Metal – genotoxicity and carcinogenicity

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By understanding the mechanisms involved in the genotoxicity and carcinogenicity in considerable detail we can predict the final outcome of exposure (Table I). Each metal has a unique mechanism of action and thus it is inappropriate and misleading to discuss metal carcinogenesis under one heading. Recent studies have shown the capacity of metal carcinogens to cause oxidative damage to DNA, to inhibit repair, to produce strand breaks both in vivo and in cell culture, and to cause chromosomal alterations. The following metals have been identified as human carcinogens, which induce mutation and abnormal gene expression, as well as abnormal cellular differentiation.

Chromium (Cr)
Chromium was the first metal suspected to be a human carcinogen in the late nineteenth century when epidemiological studies linked nasal tumours in Scottish chrome workers with chromium exposure. Since then, other chromium industries, including leather tanning, chrome plating and stainless steel production, have been implicated as potential sources of human occupational exposure to chromium.

The carcinogenicity of chromium with a hexavalent oxidation exists as an oxyanion at physiological pH and is believed to be transported into the living cells via the sulphate anion transport system. Inside the cell it is reduced to trivalent chromium eg. by thiol such as glutathione and cysteine and cytochrome P.450. After absorption, trivalent chromium is transported mainly bound to transferrin in plasma, while hexavalent chromium is partly taken up by erythrocytes, which forms adducts with DNA and the protein.

Trivalent chromium does not readily induce genotoxic effects, due to its poor uptake into living cells. However, reduced Cr(III) can alter the fidelity and kinetics of DNA replication such that the processivity is increased and fidelity is decreased. As demonstrated in Figure 1, it is the reduction of the Cr(VI) and the formation of their reactive intermediates that are thought to be the most significant genotoxins. Numerous cellular reductants including, but not limited to cytochrome P.450, NADH, glutathione (GSH), ascorbate (vit.C), cysteine, NADPH etc. are capable of reducing chromate in vitro. Chromium reduction intermediates may ultimately be genotoxic by mechanisms that eventually involve hydroxyl or thiolyl radicals.

Nickel (Ni)
The carcinogenic potency of all nickel compounds is directly related to their ability to enter cells. Water soluble nickel salts do not readily enter cells. However, recent studies have shown an increase in nickel compound related carcinogenic effects. Smelting of nickel results in the production of a nickel iron sulphide matrix that contains a high concentration of potential carcinogen, crystalline nickel subsulphide. Exposure to these compounds causes a high incidence of nasal and pharyngeal cancers. The potent carcinogenic activity of the nickel sulphide particles is due to their ability to enter cells by phagocytosis. Once nickel ions accumulate inside the cells, they bind to various peptides and amino acids which in turn lowers the oxidation potential, and generates oxygen radicals that produce damage to cells.

Recent studies have shown that Ni²⁺ can inactivate the transcription of a number of genes, presumably by inducing hypermethylation of the promoter. The mechanisms involved remain very unclear. However, the ability of nickel to turn off the transcription of selected genes if a tumour suppressor or a senescence gene is inactivated no doubt is very important in its carcinogenic action. It is interesting that nickel is synergistic at many cancer, mutagenic or genotoxic endpoints where exposure occurs together with many other types of carcinogens, such as UV light, X-rays, alkylating agents and benzopyrene, suggesting that nickel has a unique mechanism of action that is different from the effects of these other agents.

Cadmium (Cd)
Cadmium is a toxic transition metal of continuing occupational and environmental concern. Over the last 15 years, the genotoxic effect of Cd has been studied. Unfortunately, no consensus on how Cd induces genetic damage has yet emerged. At least three different hypotheses regarding this metal’s mode of action currently exist.

i. Cadmium may interact directly with chromatin to induce strand breakage, cross-linking or conformational changes in DNA.

ii. Cadmium may act indirectly, by inhibiting various proteins involved in DNA repair.

iii. Cadmium may act by catalysing cellular redox reactions whose by-products subsequently produce strand breaks, cross-links or covalent adducts in DNA.

It is, however, widely believed that proteins involved in regulating eukaryotic gene expression are composed of specific amino acid “motifs” which allow the protein to recognize particular regions of DNA. One of these “motifs” is the Zinc-finger loop. Proteins known to contain this motif include oncogene

Continued on page 15

<table>
<thead>
<tr>
<th>Metal</th>
<th>Exposure route</th>
<th>Tumour location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni</td>
<td>Pyrometallurgy, hydrometallurgy, electroplating/inhalation</td>
<td>Lung and sinonasal cancer</td>
<td>IARC 1990</td>
</tr>
<tr>
<td>Cr</td>
<td>Aromatic and chromate pigment production, chromium plating/inhalation</td>
<td>Lung and sinonasal cancer</td>
<td>IARC 1990</td>
</tr>
<tr>
<td>As</td>
<td>Production and use of arsenic trioxide and its derivatives/inhalation, skin and oral exposure</td>
<td>Lung, skin, gastrointestinal cancers, precancerous dermal keratoses</td>
<td>Sunderman 1984, Lawreys 1980</td>
</tr>
<tr>
<td>Cd</td>
<td>Production/inhalation</td>
<td>Lung</td>
<td>IARC 1994</td>
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Figure 1. Illustration of the mechanism of carcinogenicity and detoxification of chromium (vi)

Figure 2. The absorption pathway of cadmium and major organs of accumulation

(1) Cadmium decreases PTH stimulation of adenylcyclase
(2) Cadmium inhibits hydroxylation of 25-OH-D3
(3) Cadmium increases urinary calcium absorption
(4) Cadmium decreases gastrointestinal calcium absorption
(5) Cadmium affects bone mineralization directly.
CABP: Calcium binding protein
Continued from page 13

products, transcription coupling factors and enzymes involved in DNA repair.

It is quite conceivable that cadmium may exert genotoxicity by substituting for zinc in these proteins thus forming coordination complexes with thio-sulphur and imidazole-nitrogen atoms, thereby altering the conformation of the protein’s active site or via free radical formation, damaging specific regions of the genome that are critical for proper replication and/or differentiation of cells.

Figure 2 demonstrates the pathobiologic path cadmium influences after gastrointestinal absorption. Cadmium accumulates primarily in the liver and kidney where it is bound to metal. A low molecular weight metal protein is thought to detoxify the metal through high-affinity sequestration.

As cadmium often interferes with various zinc metabolic processes, a zinc treatment frequently reduces or abolishes the effects of cadmium intoxication.

ARSENIC (As)

Arsenic has long been thought to contribute to the incidence of human cancer. The major evidence for arsenic as a human carcinogen came from studies of lung cancer in arsenic ore smelters and skin cancer in people exposed to arsenic-containing drinking water. Although it has been 100 years since the carcinogenic properties of arsenic were first suggested, it is still uncertain whether inorganic arsenic causes cancers other than of skin and lung. Most of the studies on the genotoxic activity of arsenic compounds have yielded negative results for gene mutation, but positive results for chromosomal damage.

Nongenotoxic indirect carcinogens have a variety of stress-related effects that ultimately induce or effect the expression of genes controlling proliferation and differentiation. Trivalent arsenic may activate nuclear oncogenes at a certain threshold concentration, perhaps via its ability to bind to vicinal dithiols within the protein, or to bridge two thiols between two proteins as demonstrated in Figure 3.

The mechanism for the threshold activation concentration is partly controlled by the metabolism and detoxification of inorganic arsenic via methylation to less toxic metabolites, which are excreted from the body more efficiently than inorganic arsenic as demonstrated in Figure 3. The methylation process for arsenic begins to be effected at a daily intake rate of approximately 200–250 µg/day. The methylation capacity is limited by saturation of the enzymatic conversion of monomethylarsonic acid (MMA) to dimethylarsonic acid (DMA) and the inhibition of nonenzymatic conversion of trivalent arsenic to MMA by excess trivalent arsenic. However, the methylation threshold hypothesis has recently been challenged. It is concluded that regardless of the exposure level, the level of unmethylated inorganic arsenic is approximately 20% of the absorbed dose. Thus an additional threshold mechanism must be involved in the toxic effect of inorganic arsenic.

SUMMARY AND CONCLUSION

In the past 10 years, a great deal of knowledge has accumulated showing the influence of metal on the process of carcinogenesis. Among the major findings of these investigations are the following. The physiologically essential metals, particularly Mg and Zn, often counteract the activities of the carcinogenic heavy metals. Another mechanism is the induction of protective proteins serving as alternate targets to DNA for heavy metal ions. Both Zn and Ca have exerted significant protection against classical organic carcinogens by mechanisms which are not yet well understood.

Overall, carcinogenic metal derivatives are multipotent reagents capable of interacting with almost any cell constituent, including physiological metals, causing a plethora of damaging effects in mammalian genome. However, without excluding the contribution of other effects, oxidative damage seems to be slowly taking the leading role in explaining mechanisms of cancer causation and acute toxicity by other metals.

REFERENCES


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