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Review

Biochemical and medical importance of vanadium compounds

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Vanadium belongs to the group of transition metals and is present in the air and soil contaminants in large urban agglomerations due to combustion of fossil fuels. It forms numerous inorganic compounds (vanadyl sulfate, sodium metavanadate, sodium orthovanadate, vanadium pentoxide) as well as complexes with organic compounds (BMOV, BEOV, METVAN). Depending on the research model, vanadium compounds exhibit antitumor or carcinogenic properties. Vanadium compounds generate ROS as a result of Fenton's reaction or of the reaction with atmospheric oxygen. They inactivate the $Cdc25B_2$ phosphatase and lead to degradation of Cdc25C, which induces G_2/M phase arrest. In cells, vanadium compounds activate numerous signaling pathways and transcription factors, including PI3K-PKB/Akt-mTOR, NF-κB, MEK1/2-ERK, that cause cell survival or increased expression and release of VEGF. Vanadium compounds inhibit p53-dependent apoptosis and promote entry into the S phase of cells containing functional p53 protein. In addition, vanadium compounds, in particular organic derivatives, have insulin-mimetic and antidiabetic properties. Vanadium compounds lower blood glucose levels in animals and in clinical trials. They also inhibit the activity of protein tyrosine phosphatase 1B. By activating the PI3K-PKB/Akt pathway, vanadium compaunds increase the cellular uptake of glucose by the GLUT4 transporter. The PKB/Akt pathway is also used to inactivate glycogen synthase kinase-3. The impact of vanadium compounds on inflammatory reactions has not been fully studied. Vanadium pentoxide causes expression of COX-2 and the release of proinflammatory cytokines in a human lung fibroblast model. Other vanadium compounds activate NF-κB in macrophages by activating IKKβ.

Key words: vanadium, pollution, cancer, diabetes, insulin-mimetic action, inflammation

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NATURAL OCCURRENCE OF VANADIUM

Vanadium is a transition metal, owing its name to Vanadís – Norse goddess of beauty and fertility. It is estimated that more than 60 thousand tons of this element are emitted into the atmosphere each year as the result of human activities (mostly combustion of fossil fuels) (Aragón & Altamirano-Lozano, 2001). This is due to high vanadium concentrations in both crude oil (3–260 μg/g) and hard coal (14–56 μg/g). Atmospheric pollution with vanadium of natural origin is relatively low and estimated at several tons annually. The consequence of emission of large amounts of vanadium into the atmosphere is the relatively high concentration (20–300 ng/m^3) of this element in the air of big cities, with values reaching up to 10 mg/m^3 observed in the New York City and other large urban agglomerations (Aragón & Altamirano-Lozano, 2001; Lin *et al.*, 2004). Soils in areas not subject to anthropogenic changes contain small amounts of vanadium, originating mostly from volcanic rocks (Poledniok & Buhl, 2003; Nadal *et al.*, 2004). Industrial activities result in a significant increase in these levels, reaching 19.3 μg/g of soil in the vicinity of a crude oil refinery in Catalonia (Nadal *et al.*, 2004). Vanadium present in soil is accumulated in plants (Nadal *et al.*, 2004; Marcano *et al.*, 2006). Contamination with vanadium is also observed in water reservoirs: rivers, lakes and seas. Bottom sediments of the Persian Gulf contain vanadium at concentrations as high as 100 μg/g of dry sediment (Pourang *et al.*, 2005). About 10% of groundwater samples from California and some other states of the USA contain vanadium in amounts exceeding 25 μg/dm^3 (Wright & Belitz, 2010). This is due to vanadium being washed out of water-bearing rocks (Wright & Belitz, 2010).

As evidenced by studies of vanadium levels in the hair of residents of different countries, Poland's population as a whole is not significantly exposed to high levels of vanadium. The measured value is of the order of 0.055 μg/g, being three times lower than the value of 0.171 μg/g for residents of the U.S., Canada or India (Stefańska *et al.*, 2005). Hair vanadium content in students in Białystok is even lower (0.038 μg/g) due to a non-polluted environment (Stefańska *et al.*, 2005). On the other hand, vanadium pollution is observed in the Upper Silesia region (Poledniok & Buhl, 2003). Industrial pollution of the Silesian regions combined with automobile exhaust fumes is transported by rivers into the sea and are deposited in bottom sediments of the rivers. Thus, the sediments in the Bay of Szczecin are highly polluted with vanadium and other elements originating

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Abbreviations: BEOV, bis(ethylmaltolato)oxovanadium(IV); BKOV, bis(kojato)oxovanadium(IV); BMOV, bis(maltolato)oxovanadium(IV); $Cdc25B_2$, cell division control/cycle 25 homolog B_2; Cdc25C, cell division control/cycle 25 homolog C; CksHs1, human cyclin dependent kinase subunit type 1; COX-2, cyclooxygenase 2; CXCL10, C-X-C motif chemokine 10; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; E2F, Transcription factor E2F; GLUT4, Glucose transporter type 4; GSK3, glycogen synthase kinase-3; HIF-1α, hypoxia inducible factor 1α; IC_{50}, half maximal inhibitory concentration; IκBα, inhibitor of κB activity α; IKKβ, IκB kinase subunit β; IL-6 Interleukin-6; IL-8, Interleukin-8; MAPK, mitogen-activated protein kinase; MEK1/2, MAPK/ERK kinase 1 and 2; MIP-2, macrophage inflammatory protein-2; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NF-AT, nuclear factor of activated T-cells; p38, protein 38; p53, protein 53; PI3K, phosphatidylinositol 3-kinase; PKB/Akt, protein kinase B; PTP-1B, protein tyrosine phosphatase 1B; pRb, retinoblastoma protein; ROS, reactive oxygen species; SSB, single-strand break; TNFα, Tumor necrosis factor α; VEGF, vascular endothelial growth factor.

from distant regions (Glasby *et al.*, 2004). Due to the river runoff, vanadium pollution of the Bay of Szczecin is comparable to the pollution of the Persian Gulf oilfields (Glasby *et al.*, 2004; Pourang *et al.*, 2005).

VANADIUM IN LIVING ORGANISMS

After entering the circulatory system via the gastrointestinal or respiratory tract, vanadium compounds are transported by transferrin or, less commonly, by albumin or low-molecular components of plasma, such as citrates and, to a lesser extent, lactates or phosphates (Kiss *et al.*, 2000). Next, vanadium compounds are accumulated in kidneys and, to a smaller degree, in spleen, bones and liver (Hansen *et al.*, 1982). Human body contains ca. 100 μg of vanadium, with equilibrium between the amount of vanadium excreted from the body and the amount of vanadium absorbed from the outside environment (up to several dozen micrograms daily) (Byrne & Kosta, 1978; Kordowiak & Holko, 2009). For certain mammals, such as rats, vanadium is a necessary microelement; however, due to the omnipresence of this element at low concentrations, no necessity of nutritional intake of vanadium was determined in humans (Lin *et al.*, 2004; Kordowiak & Holko, 2009).

Aquatic organisms, such as ascidians, accumulate vanadium in circulatory system cells known as vanadocytes (Kawakami *et al.*, 2006; Kawakami *et al.*, 2009). Blood vanadium levels in these organisms exceed 10 mM, while the sea concentration of vanadium is about 35 nM (Kawakami *et al.*, 2009). Vanadium compounds are transported into the cytoplasm of vanadocytes, bound and reduced to the +4 oxidation state by the binding proteins – vanabins, and finally deposited in the acidic environment of vacuoles as vanadium compounds in the +3 oxidation state (Kawakami *et al.*, 2006).

In human body, vanadium has an oxidation state of +4 or +5 (Kordowiak & Holko, 2009). Vanadium compounds in the +5 oxidation state (metavanadates or orthovanadates, forming oligomers) enter cells via anionic channels, while vanadium compounds in the +4 oxidation state (vanadyl cations) permeate the cellular membrane by diffusion (Fig. 1) (Aureliano & Gândara, 2005; Kordowiak & Holko, 2009). Vanadium forms numerous derivatives with low-molecular organic compounds. Vanadium organic derivatives have been synthesized since 1990s (Thomson *et al.*, 2009). Examples of such compounds include maltol complexes such as BMOV or BEOV – compounds of insulin-mimetic activity characterized by low toxicity compared to inorganic vanadium compounds; naglivan, a cystein derivative complex, or BKOV (Fig. 2) (Scior *et al.*, 2009; Thompson *et al.*, 2009; Kordowiak & Holko, 2009). As the result of reactions with intracellular antioxidants, vanadium within the cells has predominantly an oxidation state of +4 (Aureliano & Gândara, 2005; Kordowiak & Holko, 2009).

Vanadium compounds in the +4 oxidation state are oxidized by atmospheric oxygen to the +5 oxidation state with accompanying emission of a superoxide anion radical (Cuesta *et al.*, 2011). As a result of reduction with NADPH, the reaction may proceed with generation of hydrogen peroxide (Cuesta *et al.*, 2011). Moreover, vanadium in the +4 oxidation state can be oxidized to the +5 oxidation state with generation of a hydroxyl radical via a Fenton-like reaction (Cuesta *et al.*, 2011). In cells vanadium compounds oxidized to the +5 oxidation state by atmospferic oxygen or ROS are in equilibrium with vanadium compounds reduced to the +4 oxidation state by intracellular antioxidants. Thanks to their structural similarity to phosphate anions, orthovanadium anions may act as inhibitors of protein phosphatases or bind to such molecules as ADP or NAD to form ADPV and NADV, respectively (Crans *et al.*, 2004).

VANADIUM COMPOUNDS AND DIABETES

Vanadium compounds have insulin-mimetic properties. First reports on therapeutic properties of vanadium compounds in diabetes appeared as early as in 1899 (Thompson & Orvig 2006). Many studies were conducted on inorganic and organic vanadium derivatives in induced-diabetes animal models, in which the studied compounds were found to impact the levels of glucose, cholesterol and triacylglycerols, with no harmful side effects upon prolonged administration (Yanardag *et al.*, 2003; Koyuturk *et al.*, 2005; Niu *et al.*, 2007; Wei *et al.*, 2007; Li *et al.*, 2009). The studied vanadium compounds normalize renal function and the indicator liver enzyme levels in diabetic model animals (Yanardag *et al.*, 2003; Koyuturk *et al.*, 2005). Many experiments were also performed in diabetic patients, confirming the therapeutic effect of the studied vanadium compounds on blood glucose levels with little side effects (Thompson *et al.*, 2009).

Vanadium compounds are characterized by multiple ways of action resulting in reduction of blood glucose

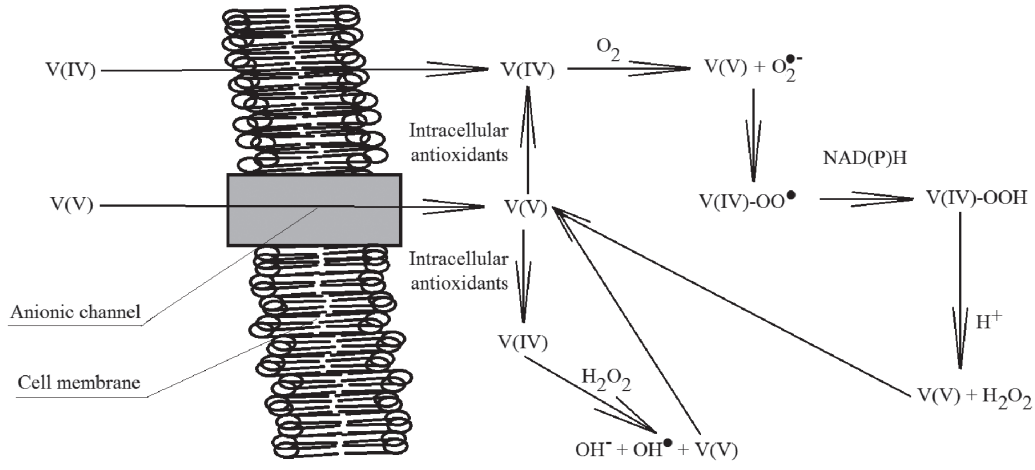

Figure 1. Biochemical pathways of inorganic vanadium compounds in the cytoplasm
According to Aureliano & Gândara, 2005; Kordowiak & Holko, 2009; Cuesta *et al.*, 2010 (modified).

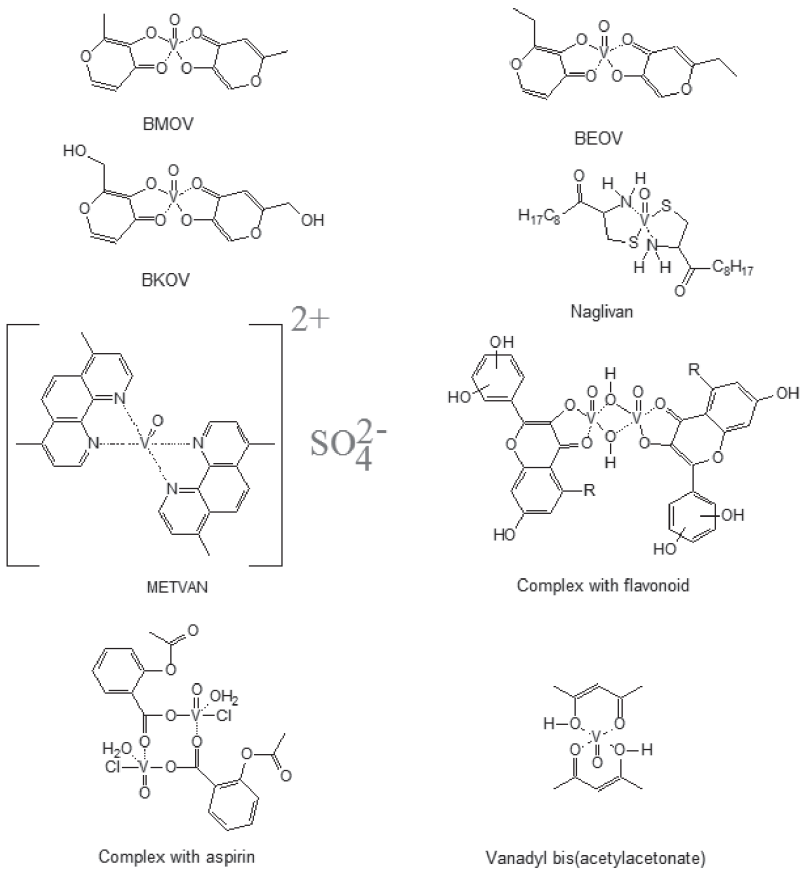

Figure 2. Examples of organic vanadium derivatives of medical importance
According to Dong *et al.*, 2000; D'Cruz & Uckun, 2001; Scior *et al.*, 2008; Thompson *et al.*, 2009, (modified).

levels (Vardatsikos *et al.*, 2009). Thanks to their structural similarity to orthophosphate anions, the orthovanadate anion and vanadium organic derivatives are inhibitors of protein phosphotyrosine phosphatases (Fig. 4). (Crans *et al.*, 2004). They may inhibit the activity of PTP-1B, which is an enzyme responsible for dephosphorylation of insulin receptors, causing insulin resistance (Scior *et al.*, 2009; Scior *et al.*, 2010). However, the mechanism of phosphotyrosine phosphatase inactivation is not yet fully understood, as it appears that this process may also be caused by free radicals (Bartosz, 2003). One may assume that vanadium compounds cause PTP-1B inhibition via ROS (Kaltschmidt *et al.*, 2000). Another mechanism of reduction of blood glucose levels by vanadium compounds is the activation of PKB/Akt leading to increased uptake of glucose by the GLUT4 transporter (Vardatsikos *et al.*, 2009). Activation of PKB/Akt results also in phosphorylation and inactivation of GSK3, leading to stimulation of the synthesis of glycogen from glucose (Vardatsikos *et al.*, 2009).

VANADIUM AND TUMOR CELLS

In chemically-induced tumor models in experimental animals, vanadium compounds show chemopreventive properties by means of optimization of phase I and phase II xenobiotic transformation enzymes (Bishayee *et al.*, 2000; Ray *et al.*, 2007; Chakraborty *et al.*, 2007). Inorganic and organic vanadium compounds were tested in human tumor cell line models. The results were promising with respect to introduction of va-

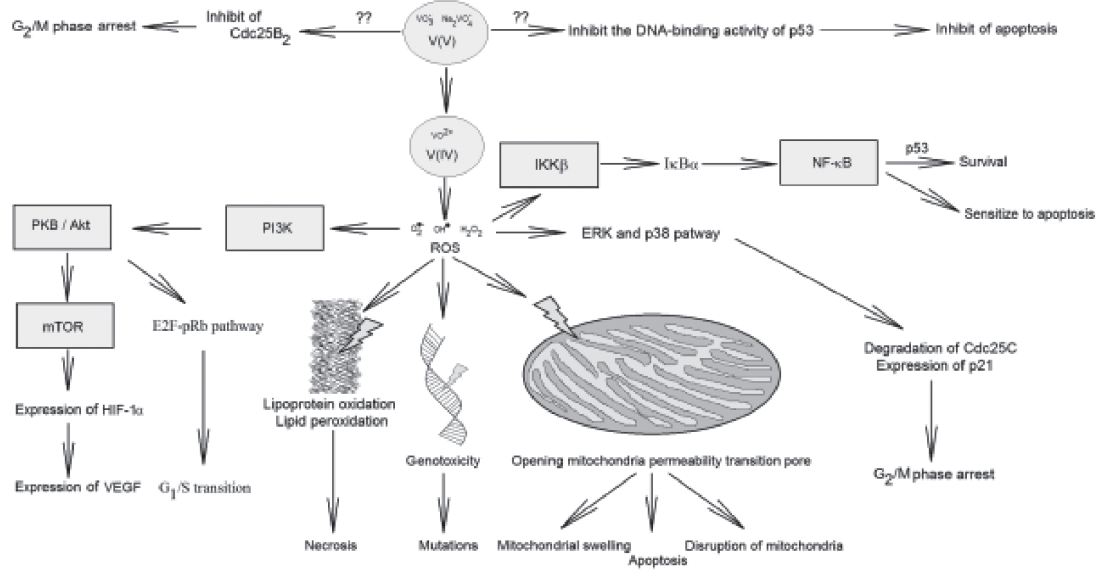

Figure 3. Some antitumor and cancerogenic pathways of inorganic vanadium compounds
According to Chen *et al.*, 1999; Woo *et al.*, 1999; Gao *et al.*, 2002; Lapenna *et al.*, 2002; Zhang *et al.*, 2003; Zhang *et al.*, 2004; Wozniak & Blasiak, 2004; Soares *et al.*, 2008; Zhao *et al.*, 2010; Morita *et al.*, 2010; Parrondo, 2010 (modified).

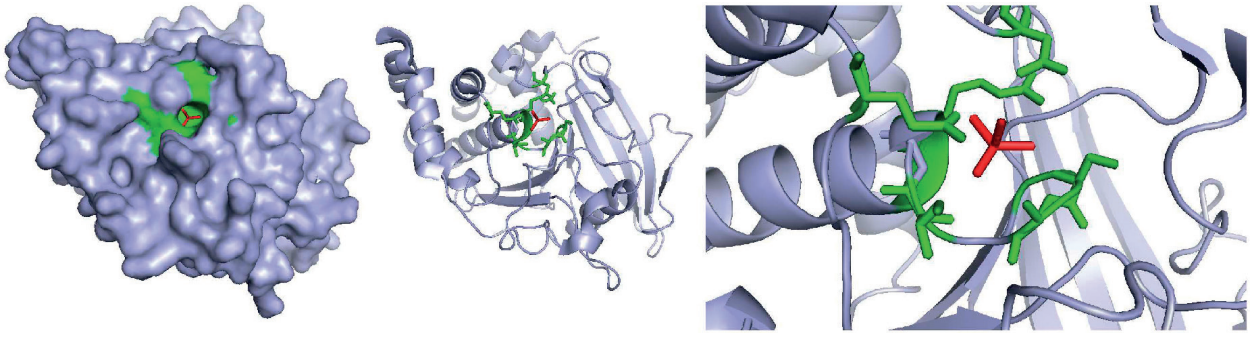

Figure 4. Phosphatase 1B with its inhibitor, the orthovanadate anion.
From left to right: model of the spatial structure of the enzyme; tertiary structure of the enzyme with the orthovanadate anion and aminoacyl residues in its catalytic center; a close-up of the catalytic center of the enzyme with a model of the orthovanadate anion and aminoacyl residues interacting with the inhibitor according to Brandão *et al.*, 2010 (modified).

nadium compounds into the therapy due to their low IC_{50} (several micromoles depending on cell line and vanadium compound), antiproliferative and proapoptotic effects (Kordowiak *et al.*, 2007; Holko *et al.*, 2008; Fu *et al.*, 2008; Klein *et al.*, 2008; Molinuevo *et al.*, 2008). Vanadium compounds are genotoxic and cause selective oxidation of pyrimidine bases and SSB-type DNA damages in tumor cells, which are characterized by less efficient DNA repair processes (Fig. 3) (Wozniak & Blasiak, 2004; Rodríguez-Mercado *et al.*, 2011). Another mechanism of action of vanadium compounds on tumor cells is the opening of mitochondrial permeability transition pores, leading to the release of cytochrome c and induction of apoptosis (Soares *et al.*, 2008; Zhao *et al.*, 2010). Vanadium compounds inhibit the activity of phosphatase $Cdc25B_2$, responsible for dephosphorylation and activation of Cdk2 in cyclin-A and -B complexes (Woo *et al.*, 1999). Inhibition of $Cdc25B_2$ induces G_2/M phase arrest. Another mechanism of action of vanadium compounds on the G_2/M phase arrest is the degradation of Cdc25C *via* MAPK cascades: ERK and p38 (Zhang *et al.*, 2003; Liu *et al.*, 2012). Another target for the vanadium compounds is CksHs1 (Arvai *et al.*, 1995). Experiments on embryonic p53-knockout fibroblasts led to conclusion that vanadium compounds promote S phase entry of cells with wild-type p53 and induce G_2/M phase arrest of p53-knockout cells (Zhang *et al.*, 2002). In addition, vanadium compounds activate NF-κB by the action of ROS in various cell types (Chen *et al.*, 1999; Jaspers *et al.*, 2000). The role of NF-κB in tumor cells is subject to discussion, as activation or overexpression of this transcription factor in non-tumor cells as well as in certain tumor cell lines leads to cell survival and inhibition of apoptosis (Parrondo, 2010). However, in prostate cancer cell lines treated with anticancer drugs, chemical activation of NF-κB increases the percentage of apoptotic cells (Parrondo, 2010). Inactivation of NF-κB in cells treated with vanadium compounds, such as pervanadate, decreases apoptotic cell death (Kaltschmidt *et al.*, 2000).

One group of organic vanadium compounds tested as antitumor drugs includes complexes of the vanadyl cation with phenanthroline derivatives, such as METVAN [bis(4,7-dimethyl-l,10-phenanthroline) sulfatooxovanadium(IV); $VO(SO_4)(Me_2\text{-}Phen)_2$] (Narla *et al.*, 2000; Narla *et al.*, 2001). These vanadium compounds are characterized by antiproliferation IC_{50} values of the order of several micromoles in many tumor cell lines and, when present at low concentrations, induce apoptosis and inhibit the cell cycle (Narla *et al.*, 2000; Dong *et al.*, 2000). METVAN is cytotoxic against many tumor cell lines (IC_{50} of less than 1 μM), reduces the invasiveness of leukemia by inhibiting the activity of metalloproteinases and damages mitochondria by generating ROS, thus causing apoptosis (Dong *et al.*, 2000; Narla *et al.*, 2001). One of side effects of the treatment is inhibition of spermatogenesis and apoptosis of male germ cells (D'Cruz & Uckun, 2001).

Vanadium compounds have carcinogenic properties and stimulate tumor development. Vanadyl cations and V_2O_5, a vanadium compound found in air pollution, generate ROS that cause DNA damage which may lead to mutations and, as a consequence, development of tumor cells (Ehrlich *et al.*, 2008). Vanadium compounds have also antiapoptotic properties (Morita *et al.*, 2010). Activation of NF-κB by ROS generated by vanadium compounds leads to cell survival and inhibition of apoptosis (Chen *et al.*, 1999; Jaspers *et al.*, 2000). In addition, by means of altered p53 phosphorylation, vanadates cause disturbances in the course of apoptosis (Suzuki *et al.*, 2007; Morita *et al.*, 2010). Another mechanism of carcinogenic action of vanadium compounds is activation of PI3K by generation of hydrogen peroxide (Gao *et al.*, 2002). PI3K activates PKB/Akt, which promotes S phase entry *via* the E2F-pRb pathway (Zhang *et al.*, 2004). In addition, activation of the PI3K-PKB/Akt-mTOR pathway results in increased expression of HIF-1α and, as a consequence, expression and release of VEGF (Gao *et al.*, 2002). Expression of VEGF stimulated by vanadium compounds is controlled not only by the PI3K-PKB/Akt pathway, but also by two other pathways: MEK1/2-ERK or increase in intracellular calcium levels (Li *et al.*, 2005). Release of VEGF causes angiogenesis and thus contributes to the development of tumor.

The effects of vanadium compounds depend on many factors, mainly on the type of cells, the type of vanadium compound and its dose. It appears that the proapoptotic or antiapoptotic effect of vanadium compounds depends largely on the cell type. The key protein, defects of which diametrically change the effects of vanadium compounds, is p53 (a large number of tumor cell types have defects in the gene encoding this protein). In p53-defective cells (tumor cells or non-tumor p53-knock out cells), vanadium compounds inhibit the cell cycle and thus induce apoptosis (Zhang *et al.*, 2002). Activation of NF-κB by ROS generated by vanadium compounds enhances the apoptotic effect (Parrondo, 2010). In contrast, in p53-functional cells, disturbed phosphorylation of p53 leads to inhibition of apoptosis (Morita *et al.*, 2010). In addition, vanadium compounds stimulate the

cell cycle, thus inhibiting apoptosis, as both processes are mutually connected (Zhang *et al.*, 2002). Moreover, NF-κB activation inhibits apoptosis of tumor cells. Another important fact is that vanadium compounds cause much more DNA damage in tumor cells compared to non-tumor cells when present at the same levels (Wozniak & Blasiak, 2004). Extensive DNA damage leads to apoptosis of tumor cells while a less intensive damage evoked by vanadium compounds in non-tumor cells may stimulate synthesis and activation of repair enzymes, thus protecting those cells from apoptosis. The above processes promote tumor cell growth at early stages of the disease and have an antitumor effect in the advanced stages of cancer. Studies in animals treated with carcinogens suggest that vanadium compounds used at low levels have selective effects on the tumor cells (Ray *et al.*, 2007; Chakraborty *et al.*, 2007).

VANADIUM COMPOUNDS AND INFLAMMATORY REACTIONS

The impact of vanadium compounds on inflammatory reactions has not been fully studied. Experiments conducted to date suggest that vanadates activate NF-κB, a transcription factor of key importance in inflammatory reactions (Chen *et al.*, 1999; Ye *et al.*, 1999). Studies conducted on RAW 264.7 macrophages showed that this was due to activation of IKKβ and degradation of IκBα (Chen *et al.*, 1999; Ye *et al.*, 1999). Activation of NF-κB leads to changes in expression of numerous genes, including TNFα and MIP-2, which belong to the CXC chemokine family (Ye *et al.*, 1999; Chong *et al.*, 2000). Another vanadium compound prevalent in air pollution and causing inflammatory reactions is vanadium pentoxide. Exposure to vanadium pentoxide-containing dust causes inflammatory reactions in lungs, leading to expression of, among others, COX-2, IL-6, IL-8 and CXCL10 (Ingram *et al.*, 2007; Rondini *et al.*, 2010). Vanadium pentoxide causes COX-2 expression in epithelial bronchial Beas-2B cells *via* the NF-AT pathway (Tang *et al.*, 2007). Another pathway for the increase in COX-2 expression, encompassing EGFR and the p38 cascade, was observed in A249 lung cancer cells (Chen *et al.*, 2006).

CONCLUSIONS AND FUTURE DIRECTIONS

Due to the ability to generate ROS, which exert nonspecific effects on different cell structures, vanadium compounds have many routes of action, sometimes diametrically opposite. They may have both antitumor and carcinogenic properties. The mechanisms of action of the vanadium compounds can be understood thanks to rapid advances in the knowledge of free radicals and the signaling pathways involving them. However, still little is known regarding the effect of vanadium compounds on the immune system and inflammatory reactions. New findings in this area may shed new light on the biochemical processes taking place in organisms treated with vanadium compounds. Currently, promising clinical trials of organic vanadium derivatives in the treatment of diabetes are under way. Soon they should be of common use. However, the effects of a long-term administration of low doses of vanadium as a potential carcinogen and correlation between the use of vanadium compounds and disorders of a free-radical background have not been fully studied yet. One of such diseases having a free-radical background is Parkinson's disease. Vanadium compounds induce ROS generation in the brain, which may contribute to degeneration of dopaminergic neuronal cells of the *substantia nigra*, which in turn leads to Parkinson's disease (Afeseh Ngwa *et al.*, 2009; Cuesta *et al.*, 2011).

It is possible that an antitumor therapy using vanadium compounds will be developed in the near future. However, due to the carcinogenic effect of vanadium, such treatment should be combined with numerous other drugs (such as anti-VEGF antibodies) to enhance the therapeutic effect of vanadium.

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