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Review Article

Metal interaction with redox regulation: an integrating concept in metal carcinogenesis?

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ABSTRACT

The carcinogenicity of cadmium, arsenic, and chromium(VI) compounds has been recognized for some decades. However, the underlying molecular mechanisms seem to be complex and are not completely understood at present. Although, with the exception of chromium(VI), direct DNA damage seems to be of minor importance, interactions with DNA repair processes, tumor suppressor functions, and signal transduction pathways have been described in diverse biological systems. In addition to the induction of damage to cellular macromolecules by reactive oxygen species, the interference with cellular redox regulation by reaction with redox-sensitive protein domains or amino acids may provide one plausible mechanism involved in metal carcinogenicity. Consequences are the distortion of zinc-binding structures and the activation or inactivation of redox-regulated signal transduction pathways, provoking metal-induced genomic instability. Nevertheless, the relevance of the respective mechanisms depends on the actual metal or metal species under consideration and more research is needed to further strengthen this hypothesis.

Contents

Introduction

Many metal compounds are carcinogenic to humans and to experimental animals. This applies not only to toxic metal compounds such as cadmium, lead, arsenic, and antimony, but includes also essential trace elements such as chromium, nickel, and cobalt on conditions of metal overload, exceeding the homeostatic capacity [1]. Nevertheless, with the exception of Cr(VI), most metal compounds are not mutagenic in bacterial test systems and mutagenic responses in mammalian cells are rather weak. Therefore, again with the exception of Cr(VI), direct interactions of metal ions with DNA seem to be of minor

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importance [1]. One mechanism frequently proposed to be involved in metal-induced tumor formation is an increase in reactive oxygen species and oxidatively damaged DNA. In addition, interference with the cellular response to DNA damage and with distinct signaling pathways has been identified for many metal compounds during the past years, including interactions with various types of DNA repair systems, cell cycle control, and tumor suppressor functions, as well as with cell proliferation and cell death [1–6]. In many cases, the inactivation of distinct proteins of the respective pathways has been demonstrated. For example, proteins with zinc-binding domains, so-called zinc-finger proteins, have been identified as potentially very sensitive targets for certain metal compounds, such as the nucleotide excision repair protein xeroderma pigmentosum A (XPA), the DNA damage signaling protein poly(ADP-ribosyl) polymerase 1 (PARP1), and the tumor suppressor protein p53 [6–16]. Respective inhibitions have frequently been observed at comparatively low concentrations. Underlying mechanisms may be explained either by disturbances of cellular redox homeostasis by metal ions, i.e., the induction of oxidative stress, or by interactions of metal ions with specific sites in proteins involved in cellular redox regulation. With respect to the latter, there has been accumulating evidence that, for example, reversible redox reactions on thiol/disulfide groups in proteins are involved in signal transduction processes similar to phosphorylation reactions [17–19]. Within this review, current evidence is summarized on the role of oxidative mechanisms in metal-induced carcinogenicity, with special emphasis on the potential impact on cellular redox regulation.

Oxidatively damaged DNA and the impact of carcinogenic metal compounds

Reactive oxygen species (ROS) such as superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical (HO•) are by-products of cellular respiration, generated by incomplete reduction of oxygen to H_2O. To enable the use of oxygen for energy production and yet to minimize oxygen-derived toxicity, a complex antioxidant network has evolved including the scavenging of reactive species by glutathione and vitamins; the enzymatic conversion of highly reactive oxygen species to less harmful ones by superoxide dismutase, catalase, and glutathione peroxidase; and finally the repair or elimination of damaged macromolecules. Oxidative stress occurs if the equilibrium between the generation of ROS and the efficiency of detoxification is disrupted. Nevertheless, even under normal cellular conditions, protection is not complete and a measurable amount of oxidatively damaged macromolecules exists in mammalian cells [5]. Especially the generation of elevated levels of DNA damage has been implicated in carcinogenicity. Oxidatively generated DNA damage includes a range of lesions such as DNA base modifications, sugar lesions, DNA single- and double-strand breaks, DNA–protein cross-links, DNA–DNA cross-links, and abasic sites. The main ROS identified so far that lead to DNA damage are HO•, singlet oxygen ($^1O_2$), and one-electron oxidants. Among these, only HO• is able to generate DNA single-strand breaks as a consequence of initial hydrogen abstraction from the 2-deoxyribose moieties, with different probabilities of hydrogen abstraction in different positions [20–23]. Concerning DNA single-base damage, $^1O_2$ reacts specifically with guanine, producing 8-oxo-7,8-dihydroguanine (8-oxoGua) without further reaction products [24]. Furthermore, 8-oxoGua, as well as 13 other singly oxidized purine and pyrimidine bases, has been detected in cellular DNA, mediated by HO• or high-intensity UVC laser pulses [25]. In addition to single-base DNA damage, HO• and one-electron oxidants have been shown to generate organic radicals such as radical cations, carbon centered or peroxyl radicals, which are able to react further with other DNA constituents or proteins, giving rise to more complex DNA lesions such as intra- and interstrand DNA cross-links as well as DNA–protein cross-links . Finally, DNA double-strand breaks (DSBs) arise from one nick in each DNA strand within one or two helix turns; they may, however, also be generated, for example, by replication of damaged DNA due to collapse of stalled replication forks (for recent reviews see [26,27]). Among these, several oxidatively generated DNA base modifications such as 8-oxoGua have miscoding and thus premutagenic properties and therefore may act as initiators in carcinogenesis [28]. Especially transition metal ions play an important role in the induction of oxidatively damaged DNA (Fig. 1). Whereas neither superoxide radical anion nor hydrogen peroxide is able to react with DNA directly, in the presence of transition metals such as iron, copper, cobalt, or nickel H_2O_2 is converted into the highly reactive HO• by Fenton-type reactions. Therefore, in the case of essential elements such as iron and copper, the controlled uptake, protein-bound transport, and intracellular sequestration of redox-active metal ions by metal-binding proteins are one important prerequisite to protect from elevated levels of oxidatively generated DNA damage. However, this protection will be overwhelmed under conditions of cellular overload by transition metals because of elevated exposure and/or nonphysiological uptake routes such as inhalation [5,29]. One unique example is Cr(VI). Under physiological conditions, Cr(VI) enters the cell as the anionic tetrahedral species chromate, CrO_4^{2-}, via anion transport systems such as the sulfate carrier, and is intracellularly reduced to Cr(III), described by the so-called "uptake–reduction" model [30–32]. Within the cell, reduction does not require enzymatic steps but is mediated by direct electron transfer from ascorbate and nonprotein thiols such as glutathione and cysteine; during this process, potentially toxic intermediates such as oxygen and sulfur radicals are generated, dependent on the intracellular reductant (for recent review see [33]). DNA lesions generated after exposure to Cr(VI) consist of two categories, namely oxidatively induced DNA damage and DNA lesions resulting from Cr(III)–DNA interactions. With respect to the formation of ROS during the intracellular reduction process, several pathways have been proposed, including the reaction of Cr(V)–glutathione complexes with hydrogen peroxide and the formation of HO• and/or a one-electron reduction of Cr(VI) to Cr(V) by NADPH-dependent flavoenzymes [34,35]. Cr(V) may either react with hydrogen peroxide in a Fenton-type reaction to yield again HO• [36], and thus induce DNA strand breaks as

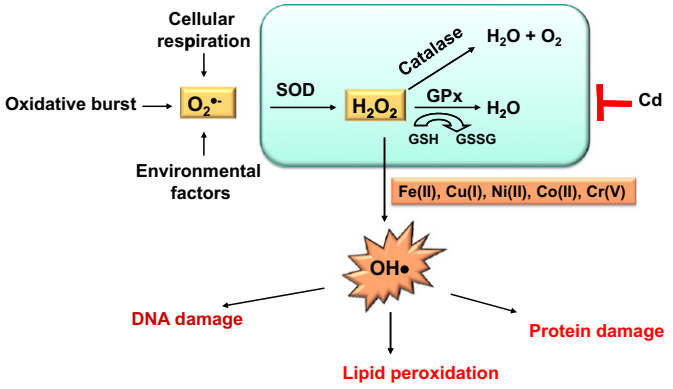

Fig. 1. Role of metal ions in the generation of cellular damage by reactive oxygen species (ROS). Whereas redox-active transition metal ions or reactive intermediates such as Cr(V) may convert H_2O_2 into highly reactive HO•, redox-inactive cadmium ions may increase the formation of ROS by inhibiting cellular defense enzymes such as superoxide dismutase (SOD), catalase, and/or glutathione peroxidase (GPx).