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Editorial

Cadmium Induced Carcinogenesis: A Molecular Preview

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Study of toxicology is an important science field that helps to understand the impact of harmful substances and pollutants towards human diseases. Environmental toxicology focuses on the occurrence, exposure and the form of toxicants in the environment and its impact on living organisms. Several different compounds / substances are regarded as toxicants or pollutants that affect the organisms directly or indirectly. One such toxicant is Cadmium (Cd), listed as one of the 126 priority pollutants and a category I carcinogen according to International Agency for Research on Cancer (IARC). Cd, a metallic element is one of the naturally occurring components in the earth's crust and waters. It is also released to the atmosphere from both natural sources and anthropogenic activities (mainly industries, fossil fuel combustion). Cd has a half-life longer than 30 years and this explains the ineffective Cd elimination pathway in humans. Numerous reports have revealed significant correlations that exist between long-term exposure (environmental and occupational) of Cd with an increased risk of prostate, genitourinary, breast, lung and colon cancers in humans.

The incidence and the mortality rates of prostate cancer have been steadily increasing till date. Chronic exposure of Cd to normal epithelial cells cultured *in vitro* transforms them to malignant cells, and this is further confirmed in animal models. At higher concentrations of Cd exposure, biosynthesis of DNA, RNA, and protein is inhibited. Although direct interaction of Cd with DNA is very minimal, it may act indirectly through epigenetic mechanisms by altering the signaling events upstream of DNA repair and apoptosis. Inhibition of DNA repair by Cd is also likely to play an important role in Cd-induced carcinogenesis. Thus, Cd is capable of inhibiting DNA repair on various levels and leads to genomic instability, which is associated with tumorigenesis.

Cd has multiple molecular targets and thus, Cd-induced prostate cancer is likely to develop through more than one signaling pathway. Cd can affect cell proliferation and differentiation, cell cycle progression, DNA synthesis and repair, apoptosis and other cellular activities and also it inhibits DNA repair in various *in vitro* models of prostate cancer.

Clinical study have reported higher concentrations of Cd in breast samples despite any significant difference in Cd levels between breast cancer patients and healthy controls, revealing the presence of Cd binding proteins in human breast tissue. However, this study fails to determine whether Cd is a major source for the etiology of breast cancer. Molecularly, Cd mimics estrogen and acute exposure to Cd is known to promote estrogen receptor (ER)-mediated pro-survival signaling and cell growth. Hence, Cd is often referred to as a metalloestrogen. However, the role of Cd acting on ER as part of a mechanism for carcinogenesis in breast remains unclear.

Epidemiological studies suggest that occupational and environmental exposure to Cd induces lung cancer in rodents as well as in humans. Chronic inhalation of Cd causes pulmonary adenocarcinomas in animal and in exposed human cell lines. Prolonged exposure of normal bronchial epithelial cells to Cd *in vitro* causes them to transform to a malignant state, and a similar observation was noted in a nude mouse model. Although the mechanisms of Cd-induced pulmonary carcinogenesis are still incompletely defined, the development of specific cell lines has greatly aided in defining the molecular events of Cd-induced lung carcinogenesis. However, the precise mechanistic details of the initiation of Cd-induced bronchial epithelial transformation are yet to be elucidated. Higher expressions of major metallothionein (MT) isoforms are associated with both Cd-induced and lung cancers. Specifically, MT-1A and MT-2A levels were shown to be significantly increased in CCT-LC as compared to control, suggesting that

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MT may increase its expression in the lung to provide protection from Cd-induced toxicity. Although Cd does not directly induce mutagenesis, chronic Cd treatment in human bronchial epithelial cells may impart DNA damage and decrease DNA repair capacity and genomic instability in an indirect manner.

The initiation and progression of Cd-induced carcinogenesis are complex processes. The factors contributing to cancer development can vary significantly in their source, duration, concentrations and route of exposure. Cd in particular acts as a double edge sword, by causing cell death as well as cell-survival. Induction of cell survival and proliferation, which leads to transformation, suggests that Cd is a potent carcinogen. On the other hand, it may enhance cell death by a variety of mechanisms, thus leading to tissue pathology and organ damage. In either case, the outcome of exposure to Cd on the cellular level is dependent not only upon the duration and level of exposure, but also on intrinsic tissue specificity and current metabolic state. The organs discussed either share some overlapping or a unique mechanistic features in response to Cd exposure and there are many open areas that needs further exploration. Identifying the possible mechanism will enhance an exceptional way towards investigating of some therapeutic intervention.