Chapter-19

Cadmium as a Carcinogen

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Abstract

Cadmium is a heavy metal introduced into the environment primarily through industrial activities. Cadmium exposure has been associated with several human diseases, such as renal dysfunction, hepatic impairment, pulmonary disease, neurodegenerative disorders, and Cancer. This chapter aims to provide insights into the various sources of cadmium exposure, its toxicological effects on human health, and its involvement in multiple types of cancer development. Cadmium is a potential carcinogen, reducing exposure and mitigating its harmful effects is crucial for human human and cancer prevention.

Keywords: Cadmium, heavy metal, Cancer, carcinogen, health.

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1. INTRODUCTION

Cadmium (Cd) is a transition metal with atomic number 48 and a silvery-white hue, belonging to Group 12 of the periodic table. This heavy metal exhibits unique chemical properties with industrial applications and significant environmental implications. With a melting point of 321.07°C and a boiling point of 765°C, cadmium is a relatively soft and ductile metal, commonly used in electroplating, as a pigment in plastics and ceramics, and in rechargeable nickel-cadmium batteries due to its ability to conduct electricity. Despite its industrial utility, cadmium is notorious for its toxic nature, lacking any known physiological function in biological systems. The toxicity of cadmium arises from its ability to interfere with essential cellular processes, leading to a myriad of adverse health effects [1]. Cadmium exposure occurs through various routes, including inhalation of contaminated air, ingesting contaminated food and water, and dermal contact with contaminated soil or dust particles. Once absorbed into the body, cadmium accumulates primarily in the kidneys, liver, gut, and bones, persisting for decades due to its slow excretion rate. Chronic exposure to cadmium has been associated with renal dysfunction, hepatic impairment, pulmonary complications, reproductive toxicity, and an increased risk of developing various cancers, including lung, kidney, and prostate cancer [2–4]. Furthermore, cadmium toxicity extends beyond its direct effects on human health, with detrimental consequences for ecosystems and wildlife. Contamination of soil and water bodies with cadmium disrupts ecological balance, affecting plant growth and biodiversity and ultimately posing risks to food chains and human consumption [5–7].

In this chapter, we will explore the toxicological aspects and environmental implications of cadmium metal and its adverse effects on human health and role in different types of Cancer. Understanding the complex interactions between cadmium and biological systems is crucial for developing effective measures to prevent and remediate cadmium contamination and protect public health.

2. CADMIUM EXPOSURE AND IMPACT ON HUMAN HEALTH

Cadmium, a ubiquitous heavy metal introduced into the environment primarily through industrial activities, poses significant health risks to humans and ecosystems alike. Half-life Cadmium in the human body is 25–30 years; thus, after entering the body, it accumulates throughout life. This chapter aims to provide insights into the various sources of cadmium exposure, its toxicological effects on human health, and strategies for managing cadmium toxicity [8–10].

Environmental Sources and Exposure Routes

Cadmium enters the environment through atmospheric deposition, mining activities, industrial processes, and agricultural practices. Contaminated water, food, and air are significant routes for human exposure to cadmium. Humans sometimes get exposed to cadmium through skin contact with cadmium-mixed products. Soil contamination, particularly in regions with historical industrial activity, can lead to elevated cadmium levels in crops and vegetables, posing risks to human health through food consumption. Notably, irrigation of rice fields with cadmium-contaminated water has been a concern, with implications for public health, as rice is a staple food in many cultures. The sources of cadmium contamination in the environment include the combustion of fossil fuels, agricultural land, leachate generated from landfill sites, and mining waste generated from zinc and lead mines [8,11].

Food and Water: High levels of cadmium can be found in seafood like crabs, oysters, and shrimp, as well as in certain organ meats like liver and kidneys. It is also present in foods like cocoa beans, certain wild mushrooms, and seeds like pumpkin or sunflower seeds. Depending on how contaminated the soil is plant-based foods like rice, wheat, leafy greens, potatoes, carrots, and celery can have higher cadmium levels than foods from animals like meat, eggs, milk, and cheese. People who do not eat meat or much shellfish might take in more cadmium than those who eat various foods. Eating rice is one of the main ways people can be exposed to cadmium. In places where the soil has much cadmium, like in Japan, flooding rice fields with water at harvest time can help reduce the amount of cadmium that gets into the rice, although this might

increase the amount of arsenic in the rice. Cadmium behaves in a certain way in water, which means it can move around quickly, especially in areas where the water is not too acidic or too basic. This can lead to cadmium getting into drinking water and rivers, especially in places near factories or mines. Cadmium can also end up in the soil from air pollution, mining activities, and using certain fertilizers or sewage sludge on farms. This can make it easier for plants and vegetables to absorb cadmium from the soil, resulting in our food [5–7].

Tobacco and Smoking: Cadmium found in tobacco smoke is recognized as a potentially significant contributing factor in lung diseases associated with smoking. According to the World Health Organization (WHO), cadmium poses a significant threat to public health, and it naturally accumulates in tobacco plants such as Nicotiana tabacum. This natural accumulation, known as "hyper-accumulation," leads to tobacco leaves containing very high cadmium concentrations, regardless of the soil's cadmium content. Typically, the cadmium content in tobacco leaves falls within 1 to 2 micrograms per gram of dry weight, resulting in approximately 0.5 to 1 microgram per cigarette. When tobacco is smoked, cadmium oxide is produced, which can either be deposited locally in lung tissue or absorbed into the bloodstream, or both. The absorption of cadmium through inhalation in the lungs is believed to be much greater than through ingestion via the intestines. As a result, cadmium concentrations in the blood of smokers can be up to four or five times higher, and concentrations in the kidneys can be up to two or three times higher compared to nonsmokers [12–15].

Occupational and Artistic Exposure: Occupational exposure and, to some extent, house dust in contaminated areas constitute essential sources of cadmium. Workers in industries such as metal smelting, battery manufacturing, and welding face heightened risks of cadmium exposure due to airborne contamination. Similarly, artists using cadmium-based pigments may inadvertently ingest hazardous amounts of cadmium. Historical figures like Claude Monet and Vincent Van Gogh famously utilized cadmium pigments in their paintings, highlighting the pervasive nature of cadmium exposure in artistic endeavors [13].

3. HEALTH EFFECTS AND TOXICITY

Exposure to low levels of cadmium can harm various parts of the body, including the kidneys, liver, bones, and heart. It can also affect eyesight and hearing. Additionally, cadmium can have harmful effects on reproduction, pregnancy, and fetal development. Cadmium can also disrupt the production of hormones related to reproduction, causing issues like menstrual irregularities, delayed puberty, pregnancy complications, and low birth weight. Women tend

to have higher levels of cadmium in their bodies than men, possibly because cadmium absorption increases when the body lacks iron. Studies have also looked into how cadmium might affect blood vessels, potentially increasing the risk of certain types of bleeding in the brain. Experimental studies using animals have shown that cadmium and cadmium compounds can cause benign and malignant tumors at various locations in the body. One study in 1983 showed that rats exposed to cadmium chloride aerosol developed lung cancer. In another study, rats were exposed to cadmium chloride through their diet for about 77 weeks. Some rats developed leukemia and testicular tumors. Overall, studies have shown that cadmium exposure can lead to tumors in various parts of the body in animals. These include cancers of the blood system, liver, lung, kidney, pancreas, prostate, and testicles. Despite its potential to cause Cancer, there have not been long-term studies on animals exposed to cadmium before birth. Since cadmium acts like estrogen and can affect children through their mothers' exposure, it is essential to consider earlier exposure times to fully understand its cancer-causing potential [8,16–18].

In human studies, the International Agency for Research on Cancer (IARC) concluded in 1993 that cadmium is carcinogenic to humans based on evidence from occupational studies [19]. These studies showed increased rates of lung cancer among workers exposed to cadmium. Despite some limitations in the studies, the IARC considered the evidence sufficient to classify cadmium as a Group 1 carcinogen. Similarly, the National Toxicology Program (NTP) 2000 also concluded that cadmium and its compounds are human carcinogens based on epidemiological and mechanistic evidence.

1. Cadmium as Carcinogen

Cadmium is a heavy environmental metal in the form of stable elements and radioactive isotopes. As we have already discussed, the half-life of cadmium is very long, so the complete elimination of cadmium from the body is complex. The route of human exposure to cadmium is generally due to the consumption of contaminated food, water, and smoking.

The first cadmium toxicity effect was highlighted in 1950. "Itai-Itai" or "Ouch-Ouch" is regarded as the first disease in the world caused by cadmium poisoning in Toyama Prefecture, Japan. In 1993, the International Agency for Research on Cancer (IARC) declared cadmium a potent group 1 carcinogen based on epidemiologic studies. Epidemiologic studies showed that cadmium causes tumors at multiple sites. It is associated with Cancer of the lungs, prostate, breast, kidney, pancreas, liver, and urinary bladder. Exposure to cadmium and its compounds, such as cadmium chloride, cadmium sulfate, cadmium nitrate, etc., leads to its accumulation in different body organs, and

this bioaccumulation interferes with many biological pathways by competing for binding sites with different vital metals. Cadmium mimics these essential metals and shows competitive binding with active sites. It can also cause damage at the genetic level. Cadmium also transforms proto-oncogenes like c-myc, c fos, and c- jun. Cadmium interferes with DNA repair systems, including mismatch repair, nucleotide excision repair, base excision repair, and non-homologous end joining (NHEJ). The complete mechanism of inhibition of cadmium's DNA repair system is unknown.

Nevertheless, it was found that cadmium interacts with the functional sulfhydryl group of DNA repair proteins, and it was also found that cadmium replaces zinc in the zinc-binding domain. Cadmium interacts with proteins like xeroderma pigmentosum complementation group A (XPA) and Replication protein A (RPA), which contains zinc finger motif DNA binding domains and is crucial in the DNA repair system. Cadmium replaces zinc from the zinc finger motif protein because it shows similarity with zinc, leading to the inactivation of these proteins. Cadmium shows its carcinogenic effects through multiple mechanisms. It interferes with the DNA repair mechanism. Cadmium induces Cancer either by genotoxic or by nongenotoxic mechanism. Long-term exposure to Cd results in DNA strand breaks, DNA protein crosslinks, chromosomal aberrations, and sister chromatid exchange. It also causes mutations, usually caused by large chromosomal deletions. This finding suggests that it could be one of the reasons for the inhibition of the DNA repair system by cadmium [20–23].

Apart from this, another study suggests that exposure to cadmium leads to the formation of reactive oxygen species and regulating heat shock genes that lead to oxidative stress and cause genomic instability. Generally, ROS is generated when oxygen is metabolized; this ROS cannot directly react with DNA. Using redox-active transition metals, ROS undergoes two chemical processes to react or cause damage. These two chemical processes are called the Fenton-type chemical reaction and the Haber-Weiss-type chemical reaction. Highly reactive radicals cause DNA to break and alter the genomic sequence, which may lead to mutation. In the case of cadmium, the direct use of a Fenton-type chemical reaction does not occur to generate highly reactive radicals like ROS. Cadmium uses two mechanisms: Firstly, it reduces the level of glutathione antioxidant, superoxide dismutase, peroxidases, and catalase enzymes. Secondly, it displaces iron and copper from different membrane proteins, and further, these ions participate in a Fenton-type reaction to increase ROS production. Usually, DNA damage is caused by many external and internal factors. ROS is an internal factor that leads to DNA damage. In normal conditions, DNA damage is further repaired by DNA repair systems like mismatch repair system (MMR), nucleotide excision repair (NER), base

excision repair (BER), non-homologous end joining (NHEJ), etc. However, in the case of cadmium-exposed cells, DNA damage cannot be repaired by the DNA repair system. Due to inhibition of the DNA repair system, damage caused by ROS, i.e., either single-strand break or double-strand break or alteration in bases, gets accumulated in the cell and eventually leads to mutation and tumor development [24–26].

It is observed that during short exposure to cadmium, the expression of some antioxidant enzymes like glutathione antioxidant, superoxide dismutase, peroxidases, etc., is reduced, creating oxidative stress in the cell. Moreover, low exposure to cadmium for extended periods causes the adaptation of genes involved in cellular antioxidant systems and elevates the expression of glutathione and metallothionein (MT). MT reduces oxidative stress by acting as a scavenger of ROS. It also helps to reduce the toxicity level of cadmium. In this way, MT acts as an anti-apoptotic factor and induces the aberrant survival of the cell. Also, it causes mobilization of cadmium from the MT complex and increases cadmium toxicity. In this way, MT functions in both ways, i.e., reducing and increasing cadmium toxicity [27,28].

Cadmium and Breast Cancer: Among all cancers, breast cancer is one of the most common cancers. Initiation and progression of breast cancer are associated with genetic as well as environmental factors. Exposure to heavy metals is one of the significant potent environmental factors that interfere with many cellular processes. Cadmium is one of the heavy metals that is present in the environment as a +2 oxidation State. As we have already discussed, the biological half-life of cadmium is very long, which makes the complete elimination of cadmium from the body complex. Heavy metals like cadmium can cause Cancer at multiple sites like the lung, prostate, liver, breast, kidney, pancreas, etc. In the case of breast cancer, one of the mechanisms by which cadmium induces carcinogenesis is through estrogen receptors. Cadmium leads to the initiation or progression of breast cancer by mimicking estrogen, and due to this property, cadmium is often known as Metallo estrogen. Metalloestrogen is a metal-induced estrogen that shows homology to natural estrogen and binds to estrogen receptors. This increases the downstream cascade of signaling that causes the progression of Cancer. Estrogen, a female sex hormone produced by the ovaries, plays a vital role in the development and differentiation of the female reproductive system. Oestrogen mainly binds with its estrogen receptor (ER) receptor and helps in growth and cell proliferation. Two types of estrogen receptors are present in cells [29,30]. One is the nuclear estrogen receptor (nER), which acts as a transcription factor. Another one is the membrane estrogen receptor (mER), which is present on the plasma membrane or membrane of the endoplasmic reticulum.

Further, nER has two isoforms, nER alpha and nER beta. Both nER alpha and nER beta show homology in the DNA and ligand binding domains but differ in NH2 terminal transactivation AF1 (Activation function 1). nER, alpha, and nER beta can regulate self-proliferation by classical and nonclassical pathways. Estrogen activates cell growth and proliferation via binding with ER Alpha, ER-beta, and GPR 30 (a seven transmembrane protein receptor on the plasma membrane and endoplasmic reticulum). ER Alpha/ ER beta activation can lead to direct or indirect (via MAPKs) transcription activation in the nucleus. However, GPR30 cannot activate transcription factors directly; it always activates MAPKs and a secondary messenger, cAMP, which leads to the expression of different transcription factors, such as c-fos. Deregulation in estrogen signaling pathways elevates the activity of transcription factors, eventually leading to the development of Cancer.

In the case of breast cancer, more than 70% are caused due to nERalpha+. ER alpha acts as an essential player in the progression of breast cancer. The role of ER beta in breast cancer is not clear due to its complexity. However, some studies concluded that the ER beta expression also causes a more advanced tumor. In the case of mER, estrogen can activate self-proliferating genes indirectly bound by DNA. In this way, heavy metals like cadmium mimic estrogen's physiological and biological properties and lead to high cell proliferation in the mammary gland. Also, it plays a role in cell cycle progression, migration, and apoptosis by activating a different transcription factor through classical or nonclassical pathways. Classical pathways include genes such as trefoil factor 1 (TFF1), cathepsin D (CTD), cyclin D1, insulin-like growth factor binding protein 1 (IGFBP1), lactoferrin (LTF), and Prolactin (PRL). These genes are also considered marker genes for breast cancer.

Moreover, nonclassical pathways include activator protein (AP1), Sp1, and NF-kB. In breast cancer, it is always a topic of discussion how cadmium interacts with estrogen receptor (ER) as metalloestrogen. Some studies suggested that cadmium interacts with estrogen receptors through ligand binding and DNA binding domain. Ligand binding domains consist of specific amino acids such as C381, C447, E523, H524, and D538. This specific amino acid is considered an interaction site of cadmium. However, in the DNA binding domain, cadmium replaces zinc because cadmium possesses chemical properties and coordination chemistry similar to zinc. In vitro, studies suggested that cadmium present in DBD (DNA binding domain) in place of zinc can slightly increase the binding affinity of estrogen receptor alpha [31–34].

Apart from estrogen signaling modulation, cadmium also induces carcinogenesis by causing aneuploidy (Aneuploidy is an aberrant no. of chromosomes present in a cell) and epigenetic changes that affect the

expression of many tumor suppressor genes and oncogenes. It is associated with histone modification, chromatin remodeling, etc. Interestingly, it was observed that estrogen also induced aneuploidy by increasing the expression of mitotic kinases Aurora A and B. In the case of breast cancer, expressive Aurora A has been found. This suggested that cadmium directly or indirectly involved in aneuploidy and over-expression of Aurora A and B is one of the causes of the progression of breast cancer.

Along with this, cadmium is also involved in breast cancer metastasis. Cadmium interferes with one of the hallmarks of Cancer: epithelial-mesenchymal transition (EMT). During EMT, the epithelial cell loses its properties and transforms itself into invasive motile mesenchymal cells and increases expression of mesenchymal marker genes, i.e., N-cadherin, fibronectin, and vimentin [33,35].

Generally, a protein called snail (containing a zinc finger DNA binding domain) plays a crucial role in EMT. Snail is a transcription factor that inhibits the E-cadherin and leads to EMT. Snail binds with three E-Box consensus sequences at the CDH1 promoter region of E-cadherin and represses its expression. In breast cancer, cadmium represses the expression of E-cadherin by up-regulating the expression of snails by interfering with different signaling pathways, i.e., wnt, TGF beta, and Notch -1. These up-regulated snails let the epithelial cell lose its markers like E-cadherin and claudin-1 and acquire a mesenchymal-like phenotype [34,36]. In this way, cadmium induces metastasis in breast cancer. Because of this, cadmium is considered a group 1 carcinogen that is involved in the initiation and progression of breast cancer.

2. Cadmium and Liver Cancer

As we know, cadmium (Cd) affects various organs of the human body and animals; the liver is the primary among them. Most of the cadmium absorbed in the intestine is delivered to the target organs through blood circulation. It binds with albumin and is transported to the hepatocytes by sinusoidal capillaries. Cadmium binds with metallothionein (MT) in the liver to form a cd-MT complex; this is involved in cadmium and heavy metal trafficking, oxidative stress, and DNA damage. The liver is the main target organ of cadmium toxicity, having both acute and chronic exposure, because it takes the most significant amount of toxicity during the initial hours of exposure. Acute exposure causes a variety of pathological changes in the liver; it causes a direct toxicity of the cadmium. At earlier exposure, it causes endothelial cell injury and later causes inflammatory injury. After acute exposure to cadmium, the buffer cells activate, and the neutrophil infiltration plays a significant role, where liver damage is unfiltered by polymorphonuclear

neutrophils (PMN), which help buffer cells by inducing necrosis and inflammatory mediators. Kuffer cells release many adhesion molecules that enhance the cellular and molecular response during secondary liver damage. When the kupffer cells are destroyed or suppressed, Cd hepatotoxicity is reduced. A variety of cytotoxicity mediators like ROS, nitric oxide, cytokines, etc, can directly target hepatocytes [22,37,38].

In the acute phase, the anti-TNF-α antibody prevents cadmium-induced secretion (TNF-α) of acute phase protein and gene expression of interleukin 1-Beta, interleukin-6, interleukin -8 in human hepatoma cell-line (HCC), HepG2. The IL-Beta and TNF-alpha are recognized proteins that stimulate the production of adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule -1 (IMAC-1), E-selection, P-selectin, β2- integrin and MAC -1 in the liver, these molecules induce the adherence and activation of circulatory inflammatory cells. Chronic exposure to cadmium results in renal diseases, osteoporosis, etc. It increases hepatotoxicity and the risk of liver cancer, leading to a high risk of mortality. The low cadmium concentration activates Notch and AKT /mTOR signaling in liver cancer. The activation of AKT/mTOR suppresses autophagy, further reducing lipotoxicity in the liver by enhancing lipid metabolism and thus cannot degrade lipid molecules. Notch signaling plays a vital role in developing the Hepatoma cell -line and the expression and activation of Notch 1, Notch 2, Notch 3, and Notch 4, which are associated with the HCC tumor aggressiveness, differentiation, and angiogenesis. The cadmium increases ROS production and activates the Notch and AKT/mTOR signaling [38,39].

Chronic exposure of cadmium-activated Notch signaling in HepG2 and SK-Hep 1 cells. The cadmium increases the mRNA expression of Notch 1 and Notch 3 in HepG2 cells and Notch 1, Notch 2, and Notch 4 in Hes 1 in SK-Hep 1 cells. Cadmium increases the expression of jagged- 1 in HepG2 cells, cleaved Notch 1, Notch 2, and Notch downstream Hes-1 protein in both cell lines. The chronic exposure of cadmium increases ps24448 mTOR and ps473-AKT in both cell lines and pG2 and LC3B in SK-Hep 1 cells. It alters the cell morphology in HepG2 cells, making them spherical, which indicates an increased tumorigenic phenotype. Cadmium also activates oncogenic mRNA protein, which induces the expression of Nanog mRNA in Sk- Hep1 cells and Nanog protein in HepG2 cells. The mRNA protein (TNFAIP8) increases HCC cell proliferation, survival, and drug resistance. Cadmium is also believed to increase the number of Cancer stem cell markers. Cd modulates the oncogenic signaling factors in HCC, increases VEGF and CD34 angiogenesis factor, and modulates CCL-4-induced HCC tumor. It inhibits tumor suppressor p16 and SLC 3843 gene expression of oncoproteins K- RAS and N-RAS and epithelial

to mesenchymal transition markers. Cd also induces the expression of proinflammatory cytokines TNF [38–40].

3. Cadmium and Lung Cancer

Lung cancer is the most common Cancer. According to data produced by the International Agency for Research on Cancer (IARC), lung cancer is the leading cause of all cancer deaths, with an estimated 1.8 million deaths (18%) in 2020. Cadmium and its compound are highly toxic, and its exposure leads to Cancer, with lung cancer being the most common. Cadmium is a natural element that can be present in food, soil, fertilizers, air, and water. There are several ways by which one can get exposed, either by cadmium-contaminated food, water or by smoking tobacco [41].

The primary route of cadmium exposure is inhalation; therefore, smoking tobacco or cigarettes is the most common source of high-dose CD exposure, increasing the risk of lung cancer. Various studies confirmed higher levels of Cd present in blood and urine in smokers than in nonsmokers. Various epidemiological studies suggest that long-term environmental and occupational exposure to Cd induces lung cancer in humans and animals. Chronic exposure to Cd causes pulmonary adenocarcinomas in animals and in exposed human cell lines. Prolonged exposure to Cd causes the normal bronchial epithelial cells to become malignant. The development of specific cell lines aids a defining feature of the development of cd-mediated lung cancer. Cd-induced, transformed lung epithelial cells known as chronic cd treated lung cells (CCT-LC) increase the MMP-2 activity, colony formation, invasion, autonomous growth, MT, and hyperproliferation. CCT-LC cells expression of p16 expression increase in cyclin D1 expression, Overexpression of CCT-LC of K-RAS, N-RAS, vimentin, and loss of SLC38A3, which are associated with lung cancer. The major metallothionein (MT) isoforms are associated with lung cancers where MT-1A and MT-2A are higher in CCT-LC cells. The CCT-LC cells have multiple characteristics of signaling networks like Oxidative stress conditions induced by antioxidative proteins Heme-oxygenase -1 (HO-1) and hypoxia-inducible factor -1 A (HIF-1 alpha). HIF-1 expression occurs through cd-induced reactive oxygen species formation associated with the transformation of bronchial epithelial cells [42–44].

The Cd activates AKT, GSK- 3β, and β-catenin signaling in BEAS-2B human bronchial epithelial cells, which causes the direct involvement of ROS in cd-induced carcinogenesis. It also activates c-myc and COX-2 along with AKT, GSK-2β, and β-catenin, leading to the development of cd-induced tumors and metastasis. The Cd causes DNA damage to the cell by decreasing DNA repair capacity and genomic instability. The cd does not directly induce mutagenesis.

The DNA repair systems are diminished, and the DNA repair capacity is lowered during cd induced transformation. The DNA sequence analysis of these cells shows the frame-shift mutations in exons of the hMSH2, ERCC1, XRCC1, and hOGG1 genes. The Cd increases the PCNA (proliferation marker genes) and cyclin D1 (cell cycle gene), which shows that the cd has mitogenic potential. The anti-apoptosis marker Bal-2 decreases in the cd-induced malignant cells in human bronchial epithelial cells. The p53 expression is also upregulated in primary epithelial lung cells. Moreover, the dysregulation of these pathways by cadmium leads to uncontrolled cell growth and tumor formation, which causes Cancer [24,45,46].

4. Cadmium and Colorectal Cancer

Cadmium is one of the hazardous heavy metals that is widely distributed in the environment. One of the significant routes of cadmium exposure is oral ingestion of contaminated food and water. Due to this, the intestinal tract is the main target of cadmium-induced toxicity. Long-term exposure to cadmium promotes metastasis of colorectal cancer cells. In colorectal Cancer, cadmium downregulated the genes related to cell junction and upregulated the genes involved in cell mobility. In short, cadmium in colorectal Cancer helps to lose the properties of epithelial cells and convert them into invasive mesenchymal cells, called epithelial-mesenchymal transition (EMT). Metastasis by cadmium in colorectal cancer cells is achieved by upregulating epidermal growth factor receptor (EGFR) signaling. In normal conditions, the presence of a ligand called epidermal growth factor (EGF) binds with its receptor EGFR and leads to activation of ERK. This ERK generates a downstream signaling cascade by activating Akt/mTOR pathways. This AKt/mTOR signaling further led to the invasion and migration of the cells. However, in cadmium-exposed cells, AKt/mTOR continued for a long term because cadmium promoted sustained EGFR signaling that enhances the metastasis property of colorectal cancer cells. Illness is another mechanism by which cadmium is considered a carcinogen for colorectal cells. It is observed that cadmium exposure is linked with inflammation. One of the diseases called inflammatory bowel disease (IBD) is also associated with cadmium exposure. Furthermore, studies indicated that inflammation is strongly associated with the progression of Cancer. Moreover, cadmium enhances inflammatory responses by increasing the expression of proinflammatory factors called cyclooxygenase-2 (COX-2) [47–49].

Among all inflammatory pathways, cyclooxygenase (COX) pathways play an important role in colorectal malignancy. There are two isoforms of COX present, i.e., COX-1 (constitutive enzyme) and COX-2 (inducible enzyme). Some data suggested that out of COX-1 and COX-2, COX-2 is involved in colorectal malignancy. In colorectal Cancer, COX-2 acts on a

metabolite called prostaglandin E2 (PGE2). In general, PGE2 binds with its receptor called E-type prostanoid (EP) receptors. There are 04 subtypes of receptors present, i.e., EP1, EP2, EP3, and EP4. However, in colorectal neoplasia, the EP4 receptor is mainly involved. In colorectal Cancer, PGE2 binds with its receptor EP4 and promotes cell proliferation, invasion, migration, and angiogenesis. As earlier mentioned, cadmium exposure leads to the production of ROS [48,50]. In colorectal Cancer, it is found that cadmium promotes malignancy by enhancing the function of two pathways. One is the ROS-p38 MAPK-COX-2-PGE2 pathway, and another is the ROS-AKT pathway. In the ROS-p38 MAPK-COX-2-PGE2 pathway, ROS accumulates in cells, eventually activating p38 MAPK. This p38 MAPK upregulated the COX-2 expression that causes the accumulation of PGE2. This PGE2 bonded with EP4, leading to cell proliferation, invasion, etc.

In another pathway, cadmium activates AKt in a dependent manner. This activated AKT plays a role in colorectal cancer cell migration. Some studies also indicated that epigenetic changes induced by cadmium also cause colorectal Cancer. It suppresses the expression of DNA methyltransferases (DNMTs) that cause hypo-methylation [47,51,52].

5. Cadmium and Skin Cancer

In the vast landscape of oncology, skin cancer stands as a significant challenge, both in its prevalence and its complexity. At the molecular level, skin cancer manifests as a complex interplay of genetic mutations, dysregulated signaling pathways, and immune evasion mechanisms. While excessive ultraviolet (UV) radiation exposure remains the primary culprit, lifestyle choices and environmental factors also shape an individual's risk profile. Among several environmental factors, heavy metal exposure is an omnipresent concern. Heavy metals, such as arsenic, cadmium, chromium, nickel, and lead, are naturally occurring elements with widespread industrial, agricultural, and environmental applications. Their toxic properties stem from their ability to accumulate in biological tissues, disrupt cellular homeostasis, induce oxidative stress, and interfere with DNA repair mechanisms, culminating in a spectrum of adverse health effects, including carcinogenesis. This chapter provides a comprehensive exploration of the relationship between cadmium exposure and skin cancer, specifically focusing on the emerging role of epigenetic alterations in driving carcinogenesis [53,54].

The skin is a complex organ composed of two distinct layers: the outermost epidermis and the underlying dermis. The epidermis consists of epithelial cells and melanocytes responsible for skin coloration, while the dermis contains connective tissue, blood vessels, hair follicles, and sweat glands.

When mutations occur in melanocytes, malignant melanoma can develop. This type of skin cancer is highly aggressive and can metastasize to other parts of the body, posing a significant health risk. Non-melanoma skin cancer (NMSC) arises from the epidermis and is the most common type of skin cancer worldwide. It encompasses two main subtypes: squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [55,56].

Cadmium can influence various cellular pathways implicated in skin cancer development, including:

- **Oxidative Stress Pathway:** Cadmium exposure leads to the generation of reactive oxygen species (ROS), which can induce oxidative stress and damage cellular components, including DNA, proteins, and lipids. Prolonged oxidative stress can contribute to carcinogenesis by promoting genetic mutations and genomic instability.
- **Cellular Signaling Pathways:** Cadmium can dysregulate multiple cellular signaling pathways involved in cell proliferation, differentiation, and survival. This includes the MAPK (Mitogen-Activated Protein and Kinase) pathway, which regulates cell growth and differentiation, and the PI3K/AKT pathway, which promotes cell survival and proliferation. Dysregulation of these pathways by cadmium can lead to uncontrolled cell growth and tumor formation.
- **DNA Repair Pathway:** Cadmium exposure can impair DNA repair mechanisms, including nucleotide excision repair (NER) and base excision repair (BER), essential for maintaining genomic integrity and preventing the accumulation of mutations. Inhibition of DNA repair pathways by cadmium can increase the likelihood of genetic alterations and contribute to skin cancer development.
- **Apoptotic Pathway:** Cadmium has been shown to modulate apoptotic pathways, which regulate programmed cell death. While cadmium exposure can induce apoptosis in some contexts, it may promote cell survival and inhibit apoptosis in others. Dysregulation of apoptotic pathways by cadmium can contribute to the survival and proliferation of cancerous cells, facilitating tumor growth and progression.
- **Epigenetic Pathways:** Cadmium exposure can induce epigenetic alterations, including changes in DNA methylation, histone modifications, and non-coding RNA expression. These epigenetic changes can affect gene expression patterns, leading to the silencing of tumor suppressor genes and activating oncogenes, thereby promoting skin cancer development and progression.

By affecting these pathways, cadmium can disrupt cellular homeostasis, promote oncogenic transformation, and contribute to the initiation and progression of skin cancer. Understanding the molecular mechanisms

underlying cadmium-induced carcinogenesis is essential for developing targeted interventions and preventive strategies to mitigate the adverse effects of cadmium exposure on skin health [55,57,58].

4. CONCLUSION

Cadmium is a metal often used in industry, but it is also very harmful to people and the environment. When exposed to cadmium, it can build up in our bodies over time, mainly in the kidneys, liver, gut, and bones, and can cause many health problems, including kidney and liver issues, trouble breathing, and even Cancer. We can be exposed to cadmium in a few different ways, i.e., through the air, contaminated food, and water, including rice, leafy greens, seafood, and even smoking tobacco. When cadmium gets into our bodies, it can mess with many essential processes, including damaging our DNA, leading to Cancer over time. Looking at its carcinogenic potential, the International Agency for Research on Cancer (IARC) 1993 declared cadmium as a group 1 carcinogen. Cadmium causes tumors at multiple sites. It is associated with the lung, prostate, breast, kidney, pancreas, liver, and urinary bladder [19].

Cadmium exposure to cells increases the production of ROS. Further, ROS creates oxidative stress and leads to single-strand and double-strand breaks in DNA. The damaged DNA accumulates in the cell because cadmium inhibits the DNA repair system. Cadmium is considered a carcinogen because it interferes with many biological pathways, like abnormal DNA methylation, cell apoptosis suppression, oxidative stress induction, destruction of antioxidant enzymes, etc. In the case of breast cancer, cadmium induces cell proliferation and growth by interfering with estrogen signaling; it acts as a mettalloestrogen and increases the level of estrogen [29,30]. Apart from this, cadmium also causes metastasis in breast cancer by enhancing the expression level of snail. In liver cancer, Cd induces hepatocellular damage to the cells. Cd leads to the imbalance of cellular redox status, which leads to oxidative stress, an increase in ROS production, and cellular damage affecting cell survival and proliferation. Acute exposure causes changes in various pathological processes, but chronic exposure to Cd results in various renal diseases, and long-term exposure leads to the risk of liver cancer. Cd leads to the dysregulation of these various signaling pathways. It activates Notch/Akt/mTOR signaling, which is the primary cause of the proliferation of liver cancer, leading to uncontrolled cell growth and tumor formation [22,49,58].

In lung cancer, long-term exposure to Cd influences various cellular and signaling pathways, where chronic exposure causes pulmonary adenocarcinomas and prolonged exposure causes normal bronchial epithelial cells to transform into malignant cells. The CCT-LC cells have multiple

characteristics like DNA damage, genomic instability, oxidative stress conditions, ROS production, etc. Cd affects critical signaling pathways like loss of p16 and increase in cyclin D1 expression. It also shows the overexpression of K-RAS, N-RAS, Vimentin, and loss of SLC38AC. The major MT isoforms MT-1A and MT-2A are high in CCT-LC cells. Bd also activates AKT, GSK- 2 β, β- catenin, leading to cell metastasis. The p53 expression is also upregulated in the lung epithelial cells, a consistent phenomenon in all Cd exposed tissue. These phenomena together lead to the activation of oncogenic signaling pathways and the development of lung cancer. Cd induces various epigenetic alterations, including changes in DNA methylation, histone modifications, frame-shift mutations, and gene expression, activating oncogenic signals and promoting lung cancer development. Cadmium also causes colorectal Cancer. Studies suggest that one of the causes of colorectal Cancer is increased expression of proinflammatory factors called cyclooxygenase-2(COX-2). Cadmium induces colorectal malignancy by enhancing ROS- p38 MAPK-COX-2- PGE2 and ROS-Akt pathway. In skin cancer, cadmium can influence several cellular pathways, such as oxidative stress, where cadmium exposure leads to the production of reactive oxygen species (ROS), causing damage to cellular components like DNA, proteins, and lipids.

Additionally, cadmium can disrupt cellular signaling pathways involved in cell growth and survival, such as the MAPK and PI3K/AKT pathways [38,49]. Dysregulation of these pathways by cadmium can lead to uncontrolled cell growth and tumor formation. Cadmium exposure can impair DNA repair mechanisms, leading to genetic alterations and mutations that can drive skin cancer development. Cadmium's impact on apoptotic pathways regulating programmed cell death is also significant. Moreover, cadmium-induced epigenetic alterations, including changes in DNA methylation, histone modifications, and non-coding RNA expression, can modify gene expression patterns, leading to the silencing of tumor suppressor genes and the activation of oncogenes, further promoting skin cancer development and progression. Thus, reducing exposure to cadmium is crucial for overall health and cancer prevention.

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