatives for cancer prevention and therapy. Cancer Lett. 2019;459:248-267.
94. Shogren-Knaak M, Ishii H, Sun JM, Pazin MJ, Davie JR, Peterson CL. Histone H4-K16 acetylation controls chromatin structure and protein interactions. Science. 2006;311(5762):844-847.
95. Falkenberg KJ, Johnstone RW. Histone deacetylases and their inhibitors in cancer, neurological diseases and immune disorders. Nat Rev Drug Discov. 2014;13(9):673-691.
96. Miyanaga A, Gemma A, Noro R, Kataoka K, Matsuda K, Nara M, et al. Antitumour activity of histone deacetylase inhibitors in non-small cell lung cancer cells: development of a molecular predictive model. Mol Cancer Ther. 2008;7(7):1923-1930.
97. Zhang J, Zhong Q. Histone deacetylase inhibitors and cell death. Cell Mol Life Sci. 2014;71:3885-3901.
98. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. Nat Rev Drug Discov. 2006;5(9):769-784.
99. Li Z, Zhu WG. Targeting histone deacetylases for cancer therapy: from molecular mechanisms to clinical implications. Int J Biol Sci. 2014;10(7):757.
100. Ryan QC, Headlee D, Acharya M, Sparreboom A, Trepel JB, Ye J, et al. Phase I and pharmacokinetic study of MS-275, a histone deacetylase inhibitor, in patients with advanced and refractory solid tumors or lymphoma. J Clin Oncol. 2005;23(17):3912-3922.
101. Kumar S, Gutierrez M, Gardner ER, Donovan E, Hwang K, Chung EJ, et al. Phase I trial of MS-275, a histone deacetylase inhibitor, administered weekly in refractory solid tumors and lymphoid malignancies. Clin Cancer Res. 2007;13(18):5411-5417.
102. Bondarev AD, Attwood MM, Jonsson J, Chubarev VN, Tarasov VV, Schiöth HB. Recent developments of HDAC inhibitors: Emerging indications and novel molecules. Br J Clin Pharmacol. 2021;87(12):4577-4597.
103. Luo M. Chemical and biochemical perspectives of protein lysine methylation. Chem Rev. 2018;118(14):6656-6705.
104. Hoy SM. Tazemetostat: first approval. Drugs. 2020;80(5):513-521.

105. Ziao Q, Yang J, Ge S, Chai P, Fan J, Jia R. Novel insights into histone lysine methyltransferases in cancer therapy: From epigenetic regulation to selective drugs. J Pharm Anal. 2023;13(2):127-141.
106. Daigle SR, Olhava EJ, Therkelsen CA, Basavapathruni A, Jin L, Boriack-Sjodin PA, et al. Potent inhibition of DOT1L as treatment of MLL-fusion leukemia. Blood. 2013;122(6):1017-1025.
107. Cao H, Li L, Yang D, Zeng L, Yewei X, Yu B, et al. Recent progress in histone methyltransferase (G9a) inhibitors as anticancer agents. Eur J Med Chem. 2019;179:537-546.
108. Szymanowska A, Rodriguez-Aguayo C, Lopez-Berestein G, Amero P. Non-Coding RNAs: Foes or Friends for Targeting Tumour Microenvironment. Non-coding RNA. 2023;9(5):52.
109. Bonneau E, Neveu B, Kostantin E, Tsongalis GJ, De Guire V. How close are miRNAs from clinical practice? A perspective on the diagnostic and therapeutic market. Electron J IFCC. 2019;30(2):114.
110. Nava VE, Perera PY, Kumar N, Jain M. Noncoding-RNA-Based Therapeutics with an Emphasis on Prostatic Carcinoma—Progress and Challenges. Vaccines. 2022;10(2):276.