Workplace Carcinogens: Metals
Part I: Mechanism of carcinogenesis

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INTRODUCTION

Exposure to heavy metals represents a significant health concern in the workplace. These metals have the ability to induce a number of adverse health effects but their role in carcinogenesis is of most concern.[1] Metals as workplace carcinogens will be discussed in two parts. Part I will focus on the mechanism of carcinogenesis, and Part II will focus on oxidative stress and the role that antioxidants can play in the prevention of occupational cancer.

MECHANISM OF CARCINOGENESIS

Carcinogenesis is a multi-sequence, complex process, changing a cell from a healthy to a precancerous state and, finally, to an early state of cancer. There are different theories of carcinogenesis.[2] Old theories describe cancer as a disease of cell differentiation or stem cell disease – this points to a single cell origin of cancer. More recently, two key mechanisms have been proposed for the induction of cancer:

1. Increased DNA synthesis and mitosis by non-genotoxic carcinogens may include mutations in dividing cells through misrepair, causing neoplasia.[2] A non-genotoxic carcinogen represents a chemical that is capable of producing cancer by some secondary mechanism not related to direct gene damage.[3]
2. Lack of equilibrium between cell death and proliferation.
   In humans, many physiological processes require a balance between cell death and cell growth, and changes in the rate of cell death can contribute to either the loss or gain of tissue. Cell proliferation is the process that results in an increase in the number of cells.
   - **Cell death (apoptosis):**
     Apoptosis plays an important role in many physiological processes, such as embryo development and aging. Uncontrolled apoptosis can be harmful, leading to the destruction of healthy cells in diseases such as Parkinson Disease or Alzheimers.[4] If the DNA damage by genotoxic agents is too great, the process of apoptosis eliminates altered cells selectively. This programmed suicide mechanism leads to many morphological changes.[2]
   - **Cell proliferation:**
     During normal cell proliferation, the tumour suppressor, protein p53, triggers mechanisms that eliminate the oxidised DNA bases that cause mutations. When the cell damage is too great, p53 triggers cell death.[2] Mutations in the gene encoding p53 result in increased proliferation instead of apoptosis of these genetically damaged cells. Mutations in the gene encoding p53 is found in half of all human tumours.[5]

Agents that damage DNA can be classified as follows:[6]

- Endogenous agents: by-products from processes such as metabolism or inflammation
- Exogenous agents: present in food, water, or air
- Physical agents: ultraviolet (UV) light and ionising radiation
- Reactive oxygen species (ROS)
- Intercalating agents: substances that inserts themselves into the DNA structure of a cell and bind to the DNA, causing DNA damage. In cancer treatment, DNA intercalating agents may kill cancer cells by damaging their DNA and stopping them from dividing[7]
- Alkylating agents: types of drugs that are used in the treatment of cancer; they interfere with the cell's DNA and inhibit cancer cell growth[7]
- Base analogues: chemicals that are structurally similar to the bases found in DNA

The carcinogenic process can be described as the imbalance between cell proliferation and cell death – shifting towards cell proliferation. It is a multi-stage process, comprising three stages: initiation, promotion and progression (Figure 1).[2]

Initiation involves a non-lethal mutation in DNA that produces an altered cell followed by at least one round of DNA synthesis to fix the damage. Oxidative DNA damage can occur via action of ROS to induce oxidative stress. This process further proceeds through oxidative stress-induced calcium changes.[2]

The promotion stage is characterised by the clonal expansion of initiated cells by cell proliferation and/or inhibition of apoptosis to form a focal lesion. This is a reversible process as this stage is dose-dependent on the tumour promoter. Several tumour promoters have an inhibiting effect on antioxidants, which are molecules that prevent oxidation. Oxidation is a process that produces free radicals, which can be harmful to cells. A high level of oxidative stress is cytotoxic as it halts cell division by inducing apoptosis, while a low level of oxidative stress can cause the opposite by stimulating proliferation during the promotion stage, thus stimulating the promotion of tumour growth. The production of ROS during this stage is the main line of ROS-related tumour promotion.[2]

The third and final stage in carcinogenesis is the progression stage. It involves molecular and cellular changes in the pre-neoplastic and neoplastic states. This stage is characterised by the disruption of chromosomal integrity and genetic instability – leading to the transformation of the cell from benign to malignant. This stage is irreversible.[2]

METALS AND OXIDATIVE STRESS

Nickel (Ni), chromium (Cr), cadmium (Cd) and arsenic (As) are some of the most widely studied heavy metals for their roles in causing oxidative stress.[8] These metals are classified as Group 1 human carcinogens according to the International Agency for Research on Cancer.[9] The major cancer sites are lung, bladder, skin, nasal cavity and sinuses (Figure 2). With environmental

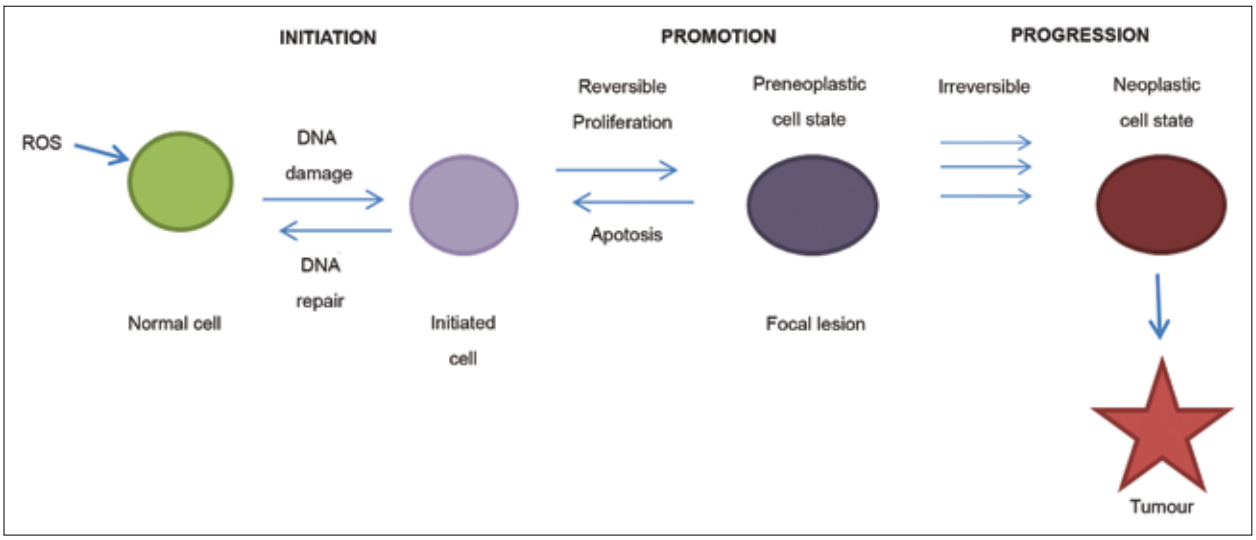

Figure 1. The three stages of carcinogenesis

pollution causing excessive exposure to these heavy metals, occupational exposure adds to the body burden of eliminating the hazardous effects of these metals. Methods to detoxify these metals should be investigated and implemented as part of a medical surveillance program.

Part II in this series will focus on oxidative stress and the role that antioxidants can play in the prevention of occupational cancer.

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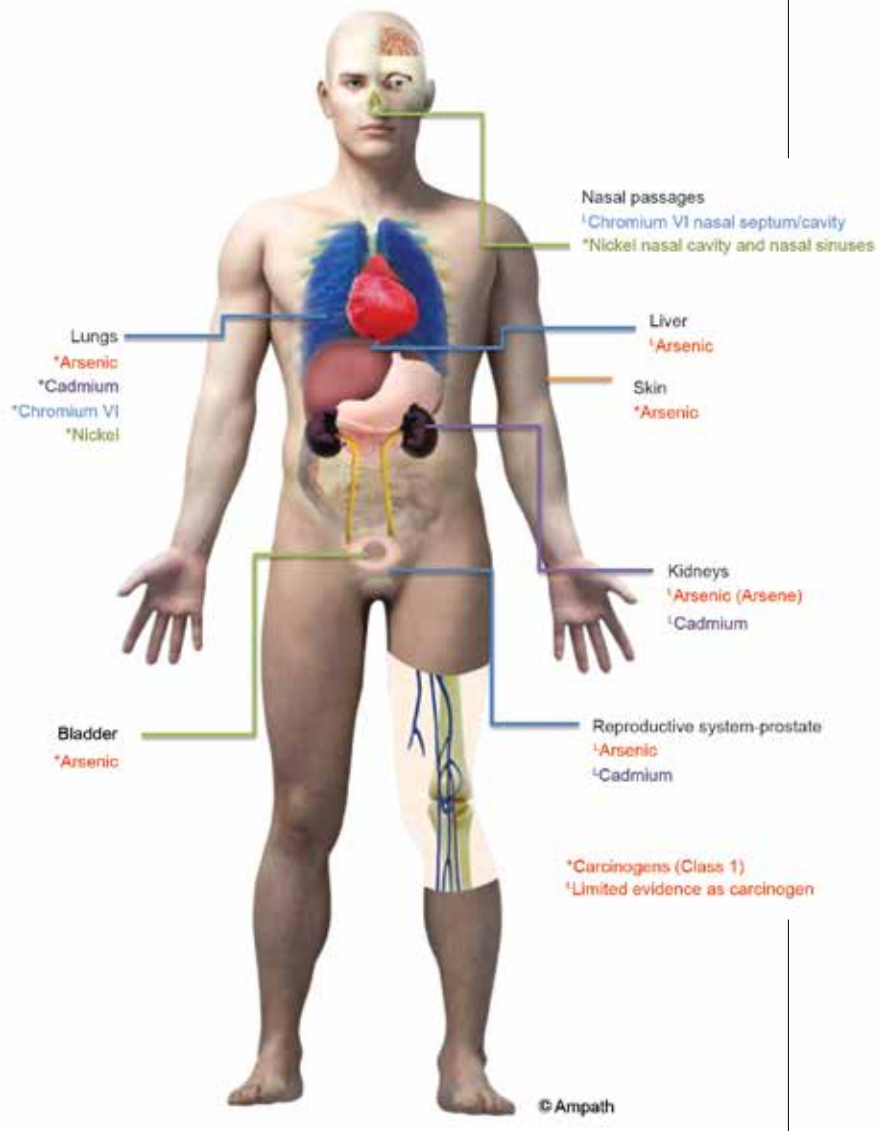

Figure 2. Workplace carcinogen: Metals