Review Article

The dynamic face of cadmium-induced Carcinogenesis: Mechanisms, emerging trends, and future directions

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ABSTRACT

Cadmium (Cd) is a malleable element with odorless, tasteless characteristics that occurs naturally in the earth's crust, underground water, and soil. The most common reasons for the anthropological release of Cd to the environment include industrial metal mining, smelting, battery manufacturing, fertilizer production, and cigarette smoking. Cadmium-containing products may enter the environment as soluble salts, vapor, or particle forms that accumulate in food, soil, water, and air. Several epidemiological studies have highlighted the association between Cd exposure and adverse health outcomes, especially renal toxicity, and the impact of Cd exposure on the development and progression of carcinogenesis. Also highlighted is the evidence for early-life and even maternal exposure to Cd leading to devastating health outcomes, especially the risk of cancer development in adulthood. Several mechanisms have been proposed to explain how Cd mediates carcinogenic transformation, including epigenetic alteration, DNA methylation, histone posttranslational modification, dysregulated non-coding RNA, DNA damage in the form of DNA mutation, strand breaks, and chromosomal abnormalities with double-strand break representing the most common DNA form of damage. Cd induces an indirect genotoxic effect by reducing p53's DNA binding activity, eventually impairing DNA repair, inducing downregulation in the expression of DNA repair genes, which might result in carcinogenic transformation, enhancing lipid peroxidation or evasion of antioxidant interference such as catalase, superoxide dismutase, and glutathione. Moreover, Cd mediates apoptosis evasion, autophagy activation, and survival mechanisms. In this review, we decipher the role of Cd mediating carcinogenic transformation in different models and highlight the interaction between various mechanisms. We also discuss diagnostic markers, therapeutic interventions, and future perspectives.

1. Introduction

Cadmium (Cd) is a silvery-white, malleable element with odorless, tasteless characteristics. It occurs naturally in the earth's crust, air, underground water, and soil (Monika et al., 2022; Wang et al., 2023). It is a non-essential toxic metal that exists as a divalent cation. It forms a complex with several organic and inorganic anions, including various chemical compounds commonly used in industry (Rafati Rahimzadeh et al., 2017). During the industrial renaissance in the 19th century, Cd was anthropogenically released to the environment in high concentration as an industrial byproduct or as a waste product that highly impacts human health, such as metal mining, alloys, smelting, welding, electroplating, Ni-Cd batteries manufacturing, cement manufacturing, cigarette smoke, fertilizer production, electronic wastes, waste incineration, and fuel combustion, which comprise the primary sources of anthropogenic cadmium emissions into the environment and represent a high risk for those areas (Afolayan, 2018; An et al., 2017; Batzer, 1983; Fishbein, 1981; Horng et al., 2002). Cadmium-containing products may enter the environment as soluble salts, vapor, or particle forms that accumulate in soil, water, and food (Bergkvist et al., 2005;

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Piol et al., 2006; Qi et al., 2018; Rafati Rahimzadeh et al., 2017; Shaari et al., 2022).

Humans are exposed to Cd in vastly different capacities. For non-smokers, industrial byproducts, waste products, or food ingestion are the primary sources of Cd contamination. Cd is a non-biodegradable metal with a long biological half-life that can be released into the environment more quickly and accumulate in the soil–plant system. Bioaccumulation increases the likelihood of incorporating cadmium into the food chain and poses dangerous health risks for humans and animals. It has long-duration endurance and is difficult to remove from the environment. Globally, several plant-based foods such as rice, tomato, potatoes, leafy vegetables, root vegetables, legumes, and nuts contribute to high Cd diet intake. In addition, seafood, such as fish, oysters, lobster, prawns, and crab, contributed to a high Cd diet in exposed populations (Gueguen et al., 2011; Kim et al., 2018; Lordan & Zabetakis, 2022; Wang et al., 2021a). A significant source of Cd contamination is tobacco smoking. Humans are primarily exposed to cadmium outside of the workplace through inhalation, while non-smokers are mainly exposed to contaminated food (Kim et al., 2018; Wang et al., 2021a). Smokers frequently have much higher levels of cadmium in their bodies. Cadmium oxide from tobacco smoking is deposited in the respiratory system and can be distributed to the circulation, resulting in high levels of cadmium (Ganguly et al., 2018; Tarhonska et al., 2022). The most common sources of Cd exposure are illustrated in Fig. 1.

Cadmium toxicity includes nephrotoxicity, cardiovascular toxicity, genotoxicity, neurotoxicity, hepatotoxicity, bone toxicity, and carcinogenicity (Nagaraju et al., 2022; Smereczanski & Brzoska, 2023; Sulayman Aboulqassim et al., 2023; Tyagi et al., 2023; Zeng et al., 2021; Zhou et al., 2023). The effect of Cd toxicity on different organs is covered in detail elsewhere (Charkiewicz et al., 2023; Genchi et al., 2020). Several epidemiological studies link cadmium exposure and various types of cancer, such as breast cancer (BC), lung cancer, liver cancer, prostate cancer (PCa), endometrial cancer, pancreatic cancer, kidney cancer, gastric cancer (GC), head and neck cancers, and ovarian cancer (Eriksen et al., 2014; Filippini et al., 2020; Lin et al., 2018; Luckett et al., 2012; McElroy et al., 2017; Men et al., 2021; Rapisarda et al., 2018; Rezapour et al., 2021; Verougstraete et al., 2003). The preponderance of evidence supports the role of Cd in promoting cell transformation and induction of cancer. The latest International Agency for Research on Cancer (IARC)/ WHO includes only three cancers for which there is limited evidence (kidney and prostate) or sufficient evidence (lung) for human carcinogenicity. While the precise mechanisms underlying cadmium-induced carcinogenesis remain unclear, DNA damage, oxidative stress, resistance to apoptosis, and epigenetic variation may contribute significantly to carcinogenesis (Bernard, 2008). This review discusses in depth the role of Cd mediating carcinogenic transformation and emphasizes the intricate interaction between mechanisms that might play a vital role in the transformation process. We also highlight the possible role of prenatal cadmium exposure in carcinogenesis, different methods for detecting Cd exposure, novel surrogate markers, therapeutic
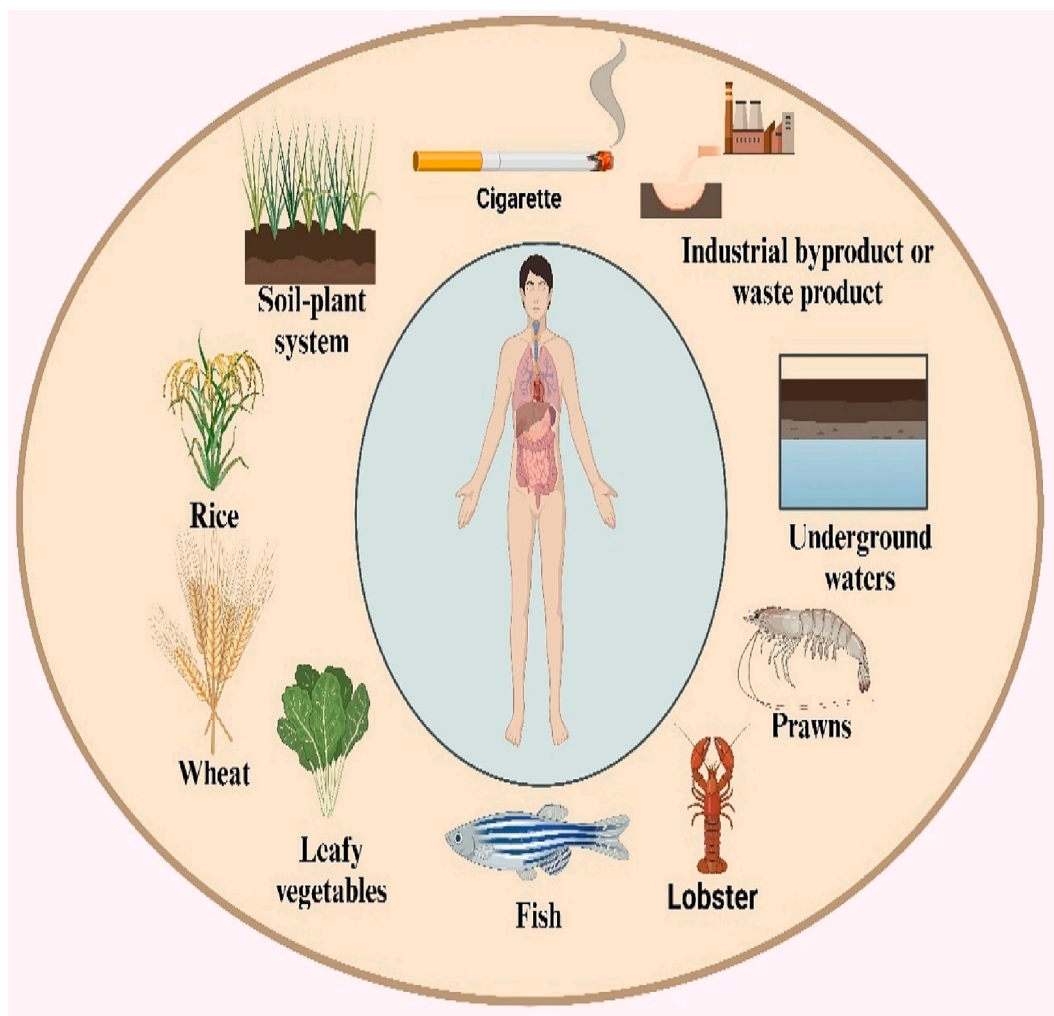

Fig. 1. Depicts various sources with high potential risk for exposure to Cd. Among them, smoking, rice, vegetables, and underground water represent the most common sources of Cd exposure. Created with BioRender.com (Accessed on 8 December 2023).

intervention, recent research trends, and future perspectives.

2. Search strategy and study selection criteria

In this review, we performed a comprehensive search of the literature using various combinations of the following search terms: (cadmium[TIAB] OR Cd[TIAB] OR cadmium compounds[TIAB] OR cadmium chloride[TIAB] OR cadmium sulfate[TIAB] OR cadmium sulfide[TIAB] OR methyl cadmium[TIAB] OR dimethyl cadmium[TIAB] OR diethyl cadmium[TIAB]) AND (carcinogenesis [TIAB] OR tumorigenesis [TIAB] OR oncogenesis [TIAB] OR tumor[TIAB] OR cancer [TIAB]) and combined the search with each set of the following search strategies: (epigenetic [TIAB] OR "DNA methylation"[MeSH Terms] OR "histone modification"[MeSH Terms] OR "noncoding RNA"[MeSH Terms] OR " long noncoding RNA"[MeSH Terms] OR "circular RNA"[MeSH Terms] OR microRNAs [MeSH Terms]) OR ("DNA damages" [MeSH Terms] OR P53[TIAB] OR "oxidative stress"[MeSH Terms] OR ROS[TIAB]) OR "PI3K/Akt signaling pathway"[TIAB] OR "MAPK cascade"[TIAB] OR "β-catenin pathway"[TIAB]) OR (apoptosis [MeSH Terms] OR "apoptosis resistance"[TIAB] OR "evading apoptosis"[TIAB] OR autophagy [MeSH Terms] OR "defective autophagy"[TIAB]) OR (biomarkers [MeSH Terms] OR " long noncoding RNA"[MeSH Terms] OR "microRNA"[TIAB] OR "circular RNA"[MeSH Terms] OR "novel biomarkers"[TIAB]) using the PubMed, Google Scholar, Connected Papers databases. We only included articles written in English. We included all mechanistic research during screening and data extraction to achieve our narrative review goal.

3. Epidemiological evidence of association between Cd exposure and risk of cancer development

A plethora of epidemiological studies have emphasized the association between Cd exposure and adverse health outcomes, especially cancer, and the impacts of Cd exposure on the development and progression of carcinogenesis. Breast cancer is the most diagnosed cancer in women and the second leading cause of cancer death among women in the United States (US) (Siegel et al., 2023). Several *in vitro* and *in vivo* studies have discussed the estrogenic effect of Cd. They concluded it could mimic estrogen, subsequently activate estrogen receptors, and induce cell proliferation and migration in BC (Aquino et al., 2012; Silva et al., 2012; Zang et al., 2009). Nevertheless, the controversial results from epidemiological studies in humans reflect the multifaceted nature of the interaction between Cd and many targets in the cell, making it difficult to determine how Cd exhibits its carcinogenic effect. Several studies uncovered a significant association between Cd exposure and the risk of BC development in various ethnic groups (Julin et al., 2012a); Nagata et al., 2013; Strumylaite et al., 2019). Furthermore, the study highlights the association between high urinary Cd (U-Cd) and mammographic density in premenopausal women supports the role of Cd in BC (Adams et al., 2011). High testosterone levels in Cd-exposed women have also been associated with an increased risk of BC development (Ali et al., 2014; Nagata et al., 2005). Those findings were supported by various *meta*-analyses suggesting that Cd exposure might be related to an increased risk of BC development (Filippini et al., 2020; Florez-Garcia et al., 2023; Larsson et al., 2015; Lin et al., 2016). Conversely, several studies also emphasized no association between airborne or dietary sources of Cd exposure and the development of BC (Adams et al., 2014; Eriksen et al., 2014; Erratum, 2020). In addition, Adams et al. also did not find an association between U-Cd and BC (Adams et al., 2016).

PCa is the second most common cause of cancer death among men and the most diagnosed cancer in men in the US (Pernar et al., 2018). Airborne or dietary exposure to Cd was strongly correlated to PCa development or aggressive cancer at the time of diagnosis (Julin et al., 2012b; Vijayakumar et al., 2021). Furthermore, higher levels of U-Cd are associated with a higher risk of PC incidence (Bede-Ojimadu et al.,

2023). A result from one *meta*-analysis substantiated the association between Cd exposure and PCa development (Zhang et al., 2016). In contrast, another *meta*-analysis showed no association between Cd exposure and the risk of PCa development (Chen et al., 2016a).

McElroy et al. (McElroy et al., 2017) uncovered that higher U-Cd levels were positively associated with an increased risk of developing endometrial cancer in Midwestern U.S. women, with a plausible estrogenic effect of Cd underlying the process of carcinogenesis. Those findings were supported by results from a study conducted by Akesson et al. showing an association between dietary Cd exposure and risk of developing endometrial cancer in women (Akesson et al., 2008). Interestingly, another study by Eriksen and colleagues also uncovered an association between Cd exposure and risk of endometrial cancer (Eriksen et al., 2014). Conversely, the results from one study exploring the role of dietary Cd exposure and the risk of endometrial cancer were inconclusive (Adams et al., 2014).

For nasopharyngeal carcinoma (NPC), Peng and colleagues explored the effects of chronic Cd exposure on the malignant progression in a Chinese patient cohort and the link between elevated levels of Cd and increased risk of developing NPC. They also correlated Cd exposure with the clinical stage and lymph node metastasis (Peng et al., 2015).

Several lines of evidence support the premise that Cd exposure may also increase the risk of pancreatic cancer (Adams et al., 2012; Buha et al., 2017; Chen et al., 2015; Garcia-Esquinas et al., 2014; Kriegel et al., 2006; Li et al., 2011; Sawada et al., 2012), lung cancer (Adams et al., 2012; Chen et al., 2016b; Garcia-Esquinas et al., 2014; Nawrot et al., 2015), renal cancer (Song et al., 2015), GC (Kim et al., 2019; Lin et al., 2018), Non-Hodgkin lymphoma, and leukemia (Adams et al., 2012). While a study by Eriksen et al. supports the association between the risk of developing ovarian cancer and exposure to Cd (Eriksen et al., 2014), contradictory results from different ethnic groups show no association observed (Adams et al., 2014; Julin et al., 2011). A large body of evidence supports the association between Cd exposure and the risk of developing various cancers despite the controversial results from some studies, mainly from either airborne or dietary sources, as shown in Table 1.

3.1. Early life exposures and cancer development risk

Early-life exposure to Cd could lead to devastating outcomes. Epidemiological studies emphasize the overly complex and far-reaching adverse effects that Cd exposure has on health outcomes, especially on children. Several epidemiological studies link Cd exposures and the risk of cancer in children (Absalon & Slesak, 2010; Infante-Rivard et al., 2001; Sherief et al., 2015). Placental Cd accumulation results in several adverse health outcomes, including low birthweight, preterm birth, and small head circumference. Despite the inconsistent results, maternal Cd exposure can affect the newborn infant's health, and this adverse effect might continue until adulthood (Young & Cai, 2020). In addition, many studies have related early life exposure to Cd during gestation and first years of life to impairment of growth (Gardner et al., 2013; Malin Igra et al., 2023), delay of pubertal development and menarche (Malin Igra et al., 2023; Reynolds et al., 2020), impaired kidney function (Rodriguez-Lopez et al., 2020; Skroder et al., 2015), and blood pressure (Young & Cai, 2020).

The role of Cd early life exposure on cancer development remains obscure. Examining the consequence of early-life Cd exposure in mice shows that prenatal to early postnatal Cd exposure increases the risk of liver cancer (Men et al., 2021). In addition, maternal exposure to Cd during pregnancy affected mammary tumorigenesis in female offspring in rat models. The study uncovered that in-utero exposure to moderate levels of Cd leads to several prominent hormonal alterations, such as reduced androgen receptor expression and elevated circulating testosterone levels in the mammary gland. The female offspring of the rat models also exhibited accelerated puberty onset and increased body weight. The data disclosed increased pre-malignant hyperplastic

Table 1

General overview of the epidemiological studies investigating the association between Cd exposure from different resources and cancer development in diverse populations.

Cancer type	Exposure measurement	Study type	Exposed population	No. of participants	Findings	Reference
Breast cancer	Urinary Cd	Case-control	White Caucasian Women	509 cases and 1170 controls	Association	(Strumylaite et al., 2019)
	Airborne Cd	Nested case-control	French E3N cohort	4,059 cases and 4,059 controls	No association	(Erratum, 2020)
	Urinary Cd	Case-control	Women's Health Initiative study	508 cases and 1,050 controls	No association	(Adams et al., 2016)
	Blood Cd and urinary Cd	Cross-sectional	Postmenopausal Swedish women	438 cases	Association	(Ali et al., 2014)
	Dietary Cd	Prospective	Danish postmenopausal women	1390 cases	No association	(Eriksen et al., 2014)
	Urinary Cd	Case-control	Japanese women	153 cases, 431 controls	Association	(Nagata et al., 2013)
	Dietary Cd	Prospective	Postmenopausal	2,112 cases	Association	(Julin, Wolk, Bergkvist, et al., 2012)
	Mammographic density and urinary Cd	Cross-sectional	Premenopausal women	190 cases	Association	(Adams et al., 2011)
	Urinary Cd and serum levels of estrogens and androgens	Prospective	Postmenopausal Japanese women.	164 cases	Association	(Nagata et al., 2005)
	Dietary Cd	Prospective	Postmenopausal women, Women's Health Initiative	155,069 cases	No association	(Adams et al., 2014)
Prostate cancer	Airborne Cd	Retrospective	Patients in the United States	230,540 cases	Association	(Vijayakumar et al., 2021)
	Dietary Cd	Prospective	Swedish men	41 089 cases	Association	(Julin, Wolk, Johansson, et al., 2012)
	Urinary Cd	Case-control	Nigerian men	PCa N = 82, BPH (N = 93), and controls (N = 98)	Association	(Bede-Ojimadu et al., 2023)
	–	Case-control	Employees of the United Kingdom Atomic Energy Authority	136 cases and 404 controls	No association	(Rooney et al., 1993)
Nasopharyngeal carcinoma	Blood Cd	Case-control	Chinese Chaoshan population	134 cases and 132 controls	Association	(Peng et al., 2015)
	Urinary Cd	Case-control	Midwestern U.S. population	631 cases and 879 controls	Association	(McElroy et al., 2017)
	Dietary Cd	Prospective	Swedish Mammography Cohort	56,030 cases	Association	(Akesson et al., 2008)
	Dietary Cd	Prospective	Postmenopausal women, Women's Health Initiative	155,069 cases	No association	(Adams et al., 2014)
Pancreatic Cancer	Blood Cd	Prospective	Pancreatic Cancer Patients from the East Nile Delta Region of Egypt	31 cases and 52 controls	Association	(Kriegel et al., 2006)
	Urinary Cd	Prospective	American Third National Health and Nutrition Examination Survey (NHANES) Cohort	Men (N = 9,388) and women (N = 10,636)	Association	(Adams et al., 2012)
	Urinary Cd	Prospective	American Indians from Arizona, Oklahoma, and North and South Dakota-The Strong Heart Study	3,792 cases	Association	(Garcia-Esquinas et al., 2014)
Lung cancer	Urinary Cd	Case-control	American Third National Health and Nutrition Examination Survey (NHANES)	Men (N = 9,388) and women (N = 10,636)	Association	(Adams et al., 2012)
	Urinary Cd	Prospective	American Indians from Arizona, Oklahoma, and North and South Dakota, Strong Heart Study from 1989 to 1991.	3,792 cases	Association	(Garcia-Esquinas et al., 2014)
Ovarian cancer	Dietary Cd	Prospective	Danish postmenopausal women	146 cases	No association	(Eriksen et al., 2014)
	Dietary Cd	Prospective	Postmenopausal women, Women's Health Initiative	155,069 cases	No association	(Adams et al., 2014)
	Dietary Cd	Prospective	Swedish Mammography Cohort	60,889 cases	No association	(Julin et al., 2011)
Non-Hodgkin lymphoma	Urinary Cd	Case-control	American Third National Health and Nutrition Examination Survey (NHANES) Cohort	Men (N = 9,388) and women (N = 10,636)	Association	(Adams et al., 2012)
Leukemia	Urinary Cd	Case-control	American Third National Health and Nutrition Examination Survey (NHANES) Cohort.	Men (N = 9,388) and women (N = 10,636)	Association.	(Adams et al., 2012)

Table 1 (*continued*)

Cancer type	Exposure measurement	Study type	Exposed population	No. of participants	Findings	Reference
Gastric cancer	Dietary Cd	Case-control	Korean population	415 cases and 830 controls	Association	(Kim et al., 2019)
	Cd and lead exposure	Case-control	Chaoshan population of Southeast China	279 cases and 112 controls	Association	(Lin et al., 2018)

alveolar nodules and terminal end buds in the mammary gland. These findings clearly show that the effects of in-utero cadmium exposure are dose-dependent (Davis et al., 2013).

Furthermore, several studies illustrate that prenatal Cd exposure could lead to the development of multigenerational adverse health outcomes. For example, Huang et al. found that prenatal Cd exposure could lead to transgenerational male reproductive problems in rats by affecting testosterone production (Huang et al., 2020). Similarly, several studies uncovered that prenatal Cd exposure could adversely affect hormonal production in rats in a cross-generation manner (Henson & Chedrese, 2004; Li et al., 2023b; Liu et al., 2020; Prins, 2008; Sun et al., 2023). While the previously discussed studies provide critical insight into the relationship between Cd exposure and health outcomes and provide evidence that Cd induces changes that are imprinted and inherited by the next generations, highlighting the role of epigenetic variation, it is also evident that further research is needed to gain a clear understanding of the mechanisms involved in Cd early life exposure and the risk of cancer.

4. Molecular mechanisms underlying Cd carcinogenesis

4.1. Epigenetic effects

The association between epigenetic alteration and Cd-induced adverse health effects is well-addressed in the literature (Manic et al., 2022). A plethora of evidence suggests that epigenetic variation is a central underlying mechanism of prenatal Cd inducing adverse effects (Vilahur et al., 2015). Three common epigenetic mechanisms that control gene expression in response to Cd exposure include DNA methylation, histone posttranslational modifications, and non-coding RNAs, as illustrated in Fig. 2. Those mechanisms control gene expression without altering the DNA sequence (Manic et al., 2022). Table 2 summarizes the effect of Cd exposure mediating epigenetic variation on carcinogenesis.

4.1.1. DNA methylation

DNA methylation is an epigenetic mark that results from the transfer of a methyl group to the C-5 position in cytosine nucleotide, usually followed by guanine nucleotide known as CpG island via DNA methyltransferase (DNMT) family of enzymes. DNA methylation either inhibits transcription factors' binding to DNA or recruits proteins that modify
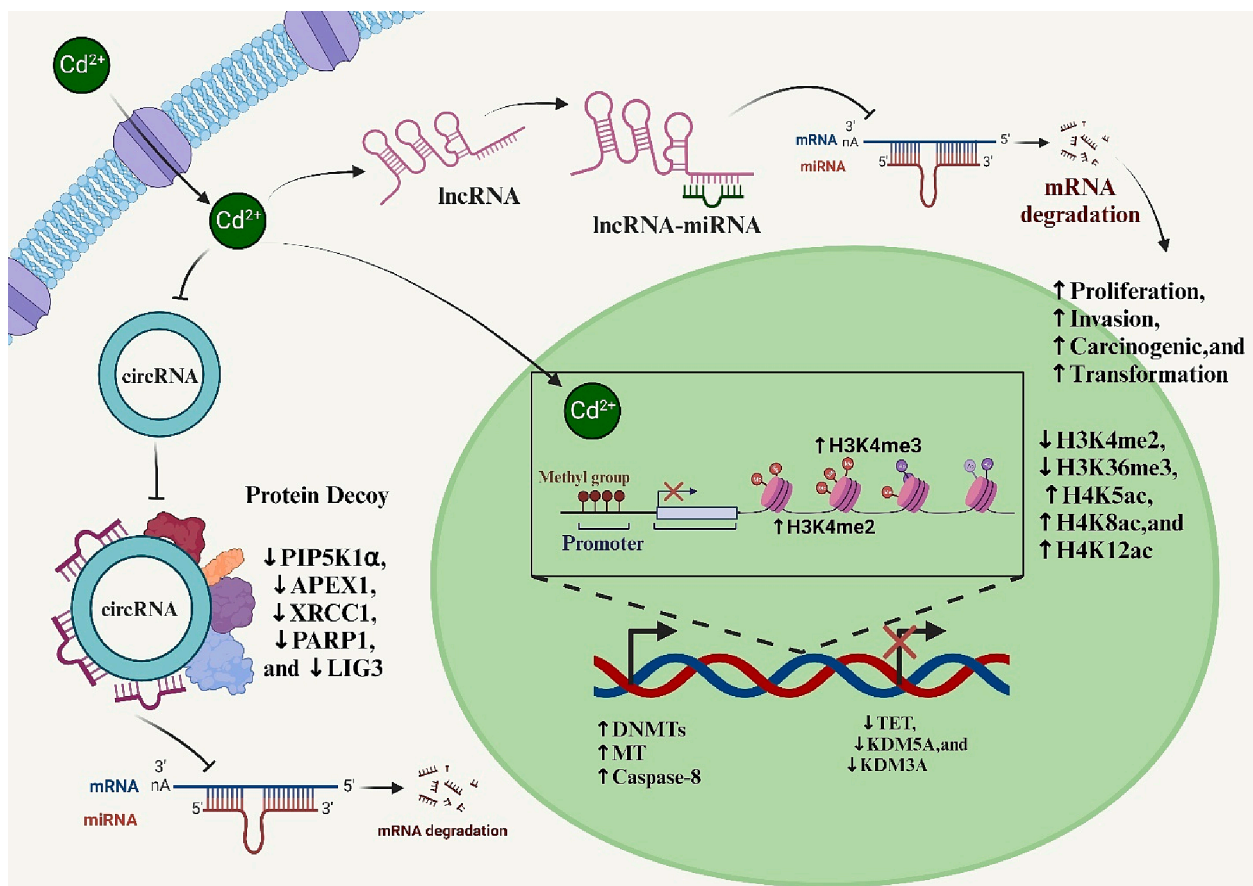

Fig. 2. Illustrate that the common epigenetic alteration mediates cd and induces tumorigenic transformation. Several epigenetic modifications can be depicted, including gene silencing by DNA methylation, histone posttranscriptional modification, and non-coding RNA such as lncRNA, circRNA, and miRNA and their role in facilitating Cd-induced transformation. Created with BioRender.com (Accessed on 9 December 2023).

Table 2

Depicts a comprehensive summary of epigenetic alterations as nongenotoxic mechanisms that regulate cellular responses and the underlying mechanisms that mediate Cd-induced carcinogenesis *in vitro* and *in vivo*, emphasizing the exposure mode, either acute or chronic, and the level of Cd concentration, either low or high.

Cells line	Cd conc.	Epigenetic alteration	Molecular events	Study Type	Exposure	References
Rat liver TRL1215 cells	2.5 μM	Hypermethylation	↑Invasiveness, ↓TET1, ↓ApoE, ↓TIMP2, and ↓TIMP3	*In vitro*	Chronic	(Hirao-Suzuki et al., 2021)
CNE-1 and CNE-2	1 μM	Hypermethylation	↓ 1α(CK1α), ↑EMT, ↑β-catenin, and ↑Wnt pathway activation	*In vitro*	Chronic	(Peng et al., 2019)
HMy2.CIR cells	0.1 μM	Hypermethylation	↓p16	*In vitro*	Chronic	(Yuan et al., 2013)
RWPE-1 cells	10 μM	Hypermethylation	↑DNMT3b ↓p21, and ↓RASSF1A	*Invitro*	Chronic	(Benbrahim-Tallaa et al., 2007)
16HBE cells	–	Hypermethylation	↑DNMT1, ↑DNMT3a ↓hMSH2, ↓ERCC1, ↓XRCC1, and↓hOGG1	*In vitro*		(Zhou et al., 2012)
HepG2, MCF7, and HEK-293 cells	1 μM	Hypomethylation	↑ PRMT5, and ↑EZH2,	*In vitro*	Acute	(Ghosh et al., 2020)
MCF-10A, MCF-7, and SKBR3 cells	2.5 μM	Hypomethylation	↓BRCA1, ↑CK5, ↑p63, ↑c-Myc, and ↑ KRAS	*In vitro*	Chronic	(Benbrahim-Tallaa et al., 2009)
BEAS-2B cells	2.0 μM	Histone methylation	↑ H3K4me3, ↑H3K9me2, ↓ KDM5A, and ↓ KDM3A	*In vitro*	Chronic	(Xiao et al., 2015)
HepG2 cells	0.1, 0.5, or 1.0 μM	Histone methylation and acetylation	↓Histone methylation and ↓acetylation	*In vitro*	Acute	(Cartularo et al., 2015)
BEAS-2B cells	1—20 μM	Histone 18 PTM	↓H3K4me2, ↓H3K36me3, ↑H3K9acS10ph, ↑H4K5ac, ↑H4K8ac, and ↑H4K12ac	*In vitro*	Chronic	(Liang et al., 2018)
16HBE cells	–	LncRNA-MALAT1	↑MALAT1, ↑proliferation, ↓FOXC2, ↓STAT3, ↓BAX, ↓EGFR, ↓TGF-β1, and ↑BCL-2	*In vitro*	Chronic	(Huang et al., 2017)
BEAS-2B cells	2.5 μM,	LncRNA -MEG3	↓MEG3), ↑ DNMTs, ↓p21, ↑Rb, and ↑Bcl-xL	*In vitro*	Chronic	(Lin, Rea, et al., 2021)
BEAS-2B cells	2.5 μM	LncRNA-DUXAP10	↑DUXAP10, ↑Hedgehog pathway, ↑Pax6, ↑KLF4, ↑KLF5, and ↑Nanog	*In vitro*	Chronic	(Wang et al., 2021b)
PC3 and DU145 cells	–	LncRNA- OIP5-AS1	↑ OIP5-AS1, ↓miR-128-3p, ↑SLC7A11, ↓cell proliferation, and ↓ferroptosis	*In vitro*	Chronic	(Zhang et al., 2021)
16HBE cells	–	LncRNA–ENST00000446135	↑ENST00000446135, ↑ ATM, vATR, ↑ ATRIP, ↓MSH2, ↓OGG1, ↓ERCC1, ↓DDB1, ↓DDB2, and↓ XRCC1	*In vitro*	Chronic	(Zhou et al., 2020)
BEAS-2B cells	2 μM	Circular RNA-circPUS7	↑CircPUS7, ↓miR-770, and ↑KRAS	*In vitro*	Chronic	(Pan et al., 2021)
BEAS-2B cells	2.0 μM	Circular RNA-circ-SHPRH	↓circ-SHPRH, ↑miR-224–5p, ↓QKI, ↓E-cadherin, ↑vimentin	*In vitro*	Chronic	(Zhou et al., 2021)
BEAS-2B cells	2.0 μM	Circular RNA- CircSPAG16	↓CircSPAG16, ↓PIP5K1α, And ↓Akt	*In vitro*	Chronic	(Wang et al., 2021b)
BEAS-2B and 16HBE cells	16HBE cells: 10 μM, BEAS-2B cells: 1 μM	Circular RNA- circCIMT	↓circCIMT, ↑γ-H2AX, ↑DNA damage, ↓APEX1, ↓XRCC1, ↓PARP1, and ↓LIG3	*In vitro*	Chronic	(Li et al., 2023a)
BEAS-2B cells	0, 2.5, 5 and 10 μM	MiR-30 family genes, miR-30a, miR-30b, miR30c-1, miR-30c2, miR-30d, and miR-30e	↓miR-30 family members, ↑SNAIL, ↓E-cadherin, ↑ZEB1, and ↑vimentin	*In vitro*	Acute	(Tanwar et al., 2019)

Model	Cd dose	Epigenetic alteration	Mechanisms	Study Type	Exposure	References
Female BALB/c mice	–	Hypermethylation	↓Caspase-8, ↓IL-1β, and ↑Itm2a	*In vivo*	Chronic	(Zhang et al., 2023)
SPF Sprague-Dawley rats	high dose: 1.225 mg/ kg, mid-dose: 0.612 mg/ kg, and low dose: 0.306 mg /kg	LncRNA-MALAT1	↑MALAT1	*In vivo*	Chronic	(Huang et al., 2017)
SPF Sprague-Dawley rats	high dose: 1.225 mg/kg, mid dose: 0.612 mg/kg, and low dose: 0.306 mg/kg	LncRNA–ENST00000446135	↑ENST000004461	*In vivo*	Chronic	(Zhou et al., 2020)
Female BALB/c mice	0.640 mg m−3	Circular RNA- circCIMT	↓circCIMT, ↑ALDH1A, and ↑Sox2	*In vivo*	Chronic	(Li et al., 2023a)

chromatin structure to control gene expression (Moore et al., 2013). This section examines how Cd exposure can affect DNA methylation patterns and facilitate carcinogenicity in different cellular models.

Several studies pointed to chronic Cd exposure mediating DNA hypermethylation and enhancing progressive tumorigenic phenotype. Zhang et al. (Zhang et al., 2023) uncovered that chronic Cd exposure mediates hypermethylation of genes associated with apoptosis and inflammation, including *caspase-8* and interleukin-1β (*Il-1β*) and

hypomethylation of the gene midline 1 (*Mid1*) in the mouse model. Rat liver cells TRL1215 cells exposed to 2.5 μM Cd for ten weeks exhibited enhanced invasiveness by downregulation of ten-eleven translocase 1 (TET1) that can reverse DNA methylation and, consequently, the downregulation of the apolipoprotein E (ApoE) by hypermethylation (Hirao-Suzuki et al., 2021). In NPC, chronic exposure of CNE-1 and CNE-2 cell lines to Cd promotes cell proliferation and cancer progression via hypermethylation of casein kinase 1α(CK1α), which leads to activation of the Wnt/β-catenin pathway (Peng et al., 2019). In addition, using *in vitro* models, lymphocyte proliferation increased due to the downregulation of p16 caused by hypermethylation of its promoter (Yuan et al., 2013). A genome-wide methylation study for the nongenotoxic carcinogen- cadmium chloride unveiled that hypermethylation of several genes in the promoter region is associated with cancer and cancer pathways (Hwang et al., 2019).

In addition, several lines of evidence suggest that Cd exposure induces the expression of DNMTs and DNA hypermethylation, facilitating the tumorigenic transformation of prostate epithelial cells, lung epithelial cells, and human embryo lung fibroblast cells (Gao et al., 2017; Jiang et al., 2008; Pelch et al., 2015). While acute Cd exposure inhibits DNMT, chronic exposure induces carcinogenesis via upregulation of DNMT and hypermethylation of genomic DNA. Surprisingly, the level of genomic hypermethylation continued for four weeks after exposing the cell to Cd-free media (Takiguchi et al., 2003). Similarly, chronic exposure of PCa cells to Cd resulted in upregulation of DNMT3b expression and hypermethylation of the tumor suppressor p16 and RASSF1A (Benbrahim-Tallaa et al., 2007). Furthermore, Zhou et al. (Zhou et al., 2012) investigated the effect of Cd exposure mediating carcinogenic transformation of bronchial epithelial cells. The authors revealed upregulation of DNMTs, including DNMT1 and DNMT3a but not DNMT3b. In addition, genomic hypermethylation was observed, especially in DNA repair genes, including *hMSH2*, *ERCC1*, *XRCC*1, and *hOGG1*. In addition, Inglot and colleagues illustrated that Cd exposure induces chromosomal aneuploidy in the pig Robertsonian translocation model through DNA hypermethylation (Inglot et al., 2012).

Hypomethylation is also a proposed mechanism for causing Cd-inducing carcinogenic transformation. Acute Cd exposure in hepatic and breast cancer in *in vitro* models demonstrated downregulation of the DNMTs, which resulted in demethylation of the CpG islands in the promoter region of protein arginine methyltransferase 5 (PRMT5) and the polycomb repressive complex 2 (PRC2) member enhancer of zeste homolog 2 (EZH2) and subsequently global hypomethylation of genomic DNA (Ghosh et al., 2020). Similarly, chronic Cd exposure induces breast cancer malignant transformation. It exhibits global hypomethylation, especially for genes that enhance aggressiveness, such as the stem cell marker cytokeratin 5 (*CK5*) and *p63*, and the oncogenic c-Myc and Kirsten rat sarcoma viral oncogene homolog (KRAS) (Benbrahim-Tallaa et al., 2009). Hypomethylation initially happens during the acute exposure phase, followed by hypermethylation in the chronic phase. In addition, DNMT might play a crucial role in Cd inducing carcinogenicity as DNMT inhibitor 5-aza-2′-deoxycytidine has been shown to induce tolerance to Cd toxicity via hypomethylation of Met-allothionein (MT) (Waalkes et al., 1988).

4.1.2. Histone modifications

Histone post-translational modification plays a crucial role in modulating gene expression. Several chemical groups can modify the histone tail, including acetylation, methylation, phosphorylation, ubiquitylation, deamination, ADP ribosylation, and isomerization. Those modifications induce intra-chromosomal changes and recruitment of remolding complexes that modify gene expression (Bannister & Kouzarides, 2011). Histone modifications also have a role in Cd-inducing cellular transformation. In immortalized normal human bronchial epithelial (BEAS-2B) cells, acute Cd exposure resulted in the upregulation of trimethylated histone H3 on lysine 4 (H3K4me3) and dimethylated histone H3 on lysine 9 (H3K9me2) compared to control

which was significantly increased with chronic exposure to low Cd concentration, and inhibition of lysine-specific demethylase 5A (KDM5A) and the lysine-specific demethylase 3A (KDM3A) demethylases respectively (Xiao et al., 2015).

Conversely, epiproteome profiling of transformed BEAS-2B through chronic exposure to Cd revealed downregulation in the methylation level of H3K4me2 and H3K36me3 and upregulation in histone acetylation (Liang et al., 2018). Another study reported that acute exposure in human hepatocellular carcinoma cells decreases histone methylation and acetylation, which was persistent for 72 h after Cd removal (Cartularo et al., 2015). Further research in this area is warranted to fully decipher the intricate mechanism of histone modification mediating Cd-induced carcinogenesis. In addition, exploring the role of other histone modifications, for example, phosphorylation and other modifications, and their role in the transformation process will be of great interest.

4.1.3. Non-coding RNAs

Non-coding RNAs(ncRNAs) refer to a group of RNAs that do not code for a protein and comprise most of the human genome. No-coding RNA can be classified into housekeeping RNAs such as rRNA, tRNA, snoRNA, and snRNA and regulatory RNAs, which can be subclassified according to their length to small non-coding RNAs such as microRNAs (miRNAs), small interfering RNAs (siRNAs), piwi interacting RNA (piRNA) and long noncoding RNAs (lncRNA) in addition to circular RNA (circRNA) (Almatroudi, 2022; Mattick & Makunin, 2006). Regulatory ncRNAs play vital roles in regulating gene expression via intricate network interactions with crucial elements, including DNA, mRNA, proteins, peptides, and small molecules and processes in the cell such as chromatin structure, transcription, RNA splicing, and protein translation (Almatroudi, 2022; Kazimierczyk et al., 2020; Mattick & Makunin, 2006).

4.1.3.1. Long noncoding RNA. Long non-coding RNAs are a group of regulatory ncRNAs with a transcript length of over 200 nucleotides. It regulates gene expression at the transcriptional and post-transcriptional levels by interfering with DNA, mRNA transcripts, sponging miRNA, or interfering proteins in different signaling pathways (Statello et al., 2021). Several studies discussed the role of lncRNA in mediating Cd-induced carcinogenic cellular transformation. For example, the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) expression was upregulated by cadmium in transformed human bronchial epithelial 16HBE cells and in a rat model, which led to increased cell proliferation, migration, invasion, and decreased apoptosis in those cells (Huang et al., 2017).

Furthermore, BEAS-2B cells exposed to low doses of Cd downregulated tumor suppressor lncRNA maternally expressed gene 3 (MEG3) expression. In addition, chronic exposure to Cd in those cells decreased p21 expression and phosphorylated retinoblastoma protein (pRB) while increasing the expression of the antiapoptotic protein Bcl-xl. Overexpression of MEG3 inhibited the transformation phenotype, implying that MEG3 might play an essential role in Cd-promoted cellular transformation and carcinogenesis (Lin et al., 2021a). In addition, the study demonstrates that the upregulation of DNMT mediates MEG3 downregulation through hypermethylation of the differentially methylated region (DMR) upstream of the MEG3 transcription start site (Lin et al., 2021a). The findings from this study are also supported by results from the NEST cohort study that show a significant correlation between elevated prenatal Cd levels and MEG3 DMR hypermethylation in maternal blood Cd (B-Cd) concentrations of infants, indicating that hypermethylation of DMR is imprinted on MEG3 (House et al., 2019).

Moreover, Lin et al. (Lin et al., 2021b) revealed that chronic low Cd exposure in the lung epithelial BEAS-2B cells induces cellular transformation, stem cell-like phenotype, and upgradation in the hedgehog pathway and induces tumor formation in a xenograft model. The authors show that the lncRNA DUXAP10 was upregulated in transformed BEAS-2B cells. The silencing of DUXAP10 resulted in the loss of transformation

and CSC-like properties, implying that the role of DUXAP10 in Cd induces carcinogenesis. Low-dose Cd exposure increases cellular growth and ferroptosis inhibition in PCa cellular models, PC3 and DU145. RNA seq data analysis unveiled that the cadmium upregulates the expression level of lncRNA OIP5-AS1 in PCa cells. Knockdown of OIP5-AS1 inhibits cell growth and induces cell death via ferroptosis. The authors revealed that OIP5-AS1 sponge the miR-128-3p, which modulates the expression of SLC7A11 and, subsequently, inhibition of ferroptosis in PCa cellular models, further confirming that lncRNA dysregulation might play a crucial role in modulating carcinogenic effect of Cd in different cellular models (Zhang et al., 2021). Studies collectively support the idea that Cd induces carcinogenesis via a nongenotoxic mechanism.

In contrast, DNA damage in the Cd-transformed human bronchial epithelial cell line16HBE cells was increased alongside the increase in damage-related genes such as *ATM*, *ATR*, and *ATRIP*. It decreased the expression of DNA repair-related genes such as *MSH2*, *OGG1*, *ERCC1*, *DDB1*, *DDB2*, and *XRCC1*. The authors demonstrate that the expression of lncRNA–ENST00000446135 was significantly upregulated in 16HBE bronchial cells and rat models, as well as in workers who faced chronic Cd exposure. Silencing of ENST00000446135 resulted in decreased cell growth and DNA damage in addition to downregulation of DNA damage-related and upregulation of DNA repair-related genes, further confirming the role of ENST00000446135 in mediating Cd-induced carcinogenesis (Zhou et al., 2020). The work by Feng and colleagues supports the role of lncRNA mediating DNA damage and Cd-induced carcinogenic effect. The authors demonstrate that the lncRNA MT1DP mediates a Cd-induced genotoxic effect. They compared residents with high U-Cd with individuals with low U-Cd and found downregulation in DNA repair genes and MT1DP (DNA damage response, genome instability, and replication fork stalling). Exposure to Cd resulted in ATR activation enhancing HIF-1α expression, leading to increased MT1DP expression and subsequent binding to chromatin, where it competitively inhibits SMARCAL1 interaction with replication protein A (RPA) complexes, ultimately causing replication stress and DNA damage (Feng et al., 2022).

Furthermore, Dai et al. performed RNA-seq analysis for the lung adenocarcinoma A549 lung cells exposed to chronic low concentrations of Cd. They found that there were 679 differentially expressed lncRNAs, out of which 375 were upregulated and 304 were downregulated, further insinuating the role of lncRNA dysregulation in modulating Cd-induced carcinogenesis (Dai et al., 2021). Those findings shed light on the complicated role of lncRNA mediating Cd carcinogenicity via non-genotoxic and genotoxic mechanisms.

4.1.3.2. Circular RNA. Circular RNA is another distinct group of ncRNAs lacking a 5′ terminal cap and 3′ polyA tail. Its closed-loop makes it more stable and resistant to exonuclease degradation than linear ncRNAs. Those characteristics render circRNA capable of regulating gene expression via different mechanisms, including sponging miRNAs, interfering with transcription, alternative splicing, and translation (Ma et al., 2021). Emerging evidence supports the role of circRNAs in cancer proliferation, progression, stemness, and resistance to chemotherapeutic agents (Su et al., 2019). Nevertheless, the role of circRNAs is to be fully elucidated. The expression of circPUS7 markedly increased in BEAS-2B cells exposed to Cd for 20 weeks. Chronic Cd exposure shows increased cell proliferation and invasiveness characteristics, markedly decreased upon circPUS7 knockdown, indicating the significant role circPUS7 plays in modulating Cd-induced cellar transformation. The mechanistic study shows that circPUS7 modulates its effect via sponging the tumor suppressor microRNA miR-770, subsequently increasing its downstream KRAS expression (Pan et al., 2021). Another study found that chronic Cd exposure in BEAS-2B cells resulted in malignant transformation and increased epithelial-mesenchymal transition (EMT). In addition, circular RNA circ-SHPRH and QKI expressions were downregulated during the transformation. The tumor suppressor protein QKI is known for

inhibiting cellular proliferation and EMT. The role of circ-SHPRH in mediating Cd-induced transformation was confirmed by overexpressing circ-SHPRH, which abrogates the transformation process and the associated EMT process. Circ-SHPRH is shown to sponge the microRNA miR-224-5p, subsequently affecting the expression of QKI and inhibiting Cd-induced transformation (Zhou et al., 2021).

The role of dysregulated circRNAs seems crucial in the Cd-induced transformation of the human bronchial epithelial cell model either by stimulating transformation, such as circPUS7, or suppressing the transformation, such as circ-SHPRH. Both circRNAs modulate Cd carcinogenesis through the sponging of microRNAs. Another mechanism includes the decoying of oncogenic proteins. CircSPAG16 is another circRNA that can abrogate the cadmium-induced transformation of BEAS-2B cells by binding to phosphatidylinositol 4-phosphate 5-kinase type-1 α (PIP5K1α), an oncogene that binds to Akt. CircCIMT is another circRNA downregulated in lung epithelial *in vitro* and *in vivo*. The expression circCIMT is decreased in the mouse lungs and transformed BEAS-2B and 16HBE cells. Overexpression of circCIMT attenuates transformation properties and reduces DNA damage associated with transformation.

In addition, the circuit binds to the endonuclease APEX1, acts as part of the base excision repair mechanism, and decreases DNA damage. Dual silencing of circCIMT and APEX1 further enhances the Cd, induces transformation, and increases DNA damage (Li et al., 2023a). Those findings support the role of circRNA in mediating Cd-induced carcinogenesis. However, further studies are warranted in different cellular *in vitro* models to fully elucidate the mechanism of circRNAs mediating carcinogenesis.

4.1.3.3. MicroRNA. MicroRNAs are 21–25-nucleotide small ncRNAs that can regulate gene expression by interfering with its mRNA transcript. The level of complementarity between miRNA and its target transcript will determine the level of inhibition, and full complementarity will result in complete silencing of the target gene, while partial complementary will result in downregulation of the target gene (Gebert & MacRae, 2019). They also regulate several essential cellular processes, such as cell growth, differentiation, and apoptosis. Dysregulation of miRNAs is associated with several pathological conditions, including cancer (Catalanotto et al., 2016). MiRNA can regulate cancer initiation, progression, treatment response, and mediate chemoresistance (Awadalla et al., 2020).

The role of Cd-mediated miRNA dysregulation in carcinogenesis is yet to be elucidated. Several studies have demonstrated that Cd exposure results in miRNA dysregulation, subsequently mediating carcinogenesis. lncRNA, such as OIP5-AS1 sponge miR-128-3p, and inhibit ferroptosis via SLC7A11 regulation (Zhang et al., 2021). Moreover, circRNAs such as circPUS7 and Circ-SHPRH sponge miRNAs, including miR-770 and miR-224-5p, thus significantly mediating Cd-induced transformation (Pan et al., 2021; Zhou et al., 2021). Awadalla et al. illustrated that the blood Cd concentration correlates with the tissue expression miRNA-21 in bladder cancer patients (Awadalla et al., 2020). Those studies provide direct evidence of the role of dysregulated miRNA in mediated carcinogenesis. At the same time, several lines of evidence also suggest miRNA's crucial role in Cd carcinogenesis. Tanwar et al. (Tanwar et al., 2019) revealed that the acute exposure of Cd to BEAS-2B cells decreases the expression of the miR-30 family, including miR-30a, miR-30b, miR30c-1, miR-30c2, miR-30d, and miR-30e. The mechanistic study found that Cd exposure upregulates the expression of EMT regulator SNAIL in those cells via downregulation of miR-30. EMT is associated with several diseases, especially cancer (Tanwar et al., 2019).

In addition, Liu et al. (Liu et al., 2015) investigated the expression profile of mRNA-miRNA using microarray profiling. They uncovered that chronic exposure to Cd in 16HBE bronchial cells resulted in dysregulation of several miRNAs upregulated hsa-miR-27b-3p, has-miR-1265, and downregulated hsa-miR-877-5p, has-miR-944, has-miR-1261,

has-miR-3960, and hsa-miR-4708-3p. Out of those dysregulated miR-NAs, the has-miR-27b-3p was the most significantly upregulated, and has-miR-944 was the most downregulated; both target CCM2, a scaffold protein that regulates lumen formation, cytoskeletal structure, and cell–cell junction.

Table 2 summarizes cadmium-induced epigenetic, nongenotoxic mechanisms described above.

4.2. Genomic instability and DNA damage

DNA damage process is essential for achieving genomic instability, a well-studied hallmark of cancer. The exposure of Cd to mammalian cells can induce DNA mutation, strand breaks, and chromosomal abnormalities (Koyama et al., 2002). The most common form of DNA damage that Cd induces is double-strand break (DSB), which can happen in normal cells (Zhang et al., 2019). The usual response to DNA damage includes the recruitment and activation of several protein complexes to the DSB site that either initiate DNA repair, induce cell cycle arrest, or drive the cell to apoptosis (Goodarzi & Jeggo, 2013). Cd-mediated carcinogenic transformation can be explained via several mechanisms, including direct genotoxic effect through direct interaction with DNA nucleotides and the formation of Cd-DNA adducts, especially with adenine and guanine nucleobases (Hossain & Huq, 2002). Indirect genotoxic effects include induction of reactive oxygen species (ROS), lipid peroxidation, and interference with antioxidants such as catalase, superoxide dismutase, and glutathione (Sanchez-Valle et al., 2013; Valverde et al., 2001). The role of Cd-mediated oxidative damage carcinogenesis is reviewed elsewhere (Henkler et al., 2010; Liu et al., 2009).

Cd can mediate carcinogenic transformation via interfering with DNA repair enzymes - the zinc finger family of proteins-either directly or indirectly. It directly interferes with DNA repair enzymes by displacing Zn or hampering their function (Anetor, 2012). Displacement of Zn by Cd in p53 results in conformational changes that decrease p53 - DNA binding activity and repair (Meplan et al., 1999). Furthermore, Cd promotes downregulation in the expression of DNA repair genes. For instance, RNA-seq data analysis from transformed bronchial epithelial cells by low Cd concentration revealed downregulation of DNA repair protein O6-methylguanine-DNA-methyltransferase (MTMG).

Further demonstrating the reduced capability to repair DNA damage reflected by MTMG downregulation, cadmium markedly decreased the viability of transformed cells caused by the alkylating agent temozolomide (Cartularo et al., 2016; Thevenod & Chakraborty, 2010). Cd disturbed the interaction between DNA and DNA repair proteins responsible for base excision repairs, such as XPA, non-homologous recombination, such as 53BP1, and homologous recombination, such as BRCA1. Interestingly, Cd exposure can also inhibit the accumulation of ubiquitination signals at the sites of DNA damage by mediating RNF168 degradation and decreasing RNF168 ubiquitin-ligase activity (Buchko et al., 2000; Hartmann & Hartwig, 1998; Zhang et al., 2019). Here, we summarize the effect of Cd-induced carcinogenic transformation via DNA damage, as depicted in Fig. 3.

4.3. Oxidative stress

Cd-mediated oxidative stress and its role in mitochondrial function have been comprehensively discussed elsewhere (Cui et al., 2021; Henkler et al., 2010; Liu et al., 2009; Nemmiche, 2017). The role of Cd mediating oxidative stress is well established in the literature.
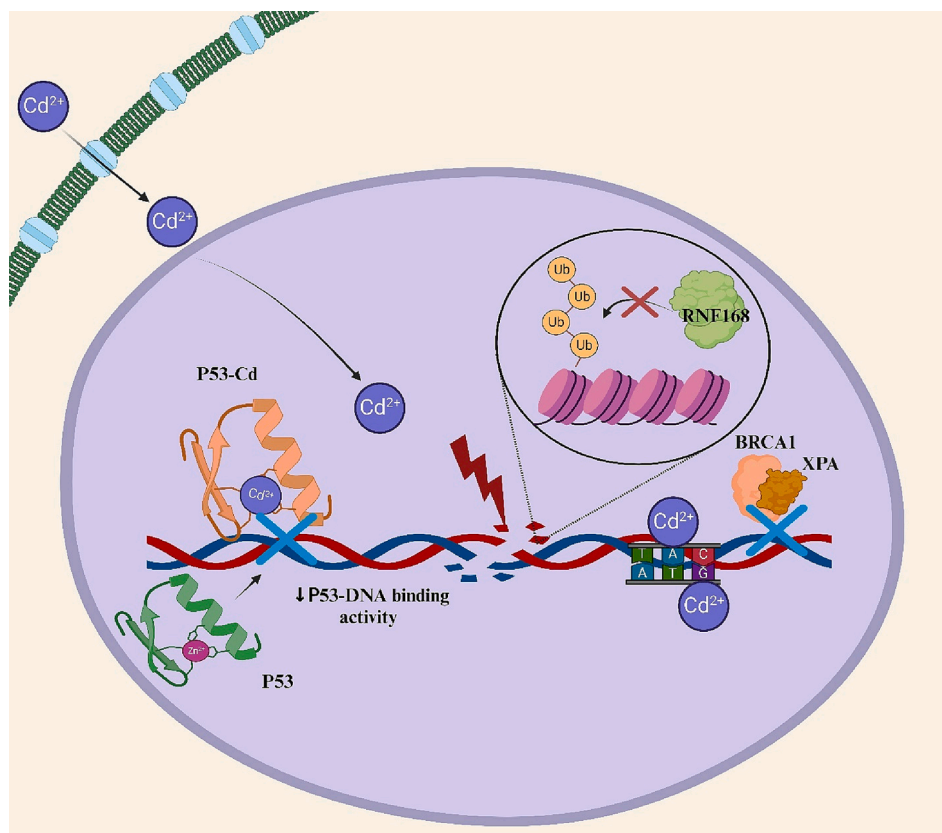

Fig. 3. Illustrates the common DNA damage mechanisms mediating Cd-induced carcinogenic transformation. Exposure to Cd induces DNA double-strand breaks, interacts with DNA nucleobase, and forms DNA adducts. In addition, Cd inhibits the accumulation of ubiquitination signals by decreasing RNF168 ubiquitin-ligase activity. Cd displaces Zn in p53, reducing p53 DNA binding activity and conformational changes, eventually leading to impaired DNA repair. It also can disturb the interaction between DNA and DNA repair proteins and hinder the recruitment of DNA damage proteins to the breaking site. Created with BioRender.com (Accessed on 9 December 2023).

Nevertheless, little was known about the mechanisms of Cd inducing oxidative stress until not long ago (Liu et al., 2008). Cd is implicated in mediating oxidative stress via direct and indirect mechanisms. Direct mechanisms include Cd replacing divalent cations, glutathione depletion, and protein-bound sulfhydryl group, which generate ROS (Liu et al., 2009; Valko et al., 2006). The indirect mechanism emphasizing the role of Cd-mediated oxidative stress comes from studying the spin-trapping technique in conjunction with electron spin resonance that involves the direct interaction between a short-lived free radical with a paramagnetic compound to form a perpetual free radical product that can be measured in acute overloaded Cd models. Along with perturbation in lipid peroxidation, activation of redox-sensitive transcription factors and redox signaling molecules such as activator protein 1 (AP-1), nuclear factor (erythroid-derived 2)-like 2, nuclear factor-κB (NF-κB), phosphoinositide 3-kinase (PI3K)/Akt (protein kinase B), mitogen-activated protein kinases (MAPK), and disparities in gene expression of several genes such as heme oxygenase-1, oxidative stress protein A170, GSH S-transferases, heat-shock proteins, GADD45, GADD153, and metallothionein provide a robust mechanism of Cd-induced ROS indirectly (Liu et al., 2009). In addition, those factors are adaptation mechanisms that reduce Cd-induced oxidative stress in chronic exposure. Nonetheless, low ROS levels can potentially result in carcinogenesis (Emami et al., 2022).

5. Cellular and molecular pathways mediating Cd induce malignant transformation

5.1. PI3K/Akt signaling pathway

The phosphatidylinositol 3-kinase (PI3K)/Akt pathway is over-activated in numerous cancers, promoting cell proliferation, invasion, metastasis, and survival capacities of tumor cells (Rascio et al., 2021). Here, we discuss the involvement of the PI3K/Akt signaling pathway in Cd-induced carcinogenic transformation in various cellular models (Fig. 4.). Chronic Cd exposure led to the transformation of cells and acquiring more aggressive tumorigenic characteristics confirmed by the development of tumors in mice. The PI3K/Akt array analysis revealed that Cd regulates the PI3K/Akt pathway on both transcriptional and translational levels, proposing that the PI3K/Akt signaling pathway plays a crucial role in the transformation of normal prostate cells into a malignant form due to Cd exposure, offering insights into potential therapeutic strategies for cadmium-induced prostate cancer (Kulkarni et al., 2020). Another study shows that KRAS silencing abrogates Cd-mediated carcinogenic transformation of prostate epithelial cells RWPE1 and downregulation of the PI3K/Akt signaling pathway, which further highlights the importance of this pathway in the transformation process (Ngalame et al., 2016).
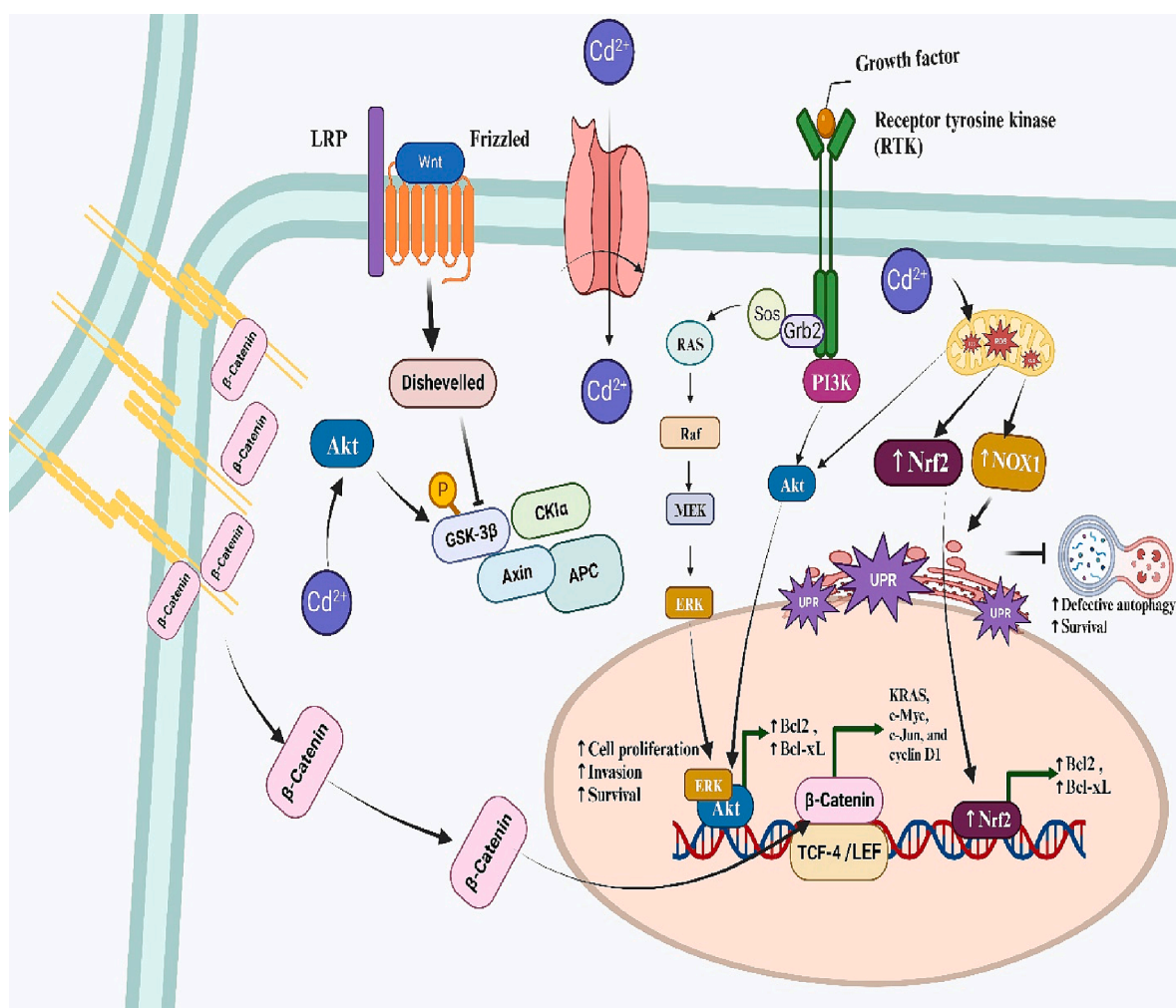
Furthermore, chronic Cd exposure induces tumorigenic

Fig. 4. Illustrates the underlying mechanism of cd-mediated carcinogenic transformation via activation of several signaling pathways. Cd induces ros generation that activates signaling pathways involved in cell proliferation and survival, such as the PI3K/Akt pathway and MAPK/Erk. In addition, Cd induces the dissociation of β-catenin from the cell membrane, resulting in localization to the nucleus, where it can activate the expression of proto-oncogenes. Cd induces ROS formation, leading to defective autophagy that mediates cell survival. created with BioRender.com (Accessed on 9 December 2023).

transformation of BEAS-2B cells and leads to the development of tumors in mice. Mechanistic studies found that Cd induces ROS formation and activates PI3K and its downstream Akt. The effect of ROS-mediated Cd activation of the PI3K/Akt signaling pathway was confirmed by transfection with the antioxidant enzymes catalase and superoxide dismutase, which resulted in abrogation of the transformation process, further ensuring the role of ROS in carcinogenic transformation (Son et al., 2012). Mohapatra et al. investigated the effect of cigarette smoke condensate containing approximately 1.011 µg Cd per cigarette equivalent on the transformation of BC cells. Their experiments showed that cigarette condensate containing heavy metals, including Cd, caused a malignant transformation of breast epithelial cells. The authors found high expression of PI3K, AKT, and NF-κB, further documenting the participation of the PI3K/Akt signaling pathway in tumorigenic transformation (Mohapatra et al., 2014). However, more mechanistic studies using different cellular and animal models are warranted to elucidate the contribution of this pathway to carcinogenesis.

5.2. MAPK signaling cascade

Mitogen-activated protein kinase (MAPK) cascades are essential in communicating signals to cellular responses. There are three well-characterized families of MAPK cascades, including the extracellular signal-regulated kinases (Erk), C-Jun N-terminal kinase (JNK), and p38 kinase (Zhang & Liu, 2002). MAPK signaling cascades modulate essential cellular processes, including cellular growth, cell differentiation, cell death, and stress responses (Guo et al., 2020). The role of MAPK signaling cascades modulating Cd to promote malignant transformation is elusive. Dasgupta et al. unveiled that chronic Cd exposure modulates malignant transformation via activating the Erk/MAPK pathway (Dasgupta et al., 2020). In addition, the activation of Erk and Akt promotes angiogenesis by inducing the expression of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (Jing et al., 2012). Further research is still warranted to decode the role of the Erk/MAPK pathway in Cd-mediated tumorigenic transformation (Fig. 4.).

Additional members of the MAPK cascades that play a crucial role in modulating Cd-mediated tumorigenesis, such as JNKs, also known as stress-activated kinases (SAPKs). The importance of JNK comes from its role in regulating essential processes such as cell growth, cell death, and DNA repair. Aberrant JNK signaling contributes to the development of several diseases, including cancer (Johnson & Nakamura, 2007). Chuang and colleagues unveiled that low Cd doses activated JNK and inhibited apoptosis (Chuang et al., 2000). Conversely, another mechanistic study disclosed that in Cd-transformed cells, the high expression of the antiapoptotic protein Bcl2 possibly attenuates JNK1/2 phosphorylation, evading apoptosis (Qu et al., 2006; Qu et al., 2007).

Furthermore, JNK is known to phosphorylate c-Jun at the N-terminal serine residues in response to stress stimuli (Johnson & Nakamura, 2007). C-Jun is as vital as an oncogene and a member of the AP-1 transcription factors that control gene expression responding to various stimuli (Johnson & Nakamura, 2007). Yang et al. uncovered that Cd exerts its malignant effect and induces cell proliferation through activating AP-1, which is mediated by JNK/c-Jun/AP-1 and ERK/Fra-1/AP-1 activation and overexpression of the anti-apoptotic protein Bcl-xL, further supporting the role of JNK in mediating apoptosis resistance in transformed cells (Yang et al., 2008). In addition, several reports showed that Cd exposure results in the upregulation of several proto-oncogenes, including but not limited to KRAS, c-Myc, c-Fos, and c-Jun (Joseph et al., 2001; Spruill et al., 2002). Both c-Fos and c-Jun are well-known proto-oncogenes combined to form an AP-1 complex that JNK can modulate to facilitate malignant phenotype in Cd-mediated transformation.

5.3. β-catenin pathway

The Wnt/β-catenin signaling pathway is crucial for tissue development and homeostasis. The dysregulation of this pathway results in the etiology of several diseases, including cancer. Its importance comes from regulating several pathways critical for cancer development, such as cancer stem cell renewal, proliferation, and differentiation. (Liu et al., 2022). The role of this pathway mediating Cd's role in tumorigenesis remains elusive. A few studies have demonstrated its involvement in Cd-induced transformation. Indeed, chronic Cd exposure promotes the transformation of BEAS-2B cells and results in tumors in mice. The authors demonstrated that Cd induces ROS formation, which subsequently activates GSK-3β/β-catenin and PI3K/Akt pathway, as previously discussed. The expression level of β-catenin and phosphorylated GSK-3β (pGSK-3β) were higher in transformed cells than in control. The effect of the Cd-mediated activation of the β-catenin pathway was confirmed by transfection with the antioxidant enzymes catalase and superoxide dismutase, which diminish the transformation process (Son et al., 2012). GSK-3β tightly regulates the activation of β-catenin. β-catenin phosphorylation by GSK-3β causes its degradation. In this study, it seemed that Cd-induced carcinogenic transformation activated the PI3K/Akt pathway that might phosphorylate GSK-3β, leading to increased levels of pGSK-3β and β-catenin stabilization (Son et al., 2012).

Chronic Cd exposure exacerbated malignant transformation by activating the Wnt/β-catenin pathway in NPC (Peng et al., 2019). Cd exposure mediates the downregulation of E-cadherin, a protein responsible for maintaining cell–cell adhesion. The downregulation of E-cadherin resulted in decreased cytoplasmic E-cadherin/β-catenin complex. It facilitated the localization of β-catenin to the nucleus, where it combines with transcription factor-4 (TCF-4) and regulates the expression of several genes responsible for tumorigenic proliferation and survival, such as *c-Jun, c-Myc,* and *cyclin D1* (Fig. 4.) (Pearson & Prozialeck, 2001).

5.4. Defective autophagy facilitates survival in Cd and induces carcinogenic transformation

Autophagy is a survival mechanism that facilitates the catabolic degradation of cellular organelles and proteins through the lysosomal-mediated degradation of loaded cargo (Saran et al., 2021). Several studies emphasized the role of autophagy in the modulation of transformation by Cd. One study highlighted that Cd induces ROS generation and upregulation of NADPH oxidase 1 (NOX1), which in turn causes endoplasmic reticulum stress and activates the unfolded protein response (UPR) that leads to defective autophagy which in turn attenuates autophagosome-lysosome fusion and facilitate survival (Tyagi et al., 2023). Similarly, Cd induces ROS generation, resulting in defective autophagy, and bestows survival advantages to transformed cells. The transformation phenotype was abrogated upon overexpression of antioxidants such as catalase and superoxide dismutase (Kolluru et al., 2019). Likewise, another study uncovered that Cd exposure induced the expression of Placenta Associated 8 (Plac8), which is a regulator of autophagosome/autolysosome fusion that leads to autophagy and increased cell proliferation and survival through the activation of pro-survival mechanisms, including Akt and NF-κβ (Kolluru et al., 2017). Psoralidin works as a chemoprotective agent by inhibiting cell proliferation autophagy and inducing downregulation of pro-survival protein NFκB and the anti-apoptotic protein Bcl2, further emphasizing the role of autophagy in Cd, mediating tumorigenesis and the crosstalk between autophagy and apoptosis resistance to facilitate Cd carcinogenesis (Pal et al., 2017). Similarly, Cd induces ROS production, resulting in autophagosome accumulation, upregulation of p61, and activation of NF-E2–related factor 2 (Nrf2). The activation of Nrf2 exhibits its effect via the upregulation of its downstream anti-apoptotic protein Bcl2 and Bcl-xL (Fig. 4.), hence inducing apoptotic resistance and enhancing cell survival (Wang et al., 2018).

6. Biomarkers and genetic factors influencing susceptibility to carcinogenesis

The adverse effect of Cd exposure on human health is well established. In our review, we discussed how Cd exposure mediates the carcinogenic transformation of normal cells. Therefore, discovering novel diagnostic biomarkers that reflect Cd exposure is crucial. Exposure to Cd results in multi-organ damage, primarily to the kidneys (50 % of cases), muscle (20 %), and liver (15 %). Blood Cd is a reliable indicator of body Cd load (Borne et al., 2019). Following exposure, much of the cadmium accumulates in the kidney, and urine levels correlate with kidney levels. As a result, U-Cd levels are frequently regarded as an indication of long-term exposure (Vacchi-Suzzi et al., 2016). The WHO recommended a health-based U-Cd exposure limit of 5 µg/g of creatinine (or 5 µg/L). Currently, the U-Cd level is considered safe for humans in most nations and is comparable to the WHO reference value (Gao et al., 2014).

Monitoring human populations for early symptoms of Cd exposure and toxicity has proven to be extremely difficult. Measuring Cd levels in blood or urine is the standard method researchers use to evaluate Cd exposure. However, several other methods include measuring Cd levels in hair, nails, and saliva. In addition, the emergence of innovative nanotechnologies, such as quantum dots, might help monitor Cd exposure (Rafati Rahimzadeh et al., 2017). Yet, discovering novel diagnostic markers, especially those associated with the possibility of cellular malignant transformation, will be immensely important.

Several studies have reported a significant association between Cd levels in blood and urine and dysregulation of ncRNAs, especially lncRNAs. The expressions of MALAT1 and ENST00000446135 are upregulated in Cd-transformed 16HBE cell rat models and in human subjects. MALAT1 and ENST00000446135 expressions correlate positively with U-Cd and B-Cd levels in both rat models and Cd-exposed workers, indicating that MALAT1 and ENST00000446135 might be used as novel biomarkers for Cd toxicity (Huang et al., 2017; Zhou et al., 2020). In addition, Moawad et al. investigated the expression signature of lncRNA-ENST00000414355 in 139 workers from Cd battery manufacturers, including 74 non-smokers and 65 smokers. ENST00000414355 expression significantly correlated with B-Cd level (Moawad et al., 2021).

MiRNAs also hold a potential role as an appropriate diagnostic marker for Cd exposure despite a lack of studies that examine the association between miRNAs and Cd-induced carcinogenic phenotype. MiRNA profiling shows that miR-122-5p and miR-326-3p may be promising biomarkers for Cd exposure (Yuan et al., 2020). Those results highlight the promising role of the ncRNA signature as a diagnostic marker for chronic Cd exposure.

Several studies explored whether genetics influence susceptibility to Cd-induced cancer. Even though the influence of genetic susceptibility of Cd induces malignant transformation, it is yet to be uncovered. Indeed, a complex network of interactions between various genes may be underlying the transformation. Our review has delineated the interaction between Cd mediate genetic modification, DNA damage, evading apoptosis, oxidative stress, carcinogenic transformation, and the reciprocal interaction between different mechanisms. Intriguingly, Cd-mediated transformation is not dominated by a single mechanism of action. Instead, there are several overlying layers of interactions that collectively modulate the transformation. Based on this premise, identifying genetic susceptibility biomarkers will enable vulnerable subpopulations to take the necessary safety measures regarding Cd exposures and decrease disease risk. The effectiveness of translation (eukaryotic) initiation factor 3 (eIF3) as a diagnostic marker for Cd exposure has been investigated in Cd-transformed 16HBE cells, rat models, and human participants. Zhou et al. found a positive correlation between eIF3 expression and B- Cd, U-Cd, and β2-microglobulin content, implying that eIF3 might be an innovative surrogate marker for Cd exposure (Zhou et al., 2016). Further research focusing on the

dysregulated proteomic, metabolomic, and transcriptomic signature in malignant transformed *in vitro* and *in vivo* models using innovative methods such as next-generation sequencing, mass spectroscopy, and microarray profiling will have a vital role in determining novel, innovative diagnostic biomarkers that are associated with carcinogenesis.

7. Strategies for Cd exposure prevention

In this review, we have highlighted the role of Cd-induced carcinogenesis and provided a comprehensive review of the literature on studies that find an association between Cd exposure and cancer development. In addition, we have discussed the risk of early life Cd exposure and cancer development. Several studies have focused on the preventive strategies that could reduce the risk of Cd exposure (Reviewed elsewhere (Mezynska & Brzoska, 2018; Nawrot et al., 2010; Schaefer et al., 2020; Sripada & Lager, 2022)), including several interventions that adopted strategies focusing on preventing Cd toxicity, especially plant-derived compounds with a particular focus on the role of flavonoid as antioxidants, bio elements including magnesium, selenium, manganese, and zinc, the antioxidants N-Acetyl Cysteine, and probiotics (Cui et al., 2021; Dubey et al., 2019; Mezynska & Brzoska, 2018; Sripada & Lager, 2022). Others focused on providing strategies that help in reducing Cd in soil and crops, such as using lime or applying amendments such as biofortification that can decrease the bioavailability of Cd in the soil, replacing phosphate-based fertilizers with zinc-based fertilizers can reduce the accumulation of Cd in crops (Schaefer et al., 2020). Genetic modification of rice, wheat, potatoes, and other staples to extract less Cd from the soil may also be helpful. The same may apply to tobacco to decrease Cd extraction from the soil. In addition, air monitoring and biomonitoring effectively reduce Cd among workforces (Lombaert et al., 2023). Even though there is a tremendous need to investigate an innovative drug that could reverse Cd-induced carcinogenicity, we discussed the promising potentials of autophagy inhibitors Psoralidin and sulforaphane in reversing Cd mediating carcinogenic transformation (Pal et al., 2017; Wang et al., 2018).

8. Beyond current paradigms: The future landscape of Cd-induced carcinogenesis

8.1. Research trends in cadmium carcinogenesis

The recent advances in diagnostic biomarkers, the genetic susceptibility field, and strategies that might mitigate Cd exposure are tremendous. Nevertheless, more research focused on deciphering the underlying mechanism mediating Cd-induced carcinogenic transformation combining different multi-omics data generated from *in vitro* and *in vivo* Cd-transformed models will help understand the multifaceted role of Cd in deriving carcinogens. Results from the multiomic data will help researchers build networks combining transcriptomics, proteomics, and metabolomics data to help determine the hub gene(s) responsible for malignant transformation. In addition, applying state-of-the-art imaging techniques such as mass spectrometry, imaging, and PET/CT scans will provide insight into the effect of Cd-mediated transformation in animal models. Current knowledge points to epigenetic aberration as a common pathway for response to Cd exposure. However, several areas are to be discovered, such as the mechanism of Cd-mediated chromatin remodeling and the exact mechanisms underlying miRNAs, circRNAs, and lncRNAs aberration in transformed cells. It will also give an insight into the heritable trait and imprinting of genes that can affect offspring. Moreover, most research focuses on medical intervention; however, shifting our paradigm toward prevention research could also highly impact health outcomes.

8.2. Translational opportunities and challenges

Furthermore, the emergence of metallomics will guide researchers to

investigate the effect of biological trace elements and inorganic elements on biological systems equipped with innovative techniques such as mass spectrometry, electrochemistry, atomic spectroscopy, chromatography, and computational modeling. Additionally, incorporating microphysiological systems will facilitate the emulation of biological systems using organ-on-a-chip technology that could collectively advance our understanding of the pathophysiology of metal-induced carcinogenesis and guide the development of groundbreaking diagnostic biomarkers and therapeutic agents.

9. Conclusion

In this review, we provided a comprehensive analysis of the effect of Cd exposure on human health, focusing on the risk of cancer development and early life exposure to cancer risk. We further discussed the mechanisms mediating Cd-induced carcinogenic transformation on *in vitro* and *in vivo* models, focusing on epigenetic aberrations, DNA damage, resisting cell death, inducing oxidative stress, and activating survival mechanisms. More research is warranted to fully understand the intricate mechanism underlying Cd-mediated carcinogenic transformation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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