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Role of metal and oxidative stress in mechanisms of Metal-induced cancer-A review

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Abstract: Humans have been in contact with metals almost since the beginning of our existence. In fact, one cannot even think on human evolution without considering the role played by metals in evolution. Consequently, the presence of a variety of metals is necessary for the normal functioning of cells and the survival of organisms. Metals play important roles in a wide variety of biological processes of living systems. Metal ion transporters participate in maintaining the required levels of the various metal ions in the cellular compartments. In order to avoid metal-related toxic effects, cells and organisms have evolved sophisticated mechanisms for sequestration and fine regulation of the available metal concentrations.

Keywords: Cancer; Oxidative stress, Metals, Iron.

Introduction:

Metals play important roles in a wide variety of biological processes of living systems. Metal ion transporters participate in maintaining the required levels of the various metal ions in the cellular compartments.[1]

Breakdown of metal-ion homeostasis can lead to the metal binding to protein sites different to those designed for that purpose or replacement of other metals from their natural binding.[2]The results have provided evidence that toxic metals can interact with DNA and proteins causing oxidative

deterioration of biological macromolecules. Thus the process of breakdown of metal-ion homeostasis has been involved in a plethora of diseases.[3-7] Metals are known to modulate gene expression by interfering with signal transduction pathways that play important roles in cell growth and development. Deregulation of cell growth and differentiation is a typical characteristic of the cancer phenotype. Actions of metals interfere with deregulation of cell proliferation by activating various transcription factors, controlling cell cycle progression and apoptosis.[8]

The generation of free radicals in living systems is closely linked with the participation of redox-active metals such as iron, copper, chromium and cobalt, the redox state of the cell is maintained within strict physiological limits.[9,10] Redox active metals may undergo cycling reactions participating in the transfer of electrons between metals and substrates and therefore may play an important role in the maintenance of redox homeostasis, a phenomenon tightly linked with metal homeostasis.[11] Disruption of metal homeostasis may lead uncontrolled metal-mediated formation of deleterious free radicals participating in the modifications to DNA bases, enhanced lipid peroxidation, and altered calcium and sulphydryl homeostasis.[12, 13]

Metal-induced oxidative stress and cancer:

Many studies have focused on metal-induced toxicity and carcinogenicity, emphasising their role in the generation of reactive oxygen and nitrogen species in biological systems. Metal-mediated formation of free radicals may cause various modifications to DNA bases, enhanced lipid peroxidation, and changes in calcium and sulphydryl homeostasis.[14-20]

1. Copper:

Copper is a cofactor of many enzymes involved in redox reactions, such as cytochrome c oxidase, ascorbate oxidase, or superoxide dismutase. It is used in biological systems for electron transport.[5] It is readily absorbed from the diet across the small intestine (~2mg/day) and stored in the liver. The major excretory route of copper stored in liver is via the biliary pathway (~80%).[21] Copper is bound to either serum albumin or histidine and trafficked through

the bloodstream for delivery to tissues or storage in the liver.[22]

Copper can induce oxidative stress by two mechanisms. First, it can directly catalyze the formation of ROS via a Fenton-like reaction.[23, 24] Second, exposure to elevated levels of copper significantly decreases glutathione levels.[25]

Because copper is an essential component of several endogenous antioxidant enzymes, and that free radicals have been proposed to play a role in the process of carcinogenesis, the effects of dietary copper levels on the development of cancer have been investigated.[26]

The weight of evidence from in vitro and in vivo assays indicates that copper (as the copper salts) is not genotoxic.[27] However, in vitro studies have shown that cancer cells in a high copper environment find it easy to proliferate into tumour.[28,29] Therefore, it has been proposed that copper-lowering drug may stabilise advanced cancer. Brewer and his group tested a drug known as tetrathiomolybdate (TM), which binds up dietary copper before it can be absorbed by the body, to see if they could reduce the spread of tumours in patients with different types of metastatic cancer. In five of six patients kept at 80% of normal copper levels for more than 90 days, existing tumours did not grow and new tumours did not form for more than 1 year. This suggests the use of TM either as the sole therapy for cancer or in conjunction with other treatments, such as surgery, chemotherapy, radiation therapy and others. Similarly to iron, copper is a well-known pro-oxidant and may participate in metal-catalyzed peroxidation of lipids.[30]

2. Chromium:

Chromium, one of the most common elements in the earth's exists in several oxidation states. [31] Chromium(III) is an essential trace element. It occures naturaly and plays an important role in regulating blood levels of glucose. Chromium(VI) is potentially toxic and carcinogenic at high doses.[32,33,34] All chromates, Cr(VI), can actively enter the cells through channels for the transfer of isoelectric and isostructural anions, such as those for $SO4^{2-}$ and $HPO4^{2-}$.[35] Certain extracellularly generated Cr(V) and Cr(III) complexes also have high permeabilities through the cell membrane. Once inside the cell, chromates are able to generate free radicals.[36] Cr(V) can also be reduced by cellular reductants (e.g.

ascorbate, GSH) to Cr(IV) (Fig. 1),[37] again participating in Fenton chemistry to generate a hydroxyl radical.[38]

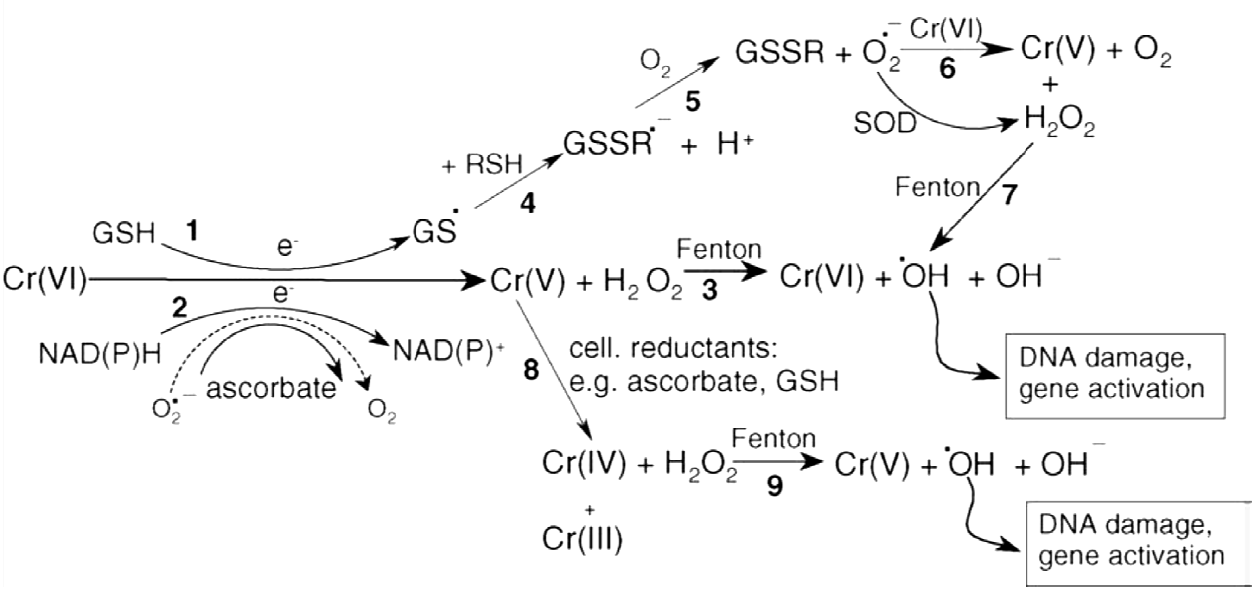

Figure 1: Biological reductants of Cr(VI) and its reactions

A series of detailed studies advocating a Cr(III)- dependent pathway in Cr(VI) carcinogenicity and mutagenicity was presented by Zhitkovich and his group who presented the evidence that intracellular reduction of Cr(VI) results in the extensive formation of Cr–DNA adducts, among which Cr(III)-mediated DNA cross-links of glutathione, cysteine, histidine and ascorbate represent a major class of DNA modifications.[39]

3. Iron:

Iron is vital for life. It can be toxic when it is present in excess. Iron homeostasis is a complex process, as there are many different proteins that respond not only to the total body burden of iron, but also to stimuli such as hypoxia, anemia and inflammation.[40] Increased levels of iron in the body cause an enhanced risk of a variety of diseases including vascular disease, cancer and certain neurological conditions. [41, 42] Iron-mediated formation of ROS leading to DNA

and lipid damage appears to result from an exaggeration of the normal function of iron, which is to transport oxygen to tissues. Iron-induced free radical damage to DNA appears to be important for the development of cancer and cancer cells are known growrapidly in response to iron. [43]

Many studies documented that mutations in superoxide dismutase enzymes[44] and iron-uptake regulator may lead to excess levels of superoxide anion radicals and iron overload. Such a condition leads to the possibility of redox active iron to participate in organic and inorganic oxygen radical reactions, such as stimulating lipid peroxidation and catalyzing the formation of damaging hydroxyl radicals with subsequent tissue damage.[45]

Nelson and Babbs proposed that intestinal exposure to ingested iron may be a principal determinant of human colorectal cancer in highly developed, meat-eating countries.[46, 47] The bile acids (deoxycholic acid), the K vitamins, iron(II) complexes and oxygen interact to induce an oncogenic effect in the colon by the generation of free radicals.[48] The association between elevated body iron stores and the development of hepatocellular carcinoma in subjects with ironoverload unrelated to genetic hemochromatosis along with the experimental evidence of a co-carcinogenic role of iron strongly support the contention that iron is involved in the development of hepatocellular carcinoma.[49, 50] Occupational exposure to asbestos containing about 30% (weight) of iron is relate to an increased risk of asbestosis — the second most important cause of lung cancer after smoking.[51] Intramuscular injections of an iron–dextran complex, frequently used for the treatment of anemia in humans, caused spindle cell sarcoma or pleomorphic sarcoma in rats at the site of injection.[52]

Permanent modification of genetic material resulting from free radical attacks represents the initial step involved in mutagenesis, carcinogenesis and ageing.[53] In fact, as it has been well documented, in various cancer tissues free radical-mediated DNA damage has occurred.[54]

4. Cobalt:

Various studies have investigated the possibility that cobalt-mediated free radical generation contributes to the toxicity of cobalt. Hanna et al. performed EPR spintrapping studies to detect the generation

of oxygen-free radicals from the reaction of hydrogen peroxide with various Co complexes under physiological conditions.[55] Cobalt is known to be toxic to the heart and suspected to be carcinogenic in animals when given in large quantities. Exposure to cobalt sulphate by inhalation resulted in increased incidence of alveolar/bronchiolar neoplasms and a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tracts of male and female rats and mice.[56] Injection of Co(II) into rats lead to a pattern of oxidative DNA base damage characteristic of hydroxyl radical attack via the Fenton reaction.[57] Trace amounts of cobalt are needed in the diet because cobalt is an integral metal of vitamin B12.[58]

5. Cadmium:

Cadmium is a heavy metal and the most common oxidation number of cadmium is +2. Food is the main source of cadmium for the non-smoking population. Estimates of dietary cadmium intake worldwide range from 10–40g/day in nonpolluted areas to several hundred micrograms in cadmiumpolluted regions.[59]

Cadmium is a highly toxic metal. Cadmium itself is unable to generate free radicals directly, however, indirect generation of various radicals involving the superoxide radical, hydroxyl radical and nitric oxide has been reported.[60] Some experiments also confirmed the generation of (non-radical) hydrogen peroxide which itself in turn may be a significant source of radicals via Fenton chemistry.[61]

Cadmium is a potent human carcinogen and occupational exposure to it has been associated with cancers of the lung, the prostate, pancreas and kidney. Cadmium also used in the pathogenesis of human pancreatic cancer and renal carcinoma.[62]

6. Arsenic:

Arsenic, known as a poison and has been discovered to be a carcinogen in humans. Many studies confirmed the generation of free radicals during arsenic metabolism in cells.[63] In recent studies concerning the mechanism of arsenite toxicity in the brain it was reported that some of its effects have been traced to the generation of the hydroxyl radicals.[64] Arsenic is a well-established human carcinogen.[65] Arsenic compounds bind to SH groups and can inhibit various enzymes, including glutathione reductase

radiation, to cause DNA mutations more effectively.[66]

Arsenic is known to induce hypoxia signalling pathways. For example in prostate cancer cells treated with arsenite induced HIF-1alpha expression in a concentration- and time-dependent manner, whereas the level of HIF-1beta remained unaffected.[67]

Arsenic is a well-documented carcinogen in a number of studies.[68] Chronic exposure to inorganic arsenic from contaminated water is responsible for various adverse health effects such as developing tumours of the lung, skin, liver, bladder and kidney. Skin lesions, peripheral neuropathy and anemia are hallmarks of chronic arsenic exposure. Arsenic is also a potential risk factor for atherosclerosis. While cardiovascular disorders following oral exposure to arsenic are well documented, there is some evidence from epidemiological trials that also inhaled inorganic arsenic can affect the cardiovascular system.[69]

7. Nickel:

Nickel is a human carcinogen that can alter gene expression by enhanced DNA methylation and compaction, rather than via mutagenic mechanisms.[70] The nickel compounds implicated as potential carcinogens are insoluble dusts of nickel subsulphides and nickel oxides, the vapor of nickel carbonyl, and soluble aerosols of nickel sulphate, nitrate, or chloride.[71] Almost all cases of acute nickel toxicity result from exposure to nickel carbonyl. Patients with severe poisoning develop intense pulmonary and gastrointestinal toxicity. The lung is the primary target organ for nickel toxicity in humans.[72]

Some other studies have shown that workers' inhalation of nickel refinery dust, which contains nickel subsulphide, has resulted in increased numbers of deaths from nasal cavity cancers, and possibly cancer of the larynx.[73]

8. Vanadium:

Vanadium is a transition metal element which occurs in various oxidative states and may participate in reactions involving formation of free radicals.[74] Vanadium in plasma is rapidly reduced to vanadium by both enzymatic (e.g. NADPH) and non-enzymatic (ascorbic acid) plasmatic antioxidants and is then transported and bound to plasma proteins.[75] The use of vanadium compounds as inhibitors of

tyrosine phosphatases in studies of signal transduction points to their potential to induce oxidative stress.[76]

9. Zinc:

Zinc is a ubiquitous trace element found in plants and animals. The adulthumanbody contains approximately 1.5–2.5 g of zinc, present in all organs, tissues, fluids and secretions. The level of free intracellular Zn(II) is as low as 0.5 nM, as estimated from measurements of the zinc-specific 19F-NMRsignal of a fluorinated metal chelating probe.[77]

The observations performed in 1961 on Iranian males have shown that zinc deficiency may cause growth retardation and hypogonadism in humans.[78] Following studies later showed that zinc was essential for humans and that zinc deficiency was prevalent in the Middle East.[79] Zinc deficiency has been associated with increased levels of oxidative damage including increased lipid, protein and DNA oxidation.[80] The zinc-supplemented group of patients with sickle cell disease had decreased incidences of infection in comparison to the placebo group.[81] After zinc supplementation, antioxidant power increased. In addition, plasma nitrite and nitrate (NOx), lipid peroxidation products, DNA oxidation products, and soluble vascular cell adhesion molecule-1 (VCAM-1) decreased compared to the placebo group.

Since oxidative stress and chronic inflammation may play important causative roles in many chronic diseases, including atherosclerosis, cancers, neurological disorders, and autoimmune diseases, more thorough studies exploring the status of zinc deficiency and supplementation are necessary.

10. Lead:

Lead is one of the heavy metals. It is a persistent metal and because of its unusual physical–chemical properties it is used in various industrial applications.[82] Well known is its use as a radiation shield. Lead is a toxic metal to humans and animals and its persistency causes prolonged occurrence in the environment – in water, soil, dust and in manufactured products containing lead. Since young organisms bear the heaviest burden of sensitivity to lead exposure, lead-based paint covers represent a serious health threat to children worldwide.[83] Soil containing lead also represents a serious

hazard for children. Gastrointestinal absorption of lead is higher in children (40–50%) than in adults (3–10%). Lead toxicity is most commonly diagnosed through elevated blood levels. Blood levels of 10g/dL (equivalent to 0.48mol/L) or higher are considered toxic and result in neurological disorders, cognitive impairments, hypertension and other disorders.[84]

Conclusions:

The current knowledge in the field of metallo-biochemistry of oxidative stress indicates that metal-induced and metal-enhanced formation of free radicals and other reactive species can be regarded as a common factor in determining metal-induced toxicity and carcinogenicity. The above discussion provides an insight into the role of metals capable of direct or indirect generation of free radicals through various mechanisms.

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