

# Cancer Epigenetics: Shifting to More Deep Action

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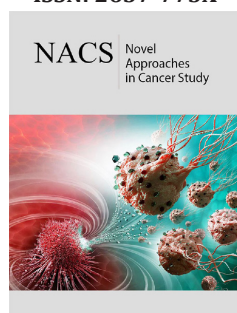
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## Abstract

Cancer is a major health problem facing the entire human population. It affects almost every race, gender, or age in the social hierarchy. Many mechanisms have been proposed for the development of cancer; either genetic or epigenetic. Over the years, a cumulative body of research indicated that epigenetic mutations (epimutations) represent a chief player in the course of cancer, where it affects cell proliferation, cancer initiation, progression, apoptosis, and metastasis. In this minireview we highlight the main mechanisms of epigenetic-mediated cancer development with emphasis on the environmental pollution role in this arena.

**Keywords:** Cancer; Epigenetics; Environment; miRNA; Methylation; Acetylation

**Abbreviations:** PAHs: Polycyclic Aromatic Hydrocarbons; AAs: Aromatic Amines; HAAs: Heterocyclic Aromatic Amines; AAS: 2-Amino-Apidic Semialdehyde; HAAs: Halo acetic acids; TSGs: Tumor Suppressor Genes; DNMT: DNA Methyltransferase; MECP2: Methyl CpG Binding Protein 2; MBD: Methyl-CpG-Binding Domain; HDAC: Histone Deacetylase; TGF: Transforming Growth Factor; LINE: Long Interspersed Nuclear Elements; Alu: Repeats characterized first in *Arthrobacter luteus*; AAP: Accumulation Associated Protein; EZH2: Enhancer of Zeste Homolog 2; TMZ: Temozolomide; JMJD2C: Jumonji Domain 2; HATs: Histone Acetyl Transferase; Gcn5: General Control Nonderepressible-5; MYST: Histone Acetyltransferase KAT6A Its acronym comes from MOZ, YBF2/SAS3, SAS2 and TIP60 protein 3; CBP: CREB-Binding Protein; PTEN: Phosphatase and Tensin Homolog; APC: Adenomatous Polyposis Coli; IGF2: Insulin-like Growth Factor 2; IGF2R: Insulin-like Growth Factor 2 Receptor; PEG3: Paternally-Expressed Gene 3 Protein; GNAS: Guanine Nucleotide Binding Protein, Alpha Stimulating Activity Polypeptide; MEST: Mesoderm Specific Transcript; LOI: Loss of imprinting; CDKN2: Cyclin-dependent kinase inhibitor; KRAS: Kirsten Rat Sarcoma; HPRT: Hypoxanthine Phosphoribosyl transferase; DAPK: Death-Associated Protein Kinase; RAR-β: Retinoic Acid Receptor Beta

## Introduction

Cancer is a large group of more 100 different diseases that can arise anywhere in the human body [1-3]. It involves uncontrolled cellular proliferation, with the potential to invade or spread to other parts of the body [4]. Cancer is considered the second common leading cause of death worldwide. This condition was responsible for about 9.6 million deaths in 2018, where about 1 in 6 deaths is due to cancer [5]. Cancer arises from accumulation of genetic mutations and/or epigenetic mutations [6,7]. Several genes are involved in the carcinogenesis process, and they are reported elsewhere. The most common causes of cancer are epimutations, where environmental pollutions are the main players [8,9]. Epigenetics is a kind of non-sequence dependent inheritance, where a change in the DNA methylation, histone modification, among others, might cause cancer to develop [10-12]. Different mechanisms are involved in epigenetic-mediated carcinogenesis, each of them was extensively studied during the last four decades [6]. Interestingly, newly developed epigenetic-based cancer therapies provide unique and validated approach to treat different types of cancers [13,14].

## Environmental Pollution and Cancer

Outdoor air pollution is a global challenging life-threatening problem, where it is classified as a class I human carcinogen [15,16]. A large number of reports shows that air pollution is

connected to increased risk of sever types of cancers including lung, head and neck, and nasopharyngeal cancers [17,18]. Other many diseases including respiratory diseases and heart disease are also correlated with prolonged exposure to polluted air [19,20]. Sources of air pollution include, but not limited to, industrial processes car fumes, and the household combustion of solid fuel [21]. All these sources contain specific chemicals that are known to be carcinogenic to humans.

### DNA adducts

The chemical substances in polluted air can cause DNA damage (*via* adducts) [22]. These substances can trigger cancer through induction of severe immune responses such as oxidative stress and long-term inflammation in the upper aerodigestive tract [22, 23]. It has been reported by several research groups that DNA adducts have been found in individuals living in polluted regions, and this adducts might be associated with cancer development [24,25]. DNA isolated from individuals working in polluted environments showed 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxo-dG) and bulky DNA adducts [26]. DNA adducts are covalent bonds occurs due to interaction of cancer-triggering chemical substances such as polycyclic aromatic hydrocarbons (PAHs) with DNA [27-29]. Some DNA adducts can be eliminated by specific repair proteins, while others are persistent, and the latter group is the main cause of pollution-related cancer initiation [30, 31]. Furthermore, persistent DNA adducts can cause base-pair substitutions, deletions and chromosomal rearrangements and other chromosomal abnormalities [32,33].

DNA adducts, however, could be used as a reliable biomarker of exposure to carcinogens. Several studies were carried out to correlate DNA adducts with the occupation of individuals exposed. Categories include police officers [23,34,35], school children [36], bus and taxi drivers [24], and gasoline salesmen and roadside residents [22]. Meanwhile, chemical substances such as aromatic amines (AAs) and heterocyclic aromatic amines (HAAs) are activated by cytochrome P450 oxidation forming N-hydroxylated intermediates, which can react with DNA directly. The resultant compounds are transformed into unstable esters that induce genetic mutations [37]. Recently, several research groups developed specific DNA biomarker to detect the mutagenic effect of prolonged exposure to polluted air. The genes used in these studies involved *CDKN2*, *p53*, *KRAS*, *HPRT*, *DAPK*, and *RAR-β* among others [38-41].

### Protein adducts

Protein adducts could also be caused by air pollution, including benzopyrene-hemoglobin adducts and 4-aminophenyl-hemoglobin adducts in polluted areas [42]. The cancer-causing effects of these adducts have yet to be investigated experimentally [43]. Hemoglobin adducts formed by 4-aminobiphenyl was reported in a group of children living in polluted areas [44]. Furthermore, air-born substances were detected in proteins of exposed individuals in a suburban group. Higher levels of 2-amino-apidic semialdehyde (AAS) was observed in plasma proteins and in hemoglobin extracted from bus drivers, while malondialdehyde was observed

in their plasma, and PAH was detected in their albumin [45]. Unfortunately, no repair mechanisms are there to handle protein adducts, and these adducts accumulate with chronic exposure to triggering factors. For that reason, hemoglobin (Hb) and serum albumin carcinogen adducts could be used straightforwardly as a biomarker for AAs and HAAs exposure. Moreover, plasma levels of p53 and p21<sup>WAF1</sup> proteins were found to be associated with exposure to PAHs and benzo[a]pyrene [46].

### Epigenetic Marks and Cancer

Epigenetics is a wide-angled mechanism by which almost all biological processes are regulated. With regard to cancer development, epigenetic-mediated gene regulation is involved in cancer initiation, progression, metastasis, and angiogenesis, along with cancer stem cell induction as a primary step towards initiating the cascade [47,48]. Players of epigenetic landscape could be classified into different classes; on DNA level, histone level, miRNA level, and imprinting.

### Cytosine Methylation

Cytosine methylation is the most common epigenetic mark in cancer [49-51]. Normally, cytosine (occurs in CpG dinucleotide) is methylated in a high percentage of human genome sequences to maintain chromosome stability, while those CpGs located in promote regions, especially of tumor suppressor genes, are normally hypomethylated [52,53]. These hypo- or un-methylated promoter regions allow for transcription of TSGs that have crucial roles in controlling cell proliferation. The methyl group in the 5mC lies in the major groove of the double helix DNA and interfere with binding of transcription factor, and hence avert gene expression [54]. Upon adding the methyl group to the fifth carbon atom in cytosine residue by the action of DNMT, methylated DNA-binding proteins such as MECP2 and the MBD protein family were recruited to bind to methylated cytosines and suppress transcription process by hindering the attachment of transcription factors [55].

Histone deacetylase (HDAC) was also recruited to remove the acetyl groups from the histone tails rendering it to closed structure in this case, it is known as heterochromatin [56,57]. If these actions took place in the promoter region, the no RNA polymerase would be able to attach its specific site to start transcription, and hence the corresponding gene in this case is said to be silenced. Methylation always occurs in CpG dinucleotides either in regions rich of these CpGs (CpG islands) or within the body of the gene [58]. Hypermethylation of tumor suppressor genes is positively correlated with the initiation of cancer in different organs [59].

Our studies indicated that global DNA methylation was increases in traffic workers with exposure to car fumes in Cairo, Egypt [60]. This study indicated that tumor (transforming) growth factor (*TGF*) was found to be hypermethylated in traffic workers exposed to car fumes for a long time (more than 6 hours/day for at least 5 years). Furthermore, *P53* was also found by our group to be dysregulated in people exposed to car fumes for a long time in a cohort population in Egypt (unpublished data). Hypermethylation and/or dysregulation of these genes might indicate a future cancer incidence in individual

with these recorded abnormalities. On the other hand, many drugs have been designed to modulate the methylome of malignant cells as a way of treatment. In our laboratory, we investigated different kind of DNMT inhibitors such as procaine and cyclophosphamide in different cancer cells including breast, colon, liver, cervical, lung, and laryngeal cancer [61-64].

### Repetitive sequences

Repetitive elements constitute a large percentage of the human genome. It is normally hypermethylated, while in cancer, it becomes hypomethylated [65]. Various types of repeats in human genome including LINE-1, Alu, centromeric tandem repeats, and juxta centromeric tandem repeats are considered the most frequently studied repetitive sequences in cancer, where it was found to be hypomethylated. In addition, hypomethylation of these repeats allows it to jump to other genomic loci [66]. Global hypomethylation of LINE-1 and Alu was associated with long term or short-term exposure to AAP. Specifically, genome wide hypomethylation of Alu and LINE-1 repeats might lead to repositioning of these sequences, leading to insertional mutations and genomic instability [67,68]. On the other hand, centromeric tandem repeats, and juxta centromeric tandem repeats play a crucial role in maintaining DNA wrapped within heterochromatin structure, where no transcription is allowed at the point of sister chromatid association. This heterochromatinization leads to chromosome stability. Therefore, hypomethylation of these repeats allows for heterochromatin to be transformed to more open form *i.e.*, euchromatin, leading to chromosome rearrangements, and hence, genomic instability [69].

### Histone methylation

The histone methylation has been widely proven to regulate transcription [70,71]. The methylation of histone tail residue is associated with both activation and suppression of transcription [72]. Histone methylation occurs in the residues of arginine and lysine on the histone tails H3 and H4 proteins [47]. Lysine methylation is stimulated by histone-lysine-N-methyltransferases also known as K-methyltransferases and involves the transport of methyl groups from the S-adenosyl methionine. EZH2 (Zeste 2) is one of the main proteins involved in the control and differentiation of stem cells, K-methyltransferase, which stimulates the trimethylation of methyl H3K27 [71,73].

EZH2 is a member of the polycomb repressive complex 2, a protein compound that contains both the K-methyltransferase protein and the reader proteins that recognizes the H3K27me3 [74,75]. H3K27me3 is usually involved in silencing genes associated with the evolution and differentiation of stem cells, including the Hox genes [76,77]. However, in many cancers, EZH2 is expressed excessively at both transcriptional and protein levels. Overexpression of EZH2 has been designated as vital in prostate cancer, where an increase in EZH2 protein staining in the cell nucleus was detected with a progression from benign to metastatic disease [78,79]. Other studies have identified excessive expression of EZH2 as a key feature of breast cancer, lymphoma and glaucoma, among other cancers [80-82]. In cancer cells, H3K27me3 was also

shown to suppress gene expression independently of the DNA methylation, whereas in normal cells, EZH2 was shown to control DNA methylation through interaction with DNMTs [83]. In addition, dysregulation has recently been described in other members of the polycomb repressive complex, including proteins that interact with polycomb repressive complex 2 after the modulation of H3K27me3 mark by EZH2 [84,85]. In contrast to H3K27me3-mediated silencing of histone, histone methylation can also be a marker associated with activation of transcription [86]. Currently, we are using temozolomide (TMZ) as a histone methylation agent in colorectal cancer cells to identify its interaction with other histone tags (unpublished data). JMJD2C is K-demethylase which stimulates the removal of methyl markers from H3K9, a histone marker that is commonly associated with suppression of gene expression [87]. JMJD2C has been detected in many types of cancers, including esophageal and breast cancers [88]. Lysine demethylase 1, a type of K-demethylase, which targets H3K9 and H3K4, has recently found to be overexpressed in ER- breast cancer caused by estrogen receptors, mesothelioma, and bladder cancer [88].

Although more research is needed to understand the functional consequences of dysregulation of histone, K-demethylases and K-methyltransferases are important in the cancer-causing process and represent new targets for treatment. Our current work involves modulating H3K27me3 to control breast cancer. We are aiming to demethylate this histone mark using demethylating agent such as 5-Aza cytidine.

### Histone acetylation

Unlike histone methylation, acetylation of histone is sturdily connected to transcription activation [89,90]. Acetylation of histone occurs on the lysine residues and is believed to enhance transcription by neutralizing the positively charged histones, thereby reducing its interaction with the negatively charged DNA [91]. The maintenance of histone marks is controlled by histone acetyl transferase (HATs), also known as K-acetyltransferases, and histone deacetylases [92]. HATs stimulate the addition of acetyl groups to lysine using acetyl coenzyme A as a cofactor, thereby transforming the chromatin structure to be euchromatin. On the other hand, HDACs remove acetyl groups and induce a closed or suppressive chromatin structure (heterochromatin) [93].

Three diverse families of HATs are known; the Gcn5 family, the MYST family, and the p300/CBP family [94,95]. It turns out that the HATs of each of these families play a role in causing cancer, either from improper activation or suppression of the target gene activity [96]. The Wnt signaling pathway, previously shown to be dysregulated in some types of cancers, is now indicated to be enhanced by HAT Gcn5 in breast cancer [97]. HDACs, in human, are a group 18 enzymes that catalyze the removal of histone acetyl marks and are involved in repressing the transcription process in several cancer-related genes such as *p53*, *PTEN*, *APC*, and *p21* [56,98]. Several cancer studies have indicated that histone deacetylation is an early step in carcinogenesis process [99-101]. In rat model with skin cancer, early loss of mono-acetylation of histone H4K16 was



detected, indicating the role of deacetylation in promoting cancer [102].

Furthermore, histone deacetylation was also observed in different malignant cell lines including breast cancer, colon cancer, and lymphoma cells signifying that histone deacetylation is a common event in cancer [103]. The deregulation of HDAC in cancer cells offers a new target for chemotherapy *i.e.*, HDAC inhibitors (HDACi). HDAC inhibitors are widely used as a therapeutic option in several diseases, including cancer. We extensively used Vorinostat (one of the FDA approved HDACi) in different cell lines to identify its role in controlling the progression of the disease [104].

### miRNAs and cancer

MicroRNAs (miRNAs) are a type of small (20-24 nucleotides) non-coding RNA molecules that play a central role in post-transcriptional regulation of gene expression [105,106]. Since its discovery in 1993, several studies have proven its role as oncogenes (oncomiRs) or tumor suppressors (anti-oncomiRs), under certain conditions in human cancers, including colorectal, liver, lung, breast, and brain cancer [107]. In these cancers, it has been shown that uncontrolled miRNAs affect the distinctive features of cancer, including the maintenance of proliferative signals, the evasion of growth inhibitors, resistance to cell death, invasion activation and metastasis (metastamiRs), and angiogenesis (angiomiRs) [108].

Convincing evidence has shown that miRNA expression is unregulated in human cancer through various mechanisms, including amplification or deletion of miRNA genes, atypical miRNA control, abnormal epigenetic changes and defects in the miRNA biosynthesis pathway [105]. Furthermore, because of their complicated role in cancer, miRNAs represent attractive candidates for cancer treatment *italic synthesizing* either miRNA antagonists or miRNA mimics to suppress or augment specific miRNA expression, respectively.

### Genomic imprinting

Genomic imprinting is type of inheritance that does not follow the usual Mendelian type of inheritance [109]. It is an epigenetic phenomenon that causes some genes to be differentially expressed based on their parent of origin [110]. This process involves DNA methylation and histone modification as epigenetic marks without affecting the sequence of DNA. Nearly 100 genes have been characterized so far, and a number of these genes have been implicated in the development of tumors. Examples of human imprinted genes are *IGF2*, *IGF2R*, *PEG3*, *GNAS*, and *MEST* [111,112]. The physiological role of many of the imprinted genes in controlling cell proliferation suggesting their potential involvement in tumor formation process [113]. Because most of the imprinted genes play central roles in cellular growth, development, and metabolism, the abnormal expression of these genes either due to genetic or epigenetic mutations often causes human ailments, including cancers [114]. For example, loss of imprinting (LOI) in *IGF2* due to abnormal methylation of differentially methylated regions has been observed in many types of tumors [115].

### Conclusion

Cancer is a disease that arise from the consecutive buildup of genetic and epigenetic changes in cells. Notwithstanding powerful studies, several questions remain unanswered about the exact role of epigenetics in cancer initiation and progression. The proposed mechanisms have accounted for a small percentage of the entire story, and the rest is demanding further investigation. Being the future field of studying cancer, epigenetic-based drugs (epidrugs) were introduced. These drugs might replace the well-known medications that target only symptoms, but not the core cause of diseases.

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