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Mini review

Oxidative stress in environmental-induced carcinogenesis

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ABSTRACT

Reactive oxygen species (ROS) are the more abundant free radicals in nature and have been related with a number of tissue/organ injuries induced by xenobiotics, ischemia, activation of leucocytes, UV exposition, etc. Oxidative stress is caused by an imbalance between ROS production and a biological system's ability to readily detoxify these reactive intermediates or easily repair the resulting damage. Thus, oxidative stress is accepted as a critical pathophysiological mechanism in different frequent human pathologies, including cancer. In fact ROS can cause protein, lipid, and DNA damage, and malignant tumors often show increased levels of DNA base oxidation and mutations.

Different lifestyle- and environmental-related factors (including, e.g., tobacco smoking, diet, alcohol, ionizing radiations, biocides, pesticides, viral infections) and other health-related factors (e.g. obesity or the aging process) may be procarcinogenic. In all these cases oxidative stress acts as a critical pathophysiological mechanism. Nevertheless it is important to remark that, in agreement with present knowledge, oxidative/nitrosative/metabolic stress, inflammation, senescence, and cancer are linked concepts that must be discussed in a coordinated manner.

Contents

1. Introduction

The increased incidence of cancer over the last 50–60 years may be largely attributed to two factors: the ageing of the population and the diffusion of carcinogenic agents, present not only in the occupational, but also in the general environment [1]. There are studies supporting evidence that lifespan exposure to carcinogenic

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agents, beginning during developmental life, produces an overall increase in carcinogenic processes [1].

Oxidative stress is caused by an imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage. Thus, oxidative stress is accepted as a critical pathophysiological mechanism in different frequent pathologies, including cardiovascular diseases, cancer, diabetes, rheumatoid arthritis, or neurological disorders such as Alzheimer or Parkinson disease [2–6].

The increasing risk of suffering pathologies related with oxidative stress confronts the scientific community about their molecular origin and nature. There are scientific evidences linking environmental changes over the time period preceding the growing incidence of some types of cancer. These changes have not stopped and the accumulation of carcinogens keeps growing [7].

Lifestyle-related factors are not considered as cancer causing agents, but are risk factors directly associated with the development of cancer. However we are frequently or constantly exposed to known and unknown environmental carcinogenic factors. How or when all these factors are critical for the genesis of cancer are problems only partially understood.

The main goal of this review is to show the procarcinogenic action of reactive oxygen species (ROS) produced by a group of environmental agents.

2. Role of ROS in oncogenesis

It is generally accepted that ROS eventually cause DNA damage, whereby insufficient cellular repair mechanisms may contribute to premature aging and apoptosis. Conversely, ROS-induced imbalances of the signalling pathways for metabolic protein turnover may also result in opposite effects to recruit malfunctioning aberrant proteins and compounds that trigger tumorigenic processes [8]. Consequently, DNA damage plays a role in the development of carcinogenesis, but is also associated with an aging process in cells and organisms [9]. Hence additional actions of ROS must be important, possibly their effects on p53, cell proliferation, invasiveness and metastasis. Chronic inflammation predisposes to malignancy, but the role of ROS in this is likely to be complex because ROS can sometimes act as anti-inflammatory agents [10].

The damaged nucleosides accumulate with age in both nuclear and mitochondrial DNA. Mitochondrial DNA (mtDNA) mutations appear involved in tumorigenesis, tumor growth promotion and/or metastatic potential [11]. An example is the mutated complex I (NADH dehydrogenase, a mtDNA gene), and its reduced activity, which in certain tumors may lead to overproduction of ROS [12], thus inducing up-regulation of different nuclear genes associated with high metastatic potential: antiapoptotic MCL-1 (myeloid cell leukemia-1), HIF-1α (hypoxia-inducible factor-1α) and VEGF (vascular endothelial growth factor) [13]. High metastatic potential is regulated by ROS-mediated reversible up-regulation of nuclear genes but not by ROS-mediated acceleration of genetic instability, which suggests that ROS scavengers may be therapeutically effective in suppressing metastasis [13].

3. Accumulation of mutations and oncogenesis is a multifactorial phenomenon

Genetic alterations, immune suppression, and malignant transformation are phenomena linked to the origin of cancer [14]. Cancer is generally believed to arise from a single cell which has become "initiated" by mutation of a few crucial genes, caused by random errors in DNA replication or a reaction of the DNA with free radicals or other chemical species of exogenous or endogenous origin. It is not obvious how the epidemiological data on cancer incidence can be interpreted within the framework of this paradigm. For example, it cannot account quantitatively for the age dependence of cancer incidence, or for the fact that the incidence of cancer in people with hereditary mutations in tumor-suppressor genes is much lower than expected, or for the observation that while in some types of cancer, like colon and pancreas, certain highly oncogenic mutations, such as that of *p53*, are prevalent, there is no significant increase in the incidence of these cancers in people who carry the mutations by heredity. The epidemiological data are consistent with the hypothesis that the rate limiting processes involve large numbers of cells. Conceivably, the mutations directly underlying neoplastic transformation may be the result of a local collapse in the system of intercellular processes on which the stability of the normal genotype and phenotype depends, and thereby trigger a cascade of mutations, among them the highly oncogenic ones. This local collapse may be due to mutations of many different genes in many cells as well as to other factors affecting the integrity of tissues [15]. This mutagenic origin of cancer may be due, in some cases, to exposition to different carcinogens present in our environment [16]. For instance, there are evidences, based on studies in murine models, showing that air contaminants may cause mutations in germinal cells [17].

In addition, accumulation of mutations appears necessary for tumor development. In this sense it is known that mutations of ~11 critical genes are required in mammary and colon cancers, whereas once tumor growth starts gene mutations keep accumulating up to ~90 [18]. Therefore it is not acceptable to think that all these mutations are caused by a single mutagen, although it is reasonable to expect a higher rate of mutations in toxic environment containing one or more carcinogens.

These mutations can affect genes of relevant xenobiotic metabolizing enzymes, produce polymorphisms leading to altered ligand affinity and activity, or influencing the expression of downstream target genes [19], thus resulting in a differential susceptibility towards environmental toxicants [19]. N-acetyltransferase isozymes (catalyzing the N-acetylation and O-acetylation of aromatic amines), isoforms of glutathione S-transferase (GST) (involved in the detoxification of PAH), cytochrome p450 and sulfotransferase isoforms, are all involved in the detoxification of active metabolites from the environment [20]. Besides, although polymorphisms in oxidative stress-related genes (e.g. mangano-type superoxide dismutase, catalase, or glutathione peroxidase) may not be directly associated with cancer risk, it is possible that accumulative defects in protection from oxidative stress may result in increased risk of the disease [21].

4. Lifestyle- and environmental-related factors, oxidative stress and carcinogenesis

4.1. Tobacco smoking

Despite widespread knowledge about high risks for health of smoking tobacco, there are still over 1 billion smokers in the world. A cigarette smoke contains thousands of chemicals, of which more than 60 are known carcinogens, i.e. polycyclic aromatic hydrocarbons, nitrosamines, aromatic amines, aldehydes, volatile organic compounds, metals, and others [22,23]. Furthermore, cigarette smoke contains high levels of free radicals which can produce lesions in DNA and generate different oxidized bases, i.e. 8-oxodG, which is a classical biomarker of oxidative DNA damage [24]. Indeed, in chronic smoking an internal oxidative environment is favored. In fact, markers of oxidative stress can be analyzed and