Mutation Research 760 (2014) 1–9

Contents lists available at ScienceDirect

Mutation Research/Genetic Toxicology and Environmental Mutagenesis

journal homepage: www.elsevier.com/locate/gentox
Community address: www.elsevier.com/locate/mutres

Minireview

Gene–environment interactions in heavy metal and pesticide carcinogenesis

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ARTICLE INFO

Article history:
Received 1 July 2013
Received in revised form
19 November 2013
Accepted 25 November 2013
Available online 3 December 2013

Keywords:
Environment
Gene
Polymorphism
Heavy metals
Pesticides

ABSTRACT

Cancer is a complex disease involving a sequence of gene–environment interactions. Lifestyle, genetics, dietary factors, and environmental pollutants can increase the risk of cancer. Gene–environment interactions have been studied by a candidate-gene approach focusing on metabolism, DNA repair, and apoptosis. Here, we review the influence of gene–environment interactions in carcinogenesis, with emphasis on heavy metal and pesticide exposures.

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http://dx.doi.org/10.1016/j.mrgentox.2013.11.002

1. Introduction

Humans are exposed to many environmental carcinogens. The increasing incidence of cancer is at least partly attributable to carcinogenic agents in the occupational and general environment [1]. How and when these agents become critical for carcinogenesis is not well understood.

Carcinogenesis is a complex, multistep, multifactorial process involving genetic alterations, immune suppression, and malignant transformation [2]. Cancers are thought to arise from a single cell, initiated by mutation of a few crucial genes caused by errors in DNA replication or exposure of DNA to free radicals or carcinogens [3]. Initiated cells undergo further genetic/epigenetic changes that provide survival advantages and ultimately lead to the conversion of normal cells to malignant cancer cells. These processes can be activated by environmental factors such as cigarette smoke, industrial pollutants, oxidative and inflammatory agents. Gene–environment interactions (GEI), broadly defined as interactions between environmental exposures and specific (risk) genotypes, are known to act in a plethora of diseases [4,5], including cancer development.

In this review, we summarize the pathways leading to cancer, GEIs, and two classes of carcinogenic environmental pollutants: heavy metals and pesticides. (Carcinogenesis induced by other agents, such as polycyclic aromatic hydrocarbons, is not within the scope of this article).

2. Multistep process of carcinogenesis:

Cancer development includes initiation, proliferation, and progression phases. The multistage process of transformation and tumorigenesis includes evasion of apoptosis, self-sufficiency in growth signals, insensitivity to antigrowth signals, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis [6,7]. Epigenetic disruption of gene expression also occurs during cancer development [8]; diet- and environment-mediated epigenetic perturbations play a crucial role in cancer progression in humans [9,10].

Accumulation of mutations seems to be necessary for tumor development [2] and one expects a higher rate of mutations with exposure to carcinogens. These mutations can affect genes encoding xenobiotic-metabolizing enzymes, produce polymorphisms leading to altered ligand affinity and activity, or influence the expression of downstream target genes, resulting in differential susceptibility to environmental toxicants [11].

Oxidative and inflammatory stresses are involved in the initiation and progression of carcinogenesis. Biomarkers of oxidative stress have been reported in cancer, due to factors such as elevated metabolism, mitochondrial mutations, cytokines, and inflammation [12]. Oxidative stress arises from increased production of reactive oxygen species (ROS) associated with decreased antioxidant capacity. ROS are constantly generated in aerobic cells by the incomplete reduction of molecular O_2 to H_2O during mitochondrial oxidative phosphorylation, as well as during processes such as inflammation, infection, mechanical or chemical stress, and exposure to ultraviolet or ionizing radiation [13]. The effect of ROS on cell depends on the level at which they are present. Low levels may be beneficial, but, at high levels, ROS can oxidatively damage macromolecules and cause detrimental effects that can lead to cell death. ROS can induce genotoxic damage, including DNA single- and double-strand breaks, DNA–protein cross-links, abasic sites, and modified bases [14–17].

Cells counteract oxidative stress by the use of several defense mechanisms, ranging from free radical scavengers and antioxidant molecules/enzymes to DNA repair mechanisms to reduce levels of ROS and prevent irreversible cellular damage [18,19]. Oxidative stress is also closely associated with carcinogenesis [20]. Increased ROS production occurs in highly proliferative cancer cells, owing to the presence of oncogenic mutations. Increased oxidative stress is well documented in transformed cells [21] and ROS regulation is crucial for transformed cells that counteract ROS accumulation by upregulating antioxidant systems [22].

Blood oxidative stress-related markers such as 8-isoprostane and 8-hydroxy-2′-deoxyguanosine (8-OHdG) are reported to be significantly increased in patients with breast cancer [23]. Over time, DNA damage can lead to an increased incidence of cancer [24]. Under normal circumstances, damaged DNA is repaired, but excess oxidative stress may result in non-repairable DNA damage, which may lead to mutations in critical genes involved in the control of cell growth. ROS act as signaling molecules to initiate inflammatory responses, which can affect cell proliferation and apoptosis. Oxidative modification of cell signal transduction by ROS may result in dysfunctional cell growth, differentiation and cell death, which can ultimately lead to the development of inflammation and cancer [16].

The effects of ROS on p53, cell proliferation, invasiveness, and metastasis are important in cancer biology. ROS are major activators of the NF-κB and AP-1 transcription factors involved in innate immune or inflammation responses [25,26]. Activation of NF-κB upregulates the expression of many inflammation-related genes, including tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8 and vascular endothelial growth factor. TNF-α and IL-1 in turn bind to tumor necrosis factor receptors and IL-1 receptors, thereby further activating the NF-κB pathway and repeating the cycle. Inflammatory chemokines act on inflammatory cells to increase their pro-tumorigenic properties and act directly on tumor cells through specific receptors expressed by those cells [27].

Investigations of oxidative stress have primarily focused on genotoxicity [14,15,19,28], but ROS also play a significant role in promotion of carcinogenesis. Many tumor promoters generate ROS [29,30].

3. Gene–environment interactions and cancer

The term Gene–environment interaction (GEI) refers to the joint influences of genetic and environmental factors on health and disease. Environmental exposures affect gene regulation and/or act as additive risk factors in conjunction with a particular allelic form of a gene (genetic polymorphism), influencing disease initiation and progression. GEI also entails the different effects of a given environmental exposure on individuals and the different effects of a genotype in people with different histories of environmental