REVIEW ARTICLE

The Role of Endocrine Disruptors and Environmental Chemicals in Causing Cancer: Focusing on Genetic and Epigenetic Mechanisms

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Abstract

Endocrine-disrupting chemicals (EDCs) and environmental pollutants are ubiquitous and increasingly linked to the aetiology of cancer. This review synthesises existing evidence on the carcinogenic potential of EDCs, including bisphenols, phthalates, pesticides, heavy metals and persistent organic pollutants, with a focus on genetic and epigenetic pathways. The molecular mechanisms by which these chemicals induce carcinogenesis, including DNA damage, chromosomal aberrations, dysregulation of oncogenes and tumour suppressor genes and alterations in DNA repair was critically accessed. Epidemiological research emphasises epigenetic changes, including aberrant DNA methylation, histone modifications and deregulated non-coding RNA expression, which mediate long-term and potentially transgenerational effects of exposure. The interplay among endocrine signalling, oxidative stress, inflammation and epigenetic reprogramming is discussed in relation to hormone-dependent and hormone-independent cancers. Epidemiological, *in vivo* and *in vitro* experimental evidence, together with high-throughput omics data, were integrated to strengthen mechanistic plausibility. This review identified important research gaps, including low-dose and mixture effects, timing of exposure and population-wide vulnerability and provides future directions for risk assessment and regulatory policy. Greater insight into the genetic and epigenetic effects of EDCs is needed to advance cancer prevention and inform evidence-based community health interventions.

Key words: Endocrine disruptors; Neoplasms; Carcinogenesis; Epigenomics; Toxic; Metals.

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Introduction

Endocrine-disrupting chemicals (EDCs) are substances, either natural or man-made, that can imitate, block, or interfere with the body's endocrine system's hormones. Numerous health problems have been linked to these substances. Based on their distinct characteristics, at least 1,000 of the approximately 85,000 man-made substances in the world may be endocrine disruptors (ED), according to the Endocrine Society.[1] Numerous health issues have increased since the Industrial Revolution due to the continuous discharge of chemicals into the environment. EDCs interfere with the hormonal system and are one class of such environmental toxins. EDCs contain a variety of substances, including flame retardants, plastic softeners, medications and insecticides. As a result, EDCs are found in a variety of bodily fluids and are regularly encountered by both humans and wildlife.[2, 3]

There is mounting evidence that if a person is exposed to EDCs in early life, especially during foetal development, it may be linked to several problems in later life, including cancer and cognitive decline.[4, 5] For example, during 1940 and 1970, women who took the synthetic oestrogen diethylstilbesterol (DES) in the early stages of pregnancy to avoid miscarriages were found to have their daughters at a higher risk of developing a rare vaginal cell adenocarcinoma during puberty.[6] There have also been studies of the adverse effects of DES even in the second generation. Sons of DES daughters, for instance, are more likely to experience hypospadias, a condition affecting the male reproductive system.[7] The mechanism by which early-life chemical exposure causes long-lasting alterations that manifest as illnesses much later in life, or even in subsequent generations, is not precisely understood. However, there is growing evidence that the long-lasting impacts of EDCs and other substances are primarily due to epigenetic processes.[8] Any long-term modification of gene function that continues even in the absence of the initial trigger and does not involve a change in gene sequence or structure is referred to as an epigenetic alteration. Epigenetic processes provide long-term transcriptional control. Numerous experimental and epidemiological studies have demonstrated that EDCs do, in fact, cause epigenetic alterations.

Concerns in society are growing that exposure to EDCs throughout development plays a significant part in the emergence of certain non-communicable diseases and the associated costs.[3, 5] According to a recent study, the annual costs of health issues related to EDC exposure in Europe were estimated to be €163 billion, or 1.28 % of the EU gross domestic product, based on their contribution to conditions like male infertility, obesity, diabetes, attention-deficit/hyperactivity disorder and autism.[3] However, only a handful of these disorders are addressed by the current methodologies for evaluating health risks associated with EDC exposure and they are not developed to measure long-term consequences resulting from exposures during early life.[8] For the chemical risk evaluation of EDCs, therefore, more precise and sensitive techniques are required, with an emphasis on mechanisms of action rather than phenotypic results. Potentially sensitive and early end-points for the long-lasting impacts of EDCs might include epigenetic modifications.[9] Currently, there is no evidence linking EDCs to adverse health outcomes and the mechanisms underlying these alterations are rarely discussed, despite numerous studies showing that they cause epigenetic modifications. However, incorporating epigenetic endpoints into chemical risk assessment requires this kind of information.[4] In addition to confirming the link between EDC exposure and epigenetic alterations, understanding the mechanisms involved would make it easier to develop techniques for screening chemicals for their capacity to influence epigenetic patterns.

EDCs and carcinogenesis

Epigenomic effects of EDCs

The United Nations World Health Organisation (UN WHO) defines EDCs as "an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub) populations".[10] Various EDCs and their mechanism are shown in Figure 1.

Cadmium (Cd)

Despite having no discernible biological purpose, cadmium (Cd) is a common element in the earth's crust and is also a pollutant resulting from human activity (electronic waste, industrial operations, phosphate fertilisers, batteries and pesticides).[10] According to the most recent statistics published by the European Food Safety Authority (EFSA), the weekly intake of Cd should not exceed 2.5 μg/kg body mass. The public is mainly exposed to cadmium through food and tobacco smoke.[11] A variety of diseases affecting the liver, kidneys, lungs, bones, brain and other organs have long been associated with long-term exposure to cadmium. Cadmium has been classified as an endocrine disruptor because it can alter hormone balance.[11] Silva and associates have demonstrated its metallo-oestrogenic action. Cadmium

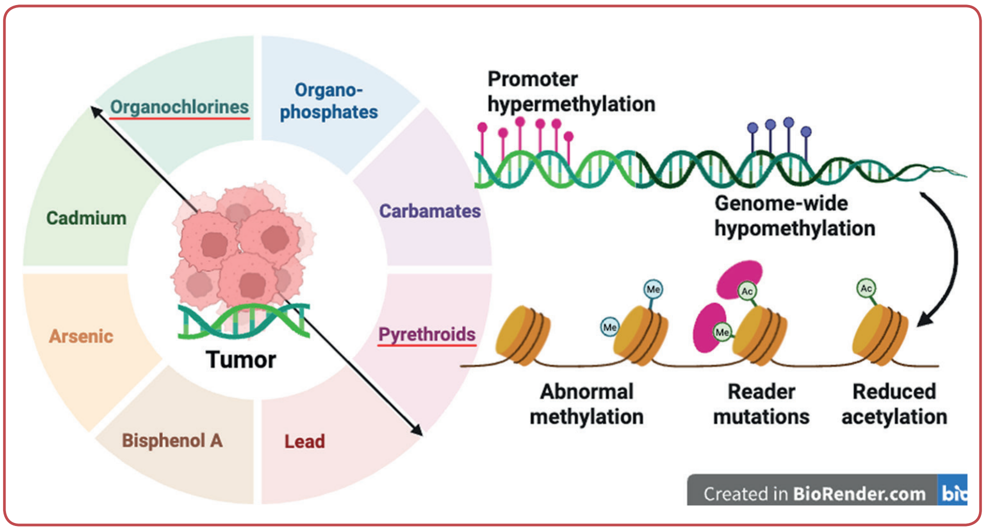

Figure 1: Endocrine-disrupting chemicals (EDCs): interaction and purposed mechanisms of action

adversely affects the thyroid gland, disrupts the male reproductive system and raises the risk of insulin resistance. Numerous epigenetic modifications, including DNA methylation, histone modifications and miRNAs, have been associated with cadmium.[12] These modifications have been observed both *in vitro* and *in vivo* and may alter gene expression. The International Agency for Research on Cancer (IARC) has designated cadmium as a known human carcinogen (Group 1). Different types of cancer are associated with cadmium, although the precise mechanism is unknown. However, epidemiological and experimental studies demonstrate that epigenetic modifications are a component of Cd-induced cancers. There is evidence that miRNAs contribute to the development of thyroid, pancreatic, kidney and prostate cancers and that Cd is associated with these cancers.[13] A 2020 study found an association between epigenetic regulation of signalling networks, such as the Wnt pathway and other metabolic pathways. Understanding the epigenomic alterations induced by cadmium is essential to determining the causes of breast cancer (BC). It has been determined that certain genes, such as TXNRD1 and CCT3, may play a crucial role in the identification and treatment of cancer.[14] This investigation supported previous studies on the metabolic characteristics of healthy and malignant breast tissue. Speedy, uncontrolled growth, proliferation and migration of cancer cells have been associated with changes. Understanding how Cd affects the epigenome may lead to more effective treatments for these types of malignancies.

Arsenic (As)

One of the most hazardous elements found in the Earth's crust is arsenic (As). Despite its use in the production of insecticides and the treatment of wood products, arsenic trioxide has been largely phased out since its toxicity was recognised. A significant public health concern, especially in countries like Bangladesh, is drinking tainted water, which is the most prevalent method by which individuals are exposed to arsenic. In 2009, the Scientific Panel on Contaminants in the Food Chain (CONTAM Panel) found that the preliminary tolerable weekly intake (PTWI), set by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at 15 µg/kg body mass, was insufficient.[15] Harmful effects were observed in individuals exposed to levels below those recommended by JECFA. The CONTAM Panel's benchmark dose lower confidence limit (BMDL01) is 0.3-8 µg As/kg body wt/day.[16]

Arsenic exposure can result in neurological diseases, skin disorders, reproductive and cardiovascular toxicity, renal and liver disorders and other health concerns in addition to its mutagenic, genotoxic and carcinogenic qualities. It functions by DNA methylation, histone modification and miRNA, just like Cd.[16] It has also been demonstrated that exposure to this metalloid alters telomerase function, which may raise the risk of cancer or cell death. Additional adverse effects could arise from As's impact on the epigenome. The link between arsenic exposure and placental DNA methylation, particularly LYRM2 methylation, is one example. To fully understand the placenta's role in shielding the embryo from As exposure, these findings require further analysis. Recently, Wallace and colleagues found a link between neurodegenerative disorders such as Parkinson disease (PD) and Alzheimer's disease (AD) and alterations in miRNA expression.[16-18]

Bisphenol A

Although bisphenol A (BPA) was first produced in 1891, its oestrogenic action was not discovered until 1936. In 2013, over 6.7 million tons of BPA were produced worldwide. Humans have been exposed to BPA for a long time and in many places, as it is used in food packaging, toy manufacturing and the production of plastics. Of the substances that affect hormones, bisphenol A has been studied the most. Luckily, BPA is rapidly broken down into non-bioactive metabolites such as glucuronide conjugates and has a short half-life of 4-5 hours.[19] In February 2022, the EFSA Panel on Food Contact Materials, Enzymes and Processing Aids proposed a daily limit of 0.04 ng BPA.[20]

According to a prenatal BPA exposure study, the primary effect of BPA exposure on male children was DNA hypermethylation, a fundamental epigenetic mechanism. In contrast, the primary impact on female infants was DNA hypomethylation.[21] According to another study, male rats exposed to BPA showed higher expression of the free fatty acid uptake gene fatty acid transporter 1 (FAT/CD36) than female or control rats.[22] By promoting hypermethylation of relevant cytosine-phosphate-guanine (CpG) sites, prenatal exposure to BPA augmented the hypermethylation of the TNFRSF25, CAPS2 and HKR1 genes, which are often the cause of obesity.[23] Meanwhile, genes involved in triglyceride production and β-oxidation, eg Cebpβ, Dgat, Cpt1a, Cebpα, Pck1, Agpat6, Acox1 and Cybb, showed reduced expression. Hepatic steatosis in male rats increased following these modifications.[24]

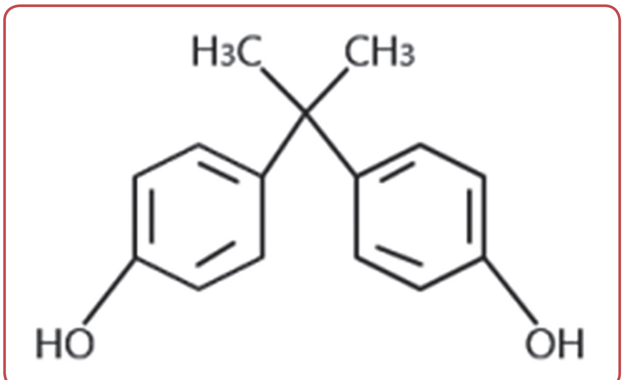

Figure 2: Chemical structure of bisphenol A ($C_{15}H_{16}O_2$)

Lead (Pb)

The Earth's crust contains naturally occurring lead (Pb). Mines and metal smelters are the primary sources of lead in the environment. After being exposed to lead, some illnesses can develop, such as abnormalities of the gastrointestinal, reproductive, haematological and neurological systems. Inorganic lead is classified by the IARC as a Group 2A carcinogen, meaning that it is expected to cause cancer in people. The FDA has established the interim reference level (IRL), which is the highest amount of lead that can be consumed in food each day. For children and adults, the IRL is 3 µg and 12.5 µg every day, respectively.[25]

The epigenome may be altered by lead exposure. A 2016 study found that early-life lead exposure may negatively affect miRNA expression, leading to overproduction of neurotoxic proteins and ultimately to AD. In a Chinese case-control study, increased miRNA expression, urine Pb levels and the onset of microalbuminuria were correlated, suggesting that miRNA may act as an intermediary in the development of Pb-induced albuminuria.[25]

Endocrine-disrupting pesticides

Pesticides include insecticides, fungicides, herbicides and fumigants and are categorised by the organisms they are intended to kill. Based on their active principles, they are further divided into groups, including carbamates, pyrethroids, organochlorines and organophosphates.

Organochlorines

Compounds classified as organochlorines have at least one chlorine atom covalently bound to them. These compounds exhibit a wide range of structural variations, resulting in distinct chemical properties.[26] Employed initially to combat typhus and malaria, these pesticides were later applied to food crops. Nevertheless, several nations have outlawed them or severely restricted their use, even in those that still permit them, because they are persistent organic pollutants (POPs) that harm the environment.[27] POPs are considered silent killers since they can bio-accumulate and remain present in the environment because they are resistant to natural degradation. Humans and other living things are affected by the majority of POPs, which are highly soluble in lipids.[28]

Exposure to organochlorine can happen through a number of methods, including ingestion, inhalation and skin contact. Consuming contaminat-

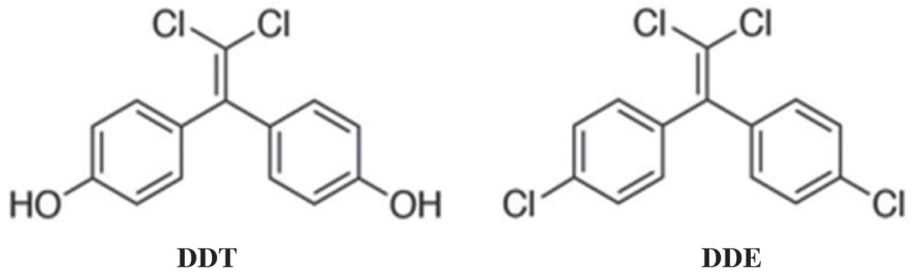

Figure 3: The chemical structures of dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE)

ed food, especially high-fat foods, is the primary way people are exposed to these chemicals. Additionally, another significant risk is ingesting contaminated breast milk. Organochlorines can also cross the placental barrier, leading to physiological changes that may appear later and foetal problems.

One of the primary organochlorine insecticides is dichlorodiphenyltrichloroethane (DDT). The WHO approved its use in 2006 to lower mortality rates in those countries in which malaria cases are high, although its use was prohibited in some nations in the 1970s.[28] Despite decades of restrictions on its use in Europe and the US, DDT, having a long half-life, is lipophilic, bioaccumulates in the food web and is still detectable in adipose tissues and the bloodstreams of both people and animals.[29] Minority groups and recent immigrants in the US had the maximum levels of dichlorodiphenyldichloroethylene (DDE), the primary metabolic product of DDT.[30]

DDT and its metabolites negatively impact the reproductive system because they are ED that hinder oestrogen and androgen pathways. The impacted species, dosage and exposure circumstances all influence reproductive toxicity. Studies also show that this pesticide has hepatotoxic and carcinogenic effects.[29, 30] All things considered, the available literature suggests that this class of pesticide has long-term adverse effects on human health.[31] Figure 3 depicts the chemical structures of DDT and DDE.

Organophosphates and carbamates

Other pesticides besides organochlorines are also commonly used in pest control and harm both humans and the environment. Glyphosate is the most prevalent member of the highly hazardous class of insecticides known as organophosphates. An estimated 100,000 fatalities annually are attributed to these toxicants. Although these substances can phosphorylate a variety of proteins and enzymes, their toxicity is associated with the inhibition of acetylcholinesterase. Organophosphate exposure can cause long-term adverse effects via a non-cholinergic mechanism. Organophosphate exposure in mothers can be transmitted to the foetus through the placenta or amniotic fluid, which can have a substantial impact on foetal development.[32]

Organophosphate exposure may promote the development of cancer in addition to congenital anomalies, cognitive deficits and neurobehavioral impairments. Acute lymphoblastic leukaemia in children was linked to maternal exposure to this kind of pesticide and exposure to it was linked to an enhanced risk of BC.[33]

Aldicarb and carbofuran are carbamate pesticides, a class that also includes endocrine-disrupting properties. Additionally, these herbicides cause toxicity by inhibiting acetylcholinesterase.[34] However, compared to organophosphate exposure, the enzyme is reactivated more quickly. Chronic adverse effects are therefore uncommon and carbamate poisoning is less severe. Infertility and endocrine disruption are among the reproductive toxicity symptoms this toxin can cause.[35] According to *in vivo* research, prenatal exposure to carbamates can influence the development of cancer in first-generation offspring whose parents were continuously exposed to these pesticides. It has also been demonstrated that other chemical pesticide classes, such as pyrethroids, triazines and neonicotinoids, may affect animal hormones and reproductive processes.[36]

Genotoxic effects of EDCs

The developmental origins of health and disease (DOHAD) hypothesis states that a hostile developmental environment might rewire cellular and tissue responses to basic physiological signals, thereby augmenting vulnerability to disease in adulthood.[37, 38] Therefore, cancer in children or adults, as well as transgenerational illnesses, may arise from foetal epigenome dysregulation caused by exposure to environmental pesticides and other EDC during pregnancy.[39] It is becoming increasingly clear that preconception exposures can result in germline epigenetic changes and increase the risk of cancer in the next generations.[39] The epigenetic mechanisms of EDCs in various cancers are illustrated in Figure 4.

Paediatric cancers

Hodgkin and non-Hodgkin lymphoma

Parental pesticide exposure has also been associated with a higher prevalence of non-Hodgkin lymphoma (NHL) in children. There is a strong correlation between higher reported household pesticide use and the risk of NHL. Pregnant females exposed to household pesticides had a higher risk of developing NHL in their offspring. Younger and older children were more likely to develop B-cell and T-cell lymphomas. Another study that revealed children whose parents were exposed to pesticides during the preconceptional period had a higher risk of getting lymphoma corroborated these findings.[40]

Insecticide-induced brain tumours in children

In addition, a number of studies show a link between children's higher risk of brain tumours and parental exposure to pesticides. For instance, prenatal exposure to flea/tick insecticides was associated with a markedly higher prevalence of brain tumours, especially in children under five at diagnosis, in a case-control study.[41] Another study with 526 matched case-control pairings revealed a link between parental pesticide exposure, two years before birth and risk of brain tumour in children below 10 years.[42]

Leukaemia

An epidemiologic study found a link between maternal pesticide exposure during pregnancy and childhood leukaemia. Although the findings were less conclusive, a link with the father's occupational pesticide exposure was also discovered.[43] In a different human cohort, however, occupational pesticide exposure during the peri-con-

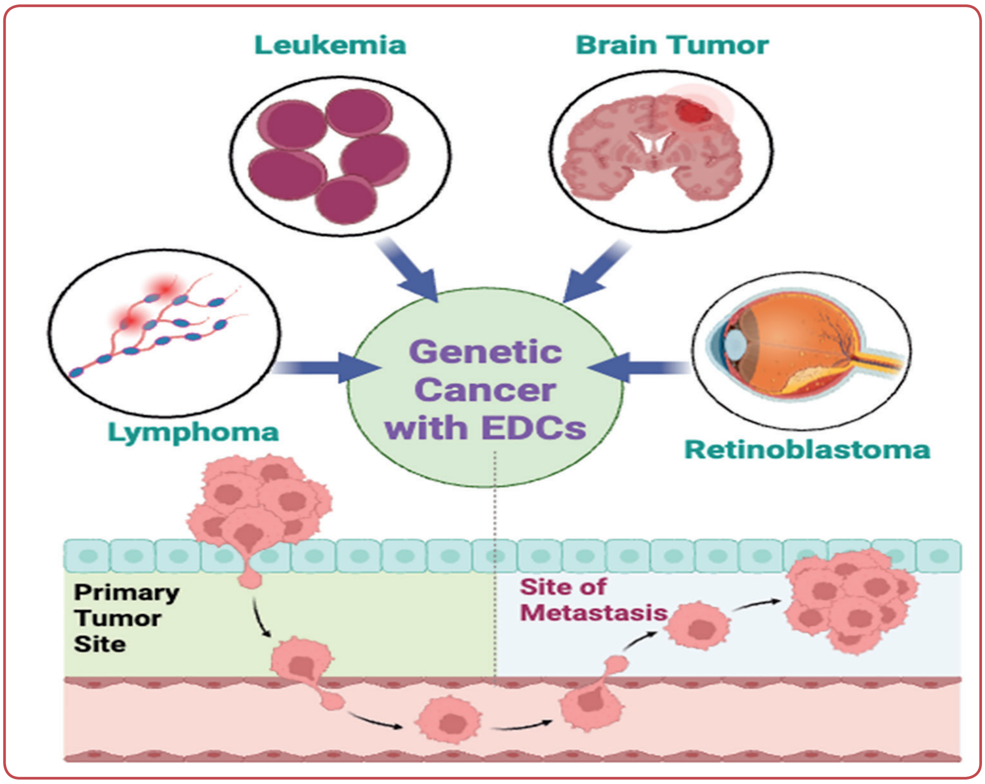

Figure 4: A schematic diagram showing the epigenetic mechanism of endocrine-disrupting chemicals (EDCs) in causing leukaemia and cancer of the brain and eye

ception period of the father was linked to the offspring's chance of developing acute lymphoblastic leukaemia (ALL). Children with T-cell ALL and those diagnosed at age five or older had more pronounced results.[44] It was found that neonates whose mothers had been exposed to pesticides during prenatal care had a considerably higher incidence of the t(8;21) translocation in their umbilical cord blood samples, which leads to juvenile acute myeloid leukaemia (AML).[45]

Retinoblastoma

Inactivation of the RB1 gene occurs during DNA replication in uncontrolled, multiplying retinal progenitor cells that proliferate only in the foetal retina, leading to retinoblastoma, as demonstrated in a case-control study. Prenatal pesticide exposure has been suggested as a potential second hit, since retinoblastoma can be induced only by the genetic inactivation of both RB1 alleles.[46]

EDC-induced cancer in the adult population

In addition to parental pesticide exposure, other EDCs have also been linked to cancers in adult offspring. The incidence of BC in three generations of progeny is increased in rats exposed to endocrine-disrupting substances during pregnancy. Changes in DNA methylation at genes linked to stem cell specification in breast tissue were associated with the BC phenotype in the progeny. These results suggest that a portion of familial BC that cannot be linked to gene defects may be caused by epigenetic inheritance resulting from prenatal exposures.

Another study found a link between BC and exposure to the endocrine disruptor diethylstilbestrol (DES) during pregnancy. Pregnant women were once given DES, a synthetic oestrogen, to help prevent miscarriages and premature births. However, severe side effects, including cancer, were later observed in the progeny as a result of its use. According to the findings, daughters of mothers exposed to DES have a BC incidence at least twice as high. Consequently, in both tumorigenic and normal mammary cells, EZH2 and histone H3K27 trimethylation expression were overrepresented when pregnant women were exposed to DES.

A Dutch study tracked 12,091 pregnant women who were exposed to DES between 1992 and 2008. According to the data analysis, there were 348 cancer cases and the median age after the follow-up was 44 years. Women who were exposed to DES showed a markedly elevated risk of melanoma (before the age of 40) and clear cell adenocarcinoma of the cervix and vagina (after the age of 40). In animal models, Newbold et al verified the intergenerational effect of DES. They found that daughters and grandchildren of women exposed to DES during pregnancy were more likely to develop reproductive tract cancers, such as uterine adenocarcinomas.[47]

Potential underlying mechanisms for the environmentally induced cancer among susceptible individuals

The development of cancer illnesses can result from environmentally induced epigenetic changes that are passed down through the parental germline. Nonetheless, it's critical to distinguish between transgenerational and intergenerational inheritance. An organism's epigenetic alterations resulting from environmental damage are inherited intergenerationally. For instance, the growing foetus or its germ line may be impacted by in utero exposures and the foetus's direct descendants may inherit these alterations. In other words, even when the stimulating stimulus is not there, inherited qualities are transmitted and preserved over generations.[48] It is important to recognise that transgenerational epigenetic inheritance faces significant challenges. In mammals, the zygote undergoes epigenetic reprogramming during germ cell formation and immediately after conception.[49]

Epigenetic mechanisms of cancer

Epigenetics is the study of modifications in gene function that are inherited mitotically and/or non-mitotically but do not alter the DNA sequence. DNA methylation, non-coding RNAs and histone modifications are the three main epigenetic information carriers.[49] In somatic cells, these epigenetic processes regulate gene expression. However, it becomes increasingly evident that epigenetic information can serve as a biological memory of past environmental exposures and be handed down through the germline from one generation to the next.[50]

DNA methylation

DNA methylation, or the covalent binding of a methyl (-CH_3) group to a DNA nucleotide, is one of the primary epigenetic markers.[51] The symmetric CpG (5'-Cytosinephosphate-Guanine-3') dinucleotide is the primary site of heritable cytosine methylation. During replication, two daughter genomes are produced, each of which has a hemimethylated CpG that serves as a substrate for the DNA methyltransferase (DNMT)1 enzyme.[52, 53]

Initially, DNA methylation patterns are formed throughout the development of embryonic life.[54] *De novo* methylation, which adds methylation to unmodified DNA, is catalysed by DNMT3a, DNMT3b and DNMT3L enzymes.[55] Once established, DNMT1 transfers the DNA methylation patterns of the daughter strand to the parent strand. Except for relatively small genomic areas known as CpG islands (CGIs), the mammalian genome is typically CpG-deficient.[56] The CpG islands exhibit focused hypomethylation, in addition to the high methylation of the sperm genome. Since highly transcribed genes contain hypomethylated DNA, methylation in the oocyte varies much more throughout the genome. But for DNA methylation to be passed down across generations, a portion of the genome would need to avoid the pre-fertilisation reprogramming.[50]

Histone modification

The nucleosome's core, the chromatin structural unit that surrounds DNA, is composed of an octamer of histone proteins. Acetylation and methylation are examples of post-translational modifications of histone tails that affect DNA interaction with these proteins to form nucleosomes. These modifications can determine how tightly histones bind to DNA and whether a genomic region is available to the transcriptional apparatus. Moreover, as essential regulators of gene expression, histones have been linked to transgenerational epigenetic inheritance. The primary processes associated with histone modifications implicated in transgenerational epigenetics are the restricted histone markers histone H3 lysine nine trimethylation (H3K9me3) and histone H3 lysine 27 trimethylation (H3K27me3).

In mammalian species, chromatin differs markedly from that in somatic cells due to extensive histone reprogramming in the male and female germlines. Both sperm and oocytes undergo substantial histone replacement, resulting in germline-specific histone composition. Sex chromosome inactivation is associated with H3K9 methylation across the chromosome, as histone modifications exhibit germline-specific patterns.[57]

Noncoding RNAs

Both transcriptional and posttranscriptional aspects of gene expression are regulated by small non-coding RNAs. By modifying a gene's epigenetic status (eg piRNAs and siRNAs) or by post-transcriptional regulation, which degrades mRNA (eg miRNAs), small RNAs can prevent gene transcription. They are both inhibitors of gene activation, independent of DNA sequence. Nonetheless, the most common RNA-based mechanisms in animals that support transgenerational epigenetic inheritance are tiny RNA silencing pathways.[58]

Mature germ cells carry extra or completely different RNA loads, even though piRNAs constitute the primary RNA route during germline development. PiRNAs are virtually non-existent in mature sperm in mammals. Rather, tsRNAs and, to a lesser level, miRNAs make up the majority of its payload. The content of the sperm RNA load is changed by environmentally induced epigenetic reprogramming events that take place in the epididymis during post-testicular maturation. Exosomes seem to transport these little RNAs made by epididymal epithelial cells to developing sperm.[59]

Several studies indicate that sperm contain numerous short non-coding RNAs essential for epigenetic inheritance.[59, 60] The sperm RNA load has been shown in some recent publications to be capable of passing on environmental traits from dads to children.[59] Certain classes of short RNAs were implicated in some of those investigations. For example, when injected into normal embryos, miRNAs overrepresented in the male sperm that are exposed to various environmental factors can replicate the effects of specific paternal exposures in their offspring. TsRNAs have been implicated in other research.[60] During the initial cell divisions, sperm short RNAs, like miRNAs, are transferred to the oocyte and alter the transcriptome, initiating a signalling cascade that may affect the development of the embryo.[61]

Novel epigenetic information among viable carriers

During embryonic development, DNA methylation patterns are lost and subsequently restored. Therefore, for environmental-induced epigenetic changes to be a viable carrier of transgenerational epigenetic transmission, they would have to withstand this widespread erasure. However, new research suggests that secondary signals, such as transcriptional factors, may restore epigenetic modifications lost during early development.[57] In line with this, a recent study showed that transcription factors prevent DNA re-methylation in demethylated regions of germ cells and early embryos.[62] These transcription factors are thought to be present when DNA is demethylated during germ-line reprogramming. Since many EDCs bind to the androgen receptor (AR) and/or the oestrogen receptor (ERα), they may then affect the recruitment patterns of these transcription factors. These transcription factors may affect cell differentiation during development and contribute to phenotypes observed following chemical exposure if they remain bound after fertilisation. The intriguing possibility that these changes could be the cause of the phenotypic effects seen after early exposure to EDs, but manifested generations later in their absence, is raised by the persistence of these novel transcription factor sites across multiple generations.[63]

Future research challenges

While there has been significant progress in EDC research, several questions and research challenges remain unanswered. First, accurately determining exposure levels and low-dose effects of complex EDC mixtures in real-world settings remains challenging, which constrains causal inference in human studies. Second, the list of epigenetic biomarkers that consistently correlate with EDC exposure and cancer risk has not yet been fully compiled. Third, inconsistencies in exposure timing, sex-specificity, genetic predisposition and vulnerability at particular life stages complicate risk assessment. Additionally, the mechanisms underlying transgenerational epigenetic inheritance and its role in cancer susceptibility have not yet been validated. Future research should focus on longitudinal cohort studies, more sophisticated integration of epigenomic and multi-omics data and more realistic *in vitro* and *in vivo* models. Addressing these difficulties is essential to fine-tune regulatory policies and preventive measures and to minimise the overall global cancer-related effects associated with endocrine-disrupting chemicals.

Conclusion

Increasing evidence indicates that EDCs are important contributors to cancer development through complex genetic and epigenetic mechanisms. Exposure to environmental EDCs, including bisphenols, phthalates, pesticides, heavy metals and persistent organic pollutants, disrupts hormonal homeostasis and induces epigenetic reprogramming, including abnormal DNA methylation, histone modifications and dysregulation of non-coding RNAs. These epigenetic modifications cause lasting changes in gene expression, leading to oncogene activation, tumour suppressor gene silencing, genomic instability and malignant transformation. In particular, epigenetic processes can provide a mechanistic link between low-dose and chronic EDC exposure and long-term cancer risk, including developmental and transgenerational effects. Combining evidence from epidemiological, experimental and omics-based research strengthens the biological plausibility of EDC-induced carcinogenesis and highlights epigenetics as a potential contributor to environmentally related cancers.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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