

Epigenetic alterations and occupational exposure to benzene, fibers, and heavy metals associated with tumor development (Review)

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Abstract. The chronic occupational exposure to contaminants and carcinogens leads to the development of cancer. Over the past decades, many carcinogens have been found in the occupational environment and their presence is often associated with an increased incidence of cancer. According to the International Agency for Research on Cancer (IARC), the majority of carcinogens are classified as 'probable' and 'possible' human carcinogens, while, direct evidence of carcinogenicity is provided in epidemiological and experimental studies. Additionally, accumulating evidence suggests that epigenetic alterations may be early indicators of genotoxic and non-genotoxic carcinogen exposure. In the present review, the relationship between exposures to benzene, mineral fibers, metals and epigenetic alterations are discussed as the most important cancer risk factors during work activities.

Contents

1. Introduction
2. Benzene
3. Natural fibers
4. Heavy metals
5. Conclusions

1. Introduction

It is known that cancer arises from multiple factors. The identification of each factor, as the specific cause of cancer development, is the one of the main goals of cancer research. Many epidemiological studies have described the association between occupational exposures to carcinogens and cancer risk (1). Although, the incidence of cancer has decreased in the western world, an increased incidence rate was observed among workers exposed to carcinogens (1-3). Since 2007 the International Agency for Research on Cancer (IARC) recognized 415 known or supposed cancerogens (2). Occupational activities associated to cancer risk may be caused by different factors; therefore, it is important to better identify every single factor implicated in this machinery to apply preventive guidelines and to better understand the pathogenic mechanism of cancer development. However, in some cases, there is a significant indication of an increased risk of development of various types of cancer with specific occupational exposure (4).

Several studies have shown that the risk of developing some cancers is associated with exposure to specific factors, such as non-ionizing radiation, 1,3-butadiene, benzene, natural fibers, air pollution, pesticides and solvents, polyaromatic hydrocarbons (PAHs), metal working fluids or mineral oil (5-11).

In addition to genetic alterations, a key role in neoplastic transformation is played by epigenetic alterations (12). For instance, it was demonstrated that chemically-induced carcinogenesis is associated with such epigenetic alterations including DNA methylation, changes of histones/chromatin structure and miRNA modifications (13-16).

Notably, several studies have shown that established occupational risk factors preferably bind to methylated DNA regions (17,18). Accordingly, epigenetic changes may be considered as a predictive biomarker of carcinogen exposure able to influence the genotoxic potential of the carcinogenic agent (18).

This review summarizes the majority of the studies focusing on the relationship among epigenetic alterations, occupational risk factors and tumor development (Table I). The

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Table I. Occupational exposure to carcinogenic agents and epigenetic alterations.

Carcinogenic agent	Uses and source	Cancer type	Epigenetic alterations	Author/(refs)
Benzene	Chemical industry, refineries, gas stations, pharmaceuticals, pesticides, plastic and dyes and cigarette	NHL, AML	Chromosomal alteration, DNA hypomethylation and hypermethylation, histones modifications, aberrant miRNA expression	Kalousová <i>et al</i> (24), Subrahmanyam <i>et al</i> (25), Zhang <i>et al</i> (26), Costa <i>et al</i> (27), Bollati <i>et al</i> (28), Fenga <i>et al</i> (29), Tabish <i>et al</i> (30), Yu <i>et al</i> (34), Bai <i>et al</i> (35), Bai <i>et al</i> (36)
Asbestos (fibrous silicate particles)	Acoustical thermal insulation, railway construction and building construction	Mesothelioma	Promoter methylation, miRNAs downregulation	Tsou <i>et al</i> (44), Jones and Baylin (45), Christensen <i>et al</i> (18), Saito <i>et al</i> (46), Lodygin <i>et al</i> (47), Busacca <i>et al</i> (48), Pass <i>et al</i> (49), Kubo <i>et al</i> (50), Christensen <i>et al</i> (51),
Chromium	Steel and end alloy production, chrome plating, dyes and pigments manufacture	Lung cancer	DNA hypomethylation	Takahashi <i>et al</i> (59), Sun <i>et al</i> (60)
Nickel	Nickel plating and battery production	Lung cancer, nasopharyngeal carcinoma	DNA hypomethylation and hypermethylation, Histone acetylation	Karaczyn <i>et al</i> (66), Golebiowski and Kasprzak (67), Kowara <i>et al</i> (68), Govindarajan <i>et al</i> (69), Broday <i>et al</i> (70), Chen <i>et al</i> (71)
Arsenic	Pesticides	Cancer of skin, liver, urinary tract, lung, colon and hematopoietic disorders	DNA hypomethylation and hypermethylation	Baylin and Herman (76), Zhao <i>et al</i> (77), Chanda <i>et al</i> (78), Cui <i>et al</i> (79)

comprehension of this phenomenon will be helpful to prevent cancer development among workers.

2. Benzene

Benzene is an aromatic hydrocarbon that is widely used in various industrial contexts such as chemical industry, refineries, plants producing tires and lubricants. It is also used in the production of pharmaceuticals, pesticides, plastics and dyes. Occupational exposure to benzene is typically cutaneous or by inhalation. The general population may also be exposed to benzene because it is in the atmosphere, particularly in the areas of high vehicular traffic and in proximity to gas stations. Cigarette smokers are also exposed to benzene as it is contained in the cigarette. It is well known

that exposure to benzene increases the risk of developing cancer in various human tissues and organs (2). In particular, it has been observed that its toxic effects may cause hematopoietic disorders such as non-Hodgkin's lymphoma, lymphocytic leukemia, acute myeloid leukemia (19-23). Chromosomal alterations have been suggested as the most common mechanisms of malignant transformation associated to benzene exposure (24-27). Most recently, epigenetic alterations, including DNA methylation, may also play a role in tumorigenesis (28,29). For instance, several studies have indicated that exposure to benzene induces loss of global genomic methylation (28) and global DNA hypomethylation in human lymphoblastoid TK6 cells (30). Similar epigenetic alterations were found in hematopoietic malignancies, particularly in patients with acute myeloid leukemia in which

other genetic alterations may occur (31,32). On the other hand, further studies indicate that benzene induces DNA hypermethylation of the tumor suppressor genes p15 and p16 in benzene poisoning workers (33).

Yu *et al* observed H4, H3, H3K4 histones modifications in the promoter region of the topoisomerase II α (Topo II α) in subjects exposed to benzene (34). Therefore, the involvement of Topo II α in benzene-induced hematotoxicity demonstrates the relationship between histone modifications and benzene exposure. Finally, association between benzene and aberrant miRNA expression was also reported in studies of benzene-exposed workers, indicating their association with benzene-induced hemotoxicity and leukemogenesis (35,36).

3. Natural fibers

Various scientific evidence has clearly demonstrated the link between the occurrence of lung cancers and malignant mesothelioma (MM) during occupational and environmental exposure to asbestos (37,38). However, information on molecular alterations in MM, in patients exposed to mineral fibers, are not yet fully known or much less compared to other malignancies. Although the use of asbestos has been banned in major world nations for >20 years, the overall incidence of MM is estimated to occur in the year 2020, with a peak of incidence for this disease in the areas of occupational or environmental exposure to asbestos (39,40).

Improved understanding of molecular genetic consequences of asbestos exposure may improve cancer prevention strategies of exposed people. To date, it is known that the asbestos fibers, are affected by macrophages, generate genotoxic reactive oxygen species that in turn are able to induce DNA damage leading to genetic alterations in MM (41-43). Furthermore, exposure to carcinogenic fibers may cause epigenetic changes that reduce the activity of tumor suppressor genes in MM (19,44,45). Accordingly, it was observed the activation of several proto-oncogenes associated with the downregulation of miRNA-127 and miRNA-34a (46,47). Indeed, several studies have indicated that aberrant expression of miRNAs play a role in MM development (48-50).

Moreover, other studies have shown that epigenetic changes significantly are associated with exposure to asbestos and significantly predict clinical outcome, discriminating the malignant phenotype from normal pleura (51).

4. Heavy metals

The carcinogenic potential of some metals is well known since the beginning of the 19th century. The economy expansion in the major industrialized countries has been accompanied by a parallel increase in consumption of metals which are now recognized as human carcinogens. Indeed, toxic metals such as chromium, nickel and arsenic are used extensively in the steel industry, the wood pressure-treated, to form alloys, for the production of coins and batteries, as catalysts for the production of carbon nanoparticles. Therefore, in highly industrialized countries the use of these metals results in increasing incidence of human cancers (2). Epigenetic mechanisms have been described in the pathogenesis of most common heavy metal-associated cancer types (52,53).

Chromium. Occupational exposure to chromium is primarily via inhalation; in fact, the relationship between chromium and risk of lung, nasal, and especially respiratory cancer is well-known (54,55). Strong mutagenic ability of chromium, due to its ability to enter the cells through the sulfate channels and to form stable chromium-DNA adducts, is also well-known (56,57). Epidemiological studies have shown that cancer may occur after chromium exposure even at lower limits than those permitted, according to the current regulation (58).

Epigenetic mechanisms, such as hypermethylation of MLH1, have been suggested as potential mechanisms of malignant transformation during chromium exposure (59). Accordingly, the inactivation of MLH1 causes loss of functional mismatch repair (MMR) in chromate-exposed lung cancer (59).

In this regard, it was suggested that the increased dimethylation of histone H3 lysine 9 at the MLH1 promoter causes the downregulation of tumor suppressor genes, including MLH1 (60).

Nickel. Nickel and nickel compounds have been classified as human carcinogens according to IARC (2012) (61). The main route of human exposure to nickel is inhalation and its toxic effects on the respiratory system are well-known (61,62). Exposure to various nickel compounds is associated with increased risks of lung cancer and nasal cancer (63) although for these cancer types the most common risk factor is tobacco smoking (64).

Several studies have demonstrated that the basis of nickel toxicity and carcinogenicity is in its ability to enter and accumulate into the cells (65). These events involve epigenetic changes such as DNA methylation as well as the activation or suppression of a number of transcription factors and histone acetylation (66,67). In particular, *in vivo* and *in vitro* studies have shown that exposure to nickel may cause hypermethylation of the tumor suppressor gene p16 and its silencing (68,69). The suppressive effects of nickel on histone H4 acetylation in both yeast and mammalian cells have also been demonstrated (70). Furthermore, previous studies have shown the loss of acetylation of H2A, H2B, H3 and H4 and the increase of H3K9 dimethylation in human lung cells exposed to soluble nickel (67,71).

Arsenic. Occupational arsenic exposure occurs mainly in the workplace through inhalation. Pesticides may contain arsenic and their effects in chronic disorders have been recently summarized (72). Effects associated with arsenic exposure include cardiovascular and peripheral vascular disease, hematologic disorders and multiple cancers (cancers of the skin, lung, liver, urinary bladder, kidney and colon) (72,73).

The oncogenic ability of arsenic is well-known for almost 30 years (74,75). Over the last ten years, various scientific evidence has shown that epigenetic changes are important in arsenic carcinogenesis. Exposure to arsenic can induce DNA methylation changes such as hypomethylation and hypermethylation. These changes are typically observed in cancer. *In vitro* human kidney cells treated with arsenic were found both hypo- and hypermethylated (76). Similar data were

observed in TRL-1215 rat liver epithelial cell line (77). Finally, other studies described a significant DNA hypermethylation of the promoter region of several genes including p53, p16, RASSF1A (78,79).

5. Conclusions

A growing body of evidence exists on occupational risk factors and cancer development. Previous studies on the association between cancer and environmental risk factors are here summarized and discussed. A better understanding of the molecular mechanisms of cancer growth in this context allow us to identify novel procedures to reduce the risk factors during work activity.

Several cancer research studies focused on cancer risk assessment, cancer epidemiology and mutational changes induced by carcinogens. Over the past decade, research interest has also been focused on epigenetic alterations for their specificity and inheritance from generation to generation. Accordingly, such alterations can be considered an appropriate biomarker of carcinogen exposure.

Based on the above, epigenetic changes, here emphasized, seem to be the most common mechanisms of carcinogenesis. In fact, the number of studies devoted to understanding the epigenetic alterations caused by exposure to chemical carcinogens is rapidly increasing.

Consequently, the role of this epigenetic alteration in carcinogenesis, involving DNA hypomethylation or hypermethylation, histones/chromatin structure alterations, different expression of microRNA and genetic changes, are detailed. However, other mechanisms, including the involvement of the tumor microenvironment, may be involved in malignant transformation after exposure to carcinogens, such as the asbestos-like fibers (80). This is the case of mesothelioma in which an early marker of malignant transformation has been recently identified (81,82).

Although, great effort has been dedicated on the knowledge of epigenetic mechanisms in carcinogenesis, further studies are always encouraged especially in the context of occupational medicine.

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