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Mini-review

The role of epigenetics in environmental and occupational carcinogenesis

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ABSTRACT

Over the last few years there has been an increasing effort in identifying environmental and occupational carcinogenic agents and linking them to the incidence of a variety of human cancers. The carcinogenic process itself is multistage and rather complex involving several different mechanisms by which various carcinogenic agents exert their effect. Amongst them are epigenetic mechanisms often involving silencing of tumor suppressor genes and/or activation of proto-oncogenes, respectively. These alterations in gene expression are considered critical during carcinogenesis and have been observed in many environmental- and occupational-induced human cancers. Some of the underlying mechanisms proposed to account for such differential gene expression include alterations in DNA methylation and/or histone modifications. Throughout this article, we aim to provide a current account of our understanding on how the epigenetic pathway is involved in contributing to an altered gene expression profile during human carcinogenesis that ultimately will allow us for better cancer diagnostics and therapeutic strategies.

Contents

1. Introduction

Over the past few decades, scientific research has linked agents of environmental and occupational exposure(s) to numerous human cancers [1]. Since the assertion in 1977 by Higginson and Muir that "80% of all cancers were due to environmental exposures" [2] researchers have attempted to quantify the exact attributable fraction between cancer deaths and such exposure(s) [1,3]. For example, studies have listed 16 occupational substances as human carcinogens, with estimates that 2% of total cancer deaths were due to pollution and 4% to occupation [3]. In 1996, a report published by the Harvard Center for Cancer Prevention updated the roster to include a total of 32 carcinogenic substances [4]. The Monographs Program on the Evaluation of Carcinogenesis Risks to Humans of the International Agency for Research on Cancer (IARC) has currently identified 88 human carcinogenic agents: 64 agents and groups of

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agents (22 drugs; 14 environmental chemicals; 14 radiation; 10 viruses, bacteria, parasites; and 4 inorganic fibers); 12 mixtures, and 13 exposure circumstances [1]. Most recently, 28 agents have been identified as definite occupational carcinogens in humans, 27 as probable occupational carcinogens and 113 as possible occupational carcinogens [5]. In addition, other research has reported that 10% of some 80,000 chemicals in use today are recognized carcinogens [6]. Finally, according to the European commission, about 100,000 man-made chemicals known to act as persistent toxic pollutants and contaminates of air, soil, water and food, have been marketed with insufficient toxicological control [5]. Thus, it is becoming of great interest not only to be able to identify carcinogenic agents but also to elucidate on the mechanisms by which they exert their effects contributing to human carcinogenesis.

2. Overview of environmental and occupational carcinogenesis

Although environmental and occupational agents are implicated as significant contributors to the increased incidence of human carcinogenesis, interpretations as to the extent of such contributions remain largely unclear. One consideration suggests that environmental pollutants play only a minor role in cancer incidence, with lifestyle influences (tobacco, high fat diet and alcohol usage) acting as major contributing factor(s) [5,7,8]. Conversely, other groups have suggested that environmental exposure to diverse physical, chemical and biological agents play a significant role in the occurrence of cancer, with lifestyle factor(s) contributing only a minor fraction [5,9]. Nevertheless, data have clearly shown that many exogenous environmental factors can significantly contribute to the causation of a variety of human cancers [1,5]. For example, natural and synthetic chemicals (i.e. fossil fuels, plastics, herbicides, pesticides, fungicides, tobacco smoke, food additives, etc.) found in the ambient environment, in drinking water and in food, have been shown to alter gene expression, as well as cellular metabolism [6,10].

Tobacco smoke, perhaps one of the most well established environmental carcinogenic factors, has been estimated to account for 30% of all cancer deaths and 85% of lung cancer deaths [6]. In fact, the mixture of tobacco smoke and tar is defined as a "complete carcinogen" due to the presence of thousands of mutagenic compounds, including polycyclic aromatic hydrocarbons (PAH) and nitrosamines [5]. On the other hand, one of the most well-established occupational carcinogenic agents known to cause mesothelioma and approximately 10% of lung cancers is asbestos. Other common agents involved in the induction of occupational carcinogenesis include: wood-dust particulates (common to cabinet makers), solvents, paints, dye products and by-products of aromatic amines and/or aminophenol groups (common to painters), gasoline, petroleum-based mixtures, benzene, mineral oils and phthalates (used for their plasticizing and emulsifying properties in medical and cosmetic devices) [5]. The combustion of a variety of these elements (i.e. vehicle exhaust, factory smoke, tobacco smoke, waste incinerators) yields a plethora of outdoor air pollutants known to adhere to fine carbon particles. Such particulates are able to remain suspended in the air and consequently penetrate into an organism and thus contributing to an increased cancer risk [5]. A recent European study showed that the risk of lung cancer due to environmental (second hand) tobacco smoke is slightly higher at work than at home, and significantly higher for ex-smokers than for never smokers [11]. Other outdoor air pollutants (such as biocides and pesticides) have also been linked to an increased risk for developing cancer. In fact, studies have revealed a causative relationship between parental and child pesticide exposure and an increased risk of developing leukemia, brain tumors, Wilm's tumors, Ewing's sarcoma and germ cell tumors [5]. Pesticides are commonly referred to as persistent organic pollutants (POPs) due to their ability to withstand environmental degradation, thereby contaminating drinking water and food [12].

The IARC has identified a variety of metals and metalloids (as antimony, arsenic, chromium, cobalt, nickel, vanadium) as being carcinogenic with an ability to contribute to a wide spectrum of cancers [5,13]. For example, whereas arsenic inhalation can cause lung cancer, its ingestion can cause bladder, kidney and lung cancers [5,14]. While the exact molecular mechanism(s) behind metal-induced carcinogenesis remain unclear, recent evidence has indicated that various metals act as catalysts in the oxidative deterioration of biological macromolecules with the ability to induce free radical generation [15]. Metal ions (such as copper, cadmium, chromium, nickel, arsenic, cobalt, vanadium, and iron) are known to generate reactive oxygen species (ROS) and thus contribute to an imbalance observed between normal and pathologic conditions where free radicals are generated [15,16]. Although ROS (i.e. superoxide radical, hydrogen peroxide, hydroxyl radical, etc.) are present in cells under normal physiological conditions, accumulative toxic effects contribute to an increased rate of ROS generation that ultimately supersedes the cellular antioxidant defense capacity thus generating a cellular toxic state known as "oxidative stress" [17]. Strong evidence supports the involvement of oxidative stress in the process of carcinogenesis [18]. For example, intracellular ROS accumulation has been shown to induce deleterious damage to a variety of biomolecules, leading to protein oxidation, lipid peroxidation, DNA damage, depletion of sulfhydryl groups and alteration(s) in signal transduction pathways [15]. In addition, evidence has linked intracellular ROS formation to carcinogenesis through either direct genotoxic effects or indirect modification(s) of signaling pathways leading to altered expression of numerous genes [16,18]. For example, recent data have suggested that certain carcinogenic metals (arsenic, cadmium, nickel, cobalt and lead) inhibit zinc finger-containing DNA repair proteins and that such damage may be regarded as a novel mechanism involved in metal-induced carcinogenesis [5]. Finally, free radical-induced damage is suggested to be involved in aberrant epigenetic changes observed during the multistage carcinogenic process [17].

3. Overview of cancer epigenetics

Cancer research has generated a body of evidence that link changes to the genome with the carcinogenic process [19]. These changes and in particular modifications in the DNA methylation machinery, have been hypothesized to serve as excellent candidates for the association between environmental exposure and cancer development [20]. In fact, epigenetic changes have been strongly implicated in virtually every step during tumor development and progression [21]. These discoveries have resulted in an increasingly accepted view that epigenetics play a fundamental role in carcinogenesis [22]. For example, much attention has been recently directed towards elucidating the connection between DNA methylation and cancer development. In fact, it is believed that aberrant DNA methylation patterns may serve as powerful detection, diagnostic and risk assessment biomarkers [22]. Evidence suggests that the normal intricate organization of DNA methylation and chromatin conformation (known to regulate the normal cellular homeostasis of gene expression patterns) somehow becomes unrecognizable in cancer cells leading to aberrant gene expression profiles [20]. More specifically, recent data indicate that hypermethylation of GC-rich DNA regions (called CpG islands) plays a major causal role in cancer development primarily through its ability to inactivate and thus silence tumor suppressor genes [23]. Under normal conditions, such CpG islands are unmethylated and their