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Cadmium toxicity in plants: Is there any analogy to its carcinogenic effect in mammalian cells?

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Abstract

Cadmium is a heavy metal, which is classified as a human carcinogen and is known to be toxic to plants. However, plants do not respond to this metal by massive cell proliferation. In this review the various aspects of cadmium toxicity in plants are compared to related processes in mammalian cells. The following issues are discussed: cellular uptake of Cd ions, their intracellular transport, the effects on cellular signaling, nucleic acids and proteins, modification of gene expression, cell cycle control and apoptosis. Reviewed data suggest that such features as: ability to remove the oxidized proteins, slightly different regulation of cell cycle genes, specific pattern of apoptosis, makes plants resistant to Cd^{2+}-induced uncontrolled cell proliferation.

Introduction

Cadmium is a heavy metal, which is widely recognized as a serious environmental pollutant. Although the existence of cadmium containing carbonic anhydrase from marine diatom *Thalassiosira weissflogii* has been recently described (Lane *et al.* 2005), it is commonly accepted that Cd^{2+} is non-essential metal. The International Agency for Research on Cancer has classified cadmium as human carcinogen (Waalkes 2000). Despite of many similar cytotoxic and genotoxic effects caused by Cd^{2+} to both plant and animal cells, the first ones generally do not respond to metal by massive cell proliferation. Plants are usually resistant to neoplastic transformation and plant-specific tumors arise only as result of interaction with pathogens, such as *Agrobacterium* or gall-forming insect (Doonan & Hunt 1996) and are not induced by environmental factors, such as heavy metals. In plants Cd^{2+} cause various effects, such as inhibition of photosynthesis, respiration, nitrogen metabolism as well as the decrease of water and mineral uptake (Sanita di Toppi & Gabbrielli 1999). Those Cd^{2+}-induced changes in plant metabolism finally lead to inhibition of plant growth. Cd^{2+} inhibits cell proliferation in mammals as well and it induces apoptosis. However, in mammalian cells Cd^{2+} may causes cancer, if metal induces mutations in critical genes and/or if it stimulates the cellular signals, which promote cell proliferation. Although the final reaction of plants and mammals to Cd^{2+} may be different, many Cd^{2+}-related processes are common in both types of cells. They include the Cd^{2+} effects on nucleic acids, proteins, gene expression and apoptosis. At least parts of them are connected with Cd^{2+}-related production of reactive oxygen species (ROS), which are responsible for damage of a variety of biomolecules (Wang *et al.* 2004). Although Cd^{2+}, unlike other heavy metals (such as Cu), seems not to act directly on the production of ROS (via Fenton and/or Harber-Weisss reaction) its toxicity is undoubtedly connected with increased level of ROS. The development of an organism, the size of its organs and tissues, depends on species-specific genetic program and environmental signals, which influence cell decision to remain quiescent, to

differentiate, to undergo programmed cell death or to enter cell division and divide. The adverse effects displayed by Cd^{2+} on growth and reproduction of plant and animal cells suggest that Cd^{2+} interferes with mechanisms regulating cell division (Waisberg *et al.* 2003; Sobkowiak & Deckert 2003, 2004).

The aim of this review is to look at those Cd^{2+}-induced processes in plants, which are known to be correlated with carcinogenesis in mammals. Cd^{2+} enters human and animal body mostly via plants, through food chain. Therefore, the understanding of Cd^{2+}-related molecular events is crucial for elaborating the efficient and targeted protection against metal toxicity for all living organisms.

Cellular uptake, intracellular transport and signaling

The heavy metal transport into plant cells is dependent on the presence of mycorrhizas, the binding properties of the cell wall and root exudates (Das *et al.* 1997; Hall 2002). However, the first active structure regulating the Cd^{2+} uptake, which seems to be target for metal toxicity is the plasma membrane (Hall 2002). The various experimental approaches, including yeast models, have been recently used to identify plant membrane transport proteins, which are involved in Cd^{2+} uptake (Williams *et al.* 2000; Clemens 2001; Hall 2002; Cobbett 2003; Mills *et al.* 2003). Cd^{2+}, similarly to other non-essential metals, is thought to enter plant cells through cation transporters with broad substrate specificity. There are informations that Cd^{2+} uptake by plant plasma membranes is mediated by ZIP proteins (IRT1 and ZNT1), Nramp (Natural resistance associated macrophage protein), LCT1 (Low-affinity cation transporter) as well as by Ca^{2+} and K^+ channels (Korshunova *et al.* 1999; Pence *et al.* 2000; Thomine *et al.* 2000; Williams *et al.* 2000; Clemens 2001; Perfus-Barbeoch *et al.* 2002; Hall & Williams 2003; Lindberg *et al.* 2004). In cytosol, Cd^{2+} is bound by chelators, such as phytochelatins and citric acid and then sequestered in the vacuole (for review, see Clemens 2001). In the latter process the participation of ABC-type (ATP-binding cassette) transporters, such as AtMRP, AtHMA4 and TcHMA4, is postulated (Bovet *et al.* 2003; Mills *et al.* 2003; Bernard *et al.* 2004) as well as the involvement of Cation diffusion facilitator (CDF) (Clemens 2001). It is also hypothesized that Cd^{2+} may reach the vacuole by direct transport, involving the Cd^{2+}/H^+ antiport activity (Rauser 1995; Clemens 2001). The same mechanism has been recently shown to operate in plasma membranes (Burzyński *et al.* 2005).

In animal cells the Cd^{2+} uptake occurs by related pathways, however, most of the Cd^{2+} enters animal cells by Ca^{2+}-channels, both the receptor-operated and voltage-sensitive type (Beyersmann & Hechtenberg 1997).

There are limited data on Cd^{2+}-induced signaling pathway in plant cells. Molecular and biochemical studies suggest that abiotic stress signaling in plants involves Ca^{2+} changes, mitogen activated protein kinase (MAPK) cascades and transcriptional activation of stress-responsive genes (Xiong & Zhu 2001). In animals Cd^{2+} induces Ca^{2+} release from internal stores and activate calcium-signaling pathway (Waisberg *et al.* 2003). It is suggested that Cd^{2+} in plants causes both the perturbation of intracellular calcium level and interfere with calcium signaling, by substituting Ca^{2+} in calmodulin regulation (Ghelis *et al.* 2001; Perfus-Barbeoch *et al.* 2002). The MAPK pathway is involved in the transduction of extracellular signals to intracellular targets in all eukaryotes. It was recently shown that Cd^{2+} activates four different MAP kinases (SIMK, MMK2, MMK3 and SAMK) in alfalfa (Jonak *et al.* 2004) and one (OsMAPK2) in rice (Yeh *et al.* 2004), whereas in animal cells Cd^{2+} activate three major MAP kinases (ERK, JNK, p38) (Wang & Shi 2001). However, it is not clear if activation of MAP kinases occurs by direct action of Cd^{2+} or through ROS, which also activate MAP kinase cascade in *Arabidopsis* (Kovtun *et al.* 2000). Recent data suggest that ROS and redox regulation play a central role in signaling in both plant and animal cells (Mahalingam & Fedoroff 2003; Laloi *et al.* 2004) and therefore they may also mediate Cd^{2+} signaling pathway. The signaling, which involves transcriptional activation of Cd^{2+}-responsive genes is described in the latter section (Modification of gene expression).

Effect on nucleic acids and proteins

It was shown that in plants moderated and relative high Cd^{2+} level (100–500 μM) increased RNA

content, which was however, due to Cd^{2+}-induced decrease of RNase activity (Hirt *et al.* 1989; Shah & Dubey 1995). The data concerning the Cd^{2+} effect on RNA level in animals is conflicting and, depending on the model system, show either the inhibition or stimulation of RNA content in cells under cadmium stress (Beyersmann & Hechtenberg 1997).

Since the Cd^{2+} is considered as human carcinogen and mutagen its effect on DNA is better known, especially in animal cells. Cd^{2+}-induced changes in DNA involve direct and/or indirect interaction with DNA. The direct interaction is result of covalent binding between Cd^{2+} and guanine and adenine moieties in DNA (Hossain & Huq 2002). The binding of Cd^{2+} to DNA is not a mutagenic event *per se*, but may lead to DNA damage indirectly. The primary targets of Cd^{2+} are proteins interacting with DNA, because of theirs easier accessibility and multiple liganding side chains. Cd^{2+} can substitute for zinc in coordination complex of zinc-finger motif of transcription factors (Hartwig 2001). The indirect interaction of Cd^{2+} on DNA is also associated with the changes in DNA synthesizing enzymes and DNA repair processes (Banfalvi *et al.* 2000) as well as oxidative damage of DNA (Filipic & Hei 2004). The Cd^{2+}-induced DNA damages have been described in tobacco (Fojtová & Kovarik 2000, Gichner *et al.* 2004), broad bean (Koppen & Verschaeve 1996) and soybean, in which it was accompanied by the decrease in DNA synthesis (Sobkowiak & Deckert 2004). It was recently shown that cadmium is a mutagen that acts by inhibiting mismatch repair (MMR) in yeast and human cells (Jin *et al.* 2003; McMurray & Tainer 2003). The components of MMR system act on lesion comprising single-base-pair mismatches, small extrahelical loops or hydrogen-bound structures, such as hairpins. Those changes, when remained un-repaired, can cause the base substitution, frameshift mutations or can form the repetitive sites near DNA breaks. These finally led to gene mutation and microsatellite instability that in animal cells are connected with predisposition to cancer (McMurray & Tainer 2003). So far it is not know which element of MMR system is poisoned by Cd^{2+}, but presumably the same mechanism may acts in plants. They contain the related set of DNA repair enzymes (Tuteja *et al.* 2001), although MMR system in plants display the higher specialization for particular mismatches and/or sequence contexts (Wu *et al.* 2003). However the only enzyme described so far to be involved in repair of Cd^{2+}-induced DNA damages in plants is telomerase (Fojtová *et al.* 2002). The emerging pattern of Cd-induced genotoxicity in plants may therefore be the same as in other organisms and includes: the Cd^{2+}-induced damage of DNA and inactivation of DNA repair machinery, which is required to deal with constant impairment of genetic material.

Apart from nucleic acids, the proteins are the targets of Cd^{2+}-induced damages. Cadmium displays the high affinity to cysteine, glutamate, aspartate and histidine and often competes with zinc for a variety of important binding sites in cells, including those, which are potentially important in gene regulation or enzyme activity (Waalkes 2000). Protein lesions can also result from Cd^{2+}-related oxidative stress. ROS, produced by Cd^{2+} action, induce the formation of disulfide bonds and thus inhibit all protein functions that depend on the presence of reduced cysteine residues. ROS can also lead to oxidation of amino acid residue side chains, formation of protein–protein cross-linkages, and oxidation of the protein backbone resulting in protein fragmentation (Berlett & Stadtman 1997). Detecting the protein carbonylation is usually used for identification of oxidized proteins. Carbonylated proteins are marked for proteolysis, but can escape degradation and form high-molecular weight aggregates that have been associated with the large number of human age-related disorders, including cancer (Nyström 2005). It was shown that Cd^{2+} caused the oxidative modification of proteins in pea plants and oxidized proteins were more efficiently degraded, which was correlated with the increased proteolytic activity (Romero-Puertas *et al.* 2002). The proteins, which in plants are most susceptible to oxidative modifications, are: HSP70, enzymes involved in photosynthesis and alleviation of oxidative stress (Romero-Puertas *et al.* 2002; Johansson *et al.* 2004). Recent data indicate that, contrary to other organisms, plants can actively remove the oxidized proteins prior to bolting and flower development (Johansson *et al.* 2004). Thus, it seems that plants can cope with Cd^{2+}-induced oxidized proteins in better way than other organisms. This feature may contribute to plant

resistance to certain Cd^{2+}-related disorders observed in humans and animals.

Modification of gene expression

The Cd^{2+}-induced modification of gene expression is regarded as a major factor responsible for various disorders in both plants and animals, including humane carcinogenesis. In the later case the two main groups of genes are activated. The first one involved proto-oncogene (immediate response genes) and the second ones are stress response genes, which participate in protective mechanism providing detoxification both by heavy metal binding and generation of antioxidant substances (Waisberg *et al.* 2003). Proto-oncogens undergo transcriptional activation when quiescent cells are exposed to cadmium. They encoded transcription factors regulating genes involved in cell proliferation and differentiation and are frequently overexpressed in tumors. Among Cd^{2+}-induced proto-oncogenes are: c-Fos, c-Jun, c-Myc and p53 as well as translation factors (Waisberg *et al.* 2003; Joseph *et al.* 2004). None of this component was shown to participate in plant cells response to Cd^{2+} stress. C-Myc and c-Jun-like proteins are involved in plants in such abiotic stress as drought and salt (Mikołajczyk *et al.* 2000; Bartels & Sunkar 2005), but there is no information on their contribution in metal response. On the other hand, the analysis of *Arabidopsis* genome showed the absence of p53 gene (Vandepoele *et al.* 2002). Screening of cadmium-responsive genes in *Arabidopsis* has shown that plants activated a set of transcription factors involved in reaction to cold, salt, dehydration and phytohormones and genes involved in oxidative and protein denaturing stress response and in sulfur metabolism (Suzuki *et al.* 2001). Transcription profiling of Cd^{2+}-treated plants have confirmed that there are few upregulated transcription factors (Kovalchuk *et al.* 2005). As metal response elements (MRE) have not been found in plants, there are not respective MRE binding transcription factors (MTF). Proteome analysis of the cadmium response was performed in *Saccharomyces cerevisiae* and indicated the following group of proteins induced by Cd^{2+}: antioxidant enzymes, heat shock proteins and chaperones, proteases, sulfur amino acid and glutathione biosynthesis enzymes (Vido *et al.* 2001). The above components are generally similar to those induced by Cd^{2+} in human and animal cells (Waisberg *et al.* 2003) and are rather involved in metal detoxification and protein refolding than in regulation of cell proliferation. Theirs effect on growth may be therefore secondary.

The lack of informations concerning the participation of proto-oncogene-like proteins in plant Cd^{2+}-response may by the crucial factor responsible for the opposite effect of this metal on proliferation and tumor formation in plants and animals. However, there are still large group of Cd^{2+}-induced genes and proteins which function is unknown in both plant and animal cells.

Modulation of cell proliferation

Cell proliferation proceeds by a coordinated process known as the cell cycle. Regulation of cell cycle plays a fundamental role in growth and development of all eukaryotic organisms, whereas the disordered cell cycle leads to many human cancers (Vermeulen *et al.* 2003). The cell cycle is governed by a highly conserved protein complex consisting of cyclin-dependent kinases (CDKs) and cyclin proteins, which act together with multiple regulatory proteins such as: CDK-inhibitory proteins, the WEE kinase, retinoblastoma-related and E2F proteins (for Review, see Inze 2005). CDK/cyclin complexes are required at two control points of the cell cycle: between G1 and S phase and between G2 and mitosis (Mironov *et al.* 1999; Stals & Inze 2001). The basic cell cycle machinery is similar in both plant and animal cells, however, certain differences exists, especially in the larger number and variety of plant CDK and cyclins, which may be connected with the plant-specific processes. In animals important role at the G1/S transition play Myb transcription factor, which regulates, among others, S-specific cyclin D and E (Pelengaris & Khan 2003). The overexpression of cyclin E is observed in many tumors, and the fact that Cd^{2+} is an inducer of c-Myb gene contribute to increased cell proliferation. However, c-Myb genes have not been found to be activated by Cd^{2+} in plants. Additionally, c-Myb-like factor in plants regulates the transcription of G2/M genes, especially mitotic cyclin B1, but not G1/S genes, like in animals (Ito *et al.* 2001; Araki *et al.* 2004). The developmental consequences related to increased

expression of cell cycle genes, such as cyclins, are also different in plants and animals. In plants overexpression of cyclin B and D cause also the acceleration of cell division, but an increase in cell number is compensated by a decrease in cell size. Finally, such changes of cell cycle genes expression do not lead to essential alteration in plant development and shape (for review, see Inze 2005). The direct effect of Cd^{2+} on plant cell cycle progression, cyclin B1 and CDK expression has been analyzed in soybean cells. It was shown that Cd^{2+} affects the S phase, by causing the earlier entry of the cells into S phase and by decreasing the rate of DNA synthesis, which was connected with DNA damage. Simultaneously, cyclin B1 mRNA was decreased, whereas CDK mRNA was not affected. It is concluded that Cd^{2+} acts on plant cell cycle at two major checkpoints: G1/S – by damaging of DNA, and G2/M – by decreasing the cyclin B1 mRNA (Sobkowiak & Deckert 2003, 2004). The presented data may therefore suggest that various effect of Cd^{2+} on proliferation of plant and animal cells may be connected with different effect of the metal on cyclin expression: in mammals Cd^{2+} induces the cyclin D and E expression by activation of Myb-type transcription factor, whereas in plants Cd^{2+} causes the inhibition of cyclin B expression. These effects seem to act independently on ROS, which impair cell cycle progression both in plant and animal cells (Reichheld *et al.* 1999; Boonstra & Post 2004).

Cadmium induced apoptosis

Cd^{2+}-induced apoptosis in mammals proceeds by mitochondria-dependent pathway and activation of caspases-3, -8 and -8 (Pulido & Parish 2003). Although the function of mitochondria is impaired in Cd^{2+}-treated plants (Sanita di Toppi & Gabbrielli 1999) it is not known if they are the primary targets in cadmium induced apoptosis. Caspase-like proteins has been recently described in plants (Sanmartin *et al.* 2005), however, theirs participation in Cd^{2+}-induced apoptosis has not been described so far. On the other side, the apoptic hallmark, as oligonukleosomal DNA fragmentation, are induced by Cd^{2+} in both plant and mammalian cells, however, the sequence of events leading to this effect differs in both types of cells. Apoptic DNA fragmentation in plant cells occurs at the higher Cd^{2+} concentrations as compared to human cells and after longer metal treatment (Fojtova & Kovarik 2000). It may suggest the higher resistance of plants to Cd^{2+}-induced degradation of DNA.

Conclusions

''Cancer is a group of genetic diseases affecting fundamental aspect of cellular function, including DNA repair, the cell cycle, apoptosis, differentiation, and cell–cell contact'' (Klug *et al.* 2005). Provided here data suggest that Cd^{2+}, at least in part, can affects all those processes, both in mammalian and plants cells. The emerging picture indicates that such features as: the ability to remove the oxidized proteins, slightly different regulation of cell cycle genes (mostly cyclins), lack of one important cell cycle regulators (p53), different pattern of apoptosis, may make plants more resistant to Cd-induced uncontrolled cell proliferation. Recently Inze (2005) stated, ''Plants have an astonishing developmental plasticity and despite the dramatic effect of some cell cycle perturbations, seeds can often be obtained''. By understanding cadmium toxicity in plants and by use this knowledge in practice we can hope that these seeds will not be contaminated by substances, which are harmful to plant-eating organisms.

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