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Epigenetic Mechanisms in Metal Carcinogenesis (Article Review)

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Abstract

Although carcinogenic metals have been demonstrated to disrupt a number of biological processes, the precise mechanism by which they cause cancer is uncertain. Research over the past decade or so suggests that epigenetic mechanisms may play a role in metal-induced carcinogenesis. This paper compiles evidence that exposure to carcinogenic metals, including nickel, arsenic, chromium, and cadmium, can change worldwide and gene-specific histone tail posttranslational modification marks and DNA methylation levels. Additionally, we would like to stress the significance of comprehending that both genetic and epigenetic mechanisms can regulate gene expression, and that both of these need to be taken into account when researching the mechanisms behind the toxicity and cell-transforming potential of carcinogenic metals and other toxicants, as well as aberrant changes in gene expression that take place during disease states like cancer.

Key words: DNA, Cancer, metal, Active

Introduction

In metal-induced carcinogenesis, epigenetic processes are crucial because they alter gene expression without altering the DNA sequence. Lead (Pb), nickel (Ni), chromium (Cr), arsenic (As), and cadmium (Cd) are among the many known hazardous metals. to induce epigenetic modifications that contribute to cancer development. The major epigenetic mechanisms involved include:

1. DNA Methylation

- **Global Hypomethylation:** Many metals cause worldwide DNA hypomethylation, important to genomic variability and start of oncogenes.
- **Promoter Hyper methylation:** Metals like nickel and arsenic induce hypermethylation of tumor suppressor gene promoters (e.g., p16, RASSF1A), leading to gene silencing and uncontrolled cell proliferation.

2. Histone Modifications

- Metals disrupt histone methylation, acetylation, and phosphorylation, altering chromatin structure and gene expression.
- **Nickel** inhibits histone demethylation, leading to persistent gene silencing.
- **Arsenic** reduces histone acetylation, repressing tumor suppressor genes.

3. Non-Coding RNAs (ncRNAs)

- MicroRNAs (miRNAs) play a key role in metal-induced carcinogenesis by regulating gene expression.
- **Cadmium and arsenic** deregulate miRNAs complicated in apoptosis, cell series switch, and DNA overhaul, promoting growth progression.

4. Chromatin Remodeling

- Metals interfere with chromatin-modifying enzymes, leading to altered chromatin accessibility.
- Changes in chromatin structure can either promote oncogene activation or suppress tumor suppressor genes.

Implications for Cancer Therapy

Understanding these epigenetic alterations provides potential targets for cancer prevention and therapy. Drugs targeting DNA methylation (e.g., 5-azacytidine) or histone modifications (e.g., histone deacetylase inhibitors) could reverse metal-induced epigenetic changes.

Epigenetic Carcinogenesis refers to the part of epigenetic changes now the development and evolution of tumor. Unlike genetic mutations, epi genetic modifications do not adjust the DNA order but affect gene expression, often leading to tumor formation and progression.

Key Epigenetic Apparatuses in Tumor

1. **DNA Methyliation**
    - Hypermethylation of growth suppressor genetic factor (e.g., *p16*, *MLH1*) leads to gene silencing.
    - Hypomethylation of oncogenes and repetitive DNA sequences results in genome instability and activation of cancer-related genes.
2. **Histone Changes**
    - Aceitylation, methyliation, phosphorylatian, and ubiquitination of histones can either activate or repress gene expression.
    - Aberrant histone alterations can stillness tumor suppressor DNA segment or start oncogenes.
3. **Non-Coding RNAs (ncRNAs)**

- MicroRNAs (miRNAs) can function as oncogenes or tumor suppressors by regulating target gene expression.
- Long non-coding RNAs (lncRNAs) influence chromatin structure and gene regulation in cancer.

Role of Epigenetic Changes in Cancer Development

- **Initiation**: Epigenetic changes silence DNA repair genes, leading to accumulation of mutations.
- **Promotion**: Oncogene activation and tumor suppressor gene inactivation drive abnormal cell growth.
- **Progression**: Epigenetic instability contributes to metastasis and drug resistance.

Epigenetic Therapy in Cancer

Since epigenetic changes are reversible, they serve as targets for cancer treatment. Some FDA-approved epigenetic drugs contain:

- **DNA Methyl transferase Inhibeitors (DNMTi)**: Azaciitidine, Gemcitabine.
- **Histone Deacietylase Inhibetors (HDACi)**: Voriinostat, Romiidepsin.

These therapies aim to restore normal gene expression patterns, making them promising for treating various cancers.

A. Lead

Lead is a well-known environmental toxin and carcinogen, and its part in carcinogenesis (the course by which usual cells are distorted into growth cells) has been studied extensively. Chronic exposure to lead, even at low levels, can have serious health consequences, including an increased risk of cancer. Here's an overview of how lead contributes to carcinogenesis:

Mechanisms of Lead-Induced Carcinogenesis

1. **Generation of Reactive Oxygen Species (ROS)**:
   - Lead exposure can bring oxidative pressure by making reactive oxygen class (ROS).
   - ROS can harm DNA, proteins, and fats, leading to mutations then genomic instability, which are key drivers of cancer development.
2. **DNA Damage and Inhibition of DNA Repair**:
   - Lead can directly or indirectly cause DNA damage, such as strand breaks and base modifications.
   - It also interferes with DNA overhaul mechanisms, creation cells extra susceptible to gathering mutations.
3. **Epigenetic Changes**:

- Lead exposure can alter epigenetic regulation, such as DNA methiylation and histone alteration.
- These changes can lead to the activation of oncogenes or the silencing of tumor suppressor genes.

B. Nickel

Nickel besides certain nickel mixes are confidential as **carcinogenic** to persons by the **Worldwide Agency for Enquiry on Tumor (IARC)** and other controlling bodies. Here's a breakdown of the carcinogenic potential of nickel:

1. IARC Classification

- **Nickel mixes**: Confidential as **Cluster 1** (carcinogenic to persons).
- **Iron nickel**: Secret as **Cluster 2B** (perhaps carcinogenic to persons).

They IARC has concluded that exposure to nickel compounds, particularly in work-related settings, is related with an increased danger of lung tumor and nasal growth.

2. Mechanism of Carcinogenicity

- Nickel can reason DNA injury and oxidative stress, leading near mutations and cancer development.
- It can also disrupt cellular courses, such as DNA overhaul mechanisms, and promote tumor growth.

3. Routes of Exposure

- **Inhalation**: The main route of contact in working settings (e.g., mining, refining, welding, and battery manufacturing).
- **Skin contact**: Nickel is a common allergen and can cause contact dermatitis, but skin exposure is not strongly linked to cancer.
- **Ingestion**: Less common, but possible through contaminated food or water.

C. Radium

Radium is a highly radioactive element and is well-known for its **carcinogenic** properties. It emits **alpha particles**, which can cause significant damage to living tissues, leading to cancer. Here's an overview of radium's carcinogenicity:

1. IARC Classification

- Radium and its isotopes (e.g., Radium-226, Radium-228) are secret as **Group 1** (carcinogenic to persons) by the **Global Agency for Research on Growth (IARC)**.

2. Mechanism of Carcinogenicity

- Radium emits **alpha radiation**, which is highly damaging to DNA and other cellular structures.
- When radium is ingested or inhaled, it accumulates in bones (because it behaves similarly to calcium), where it continues to emit radiation.
- This prolonged exposure to radiation can lead to mutations, uncontrolled cell growth, and ultimately cancer, particularly **bone cancer** (osteosarcoma) and **cancers of the head and sinuses**.

- **D. Arsenic**

Arsenic is a well-known **carcinogen** and is classified as such by major fitness organizations, with the **Worldwide Agency for Research on Tumor (IARC)**. Contact to arsenic, particularly **inorganic arsenic**, is strongly allied to several kinds of cancer. Here's a detailed overview:

1. IARC Classification

- **Inorganic arsenic mixes**: Confidential as **Cluster 1** (carcinogenic to persons).
- **Organic arsenic compounds**: Generally considered less toxic, but some forms may still pose health risks.

2. Mechanism of Carcinogenicity

- Arsenic interferes with cellular processes, including DNA repair and methylation, leading to genetic mutations.
- It generates **sensitive oxygen class (ROS)**, which reason oxidative pressure and damage to DNA, proteins, and fats.
- Arsenic can also disrupt cell signaling pathways, promoting uncontrolled cell growth and cancer development.

3. Routes of Exposure

- **Drinking water**: The most common source of exposure, especially in areas with naturally high levels of arsenic in groundwater (e.g., Bangladesh, India, parts of the U.S.).
- **Food**: Contaminated crops irrigated with arsenic-laden water (e.g., rice).
- **Occupational exposure**: Workers in industries like mining, smelting, and pesticide manufacturing.
- **Air**: Inhalation of arsenic-containing dust or fumes in polluted areas or workplaces.

- **E. Beryllium**

Beryllium is a lightweight metal that is classified as a **carcinogen** due to its ability to cause cancer, particularly **lung cancer**, in humans. Here's a detailed overview of beryllium's carcinogenic properties:

1. IARC Classification

- Beryllium and beryllium compounds are secret as **Group 1** (carcinogenic to people) by the **Universal Agency for Exploration on Growth (IARC)**.

2. Mechanism of Carcinogenicity

- Beryllium exposure can chief to **chronic irritation** then **immune system activation**, which contribute to cancer development.
- It causes **DNA damage** and **chromosomal abnormalities** by generating reactive oxygen species (ROS).
- Beryllium particles, when inhaled, can persist in the lungs, leading to long-term tissue damage and increased cancer risk.

3. Routes of Exposure

- **Inhalation**: The chief route of contact, especially in working settings. Beryllium particles can be inhaled during machining, grinding, or other processes that generate dust or fumes.
- **Skin contact**: Less common, but beryllium can cause skin irritation or sensitization.
- **Ingestion**: Rare, as beryllium is poorly absorbed through the digestive system.

4. Types of Cancer Linked to Beryllium Exposure

- **Lung cancer**: The most well-documented cancer associated with beryllium exposure.
- **Other cancers**: Some studies suggest a potential link to other cancers, but the evidence is less conclusive.

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