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Review

Environmental carcinogenesis and pH homeostasis: Not only a matter of dysregulated metabolism

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ABSTRACT

According to the World Health Organization, around 20% of all cancers would be due to environmental factors. Among these factors, several chemicals are indeed well recognized carcinogens. The widespread contaminant benzo[a]pyrene (B[a]P), an often used model carcinogen of the polycyclic aromatic hydrocarbons' family, has been suggested to target most, if not all, cancer hallmarks described by Hanahan and Weinberg. It is classified as a group I carcinogen by the International Agency for Research on Cancer; however, the precise intracellular mechanisms underlying its carcinogenic properties remain yet to be thoroughly defined. Recently, the pH homeostasis, a well known regulator of carcinogenic processes, was suggested to be a key actor in both cell death and Warburg-like metabolic reprogramming induced upon B[a]P exposure. The present review will highlight those data with the aim of favoring research on the role of H^+ dynamics in environmental carcinogenesis.

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Abbreviations: AhR, aryl hydrocarbon receptor; B[a]P, benzo[a]pyrene; CYP, cytochrome P450; EMT, epithelial-to-mesenchymal transition; Cx43, connexin 43; GJIC, gap junction intercellular communication; HMGCoA reductase, 3-hydroxy-3-methylglutaryl-CoA reductase; NHE1, Na^+/H^+ exchanger 1; PAH, polycyclic aromatic hydrocarbon; pH_i, intracellular pH; pH_e, extracellular pH; TCA cycle, tricarboxylic acid cycle; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; $\Delta\Psi m$, mitochondrial membrane potential; Δp, proton motive force; ΔpHm, cytosol-mitochondrial proton gradient.

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1. Introduction

An increased human lifespan along with the improvement of screening and diagnostic methods cannot alone explain the increasing incidence of certain types of cancers. Several studies have pointed out that factors related to the so-called western lifestyle such as a high-fat diet, alcohol consumption and cigarette smoking, represent important risk factors with regard to the development of several of these cancers. Some occupational activities are also responsible for cancer development; in line with this, it is worth noting that the chimney sweepers' cancer, also called "soot wart", has been the first reported form of occupational cancer; this cancer targets the skin of scrotum, and was initially identified by Percivall Pott in 1773 [1]. As a result of this knowledge and following restriction campaigns, smoking and for some countries also alcohol consumption have been declining for several years, thus leading to a decrease in the number of aero-digestive tract and esophageal cancers. Regulations have also been set up to limit or prevent the chemical exposure of workers. However, the incidence of several other cancers including hepatocellular carcinoma (HCC) (European Cancer Observatory, http://eu-cancer.iarc.fr) is still increasing. Important risk factors notably for development of HCC, in addition to those mentioned above, include infections like Hepatitis C and B viruses, and natural compounds like the mycotoxin aflatoxin B1 [2].

During the last decades, intensive chemical testing and regulations have most probably reduced the likelihood of being exposed to complete genotoxic chemical carcinogens. However, spontaneous DNA damage occurs in all tissues at a high frequency, and various types of genetically predispositions exist. As cancer is due to a combined action of several factors, there is a growing awareness that chemically-induced DNA damage may not always be the limiting factor for cancer development. Furthermore, we are still exposed to an increasing amount of chemicals for which the combined actions are often unknown. Thus, this type of involuntary exposure could contribute to the increasing incidence of different types of cancers in industrialized countries. Indeed, according to data obtained through the World Health Organization, approximately 20% of cancer deaths would be due to environmental factors [3].

The complete elimination of environmental chemicals, either synthetic or natural, which contribute to the carcinogenic processes, is technically unfeasible. In this context, human exposure to toxic chemicals is therefore inevitable, particularly due to food contamination and air pollution. Important combined factors associated with lifestyle are well identified and accessible to epidemiological studies using traditional epidemiological methods. This is not the case for examination of the effects of low doses of individual chemicals that may differentially be involved in the carcinogenic process. Furthermore, as stated above, the combined effects of environmental chemicals due to their diversity and widespread distribution may potentially make an important contribution to the overall process of cancer development. Hence, as recently stressed by the Halifax project consortium [4,5], there is an urgent need to develop studies on the biological and toxicological effects of these contaminants to increase our knowledge about their action mechanisms, notably with regard to carcinogenesis.

The precise sequencing of the carcinogenic process is still not fully elucidated, and in a recent comprehensive review, the process was suggested to include tumor initiation, tumor formation and progression, matrix remodeling, intravasation, extravasation and metastasis [4]. Important acquisition hallmarks are genetic instability, tumor-promoting inflammation, sustained proliferative signaling, insensitivity to antigrowth signals, replicative immortality, dysregulated metabolism, resistance to cell death, angiogenesis, tissue invasion and metastasis [6]. One key parameter for the occurrence of several of these cancer hallmarks is intracellular pH (pH_i) [7–12]. Based upon the fact that alterations in cell H^+ homeostasis could also result from exposure to environmental carcinogens, it is important to review the role of these alterations in the occurrence of some of the cancer hallmarks in order to bring some new clues to the understanding of environmentally-linked cancer development. This review will mainly focus on the impact of pH homeostasis in polycyclic aromatic hydrocarbons (PAHs)-induced effects on resistance to cell death and dysregulated metabolism/cellular energetics. Indeed the PAHs are among the molecules worth considering when focusing on the etiology of diverse cancers since they are widespread in our environment and constitute the largest class of environmental carcinogens. However, when necessary, reference to other environmental carcinogens will also be made.

2. Generalities on the PAH family

2.1. Sources and exposure

PAHs are major environmental pollutants which are primarily formed during incomplete combustion or pyrolysis of organic material such as gasoline, diesel fuel, coal, oil, food (grilled, barbecued or smoked) and tobacco. These substances are therefore found in polluted air, water, soil and food. In the air, they are often

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