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Review Article

Oxidative stress and metal carcinogenesis

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ABSTRACT

Occupational and environmental exposures to metals are closely associated with an increased risk of various cancers. Although carcinogenesis caused by metals has been intensively investigated, the exact mechanisms of action are still unclear. Accumulating evidence indicates that reactive oxygen species (ROS) generated by metals play important roles in the etiology of degenerative and chronic diseases. This review covers recent advances in (1) metal-induced generation of ROS and the related mechanisms; (2) the relationship between metal-mediated ROS generation and carcinogenesis; and (3) the signaling proteins involved in metal-induced carcinogenesis, especially intracellular reduction–oxidation-sensitive molecules.

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Abbreviations: AP-1, activator protein-1; ARE, antioxidant response element; CAT, catalase; CBD, chronic beryllium disease; DFX, desferoxamine; EGF, epidermal growth factor; ERK, extracellular signal-regulated kinase; ESR, electron spin resonance; GF, growth factor; GPx, glutathione peroxidase; GSH, reduced glutathione; HIF-1, hypoxia-inducible factor 1; IL, interleukin; JNK, c-Jun-NH₂-terminal kinase; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; NADPH, reduced nicotinic adenine dinucleotide phosphate; NFAT, nuclear factor of activated T cells; NF-κB, nuclear transcription factor κB; 8-OHdG, 8-hydroxydeoxy guanosine; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; RNS, reactive nitrogen species; ROS, reactive oxygen species; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor; XO, xanthine oxidase.

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Introduction

Carcinogenic metals present in occupational and general environments are believed to be critical factors involved in the increased incidence of cancers over the last half century [1]. Potential sources of metal exposure include groundwater contamination, metal working, leather tanning, and mining [1–4]. In addition to environmental and occupational settings, a variety of uses in medicine can result in exposure to different forms of metals [5,6]. Many metals, such as arsenic (As), beryllium (Be), cadmium (Cd), chromium (Cr), cobalt (Co), lead (Pb), mercury (Hg), Nickel (Ni), and vanadium (V), are toxic even at low levels of exposure [1,7–9]. These metals are known to induce cellular damage, inflammation, and cancers mainly in the kidney, liver, lung, prostate, and skin [8,10,11]. Even though metals, such as copper (Cu), iron (Fe), selenium (Se), and zinc (Zn), are essential to living organisms in trace amounts, chronic and extensive exposure causes detrimental effects to tissues and organs, eventually resulting in carcinogenesis [8,12,13].

Although the molecular mechanisms are not completely understood, the potential of metals to generate reactive oxygen species (ROS) and thus to alter cellular reduction–oxidation (redox) states is considered the most important mechanism involved in metal-induced carcinogenicity [11,13–16]. Recent research suggests that chronic exposure to ROS causes oxidative stress by disrupting the balance between the levels of ROS produced and the potential of cellular antioxidant systems to remove them. Prolonged and persistent oxidative stress causes changes in cellular redox homeostasis and leads to abnormal activation of redox-sensitive signaling molecules [17]. Oxidative stress also damages biomacromolecules, such as DNA, proteins, and lipids, and eventually induces a variety of chronic and degenerative diseases including cancer, cardiovascular disorders, diabetes, rheumatoid arthritis, and Alzheimer's and Parkinson's disease [18–20]. Most carcinogenic metals have been shown to produce the superoxide anion radical ($O_2^{\cdot-}$) and hydroxyl radical ($\cdot OH$) mostly via the Fenton reaction [8]. Metal-induced ROS production has also been implicated in the initiation of cellular injury and the stimulation of inflammatory processes, which can lead to cancer development [21]. Further, oxidative stress causes genetic and epigenetic changes, uncontrolled cell growth, and abnormal cellular signaling, all of which are primary mechanisms involved in metal-mediated carcinogenesis [22–24].

Accumulating evidence provides a correlation between metal-induced oxidative stress and increased cancer risk. Due to the increasing utilization of toxic metals in industry and medicine as well as their inefficient recycling, environmental accumulation of carcinogenic metals may result in subsequent increases in cancer incidence [8,25]. This makes understanding the relationships among metals, oxidative stress, and carcinogenicity of great interest. Such knowledge could improve risk assessment and the design of anticancer therapeutics. This review offers a brief overview of the current knowledge regarding oxidative damage

and carcinogenicity induced by metals. This review also covers recent evidence for the involvement of oxidative stress in the unregulated activation of redox-sensitive signal transduction and gene expression, especially in metal-induced carcinogenesis.

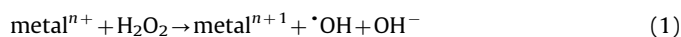
Metals and ROS generation

General sources of ROS production

Cellular ROS can be distinguished by whether they are endogenously or exogenously generated. The mitochondrial respiratory chain, the cytochrome P450 metabolic pathway, and the inflammatory response are important endogenous sources [26,27]. $O_2^{\cdot-}$, the simplest form of ROS, is produced from complexes I and III of the electron transport chain in mitochondria by the addition of one electron to molecular oxygen. The mitochondria produce approximately 2–3 nmol of superoxide/min per milligram of protein [28,29]. This radical reacts with cellular molecules to generate hydrogen peroxide (H_2O_2) as well as reactive radicals such as hydroxyl radicals ($\cdot OH$) and peroxy radicals ($ROO\cdot$) [28,29]. Xanthine oxidase (XO), a highly versatile enzyme, is also an important source of oxygen-free radicals [30]. XO catalyzes the reaction of hypoxanthine to xanthine and to uric acid by forming $O_2^{\cdot-}$ in the first step and H_2O_2 in the second step [30]. Immune cells including macrophages and neutrophils, as well as microsomes, generate intracellular ROS [31,32]. Peroxisomes are also capable of producing H_2O_2 , but not $O_2^{\cdot-}$, under physiological conditions [33]. In addition to these sources, various chemicals and xenobiotics, such as chlorinated compounds, metal ions, and radiation, are other important exogenous sources of cellular ROS generation. While the generation of ROS induced by endogenous sources is mostly related to normal metabolism and/or functions of immune cells, exogenous sources, especially metals, not only produce ROS directly and/or stimulate ROS generation by endogenous sources, but also have toxic and carcinogenic properties [8,11,15,22–25].

Common mechanisms of metal-mediated ROS generation

Metal ions produce intracellular ROS in a direct and indirect manner, where the Fenton-type reaction is one of the most well-known mechanisms. During this reaction, a transition metal ion reacts with H_2O_2 to generate the highly toxic $\cdot OH$ and an oxidized metal ion.



Many metals, such as Fe(II), Cu, Cr(III), (V), and (IV), Co(II), Ni(II), and V(IV), can generate free radicals via the Fenton-type reaction, although their abilities to generate free radicals differ [10]. While the efficiencies of Co(II) and Ni(II) to generate $\cdot OH$ are very low due to their high redox potentials, Fe(II) produces

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