

CADMIUM CARCINOGENESIS – SOME KEY POINTS

RAKOTWÓRCZOŚĆ KADMU – KLUCZOWE ZAGADNIENIA

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Abstract

The article presents briefly the main mechanisms of cadmium carcinogenesis and the most important sites of cancer (lung, breast, prostate, testes, kidney) induced by cadmium. In spite of some evidence showing carcinogenic potential of cadmium, further research is still required to elucidate the relative contributions of various molecular mechanisms involved in cadmium carcinogenesis.

Keywords: cadmium, cancer, carcinogenesis

Streszczenie

Przedstawiono w skrócie główne mechanizmy karcinogenezy wywołanej przez kadm oraz najbardziej częste miejsca występowania nowotworu indukowanego przez kadm (płuca, piersi, prostata, jądra, nerki). Mimo wielu dowodów wykazujących działanie karcinogenne kadmu konieczne są dalsze badania, aby wyjaśnić względny udział różnych mechanizmów molekularnych biorących udział w karcinogenezie wywołanej przez kadm.

Słowa kluczowe: kadm, nowotwory, karcinogeneza

Cadmium is a toxic, nonessential, and bioaccumulating heavy metal widely used in industry as a colour pigment, in several alloys and most commonly in re-chargeable nickel-cadmium batteries. Metallic cadmium has mostly been used as an anti-corrosion agent. Production, consumption and emission of this metal to the environment worldwide have increased dramatically during 20th century [1, 2].

Since cadmium is highly persistent in the environment, it affects human health both through occupational and environmental exposures. Cadmium exerts multiple toxic effects, and has been classified as a human carcinogen by the International Agency for Research on Cancer [2].

Cadmium accumulates primarily in liver and kidney where it is bound to metallothioneins, a low molecular weight metal binding proteins thought to detoxify the metal through high affinity sequestration [3]. There is evidence, that the metal may play a role in the initiation of cancer, by increasing the metastatic potential of existing cancer cells. It has been demonstrated that cadmium induces cancer by multiple mechanisms: (1) aberrant gene expression, (2) inhibition of DNA damage repair, (3) induction of oxidative stress, and (4) inhibition of apoptosis. The most important among them is oxidative stress because of its involvement in Cd-induced aberrant gene expression, inhibition of DNA damage repair, and apoptosis [4]. Results of

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experimental studies have shown that depending on the dose, route and duration of exposure, cadmium can cause damage to various organs including the lung, breast, liver, kidney, bones, testes and placenta [4].

Several studies show that inhaled cadmium is a potent pulmonary carcinogen in the rats, supporting its potential as a human carcinogen. Large numbers of studies found that occupational cadmium exposure is associated with lung cancer in humans [2]. It is estimated that workers in certain occupations are exposed to cadmium at significantly higher levels than the general public. Similarly, people living in areas contaminated with cadmium are exposed to higher amounts of the metal. In this way chronic inhalation of cadmium causes pulmonary adenocarcinomas [5, 6]. There is evidence that carcinogenicity due to metals is the result of the production of the reactive oxygen species. Inhaled metals are not biodegradable. Therefore, they are deposited and remain for long periods in various areas of the pulmonary tissue.

Some studies have looked at the influence of cadmium as one of environment risk factor on breast cancer. There is evidence that cadmium may have estrogenicity [7, 8]. *In vivo* and *in vitro* studies show cadmium acting like an estradiol activating estrogens receptor through a high-affinity interaction with the hormone binding domain of the receptor. Regulation of expression and activity of estrogens receptors plays an essential role in the growth, differentiation and prognosis of human breast cancer. Some studies reported that cadmium exposure increased uterine weight, induced the expression of progesterone receptor, increased the proliferation of the endometrium and promoted growth and development of the mammary glands increasing the formation of side branches and alveolar buds as well as the production of casein and whey acidic protein in mice [9]. Greater concentration of cadmium was determined in urine, blood, and breast tissue of breast cancer patients than in controls [10, 11]. Epidemiological study revealed twice as high risk of breast cancer in women with creatinine-adjusted urine cadmium $>0.58 \mu\text{g/g}$ compare to those with cadmium $<0.26 \mu\text{g/g}$ [12].

Cadmium exposure has also been linked to human prostate cancer [1]. Cadmium relation between cancer of the prostate or testes in humans is unclear in spite of suggestive results in rats. Parenteral administration or oral exposure to cadmium resulted in proliferative lesions or tumours of the prostate and testes in rats. The pathogenesis of cadmium-induced prostate cancer involved the effect of cadmium on the testes manifested by a positive dose response with low doses of cadmium but not

with high doses. High doses of cadmium produced testicular degeneration reducing testosterone production. Cadmium induced testicular hemorrhagic necrosis in rat testes if it was given parenterally, oral cadmium exposure resulted in testes tumours [2, 13, 14].

Recent studies suggest that cadmium may be a cause of renal cancer. It accumulates in kidney cells, particularly those of the proximal tubular epithelium, and the damage caused is associated with development of chronic kidney disease, characterized by proximal tubular necrosis and proteinuria. Some epidemiologic studies showed positive associations between occupational exposure to cadmium and the risk of renal cancer [13, 15, 16].

Other target sites for cadmium carcinogenesis in humans (liver, stomach) are still investigated [4].

In conclusion, large results of studies show carcinogenic potential of cadmium to experimental animals and human beings. However, further research is still required to elucidate relative contributions of various molecular mechanisms involved in cadmium carcinogenesis.

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