IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Recent Developments In Metal Carcinogenicity And Potential Molecular Markers

Ms. Mane Rutuja. H,

Ms. Jain Alfa, Ms. Gaikwad Rucha, Ms. Kokane Rutuja.

Institute of pharmaceutical science and Research (for girls) (college code-6914) pune- solapur highway, swami chincholi (Bhigwan), Tal- Daund, Dist-pune 413130

Abstract:

Metal compounds that are carcinogenic and harm human health through occupational and environmental exposure include arsenic, cadmium, chromium, cobalt, lead, mercury, and nickel. However, the fundamental processes leading to tumor development remain poorly understood. Oxidative stress, which is a discrepancy between the system's capacity to quickly detoxify reactive intermediates and the rate at which free radicals are produced, may be caused by interference with metal homeostasis. As a result, this incident results in protein modification, lipid peroxidation, DNA damage, and maybe symptoms of numerous diseases, including cancer. Numerous molecular markers and common mechanisms of action are included in this overview. Free radicals produced by metals, oxidative stress, protein, lipid, and DNA damage, responsive signal transduction pathways important for cell growth and development, and the functions of antioxidant enzymes and DNA repair systems are all discussed. It is also discussed how certain regulatory factors, such as AP-1, NF-B, Ref-1, and p53, interact with non-enzymatic antioxidants, such as carotenoids, flavonoids, glutathione, selenium, vitamin C, and vitamin E. Cellular oxidative stress markers, such as catalase, glutathione peroxidase, and superoxide dismutase, are also discussed. Oncogenic stimulation is associated with dysregulation of defensive mechanisms, including the cellular antioxidant network against free radicals and a deficit in DNA repair. These findings support the hypothesis that DNA repair proteins and newly developing regulatory factors responsive to oxidative stress serve as possible predictors of tumor initiation and progression.

Keywords: carcinogenicity; DNA damage; DNA repair; genotoxicity; heavy metal; oxidative stress.

Introduction

1. General Characteristics of Cancer-Producing Metal Compounds

Environmentally speaking, metal complexes are present everywhere. Human exposure to metals is strongly influenced by industrial usage[1]. Arsenic, cadmium, chromium, cobalt, lead, mercury, and nickel are a few of the metals that the German MAK Commission and the International Agency for Research on Cancer have designated as human carcinogens or are thought to be human carcinogens[2]. Their ability to cause cancer is mostly influenced by their oxidation state, solubility, urea to hazardous metals is strongly linked to the production of free radicals in ligand complex shape[3]. Uptake, intracellular transport and distribution, and bioavailability are all governed by physicochemical qualities[4] . Similar in charge and size to necessary metal ions, toxic metal ions may challenge them for biological binding sites, causing disruptions in metal homeostasis as well as changes in biomolecular structure and function. Directly or indirectly, exposing things[5]. Oxidative stress, which is caused by the accumulation of free radicals such reactive oxygen species (ROS) and reactive nitrogen species (RNS), is connected to the development of cancer. Induction of oxidative stress and damage to cellular components, particularly DNA; interference with DNA repair mechanisms; genomic instability; and (3) inhibition of cell growth and proliferation via signaling pathways and dysregulation of oncogenes or tumor suppressor genes are the main mechanisms by which metals cause cancer[6]. More information is provided on these potential common processes of metal-induced carcinogenicity with special variations with respect to particular metals[7].

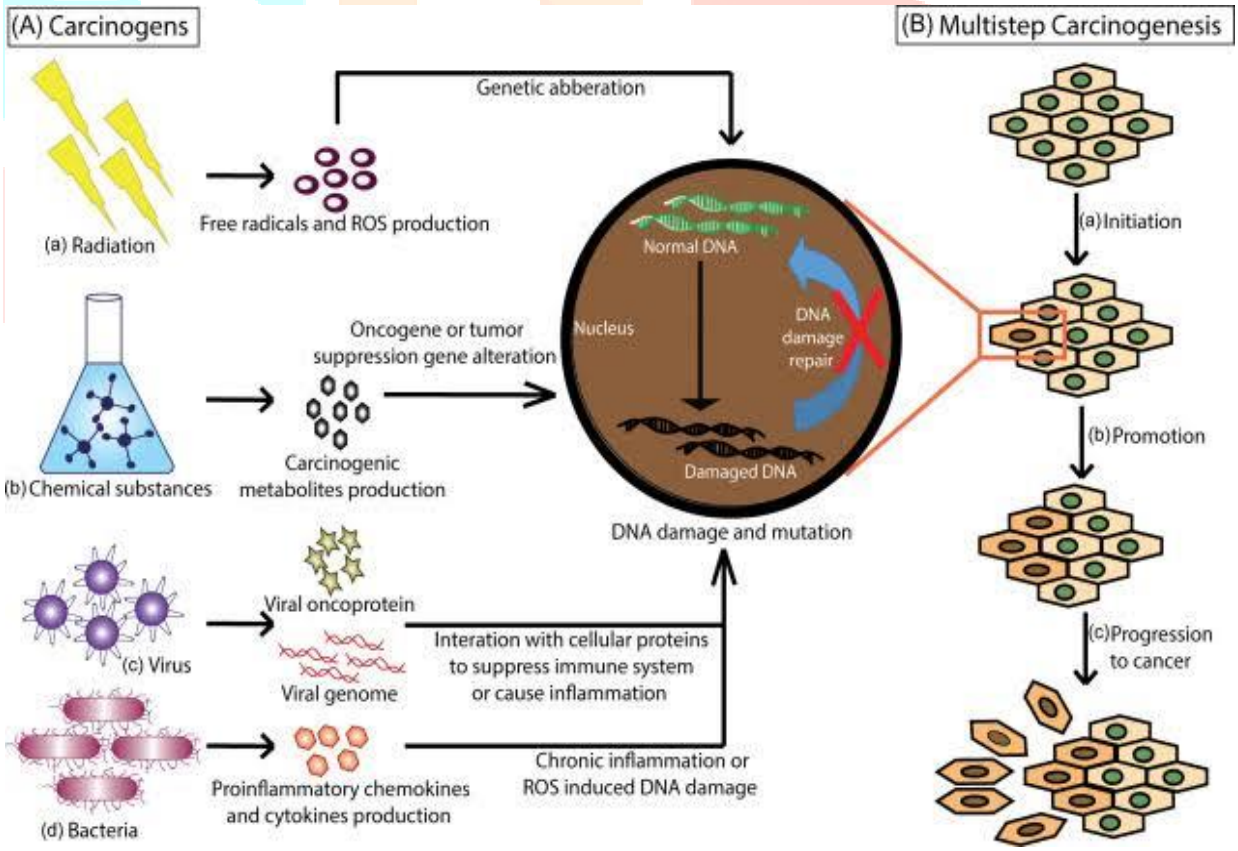

Fig : causes of cancer : physical ,chemical, biological carcinogens,and viruses.

2. General Mechanisms of Genotoxicity and Carcinogenicity Caused by Metals

The bulk of metal-induced carcinogenicity is caused by common processes of diverse carcinogenic metals that result in oxidative stress, compromise DNA repair systems, and disrupt signaling pathways (Figure)[8]. It is impossible to rule out specific carcinogenic metals' specific mechanisms, such as arsenic's replacement of inorganic phosphate in oxidative phosphorylation pathways, cadmium's disruption of cell-cell adhesion, trivalent chromium's direct DNA binding, and nickel's interference with DNA methylation and histone acetylation[9].

2.1 Induction of Oxidative Stress, a Causative Source for Metal Toxicity, is discussed in Section

A unique phenomenon that explains metal-induced genotoxicity and mutagenicity is the induction of oxidative stress. Redox reactions are brought on in living systems by a number of carcinogenic metals, including arsenic, cobalt, chromium, lead, mercury, and nickel[10]. These metals cause the generation of RNS (such as nitric oxide, proximities, and S-nitroso thiols) and ROS (such a Fenton- and Haber-Weiss-type reactions have been primarily responsible for the formation of hydroxyl radicals. These radicals have caused DNA, proteins, and lipids to oxidatively deteriorate[11]. Cadmium is a redox-inert metal that cannot carry out redox reactions in living things. Although it inhibits antioxidant enzymes including catalase, glutathione peroxidase, glutathione reductase, and superoxide dismutase through interactions with their thiol groups, both in vivo and in vitro, it is able to promote oxidative stresses hydroxyl peroxide and superoxide radicals) in both in vivo and in vitro systems[12]. Additionally, cadmium has the ability to replace copper and iron in a variety of cytoplasmic and membrane proteins (such as ferritin and apoferritin), which increases the quantity of free or inadequately chelated copper and iron ions and triggers Fenton reactions that cause oxidative stress[13]. DNA single-strand breaks and cellular DNA damage were caused by cadmium treatment in a sizable number of cells. Indeed, a Cd (II)-administered animal system experiences temporary oxidative damage. It's interesting to note that cobalt has a reversal effect on free radical production. The production of free radicals as well as the oxidation of lipids and proteins are both markedly reduced by cobalt intake[14]. Low amounts of ROS operate as a mitogenic signal to activate redox-sensitive transcription factors in addition to causing direct DNA damage. Chronic poisoning from repeated contact with hazardous metals causes their accumulation in living systems and raises health concerns for the general public. In vitro, exposure to so-called nanoparticles made of metallic compounds, such as cobalt and nickel, caused cytotoxicity in a concentration-dependent manner[15]. Numerous research projects have been carried out to examine the harmful effects of different metallic nanoparticles or nanomaterials on the production of free radicals as well as their modes of action both in vitro and in vivo[16]. These results point to many forms of DNA damage, including chromosomal abnormalities, DNA adduct formation, and the production of micronuclei According to the findings of the investigation of the expression of proteins and mRNA by nanoparticles, specific signaling pathways involving apoptosis, cell cycle regulation, embryogenesis, growth, and inflammation are severely disrupted[17].

2.2. Impairment of DNA Repair Systems and Involvement in Carcinogenesis: Environmental stimuli (such as UV, chemical toxins, and biological toxins) and endogenous substances produced during oxidative metabolism constantly damage DNA molecules[18]. As a result, a number of endogenous DNA repair systems continuously carry out some of their partially overlapping tasks. Base excision repair (BER), also known as single strand break repair, nucleotide excision repair (NER), base mismatch repair, and recombinational (double strand break) repair, are the four primary types of these[19]. Except for Cr (VI), the majority of carcinogenic metals are modest mutagens in mammalian cells and frequently commutate because other genotoxic substances accelerate their own mutagenicity[20]. A closer examination reveals contradictory phenomena under the heading of DNA repair impairment in metal-mediated carcinogenesis, including the occurrence of oxidative damage induced by redox-inert metals such as cadmium, differences between low mutagenicity and high carcinogenicity for nickel compounds, and synergistic effects of exposure to non-carcinogenic chemicals like polyaromatic hydrocarbons and cobalt[21]. In fact, recent studies have shown that some carcinogenic metals can prevent DNA damage

caused by both endogenous and external causes from being repaired at low doses. A growing body of research has shown that carcinogenic metals such as (III)/As(V), Cd (II), Cr (VI), Ni (II), Hg (II), and Pb (II) might interfere with DNA repair processes. individual metals can also be selectively inhibited by various repair techniques. Co (II) hinders the incision as well as the polymerization step in the NER system, whereas Cd (II) and Ni (II) obstruct the detection of DNA lesions. At low concentrations, as (III) inhibits the incision stage, while at larger concentrations, it inhibits the ligation step. The incision stage is similarly reduced by these three metals, Cd (II), Hg (II), and Pb (II). Water soluble Cd (II) has been found to disrupt the assembly and disassembly of the NER machinery, which is evidence of the disassembly inhibition of XPA and XPC, key elements in the global genome NER[22]. In vitro BER, NER, and strand break repair can all be inhibited by metalloids like methylated arenites, arsenates, and particulate arsenic. In human cells, chromium reduces NER and simultaneously increases the mutagenicity of benzo[a]pyrene. Human populations have been found to have higher susceptibility to chromate due to an OGG1 enzyme polymorphism implicated in the BER process. Deficits in these repair mechanisms that are inherited or acquired might start cancerous development[23]. Human cancer is significantly correlated with genetic flaws and polymorphisms in the DNA repair component genes (e.g., ERCC1, MGMT, MLH1, MSH2, MSH6, and XRCC4). Genomic instability results from repeated disruptions of repair and enduring DNA damage, which may enable abnormal cell growth and/or ineffective apoptosis[24].

2.3. Cell Growth Signaling Interference and Carcinogenesis Promotion

Dysregulation of cell proliferation and differentiation is most likely a factor in the genesis of tumors. Metals that cause cancer may have an impact on cell growth through mechanisms such altered expression of growth-related factors and deactivation of growth control. Several pathways, including the mitogen-activated protein kinase (MAPK) pathways, are supported by certain metals[25]. Nuclear transcription factors (AP-1, NF-B, p53, NFAT, and HIF-1) that control the expression of cytoprotective genes with regard to DNA repair, immunological response, cell cycle arrest, and apoptosis are activated as a result of this. In many different phosphatases, particularly serine/threonine-, phosphoserine-, and phospholipid-phosphatases, which are oxidized to create disulfide bonds, thiol groups are likely to interact with toxic metals and ROS [26]. This causes protein conformational changes, which in turn activate specific redox-regulated transcription factors as previously described and up-regulate a number of signaling cascades. factor nuclear transcription Apoptosis and cell proliferation are both critically dependent on AP-1. The JNK and p38 MAPK pathways are responsible for increasing AP-1 activity in response to certain metals, hydrogen peroxide, cytokines, and other stimuli. The inflammatory response, cell transformation, and cell survival are only a few of the processes in which nuclear factor NF-B plays a significant role[27]. NF-B activation has been linked to the development of cancer in response to environmental factors such UV rays, toxic metals, and benzo[a]pyrene. The discovery that various stimuli, including thiols and vitamin E, frequently prevent the activation of NF-B, has been shown to support the impact of metals and ROS on NF-B activation. In rats given nanoparticle treatment, administration of the antioxidant N-acetyl-l-cysteine (NAC) greatly reduces ROS production as well as NF-B, p38 MAPK, and protein kinase C-mediated signaling pathways, which eliminates inflammation. The majority of human malignancies are associated with p53 gene alterations. Environmental toxins like nickel, cigarette smoke, and UV radiation can cause p53 mutation. Mechanisms of p53 activation in response to carcinogenic metals have determined in multiple ways[28]. The nuclear factor of activated T cells (NFAT) controls cytokine production, muscle growth and differentiation, and angiogenesis. Previous studies have determined that various metals such as nickel increase intracellular calcium, representing a plausible mode of action for metal-activated NFAT. Certain metals activate NFAT not only via a calcium-dependent pathway but also through formation of hydrogen peroxide. Hypoxia-induced component by regulating the expression of numerous cancer-related genes, including as heme oxygenase1 and vascular endothelial growth factor, HIF-1 regulates precise oxygen homeostasis. It is known that hydrogen peroxide and carcinogenic metals like nickel or chromium activate HIF-1. According to an in vitro investigation, nickel stimulates HIF-1 by replacing the iron in the oxygen carrier with nickel, which results in permanent hypoxia and activates HIF1. Indeed, changes in gene expression

patterns may result from epigenetic mechanisms including hypo- or hypermethylation of DNA or changed histone acetylation. Tumor symptoms are associated with persistent alteration of gene regulation by carcinogenic metals. Some carcinogenic metals inhibit the tumor suppressor p53 and/or lower the expression of senescence-related genes as well as tumor suppressor genes (including p16 and p53). As a result, metals may promote cell growth by preventing apoptosis and enabling cell tolerance to metal toxicity[29]. Nickel disrupts the epigenetic pathways that regulate proper growth. Recent research has shown that nickel compounds increase the proliferation of mammalian cells by increasing the methylation of cytosine bases and decreasing the expression of tumor suppressor genes. DNA hypermethylation has been identified in nickel-induced malignancies together with decreased expression of the tumor suppressor genes p16 and Fit. The inhibition of various histones' acetylation and subsequent chromatin condensation in vitro by nickel compounds has been discovered as a second epigenetic mechanism. This inhibition is likely caused by nickel ions binding to the histone proteins. Inhibiting histone acetylation appears to contribute to the silencing of telomeric genes because it makes it easier for transcription factors to reach DNA[30].

3. Reviewing Protein-Protein Interactions with Zinc Finger Proteins as Potential Biomarkers for Metal-Genotoxicity and Carcinogenicity

In the human genome, over 10% of genes encode zinc finger proteins that serve a variety of purposes, such as DNA recognition and repair, RNA packaging, transcriptional activation, apoptotic regulation, protein folding and assembly[31]. Zinc is complexed to four cysteines (Cyst) or/and histidine's (His) within zinc finger structures in their DNA-binding motifs, enabling appropriate folding of various structural domains and promoting DNA-protein as well as protein-protein interactions. We'll review the most recent information on hazardous metal interference with zinc finger DNA repair proteins. In fact, rather than directly binding to DNA, interactions with zinc finger proteins, particularly DNA repair proteins, transcription factors, and tumor suppressors, are regarded to be more pertinent for metal-mediated carcinogenesis . The production of mixed complexes, isostructural substitution, replacement with changed geometry, and catalysis of thiol oxidation are examples of possible pathways for zinc finger interference by carcinogenic metals. These metal carcinogenesis-related mechanisms focus on altered gene expression[32]. Certain zinc finger proteins could be thought of as direct biomarkers that can predict the development of cancer (Figure 1). Mammalian DNA Repair Protein XPA, Section 3.1For the NER pathway's DNA lesion identification, Xerodermapigmentosum A (XPA) is a well-known protein with a single Cys4 zinc finger domain. One of the most adaptable repair mechanisms for diverse large DNA lesions caused by UV light, environmental carcinogens, and certain anticancer drugs is the NER. By attracting other proteins to the damaged DNA region in the first phase, XPA plays a crucial role in the formation of the pre-incision complex. These include replication protein A, transcription factor IIH, and excision repair cross-complementing protein 1. UVC, benzo[a]pyrene, or cis-platinum-induced DNA lesions are the only ones that XPA exclusively binds to. The minimum DNA-binding domain of XPA includes a single zinc finger motif where four Cyst residues are complexed with zinc[33]. Replacement of each of these Cycloadds results in a significant decline in NER activity. Systematic studies concentrating on metal-inhibited XPA binding to a UV-irradiated oligonucleotide using a gel mobility shift test have demonstrated that DNA binding activity is decreased by adding Cd (II), Co (II), and Ni (II), but is not impacted by as (III), Hg (II), or Pb (II). Inhibition of XPA by Cd (II), Co (II), and Ni (II) can be effectively avoided by concurrent Zn (II) treatment. Parallel studies with a bacterial version of the well-studied zinc finger protein aminopyrimidine-DNA glycosylase (Fig), which is responsible for BER, have shown susceptibilities to Cd (II) and Hg (II), but no inhibitory effect of the other metals tested. This illustrates how each zinc finger protein reacts differently to various hazardous metals[34]. A structural model of the 37-peptide XPA zinc finger motif (Paz) has been used in additional molecular investigations to enable quantitative comparisons of Zn (II) with Cd (II), Co (II), and Ni (II). It has been discovered to encourage Paz oxidation in the presence of Ni (II), which results in the loss of Zn (II). Changes in the tetrahedral geometry of the metal site and the irreversible creation of intramolecular disulfide bonds catalyzed by Ni (II) could be the cause of this. In contrast to Ni (II), Co (II) exhibits reduced

efficiency for Zn (II) substitution. It has been reported to indirectly promote substantial Paz oxidation at high Co (II) concentrations. Due to Cd (II)'s extremely high binding affinity, it is conceivable to quantitatively substitute Zn (II) and subsequently alter the peptide structure without Cd (II)-mediated oxidation of thiol groups. These three metals each have a unique way of hindering XPA. According to recent studies, soluble cadmium chloride obstructs the disassembly of XPA and XPC, two important initiators in the global genome NER[35]. Additionally, it is still unclear how carcinogenic metals interfere with the zinc finger motif of DNA-protein interactions to worsen such interactions. DNA strand break repair protein Poly (ADP-Ribose) Polymerase (PARP) 3.2 The primary function of PARP's two distinct Cys3His1-type zinc finger domains is to identify and signal DNA strand breaks to the enzymatic components of BER. Long chains of poly (ADP-ribose) polymers are added to target proteins involved in chromatin architecture and DNA metabolism by PARP after a DNA strand breaks[36] . For the purpose of identifying and/or detecting nicked DNA, this alteration step appears to be necessary. Through cell cycle arrest and subsequent interaction with DNA repair enzymes, PARP continues the DNA repair process in response to mild to moderate genotoxic stimuli. Severe DNA damage may cause PARP to become hyperactivated, which finally triggers the apoptotic process. Furthermore, although it is still not completely understood, PARP probably plays a significant role in both spontaneous and anticancer agent-induced apoptosis. An analysis of the inhibitory effects of anticancer metal complexes on the PARP activity produced from human cancer cells very recently revealed a high correlation between the ability of these complexes to bind to the zinc finger motif through zinc competition and the inhibition of PARP. These findings provide credence to the idea that the zinc finger motif's activity is decreased by zinc displacement with other metals[37]. This finding highlights the potential role of PARP as a mediator in cancer cell chemotherapies' drug resistance. As (III) decreases PARP activity in a human lymphoma cell line. Similar studies have shown that as (II), Co (II), Cd (II), and Ni (II), but not Pb (II) or Hg (II), selectively inhibit hydrogen peroxide-induced PARP activity in HeLa cells. It is important to conduct additional molecular research based on inhibition via interactions with the zinc finger motif. DNA strand break repair protein Poly (ADP-Ribose) Polymerase (PARP) 3.2 The primary function of PARP's two distinct Cys3His1-type zinc finger domains is to identify and signal DNA strand breaks to the enzymatic components of BER . Long chains of poly (ADP-ribose) polymers are added to target proteins involved in chromatin architecture and DNA metabolism by PARP after a DNA strand breaks. For the purpose of identifying and/or detecting nicked DNA, this alteration step appears to be necessary. Through cell cycle arrest and subsequent interaction with DNA repair enzymes, PARP continues the DNA repair process in response to mild to moderate genotoxic stimuli. Severe DNA damage may cause PARP to become hyperactivated, which finally triggers the apoptotic process[38]. Furthermore, although it is still not completely understood, PARP probably plays a significant role in both spontaneous and anticancer agent-induced apoptosis. An analysis of the inhibitory effects of anticancer metal complexes on the PARP activity produced from human cancer cells very recently revealed a high correlation between the ability of these complexes to bind to the zinc finger motif through zinc competition and the inhibition of PARP. These findings provide credence to the idea that the zinc finger motif's activity is decreased by zinc displacement with other metals. This finding highlights the potential role of PARP as a mediator in cancer cell chemotherapies' drug resistance[39]. As (III) decreases PARP activity in a human lymphoma cell line Similar studies have shown that as (II), Co (II), Cd (II), and Ni (II), but not Pb (II) or Hg (II), selectively inhibit hydrogen peroxide-induced PARP activity in HeLa cells. It is important to conduct additional molecular research based on inhibition via interactions with the zinc finger motif. Tumor Suppressor Protein p53, Section 3.3Through the NER and genomic stability, the p53 protein, which has a zinc finger domain of the Cys3His1 type, plays a significant part in DNA repair[40]. Depending on the physiological condition and type of cell, p53 regulates a number of crucial processes to induce DNA repair processing, cell cycle arrest, or apoptosis through coordinated pathways. Indeed, a variety of stress signals, including DNA damage, activate p53. By binding to certain response regions, p53 controls the transcription of multiple downstream genes, including XPA. By preventing damaged cells from reproducing, damaged DNA is repaired, or cells with severe damage undergo apoptosis. Additionally, certain proteins involved in DNA replication, transcription, and repair interact directly with p53. Sequence-specific DNA binding is dependent on metal and redox control due to

its primary biochemical characteristic. Zinc is thought to be necessary for correct folding of p53 into its native conformation and subsequent functioning because p53-DNA interaction is mediated by tetrahedral coordination of zinc with three Cyst and one Hys. In the presence of DNA damage, selenium compounds, acting as redox stimulators, may promote p53-specific DNA binding as well as p53-mediated DNA repair through a redox regulation at certain Cyst residues. Due to the disturbance of p53's native conformation, Co (II) and Ni (II) reduce the ability of p53 to bind DNA and prevent cell cycle arrest. The conformation of p53 at the zinc finger motif was also changed by water-soluble cadmium chloride and particulate cadmium oxide compounds in human cells[41]. When combined, zinc finger motifs take role in interactions between proteins and DNA in a number of protein families, including those that are involved in DNA repair, transcription, and tumor suppression. These zinc finger proteins are differently inhibited by known carcinogens like arsenic, cadmium, cobalt, lead, and nickel, which results in misaligned zinc finger domains and subsequent malfunctioning of the proteins. As a result, this reactivity might be thought of as a probable molecular pathway in the development of cancer. In fact, only a small amount of data has been used to define reference concentrations (Race) or reference doses (RfD) for the exposure of specific carcinogenic metals, demonstrating that there is no reliable correlation between metal concentrations and human carcinogenicity. In addition to directly measuring metal concentrations in human samples, these zinc finger proteins may be used as genetic risk factors for carcinogenesis because of changes in their binding constants or stability constants when complexed with Zn (II) or thiol-typed antioxidants (such as glutathione and thioredoxin). As an alternative, measuring DNA repair capacity using assays of specific enzymes (DNA polymerase "pol" and XPG or ERCC5) involved in known zinc finger protein-modulated repair pathways, with the use of protein extracts from human tissues or cells, may be useful for partially evaluating cancer risk[42].

4. Improving Antioxidant Defense Mechanisms to Lower Metal-Induced Carcinogenicity

Different cancer-causing metals interact intricately with biological elements. The cellular components of antioxidant defenses are crucial because they balance prooxidants, ROS, and RNS, which are brought on by the actions of non-enzymatic antioxidants as well as antioxidant enzymes , and they scavenge them[43]. This ensures that biological sites are protected to the fullest extent possible. Catalase, glutathione peroxidase, and superoxide dismutase are the three most effective enzymatic antioxidants. Vitamin C, vitamin E, thiol antioxidants (glutathione, thioredoxin, and lipoic acid), natural flavonoids, melatonin, and selenium are examples of non-enzymatic antioxidants. Vitamin E and -lipoic acid are examples of antioxidants that function in a hydrophobic phase, while vitamin C and vitamin E are examples of antioxidants that act in both phases. Redox potentials are responsible for an antioxidant network's ability to replenish one antioxidant after another. Increased ROS levels and eliminated enzymatic and non-enzymatic antioxidant activity in tumor cells are related. Enzymatic Antioxidants and Their Physiological Reaction to Metal toxicity, Section[44].

4.1Animals exposed to arsenic have been shown to have altered amounts of reduced glutathione and glutathione peroxidase [4,103,104]. Catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase, and Cu, Zn-superoxide dismutase activity have all been found to vary in rats exposed to cadmium. In animal models, lead exposure alters the levels of reduced glutathione as well as the oxidative stress indicators catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. While the addition of antioxidant enzymes like catalase and superoxide dismutase (75 and 150 g/mL, respectively) does not seem to protect lymphocytes against organic mercury-induced genotoxicity in vitro, epidemiological observations have shown that the activity of these enzymes' changes in exposed populations with a consequent genotoxic alteration[45]. These findings highlight how persistent oxidative stress brought on by long-term exposure to relatively low mercury levels may limit antioxidant enzyme activity. This phenomenon may provide as a significant peripheral target for populations exposed to mercury exposure[46].

4.2Non-enzymatic antioxidants and their improvement in the development of cancer

The reduction in ROS level in rat testicular tissues demonstrates how vitamin C and/or E supplementation can prevent cadmium poisoning. In rats exposed with cadmium, dietary intake of a mixture of these vitamins returns the testicles to normal function. By lowering lipid peroxidation and preserving physiological homeostasis, powerful antioxidants and free radical scavengers such melatonin, methyl gallate, and quercetin also have cytoprotective effects against cadmium poisoning[47]. Cobalt particles that are inhaled predominantly interact with antioxidants and surfactants on the lung surface. One of the first lines of defense against lung injury brought on by excessive ROS generation is reduced glutathione, a ROS scavenger. The amount of dust present and the resulting surface area exposed are related to how much the thiol concentration is reduced. Additionally, intracellular ascorbate is depleted as a result of Co (II) exposure. It's interesting to note that while the efflux is a metal-independent process, cobalt inhibits the influx of ascorbate[48]. Superoxide and hydroxyl radicals produced by cobalt can be neutralized by reduced glutathione and ascorbate, respectively. Additionally, in reaction to cobalt in the form of a cobalt/tungsten (Co/WC) combination, reduced glutathione and Cyst residues in proteins also play a significant role in redox regulation. According to earlier studies, ascorbate is thought to be the main reducer of Cr (VI) in cells. Ascorbate, on the other hand, plays two conflicting roles in Cr (VI) poisoning, acting as a prooxidant inside of cells and a protective-antioxidant outside. High levels of chromium-DNA adduct are produced by the ascorbate-initiated reduction of Cr (VI) inside cells, which permits DNA mutation. Additionally, non-enzymatic interactions between Cyst and glutathione diminish Cr (VI) as well. NAD(P)H appears to be the main reductant of Cr (VI) in mitochondria, producing stable Cr (III) with a considerably higher DNA affinity than Cr (VI). Glutathione metabolism is mostly responsible for lead poisoning. In animal studies, lead exposure changes the reduced glutathione level. A crucial substrate, glutathione influences how many medications and poisons work through its conjugation in the liver. Following lead exposure in humans, a rise in the prevalence of hypertension has been noted, which may be related to the major impact of RNS such nitric oxide. Nitric oxide availability can be reduced by using antioxidants. When given to hypertensive rats with inhibited glutathione production, vitamins E (5000 IU/kg) and C (3 mmol/L of drinking water) completely reverse hypertension. Nitric oxide availability can be reduced by using antioxidants[49]. When given to hypertensive rats with inhibited glutathione production, vitamins E (5000 IU/kg) and C (3 mmol/L of drinking water) completely reverse hypertension. Superoxide dismutase levels are restored by zinc supplementation in lead-exposed rats, indicating that zinc functions as an antioxidant and a likely chelating agent for lead poisoning. Animals are protected when given selenium before being exposed to lead. In addition to reduced glutathione, selenium increases the levels of glutathione peroxidase, superoxide dismutase, and reduced glutathione in kidney and liver tissues. Selenium produces a stable lead-selenium complex, suggesting that it has anti-toxic properties against lead. An excellent antioxidant with chelating effects is alpha-lipoic acid. The adverse effects of lead exposure on glutathione and oxidative stress indicators in liver and kidney tissues are suppressed by alpha-lipoic acid in response to lead exposure[50].

A significant line of cell defense against mercury toxicity appears to be glutathione, which may protect cells by acting as an antioxidant and chelating mercury, according to research on mercury-induced toxicity. High intracellular glutathione levels may help provide neural protection after exposure to mercury chemicals, according to prior research. In vivo studies have shown that communities of people who consume methylmercury-contaminated fish (levels of mercury content in hair of 12–15 g/g) have higher glutathione levels. Additionally, a direct correlation between blood levels of glutathione and mercury has been discovered. Ascorbate is an example of an antioxidant that exhibits its anti-mercury genotoxicity properties in vitro by suppressing sister chromatid swaps and aberrant mitosis. Intriguingly, in communities exposed to mercury, a strong negative connection was found between blood levels of mercury and consumption of tropical fruits, especially oranges high in vitamin C. This illustrates yet another facet of the antioxidant molecules' protective function. However, inconsistent results between experimental studies (both in vitro and in vivo) and human

clinical trials regarding the association between antioxidant supplements and the risk of carcinogenesis have been found by a meta-analysis of randomized controlled trials, suggesting that experimental studies showing the effects of antioxidant substances cannot be directly applied to humans because these substances may exert negative properties or promote carcinogenesis. The use of antioxidant supplements for the primary and secondary prevention of cancer is currently not supported by any clinical data. The possible impacts of antioxidant supplements on human health, particularly in relation to cancer risk, must be noted, even though many populations consume them to enhance their health and prevent cancer[51].

5. Finalization

Growing attention has been paid to the connection between metal-induced interference and carcinogenesis in living systems. It is extremely important to comprehend the mechanisms underlying the toxicity caused by various carcinogenic metals and metallic nanoparticles. Metallic nanoparticle toxicity and recommended practices are little understood, despite an increasing trend in their utilization. Chronic exposure to hazardous metals can enter live organisms through a variety of mechanisms, accumulating and leading to serious sickness. Toxic metal biomonitoring in bodily fluids like blood and urine in children may offer adequate assessments to stop such illness or suffering that causes severe mental retardation. Complex mechanisms underlie metal carcinogenicity, and it is believed that oxidative stress, cellular redox equilibrium, DNA repair, and certain signal transduction pathways are interrelated[52]. It is likely more important for metal-mediated carcinogenesis than direct interactions with DNA that hazardous metals interfere with zinc finger proteins, particularly DNA repair proteins. Epidemiological findings indicating a wide number of human populations, especially in industrialized nations, have increased cancer incidence highlight the pertinent issue of zinc finger proteins operating in DNA repair systems. Zinc finger motifs are found in zinc finger proteins, such as DNA repair enzymes, nuclear transcription factors, and tumor suppressors. Zinc deprivation likely causes an increase in displacement and a decrease in restoration of these motifs. Therefore, a wide range of these zinc finger proteins may be considered viable biomarkers for determining the risk of exposure to specific carcinogenic metals in the environment and at work. For the development of a test to be as effective as feasible, finding novel markers or a group of particular markers will also be necessary. These investigations will be beneficial for strengthening a thorough risk assessment and enhancing public health protection. Non-enzymatic antioxidants appear to work in tandem with cellular antioxidant enzymes to significantly lower cancer incidence related to oxidative stress. Keeping yourself as little as possible exposed to oxidative stressors, especially from exogenous sources, is the most crucial step in cancer prevention[53].

Conclusion:

There has been a growing body of research on the connection between carcinogenesis in living systems and interference caused by metals. It is extremely important to comprehend the reasons behind the toxicity caused by various metallic nanoparticles and carcinogenic metals. While metallic nanoparticles are becoming more and more common, little is known regarding their toxicity and recommended uses. Hazardous disease accumulation can result from long-term exposure to toxic metals entering living organisms through a variety of pathways. In order to prevent severe mental retardation in children, toxic metal biomonitoring in physiological tissues like blood and urine may offer sufficient assessments to stop such illness/suffering. Complex mechanisms underlie metal carcinogenicity, with specialized signal transduction pathways, cellular redox balance, oxidative assault, and DNA repair all believed to be interdependent.It is probable that hazardous metal-induced carcinogenesis is more closely related to the disruption of zinc finger proteins—specifically, DNA repair proteins—than to direct interactions with DNA. Epidemiological data showing higher cancer incidence in many human populations—even in affluent nations—with insufficient dietary zinc further lends weight to the pertinent question of zinc finger proteins operating in DNA repair mechanisms..Further work will be needed to identify novel markers or a set of specialized markers in order to design a test that will discover faults as soon as possible. These investigations will be beneficial for strengthening public health protection and creating a more thorough risk assessment. Non-

enzymatic antioxidants working with cellular antioxidant enzymes appear to neutralize significant action to lower cancer incidence related to oxidative stress. Preventing cancer mostly involves reducing exposure to oxidative stressors, especially those originating from external sources.

Reference:

1.Beyersmann D, Hartwig A. Carcinogenic metal compounds: recent insight into molecular and cellular mechanisms. Arch Toxicol. 2008; 82: 493–512.

2.Achanzar WE, Webber MM, Waalkes MP (2002) Altered apoptotic gene expression and acquired apoptotic resistance in cadmium-transformed human prostate epithelial cells. Prostate 52:236–244

3.Neha, K.; Haider, M.R.; Pathak, A.; Yar, M.S. Medicinal prospects of antioxidants: A review. Eur. J. Med. Chem. 2019, 178, 687–704.

4.C. Hansch et al.

Substituent Constants for Correlation Analysis in Chemistry and Biology

(1979)

5.Waldron, K. J. & Robinson, N. J. How do bacterial cells ensure that metalloproteins get the correct metal? Nature Rev. Microbiol. 7, 25–35 (2009)

6.J.M. McCord et al.

Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein)

J. Biol. Chem.

(1969)

7.Satarug S, Baker JR, Reilly PE, Moore MR, Williams DJ: Cadmium levels in the lung, liver, kidney cortex, and urine samples from Australians without occupational exposure to metals. Arch Environ Health 57: 69–77, 2002

8.Halliwell, S.; Gutteridge, J.M.C. Free Radicals in Biology and Medicine, 4th ed.; Oxford University Press: New York, NY, USA, 2007.

9.Bal W, Liang R, Lukszo J, Lee SH, Dizdaroglu M, Kasprzak KS (2000) Ni(II) specifically cleaves the C-terminal tail of the major variant of histone H2A and forms an oxidative damage-mediating complex with the cleaved-off octapeptide. Chem Res Toxicol 13:616–624

10.Sunderman FW, Jr. Carcinogenicity and mutagenicity of some metals and their compounds. International Agency for Research on Cancer Scientific Publications, Vol 71. IARC, Lyon 1986; 17–43

11.Hey, D.H., and W.A. Waters, Some Organic Reactions Involving the Occurrence of Free Radicals in Solution, Chem. Rev. 21: 169–208 (1937).

12.Anderson CP, Shen M, Eisenstein RS, Leibold EA (2012) Mammalian iron metabolism and its control by iron regulatory proteins. Biochim Biophys Acta 1823:1468–1483. doi:10.1016/j.bbamcr.2012.05.010

13.J.E. Chipuk et al.

How do BCL-2 proteins induce mitochondrial outer membrane permeabilization?

Trends Cell Biol

(2008)

14.Beyersmann, D.; Hartwig, A. Carcinogenic metal compounds: Recent insight into molecular and cellular mechanisms. Arch. Toxicol 2008, 82, 493-512.

15.J. G. Kusters, A H. Vliet and E. J. Kuipers, Clin. Microbiol. Rev 19, 449

(2006)https://doi.org/10.1128/CMR.00054-05

16. Ahamed M, Karns M, Goodson M, Rowe J, Hussain SM, Schlager JJ, 2008. DNA damage response to different surface chemistry of silver nanoparticles in mammalian cells. Toxicol Appl Pharmacol 233:404-410.

17.M. Fenech et al.The Human micronucleus project-an international collaborative study on the use of the micronucleus technique for measuring DNA damage in humans

Mutat. Res(1999)

18.H. Sato, H. Shibata, T. Shimizu, S. Shibata, H. Toriumi, and T. Ebine, "Differential cellular localization of antioxidant enzymes in the trigeminal ganglion, Neuroscience, vol. 248, pp. 345-358, 2013.

19. Zhou BB, Elledge SJ (2000) The DNA damage response: putting checkpoints in perspective. Nature 408(6811):433-439

20.Abbott BD, Held GA, Wood CR, Buckalew AR, Brown JG, Schmid J. AhR, ARNT, and CYP1A1 mRNA quantitation in cultured human embryonic palates exposed to TCDD and comparison with mouse palate in vivo and in culture. Toxicological Sciences.

1999:47:62-75

21.Akaike et al., 2015

Akaike Y, Kuwano Y., Nishida K, Kurokawa K., Kajita K., Kano S, et al.

Homeodomain-interacting protein kinase 2 regulates DNA damage response through interacting with heterochromatin protein 1 gamma.

Oncogene, 34 (2015), pp. 3463-3473, 10.1038/onc.2014.278

22.Adamo A, Collis S.J, Adelman CA, Silva N, Horejsi Z, Ward JD, Martinez-Perez E,

Boulton SJ, La Volpe A. 2010. Preventing nonhomologous end joining suppresses DNA

repair defects of Fanconi anemia. Mol Cell 39: 25-35.

23.Angelini S, Kumar R, Carbone F, Maffei F, Forti GC, Violante FS, Lodi V, Curti S, Hemminki K, Hrelia P (2005) Micronuclei in humans induced by exposure to low level of ionizing radiation: influence of polymorphisms in DNA repair genes. Mutat

Res 570:105–117

24.Collis SJ, Boulton SJ. Emerging links between the biological clock and the DNA damage response. Chromosoma (2007) 116:331–9. doi: 10.1007/s00412-007-0108-6

25.Shih, C. & Weinberg, R. A. Isolation of a transforming sequence from a human bladder carcinoma cell line. Cell 29, 161–169 (1982).

26.Anand P, Kunnumakkara AB, Sundaram C, Harikumar KB, Tharakan ST, Lai OS, Sung B, Misra K, Aggarwal BB (2008) Cancer is a preventable disease that requires major life style changes. Pharm Res 25(9):2097–2116

27.J.J. Haddad et al.

Biochem. Biophys. Res. Commun.

(2000)

28.BarnesP.J. et al.

NF-κB: a pivotal role in asthma and a new target for therapy

Trends Pharmacol. Sci.

(1997)

29.Bouck, N., V. Stellmach, and S.C. Hsu. 1996. How tumors become angiogenic. Adv. Cancer Res. 69:135–174.

30.M. Esteller, R. Risques, M. Toyota, G. Capella, V. Moreno, M. Peinado, S. Baylin and J. Herman, Promoter hypermethylation of the DNA repair gene 0(6)-methylguanine-DNA methyltransferase is associated with the presence of G:C to A:T transition mutations in p53 in human colorectal tumorigenesis, Cancer Res., 2001, 61, 4689–4692

31.Beerli, R.R. & Barbas, C.F. III. Engineering polydactyl zinc-finger transcription factors. Nat. Biotechnol. 12, 632–641 (2002).

32.Bothos J, Summers MK, Venere M, Scolnick DM, Halazonetis TD . (2003). The Chfr mitotic checkpoint protein functions with Ubc13-Mms2 to form Lys63-linked polyubiquitin chains. Oncogene 22: 7101–7107.

33.Prakash A., Doublie S., Wallace S.S.. The Fpg/Nei family of DNA glycosylases: substrates, structures, and search for damage, Progress Mol. Biol. Trans. Sci., 2012, vol. 110 (pg. 71-91)

34.Corentin Lefebvre, Clément Michelin, Thomas Martzel, Vaneck Djou'ou Mvondo, Véronique Bulach, Manabu Abe, and Norbert Hoffmann . Photochemically Induced Intramolecular Radical Cyclization Reactions with Imines. The Journal of Organic Chemistry 2018, 83 (4) , 1867-1875.

35.Achanzar WE, Webber MM, Waalkes MP. 2002. Altered apoptotic gene expression and acquired apoptotic resistance in cadmium-transformed human prostate epithelial cell. Prostate. 52:236–244.

36.Lord CJ, Ashworth A . The DNA damage response and cancer therapy. Nature 2012; 481: 287–294.

37.Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; 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, 394–424. [Google Scholar] [CrossRef] [PubMed][Green Version]

38.Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci USA. 1990;87:1620–4.

39.X. Ding et al.

Differential sensitivities of cellular XPA and PARP-1 to arsenite inhibition and zinc rescue

Toxicol. Appl. Pharm.(2017)

40.B.N. Ames

DNA damage from micronutrient deficiencies is likely to be a major cause of cancer

Mutation Research,

(2001)

41.Ganther, H.E. (1999) Selenium metabolism, selenoproteins and mechanisms of cancer prevention: complexities with thioredoxin reductase. Carcinogenesis 20, 1657–1666.

42.Thomson, C.D. (2004) Assessment of requirements for selenium and adequacy of selenium status: a review. Eur. J. Clin. Nutr. 58, 391–402.

43.Flora SJ. Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure. Oxid Med Cell Longev. 2009;2:191–206.

44.Diplock A. T., Machlin L. J., Packer L., Pryor W. A. Vitamin E: biochemistry and health implications. Ann. N.Y. Acad. Sci. 1989; 570

45.M. Arita, Y. Sato, H. Arai, K. Inoue

Binding of atocopherylquinone, an oxidized form of a-tocopherol, to glutathione S-transferase in the liver cytosol

FEBS Lett., 436 (1998), pp. 424-426

46.F.Z. Avval et al.

Molecular mechanisms of thioredoxin and glutaredoxin as hydrogen donors for mammalian S phase ribonucleotide reductase

J. Biol. Chem.

(2009)

47.Thoreux-Manlay A, de la Calle JFV, Olivier MF, Soufir JC, Masse R, Pinon-Lataillade G: Impairment of testicular endocrine function after lead intoxication in the adult rat. Toxicology. 1995, 26: 101-109.

48.Beyersmann, D.; Hartwig, A. Carcinogenic metal compounds: Recent insight into molecular and cellular mechanisms. Arch. Toxicol 2008, 82, 493–512. [Google Scholar]

49.Shukla, D.; Saxena, S.; Jayamurthy, P.; Sairam, M.; Singh, M.; Jain, S.K.; Bansal, A.; Ilavazaghan, G. Hypoxic preconditioning with cobalt attenuates hypobaric hypoxia-induced oxidative damage in rat lungs. High Alt. Med. Biol 2009, 10, 57–69. [Google Scholar]

50.Hamdan, M., Noorhamdani, A. S., Rahayu, M. & Machfoed, M. H. The effect of Ginkgo Biloba (Egb) extracts on the expression of Hsp 90, Vegf and Bdnf in the Rattus Novergicus with lead (Pb) exposure. J. Int. Dent. Med. Res. 13(1), 17–22 (2020).

51.Robins, P.; Jones, C.J.; Biggerstaff, M.; Lindahl, T.; Wood, R.D. Complementation of DNA repair in xerodermapigmentosum group A cell extracts by a protein with affinity for damaged DNA. EMBO J 1991, 10, 3913–3921.

52.Pande, M.; Flora, S.J.S. Lead induced oxidative damage and its response to combined administration of alpha-lipoic acid and succimers in rats. Toxicology 2002, 177, 187–196.

53.M. Asmuss et al.

Differential effects of toxic metal compounds on the activities of Fpg and XPA, two zinc finger proteins involved in DNA repair

Carcinogenesis

(2000)

Acknowledgments

The Ministry of Environment of Korea provided funding for this work under grant number 2010-090001-0083-0. The Korea Research Foundation Grant, funded by the Korean government (MOEHRD, Basic Research Promotion Fund) (KRF-2008-313-E00139), also provided funding for this review. Additionally, it was funded by a grant from the Ministry of Education, Science and Technology's Basic Science Research Program through the National Research Foundation of Korea (NRF) (award numbers 2011-0017246 and 2011-0004481).